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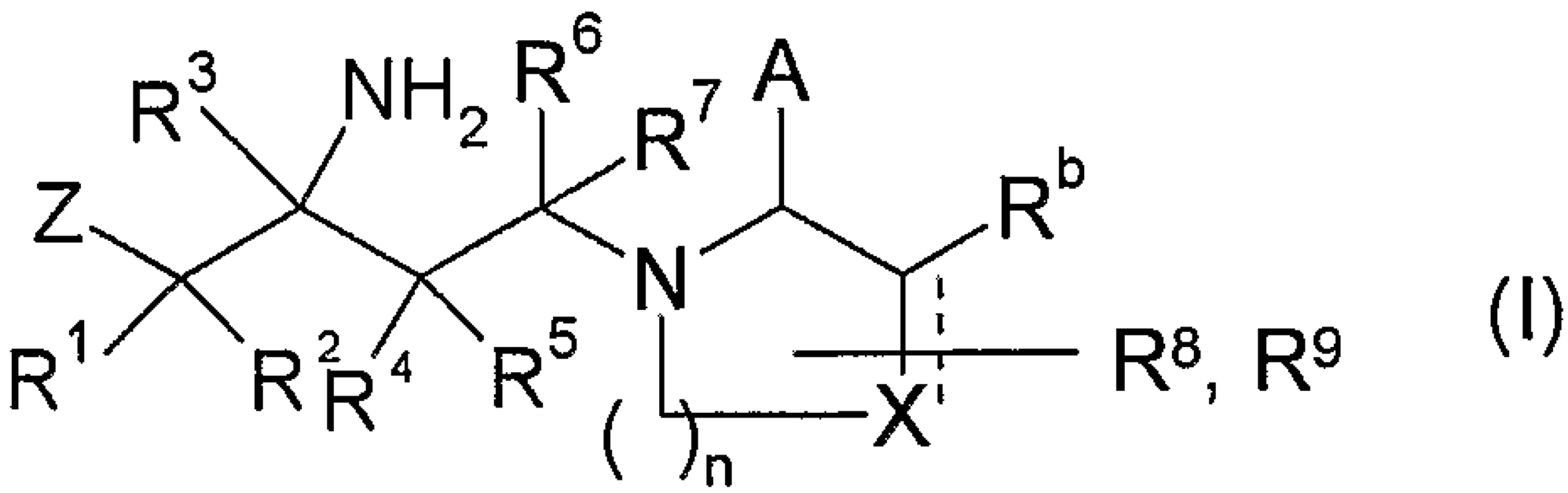
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(54) Titre : DERIVES DE 1-`(3R)-AMINO-4-(2-FLUORO-PHENYL)-BUTYL]-PYRROLIDINE-(2R)-ACIDE CARBOXILIQUE-BENZYLAMINE ET COMPOSES APPARENTES UTILISES COMME INHIBITEURS DE LA DIPEPTIDYL-PEPTIDASE IV (DPP-IV) DESTINES AU TRAITEMENT DU DIABETE NON INSULINO-DEPENDANT

(54) Title: 1-`(3R)-AMINO-4-(2-FLUORO-PHENYL)-BUTYL]-PYRROLIDINE-(2R)-CARBOXILIC ACID-BENZYL AMINE DERIVATIVES AND RELATED COMPOUNDS AS DIPEPTIDYL-PEPTIDASE IV (DPP-IV) INHIBITORS FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS



(I)

(57) Abrégé/Abstract:
The invention relates to compounds of formula (I), wherein R^{1-9},Z, n, X, A, and R^b have the meaning as cited in the description and the claims. Said compounds are useful as DPP-IV inhibitors. The invention also relates to the preparation of such compounds as well as the production and use thereof as medicament for the treatment of type 2 diabetes mellitus, obesity and lipid disorders.

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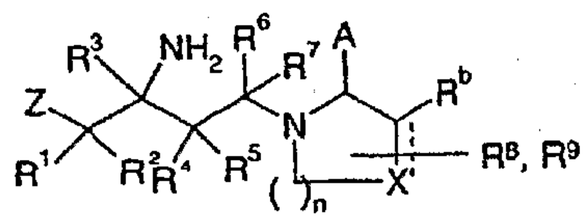
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(54) Title: 1-'(3R)-AMINO-4-(2-FLUORO-PHENYL)-BUTYL !-PYRROLIDINE-(2R)-CARBOXILIC ACID-BENZYL AMINE DERIVATIVES AND RELATED COMPOUNDS AS DIPEPTIDYL-PEPTIDASE IV (DPP-IV) INHIBITORS FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS



(I)

(57) Abstract: The invention relates to compounds of formula (I), wherein R^{1-9},Z, n, X, A, and R^b have the meaning as cited in the description and the claims. Said compounds are useful as DPP-IV inhibitors. The invention also relates to the preparation of such compounds as well as the production and use thereof as medicament for the treatment of type 2 diabetes mellitus, obesity and lipid disorders.

1-'(3R)-AMINO-4-(2-FLUORO-PHENYL)-BUTYL!-PYRROLIDINE-(2R)-CARBOXYLIC ACID-BENZYL AMINE DERIVATIVES ÄND RELATED COMPOUNDS AS DIPEPTIDYL-PEPTIDASE IV (DPP-IV) INHIBITORS FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

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.

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 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 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 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 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 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 sulphonylureas (*e.g.*, tolbutamide and glipizide) or meglitinide, which stimulate the pancreatic β-cells to secrete more insulin, and/or by injection of insulin when sulphonylureas 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 (sulphonylureas 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

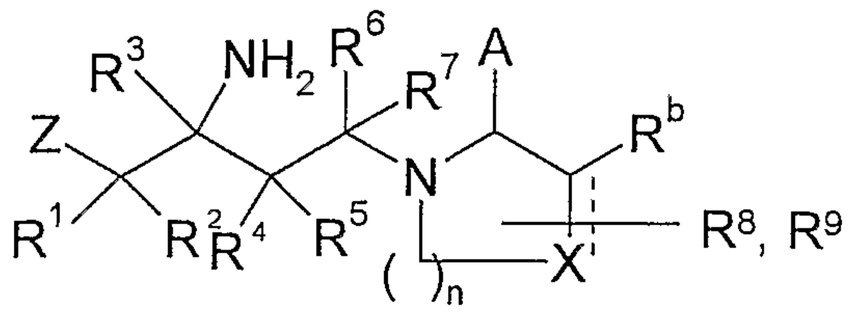
biochemical approaches that have been recently introduced or are still under development include treatment with alpha-glucosidase inhibitors (*e.g.*, acarbose) and protein tyrosine phosphatase-1B (PTP-1B) inhibitors.

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):



(I)

or a pharmaceutically acceptable salt thereof, wherein a dotted line indicates an optionally present double bond and wherein

Z is selected from the group consisting of phenyl; naphthyl; indenyl; C_{3-7} cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle, wherein Z is optionally substituted with one or more R^{10}, wherein R^{10} is independently selected from the group consisting of halogen; CN; OH; NH_2; oxo (=O), where the ring is at least partially saturated; R^{11}; and R^{12};

R^{11} is selected from the group consisting of C_{1-6} alkyl; O-C_{1-6} alkyl; and S-C_{1-6} alkyl, wherein R^{11} is optionally interrupted by oxygen and wherein R^{11} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{12} is selected from the group consisting of phenyl; heterocycle; and C_{3-7} cycloalkyl, wherein R^{12} is optionally substituted with one or more R^{13}, wherein R^{13} is independently selected from the group consisting of halogen; CN; OH; NH_2; oxo (=O), where the ring is at least partially saturated; C_{1-6} alkyl; O-C_{1-6} alkyl; and S-C_{1-6} alkyl;

R^1, R^4 are independently selected from the group consisting of H; F; OH; and R^{14};

R^2, R^5, R^6, R^7 are independently selected from the group consisting of H; F; and R^{15};

R^{14} is independently selected from the group consisting of C_{1-6} alkyl; O-C_{1-6} alkyl; N(R^{14a})-C_{1-6} alkyl; S-C_{1-6} alkyl; C_{3-7} cycloalkyl; O-C_{3-7} cycloalkyl; N(R^{14a})-C_{3-7} cycloalkyl; S-C_{3-7} cycloalkyl; -C_{1-6} alkyl-C_{3-7} cycloalkyl; O-C_{1-6} alkyl-C_{3-7} cycloalkyl; N(R^{14a})-C_{1-6} alkyl-C_{3-7} cycloalkyl; S-C_{1-6} alkyl-C_{3-7} cycloalkyl; heterocycle; O-heterocycle; N(R^{14a})-heterocycle; S-heterocycle; C_{1-6} alkyl-heterocycle; O-C_{1-6} alkyl-heterocycle; N(R^{14a})-C_{1-6} alkyl-heterocycle; S-C_{1-6} alkyl-heterocycle;

wherein R^{14} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{14a} is selected from the group consisting of H; and C_{1-6} alkyl;

optionally R^6 is selected from the group consisting of $-C(R^{6a}R^{6b})-O-C_{1-6}$ alkyl; $-C(R^{6a}R^{6b})-O-C_{3-7}$ cycloalkyl; $-C(R^{6a}R^{6b})-S-C_{1-6}$ alkyl; $-C(R^{6a}R^{6b})-S-C_{3-7}$ cycloalkyl; $-C(R^{6a}R^{6b})-N(R^{6c})-C_{1-6}$ alkyl; and $-C(R^{6a}R^{6b})-N(R^{6c})-C_{3-7}$ cycloalkyl, wherein each C_{1-6} alkyl and C_{3-7} cycloalkyl is optionally substituted with one or more R^{6d}, wherein R^{6d} is independently selected from the group consisting of halogen; C_{1-6} alkyl; and C_{3-7} cycloalkyl;

R^{6a}, R^{6b}, R^{6c} are independently selected from the group consisting of H; and C_{1-6} alkyl;

R^{15} is independently selected from the group consisting of C_{1-6} alkyl; C_{3-7} cycloalkyl; and $-C_{1-6}$ alkyl-C_{3-7} cycloalkyl, wherein R^{15} is optionally substituted with one or more R^{15a}, wherein R^{15a} 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, R^4, R^5, R^6, R^{6a}, R^{6b}, R^7 independently selected from the group consisting of R^1/R^2; R^2/R^3; R^3/R^4; R^4/R^5; R^5/R^6; R^{6a}/R^{6b} and R^6/R^7 form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more of R^{15b}, wherein R^{15b} is independently selected from the group consisting of F; Cl; and OH;

n is 0, 1, 2 or 3;

X is selected from the group consisting of $-C(R^{16}R^c)-$; $-C(R^a)=CR^c-$; $-C(R^{16}R^a)-CR^c=$, $-C(R^{16}R^a)-O-$; $-C(R^{16}R^a)-S-$; $-C(R^{16}R^a)-S(O)-$; $-C(R^{16}R^a)-S(O)_2-$; $-C(R^{16}R^a)-NR^c-$; and $-C(R^{16}R^a)-CR^{17}R^c-$;

R^8 is selected from the group consisting of H; F; OH; and C_{1-6} alkyl, optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

R^9, R^{16}, R^{17} are independently selected from the group consisting of H; F; and C_{1-6} alkyl, optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

R^a, R^b, R^c, A are independently selected from the group consisting of H; F; Cl; CN; -Y-H; and -Y-T, provided that at most two of R^a, R^b, R^c, A are independently -Y-T;

optionally R^c is selected from the group consisting of -O-C_{1-6} alkyl; -O-C_{3-7} cycloalkyl; -S-C_{1-6} alkyl; -S-C_{3-7} cycloalkyl; -N(R^{18})-C_{1-6} alkyl; and -N(R^{18})-C_{3-7} cycloalkyl, wherein each C_{1-6} alkyl and C_{3-7} cycloalkyl is optionally substituted with one or more R^{18a}, wherein R^{18a} is independently selected from the group consisting of halogen; C_{1-6} alkyl; and C_{3-7} cycloalkyl, provided that n is 1;

R^{18} is independently selected from the group consisting of H; C_{1-6} alkyl;

optionally a pair of R^a, R^b, R^c selected from the group consisting of R^a/R^c; and R^b/R^c forms a ring Z^1;

Z^1 is selected from the group consisting of Z^2; and Z^3;

Z^2 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein Z^2 is optionally substituted with one or more R^{19}; wherein R^{19} is independently selected from the group consisting of halogen; CN; $COOR^{20}$; OR^{20}; $C(O)N(R^{20}R^{20a})$; $S(O)_2N(R^{20}R^{20a})$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{20})$-C_{1-6} alkyl; $S(O)_2N(R^{20})$-C_{1-6} alkyl; $S(O)N(R^{20})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{20})S(O)_2$-C_{1-6} alkyl; and $N(R^{20})S(O)$-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

Z^3 is selected from the group consisting of C_{3-7} cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle; wherein Z^3 is optionally substituted with one or more R^{21}, wherein R^{21} is independently selected from the group consisting of halogen; CN; OR^{22}; oxo (=O), where the ring is at least partially saturated; $N(R^{22}R^{22a})$; $COOR^{22}$; $C(O)N(R^{22}R^{22a})$; $S(O)_2N(R^{22}R^{22a})$; $S(O)N(R^{22}R^{22a})$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $N(R^{22})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{22})$- C_{1-6} alkyl;

$N(R^{22})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{22})$-C_{1-6} alkyl; $S(O)N(R^{22})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{22})S(O)_2$-C_{1-6} alkyl; and $N(R^{22})S(O)$-C_{1-6} alkyl; 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^{21} is $C(O)R^{22}$, provided that $C(O)R^{22}$ is bound to a nitrogen, which is a ring atom of a heterocycle or heterobicycle;

R^{20}, R^{20a}, R^{22}, R^{22a} 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;

Y is selected from the group consisting of a covalent bond; -C_{1-6} alkyl-T^0-; -C_{1-6} alkyl-O-T^0-; -C_{1-6} alkyl-S-T^0-; -C_{1-6} alkyl-S(O)-T^0-; -C_{1-6} alkyl-$S(O)_2$-T^0-; -C_{1-6} alkyl-$N(R^{23})$-T^0-; -C(O)-O-; -C(O)O-C_{1-6} alkyl-T^0-; -C_{1-6} alkyl-C(O)O-; -C_{1-6} alkyl-C(O)O-C_{1-6} alkyl-T^0-; $-C(O)N(R^{23})$-; $-C(O)N(R^{23})$-C_{1-6} alkyl-T^0-; -C_{1-6} alkyl-$C(O)N(R^{23})$-; and -C_{1-6} alkyl-$C(O)N(R^{23})$-C_{1-6} alkyl-T^0-; wherein each C_{1-6} alkyl is optionally substituted with one or more F;

T^0 is selected from the group consisting of a covalent bond; -C_{1-6} alkyl-; -C_{1-6} alkyl-O-; -C_{1-6} alkyl-$N(R^{23})$-; -C(O)-; -C(O)-C_{1-6} alkyl-; -C(O)-C_{1-6} alkyl-O-; -C(O)-C_{1-6} alkyl-$N(R^{23})$-; -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-$N(R^{23})$-; $-C(O)N(R^{23})$-; $-C(O)N(R^{23})$-C_{1-6} alkyl-; $-C(O)N(R^{23})$-C_{1-6} alkyl-O-; $-C(O)N(R^{23})$-C_{1-6} alkyl-$N(R^{24})$-; -$S(O)_2$-; -$S(O)_2$-C_{1-6} alkyl-; -$S(O)_2$-C_{1-6} alkyl-O-; and -$S(O)_2$-C_{1-6} alkyl-$N(R^{23})$-; wherein each C_{1-6} alkyl is optionally substituted with one or more F;

R^{23}, R^{24} are independently selected from the group consisting of H; and C_{1-6} alkyl;

T is selected from the group consisting of T^1; and T^2;

T^1 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T^1 is optionally substituted with one or more R^{25}; wherein R^{25} is independently selected from the group consisting of halogen; CN; R^{26}; COOH; OH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; $COOT^3$; OT^3; ST^3; $C(O)N(R^{27})T^3$; $S(O)_2N(R^{27})T^3$; $S(O)N(R^{27})T^3$ and T^3;

T^2 is selected from the group consisting of C_{3-7} cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle; wherein T^2 is optionally substituted with one or more R^{28}, wherein R^{28} is independently selected from the group consisting of halogen; CN; R^{29}; OH; oxo (=O), where the ring is at least partially saturated; NH_2; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; $COOT^3$; OT^3; $C(O)N(R^{30})T^3$; $S(O)_2N(R^{30})T^3$; $S(O)N(R^{30})T^3$; $N(R^{30})T^3$; and T^3;

optionally R^{28} is $C(O)R^{30}$, provided that $C(O)R^{30}$ is bound to a nitrogen, which is a ring atom of a heterocycle or heterobicycle;

R^{26} is selected from the group consisting of C_{1-6} alkyl; $O\text{-}C_{1-6}$ alkyl; $S\text{-}C_{1-6}$ alkyl; $COO\text{-}C_{1-6}$ alkyl; $OC(O)\text{-}\ C_{1-6}$ alkyl; $C(O)N(R^{31})\text{-}C_{1-6}$ alkyl; $S(O)_2N(R^{31})\text{-}C_{1-6}$ alkyl; $S(O)N(R^{31})\text{-}C_{1-6}$ alkyl; $S(O)\text{-}C_{1-6}$ alkyl; $S(O)_2\text{-}C_{1-6}$ alkyl; $N(R^{31})S(O)_2\text{-}C_{1-6}$ alkyl; and $N(R^{31})S(O)\ \text{-}C_{1-6}$ alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more R^{32}, wherein R^{32} is independently selected from the group consisting of F; $COOR^{33}$; $C(O)N(R^{33}R^{34})$; $S(O)_2N(R^{33}R^{34})$; OR^{33}; $N(R^{33}R^{34})$; T^3; $O\text{-}T^3$; and $N(R^{33})\text{-}T^3$;

R^{29} is selected from the group consisting of C_{1-6} alkyl; $O\text{-}C_{1-6}$ alkyl; $S\text{-}C_{1-6}$ alkyl; $N(R^{35})\text{-}C_{1-6}$ alkyl; $COO\text{-}C_{1-6}$ alkyl; $OC(O)\text{-}\ C_{1-6}$ alkyl; $C(O)N(R^{35})\text{-}\ C_{1-6}$ alkyl; $N(R^{35})\text{-}C(O)\text{-}\ C_{1-6}$ alkyl; $S(O)_2N(R^{35})\text{-}C_{1-6}$ alkyl; $S(O)N(R^{35})\text{-}C_{1-6}$ alkyl; $S(O)\text{-}C_{1-6}$ alkyl; $S(O)_2\text{-}C_{1-6}$ alkyl; $-N(R^{35})S(O)_2\text{-}C_{1-6}$ alkyl; and $-N(R^{35})S(O)\text{-}C_{1-6}$ alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more R^{32a}, wherein R^{32a} is independently selected from the group consisting of F; $COOR^{36}$; $C(O)N(R^{36}R^{37})$; $S(O)_2N(R^{36}R^{37})$; $S(O)N(R^{36}R^{37})$; OR^{36}; $N(R^{36}R^{37})$; T^3; $O\text{-}T^3$; and $N(R^{36})\text{-}T^3$;

R^{27}, R^{30}, R^{31}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37} are independently selected from the group consisting of H; and C_{1-6} alkyl;

T^3 is selected from the group consisting of T^4; and T^5;

T^4 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T^4 is optionally substituted with one or more R^{38}, wherein R^{38} is independently selected from the group consisting of halogen; CN; $COOR^{39}$; OR^{39}; $C(O)N(R^{39}R^{40})$; $S(O)_2N(R^{39}R^{40})$; C_{1-6} alkyl; $O\text{-}C_{1-6}$ alkyl; $S\text{-}C_{1-6}$ alkyl; $COO\text{-}C_{1-6}$ alkyl; $OC(O)\text{-}C_{1-6}$ alkyl; $C(O)N(R^{39})\text{-}C_{1-6}$ alkyl; $S(O)_2N(R^{39})\text{-}C_{1-6}$ alkyl; $S(O)N(R^{39})\text{-}C_{1-6}$ alkyl; $S(O)_2\text{-}C_{1-6}$ alkyl;

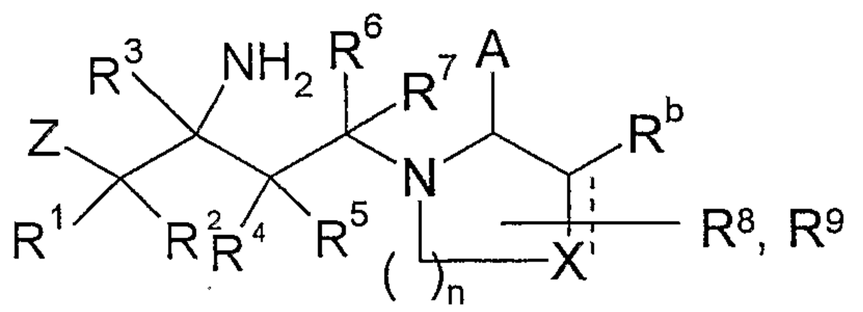
$S(O)$-C_{1-6} alkyl; $N(R^{39})S(O)_2$-C_{1-6} alkyl; and $N(R^{39})S(O)$-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

T^5 is selected from the group consisting of heterocycle; heterobicycle; C_{3-7} cycloalkyl; indanyl; tetralinyl; and decalinyl; wherein T^5 is optionally substituted with one or more R^{41}, wherein R^{41} is independently selected from the group consisting of halogen; CN; OR^{42}; oxo (=O), where the ring is at least partially saturated; $N(R^{42}R^{43})$; $COOR^{42}$; $C(O)N(R^{42}R^{43})$; $S(O)_2N(R^{42}R^{43})$; $S(O)N(R^{42}R^{43})$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $N(R^{42})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{42})$-C_{1-6} alkyl; $N(R^{42})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{42})$-C_{1-6} alkyl; $S(O)N(R^{42})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{42})S(O)_2$-C_{1-6} alkyl; and $N(R^{42})S(O)$-C_{1-6} alkyl; 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^{41} is $C(O)R^{42}$, provided that $C(O)R^{42}$ is bound to a nitrogen, which is a ring atom of a heterocycle or heterobicycle;

R^{39}, R^{40}, R^{42}, R^{43}, are independently selected from the group consisting of H; and C_{1-6} alkyl; C_{3-7} cycloalkyl; and -C_{1-6} alkyl-C_{3-7} cycloalkyl.

The invention further relates to compounds according to formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein a dotted line indicates an optionally present double bond and wherein

Z is selected from the group consisting of phenyl; naphthyl; indenyl; C_{3-7} cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle, wherein Z is optionally substituted with one or more R^{10}, wherein R^{10} is independently selected from the group

consisting of halogen; CN; OH; NH_2; oxo (=O), where the ring is at least partially saturated; R^{11}; and R^{12};

R^{11} is selected from the group consisting of C_{1-6} alkyl; O-C_{1-6} alkyl; and S-C_{1-6} alkyl, wherein R^{11} is optionally interrupted by oxygen and wherein R^{11} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{12} is selected from the group consisting of phenyl; heterocycle; and C_{3-7} cycloalkyl, wherein R^{12} is optionally substituted with one or more R^{13}, wherein R^{13} is independently selected from the group consisting of halogen; CN; OH; NH_2; oxo (=O), where the ring is at least partially saturated; C_{1-6} alkyl; O-C_{1-6} alkyl; and S-C_{1-6} alkyl;

R^1, R^4 are independently selected from the group consisting of H; F; and R^{14};

R^2, R^5, R^6, R^7 are independently selected from the group consisting of H; F; and R^{15};

R^{14} is independently selected from the group consisting of C_{1-6} alkyl; O-C_{1-6} alkyl; N(R^{14a})-C_{1-6} alkyl; S-C_{1-6} alkyl; C_{3-7} cycloalkyl; O-C_{3-7} cycloalkyl; N(R^{14a})-C_{3-7} cycloalkyl; S-C_{3-7} cycloalkyl; -C_{1-6} alkyl-C_{3-7} cycloalkyl; O-C_{1-6} alkyl-C_{3-7} cycloalkyl; N(R^{14a})-C_{1-6} alkyl-C_{3-7} cycloalkyl; S-C_{1-6} alkyl-C_{3-7} cycloalkyl; heterocycle; O-heterocycle; N(R^{14a})-heterocycle; S-heterocycle; C_{1-6} alkyl-heterocycle; O-C_{1-6} alkyl-heterocycle; N(R^{14a})-C_{1-6} alkyl-heterocycle; S-C_{1-6} alkyl-heterocycle; wherein R^{14} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{14a} is selected from the group consisting of H; and C_{1-6} alkyl;

optionally R^6 is selected from the group consisting of -C($R^{6a}R^{6b}$)-O-C_{1-6} alkyl; -C($R^{6a}R^{6b}$)-O-C_{3-7} cycloalkyl; -C($R^{6a}R^{6b}$)-S-C_{1-6} alkyl; -C($R^{6a}R^{6b}$)-S-C_{3-7} cycloalkyl; -C($R^{6a}R^{6b}$)-N(R^{6c})-C_{1-6} alkyl; and -C($R^{6a}R^{6b}$)-N(R^{6c})-C_{3-7} cycloalkyl, wherein each C_{1-6} alkyl and C_{3-7} cycloalkyl is optionally substituted with one or more R^{6d}, wherein R^{6d} is independently selected from the group consisting of halogen; C_{1-6} alkyl; and C_{3-7} cycloalkyl;

R^{6a}, R^{6b}, R^{6c} are independently selected from the group consisting of H; and C_{1-6} alkyl;

R^{15} is independently selected from the group consisting of C_{1-6} alkyl; C_{3-7} cycloalkyl; and -C_{1-6} alkyl-C_{3-7} cycloalkyl, wherein R^{15} is optionally substituted with one or more R^{15a}, wherein R^{15a} 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, R^4, R^5, R^6, R^{6a}, R^{6b}, R^7 independently selected from the group consisting of R^1/R^2; R^2/R^3; R^3/R^4; R^4/R^5; R^5/R^6; R^{6a}/R^{6b} and R^6/R^7 form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more of R^{15b}, wherein R^{15b} is independently selected from the group consisting of F; Cl; and OH;

n is 0, 1, 2 or 3;

X is selected from the group consisting of -$C(R^{16}R^c)$-; -$C(R^a)$=CR^c-; -$C(R^{16}R^a)$-CR^c=, -$C(R^{16}R^a)$-O-; -$C(R^{16}R^a)$-S-; -$C(R^{16}R^a)$-S(O)-; -$C(R^{16}R^a)$-$S(O)_2$-; -$C(R^{16}R^a)$-NR^c-; and -$C(R^{16}R^a)$-$CR^{17}R^c$-;

R^8 is selected from the group consisting of H; F; OH; and C_{1-6} alkyl, optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

R^9, R^{16}, R^{17} are independently selected from the group consisting of H; F; and C_{1-6} alkyl, optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

R^a, R^b, R^c are independently selected from the group consisting of H; F; Cl; CN; -Y-H; and -Y-T,

A is selected from the group consisting of –Y-H and –Y-T;

provided that at most two of R^a, R^b, R^c, A are independently -Y-T;

optionally R^c is selected from the group consisting of -O-C_{1-6} alkyl; -O-C_{3-7} cycloalkyl; -S-C_{1-6} alkyl; -S-C_{3-7} cycloalkyl; -N(R^{18})-C_{1-6} alkyl; and -N(R^{18})-C_{3-7} cycloalkyl, wherein each C_{1-6} alkyl and C_{3-7} cycloalkyl is optionally substituted with one or more R^{18a}, wherein R^{18a} is independently selected from the group consisting of halogen; C_{1-6} alkyl; and C_{3-7} cycloalkyl, provided that n is 1;

R^{18} is independently selected from the group consisting of H; C_{1-6} alkyl;

Optionally a pair of R^a, R^b, R^c selected from the group consisting of R^a/R^c; and R^b/R^c forms a ring Z^1;

Z^1 is selected from the group consisting of Z^2; and Z^3;

Z^2 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein Z^2 is optionally substituted with one or more R^{19}; wherein R^{19} is independently selected from the group consisting of halogen; CN; $COOR^{20}$; OR^{20}; $C(O)N(R^{20}R^{20a})$; $S(O)_2N(R^{20}R^{20a})$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{20})$-C_{1-6} alkyl; $S(O)_2N(R^{20})$-C_{1-6} alkyl; $S(O)N(R^{20})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{20})S(O)_2$-C_{1-6} alkyl; and $N(R^{20})S(O)$-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

Z^3 is selected from the group consisting of C_{3-7} cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle; wherein Z^3 is optionally substituted with one or more R^{21}, wherein R^{21} is independently selected from the group consisting of halogen; CN; OR^{22}; oxo (=O), where the ring is at least partially saturated; $N(R^{22}R^{22a})$; $COOR^{22}$; $C(O)N(R^{22}R^{22a})$; $S(O)_2N(R^{22}R^{22a})$; $S(O)N(R^{22}R^{22a})$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $N(R^{22})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{22})$-C_{1-6} alkyl; $N(R^{22})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{22})$-C_{1-6} alkyl; $S(O)N(R^{22})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{22})S(O)_2$-C_{1-6} alkyl; and $N(R^{22})S(O)$-C_{1-6} alkyl; 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^{21} is $C(O)R^{22}$, provided that $C(O)R^{22}$ is bound to a nitrogen, which is a ring atom of a heterocycle or heterobicycle;

R^{20}, R^{20a}, R^{22}, R^{22a} 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;

Y is selected from the group consisting of a covalent bond; -C_{1-6} alkyl-T^0-; -C_{1-6} alkyl-O-T^0-; -C_{1-6} alkyl-S-T^0-; -C_{1-6} alkyl-S(O)-T^0-; -C_{1-6} alkyl-$S(O)_2$-T^0-; -C_{1-6} alkyl-$N(R^{23})$-T^0-; -C(O)-O-; -C(O)O-C_{1-6} alkyl-T^0-; -C_{1-6} alkyl-C(O)O-; -C_{1-6} alkyl-C(O)O-C_{1-6} alkyl-T^0-; -C(O)$N(R^{23})$-; -C(O)$N(R^{23})$-C_{1-6} alkyl-T^0-; -C_{1-6} alkyl-C(O)$N(R^{23})$-; and -C_{1-6} alkyl-C(O)$N(R^{23})$-C_{1-6} alkyl-T^0-; wherein each C_{1-6} alkyl is optionally substituted with one or more F;

T^0 is selected from the group consisting of a covalent bond; -C_{1-6} alkyl-; -C_{1-6} alkyl-O-; -C_{1-6} alkyl-$N(R^{23})$-; -C(O)-; -C(O)-C_{1-6} alkyl-; -C(O)-C_{1-6} alkyl-O-; -C(O)-C_{1-6} alkyl-$N(R^{23})$-; -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-$N(R^{23})$-; -C(O)$N(R^{23})$-; -C(O)$N(R^{23})$-C_{1-6} alkyl-; -C(O)$N(R^{23})$-C_{1-6} alkyl-O-; -C(O)$N(R^{23})$-C_{1-6} alkyl-$N(R^{24})$-; -$S(O)_2$-; -$S(O)_2$-C_{1-6} alkyl-; -$S(O)_2$-C_{1-6} alkyl-O-; and -$S(O)_2$-C_{1-6} alkyl-$N(R^{23})$-; wherein each C_{1-6} alkyl is optionally substituted with one or more F;

R^{23}, R^{24} are independently selected from the group consisting of H; and C_{1-6} alkyl;

T is selected from the group consisting of T^1; and T^2;

T^1 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T^1 is optionally substituted with one or more R^{25}; wherein R^{25} is independently selected from the group consisting of halogen; CN; R^{26}; COOH; OH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; $COOT^3$; OT^3; ST^3; $C(O)N(R^{27})T^3$; $S(O)_2N(R^{27})T^3$; $S(O)N(R^{27})T^3$ and T^3;

T^2 is selected from the group consisting of C_{3-7} cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle; wherein T^2 is optionally substituted with one or more R^{28}, wherein R^{28} is independently selected from the group consisting of halogen; CN; R^{29}; OH; oxo (=O), where the ring is at least partially saturated; NH_2; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; $COOT^3$; OT^3; $C(O)N(R^{30})T^3$; $S(O)_2N(R^{30})T^3$; $S(O)N(R^{30})T^3$; $N(R^{30})T^3$; and T^3;

optionally R^{28} is $C(O)R^{30}$, provided that $C(O)R^{30}$ is bound to a nitrogen, which is a ring atom of a heterocycle or heterobicycle;

R^{26} is selected from the group consisting of C_{1-6} alkyl; $O\text{-}C_{1-6}$ alkyl; $S\text{-}C_{1-6}$ alkyl; $COO\text{-}C_{1-6}$ alkyl; $OC(O)\text{-}C_{1-6}$ alkyl; $C(O)N(R^{31})\text{-}C_{1-6}$ alkyl; $S(O)_2N(R^{31})\text{-}C_{1-6}$ alkyl; $S(O)N(R^{31})\text{-}C_{1-6}$ alkyl; $S(O)\text{-}C_{1-6}$ alkyl; $S(O)_2\text{-}C_{1-6}$ alkyl; $N(R^{31})S(O)_2\text{-}C_{1-6}$ alkyl; and $N(R^{31})S(O)\text{-}C_{1-6}$ alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more R^{32}, wherein R^{32} is independently selected from the group consisting of F; $COOR^{33}$; $C(O)N(R^{33}R^{34})$; $S(O)_2N(R^{33}R^{34})$; OR^{33}; $N(R^{33}R^{34})$; T^3; $O\text{-}T^3$; and $N(R^{33})\text{-}T^3$;

R^{29} is selected from the group consisting of C_{1-6} alkyl; $O\text{-}C_{1-6}$ alkyl; $S\text{-}C_{1-6}$ alkyl; $N(R^{35})\text{-}C_{1-6}$ alkyl; $COO\text{-}C_{1-6}$ alkyl; $OC(O)\text{-}C_{1-6}$ alkyl; $C(O)N(R^{35})\text{-}\ C_{1-6}$ alkyl; $N(R^{35})\text{-}C(O)\text{-}C_{1-6}$ alkyl; $S(O)_2N(R^{35})\text{-}C_{1-6}$ alkyl; $S(O)N(R^{35})\text{-}C_{1-6}$ alkyl; $S(O)\text{-}C_{1-6}$ alkyl; $S(O)_2\text{-}C_{1-6}$ alkyl; $-N(R^{35})S(O)_2\text{-}C_{1-6}$ alkyl; and $-N(R^{35})S(O)\text{-}C_{1-6}$ alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more R^{32a}, wherein R^{32a} is independently selected from the group consisting of F; $COOR^{36}$; $C(O)N(R^{36}R^{37})$; $S(O)_2N(R^{36}R^{37})$; $S(O)N(R^{36}R^{37})$; OR^{36}; $N(R^{36}R^{37})$; T^3; $O\text{-}T^3$; and $N(R^{36})\text{-}T^3$;

R^{27}, R^{30}, R^{31}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37} are independently selected from the group consisting of H; and C_{1-6} alkyl;

T^3 is selected from the group consisting of T^4; and T^5;

T^4 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T^4 is optionally substituted with one or more R^{38}, wherein R^{38} is independently selected from the group consisting of halogen; CN; $COOR^{39}$; OR^{39}; $C(O)N(R^{39}R^{40})$; $S(O)_2N(R^{39}R^{40})$; C_{1-6} alkyl; $O\text{-}C_{1-6}$ alkyl; $S\text{-}C_{1-6}$ alkyl; $COO\text{-}C_{1-6}$ alkyl; $OC(O)\text{-}C_{1-6}$ alkyl; $C(O)N(R^{39})\text{-}C_{1-6}$ alkyl; $S(O)_2N(R^{39})\text{-}C_{1-6}$ alkyl; $S(O)N(R^{39})\text{-}C_{1-6}$ alkyl; $S(O)_2\text{-}C_{1-6}$ alkyl; $S(O)\text{-}C_{1-6}$ alkyl; $N(R^{39})S(O)_2\text{-}C_{1-6}$ alkyl; and $N(R^{39})S(O)\text{-}C_{1-6}$ alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

T^5 is selected from the group consisting of heterocycle; heterobicycle; C_{3-7} cycloalkyl; indanyl; tetralinyl; and decalinyl; wherein T^5 is optionally substituted with one or more R^{41}, wherein R^{41} is independently selected from the group consisting of

halogen; CN; OR^{42}; oxo (=O), where the ring is at least partially saturated; $N(R^{42}R^{43})$; $COOR^{42}$; $C(O)N(R^{42}R^{43})$; $S(O)_2N(R^{42}R^{43})$; $S(O)N(R^{42}R^{43})$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $N(R^{42})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; $OC(O)$-C_{1-6} alkyl; $C(O)N(R^{42})$- C_{1-6} alkyl; $N(R^{42})$-$C(O)$-C_{1-6} alkyl; $S(O)_2N(R^{42})$-C_{1-6} alkyl; $S(O)N(R^{42})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; $S(O)$-C_{1-6} alkyl; $N(R^{42})S(O)_2$-C_{1-6} alkyl; and $N(R^{42})S(O)$-C_{1-6} alkyl; 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^{41} is $C(O)R^{42}$, provided that $C(O)R^{42}$ is bound to a nitrogen, which is a ring atom of a heterocycle or heterobicycle;

R^{39}, R^{40}, R^{42}, R^{43}, 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,

provided that if Z is phenyl, R^1 to R^9 are hydrogen, n is 1, X is CH_2 and R^b is hydrogen, then A is not –C(O)-NH_2 or –C(O)-NH(*t*-butyl).

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.

"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_{1-4} Alkyl" means an alkyl chain having 1 - 4 carbon atoms, e.g. at the end of a molecule methyl, ethyl, -$CH=CH_2$, -$C\equiv CH$, n-propyl, isopropyl, -$CH=CH-CH_3$, -CH_2-$CH=CH_2$, n-butyl, isobutyl, -$CH=CH-CH_2-CH_3$, -$CH=CH-CH=CH_2$, sec-butyl tert-butyl or amid, e.g. -CH_2-, -CH_2-CH_2-, -CH=CH-, -$CH(CH_3)$-, -$C(CH_2)$-, -$CH_2-CH_2-CH_2$-, -$CH(C_2H_5)$-, -$CH(CH_3)_2$-.

"C_{1-6} Alkyl" means an alkyl chain having 1 - 6 carbon atoms, e.g. C_{1-4} alkyl, methyl, ethyl, -$CH=CH_2$, -$C\equiv CH$, n-propyl, isopropyl, -$CH=CH-CH_3$, -$CH_2-CH=CH_2$, n-butyl, isobutyl, -$CH=CH-CH_2-CH_3$, -$CH=CH-CH=CH_2$, sec-butyl tert-butyl, n-pentane, n-hexane, or amid, e.g. -CH_2-, -CH_2-CH_2-, -CH=CH-, -$CH(CH_3)$-, -$C(CH_2)$-,

-CH_2-CH_2-CH_2-, -$CH(C_2H_5)$-, -$CH(CH_3)_2$-. Each hydrogen of a C_{1-6} alkyl carbon may be replaced by a substituent.

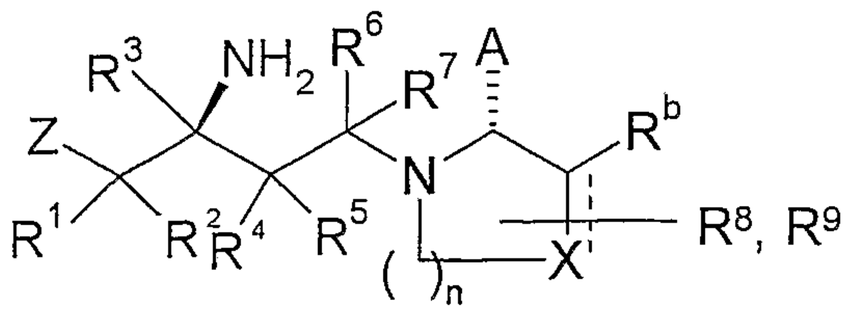
"C_{3-7} Cycloalkyl" or "C_{3-7} Cycloalkyl ring" means a cyclic alkyl chain having 3 - 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl. Each hydrogen of a cycloalkyl carbon may be replaced by a substituent.

"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 sulphur (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, sulpholane, pyran, dihydropyran, tetrahydropyran, imidazolidine, pyridine, pyridazine, pyrazine, pyrimidine, piperazine, piperidine, morpholine, tetrazole, triazole, triazolidine, tetrazolidine, azepine or homopiperazine. "Heterocycle" means also azetidine.

"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.

A preferred stereochemistry of compounds or a pharmaceutically acceptable salt thereof according to the present invention is shown in formula (Ia)



(Ia)

wherein Z, R^{1-9}, n, A, X and R^b have the meaning as indicated above.

Preferred compounds of formula (I) or (Ia) 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) or (Ia) 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 Z, R^{1-9}, n, A, X and R^b of the formula (I) or (Ia) independently have the following meaning. Hence, one or more of the substituents Z, R^{1-9}, n, A, X and R^b can have the preferred or more preferred meanings given below.

Preferably, Z is selected from the group consisting of phenyl; and heterocycle, wherein Z is optionally substituted with up to 3 R^{10}, which are the same or different. More preferred, Z is phenyl substituted with up to 2 R^{10}.

Preferably, R^{10} is selected from the group consisting of F; Cl; CN; and C_{1-6} alkyl.

It is preferred that R^1, R^2, R^4, R^5, R^6, R^7 are independently selected from the group consisting of H; F; and C_{1-6} alkyl.

Preferably, R^3 is H.

Preferably, n is 0 or 1. More preferably, n is 1.

Preferably, X is selected from the group consisting of $-C(R^{16}R^c)-$; $-C(R^{16}R^a)-O-$; $-C(R^{16}R^a)-NR^c-$; $-C(R^{16}R^a)-CR^{17}R^c$; and $-C(R^a)=CR^c-$.

More preferably, X is selected from the group consisting of -CH(R^c)-; -CH(R^a)-N(R^c)-; and -C(R^a)=C(R^c)-.

In a further preferred embodiment, X is selected from the group consisting of –CH(R^a)-CH(R^c)-; and –CH_2-O-.

Preferably, R^8 and R^9 are independently selected from the group consisting of H; F; and C_{1-6} alkyl. More preferably, R^8 and R^9 are independently selected from the group consisting of H; and F.

Preferably, R^a, R^b, R^c are H.

Preferably, R^c is -Y-T and T is phenyl. More preferably, R^c is C_{1-6} alkyl-T.

Preferably, the pair R^a and R^c form a ring Z^1.

Preferably, Z^1 is selected from the group consisting of phenyl; C_{3-7} cycloalkyl; and heterocycle. More preferably, Z^1 is phenyl.

Preferably, A is selected from the group consisting of -Y-T; and -Y-H.

Preferably, Y is selected from the group consisting of -C(O)NH-; -C(O)NH-C_{1-6} alkyl-; -C_{1-6} alkyl-NHC(O)-C_{1-6} alkyl-; -C_{1-6} alkyl-NHC(O); C_{1-6} alkyl-NHS$(O)_2$-C_{1-6} alkyl; -C_{1-6} alkyl-O-; and -C_{1-6} alkyl-O-C_{1-6}alkyl-. More preferably, Y is selected from the group consisting of -C(O)NH-CH_2-; -CH_2-NHC(O)-CH_2-; -CH_2-NHC(O)-; -CH_2-NHS$(O)_2$-CH_2-; -CH_2-O-; and -CH_2-O-CH_2-.

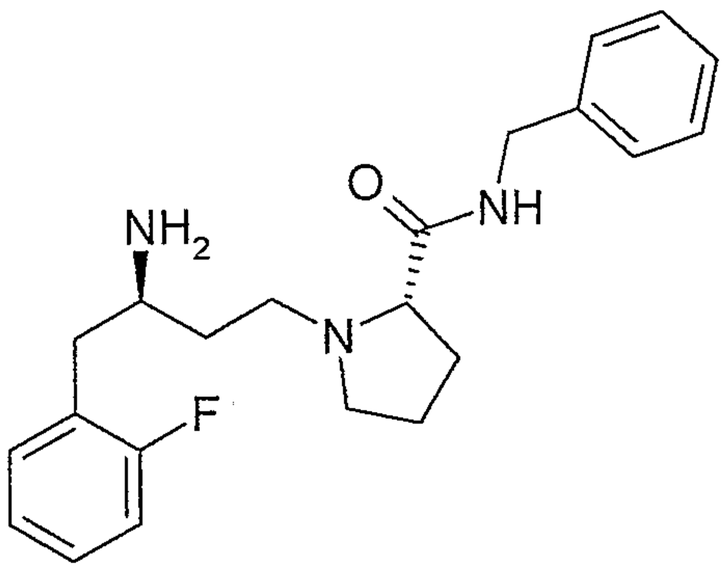
In a further preferred embodiment, Y is C_{1-6} alkyl-NHS$(O)_2$-.

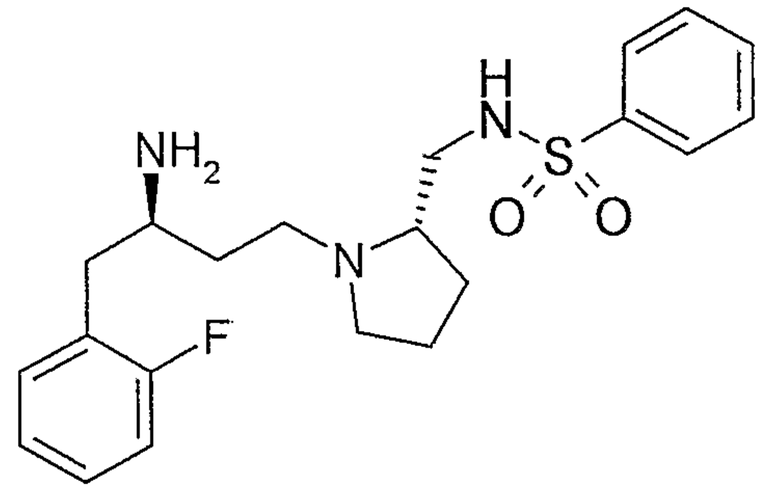
Preferably, T is selected from the group consisting of phenyl; C_{3-7} cycloalkyl; and heterocycle, wherein T is optionally substituted with one or more radicals selected from the group consisting of halogen; CN; S$(O)_2$-C_{1-6} alkyl; and C_{1-6} alkyl.

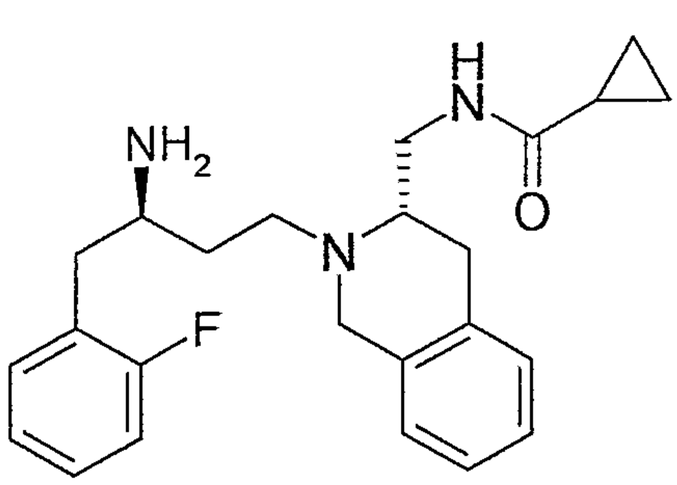
More preferably, T is selected from the group consisting of phenyl; C_{3-7} cycloalkyl wherein T is optionally substituted with one or more F. Further, C_{3-7} cylcoalkyl is preferably cyclopropyl.

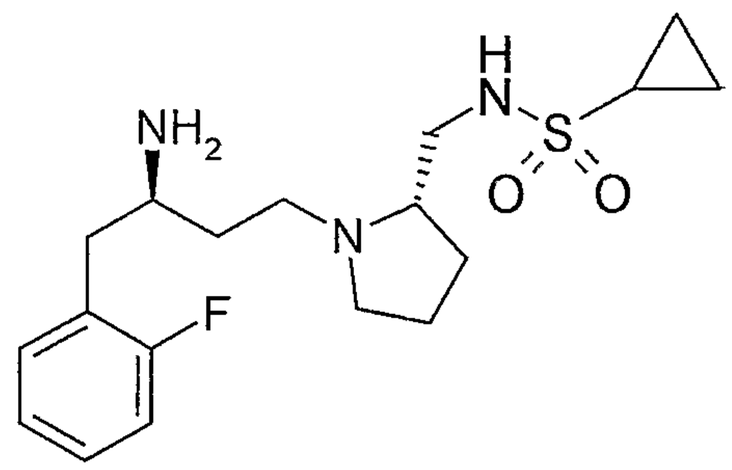
Compounds of the formula (I) or (Ia) in which some or all of the above-mentioned groups have the preferred or more preferred meanings are also an object of the present invention.

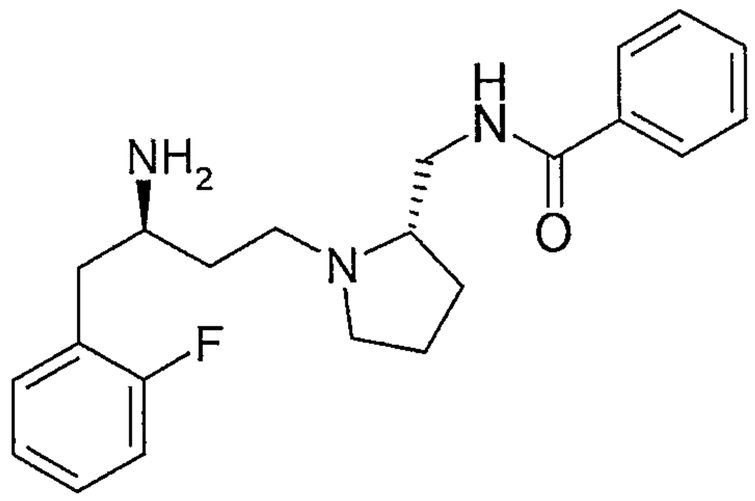
Preferred embodiments of the compounds according to the present invention are:

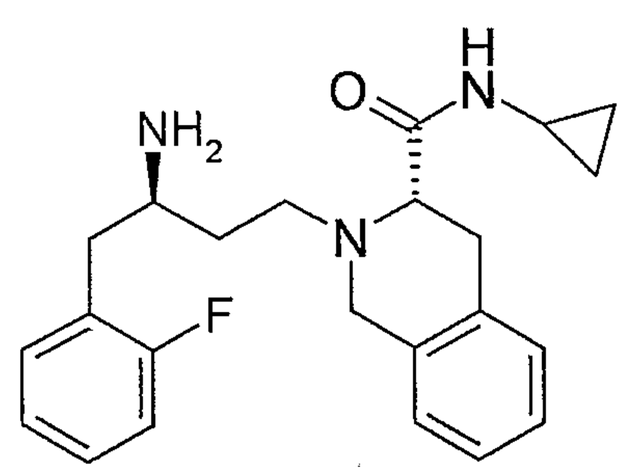


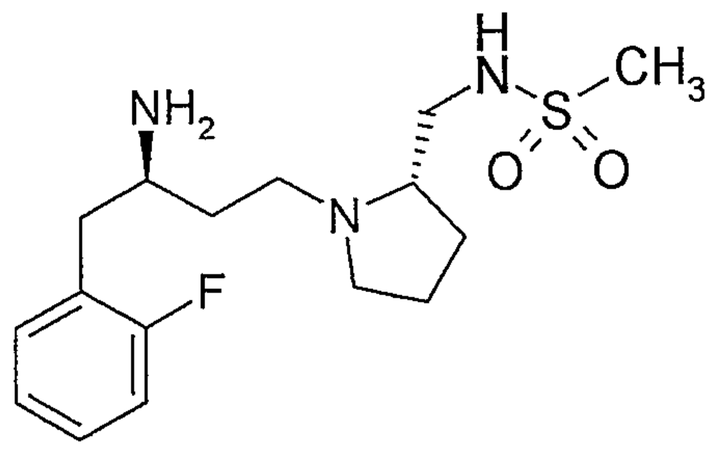


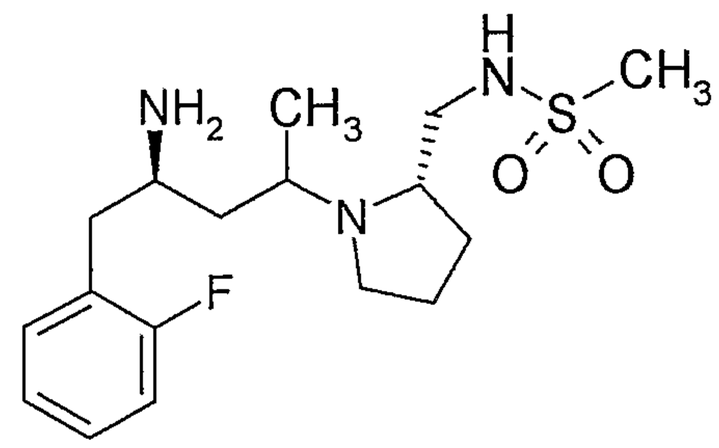


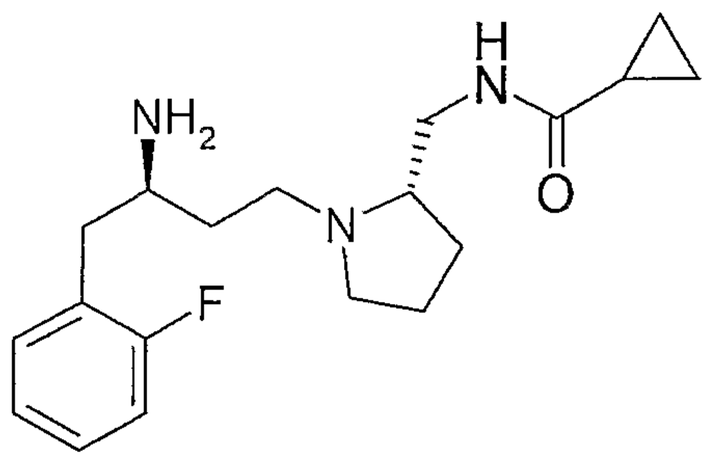


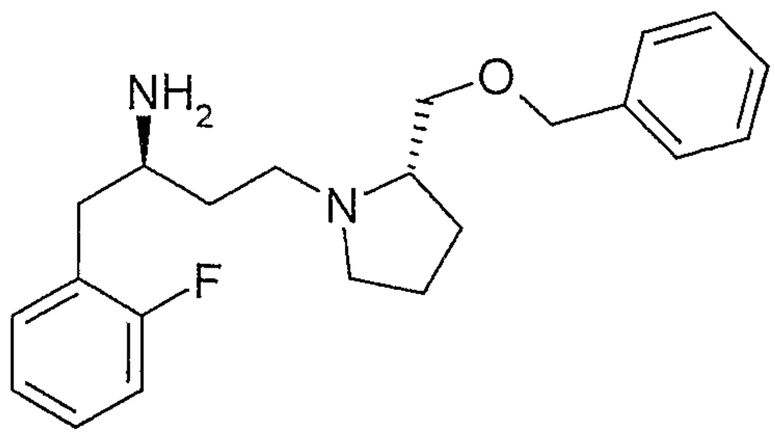


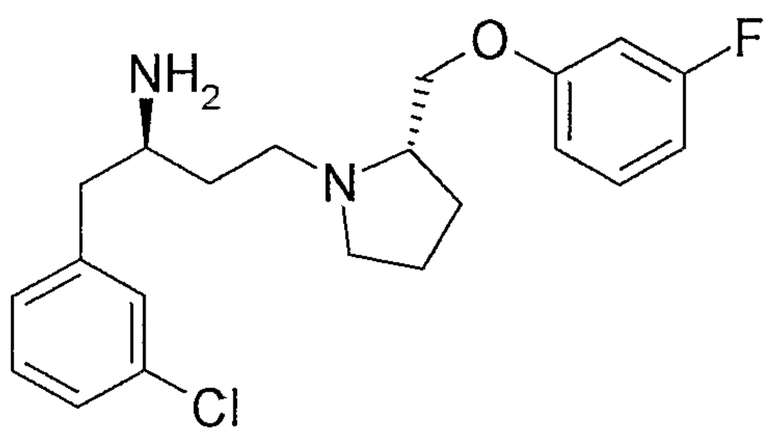


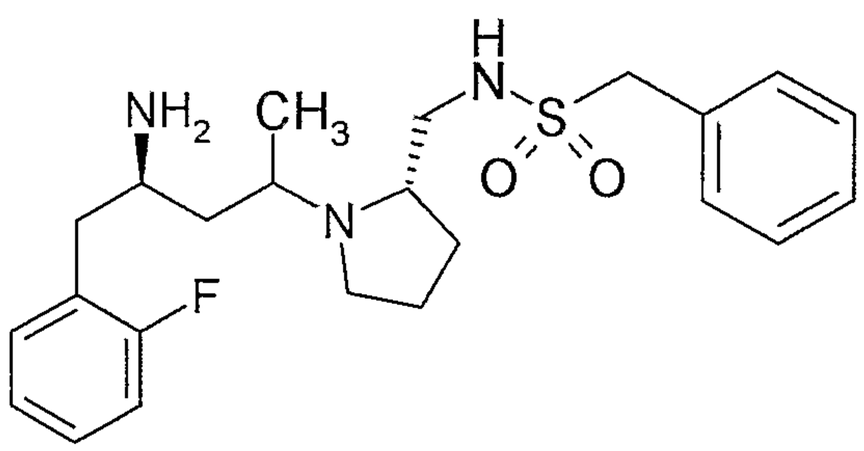


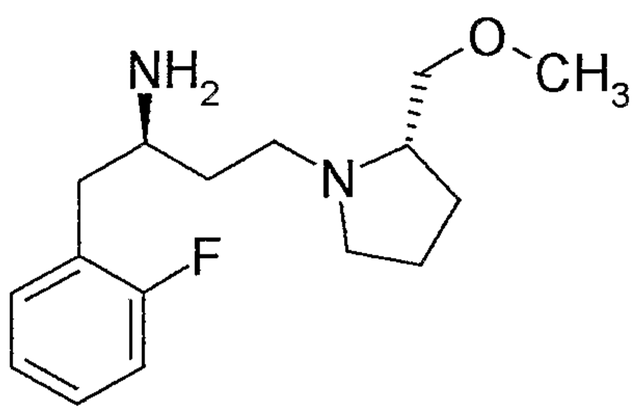


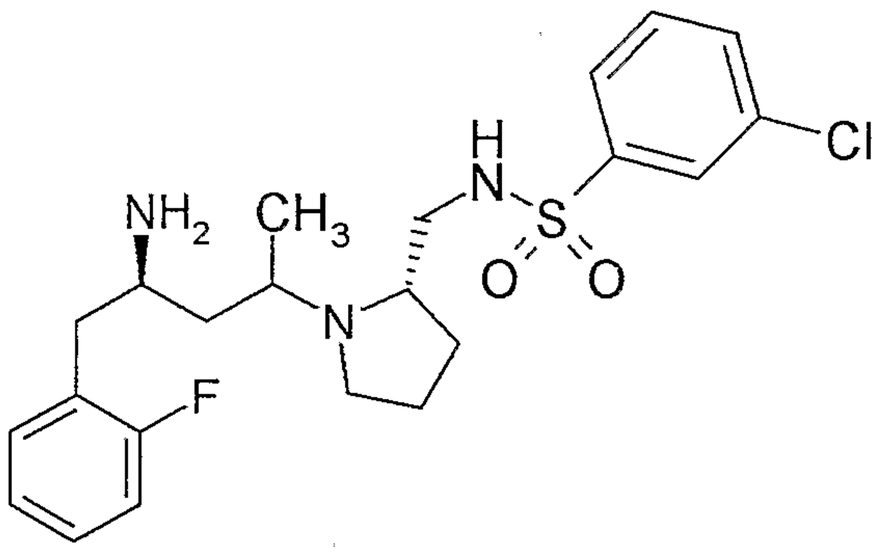


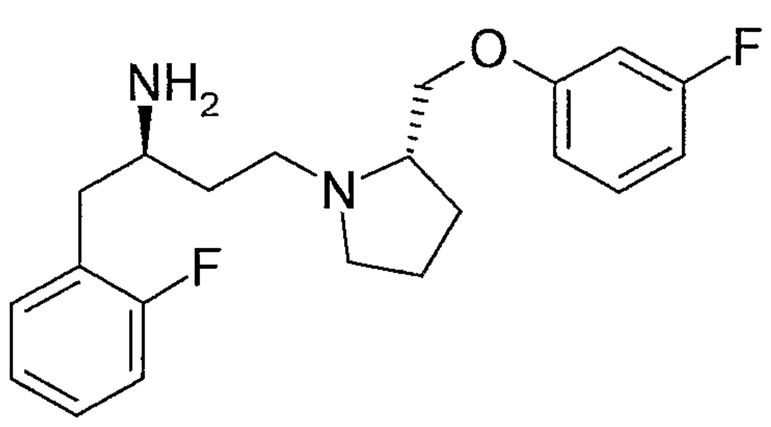


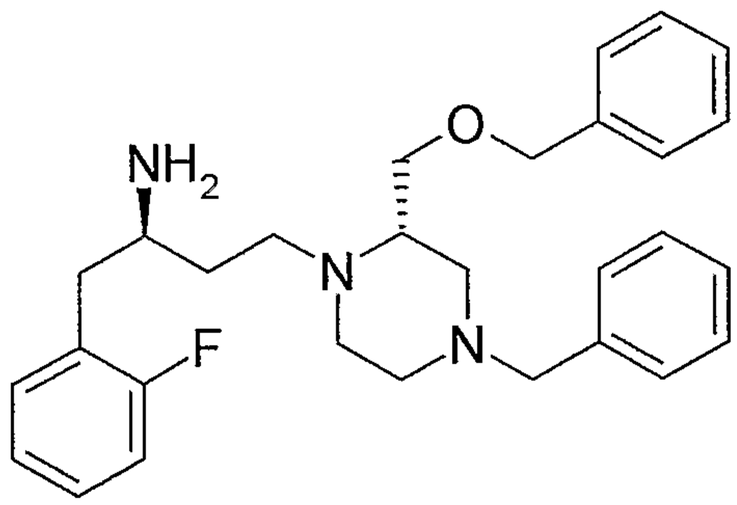


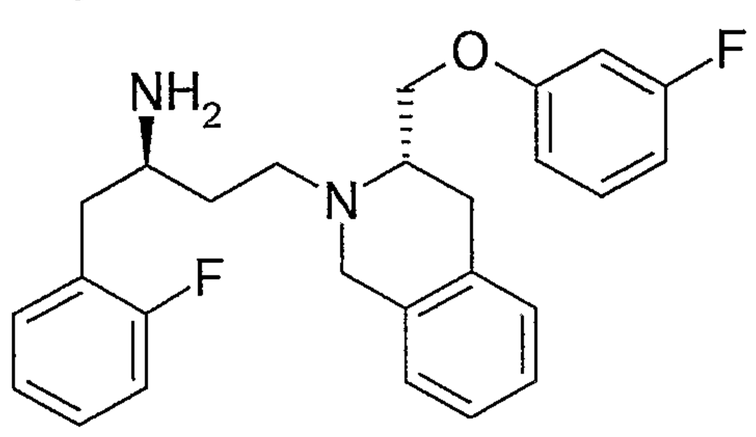


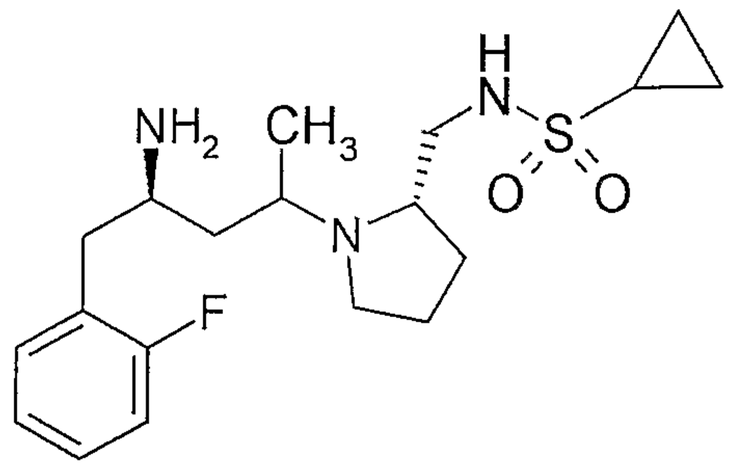


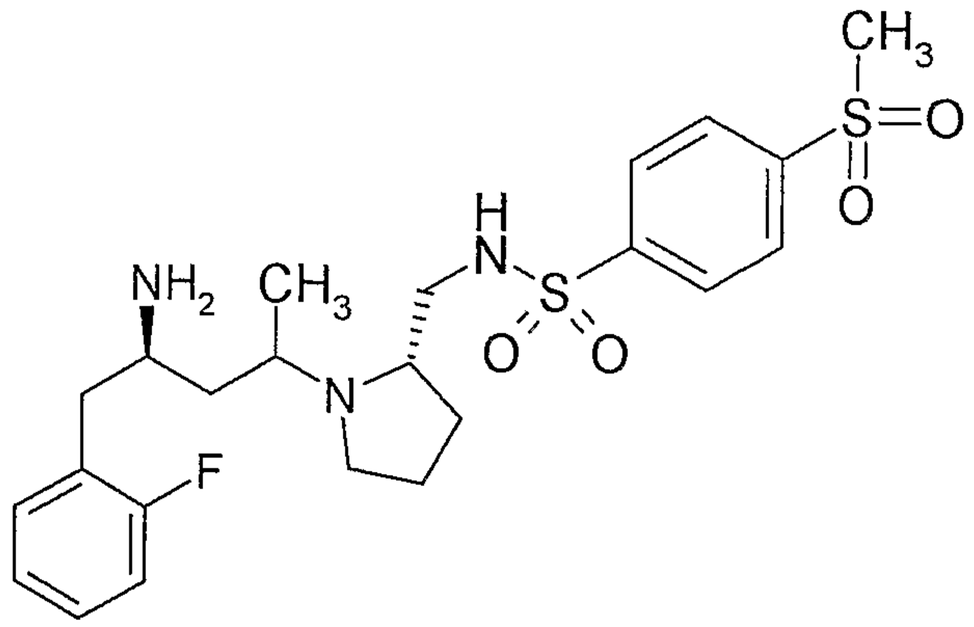


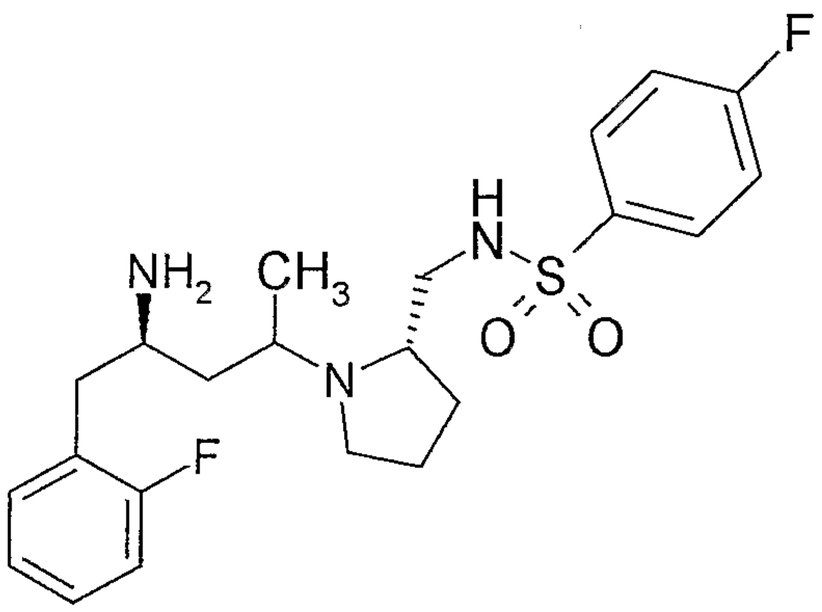


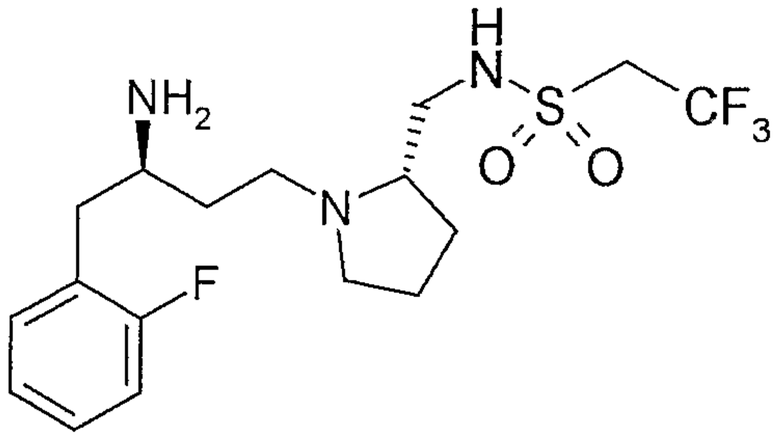


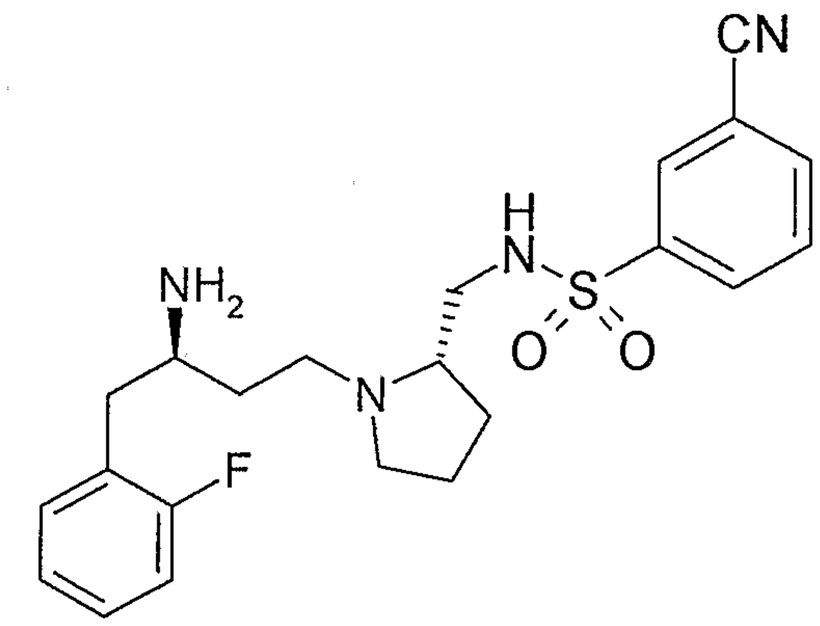


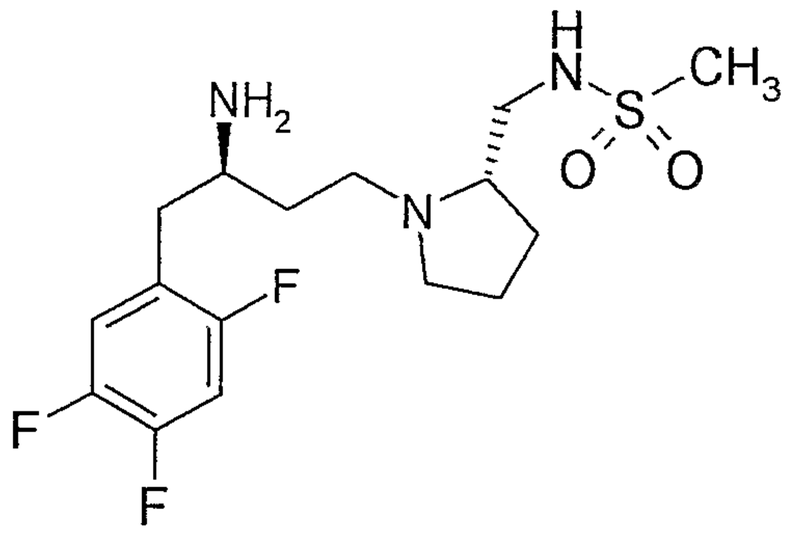


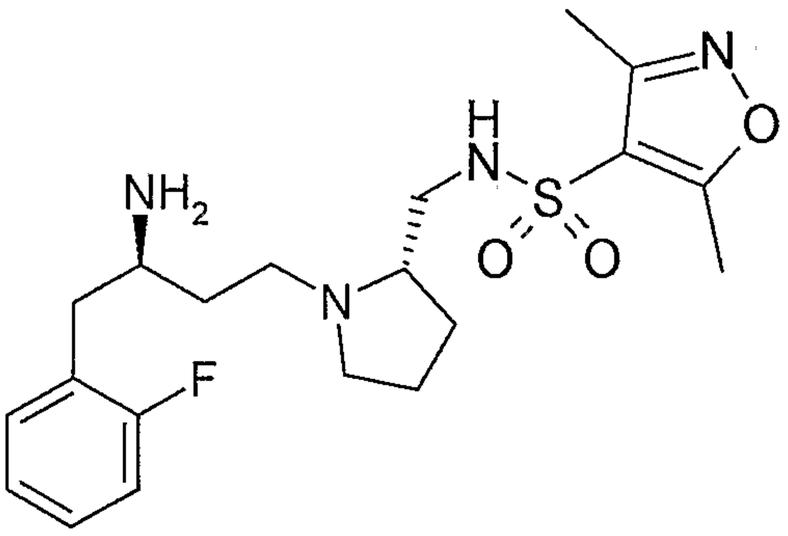


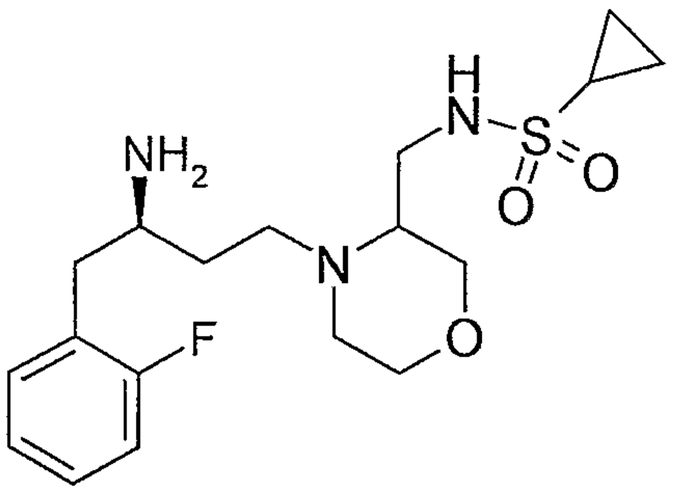


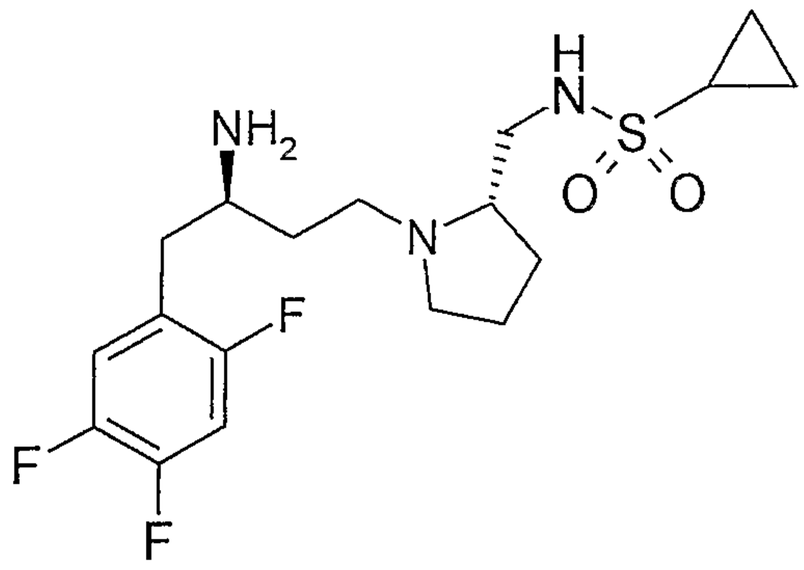


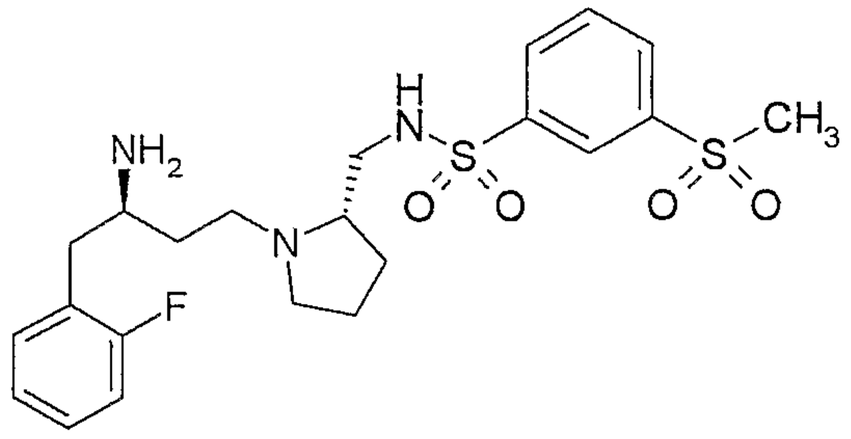












Furthermore, the present invention provides prodrug compounds of the compounds of the invention as described above.

"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, alanylamino, 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) or (Ia) are also within the scope of the present invention.

Where tautomerism, like e.g. keto-enol tautomerism, of compounds of general formula (I) or (Ia) 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) or (Ia) may be obtained from stereoselective synthesis using optically pure starting materials.

In case the compounds according to formula (I) or (Ia) 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) or (Ia) 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) or (Ia) 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, sulphuric acid, nitric acid, methanesulphonic acid, p-toluenesulphonic acid, naphthalenedisulphonic 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, sulphaminic 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) or (Ia) 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) or (Ia) 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) or (Ia) 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 (Ia) 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 (Ia) 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 (Ia) 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; hypercholestrerolemia; 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. Preferred is non-insulin dependent (Type II) diabetes mellitus and obesity.

The present invention provides pharmaceutical compositions comprising a compound of formula (I) or (Ia), 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 (Ia), 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-IB (PTP-1B) inhibitors; insulin and insulin mimetics; sulphonylureas and other insulin secretagogues; alpha-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-alpha agonists; PPAR-alpha/gamma dual agonists; inhibitors of cholesterol absorption; acyl CoA : cholesterol acyltransferase inhibitors; anti-oxidants; PPAR-gamma 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) or (Ia) 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 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, 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 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 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.

Compounds of formula (I) or (Ia) 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 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 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 (Ia) 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.

Preferred embodiments of compounds having formula (I) of the present invention can be prepared from beta amino acid intermediates such as those of formula (VI). The preparation of these intermediates is described in the following schemes.

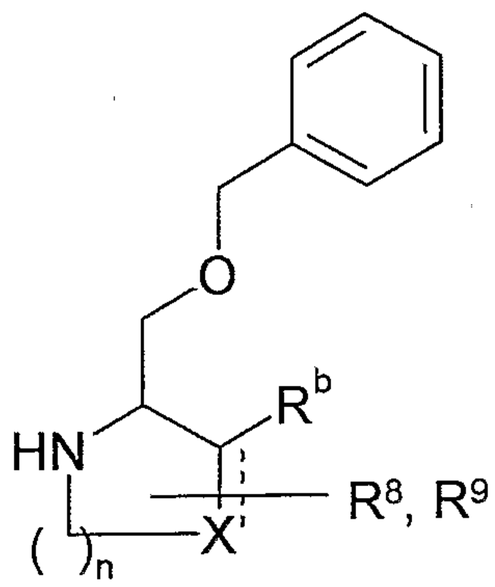
Some abbreviations that may appear in this application are as follows.

ABBREVIATIONS

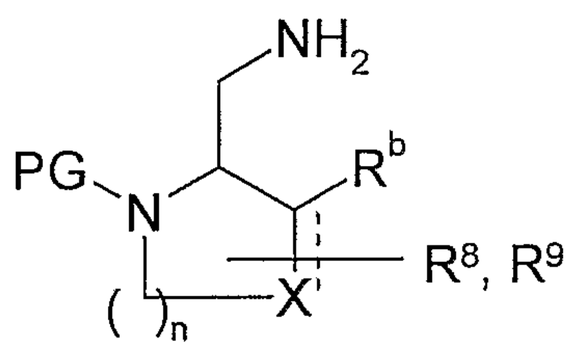
Designation	
Boc (or BOC)	*tert*-Butoxycarbonyl
Bn	Benzyl-
*t*BuOH	*tert*-Butanol
bs	Broad singlet
CDI	1,1´-Carbonyldiimidazole
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIEA	Diisopropylethylamine
DMF	N,N-Dimethylformamide
DPPA	Diphenylphosphoryl azide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
Et_3N	Triethylamine
h	Hour
HATU	O-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HOBt	1-Hydroxybenzotriazole
HPLC	High pressure liquid chromatography
$LiAlH_4$	Lithium aluminiumhydride,
$NaBH_4$	Sodium borohydride
NaH	Sodium hydride
$NaHB(AcO)_3$	Sodium triacetoxyborohydride
PG	Protecting group
PPh_3	Triphenylphosphine

PS-NM_eHCO_3	(Polystyrylmethyl)trimethylammonium bicarbonate
rt	Retention time
TEOF	Triethyl orthoformate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Ti (O*i*$Pr)_4$	Titanium tetraisopropoxide
TMOF	Trimethyl orthoformate

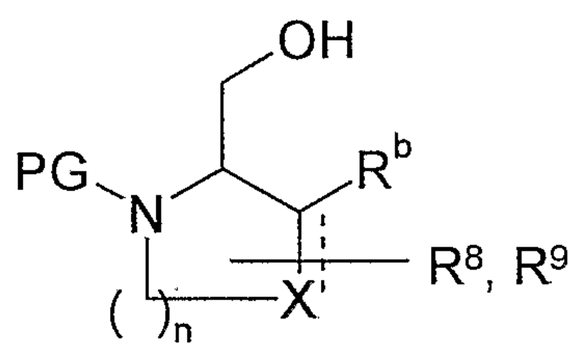
Available starting materials may be amines having the formula (II) or (III) and alcohols with formula (IV).



(II)



(III)

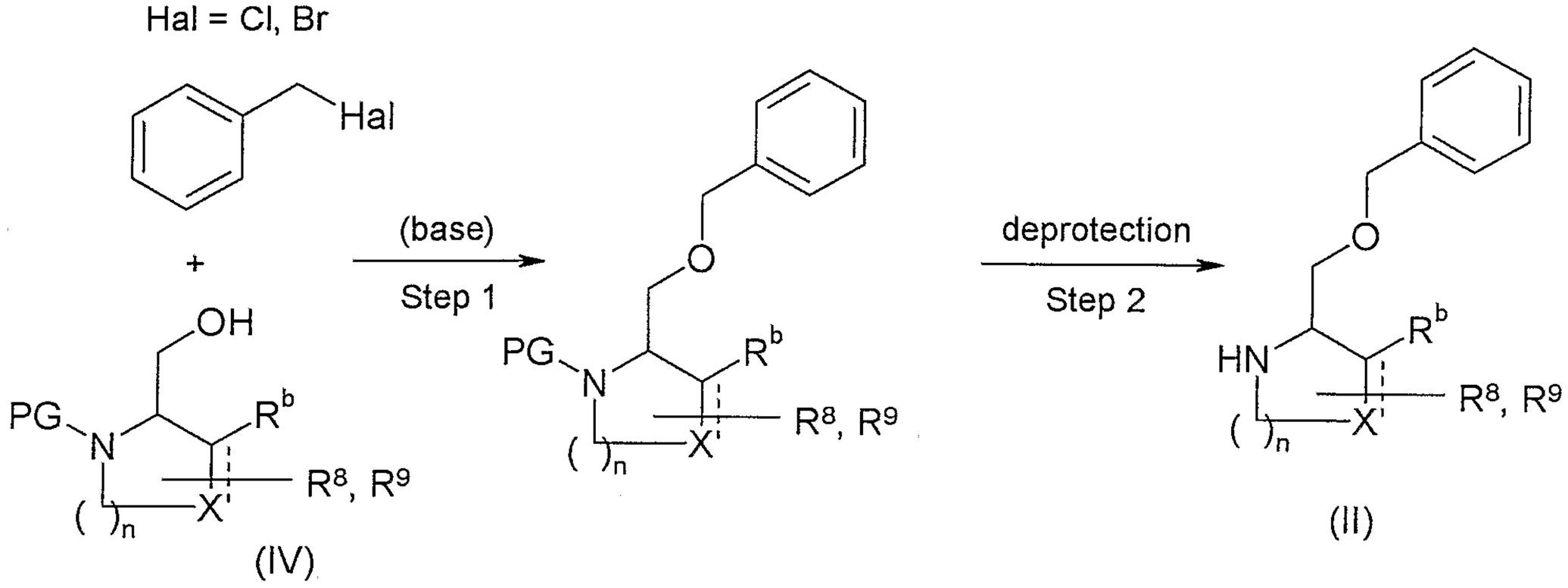


(IV)

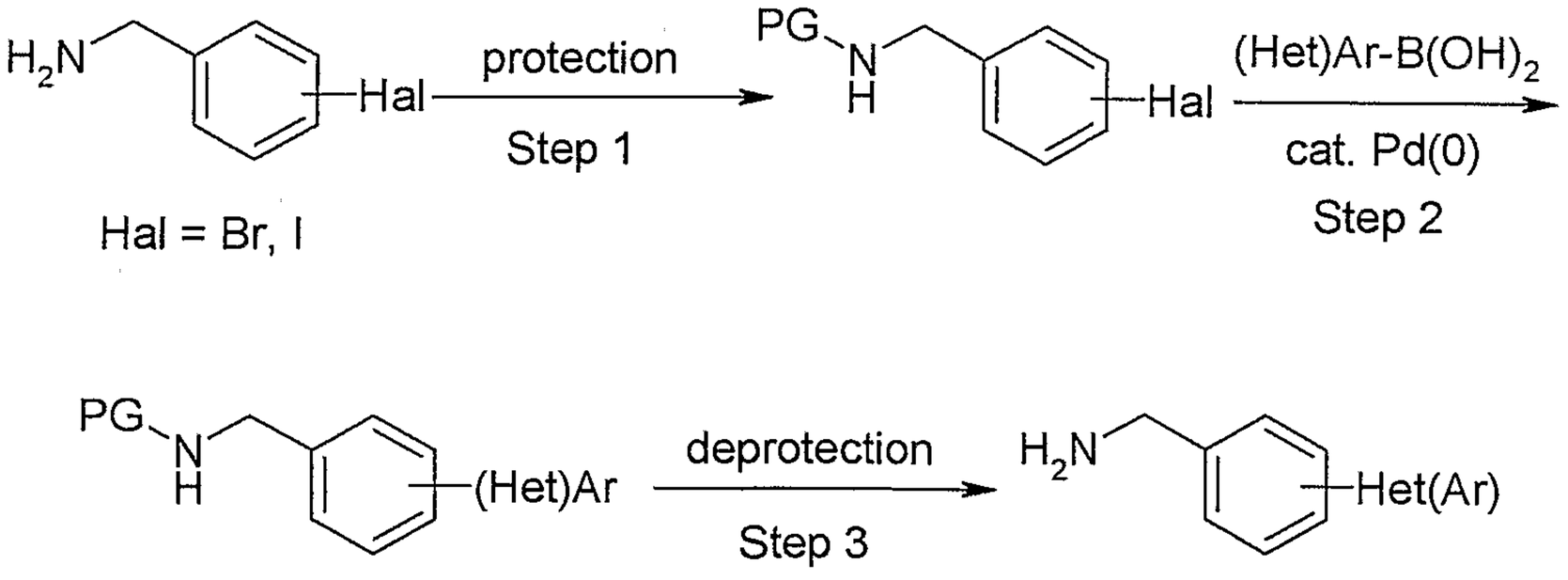
They may be purchased from commercially available sources such as ABCR, Array, Astatech, Sigma-Aldrich, Fluka or be synthesised using common nucleophilic substitution reactions between compounds containing suitable leaving groups and nucleophiles (eg. halogenide, mesylate or tosylate reacting with an amine). The conversion of some functional groups (eg. esters into acids, alcohols or amides; alcohols into mesylates, tosylates or azides) may allow the preparation of diverse intermediates which may be further modified to amines (eg. by reduction of amides, nitriles or azides). Novel carbon-nitrogen palladium-catalysed coupling reactions with suitable functionalised starting materials may also afford valuable intermediates. 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, eg. transition-metal catalysed reactions, conventional techniques for ring closure or formylation of (hetero)aryls. Schemes A to F show some general procedures for the suggested synthetical routes to amines and alcohols and more specifically for the synthesis of some compounds described below.

Unless otherwise indicated in the schemes, the variables have the same meaning as described above.

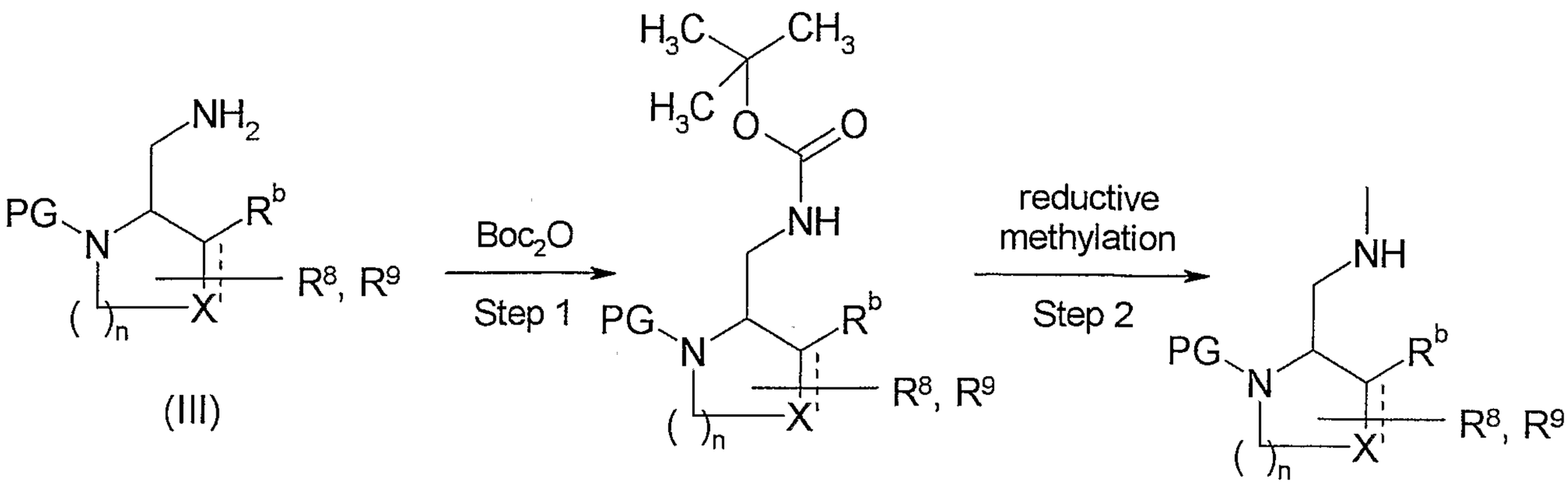
Scheme A



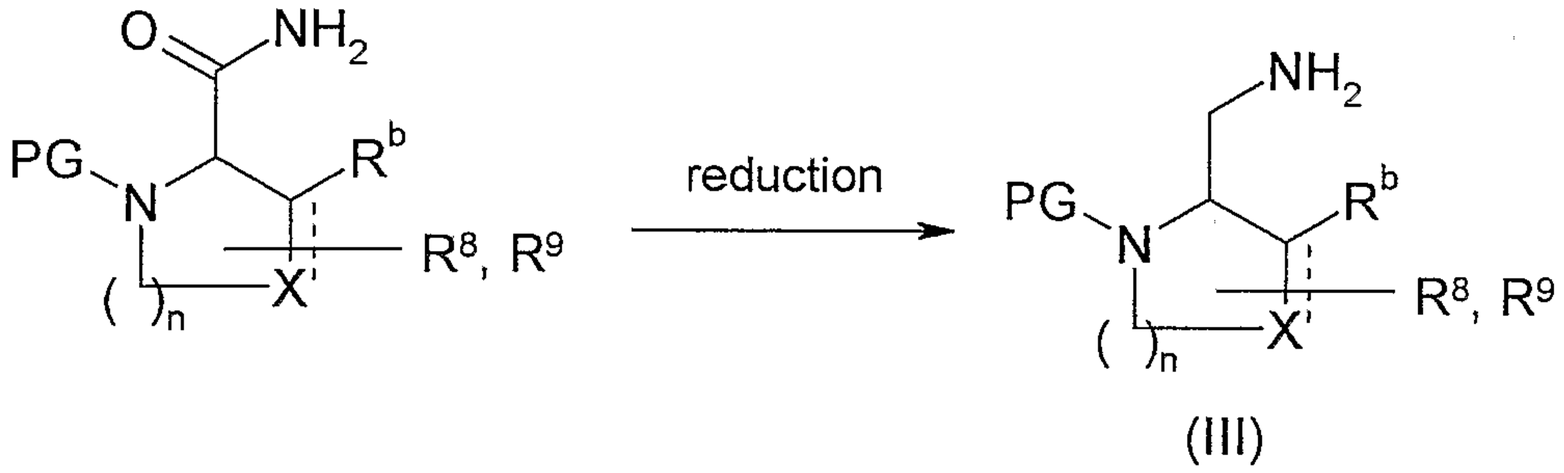
Scheme B



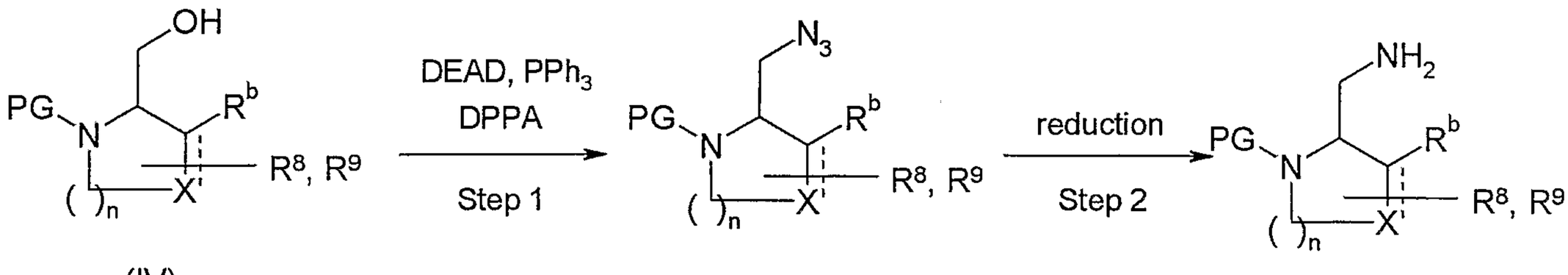
Scheme C



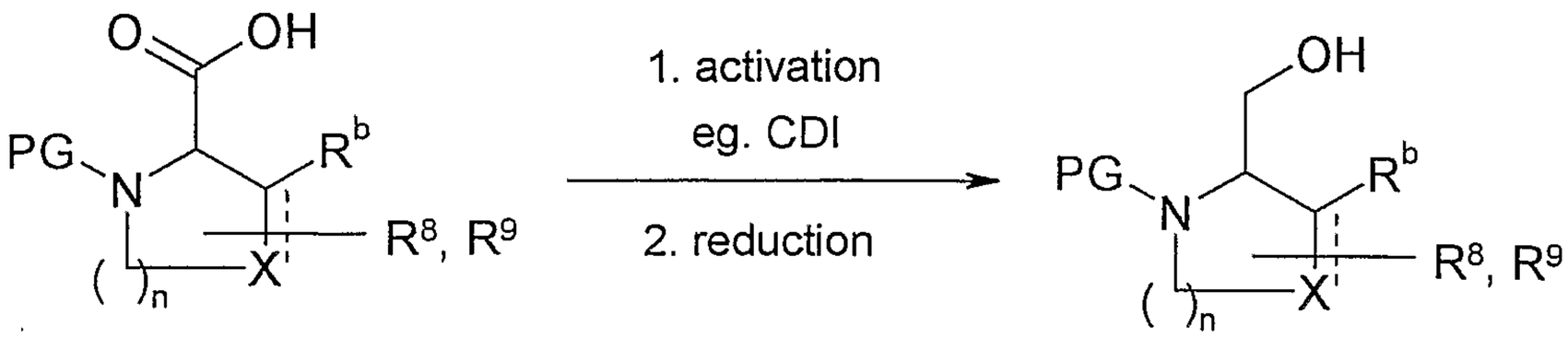
Scheme D



Scheme E

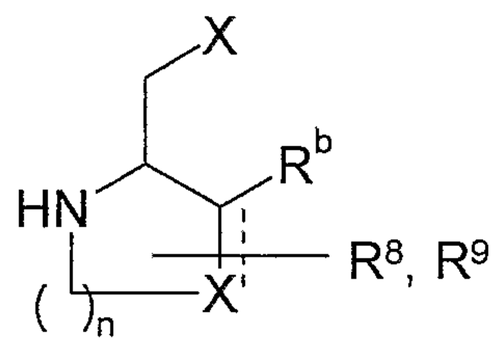


Scheme F



The protective group may be removed with, for example, diethylamine in dichloromethane in the case of Fmoc or using acidic conditions (such as trifluoroacetic acid in dichloromethane or hydrochloric acid in dioxane) in the case of Boc, as described in *Protective Groups in Organic Synthesis* 3rd ed., Ed. Wiley-VCH, New York; 1999.

Available starting materials may be amines having the formula (V):



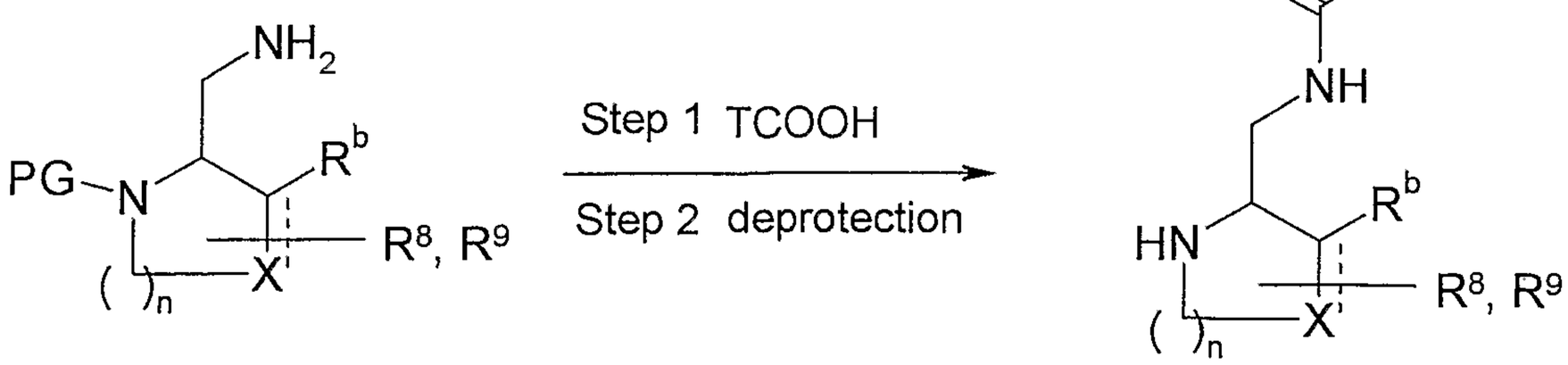
(V)

$X = NH_2$ or OH

They may be purchased from commercially available sources such as Array, Sigma-Aldrich, Fluka, ABCR or be synthesised by one skilled in the art. Common reactions between compounds containing amino functionalities (eg. prepared according to Schemes A to F) and carboxyl, sulphonyl or isocyanate functionalities may be employed for their synthesis with suitable functionalised starting materials. Nucleophilic substitution reactions between compounds containing a suitable leaving group (e.g. halogenide, mesylate, tosylate) and nucleophiles (e.g. amines, alcoholates) may be also employed. The conversion of diverse functional groups (such as esters, alcohols, amides, nitriles, azides) may allow the synthesis of some intermediates or final compounds.

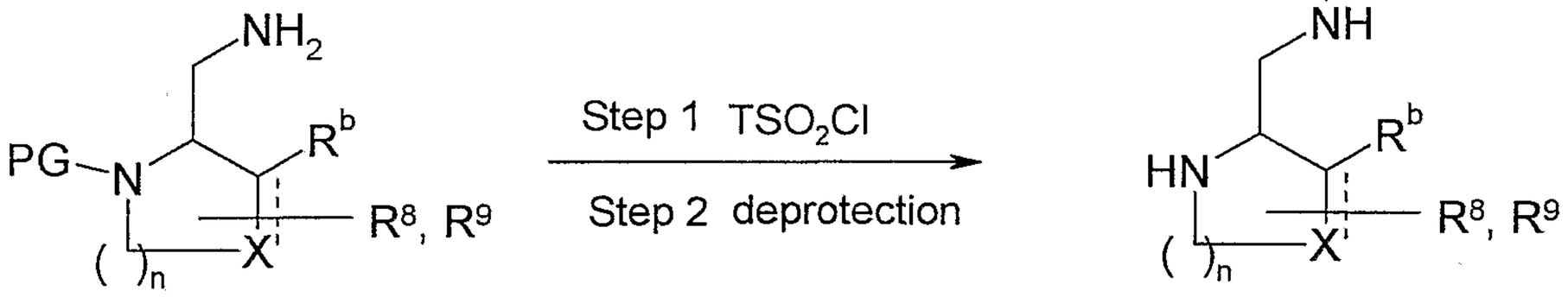
Schemes G to L outline general procedures for the synthesis of some compounds described below. Unless otherwise indicated in the schemes, the variables have the same meaning as described above.

Scheme G



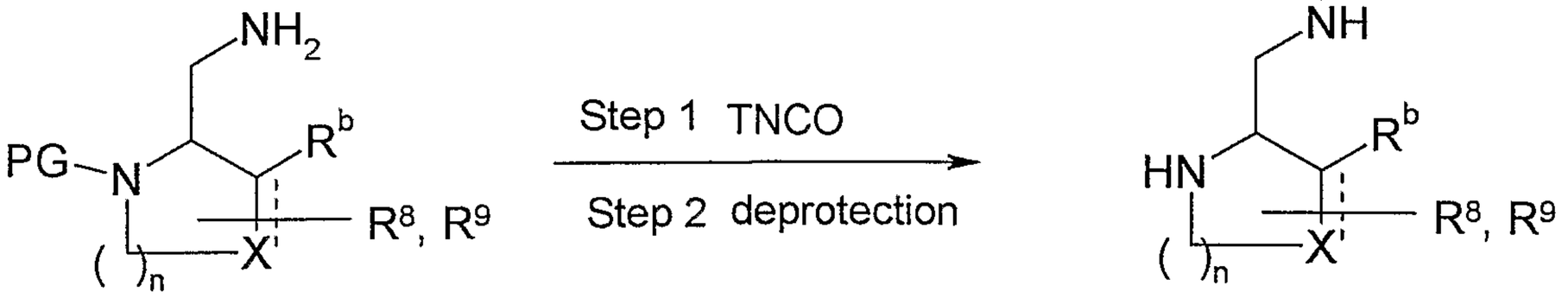
(III)

Scheme H



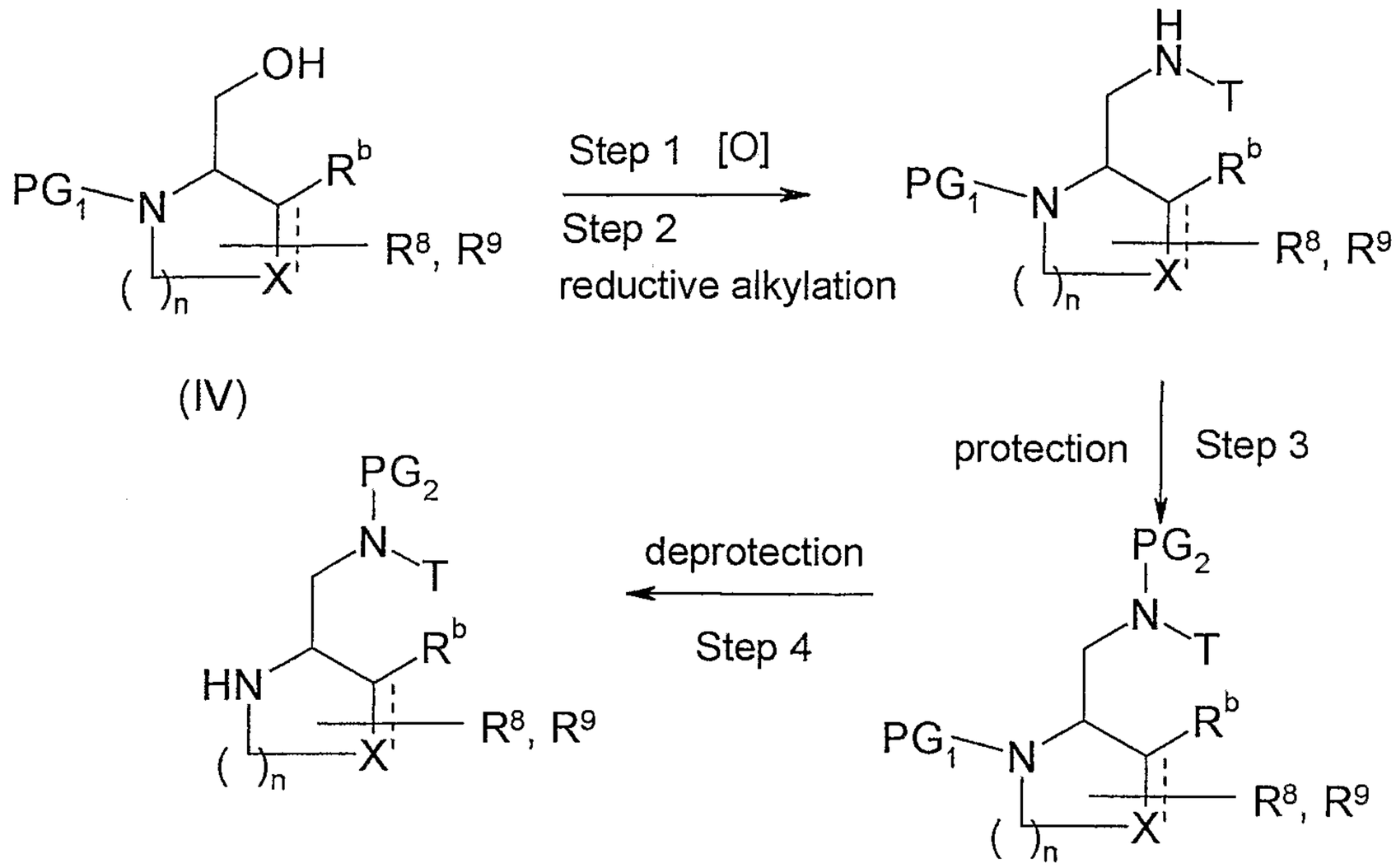
(III)

Scheme I

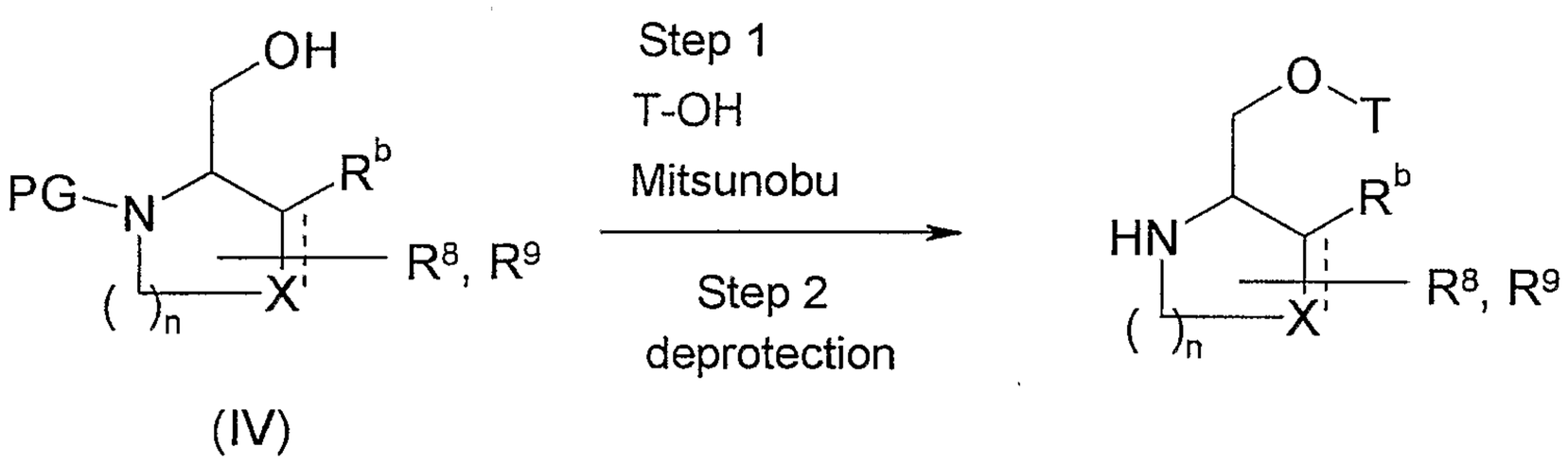


(III)

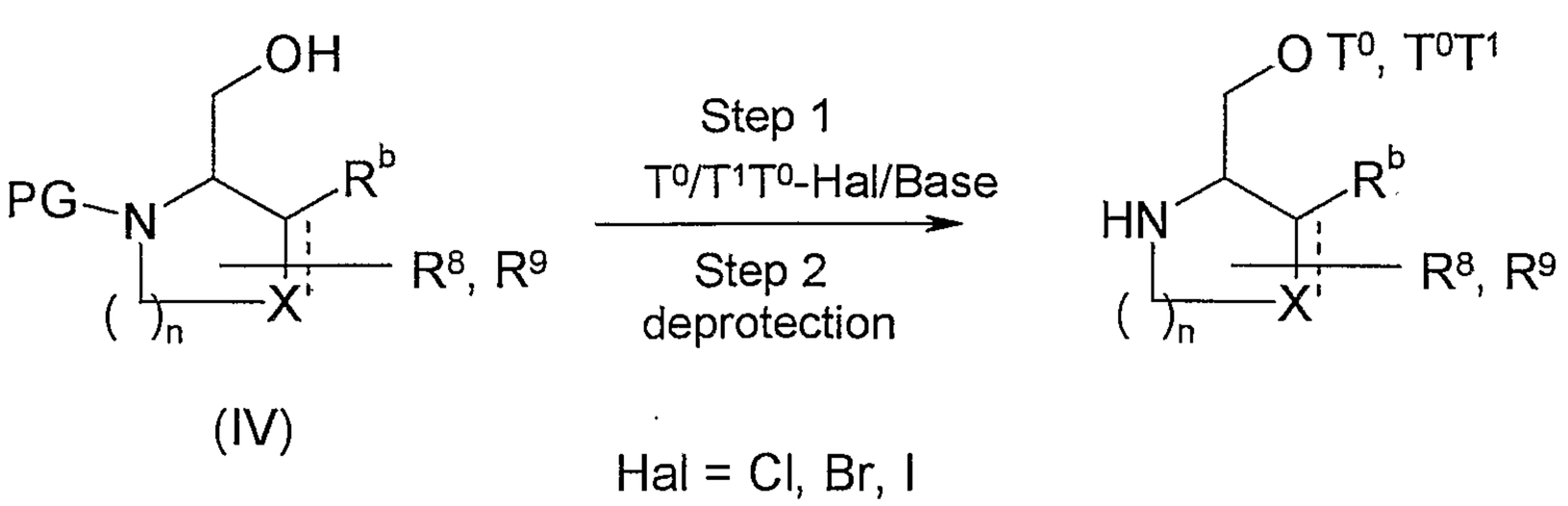
Scheme J



Scheme K

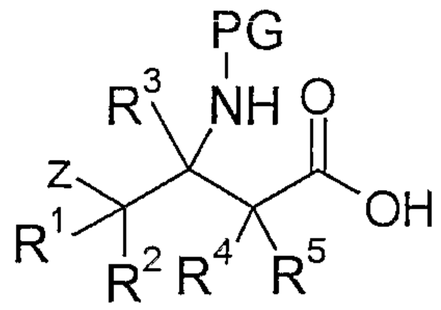


Scheme L



Hal = Cl, Br, I

Enantiomerically pure beta amino acids having the formula (VI)

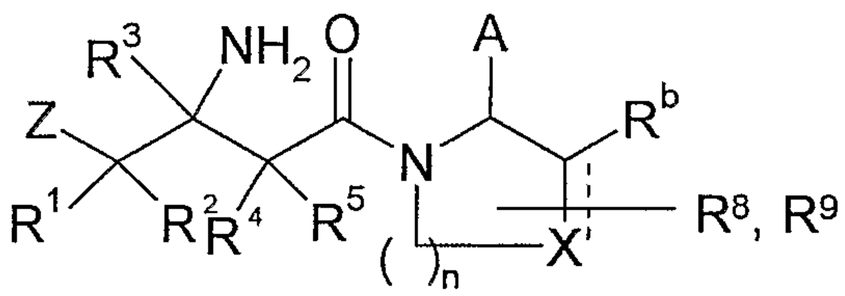


(VI)

may be commercially available, known in the literature or may be conveniently synthesized using one of the methods already published and reviewed in e.g., Cole, *Tetrahedron*, 32, 9517 (1994), Juaristi et al., *Aldrichimica Acta*, 27, 3, 1994, or Juaristi, *Enantioselective Synthesis of β-Amino Acids*, Ed. Wiley-VCH, New York, 1997.

In particular, 3-amino-4-(2,4,5-trifluoro-phenyl)-butyric acid may be synthesized by a variety of methods as reported in the patent applications WO 2004069162, WO 2004064778, WO 2004037169, WO 2004032836 and in the articles *JACS*, 126, 3048 (2004) and *JACS*, 126, 9918 (2004).

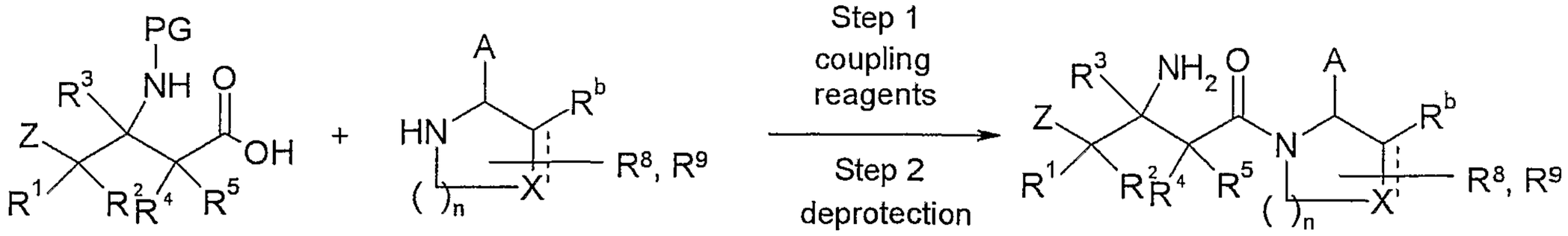
Amides with formula (VII)



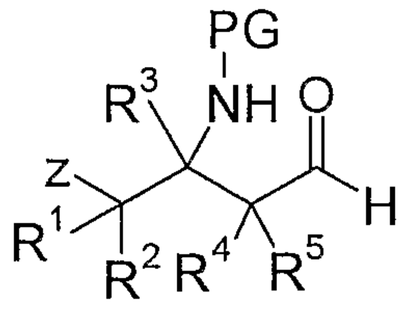
(VII)

may be prepared by amide coupling between beta amino acids with formula (VI) and suitable amines (eg. prepared according to Schemes A to E and G to L), as shown in Scheme M. For example, it may be possible to synthesize compunds of formula (VII) using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) in combination with 1-hydroxybenzotriazole (HOBt) and a base (triethylamine or diisopropylethylamine) or O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) in the presence of a base, in solvents such as dichloromethane or *N,N*-dimethylformamide.

Scheme M



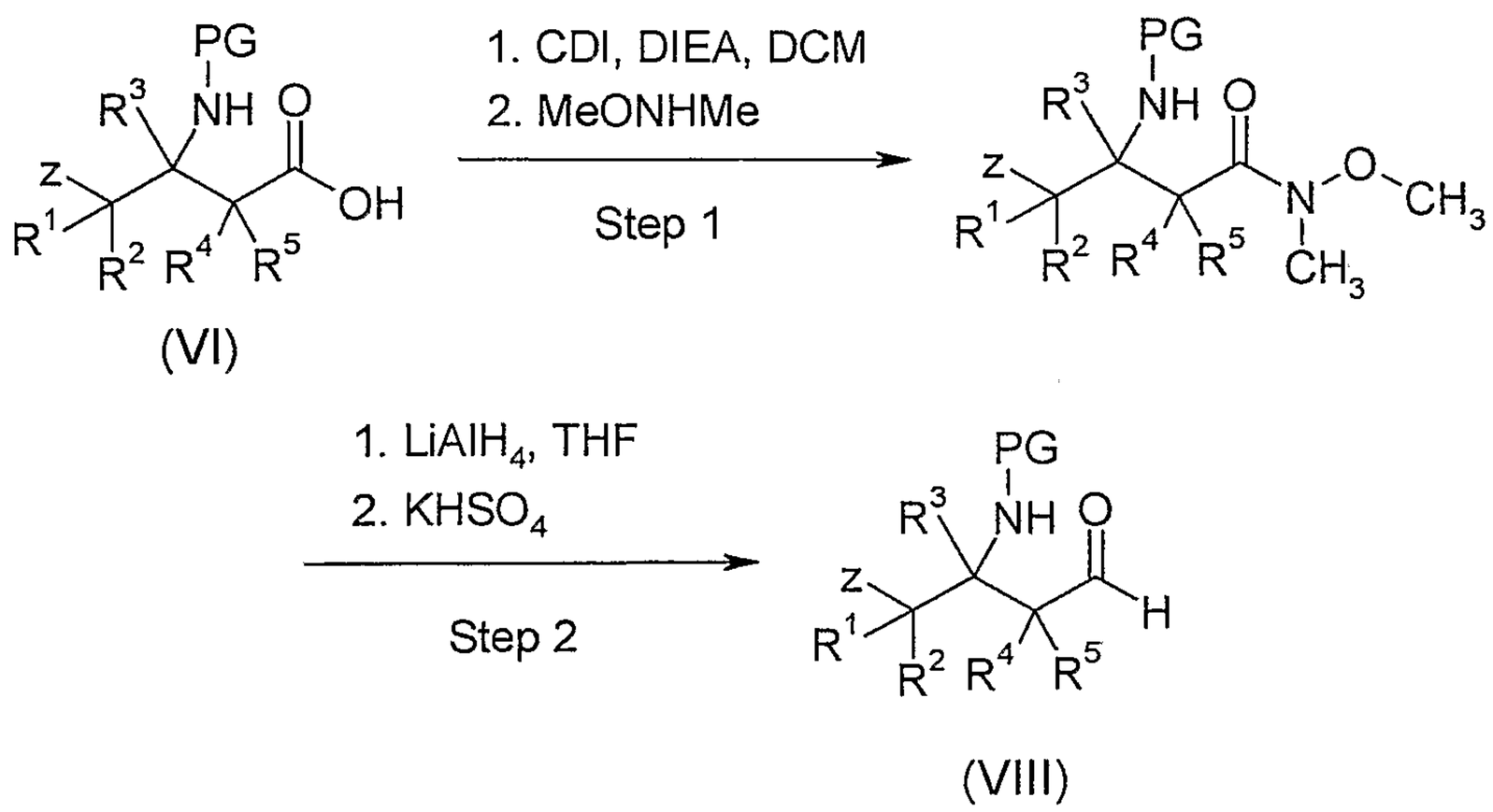
Enantiomerically pure beta amino aldehydes having the formula (VIII)



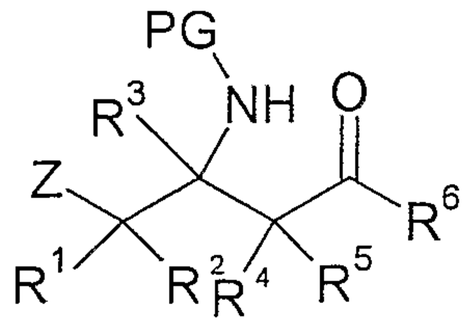
(VIII)

may be commercially available or synthesised by one skilled in the art using as starting material the conveniently substituted acids e.g. (VI) through direct reduction with diisobutylaluminium hydride or through formation of the Weinreb amide and further reduction with lithium aluminiumhydride, as depicted in Scheme N.

Scheme N



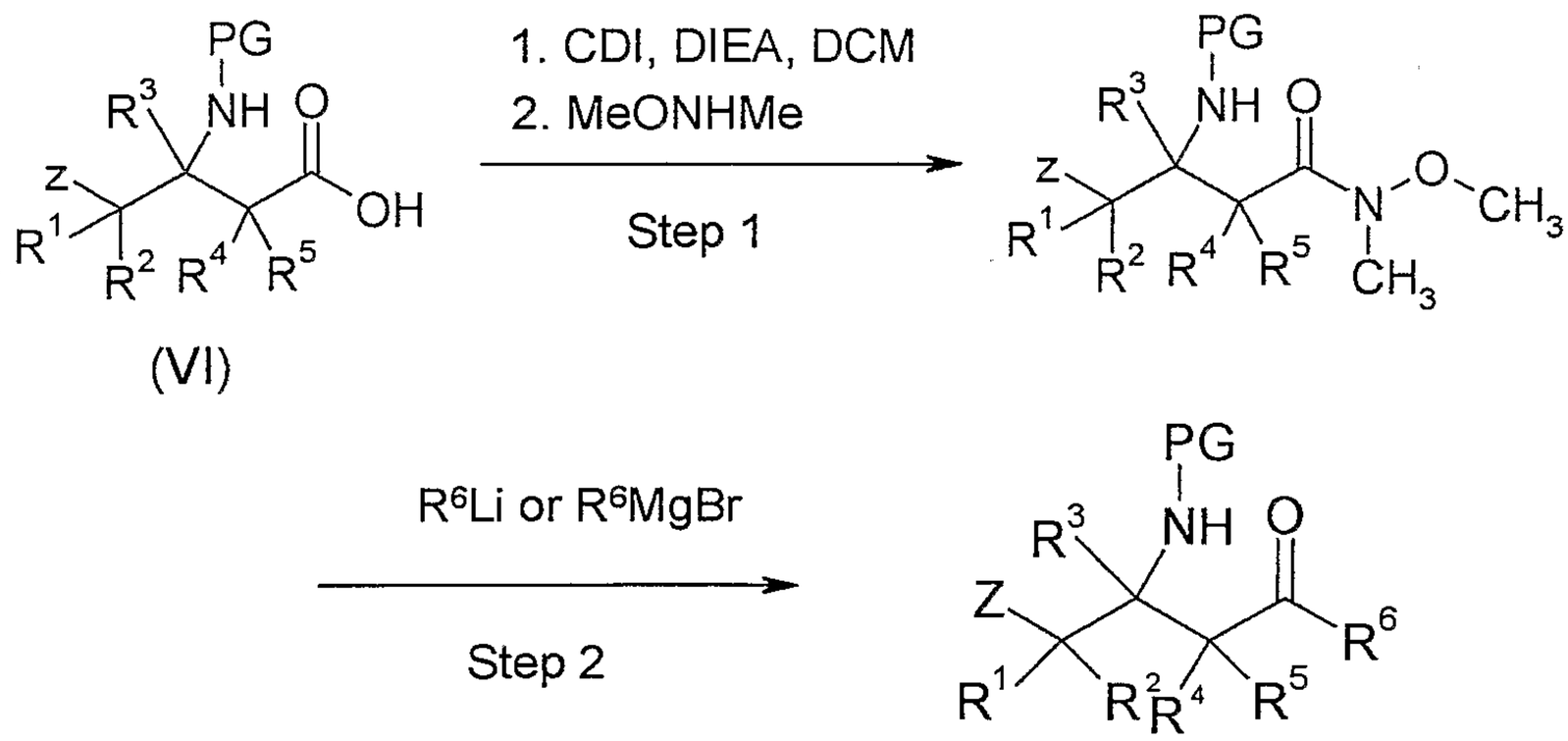
Enantiomerically pure beta amino ketones having the formula (IX)



(IX)

may be commercially available or synthesised by one skilled in the art using as starting material the conveniently substituted acids *e.g.* through formation of the Weinreb amide and addition of an alkyl lithium or alkyl magnesiumbromide reagent, as depicted in Scheme O.

Scheme O



(VI)

Unless otherwise noted, all non-aqueous reactions were carried out under 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 Reprosil-Pur ODS3, 5 µm, 20 x 125 mm column with Shimadzu LC8A-Pump and SPD-10Avp UV/Vis diode array detector. The ^{1}H-NMR spectra were recorded on a Varian VXR-S (300 MHz for ^{1}H-NMR) using d_6-dimethylsulphoxide as solvent; chemical shifts are reported in ppm relative to tetramethylsilane. Analytical LC/MS was performed using Reprosil-Pur ODS3, 5 µM, 1 x 60 mm columns with a linear gradient from 5% to 95% acetonitrile in water (0.1% TFA) at a flow rate of 250 µl/min; retention times are given in minutes. Methods are:

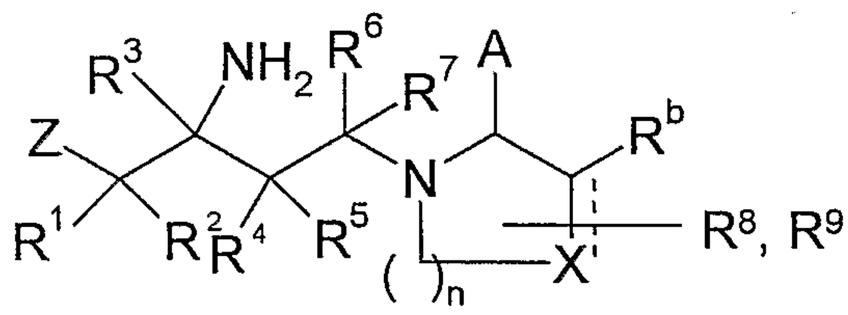
(I) runs on a LC10Advp-Pump (Shimadzu) with SPD-M10Avp UV/Vis diode array detector and QP2010 MS-detector in ESI+ modus with UV-detection at 214, 254 and 275 nm, 10 min. linear gradient; (II) idem but 5 min. linear gradient; (III) runs on a LC10Advp-Pump (Shimadzu) with SPD-10Avp dual wavelength UV-detector and QP2010 MS-detector in ESI+ modus with UV-detection at 214 and 254 nm, 10 min. linear gradient; (IV) idem but 5 min. linear gradient; (V) runs on a LC10Advp-Pump (Shimadzu) with SPD-M10Avp UV/Vis diode array detector and QP2010 MS-detector in ESI+ mode with UV-detection at 214, 254 and 275 nm, with a linear gradient different from 5% to 95% acetonitrile in water (0.1% TFA or formic acid). In this case the data will be reported as follows:

LC/MS (V) (5-90%, 5 min): rt 1.60, m/z 171 $(M+H)^+$; (VI) runs on a LC10Advp-Pump (Shimadzu) with SPD-10Avp dual wavelength UV-detector and QP2010 MS-detector in ESI+ modus with UV-detection at 214 and 254 nm, with a linear gradient different from 5% to 95% acetonitrile in water (0.1% TFA or formic acid). In this case the data will be reported as follows:

LC/MS (VI) (5-90%, 5 min): rt 1.60, m/z 171 $(M+H)^+$.

General procedure for making compounds of the invention

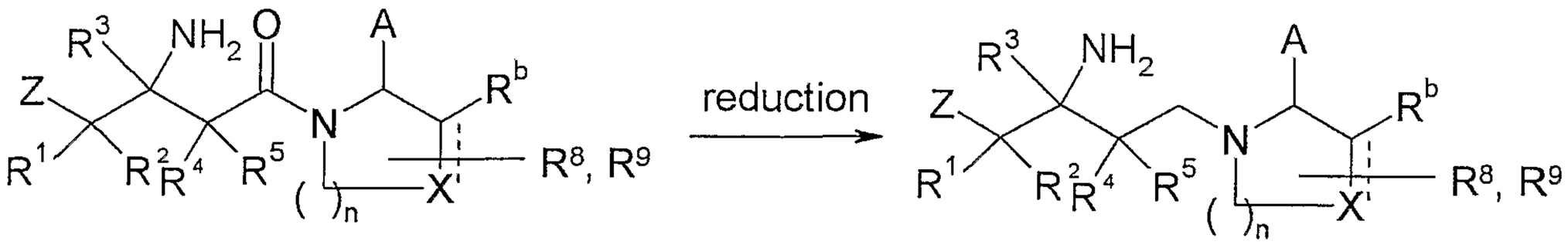
In general, compounds having the structure (I)



wherein the variables have the above described meanings, may be prepared by reduction of suitable amides (eg. with lithium aluminiumhydride in tetrahydrofuran), by reductive amination reducing the imine formed from a conveniently substituted aldehyde or ketone and an amine (eg. in acidic medium with a triacetoxyborohydride salt or sodium borohydride in dichloromethane, methanol or ethanol) or by the Kulinkovic reaction with an alkylmagnesium halide in the presence of titanium tetraisopropoxide in aprotic solvents such as tetrahydrofuran.

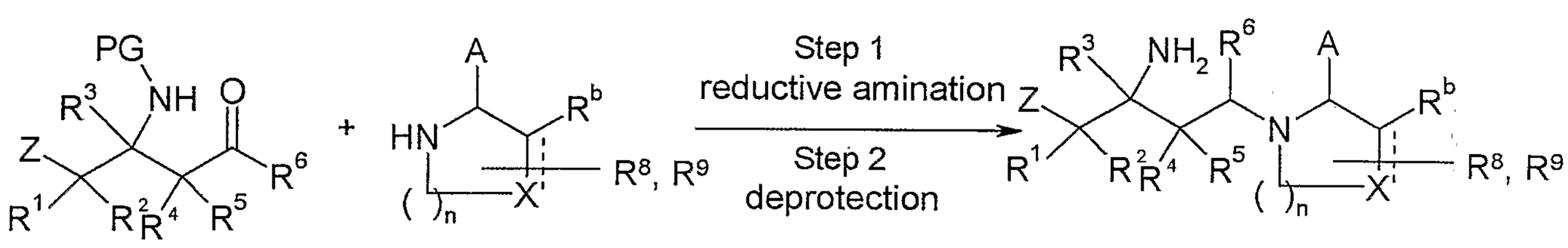
Scheme P outlines a procedure for using the amides formed according to Scheme M to synthesise compounds that are embodiments of the invention.

Scheme P



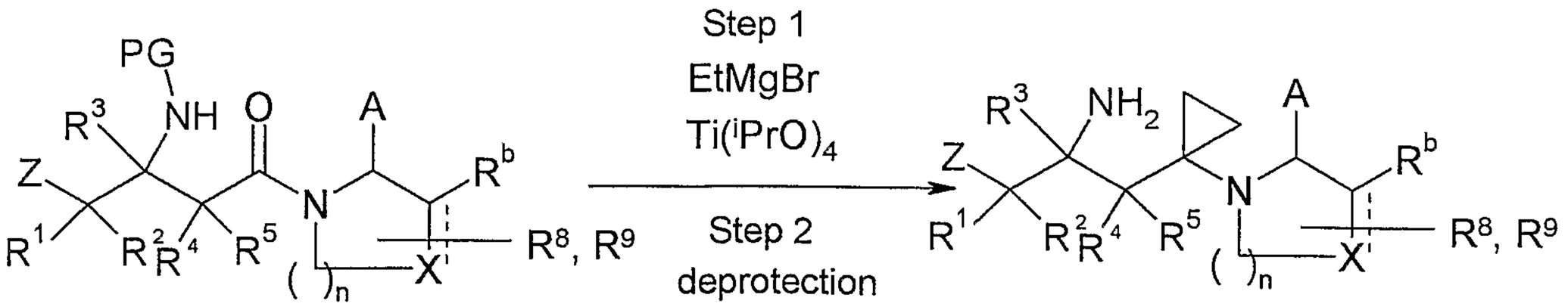
Scheme Q outlines a procedure for reducing the imines obtained by reacting suitable amines (e.g., prepared according to Schemes G to L) and aldehydes with formula (VIII) or ketones with formula (IX).

Scheme Q



Scheme R outlines a procedure for the use of the Kulinkovic reaction with amides prepared according to Scheme M.

Scheme R



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 or formic acid salts.

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.

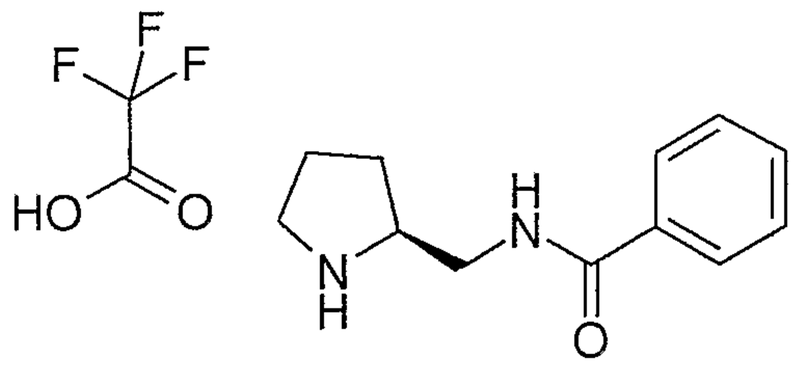
EXAMPLES

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

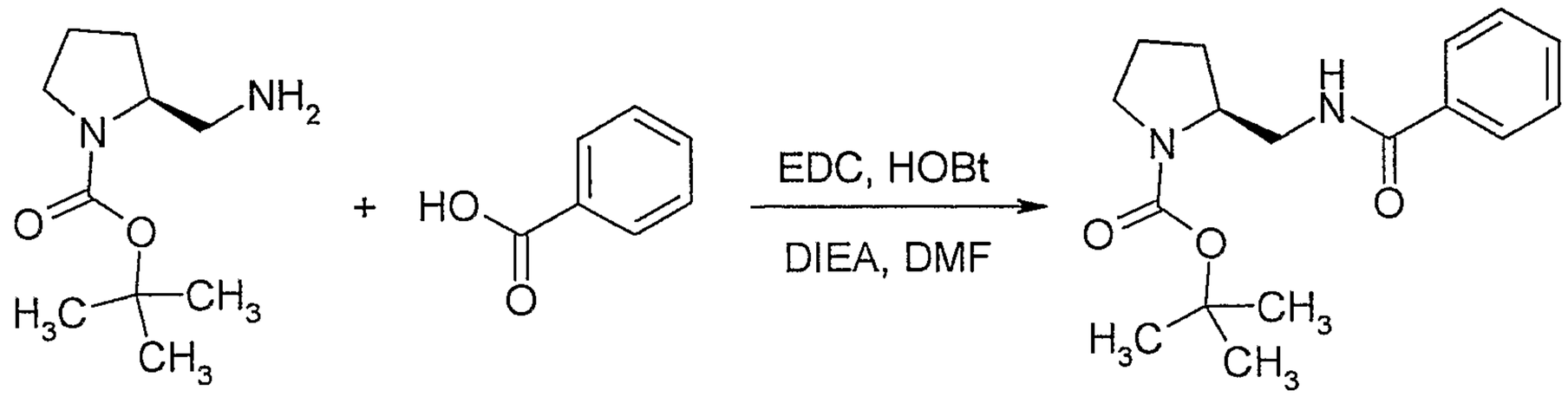
Example 1

The following representative example illustrates the synthesis of an amine educt which contains an amide bond.



Procedure for making an intermediate according to Scheme G.

Step 1



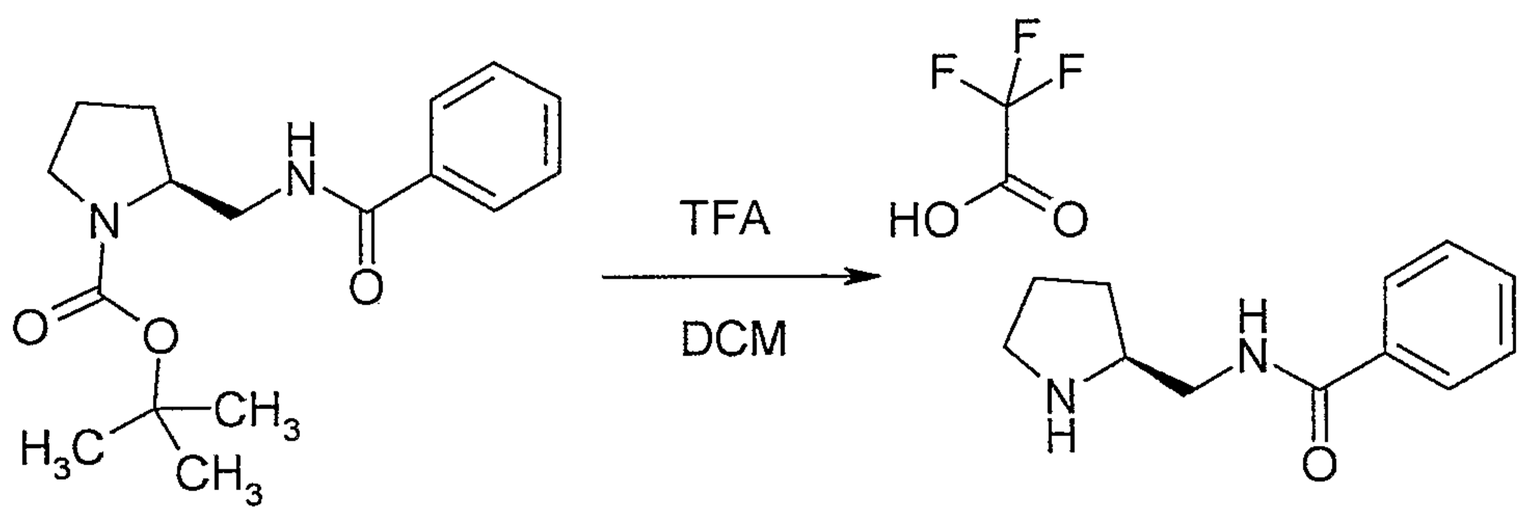
(2*S*)-(Benzoylamino-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

A mixture of 127 mg (1.04 mmol) of benzoic acid, 219 mg (1.14 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 154 mg (1.14 mmol) of 1-hydroxy-benzotriazole and 271 µL (1.56 mmol) of diisopropylethylamine in 2 mL of *N,N*-dimethylformamide is stirred at room temperature for 10 minutes, before a solution of 250 mg (1.24 mmol) of (2*S*)-aminomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester in 2 mL of *N,N*-dimethylformamide is added and stirring is continued overnight. The solution is diluted with 50 mL of ethyl acetate, washed sequentially with 5% citric acid aqueous solution, saturated aqueous sodium bicarbonate solution and brine, dried over sodium sulphate and the solvent is removed under vacuum. Purification of the crude product by flash chromatography (silica gel, 0% to 10 % of ethyl acetate in cyclohexane) affords the title compound.

^{1}H-NMR, δ (ppm) = 1.40 (s, 9H), 1.75-1.88 (m, 4H), 3.20-3.28 (m, 3H, together with water), 3.39-3.50 (m, 1H), 3.90-3.98 (m, 1H), 7.41-7.47 (m, 4H), 7.78-7.81 (m, 1H), 8.34-8.39 (m, 1H).

LC/MS (IV) rt 2.79, m/z 368 $[M+Na+CH_3CN]^+$.

Step 2



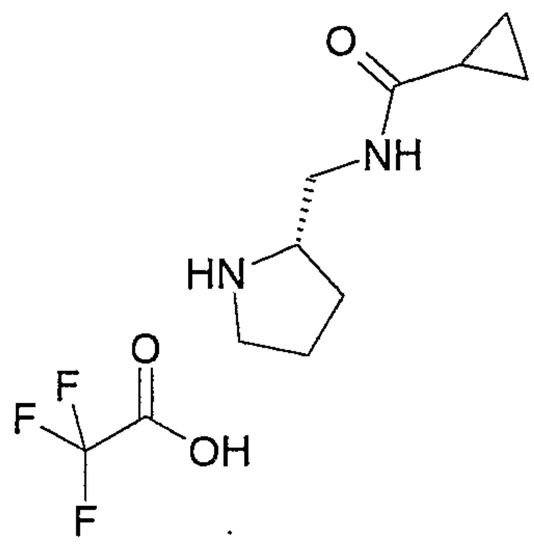
N-Pyrrolidin-(2*S*)-ylmethyl-benzamide (TFA salt).

A solution of 20.0 mg (0.07 mmol) of (2*S*)-(benzoylamino-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (Step 1) in 0.5 mL of trifluoroacetic acid and 1.0 mL of dichloromethane is stirred at room temperature for 30 minutes and then evaporated under reduced pressure to yield the title compound.

LCMS (IV) rt 1.94, m/z 205 $(M+H)^+$.

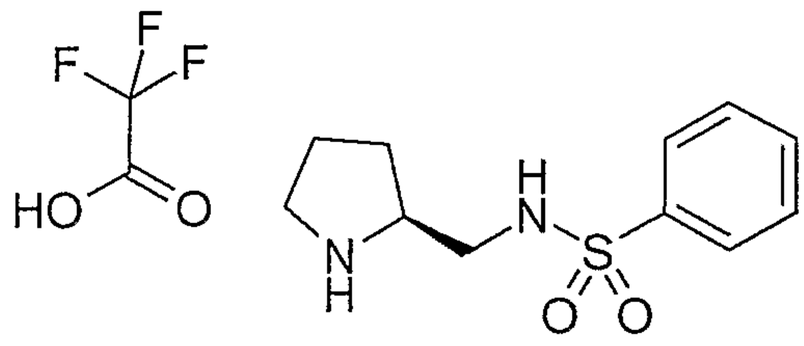
The intermediate in Table 1 is synthesized according to the procedure shown for Example 1.

TABLE 1

Example	Structure	LC-MS	NMR
2		LC/MS (II) rt 0.90 and 1.20, m/z 169 $(M+H)^+$.	Boc-protected compound (Step 1): ^{1}H-NMR δ (ppm) = 0.61-0.65 (m, 4H), 1.40 (s, 9H), 1.49- 1.61 (m, 1H), 1.63-1.85 (m, 4H), 2.85-3.10 (m, 1H), 3.15-3.30 (m, 2H), 3.39-3.50 (m, 1H), 3.68-3.78 (m, 1H), 8.08 (bs, 1H).

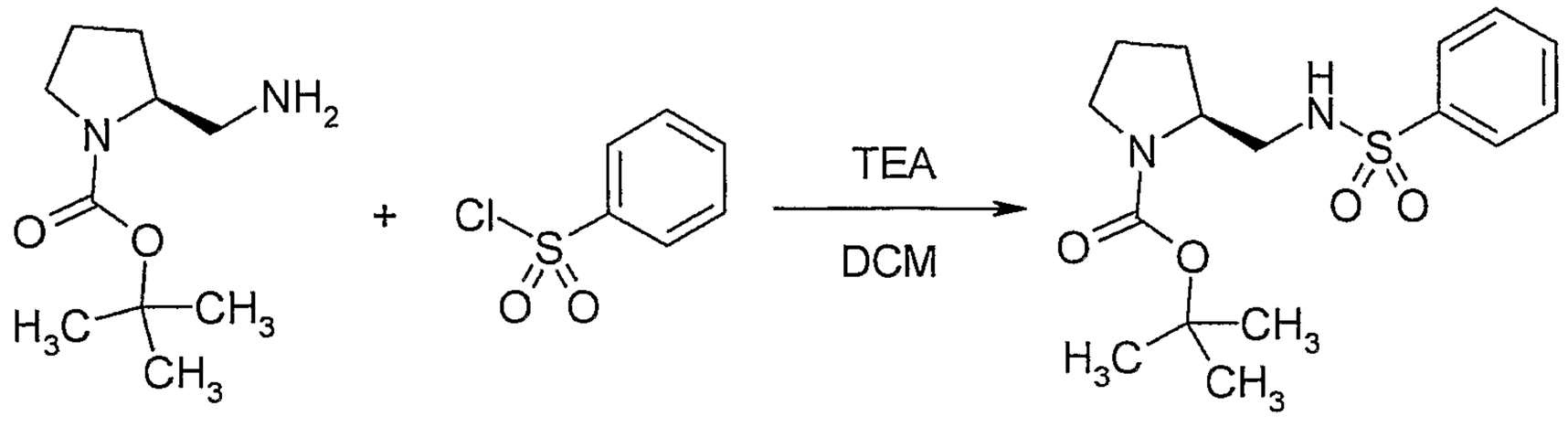
Example 3

The following representative example illustrates the synthesis of an amine educt which contains a sulphonamide bond.



Procedure for making an intermediate according to Scheme H.

Step 1

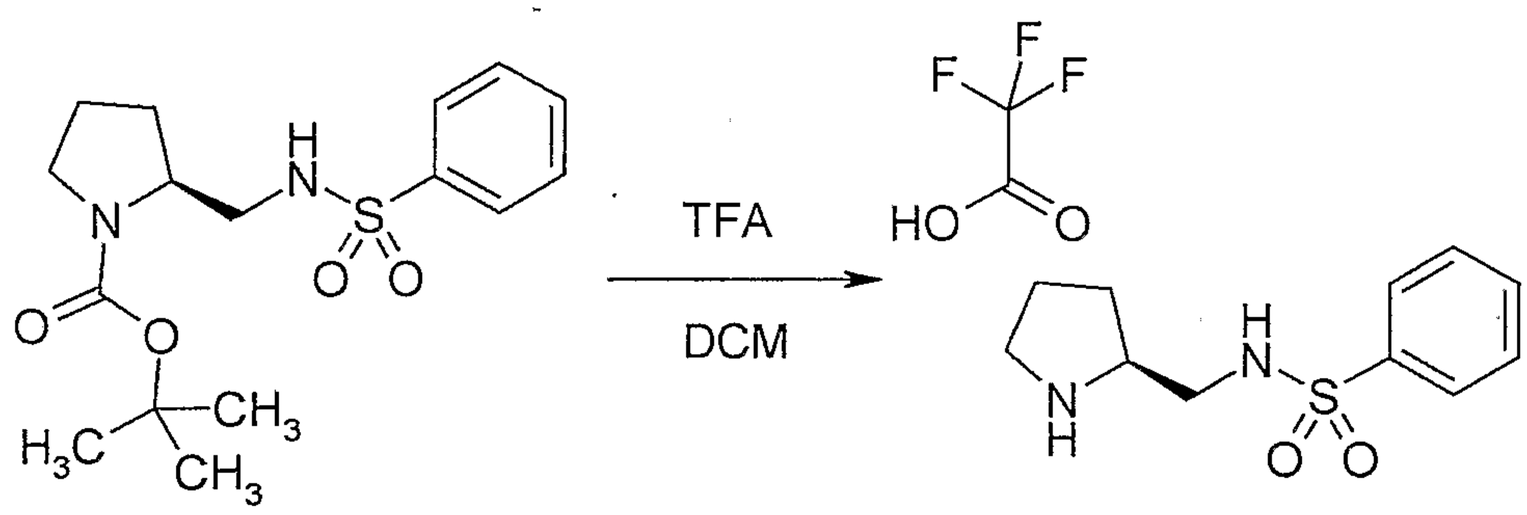


(2*S*)-(Benzenesulphonylamino-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

To a solution of 150 mg (0.75 mmol) of (2*S*)-aminomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester and 117 µL (0.90 mmol) of triethylamine in 3 mL of dichloromethane at 0°C is added 62 µL (0.80 mmol) of benzenesulphonylchloride. The mixture is stirred for 1.5 h at room temperature and then evaporated under reduced pressure to give a crude mixture containing approximate 70% of the title compound, which is taken directly onto the next step.

LC/MS (I) rt 4.34, m/z 241 $[M\text{-Boc}+H]^+$.

Step 2



N-Pyrrolidin-(2*S*)-ylmethyl-benzensulphonamide (TFA salt).

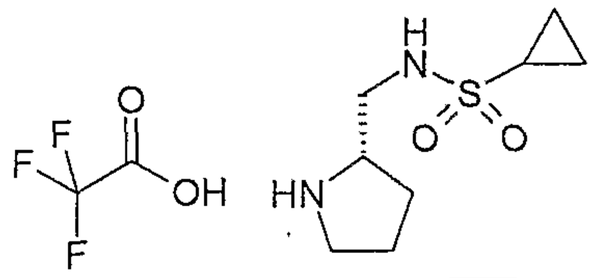
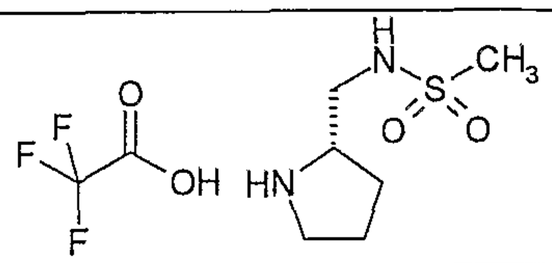
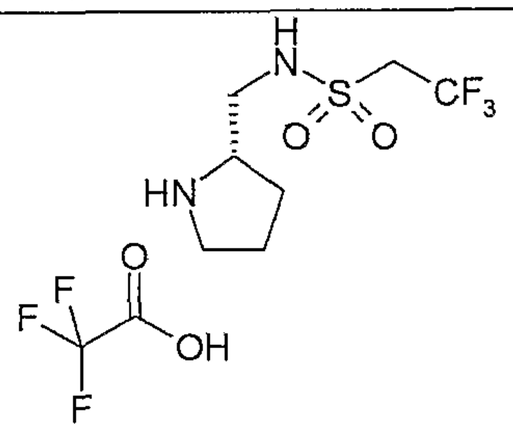
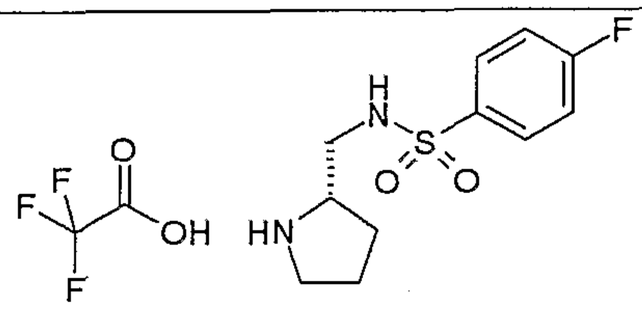
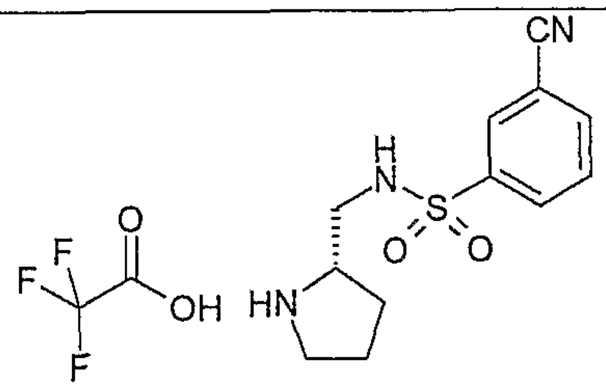
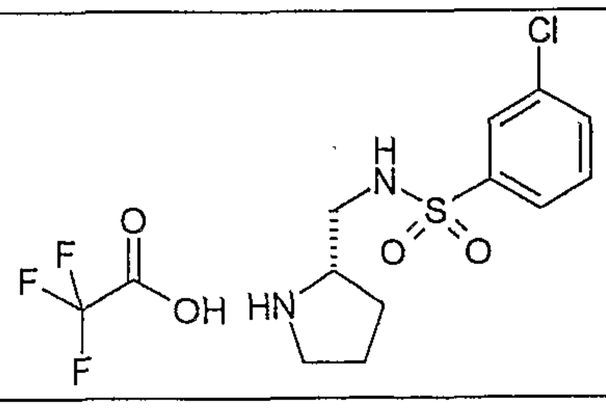
A solution of 231 mg (approximate 70% purity, 0.47 mmol) of (2*S*)-(benzene-sulphonylamino-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (Step 1) in 0.5 mL of trifluoroacetic acid and 1.5 mL of dichloromethane is stirred at room temperature for 2 h and then evaporated under reduced pressure. The oily product is diluted in 5 mL of dichloromethane and filtered through aluminium oxide (0% to 10% methanol in dichloromethane) and the collected fractions are concentrated to give the title compound.

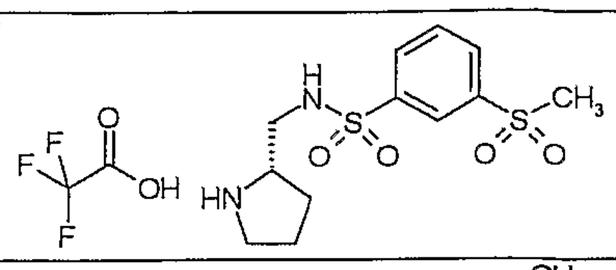
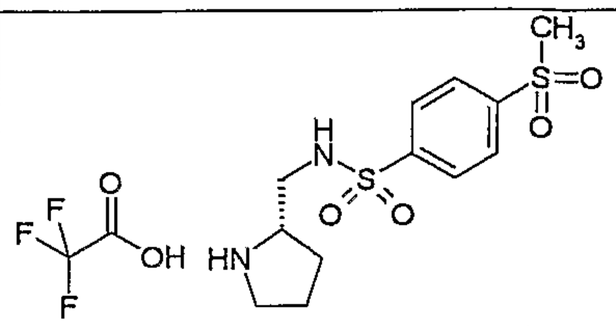
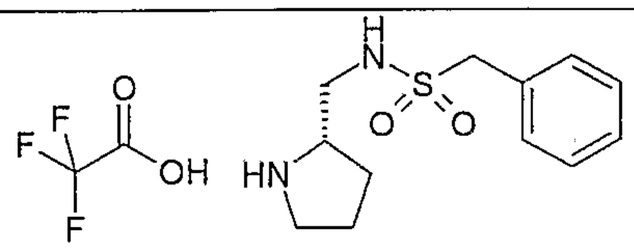
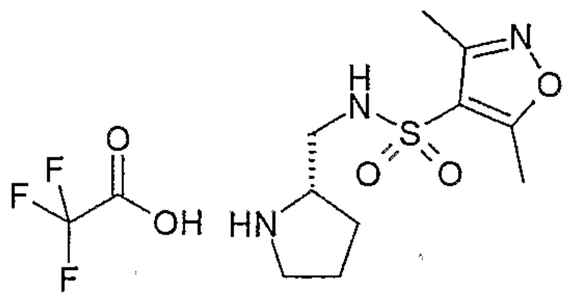
^{1}H-NMR, δ (ppm) =1.53-1.65 (m, 1H), 1.81-2.05 (m, 3H), 2.91-3.16 (m, 5H), 3.50-3.55 (m, 1H), 7.27-7.29 (m, 1H), 7.58-7.60 (m, 2H), 7.78-7.80 (m, 2H), 7.99 (t, 1H), 9.15 (bs, 1H).

LC/MS (Method I) rt 2.11, m/z 241 $[M+H]^+$.

The intermediates in Table 2 are synthesized according to the procedure shown for Example 3.

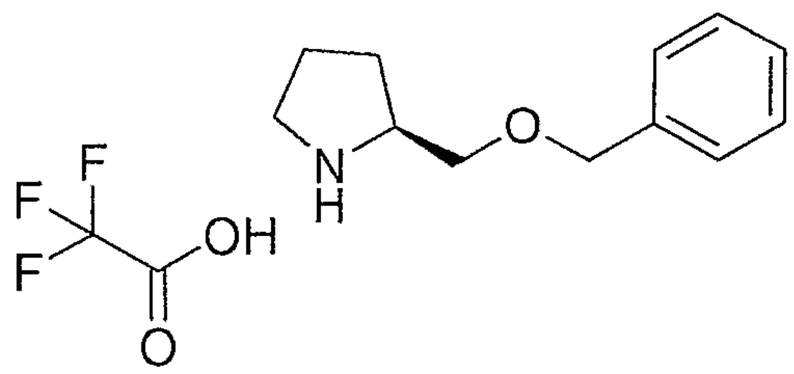
TABLE 2

Example	Structure	LC-MS	NMR
4		LC/MS (II) rt 1.60, m/z 206 $(M+H)^+$.	
5		LC/MS (II) rt 0.40, m/z 196 $(M+H)^+$.	
6		LC/MS (IV) rt 1.20, m/z 247 $(M+H)^+$.	Boc-protected compound (step 1): ^{1}H-NMR δ(ppm)= 1.40 (s, 9H), 1.73-1.86 (m, 4H), 2.83-2.96 (m, 1H), 3.18-3.21 (m, 3H), 3.67-3.78 (m, 1H), 4.32-4.38 (m, 2H), 7.88 (bs, 1H).
7		LC/MS (II) rt 1.72, m/z 275 $(M+H)^+$.	
8		LC/MS (IV) rt 1.83, m/z 266 $(M+H)^+$.	
9		LC/MS (II) rt 1.88, m/z 275 $(M+H)^+$.	

10		LC/MS (IV) rt 1.85, m/z 319 $(M+H)^+$.	
11		LC/MS (II) rt 1.67, m/z 319 $(M+H)^+$.	
12		LC/MS (II) rt 1.74, m/z 255 $(M+H)^+$.	
13		LC/MS (IV) rt 1.79, m/z 260 $(M+H)^+$.	

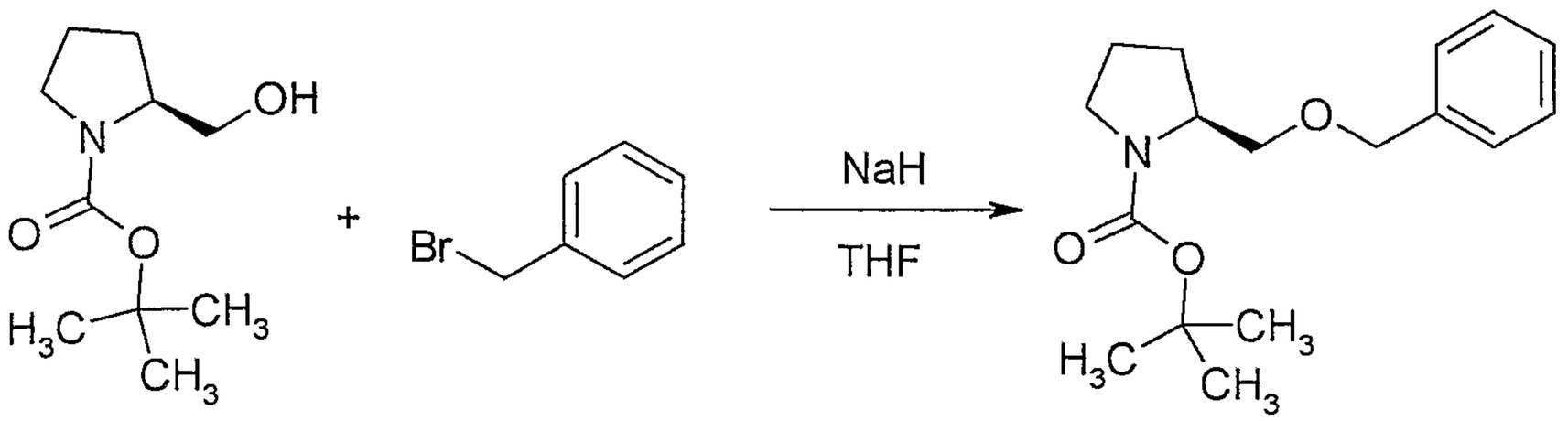
Example 14

The following representative example illustrates the synthesis of an amine educt which contains an ether bond.



Procedure for making an intermediate according to Scheme L.

Step 1



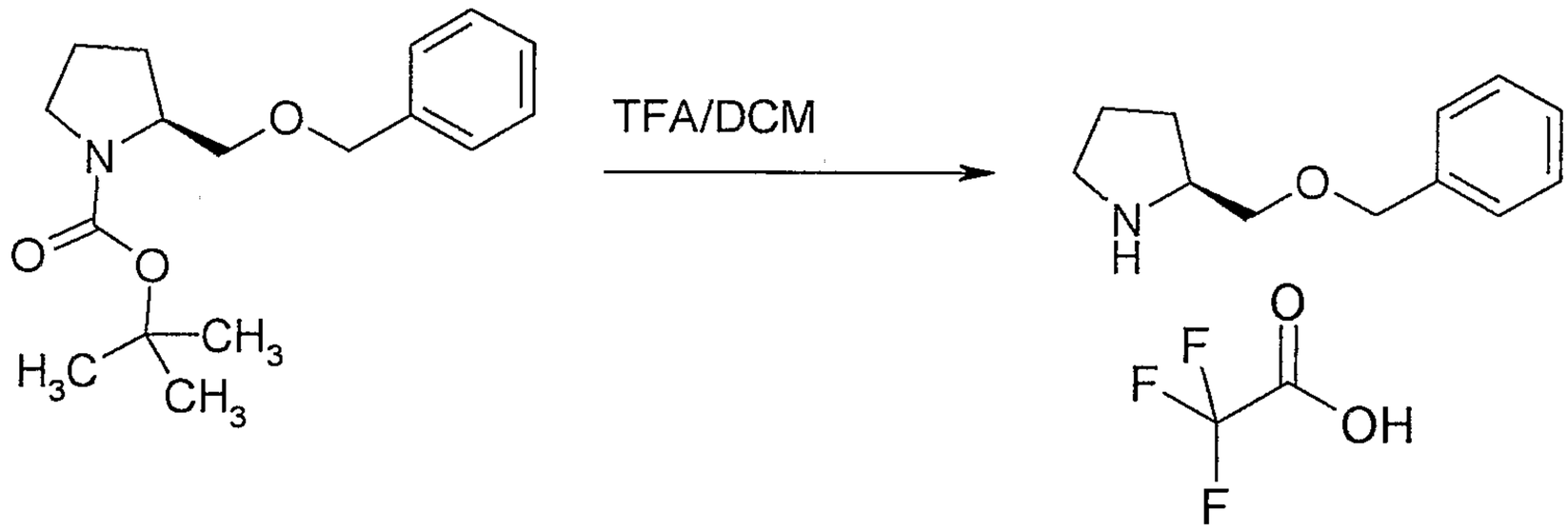
(2*S*)-Benzyloxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

(For the synthesis see also *J. Med. Chem.*; 42; 4; 1999; 677-690)

A solution of 500 mg (2.48 mmol) of (2*S*)-hydroxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester in 2 mL of tetrahydrofuran is added dropwise to a slurry of 119.2 mg (60% dispersion in oil, 2.98 mmol) of sodium hydride in 2 mL of tetrahydrofuran at 0°C and the mixture is stirred for 5 minutes. 325 µL (119 mg, 2.73 mmol) of benzylbromide is added to the solution and the reaction is allowed to warm to room temperature and stirred overnight. Water and 1N hydrochloric acid solution are added and the mixture is extracted with ethyl acetate. The collected organic phases are washed sequentially with a saturated aqueous sodium bicarbonate solution, brine and water, then dried over sodium sulphate and evaporated under reduced pressure. The crude mixture is purified using flash chromatography (silica gel, 0% to 10% ethyl acetate in cyclohexane) to afford the title compound.

LC/MS (IV) rt 3.41, m/z 233 $[M-^tBuOH]^+$.

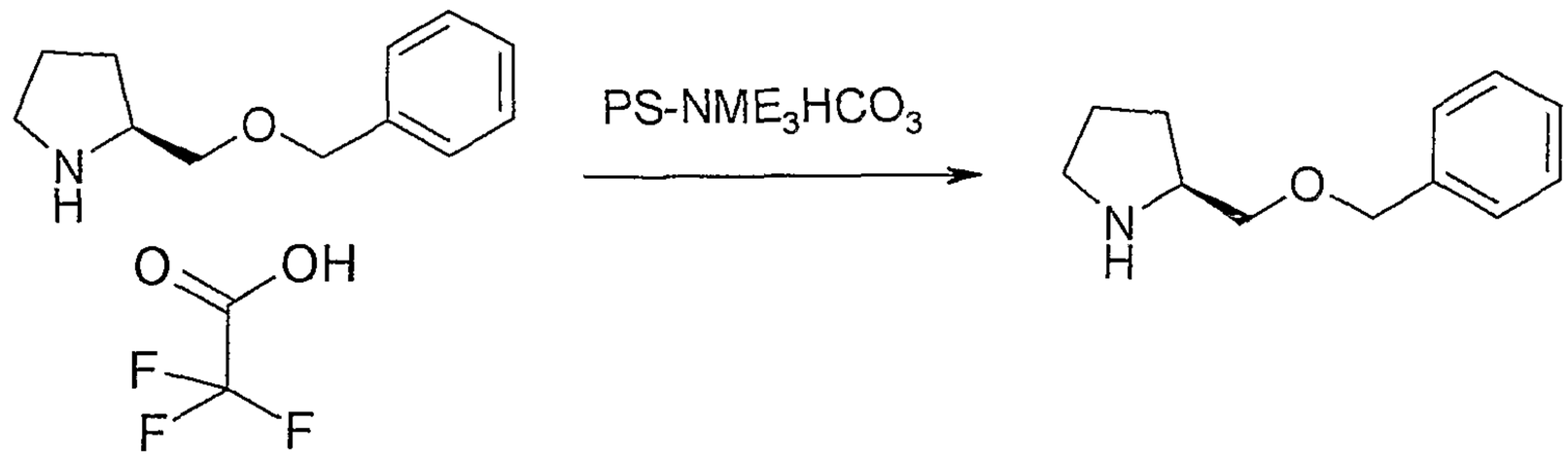
Step 2



(2*S*)-Benzyloxymethyl-pyrrolidine (TFA salt)

A solution of 300 mg (1.03 mmol) of (2*S*)-benzyloxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (Step 1) in 1.5 mL of trifluoroacetic acid and 1.5 mL of dichloromethane is stirred at room temperature for 1 h and then evaporated under reduced pressure to yield the title compound which was used without further purification in the next step.

Step 3



(S)-2-Benzyloxymethyl-pyrrolidine

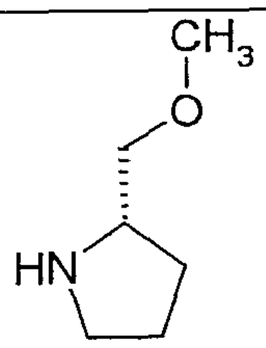
The TFA salt from step 2 is diluted in 5 mL of dichloromethane and stirred for 1 h with 1.43 g (4.12 mmol) of (polystyrylmethyl)trimethylammonium bicarbonate (Separtis, 2.73 mmol/g), then filtered and evaporated under reduced pressure to yield the title compound.

^{1}H-NMR, δ (ppm) = 1.34-1.42 (m, 1H), 1.59-1.81 (m, 3H), 2.76-2.86 (m, 2H), 3.27-3.33 (m, 4H), 4.47 (s, 2H), 7.29-7.24 (m, 5H).

LC/MS (III) rt 2.62, m/z 192 $[M+H]^+$.

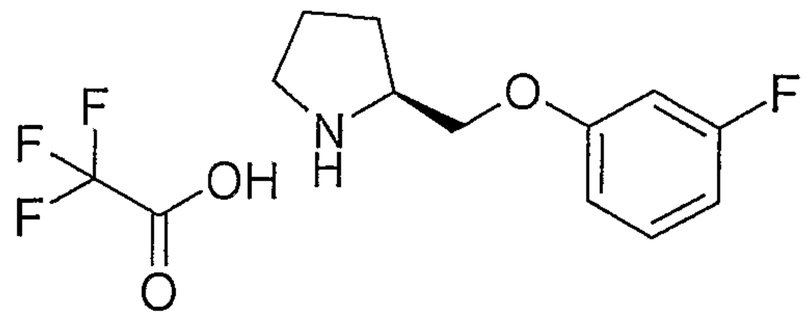
The intermediate in Table 3 is synthesized according to the procedure shown for Example 14.

TABLE 3

Example	Structure	LC-MS	NMR
15		Boc-protected compound (step 1) : LC/MS (II) rt 4.46, m/z 201 $(M+H-CH_3)^+$.	TFA salt: ^{1}H-NMR δ (ppm) = 1.50-1.65 (m, 1H), 1.80-2.10 (m, 3H), 3.05-3.25 (m, 2H), 3.30 (s, 3H), 3.40-3.46 (m, 1H), 3.51-3.56 (m, 1H), 3.60-3.75 (m, 1H), 8.55 (s, 3H), 9.18 (s, 3H).

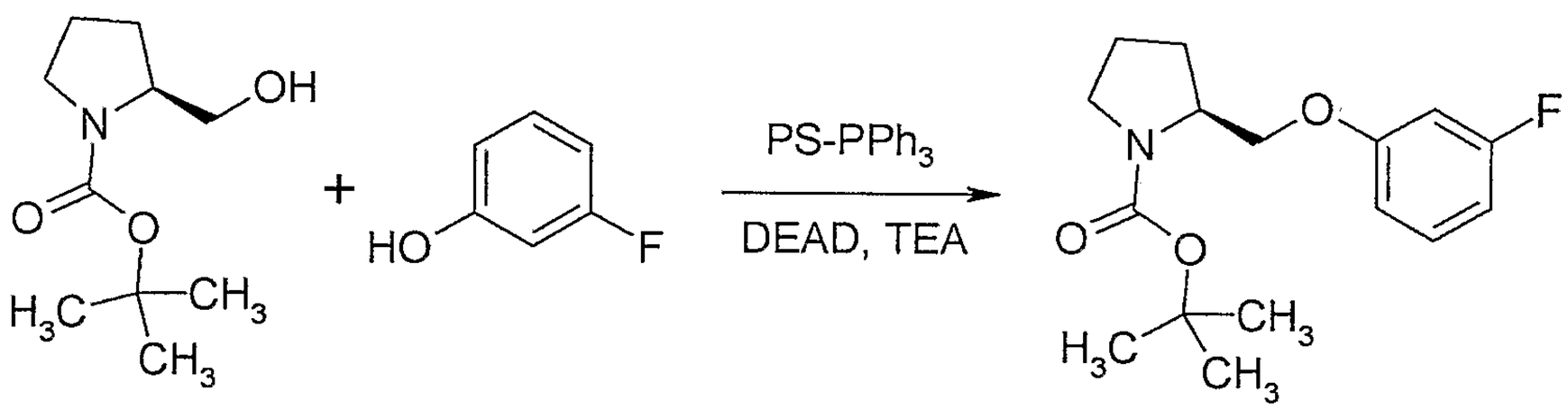
Example 16

The following representative example illustrates the synthesis of an amine educt which contains an ether bond.



Procedure for making an intermediate according to Scheme K.

Step1

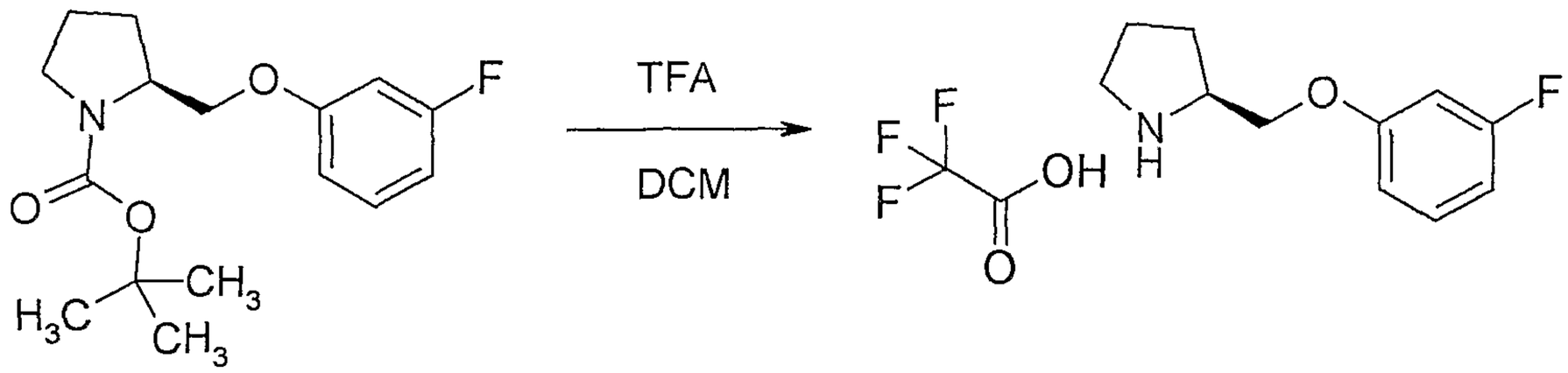


(2*S*)-(3-Fluoro-phenoxymethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

A mixture of 1.20 g (1.12 mmol) triphenylphosphine polystyrene in 4 mL dichloromethane is cooled to 0°C, at this temperature is added dropwise 155.7 mg (0.89 mmol) of diethyl azodicarboxylate and the reaction mixture is stirred for 30 minutes. To the reaction mixture is given sequentially 150.0 mg (0.75 mmol) of (2*S*)-hydroxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester dissolved in dichloromethane, 83.5 mg (0.75 mmol) of 3-fluorophenol and 116 μL (1.13 mmol) of triethylamine. The mixture is stirred overnight. As the reaction was not complete (detected by TLC, eluent 2% methanol in dichloromethane) it is cooled again to 0°C and another 50 μL of diethyl azodicarboxylate and 29 mg of 3-flourophenol is added. The reaction mixture is stirred for 48 hours and 5 mL dichlorormethane is added. The mixture is filtered over celite. The solvent is removed under reduced pressure and the residue is purified by flash chromatography (silica gel, 0-20% ethyl acetate in cyclohexane) to yield the title compound, used directly in next step without further purification.

LCMS (II) rt 3.48, m/z 281 $[M-CH_3+H]^+$.

Step 2



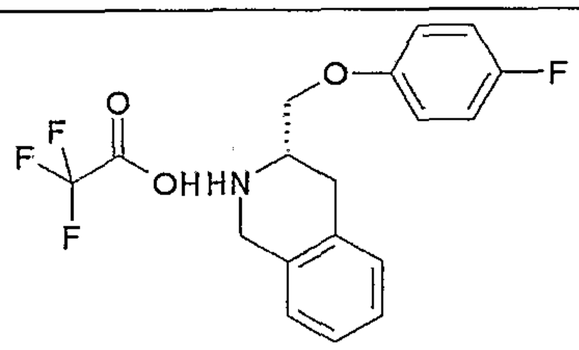
(2*S*)-(3-Fluoro-phenoxymethyl)-pyrrolidine (TFA salt)

To a solution of 20.0 mg (0.06 mmol) of (2*S*)-(3-Fluoro-phenoxymethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (Step 1) in 1mL dichloromethane, 0.5 mL of trifluoroacetic acid is added at room temperature and stirred until the reaction is complete (monitored by TLC). Removal of the solvents under reduced pressure affords the title compound.

LCMS (II) rt 1.78, m/z 196 $[M+H]^+$.

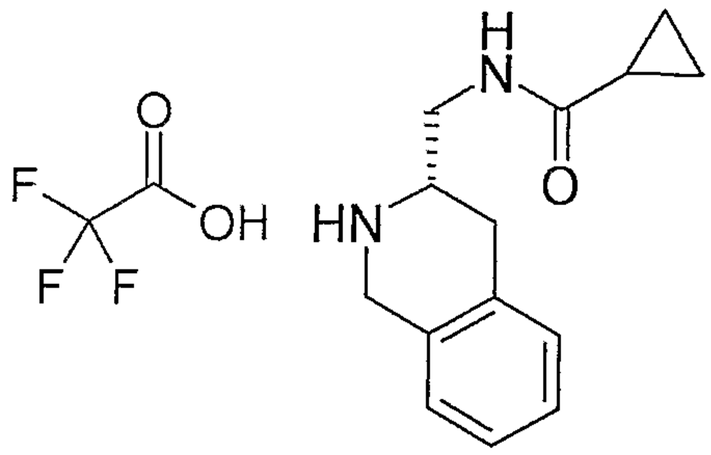
The intermediate in Table 4 is synthesized according to the procedure shown for Example 16.

TABLE 4

Example	Structure	LC-MS	NMR
17		LC/MS (II) rt 2.19, m/z 258 $(M+H)^+$.	

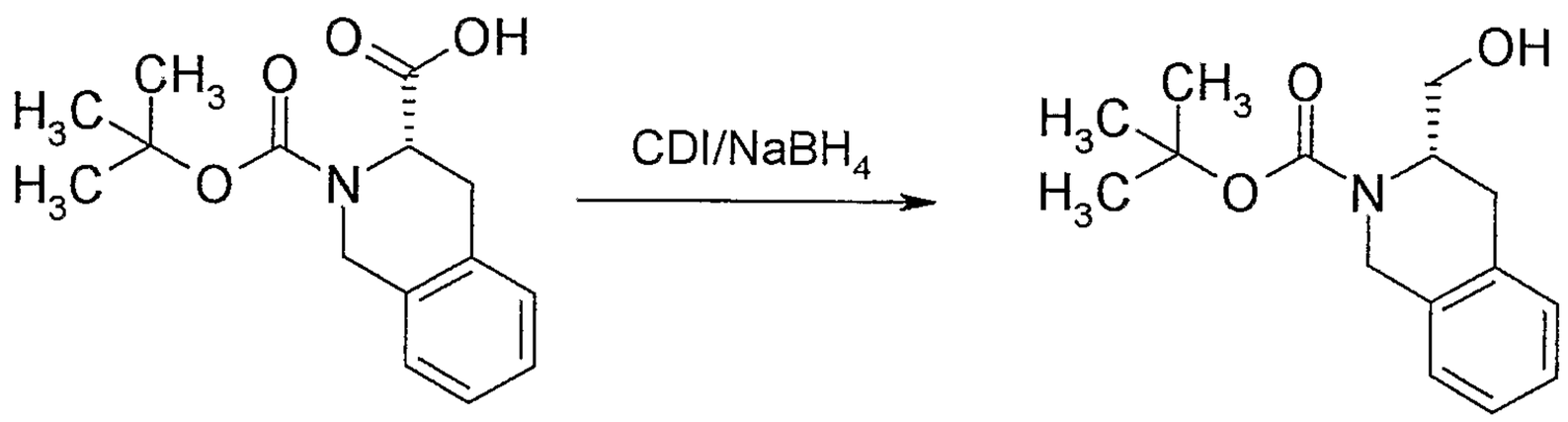
Example 18

The following representative example illustrates the synthesis of an amine educt in the tetrahydroisoquinoline series.



Procedure for making an intermediate according to Scheme F and E.

Step 1



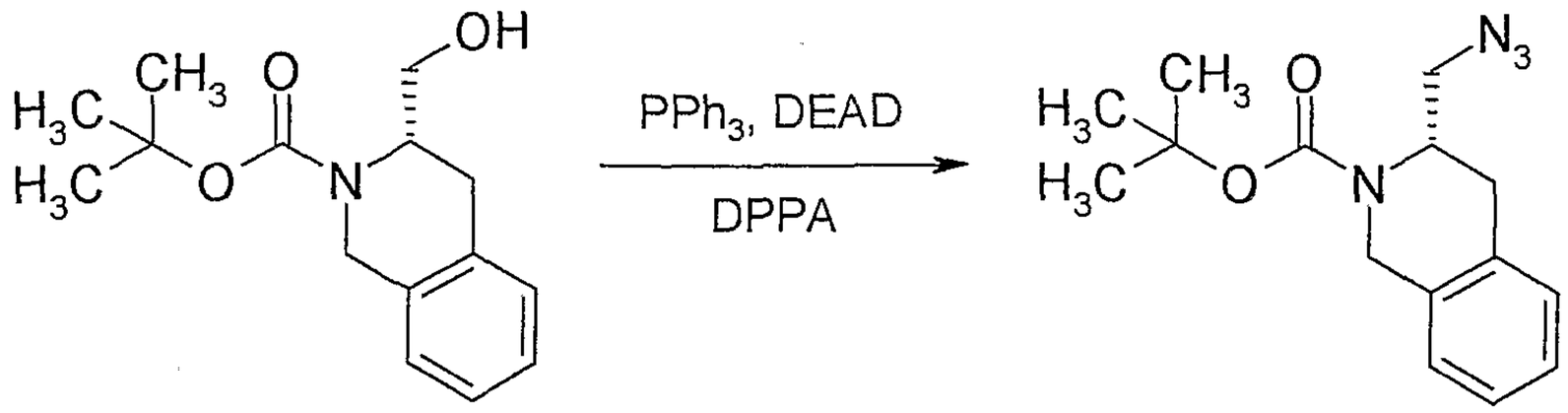
(3*S*)-Hydroxymethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

437 mg (1.58 mmol) of (2*S*)-3,4-Dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-*tert*-butyl ester is dissolved in 20 mL absolute tetrahydrofuran, then 384 mg (2.37 mmol) of 1,1'-carbonyldiimidazole is added and the mixture is stirred at ambient temperature for 30 minutes. The flask is transferred into an ice bath and 90 mg (2.37 mmol) of sodium borohydride in 1 mL water is added. After stirring for 10 minutes at 0°C, acetone is added and the solvent is removed under reduced pressure. The solid residue is taken into water/ethyl acetate and the layers are separated. The organic layer is washed sequentially with 5% aqueous citric acid solution, saturated aqueous sodium bicarbonate solution, brine and dried over sodium sulphate. The solvent is removed and the residue is purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 2:1) to yield the title compound.

^{1}H-NMR, δ = 1.43 (s, 9H), 2.85 (m, 2H), 3.13 (m, 1H), 3.30 (m, 1H), 4.13–4.30 (m, 2H), 4.60 (d, 1H), 4.68 (bs, 1H), 7.13 (s, 4H).

LCMS (II) rt 2.62, m/z 164 $[M\text{-Boc}+H]^+$.

Step 2

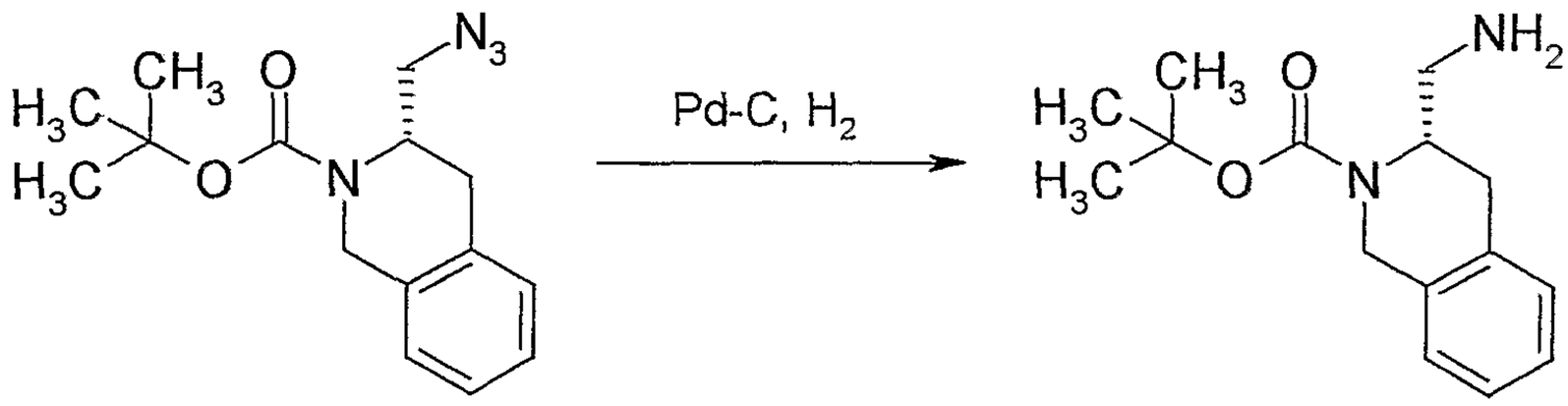


(3*S*)-Azidomethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

Following the procedure from Page et al., *J. Med. Chem.* 44, 2387 (2001) the alcohol from step 1 was transformed into the title compound.

LCMS (II) rt 3.35, m/z 230 $[M -Boc+CH_3CN+H]^+$.

Step 3



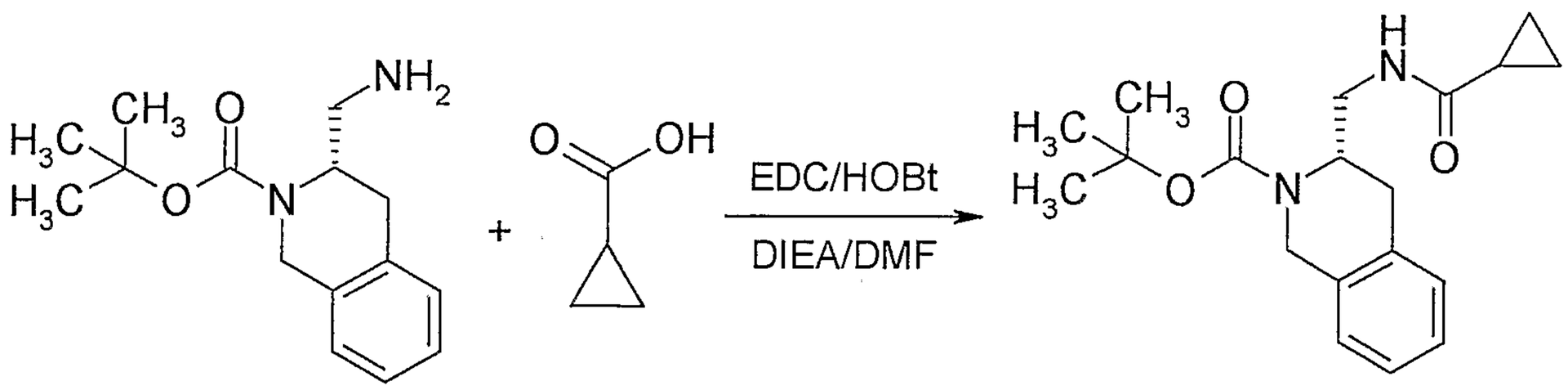
(3*S*)-Aminomethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

6.02 mg (2.09 mmol) of (3*S*)-azidomethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (Step 2) is dissolved in 20 mL methanol, 10% Palladium on carbon is added and the reaction is stirred for 1.5 h under hydrogen atmosphere. The mixture is filtered over Celite and the solvent is removed under reduced pressure. Flash chromatography (silica gel, dichloromethane/methanol with 3% ammonia) affords the title compound.

^{1}H-NMR, δ = 1.43 (s, 9H), 2.37 (dd, 1H), 2.48 (m together with DMSO, 1H), 2.84 (m, 2H), 4.13–4.20 (m, 2H), 4.63 (d, 1H), 7.11 (s, 4H).

LCMS (II) rt 2.21, m/z 263 $(M+H)^+$.

Step 4

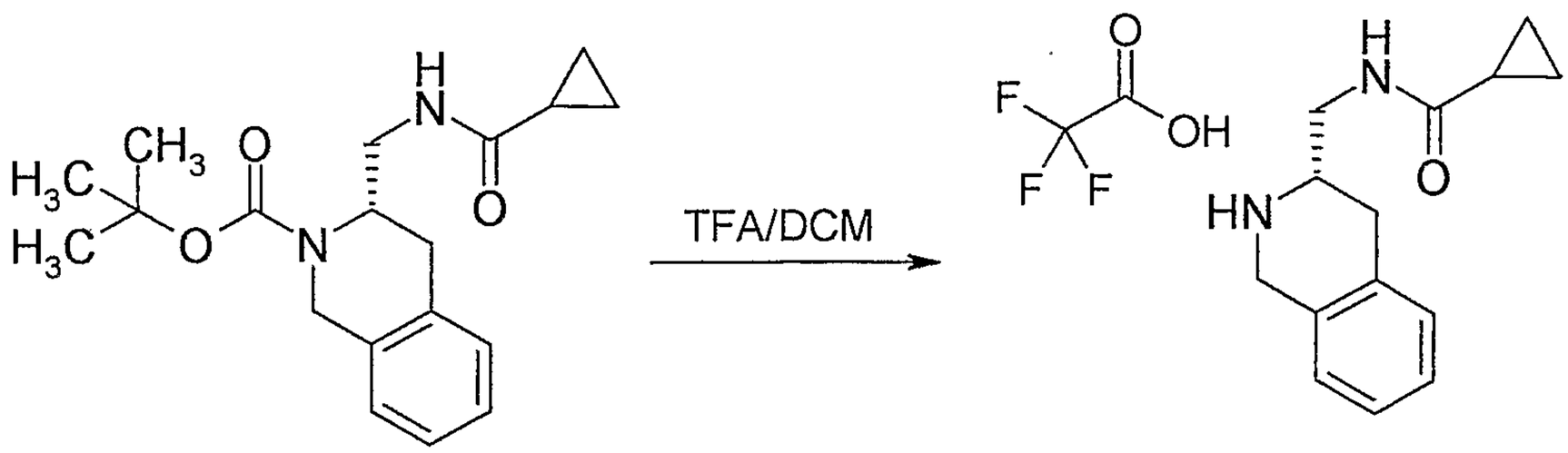


(3*S*)-[(Cyclopropanecarbonyl-amino)-methyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester

A mixture of 12 mg (0.14 mmol) cyclopropanecarboxylic acid, 31 mg (0.16 mmol) 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride, 22 mg (0.16 mmol) 1-hydroxybenzotriazole and 66 µL (0.35 mmol) diisopropylethylamine in 2 mL *N,N*-dimethylformamide is stirred at ambient temperature for 10 minutes before 38 mg (0.14 mmol) (3*S*)-Aminomethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (Step 3) in 1 mL *N,N*-dimethylformamide is added and stirring is continued overnight. The solution is diluted with 50 mL ethyl acetate, washed sequentially 5% aqueous citric acid solution, saturated aqueous sodium bicarbonate solution and brine and dried over sodium sulphate. The solvent is removed under reduced pressure and the residue is purified by flash chromatography (silica gel, cyclohexane/ethylacetate 2:1) to yield the title compound.

LCMS (II) rt 2.71, m/z 394 $[M+Na+CH_3CN+H]^+$.

Step 5



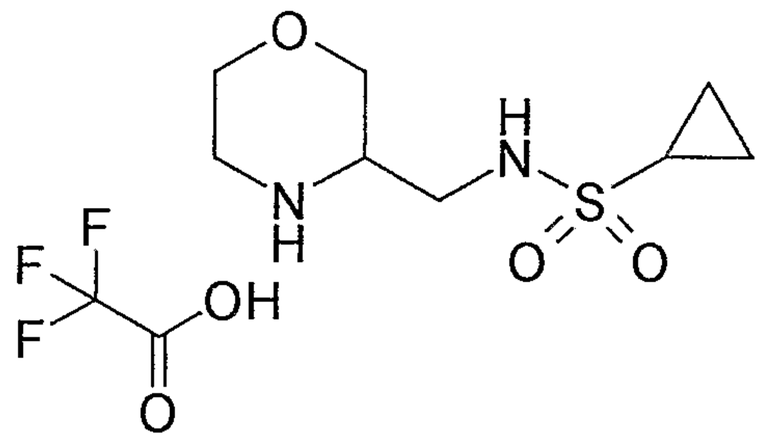
Cyclopropanecarboxylic acid (1,2,3,4-tetrahydro-isoquinolin-(3*S*)-ylmethyl)-amide (TFA salt)

25 mg (0.08 mmol) of (3*S*)-[(cyclopropanecarbonyl-amino)-methyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (Step 4) is dissolved in 1 mL dichloromethane and 0.5 mL of trifluoroacetic acid is added. The solution is stirred for 30 min at ambient temperature, then the solvents are removed under reduced pressure. The crude material is taken directly onto the next synthetic step.

LCMS (II) rt 1.66, m/z 231 $(M+H)^+$.

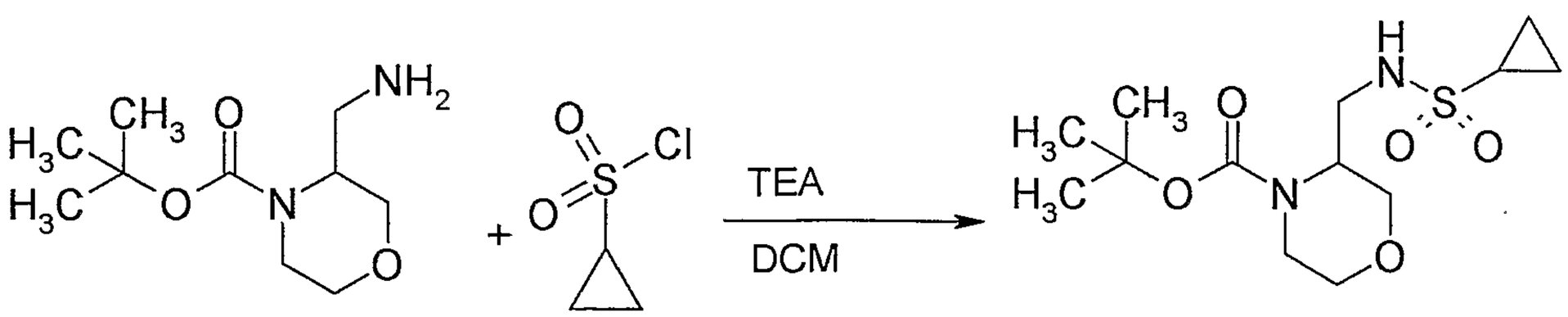
Example 19

The following representative example illustrates the synthesis of an amine educt in the morpholine series.



Procedure for making an intermediate according to Scheme H.

Step 1



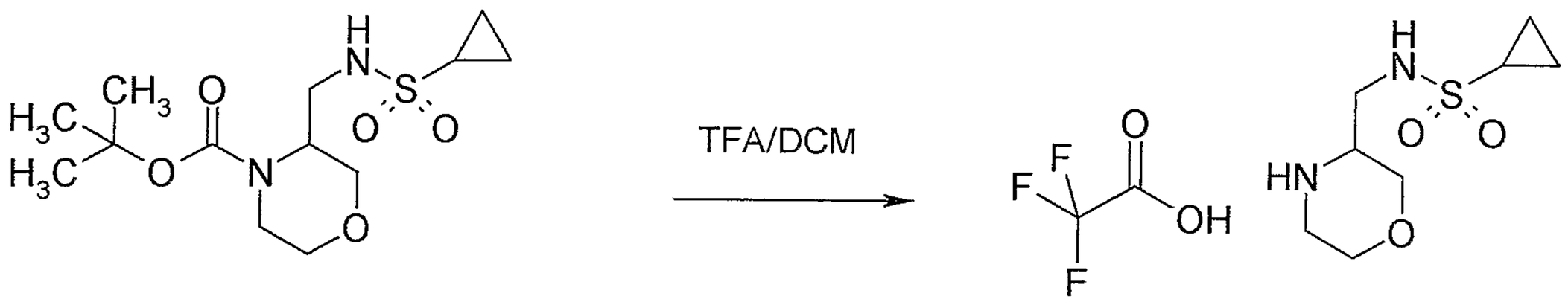
3-(Cyclopropanesulphonylamino-methyl)-morpholine-4-carboxylic acid tert-butyl ester

To a solution of 21 mg (0.10 mmol) 3-Aminomethyl-morpholine-4-carboxylic acid tert-butyl ester (prepared according to Example 18, steps 1, 2 and 3) and 15 µL (0.12 mmol) of triethylamine in 3 mL of dichloromethane at 0°C is added 15 mg (0.11 mmol)

of cyclopropanesulphonyl chloride. After stirring for 1.5 h at room temperature dichlorometahne is added. The organic solution is washed successively with a 5% aqueous citric acid solution, with a saturated aqueous sodium bicarbonate solution and with brine. After drying over sodium sulphate and evaporating the solvent under reduced pressure, the title compound, was obtained which was used crude in the next step without further purification.

LC/MS (II) rt 2.26, m/z 384 $[M+H+CH_3CN]^+$.

Step 2



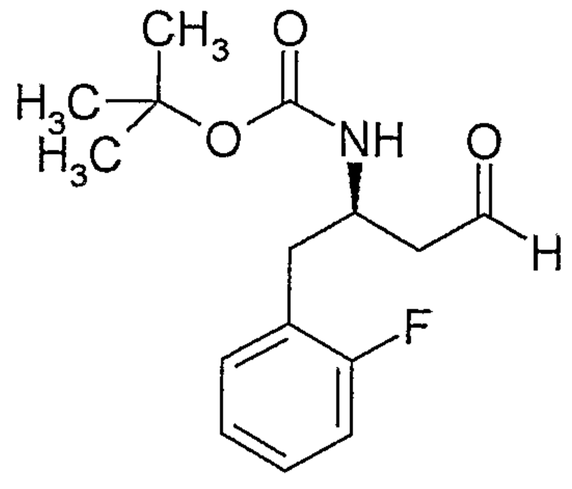
Cyclopropanesulphonic acid (morpholin-3-ylmethyl)-amide

19 mg (0.06 mmol) 3-(cyclopropanesulphonylamino-methyl)-morpholine-4-carboxylic acid tert-butyl ester (Step 1) are dissolved in 1 mL of a 30% solution of TFA in dichloromethane. The solution is stirred for 30 min at ambient temperature, then the solvents are removed under reduced pressure.

LCMS (II) rt 1.19, m/z 201 $(M+H)^+$.

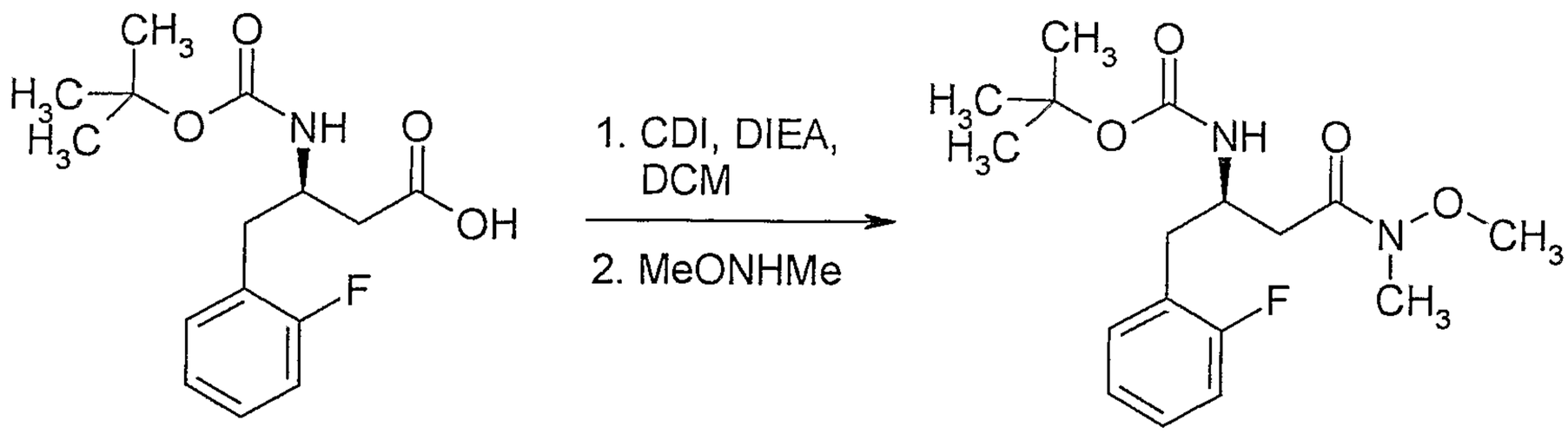
Example 20

The following representative example illustrates the synthesis of an aldehyde educt.



Procedure for making an intermediate according to Scheme N.

Step 1

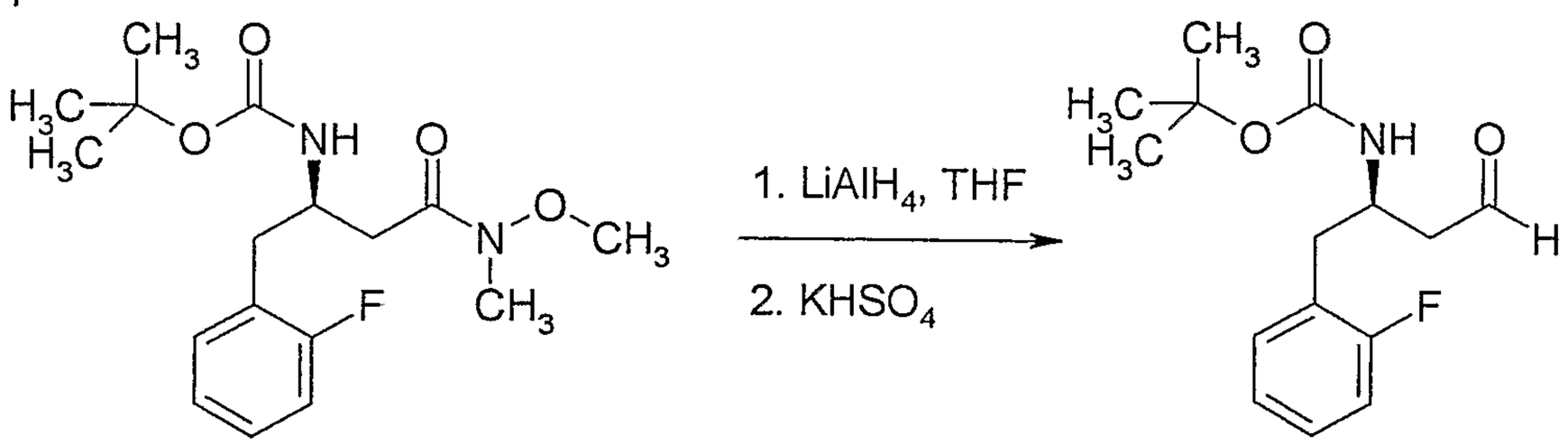


{(2*R*)-(2-Fluoro-phenyl)-1-[(methoxy-methyl-carbamoyl)-methyl]-ethyl}-carbamic acid *tert*-butyl ester.

To a solution of 29.0 mg (0.097 mmol) of (3*R*)-*tert*-butoxycarbonylamino-4-(2-fluoro-phenyl)-butyric acid in 1 mL of dichloromethane is added under argon 17.4 mg (0.107 mmol) 1,1'-carbonyldiimidazole. The solution is stirred for 1h and then 19 µL (0.107 mmol) of diisopropylethylamine and 10.7 mg (0.107 mmol) of *N,O*-dimethyl-hydroxylamine hydrochloride are added. The resulting mixture is stirred overnight at room temperature and then diluted with dichloromethane and washed sequentially with a saturated sodium bicarbonate aqueous solution, a 5% aqueous citric acid solution and brine. The combined organic phases are dried over sodium sulphate, filtered and concentrated under reduced pressure to afford the title compound which was used directly in the next step without further purification.

LC/MS (IV) rt 2.79, m/z 241 $[M\text{-}Boc+H]^+$.

Step 2



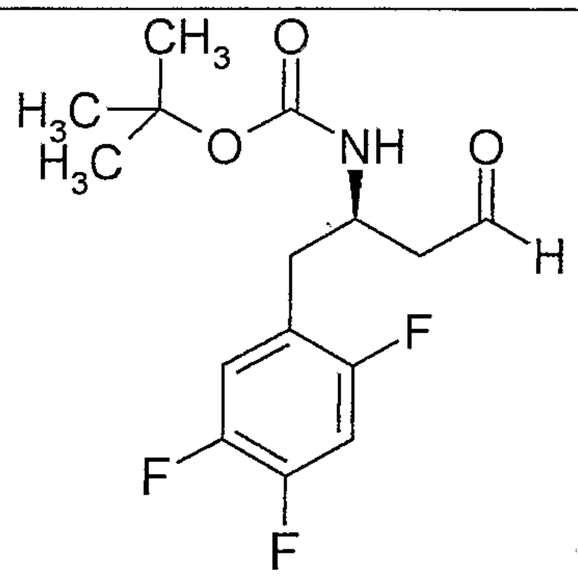
(1R)-[(2-Fluoro-benzyl)-3-oxo-propyl]-carbamic acid *tert*-butyl ester.

A solution of 23.0 mg (0.068 mmol) of {*(2R)*-(2-fluoro-phenyl)-1-[(methoxy-methyl-carbamoyl)-methyl]-ethyl}-carbamic acid *tert*-butyl ester (Step 1) in 1 mL of tetrahydrofuran is cooled down to -10 °C and then 34 µL (0.034 mmol) of a 1 M lithium aluminium tetrahydride solution in tetrahydrofuran is added. The solution is stirred for

30 minutes, cooled down again to -10 °C and quenched with 5 mL of a saturated sodium hydrogensulphate aqueous solution. The crude mixture is extracted with diethyl ether, the organic layer is separated and washed with brine, dried over sodium sulphate and filtered, evaporated under reduced pressure to afford the title compound. LC/MS (II) rt 2.66, m/z 226 $[M-C_3H_9+H]^+$.

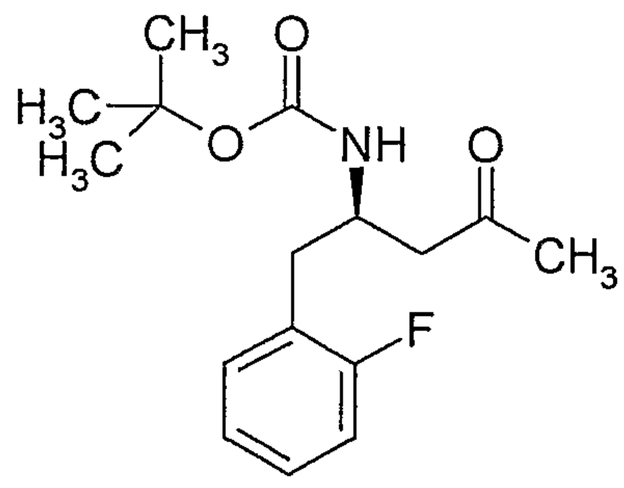
The compound in Table 5 is synthesized according to the procedure shown for example 20.

TABLE 5

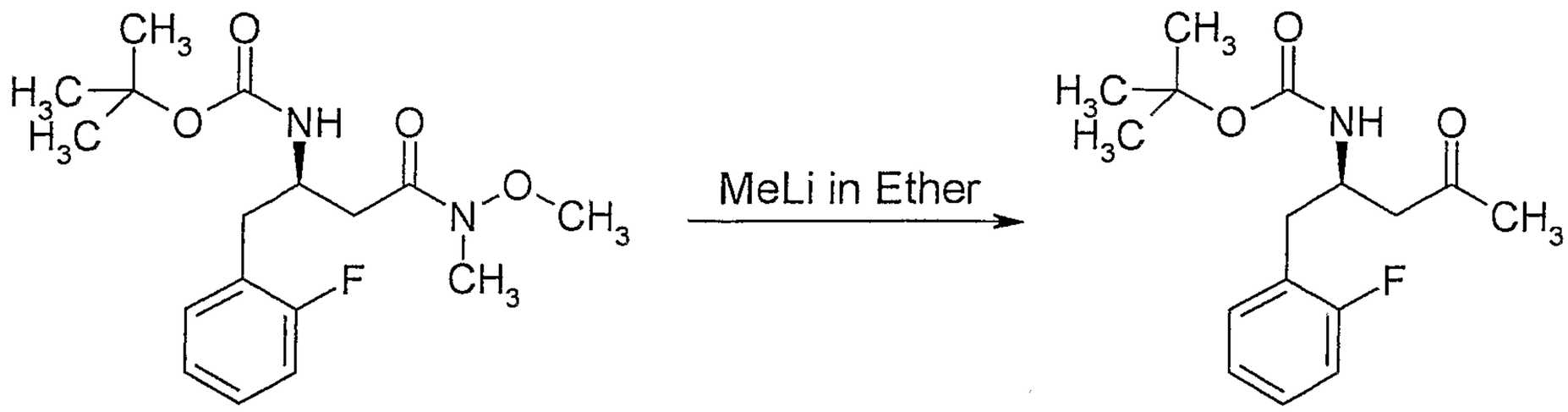
Example	Structure	LC-MS	NMR
21		LC/MS (II) (15-95%, 5 min) rt 2.59, m/z 363 $(M+CH_3+OCH_3)^+$.	

Example 22

The following representative example illustrates the synthesis of an alkylketone educt.



Procedure for making an intermediate according to Scheme O.



[*(1R)*-(2-Fluoro-benzyl)-3-oxo-butyl]-carbamic acid *tert*-butyl ester

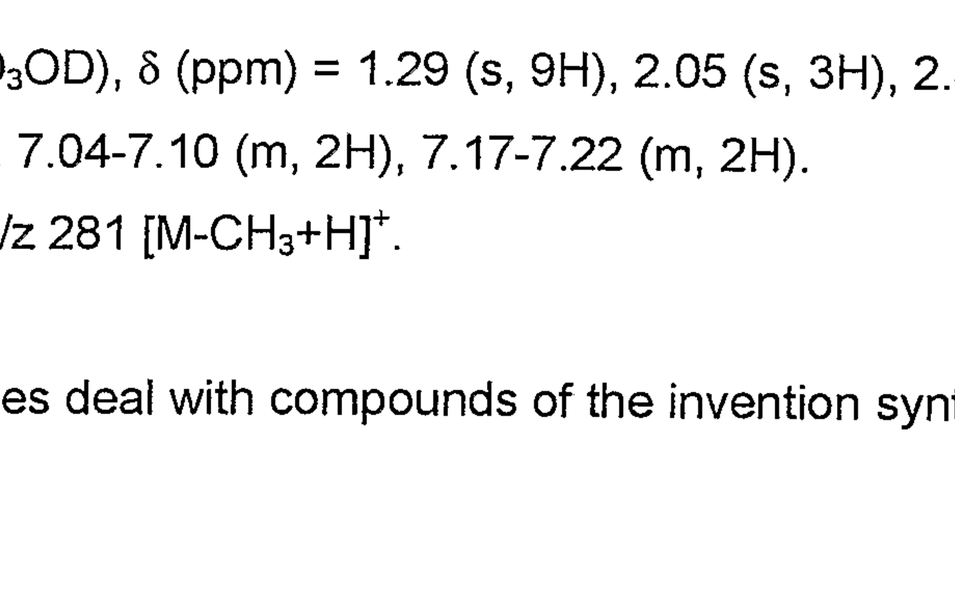
1218 µL (1.82 mmol) of a 1.5 M solution of methy lithium in ether is added dropwise at 0°C to a solution of 203 mg (0.61 mmol) of {*(2R)*-(2-fluoro-phenyl)-1-[(methoxy-methyl-carbamoyl)-methyl]-ethyl}-carbamic acid *tert*-butyl ester (Example 20, Step 1) in 1.3 mL absolute tetrahydrofuran. After the addition is complete the reaction mixture is stirred for 1h at room temperature, cooled again to 0°C and quenched with 2 mL methanol. The solvent is evaporated under reduced pressure, the residue is dissolved in dichloromethane, washed four times with brine, dried over sodium sulphate, filtered and concentrated under reduced pressure to afford the title compound as a yellow solid.

^{1}H-NMR (solvent: CD_3OD), δ (ppm) = 1.29 (s, 9H), 2.05 (s, 3H), 2.46-2.85 (m, 4H), 4.06 (m, 1H), 6.68 (d, 1H), 7.04-7.10 (m, 2H), 7.17-7.22 (m, 2H).

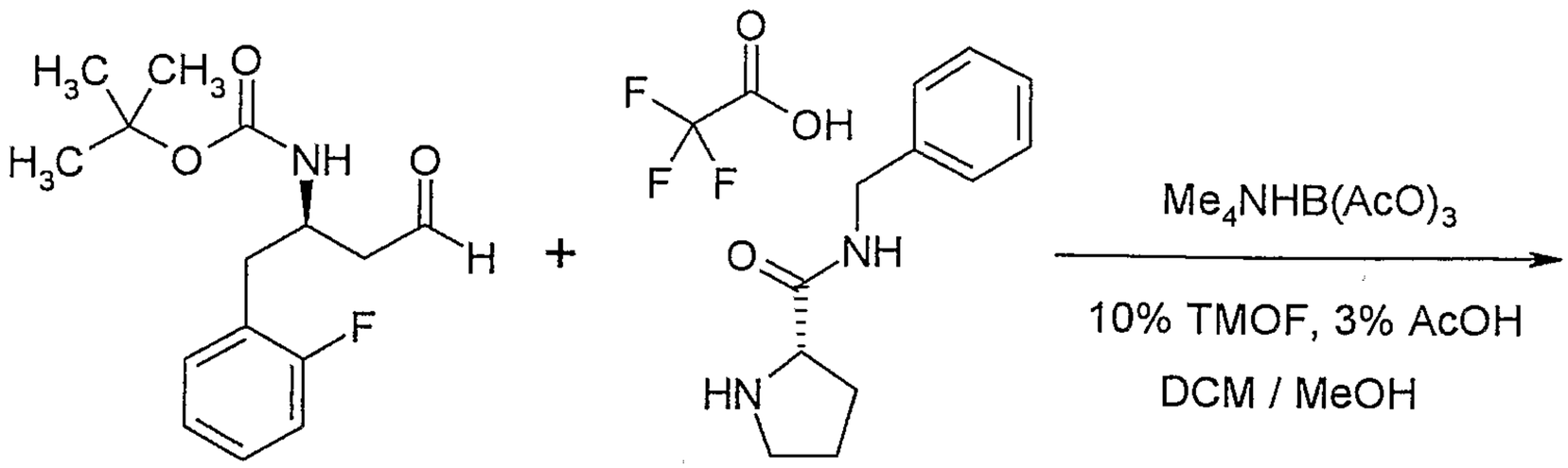
LC/MS (III) rt 4.81, m/z 281 $[M-CH_3+H]^+$.

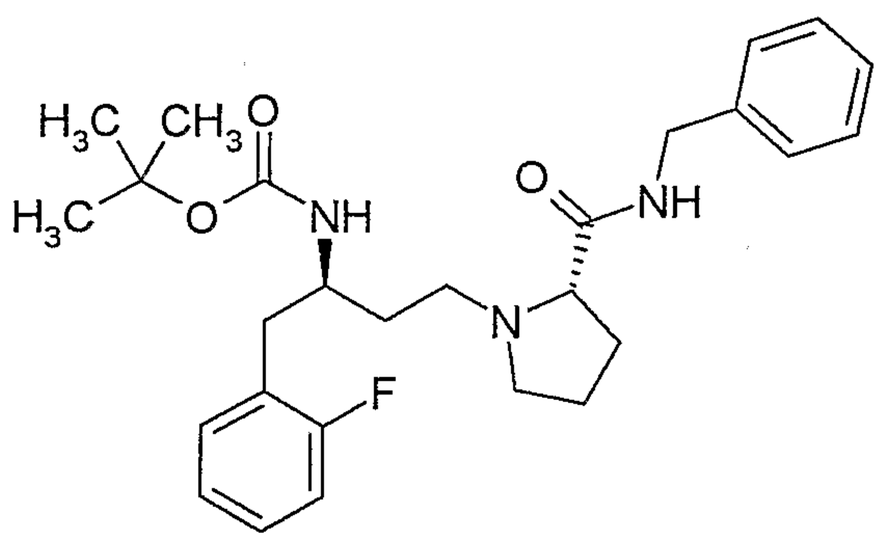
The following examples deal with compounds of the invention synthesised according to Scheme Q.

Example 23



Step 1



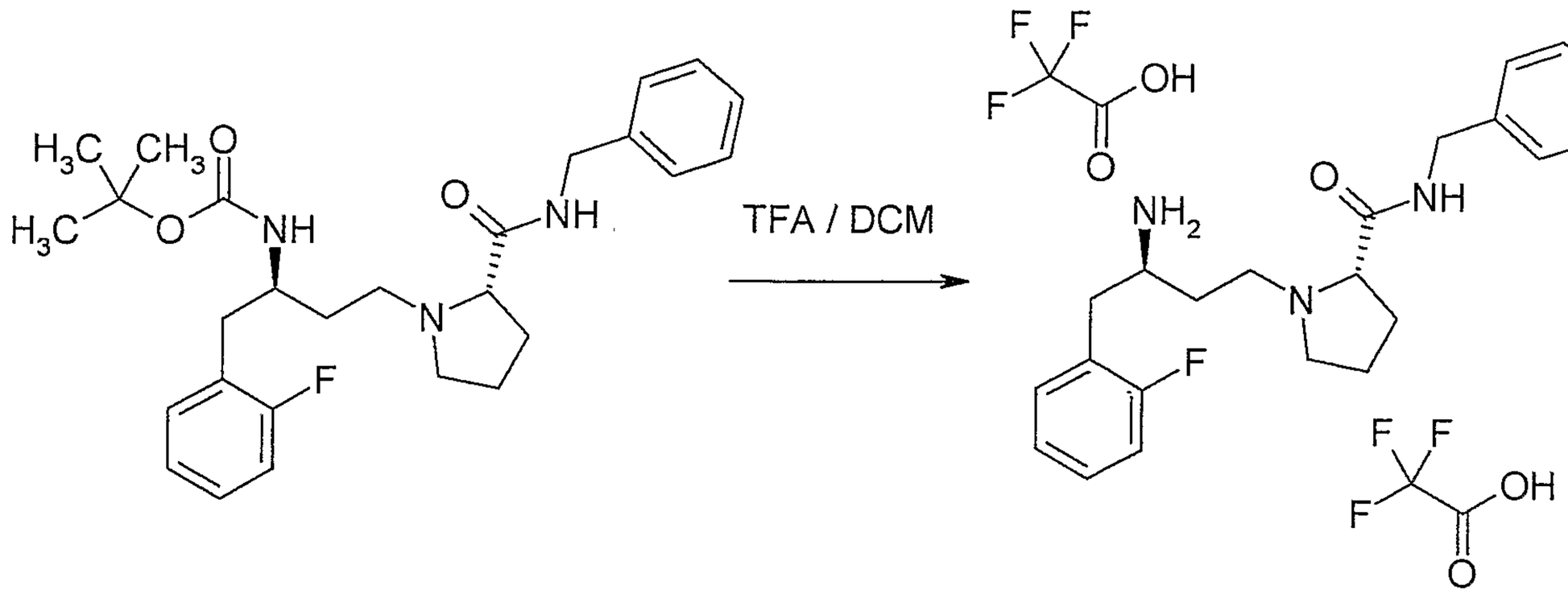


{3-[(2*S*)-2-Benzylcarbamoyl-pyrrolidin-1-yl]-(1*R*)-(2-fluoro-benzyl)-propyl]-carbamic acid *tert*-butyl ester.

To a solution of 12.0 mg (0.057 mmol) of pyrrolidine-(2*S*)-carboxylic acid benzylamide, TFA salt (synthesised according a standard procedure for amide coupling, compare Example 18, step 4, 5 with commercially available starting materials) in 3 mL of a mixture of dichloromethane/methanol (3:1) containing 10% of trimethyl orthoformate and 3% of acetic acid, 19.0 mg (0.068 mmol) of [(1*R*)-(2-fluoro-benzyl)-3-oxo-propyl]-carbamic acid *tert*-butyl ester (Example 20) is added. The solution is stirred overnight at room temperature, quenched with methanol and concentrated under reduced pressure. The crude mixture is dissolved in ethyl acetate and washed with brine and water. The organic layer is dried over sodium sulphate, filtered and under reduced pressure. Purification of the crude mixture using preparative LC/MS (5% to 95% of acetonitrile in water, 0.1% trifluoroacetic acid) affords the title compound.

LC/MS (II) rt 2.55, m/z 470 $[M+H]^+$.

Step 2

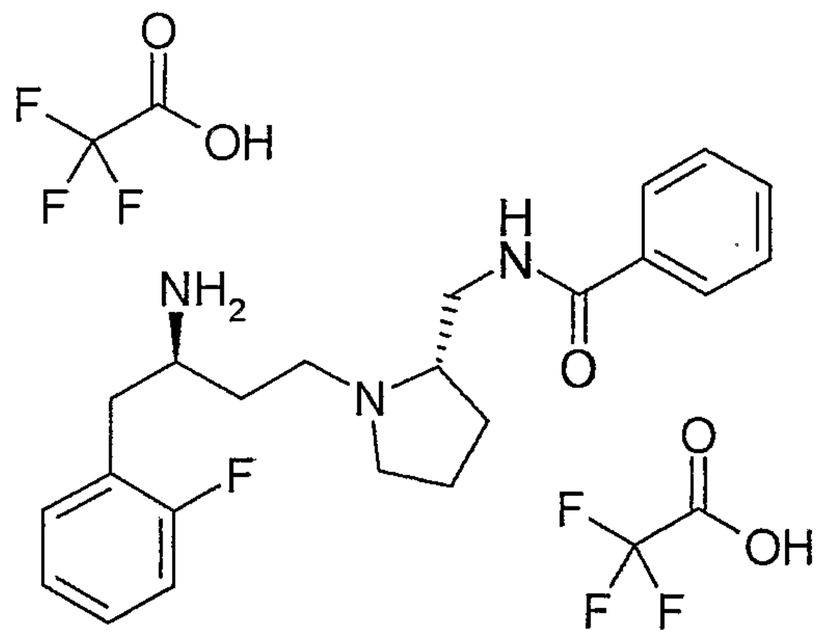


1-[(3*R*)-Amino-4-(2-fluoro-phenyl)-butyl]-pyrrolidine-(*2R*)-carboxylic acid benzyl-amine (2 x TFA salt)

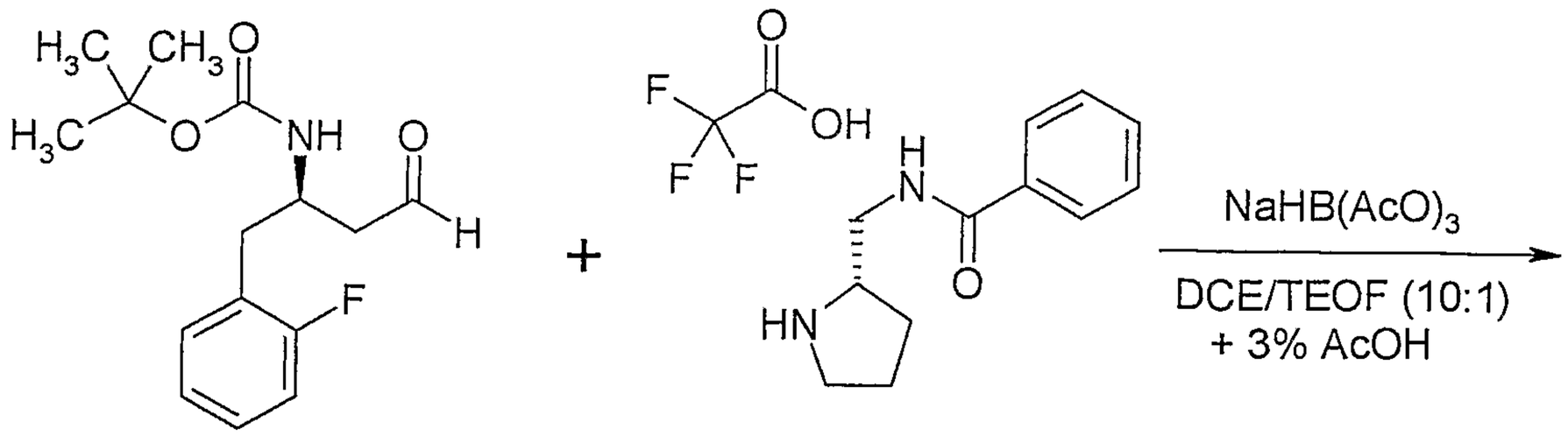
A solution of 15.9 mg (0.032 mmol) of {3-[(*2S*)-2-benzylcarbamoyl-pyrrolidin-1-yl]-(1*R*)-(2-fluoro-benzyl)-propyl]-carbamic acid *tert*-butyl ester (Step 1) in 2 mL of a mixture of dichloromethane/trifluoroacetic acid (2:1) is stirred for 1 h at room temperature. The solvents are evaporated under reduced pressure to afford the title compound.

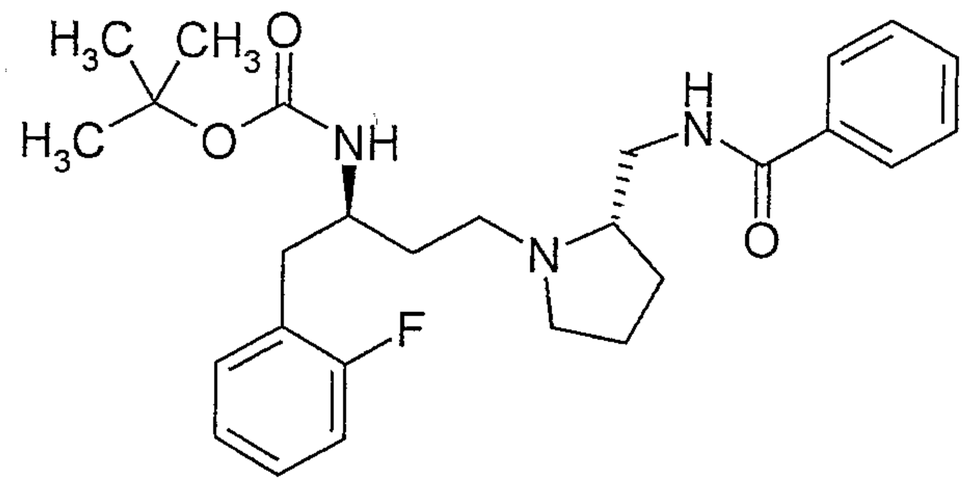
LC/MS (IV) rt 1.93, m/z 370 $[M+H]^+$.

Example 24



Step 1



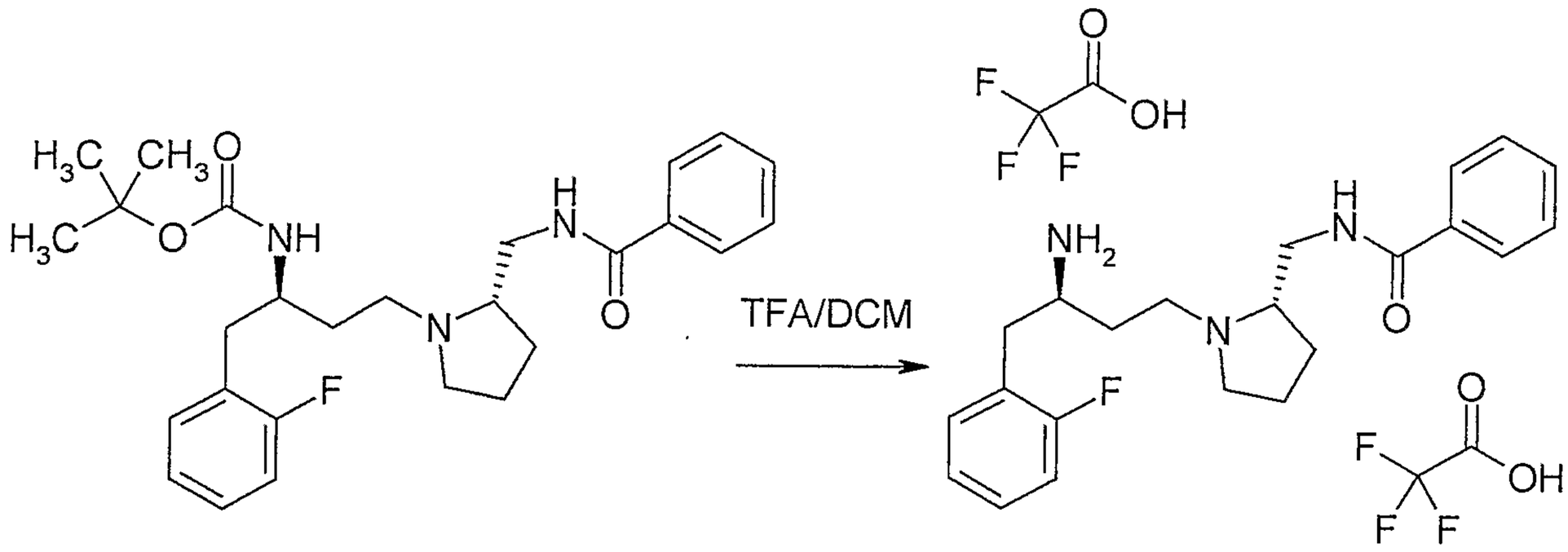


[3-[(2*S*)-(Benzoylamino-methyl)-pyrrolidin-1-yl]-(1*R*)-(2-fluoro-benzyl)-propyl]-carbamic acid *tert*-butyl ester

To a solution of 23.2 mg of [(1*R*)-(2-fluoro-benzyl)-3-oxo-propyl]-carbamic acid *tert*-butyl ester in dichloroethane/triethyl orthoformate (10:1) containing 3% acetic, 20.0 mg (0.10 mmol) of *N*-pyrrolidin-(2*S*)-ylmethyl-benzamide, (TFA salt, Example 1) dissolved in the same solvent mixture and 41.5 mg (0.20 mmol) of powdered sodium triacetoxyborohydride are added The reaction mixture is stirred overnight at room temperature, cooled to 0°C and quenched with saturated aqueous sodium bicarbonate solution. The crude reaction mixture is extracted with ethyl acetate. The organic layer is dried over sodium sulphate, filtered and concentrated under reduced pressure to dryness. The residue is purified using flash chromatography (silica gel, 0%-10% methanol in dichloromethane) to afford the title compound.

LC/MS (IV) rt 2.58, m/z 470 $[M+H]^+$.

Step 2



N-{1-[(3*R*)-Amino-4-(2-fluoro-phenyl)-butyl]-pyrrolidin-(2*S*)-ylmethyl}-benzamide (2 x TFA salt)

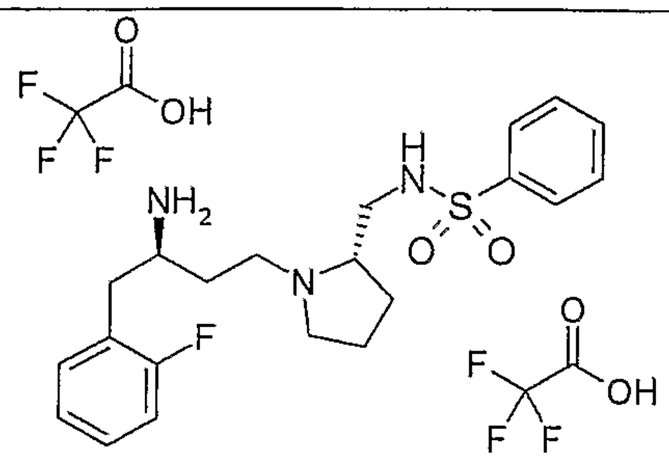
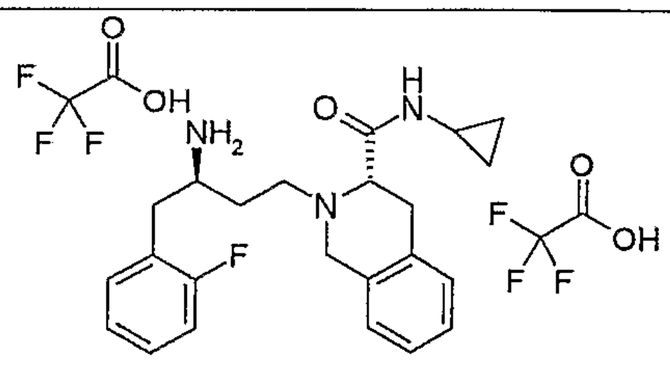
To a solution of 3.3 mg (0.01 mmol) of [3-[(2*S*)-(benzoylamino-methyl)-pyrrolidin-1-yl]-(1*R*)-(2-fluoro-benzyl)-propyl]-carbamic acid *tert*-butyl ester (Step 1) in 1mL dichloromethane, 0.5 mL of trifluoroacetic acid is added at room temperature and stirred until the reaction is complete (monitored by TLC, eluent: dichloromethane/methanol 95/5). After removal of the solvents under reduced pressure, 0.5 mL of methanol is added and the crude material is purified using preparative HPLC with a 15 minute linear gradient from 10%-60% acetonitrile in water (0.1% TFA) to afford the title compound.

^{1}H-NMR, δ (ppm) = 1.79-2.00 (m, 5H), 2.12 (m, 1H), 2.89-3.06 (m, 3H), 3.20 (m, 1H), 3.46-3.65 (m, 6H), 7.14-7.21 (m, 2H), 7.30-7.38 (m, 2H), 7.42-7.56 (m, 3H), 7.78-7.81 (m, 2H), 8.18 (bs, 3H), 8.82 (m, 1H), 9.46 (bs, 1H).

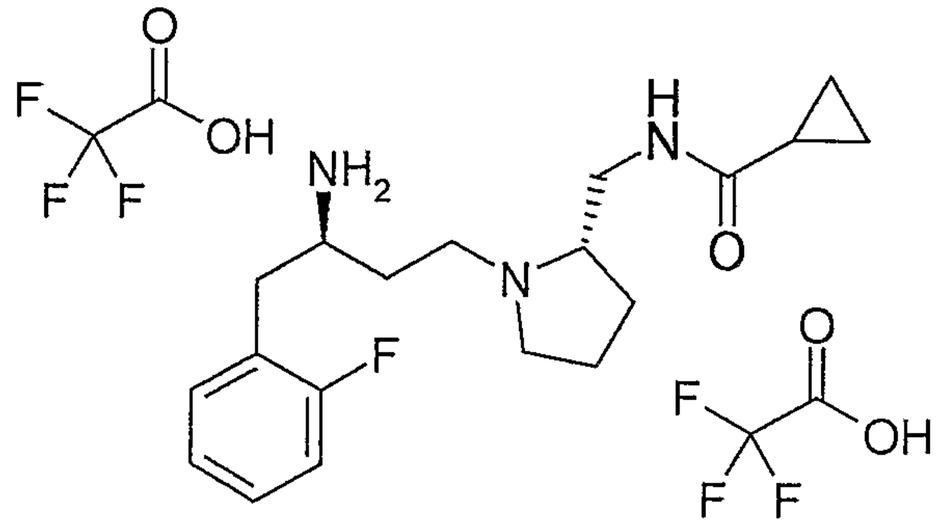
LC/MS (II) rt 1.85, m/z 370 $[M+H]^+$.

The compounds in Table 6 are synthesized according to the procedure shown for example 24

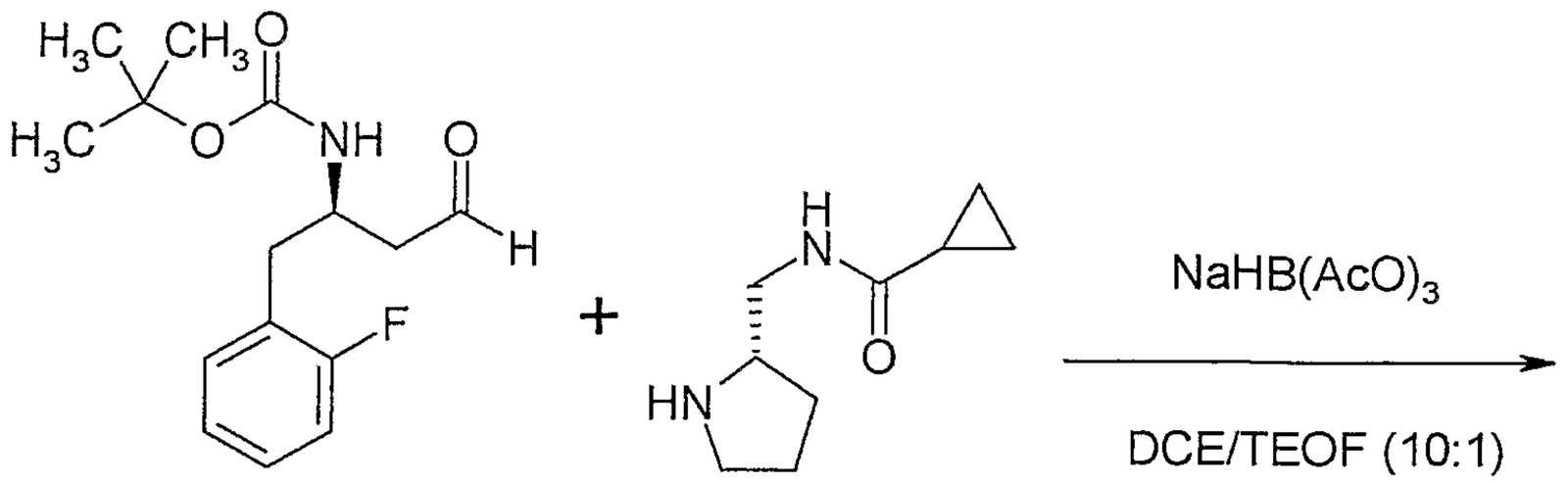
TABLE 6

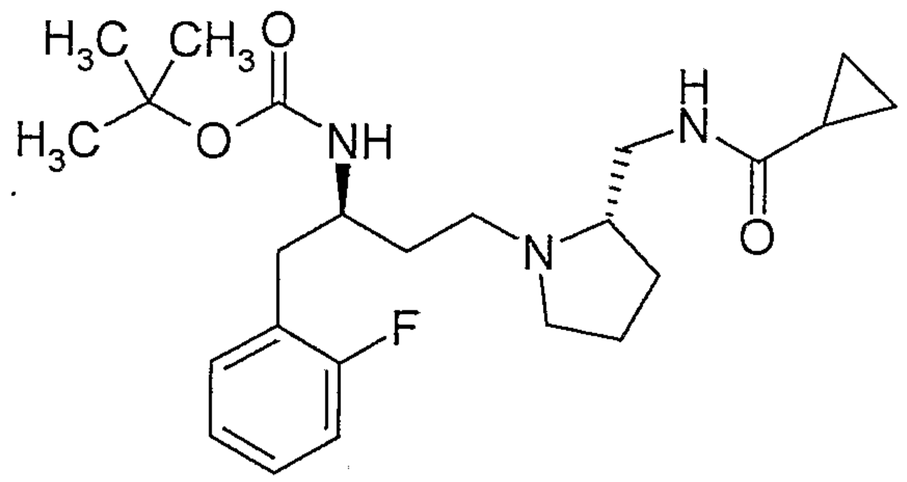
Example	Structure	LC-MS	NMR
25		LC/MS (II) rt 1.76, m/z 406 $(M+H-CH_3)^+$.	^{1}H-NMR, δ (ppm) = 1.69-2.00 (m, 5H), 2.11 (m, 1H), 2.85-3.21 (m, 6H), 3.36-3.53 (m, 4H), 7.10-7.20 (m, 2H), 7.29-7.37 (m, 2H), 7.54-7.68 (m, 3H), 7.75-7.81 (m, 2H), 8.03-8.12 (m, 4H), 9.63 (bs, 1H).
26		LC/MS (II) rt 1.82, m/z 382 $[M+H]^+$.	Partial spectra: ^{1}H-NMR, δ (ppm) = 0.42-0.57 (m, 2H), 0.65-0-75 (m, 2H), 1.87-1,93 (m, 2H), 2.72 (m, 1H), 2.80-3.20 (m, 6H), 3.52 (m, 1H), 4.25-4.40 (m, 2H), 7.16-7.35 (m, 8H), 8.09 (bs, 3H), 8.61 (bs, 1H).

Example 27



Step 1



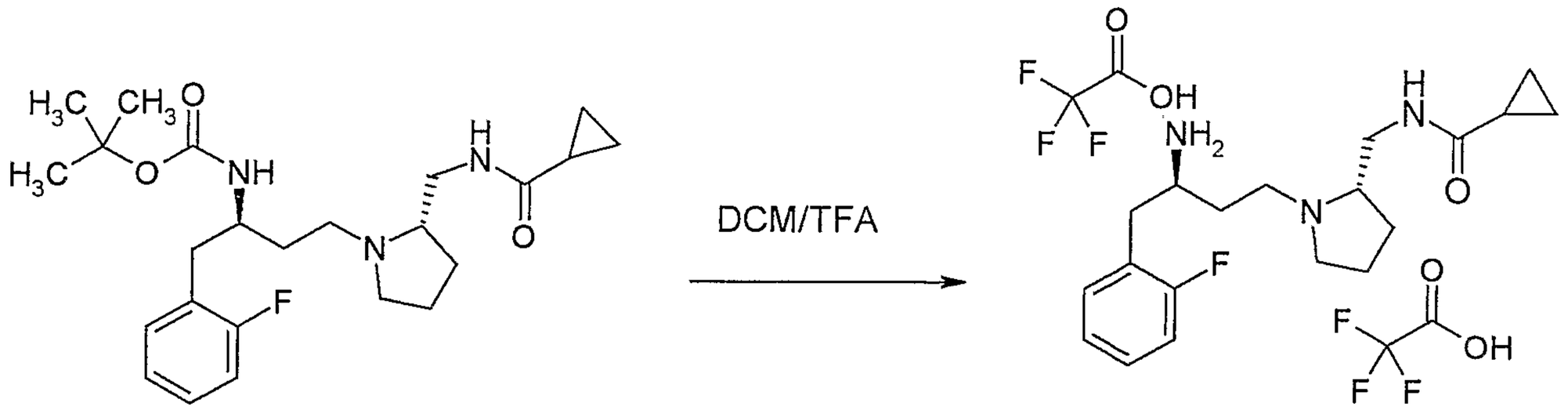


[3-{(2*S*)-[(Cyclopropanecarbonyl-amino)-methyl]-pyrrolidin-1-yl}-(1*R*)-(2-fluoro-benzyl)-propyl]-carbamic acid *tert*-butyl ester

To a solution of 26.0 mg of [(1*R*)-(2-fluoro-benzyl)-3-oxo-propyl]-carbamic acid *tert*-butyl ester (Example 20) in dichloroethane/triethyl orthoformate (10:1) is added 25.9 mg (0.15 mmol) of cyclopropanecarboxylic acid (pyrrolidin-(2*S*)-ylmethyl)-amide (Example 2, free base according to Example 14, Step 3)) dissolved in the same solvent mixture. 65.3 mg (0.31 mmol) of powdered sodium triacetoxyborohydride is added and the reaction mixture is stirred overnight at room temperature. It is then cooled to 0°C and quenched with saturated sodium bicarbonate solution. The crude reaction mixture is extracted with ethyl acetate. The organic layer is dried over sodium sulphate, filtered and evaporated under reduced pressure. The residue is purified using flash chromatography (silica gel, 0%-10% methanol in dichloromethane) to afford the title compound.

LC/MS (II) rt 2.29, m/z 434 $[M+H]^+$.

Step 2



Cyclopropanecarboxylic acid {1-[(3*R*)-amino-4-(2-fluoro-phenyl)-butyl]-pyrrolidin-(2*S*)-ylmethyl}-amide (2 x TFA salt)

Obtained from [3-{(2*S*)-[(cyclopropanecarbonyl-amino)-methyl]-pyrrolidin-1-yl}-(1*R*)-(2-fluoro-benzyl)-propyl]-carbamic acid *tert*-butyl ester according to step 2 in the procedure described for Example 24.

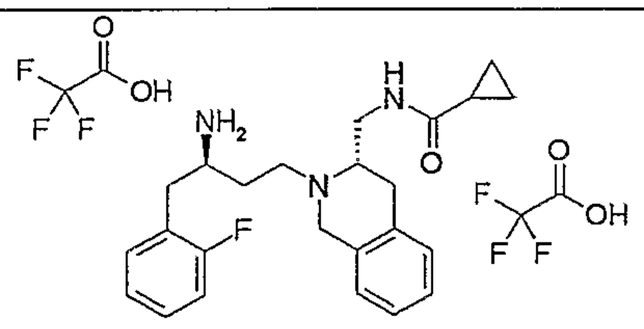
The crude material is purified using preparative HPLC with a 10 minute linear gradient from 5%-35% acetonitrile in water (0.1% TFA) to afford the title compound.

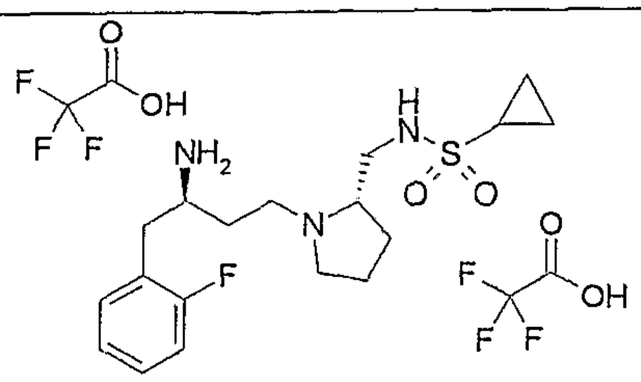
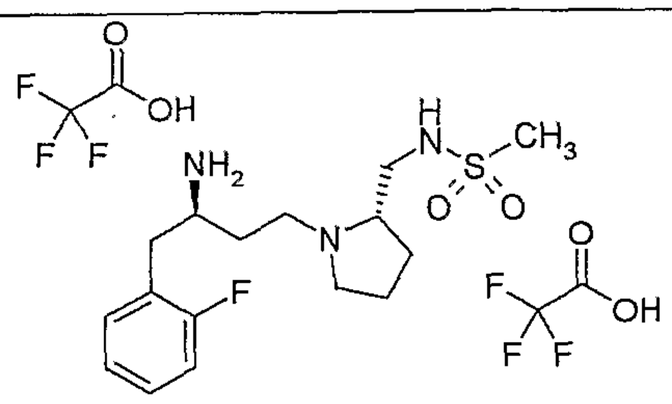
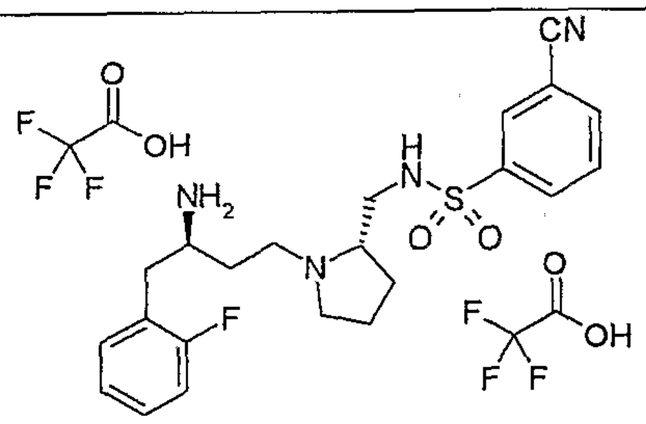
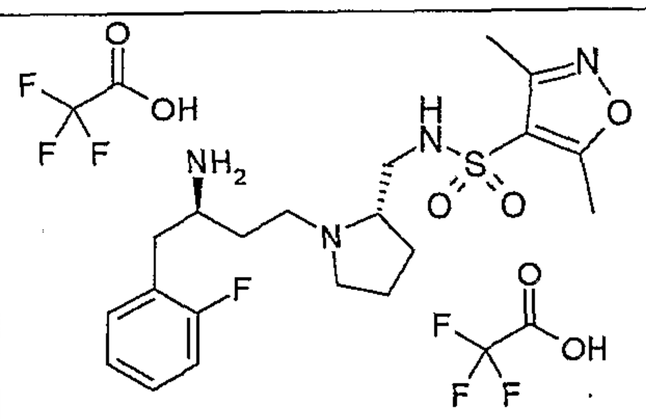
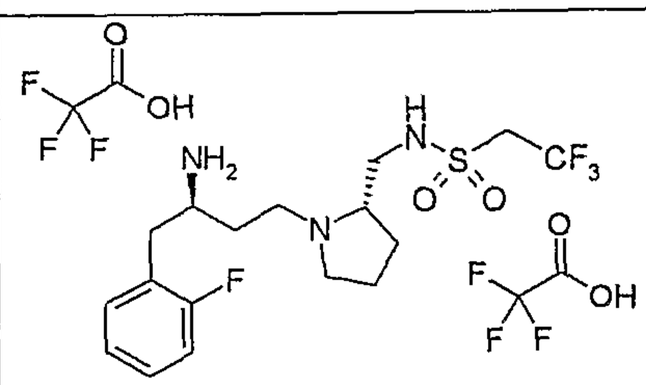
^{1}H-NMR, δ (ppm) = 0.68-0.74 (m, 4H), 1.57 (m, 1H), 1.68-2.17 (m, 6H), 2.85-3.04 (m, 3H), 3.16 (m, 1H), 3.29-3.55 (m, 6H), 7.05-7.20 (m, 2H), 7.28-7.40 (m, 2H), 8.18 (bs, 3H), 8.51 (m, 1H), 9.68 (bs, 1H).

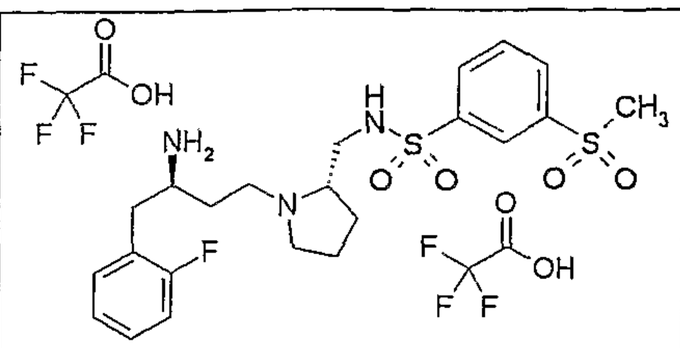
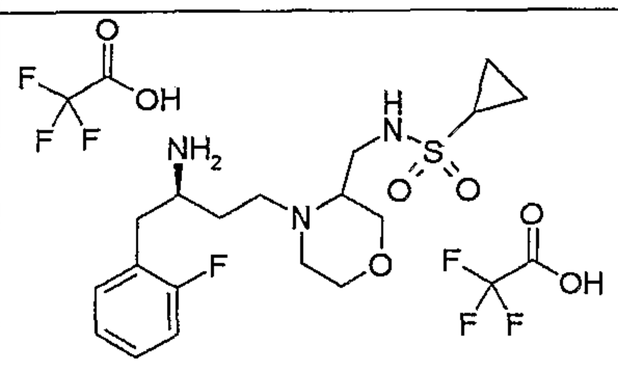
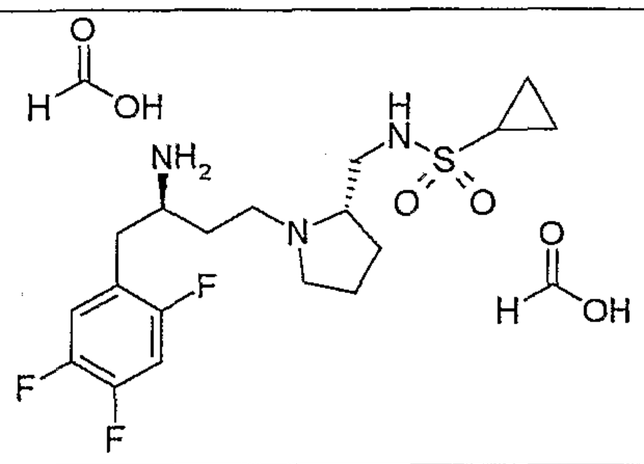
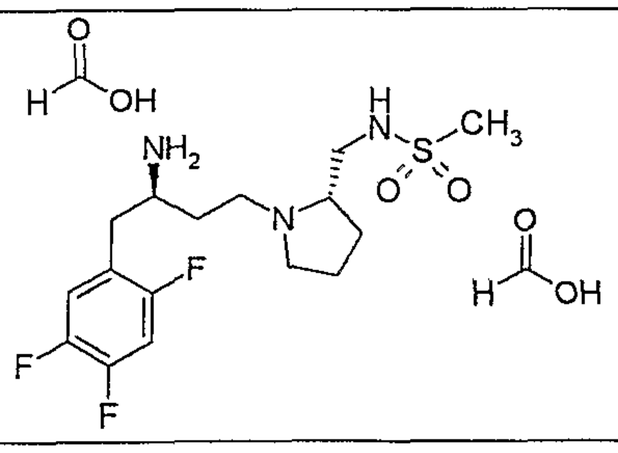
LC/MS (II) rt 1.68, m/z 334 $[M+H]^+$.

The compounds in Table 7 are synthesized according to the procedure shown for example 27.

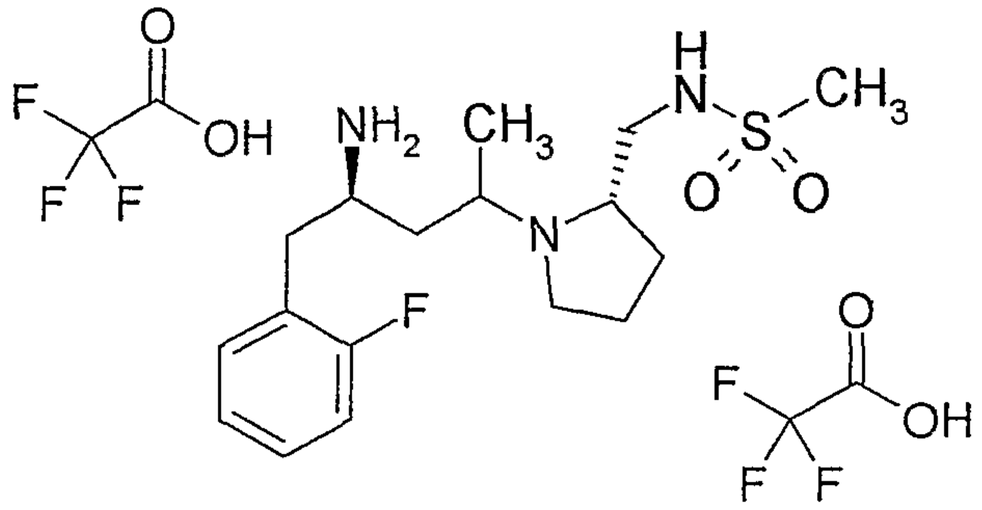
TABLE 7

Example	Structure	LC-MS	NMR
28		LC/MS (II) rt 1.61, m/z 396 $[M+H]^+$.	Partial spectra: ^{1}H-NMR, δ (ppm) =0.64-0.72 (m, 4H), 1.55 (m, 1H), 2.00-2.08 (m, 2H), 2.88-3.16 (m, 6H), 3.36 (m, 1H), 3.42-3.58 (m, 2H), 3.69 (m, 1H), 4.22-4.46 (m, 2H), 7.12-7.34 (m, 8H), 8.8 (bs, 3H), 8.41 (bs, 1H).

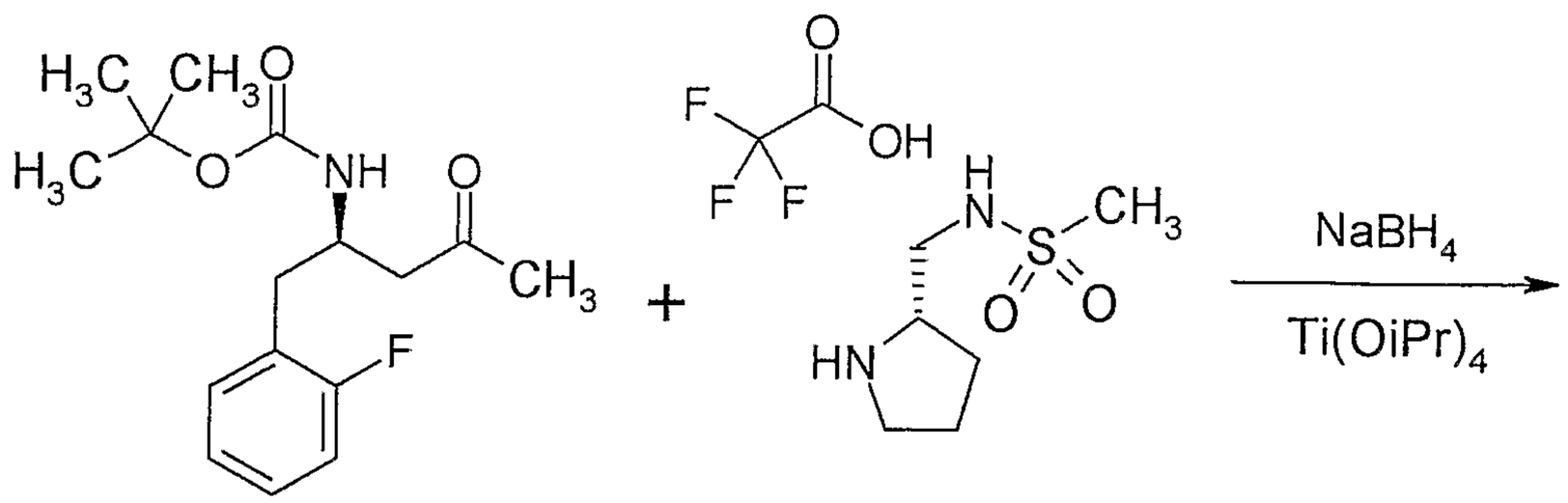
29		LC/MS (II) rt 1.70, m/z 370 $[M+H]^+$.	^{1}H-NMR, δ (ppm) = 0.94-0.99 (m, 4H), 1.74-2.00 (m, 6H), 2.15 (m, 1H), 2.60 (m, 1H), 2.85-3.29 (m, 5H), 3.39-3.61 (m, 4H), 7.12-7.22 (m, 2H), 7.28-7.36 (m, 2H), 7.42 (bs, 1H), 8.09 (bs, 3H), 9.54 (bs, 1H).
30		LC/MS (II) rt 1.62, m/z 344 $[M+H]^+$.	^{1}H-NMR, δ (ppm) = 1.72-1.81 (m, 1H), 1.85-2.00 (m, 3H), 2.10-2-19 (m, 2H), 2.86-3.06 (m, 2H), 2.95 (s, 3H), 3.06-3.16 (m, 2H), 3.33-3.55 (m, 6H), 7.13-7.20 (m, 2H), 7.30-7.41 (m, 3H), 9.11 (bs, 3H), 9.56 (bs, 1H).
31		LC/MS (IV) rt 2.16, m/z 431 $[M+H]^+$.	^{1}H-NMR, δ (ppm) = 1.72-2.12 (m, 6H), 2.82-3.51 (m, 10H), 7.12 (m, 2H), 7.33 (m, 2H), 7.81 (m, 1H), 8.06-8.30 (m, 3H).
32		LC/MS (IV) rt 2.08, m/z 426 $[M+H]^+$.	^{1}H-NMR, δ (ppm) = 1.74-2.14 (m, 6H), 2.32 (s, 3H), 2.58 (s, 3H), 2.84-3.55 (m, 10H), 7.15 (m, 2H), 7.30 (m, 2H), 8.12 (m, 3H).
33		LC/MS (IV) rt 1.96, m/z 412 $[M+H]^+$.	^{1}H-NMR, δ (ppm) = 1.77-2.17 (m, 6H), 2.85-3.43 (m, 10H), 4.45 (m, 2H), 7.13 (m, 2H), 7.31 (m, 2H), 8.14 (m, 3H).

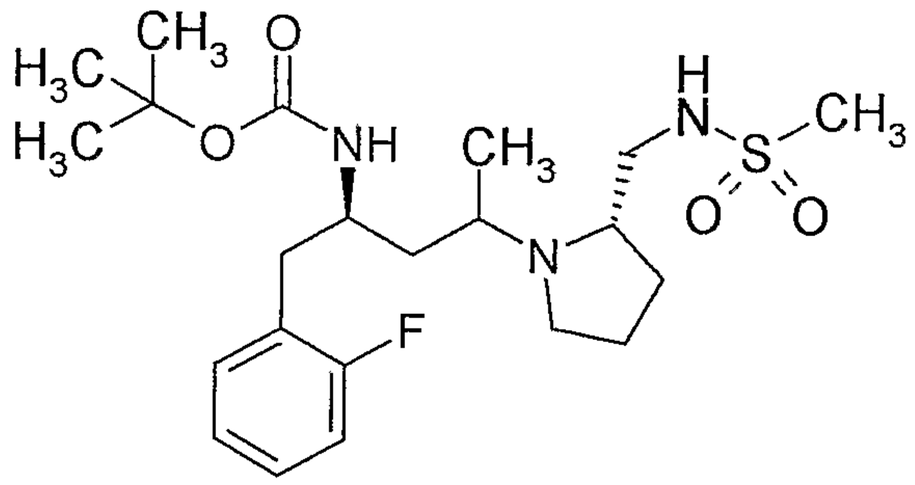
34		LC/MS (II) rt 2.62, m/z 484 $[M+H]^+$.	^{1}H-NMR, δ (ppm) = 1.70-2.12 (m, 4H), 2.84-3.50 (m, 12H), 3.29 (s, 3H), 7.13 (m, 2H), 7.31 (m, 2H), 7.88 (m, 1H), 8.09-8.31 (m, 4H).
35		LC/MS (II) rt 1.62, m/z 386 $[M+H]^+$.	^{1}H-NMR, δ (ppm) = 0.96 (m, 4H), 1.86 (m, 2H), 2.60 (m, 1H), 2-94-3.45 (m, 11H), 3.64-3.82 (m, 4H), 7.14 (m, 2H), 7.34 (m, 2H), 8.05 (m, 3H).
36		LC/MS (VI) (1-30%, 10 min): rt 4.32, m/z 406 $[M+H]^+$.	
37		LC/MS (VI) (1-30%, 10 min): rt 3.2, m/z 380 $[M+H]^+$.	

Example 38



Step 1





{(1*R*)-(2-Fluoro-benzyl)-3-[(2*S*)-(methanesulphonylamino-methyl)-pyrrolidin-1-yl]-butyl}-carbamic acid *tert*-butyl ester

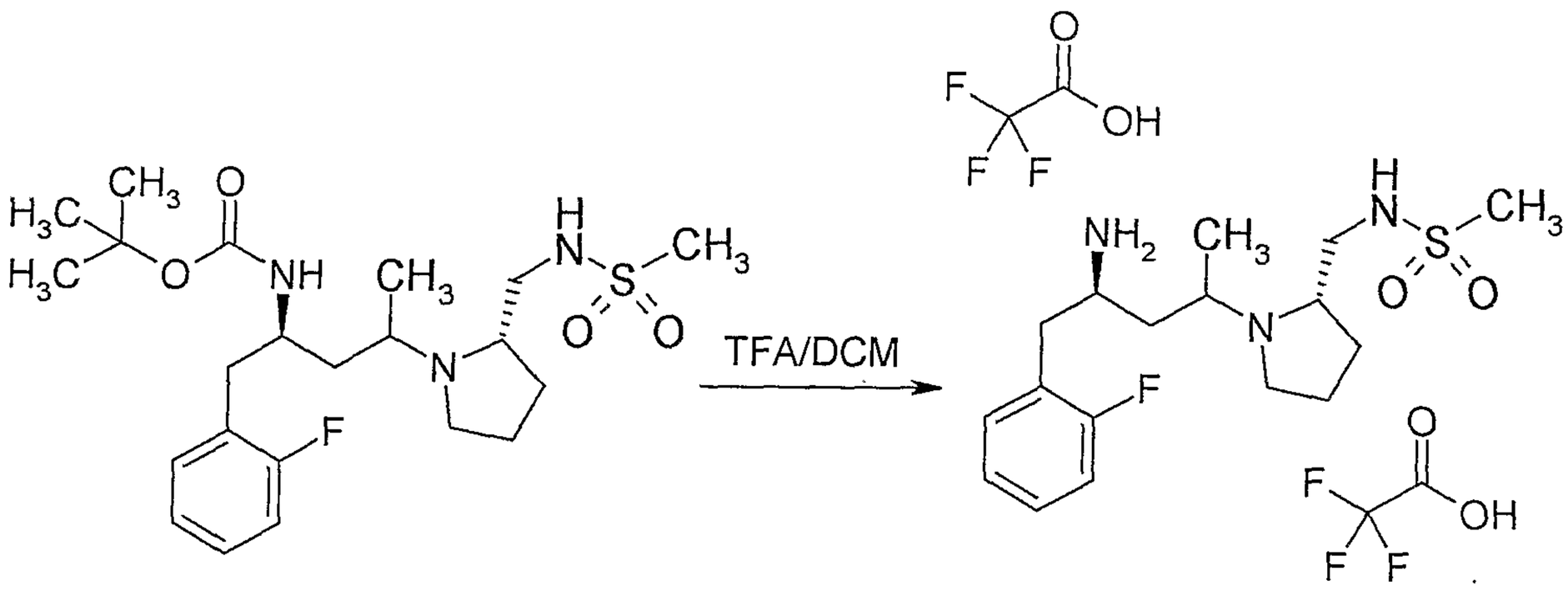
Prepared as a mixture of diastereoisomers.

A slurry mixture containing 127 mg (0.43mmol) of [(1*R*)-(2-fluoro-benzyl)-3-oxo-butyl]-carbamic acid *tert*-butyl ester (Example 22), 93 mg (0.52 mmol) of *N*-Pyrrolidin-(2*S*)-ylmethyl-methanesulphonamide (Example 5), 245 μL (0.86 mmol) titanium tetraisopropoxide and 500 μL triethylamine is stirred 6h at room temperature. Then 1.5 mL ethanol and 66 mg (0.86 mmol) of sodium borohydride are added. After stirring 30 minutes at room temperature the solvent is evaporated under reduced pressure. The residue is dissolved with ethyl acetate, then washed three times with saturated sodium bicarbonate solution, two times with brine, dried over sodium sulphate, filtered and evaporated under reduced pressure.

The residue is purified using flash chromatography (silica gel, ethyl acetate) to afford the title compound.

LC/MS (II) rt 2.30, m/z 458 $[M+H]^+$.

Step 2:



N-{1-[(3*R*)-Amino-4-(2-fluoro-phenyl)-1-methyl-butyl]-pyrrolidin-(2*S*)-ylmethyl}-methanesulphonamide (2 x TFA salt)

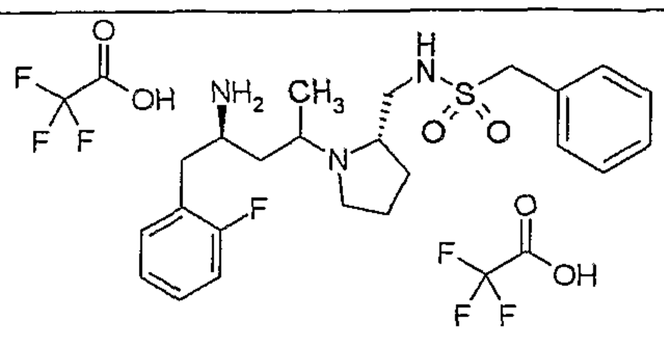
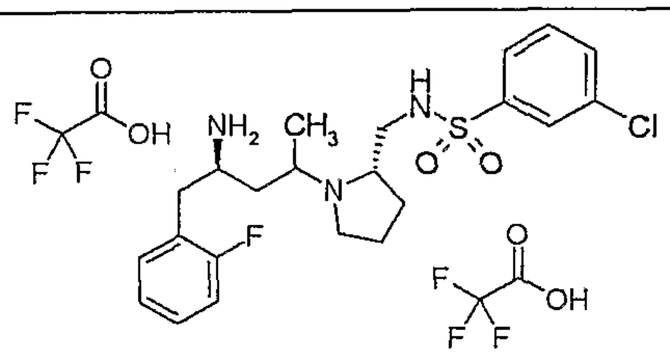
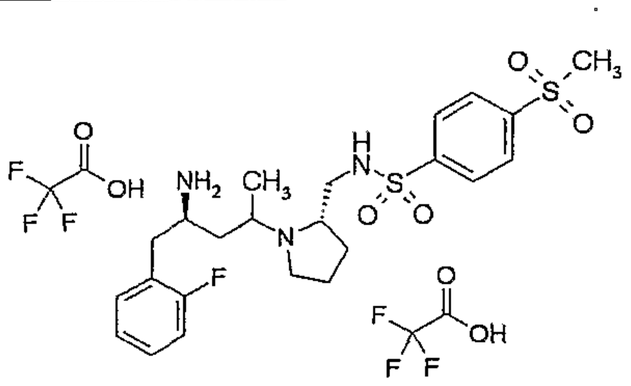
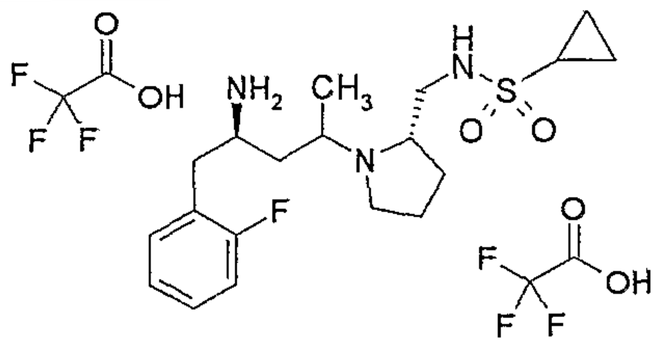
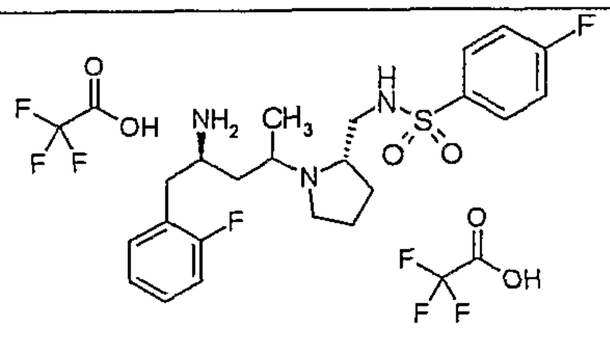
To a solution of 53 mg (0.12 mmol) of {(1*R*)-(2-fluoro-benzyl)-3-[(2*S*)-(methanesulphonylamino-methyl)-pyrrolidin-1-yl]-butyl}-carbamic acid *tert*-butyl ester (Step 1) in dichloromethane, 300 µL of trifluoroacetic acid is added at room temperature and stirring continued until the reaction is complete (monitored by LCMS). The solvent is evaporated under reduced pressure. The mixture of diastereomers could be resolved by HPLC with a 20 min linear gradient from 5%-30% acetonitrile in water (0.1% TFA).

^{1}H-NMR (major diastereoisomer), δ (ppm) = 1.20 (d, 3H), 1.63 (m, 1H), 1.82-1.95 (m, 3H), 2.01-2.15 (m, 2H), 2.84-2.92 (m, 1H), 2.96 (s, 3H), 3.02-3.09 (m, 1H), 3.10-3.18 (m, 1H), 3.23-3.34 (m, 1H), 3.42-3.52 (m, 2H), 3.56-3.70 (m, 3H), 7.15-7.21 (m, 2H), 7.30-7.39 (m, 3H), 8.14 (bs, 3H), 9.58 (bs, 1H).

LC/MS (I) (minor diastereoisomer) rt 2.25, m/z 358 $[M+H]^+$, (major diastereoisomer) rt 2.39, m/z 358 $[M+H]^+$.

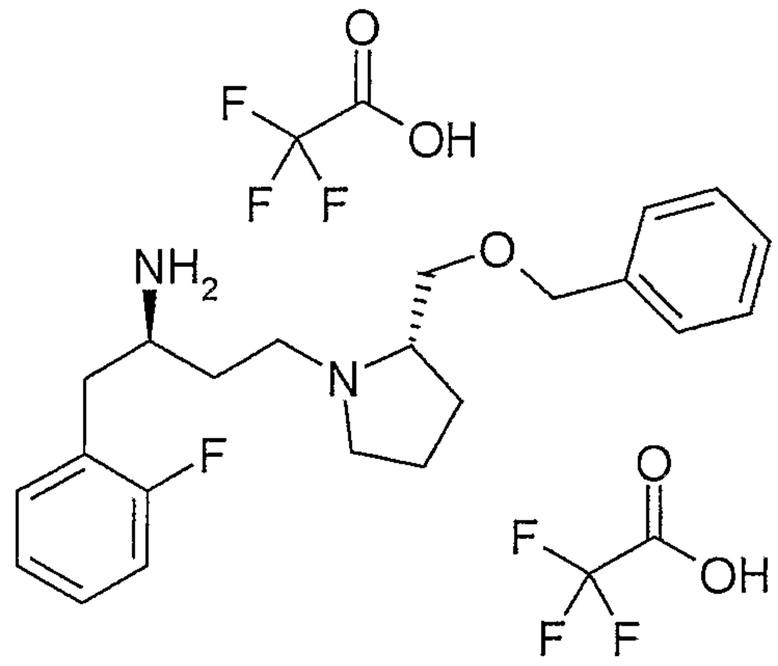
The compounds in Table 8 are synthesized according to the procedure shown for example 38.

TABLE 8

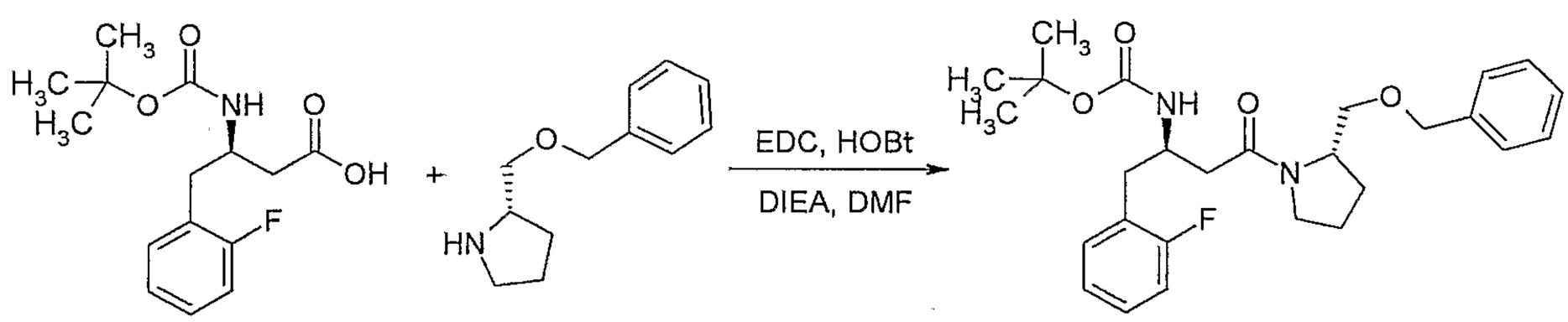
Example	Structure	LC-MS	NMR
39		LC/MS (V) (5-30%, 15 min) major rt 6.05, m/z 456 $[M+Na]^+$; minor rt 6.18, m/z 456 $[M+Na]^+$	^{1}H-NMR, δ (ppm) minor = 0.79 (m, 3H), 1.08-1.70 (m, 4H), 2.35 (m, 2H), 2.58-3.15 (m, 8H), 4.27 (s, 2H), 7.09-7.35 (m, 9H).
40		LC/MS (V) (5-30%, 15 min) major rt 6.90, m/z 455 $[M+H]^+$; minor rt 7.12, m/z 455 $[M+Na]^+$	^{1}H-NMR, δ (ppm) minor = 0.73 (m, 3H), 1.10-1.66 (m, 6H), 2.31 (m, 2H), 2.63-2.74 (m, 5H), 3.05 (m, 2H), 7.10 (m, 2H), 7.22 (m, 2H), 7.55 (m, 1H), 7.71 (m, 2H).
41		LC/MS (V) (5-30%, 15 min) major rt 6.72, m/z 498 $[M+H]^+$, minor rt 6.47, m/z 498 $[M+H]^+$	^{1}H-NMR, δ (ppm) minor = 0.71 (m, 3H), 1.30-1.66 (m, 4H), 2.28 (m, 2H), 2.65-3.26 (m, 9H), 7.10 (m, 2H), 7.24 (m, 2H), 7.98 (m, 2H), 8.06 (m, 2H).
42		LC/MS (V) (5-30%, 15 min) major rt 5.86, m/z 406 $[M+Na]^+$; minor rt 5.97, m/z 406 $[M+Na]^+$	^{1}H-NMR, δ (ppm) minor = 0.82-0.90 (m, 7H), 1.25-1.72 (m, 5H), 2.24 (m, 2H), 2.52-2.91 (m, 6H), 3.10 (m, 1H), 7.10 (m, 2H), 7.24 (m, 2H).
43		LC/MS (V) (10-60%, 10 min) rt 2.95, m/z 438 $[M+H]^+$.	^{1}H-NMR, δ (ppm) minor = 1.04-1.28 (m, 4H), 1.52-2.08 (m, 6H), 2.66-3.20 (m, 5H), 3.47-3.65 (m, 3H), 7.15 (m, 2H), 7.30-7.45 (m, 4H), 7.86 (m, 2H), 7.99 (bs, 3H).

The following examples deal with compounds of the invention synthesised according to Scheme P.

Example 44



Step 1

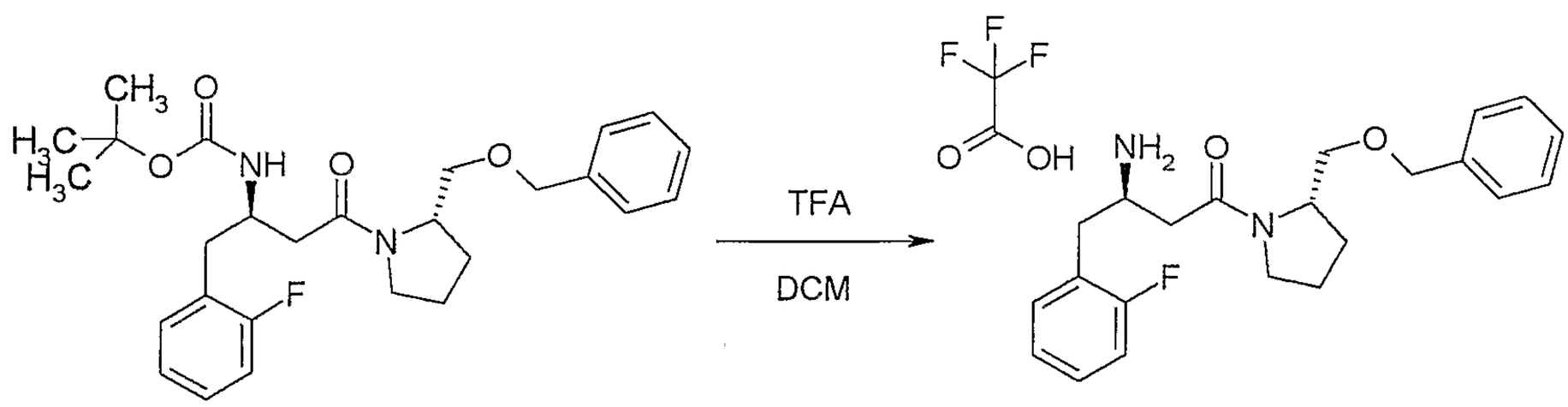


{*(3R)*-[*(2S)*-Benzyloxymethyl-pyrrolidin-1-yl]-1-(2-fluoro-benzyl)-3-oxo-propyl}-carbamic acid *tert*-butyl ester.

A mixture of 44.8 mg (0.15 mmol) of *(3R)-tert*-butoxycarbonylamino-4-[2-fluoro-phenyl]-butyric acid, 28.3 mg (0.21 mmol) of 1-hydroxybenzotriazole (HOBt), 39.9 mg (0.21 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 100 µL (98.2 mg, 0.76 mmol) of diisopropylethylamine in 2.5 mL of *N,N*-dimethylformamide is stirred for 5 minutes. After addition of 50.0 mg (0.17 mmol) of *(2S)*-benzyloxymethylpyrrolidine (Example 14) in 0.5 mL of *N,N*-dimethylformamide, the mixture is stirred for further 16 h. The solution is diluted with 5 mL of 1N hydrochloric acid solution and extracted twice with 10 mL of dichloromethane. The collected organic phases are washed with brine and water, dried over sodium sulphate and evaporated under reduced pressure. The residue is purified using flash chromatography (silica gel, 0% to 10% methanol in dichloromethane) to afford the title compound.

LC/MS (I) rt 5.68, m/z 471 $(M+H)^+$.

Step 2



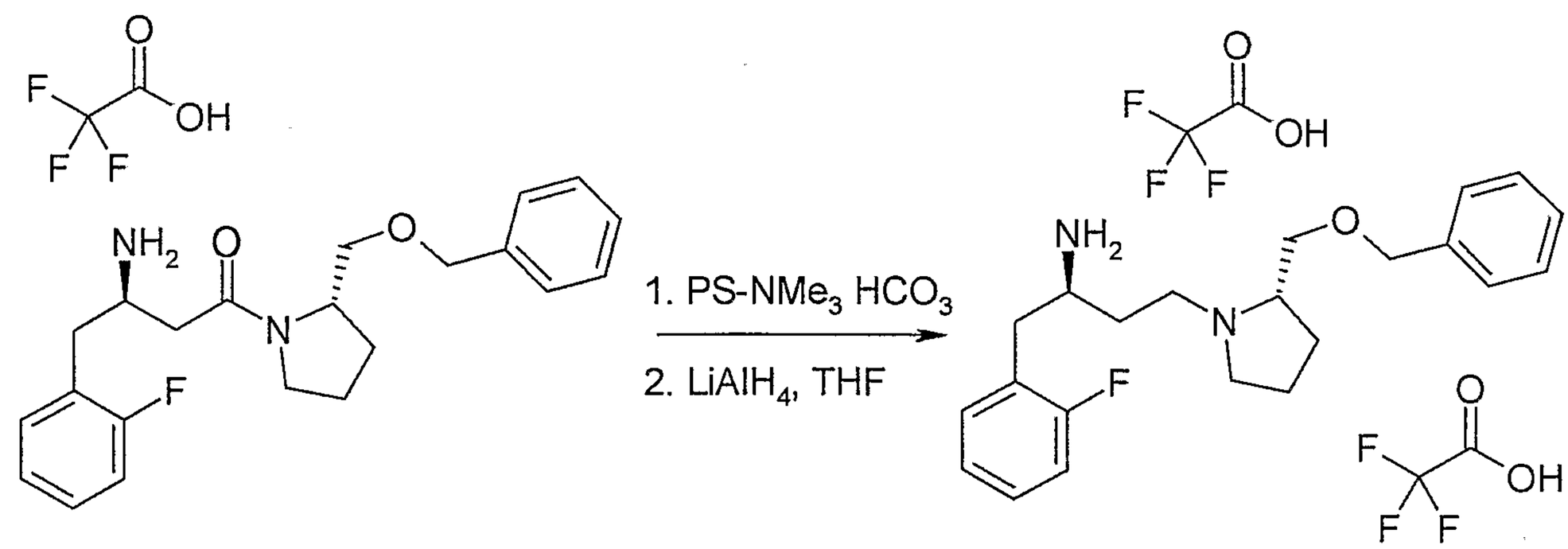
(3R)-Amino-1-[(2S)-benzyloxymethyl-pyrrolidin-1-yl]-4-(2-fluoro-phenyl)-butan-1-one (TFA salt).

A solution of 8.00 mg (0.017 mmol) of {(3R)-[(2S)-benzyloxymethyl-pyrrolidin-1-yl]-1-(2-fluoro-benzyl)-3-oxo-propyl}]-carbamic acid *tert*-butyl ester (Step 1) in 0.5 mL of trifluoroacetic acid and 1 mL of dichloromethane is stirred at room temperature for 1 h. The mixture is then evaporated under reduced pressure. The crude mixture is purified using HPLC (eluent: 5% to 95% acetonitrile in water with 0.1% of trifluoroacetic acid) to afford the title compound.

^{1}H-NMR δ (ppm) = 1.79-1.87 (m, 3H), 2.85-2.92 (m, 1H), 2.98-3.05 (m, 1H), 3.21-3.32 (m, 5H), 3.43-3.47 (m, 1H), 3.69 (bs), 3.93-3.95 (m, 0.3H), 4.05-4.10 (m, 0.7H), 4.41-4.45 (m, 3H), 7.11-7.18 (m, 2H), 7.21-7.32 (m, 7H), 7.94 (bs, 2H).

LC/MS (I) rt 3.60, m/z 371 $(M+H)^+$.

Step 3



(1R)-3-[(2S)-2-Benzyloxymethyl-pyrrolidin-1-yl]-1-(2-fluoro-benzyl)-propylamine (2 x TFA salt)

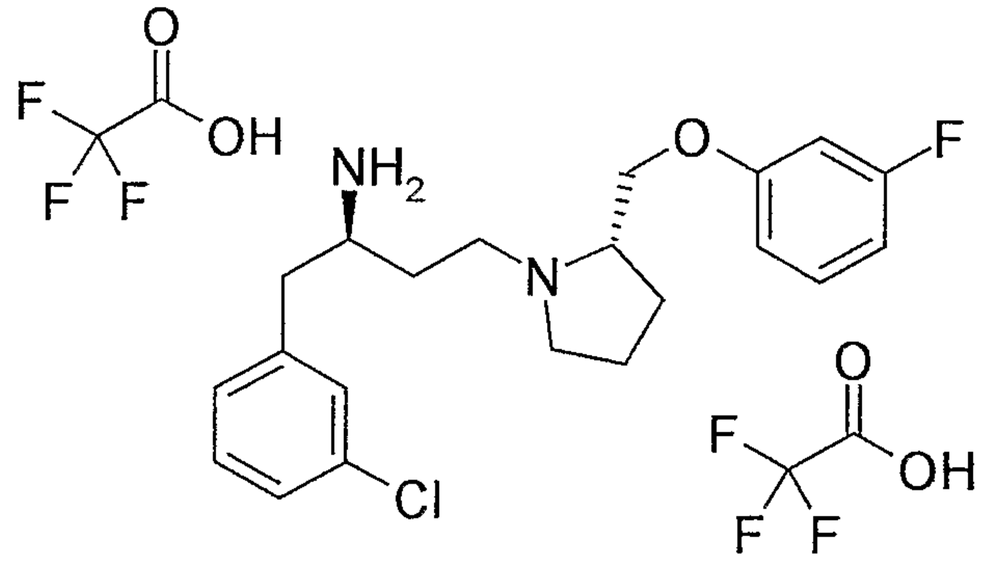
To a stirred solution of 8.20 mg (0.017 mmol) of (3R)-amino-1-[(2S)-2-benzyloxymethyl-pyrrolidin-1-yl)-4-(2-fluoro-phenyl)-butan-1-one (Step 2) in 1 mL of

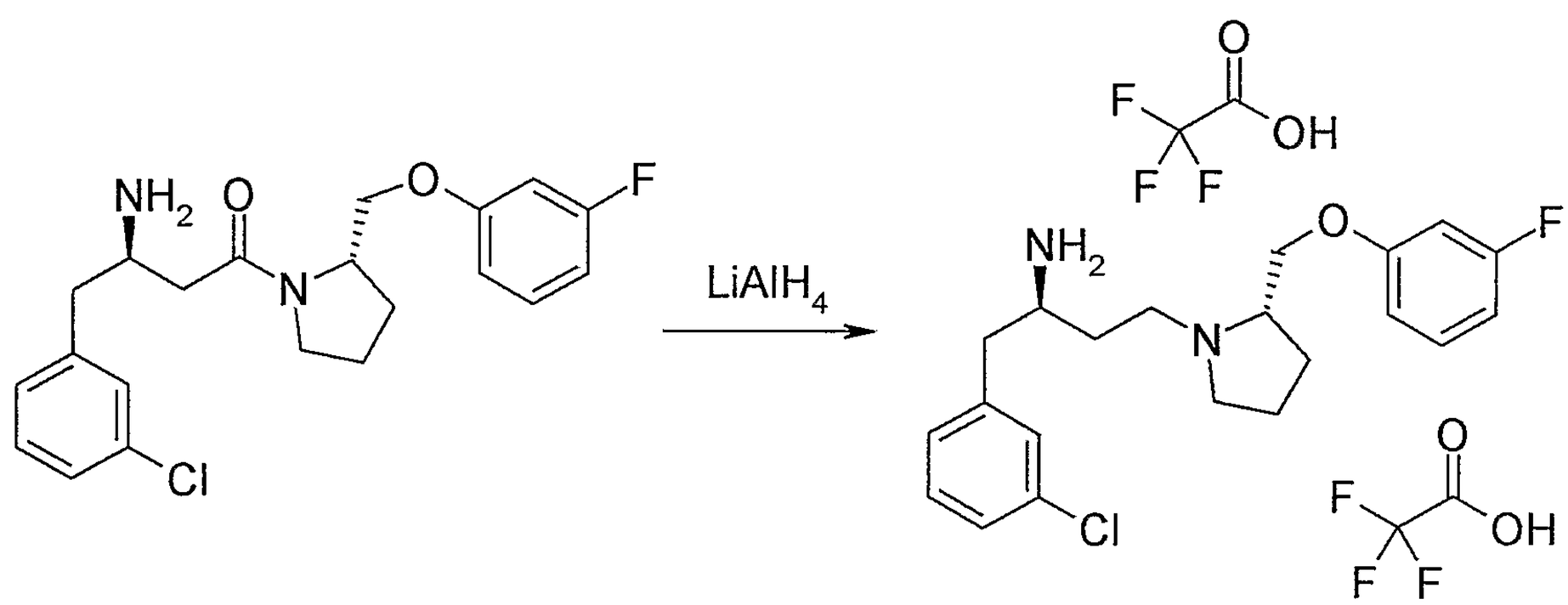
dichloromethane at room temperature is added 55 mg (0.144 mmol) of (polystyryl-methyl)trimethylammonium bicarbonate (Novabiochem, 2.64 mmol/g). The suspension is stirred for 1 h, filtered and evaporated under reduced pressure. The residue is then dissolved in a few microliters of tetrahydrofuran and 63 μL (0.063 mmol) of a 1 M lithium aluminiumhydride solution in tetrahydrofuran is added under argon. The resulting solution is refluxed for 5 h and then quenched with methanol. The solvents are evaporated under reduced pressure, the crude mixture is dissolved in ethyl acetate and washed with water, saturated sodium bicarbonate aqueous solution and brine. The combined organic layers are dried over sodium sulphate, filtered and evaporated under reduced pressure.

Purification using preparative LC/MS (5% to 95% of acetonitrile in water, 0.1% trifluoroacetic acid) affords the title compound.

LC/MS (IV) rt 2.18, m/z 357 $[M+H]^+$.

Example 45





(1*R*)-(3-Chloro-benzyl)-3-[(2*S*)-(3-fluoro-phenoxymethyl)-pyrrolidin-1-yl]-propylamine (2 x TFA salt)

To 131 µL (0.13 mmol) of a 1 M lithium aluminium tetrahydride solution in tetrahydrofuran is added a solution of 34.0 mg (0.087 mmol) of (3*R*)-amino-4-(3-chloro-phenyl)-1-[(2*S*)-(3-fluoro-phenoxymethyl)-pyrrolidin-1-yl]-butan-1-one one (synthesised according to Example 44, with Example 16 as amine component) in tetrahydrofuran. The reaction mixture is refluxed for 2 h and then quenched with methanol. The solution was made alkaline with 5N sodium hydroxide aqueous solution to pH 11-14 and extracted with dichloromethane. The combined organic layers are dried over sodium sulphate, filtered and evaporated under reduced pressure.

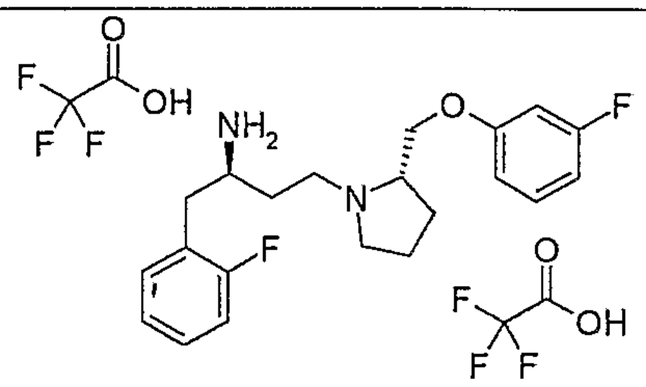
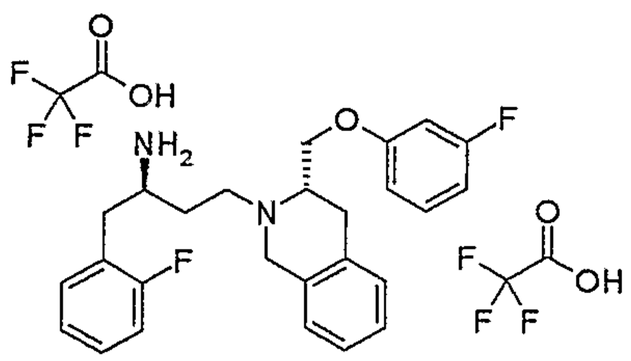
The crude material is purified using preparative HPLC with a 15 minute linear gradient from 10%-60% acetonitrile in water (0.1% TFA) to afford the title compound.

^{1}H-NMR, δ (ppm) =1.78-2.05 (m, 5H), 2.24 (m, 1H), 2.87-2.95 (m, 2H), 3.13 (m, 1H), 3.34 (m, 1H), 3.45-3.57 (m, 3H), 3.85 (m, 1H), 4.15 (m, 1H), 4.31 (m, 1H), 6.76-6.86 (m, 3H), 7.21-7.37 (m, 5H), 8.13 (bs, 3H), 10.02 (bs, 1H).

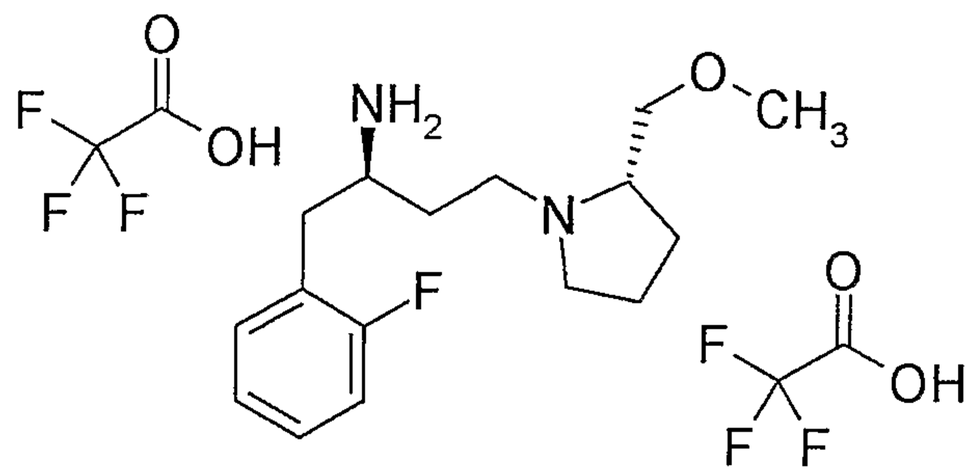
LC/MS (II) rt 2.10, m/z 377 $[M+H]^+$.

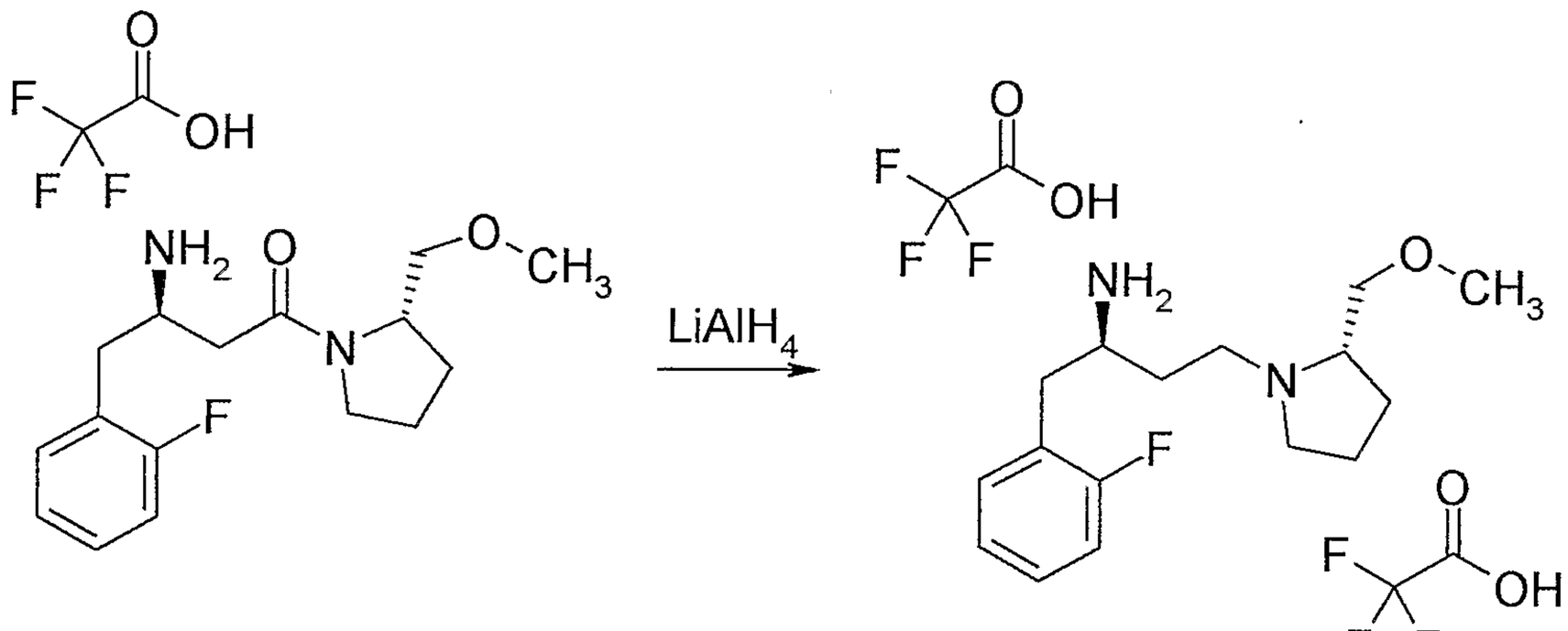
The compounds in Table 9 are synthesized according to the procedure shown for example 45.

TABLE 9

Example	Structure	LC-MS	NMR
46		LC/MS (IV) rt 1.93, m/z 361 $[M+H]^+$.	
47		LC/MS (IV) rt 2.11, m/z 423 $[M+H]^+$.	

Example 48





(1*R*)-(2-Fluoro-benzyl)-3-(2*S*)-methoxymethyl-pyrrolidin-1-yl)-propylamine (2 xTFA salt)

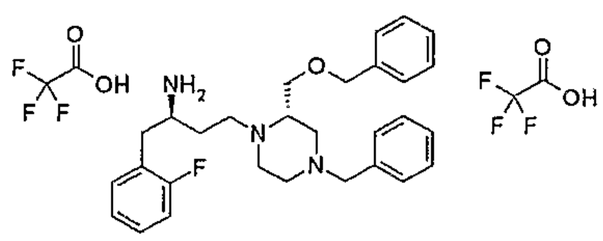
To a solution of 19 mg (0.05 mmol) of (*3R*)-amino-4-(2-fluoro-phenyl)-1-(2-methoxymethyl-pyrrolidin-1-yl)-butan-1-one (TFA salt) (synthesised according to Example 44, steps 1 and 2, with Example 15 as amine component) in tetrahydrofuran under argon is added 70 µL of a 1.0M lithium aluminium tetrahydride solution in tetrahydrofuran. The reaction mixture is refluxed for 1.5 h and then quenched with methanol. The solution is made alkaline with sodium hydroxide aqueous solution to pH 11-14, diluted with ethyl acetate and washed with saturated sodium bicarbonate solution and brine. The organic layer is dried over sodium sulphate, filtered and evaporated under reduced pressure.

The crude material is purified using preparative HPLC with a 13 min linear gradient from 3%-35% acetonitrile in water (0.1% TFA) to afford the title compound.

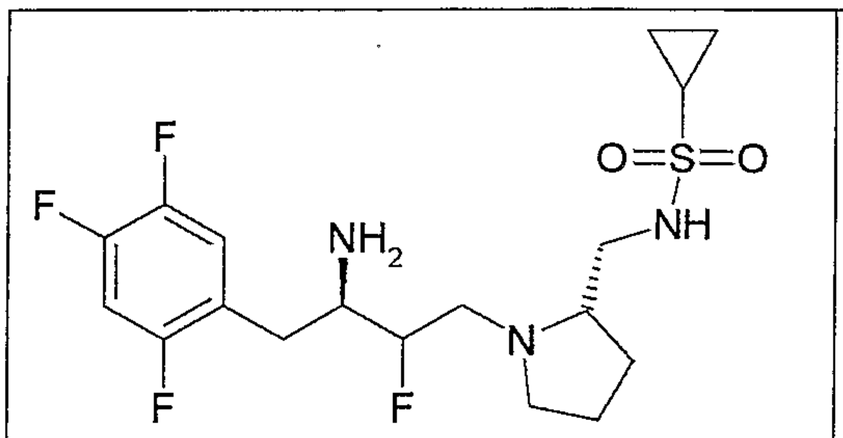
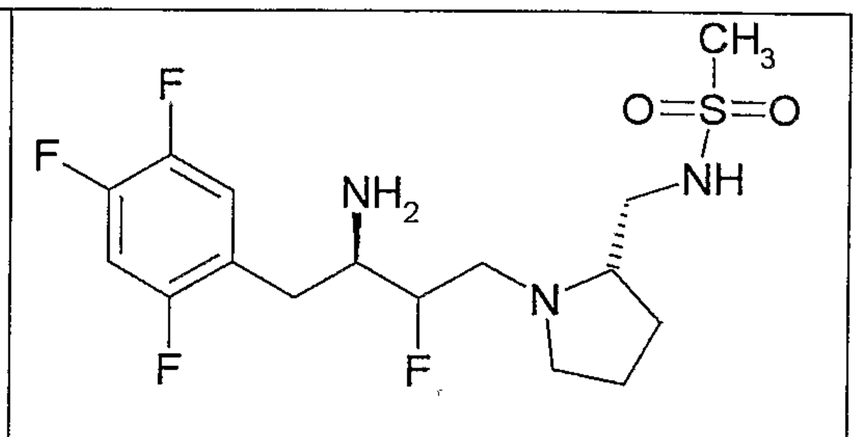
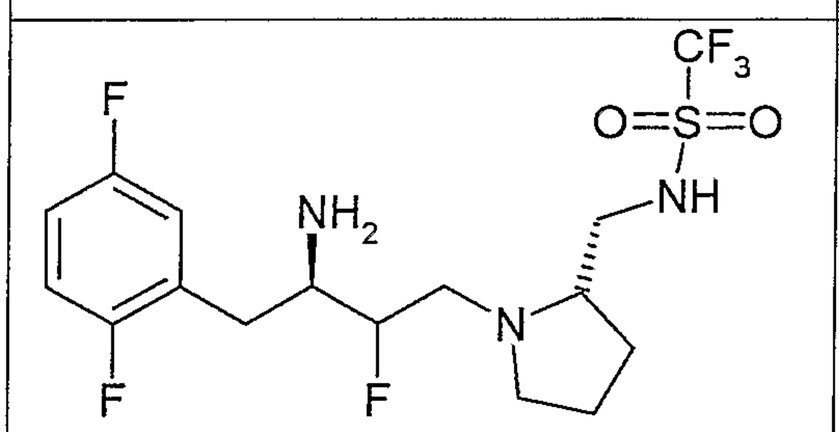
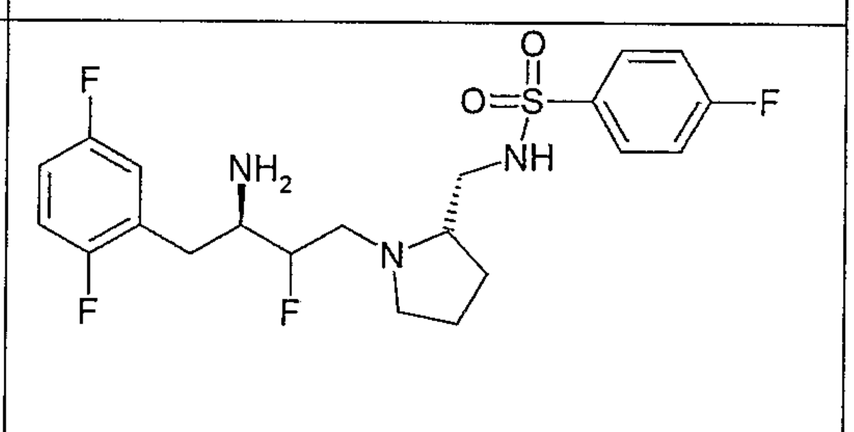
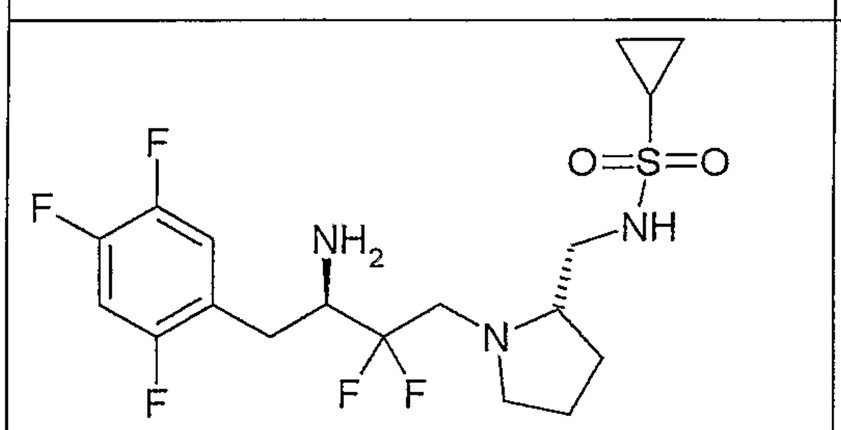
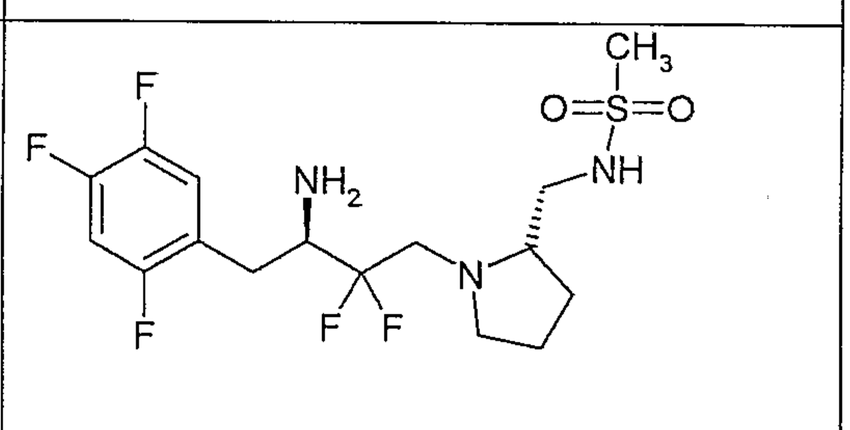
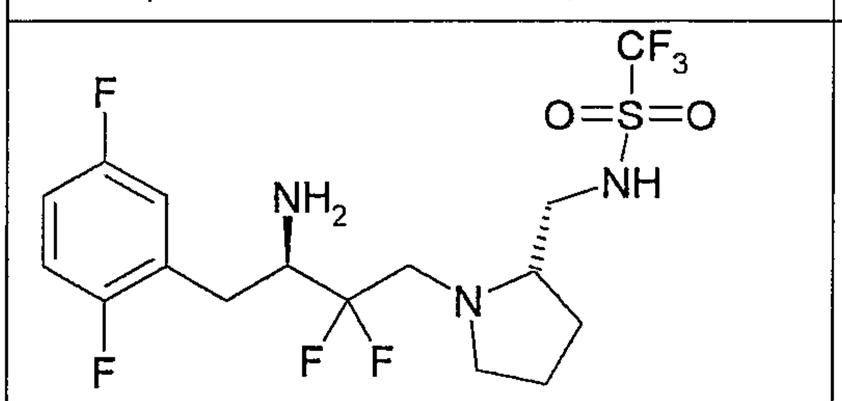
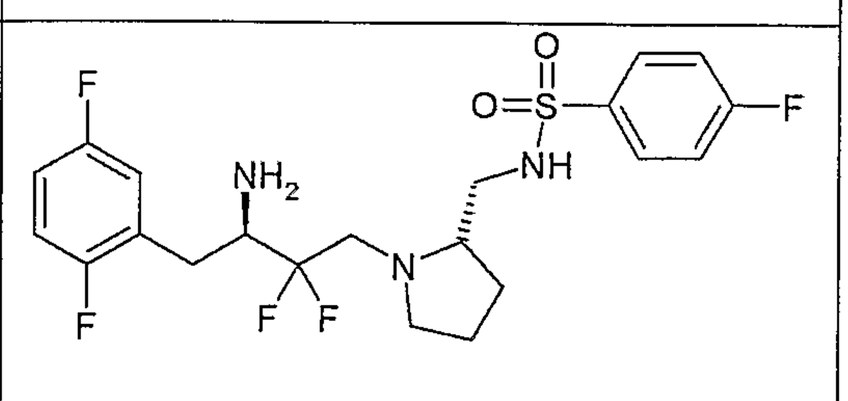
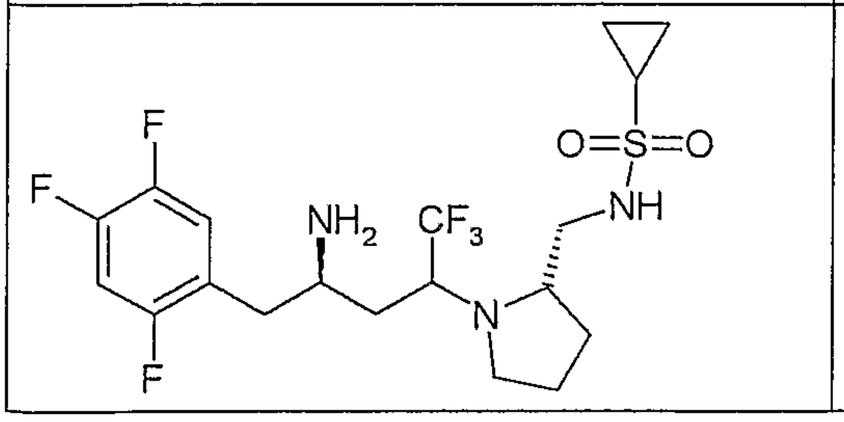
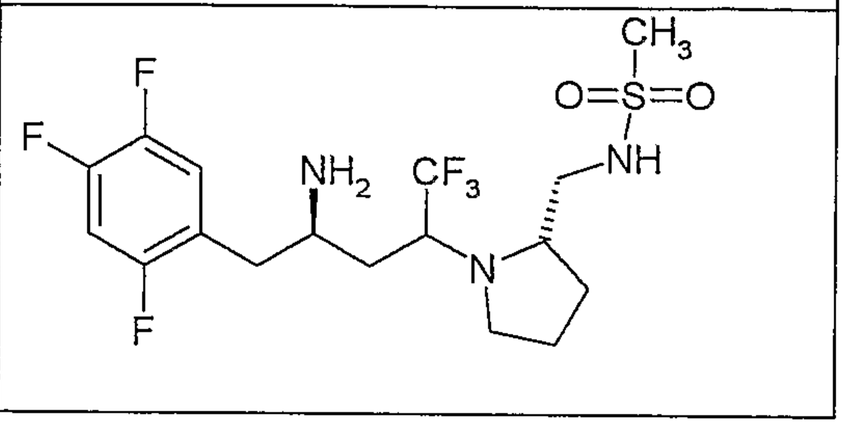
LC/MS (I, gradient 5-50%) rt 2.63, m/z 281 $[M+H]^+$.

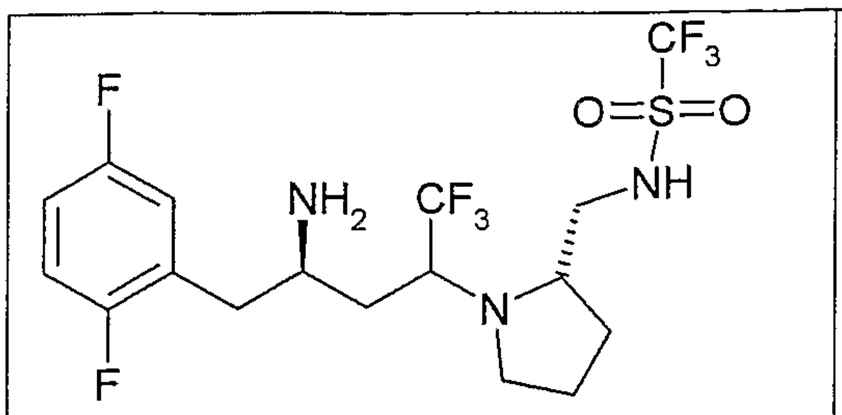
The compound in Table 10 is synthesized according to the procedure shown for example 48.

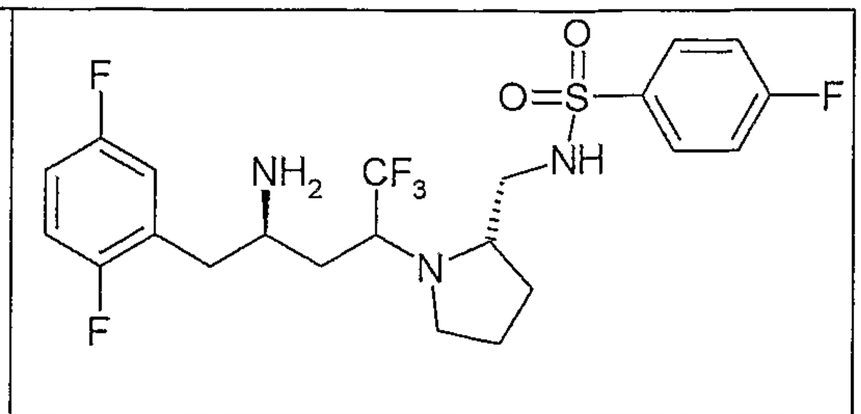
TABLE 10

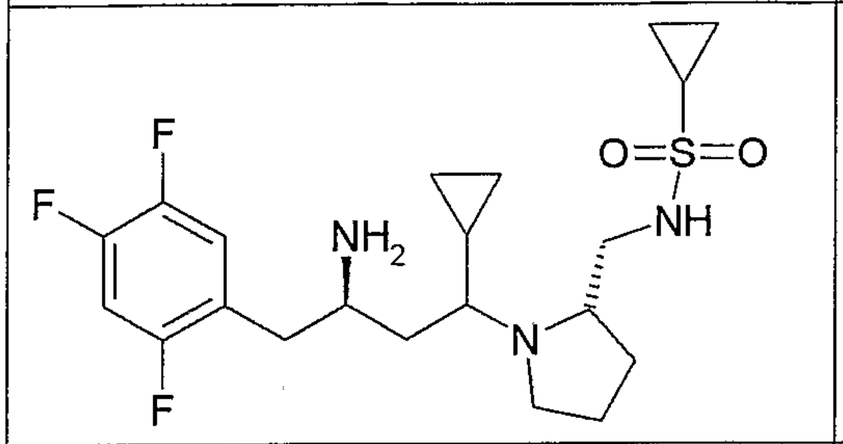
Example	Structure	LC-MS	NMR
49		LC/MS (IV) rt 2.21 min, m/z 462 $[M+H]^+$.	

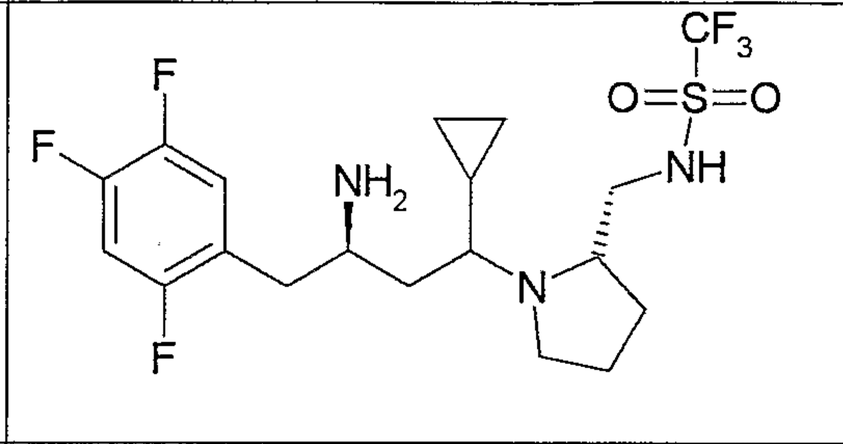
Further examples from this series are exemplified below:

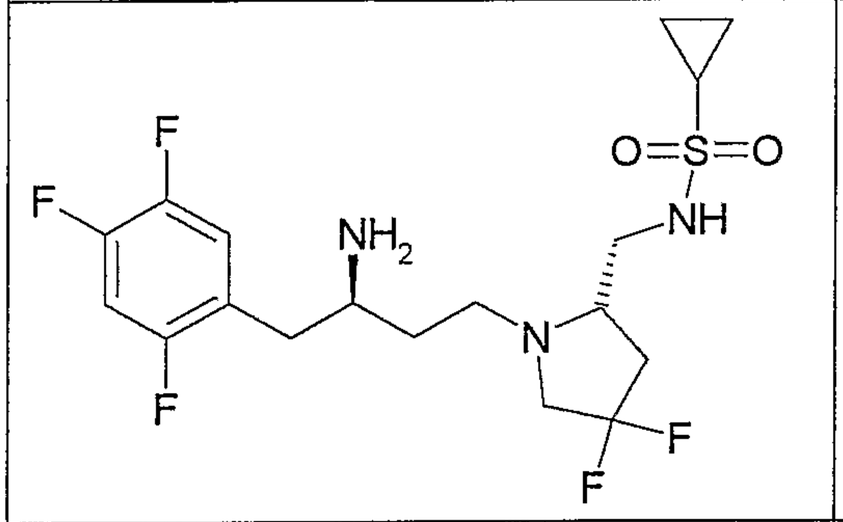
	
	
	
	
	

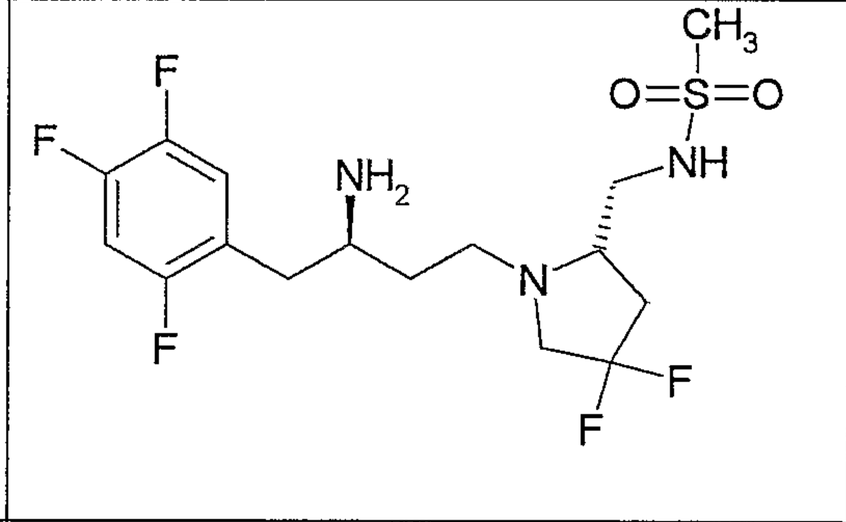


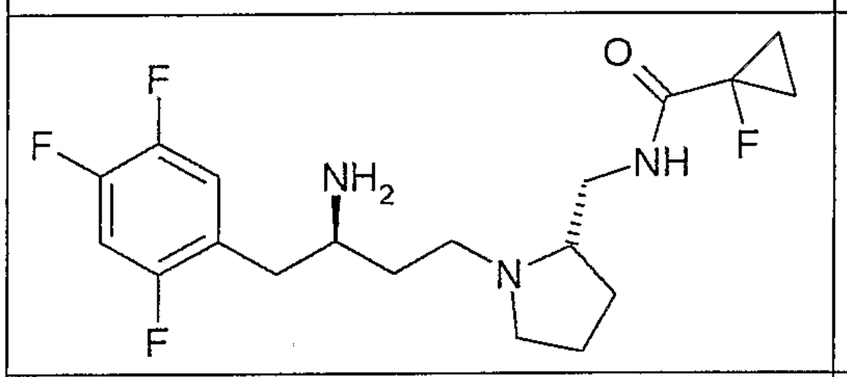


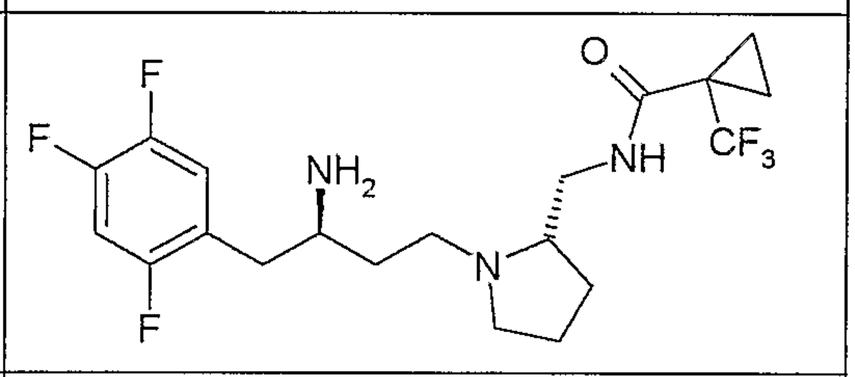


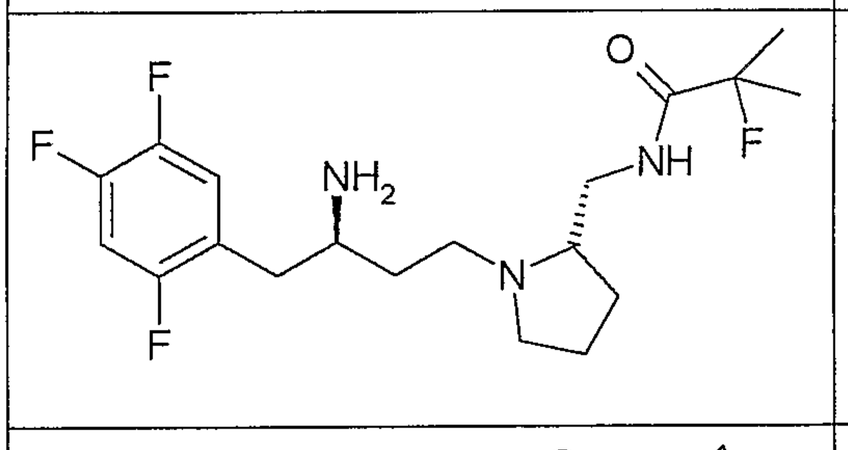


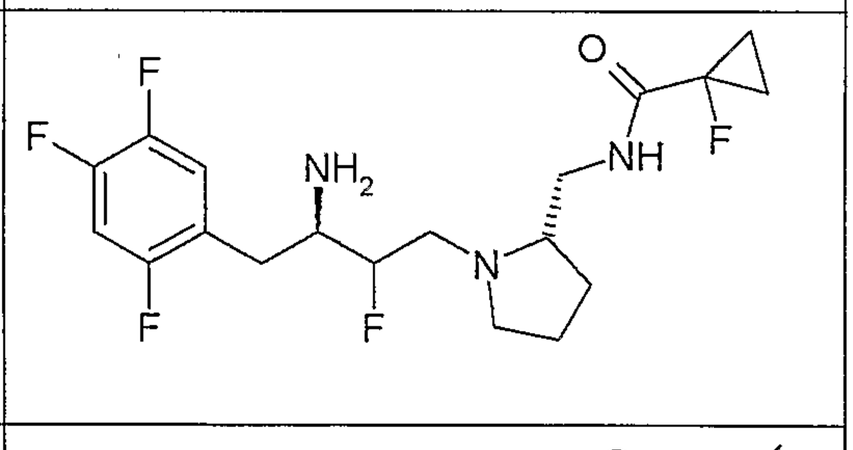


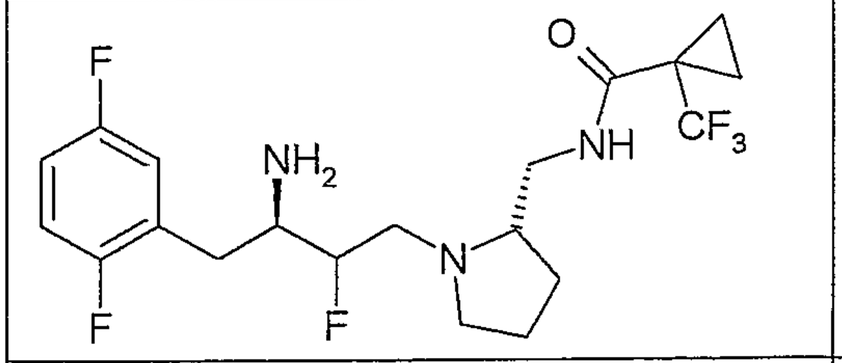


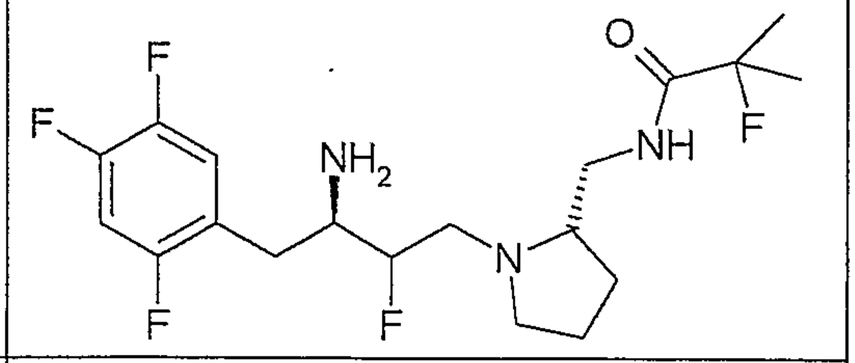


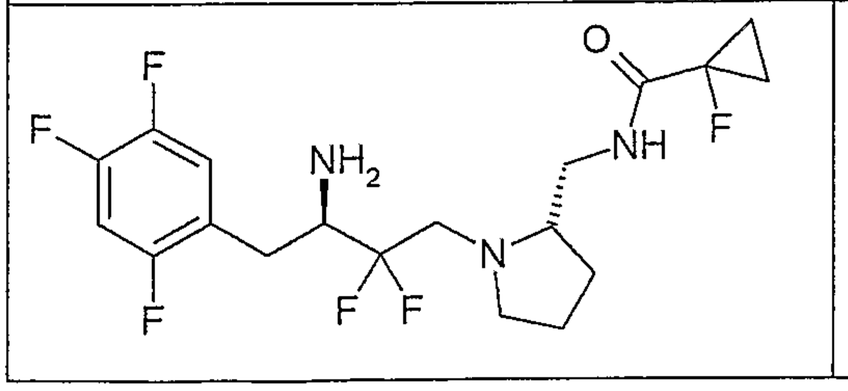


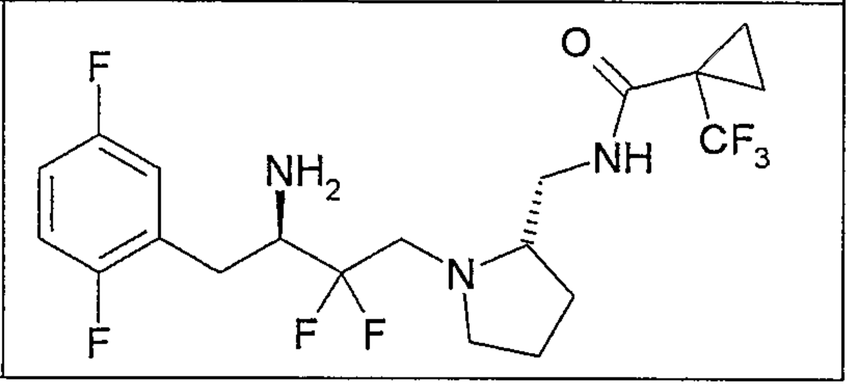


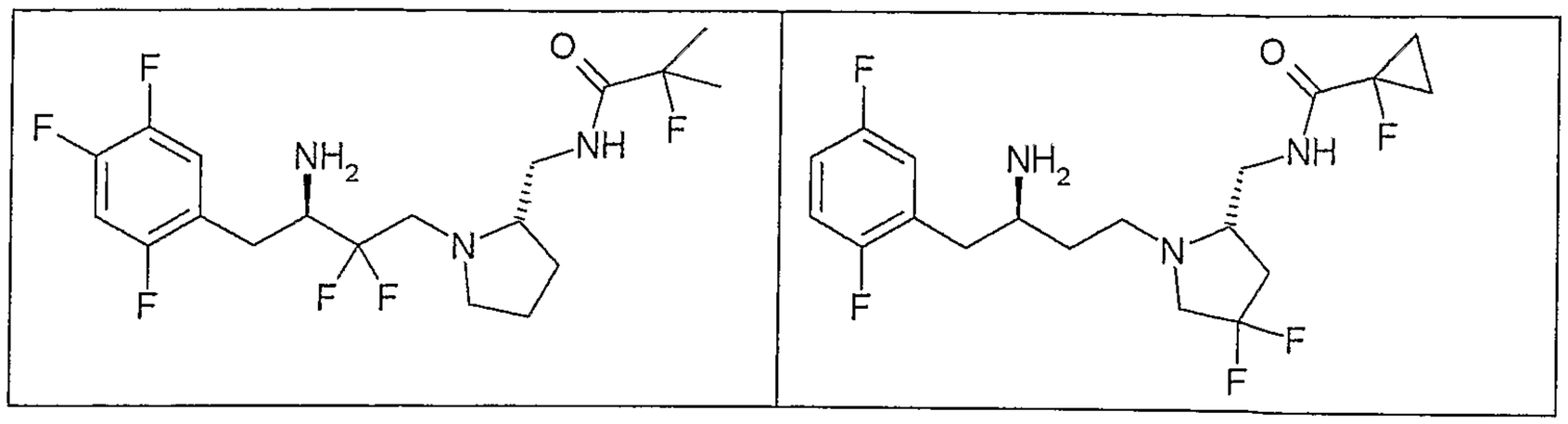












ASSAYS

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 µL, 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 µM substrate and the fluorescence of liberated AMC is detected for 10 minutes at 25 °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-include.

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) and used for inhouse screening.

In the table are listed the IC_{50} values for inhibition of DPP-IV peptidase activity determined in assays as described above. The IC_{50} values were grouped in 3 classes: a ≤ 100 nM; b ≥101 nM and ≤ 1000 nM ; c ≥1001 nM and ≤ 2000 nM; d ≥ 2001 nM and ≤ 2200 nM.

Example	IC_{50}
23	b
24	a
25	a
26	b
27	a
28	b
29	a
30	a
31	a
32	a
33	a
42 major	b
42 minor	a
43	a
44	b
45	a
46	a
47	b
48	b

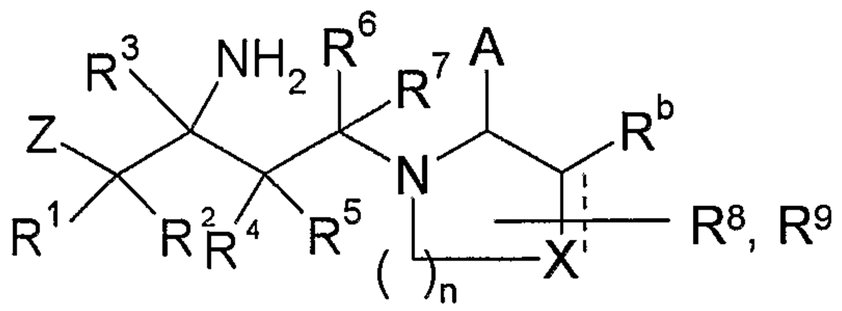
Example	IC_{50}
34	a
35	b
36	a
37	a
38 major	b
38 minor	a
39 major	b
39 minor	a
40 major	b
40 minor	a
41 minor	a
49	d

5

AMENDED CLAIMS

[received by the International Bureau on 21 September 2005 (21.09.2005);
original claims 1-27 replaced by amended claims 1-26 (14 pages)]

1. A compound of the formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein a dotted line indicates an optionally present double bond and wherein

Z is selected from the group consisting of phenyl; naphthyl; indenyl; C_{3-7} cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle, wherein Z is optionally substituted with one or more R^{10}, wherein R^{10} is independently selected from the group consisting of halogen; CN; OH; NH_2; oxo (=O), where the ring is at least partially saturated; R^{11}; and R^{12};

R^{11} is selected from the group consisting of C_{1-6} alkyl; O-C_{1-6} alkyl; and S-C_{1-6} alkyl, wherein R^{11} is optionally interrupted by oxygen and wherein R^{11} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{12} is selected from the group consisting of phenyl; heterocycle; and C_{3-7} cycloalkyl, wherein R^{12} is optionally substituted with one or more R^{13}, wherein R^{13} is independently

selected from the group consisting of halogen; CN; OH; NH_2; oxo (=O), where the ring is at least partially saturated; C_{1-6} alkyl; O-C_{1-6} alkyl; and S-C_{1-6} alkyl;

R^1, R^4 are independently selected from the group consisting of H; F; and R^{14};

R^2, R^5, R^6, R^7 are independently selected from the group consisting of H; F; and R^{15};

R^{14} is independently selected from the group consisting of C_{1-6} alkyl; O-C_{1-6} alkyl; N(R^{14a})-C_{1-6} alkyl; S-C_{1-6} alkyl; C_{3-7} cycloalkyl; O-C_{3-7} cycloalkyl; N(R^{14a})-C_{3-7} cycloalkyl; S-C_{3-7} cycloalkyl; -C_{1-6} alkyl-C_{3-7} cycloalkyl; O-C_{1-6} alkyl-C_{3-7} cycloalkyl; N(R^{14a})-C_{1-6} alkyl-C_{3-7} cycloalkyl; S-C_{1-6} alkyl-C_{3-7} cycloalkyl; heterocycle; O-heterocycle; N(R^{14a})-heterocycle; S-heterocycle; C_{1-6} alkyl-heterocycle; O-C_{1-6} alkyl-heterocycle; N(R^{14a})-C_{1-6} alkyl-heterocycle; S-C_{1-6} alkyl-heterocycle; wherein R^{14} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{14a} is selected from the group consisting of H; and C_{1-6} alkyl;

optionally R^6 is selected from the group consisting of -C($R^{6a}R^{6b}$)-O-C_{1-6} alkyl; -C($R^{6a}R^{6b}$)-O-C_{3-7} cycloalkyl; -C($R^{6a}R^{6b}$)-S-C_{1-6} alkyl; -C($R^{6a}R^{6b}$)-S-C_{3-7} cycloalkyl; -C($R^{6a}R^{6b}$)-N(R^{6c})-C_{1-6} alkyl; and -C($R^{6a}R^{6b}$)-N(R^{6c})-C_{3-7} cycloalkyl, wherein each C_{1-6} alkyl and C_{3-7} cycloalkyl is optionally substituted with one or more R^{6d}, wherein R^{6d} is independently selected from the group consisting of halogen; C_{1-6} alkyl; and C_{3-7} cycloalkyl;

R^{6a}, R^{6b}, R^{6c} are independently selected from the group consisting of H; and C_{1-6} alkyl;

R^{15} is independently selected from the group consisting of C_{1-6} alkyl; C_{3-7} cycloalkyl; and -C_{1-6} alkyl-C_{3-7} cycloalkyl, wherein R^{15} is optionally substituted with one or more R^{15a}, wherein R^{15a} 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, R^4, R^5, R^6, R^{6a}, R^{6b}, R^7 independently selected from the group consisting of R^1/R^2; R^2/R^3; R^3/R^4; R^4/R^5; R^5/R^6; R^{6a}/R^{6b} and R^6/R^7 form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more of R^{15b}, wherein R^{15b} is independently selected from the group consisting of F; Cl; and OH;

n is 0, 1, 2 or 3;

X is selected from the group consisting of $-C(R^{16}R^c)-$; $-C(R^a)=CR^c-$; $-C(R^{16}R^a)-CR^c=$, $-C(R^{16}R^a)-O-$; $-C(R^{16}R^a)-S-$; $-C(R^{16}R^a)-S(O)-$; $-C(R^{16}R^a)-S(O)_2-$; $-C(R^{16}R^a)-NR^c-$; and $-C(R^{16}R^a)-CR^{17}R^c-$;

R^8 is selected from the group consisting of H; F; OH; and C_{1-6} alkyl, optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

R^9, R^{16}, R^{17} are independently selected from the group consisting of H; F; and C_{1-6} alkyl, optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

R^a, R^b, R^c, are independently selected from the group consisting of H; F; Cl; CN; -Y-H; and -Y-T,

A is selected from the group consisting of –Y-H and –Y-T,

provided that at most two of R^a, R^b, R^c, A are independently -Y-T;

optionally R^c is selected from the group consisting of $-O-C_{1-6}$ alkyl; $-O-C_{3-7}$ cycloalkyl; $-S-C_{1-6}$ alkyl; $-S-C_{3-7}$ cycloalkyl; $-N(R^{18})-C_{1-6}$ alkyl; and $-N(R^{18})-C_{3-7}$ cycloalkyl, wherein each C_{1-6} alkyl and C_{3-7} cycloalkyl is optionally substi-

tuted with one or more R^{18a}, wherein R^{18a} is independently selected from the group consisting of halogen; C_{1-6} alkyl; and C_{3-7} cycloalkyl, provided that n is 1;

R^{18} is independently selected from the group consisting of H; C_{1-6} alkyl;

optionally a pair of R^a, R^b, R^c selected from the group consisting of R^a/R^c; and R^b/R^c forms a ring Z^1;

Z^1 is selected from the group consisting of Z^2; and Z^3;

Z^2 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein Z^2 is optionally substituted with one or more R^{19}; wherein R^{19} is independently selected from the group consisting of halogen; CN; $COOR^{20}$; OR^{20}; $C(O)N(R^{20}R^{20a})$; $S(O)_2N(R^{20}R^{20a})$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{20})$-C_{1-6} alkyl; $S(O)_2N(R^{20})$-C_{1-6} alkyl; $S(O)N(R^{20})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{20})S(O)_2$-C_{1-6} alkyl; and $N(R^{20})S(O)$-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

Z^3 is selected from the group consisting of C_{3-7} cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle; wherein Z^3 is optionally substituted with one or more R^{21}, wherein R^{21} is independently selected from the group consisting of halogen; CN; OR^{22}; oxo (=O), where the ring is at least partially saturated; $N(R^{22}R^{22a})$; $COOR^{22}$; $C(O)N(R^{22}R^{22a})$; $S(O)_2N(R^{22}R^{22a})$; $S(O)N(R^{22}R^{22a})$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $N(R^{22})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{22})$-C_{1-6} alkyl; $N(R^{22})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{22})$-C_{1-6} alkyl; $S(O)N(R^{22})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{22})S(O)_2$-C_{1-6} alkyl; and $N(R^{22})S(O)$-C_{1-6} alkyl; 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^{21} is $C(O)R^{22}$, provided that $C(O)R^{22}$ is bound to a nitrogen, which is a ring atom of a heterocycle or heterobicycle;

R^{20}, R^{20a}, R^{22}, R^{22a} 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;

Y is selected from the group consisting of a covalent bond; -C_{1-6} alkyl-T^0-; -C_{1-6} alkyl-O-T^0-; -C_{1-6} alkyl-S-T^0-; -C_{1-6} alkyl-S(O)-T^0-; -C_{1-6} alkyl-$S(O)_2$-T^0-; -C_{1-6} alkyl-$N(R^{23})$-T^0-; -C(O)-O-; -C(O)O-C_{1-6} alkyl-T^0-; -C_{1-6} alkyl-C(O)O-; -C_{1-6} alkyl-C(O)O-C_{1-6} alkyl-T^0-; -C(O)$N(R^{23})$-; -C(O)$N(R^{23})$-C_{1-6} alkyl-T^0-; -C_{1-6} alkyl-C(O)$N(R^{23})$-; and -C_{1-6} alkyl-C(O)$N(R^{23})$-C_{1-6} alkyl-T^0-; wherein each C_{1-6} alkyl is optionally substituted with one or more F;

T^0 is selected from the group consisting of a covalent bond; -C_{1-6} alkyl-; -C_{1-6} alkyl-O-; -C_{1-6} alkyl-$N(R^{23})$-; -C(O)-; -C(O)-C_{1-6} alkyl-; -C(O)-C_{1-6} alkyl-O-; -C(O)-C_{1-6} alkyl-$N(R^{23})$-; -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-$N(R^{23})$-; -C(O)$N(R^{23})$-; -C(O)$N(R^{23})$-C_{1-6} alkyl-; -C(O)$N(R^{23})$-C_{1-6} alkyl-O-; -C(O)$N(R^{23})$-C_{1-6} alkyl-$N(R^{24})$-; -$S(O)_2$-; -$S(O)_2$-C_{1-6} alkyl-; -$S(O)_2$-C_{1-6} alkyl-O-; and -$S(O)_2$-C_{1-6} alkyl-$N(R^{23})$-; wherein each C_{1-6} alkyl is optionally substituted with one or more F;

R^{23}, R^{24} are independently selected from the group consisting of H; and C_{1-6} alkyl;

T is selected from the group consisting of T^1; and T^2;

T^1 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T^1 is optionally substituted with one or more R^{25}; wherein R^{25} is independently selected from the group consisting of halogen; CN; R^{26}; COOH; OH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; $COOT^3$; OT^3; ST^3; C(O)$N(R^{27})T^3$; $S(O)_2N(R^{27})T^3$; S(O)$N(R^{27})T^3$ and T^3;

T^2 is selected from the group consisting of C_{3-7} cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle; wherein T^2 is optionally substituted with one or more R^{28}, wherein R^{28} is independently selected from the group consisting of halogen; CN;

R^{29}; OH; oxo (=O), where the ring is at least partially saturated; NH_2; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; $COOT^3$; OT^3; $C(O)N(R^{30})T^3$; $S(O)_2N(R^{30})T^3$; $S(O)N(R^{30})T^3$; $N(R^{30})T^3$; and T^3;

optionally R^{28} is $C(O)R^{30}$, provided that $C(O)R^{30}$ is bound to a nitrogen, which is a ring atom of a heterocycle or heterobicycle;

R^{26} is selected from the group consisting of C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{31})$-C_{1-6} alkyl; $S(O)_2N(R^{31})$-C_{1-6} alkyl; $S(O)N(R^{31})$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; $N(R^{31})S(O)_2$-C_{1-6} alkyl; and $N(R^{31})S(O)$ -C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more R^{32}, wherein R^{32} is independently selected from the group consisting of F; $COOR^{33}$; $C(O)N(R^{33}R^{34})$; $S(O)_2N(R^{33}R^{34})$; OR^{33}; $N(R^{33}R^{34})$; T^3; O-T^3; and $N(R^{33})$-T^3;

R^{29} is selected from the group consisting of C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $N(R^{35})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{35})$- C_{1-6} alkyl; $N(R^{35})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{35})$-C_{1-6} alkyl; S(O) $N(R^{35})$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; $-N(R^{35})S(O)_2$-C_{1-6} alkyl; and $-N(R^{35})S(O)$-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more R^{32a}, wherein R^{32a} is independently selected from the group consisting of F; $COOR^{36}$; $C(O)N(R^{36}R^{37})$; $S(O)_2N(R^{36}R^{37})$; $S(O)N(R^{36}R^{37})$; OR^{36}; $N(R^{36}R^{37})$; T^3; O-T^3; and $N(R^{36})$-T^3;

R^{27}, R^{30}, R^{31}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37} are independently selected from the group consisting of H; and C_{1-6} alkyl;

T^3 is selected from the group consisting of T^4; and T^5;

T^4 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T^4 is optionally substituted with one or more R^{38}, wherein R^{38} is independently selected from the group consisting of halogen; CN; $COOR^{39}$; OR^{39}; $C(O)N(R^{39}R^{40})$; $S(O)_2N(R^{39}R^{40})$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl;

$C(O)N(R^{39})$-C_{1-6} alkyl; $S(O)_2N(R^{39})$-C_{1-6} alkyl; $S(O)N(R^{39})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; $S(O)$-C_{1-6} alkyl; $N(R^{39})S(O)_2$-C_{1-6} alkyl; and $N(R^{39})S(O)$-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen selected from the group consisting of F; and Cl;

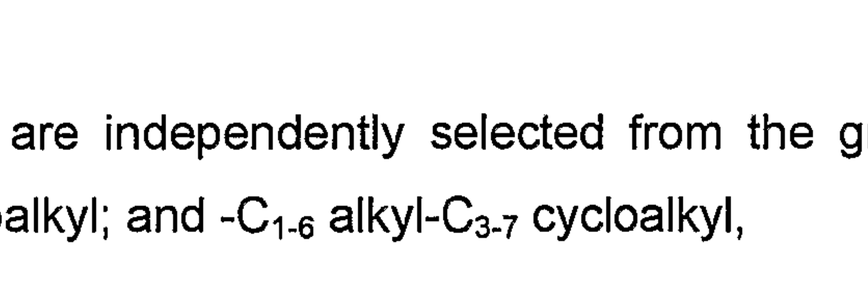
T^5 is selected from the group consisting of heterocycle; heterobicycle; C_{3-7} cycloalkyl; indanyl; tetralinyl; and decalinyl; wherein T^5 is optionally substituted with one or more R^{41}, wherein R^{41} is independently selected from the group consisting of halogen; CN; OR^{42}; oxo (=O), where the ring is at least partially saturated; $N(R^{42}R^{43})$; $COOR^{42}$; $C(O)N(R^{42}R^{43})$; $S(O)_2N(R^{42}R^{43})$; $S(O)N(R^{42}R^{43})$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $N(R^{42})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{42})$-C_{1-6} alkyl; $N(R^{42})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{42})$-C_{1-6} alkyl; $S(O)N(R^{42})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{42})S(O)_2$-C_{1-6} alkyl; and $N(R^{42})S(O)$-C_{1-6} alkyl; 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^{41} is $C(O)R^{42}$, provided that $C(O)R^{42}$ is bound to a nitrogen, which is a ring atom of a heterocycle or heterobicycle;

R^{39}, R^{40}, R^{42}, R^{43}, are independently selected from the group consisting of H; and C_{1-6} alkyl; C_{3-7} cycloalkyl; and -C_{1-6} alkyl-C_{3-7} cycloalkyl,

provided that if Z is phenyl, R^1 to R^9 are hydrogen, n is 1, X is CH_2 and R^b is hydrogen, then A is not –C(O)-NH_2 or –C(O)-NH(*t*-butyl).

2. A compound according to claim 1 of formula (Ia)



(Ia)

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or a pharmaceutical acceptable salt thereof, wherein Z, R^{1-9}, X, n, R^b and A have the meaning as indicated in claim 1.

3. A compound according to claim 1 or 2, wherein Z is selected from the group consisting of phenyl; and heterocycle, and wherein Z is optionally substituted with up to 2 R^{10}, which are the same or different.

4. A compound according to any of the preceding claims, wherein R^{10} is selected from the group consisting of F; Cl; CN; and C_{1-6} alkyl.

5. A compound according to any of the preceding claims, wherein R^1, R^2, R^4, R^5, R^6, R^7 are independently selected from the group consisting of H; F; and C_{1-6} alkyl.

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

7. A compound according to any of the preceding claims, wherein n is 0 or 1.

8. A compound according to any of the preceding claims, wherein X is selected from the group consisting of $-CH(R^c)-$; $-CH(R^a)-N(R^c)-$; and $-C(R^a)=C(R^c)-$.

9. A compound according to any of the preceding claims, wherein R^8, R^9 are independently selected from the group consisting of H, and F.

10. A compound according to any of the preceding claims, wherein R^a, R^b, R^c are H.

11. A compound according to any of the preceding claims, wherein R^c is -Y-T.

12. A compound according to claim 11, wherein R^c is C_{1-6} alkyl-T.

13. A compound according to claim 11 or 12, wherein T is phenyl.

14. A compound according to any of the preceding claims, wherein the pair R^a and R^c forms a ring Z^1.

15. A compound according to any of the preceding claims, wherein Z^1 is selected from the group consisting of phenyl; C_{3-7} cycloalkyl; and heterocycle.

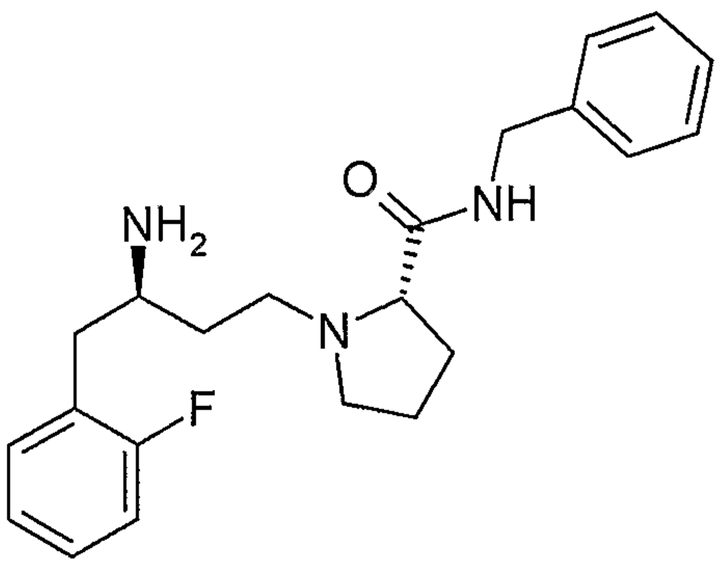
16. A compound according to any of the preceding claims, wherein Y is selected from the group consisting of -C(O)NH-; -C(O)NH-C_{1-6} alkyl-; -C_{1-6} alkyl-NHC(O)-C_{1-6} alkyl-; -C_{1-6} alkyl-NHC(O); C_{1-6} alkyl-NHS$(O)_2$-C_{1-6} alkyl; -C_{1-6} alkyl-O-; and -C_{1-6} alkyl-O-C_{1-6}alkyl-.

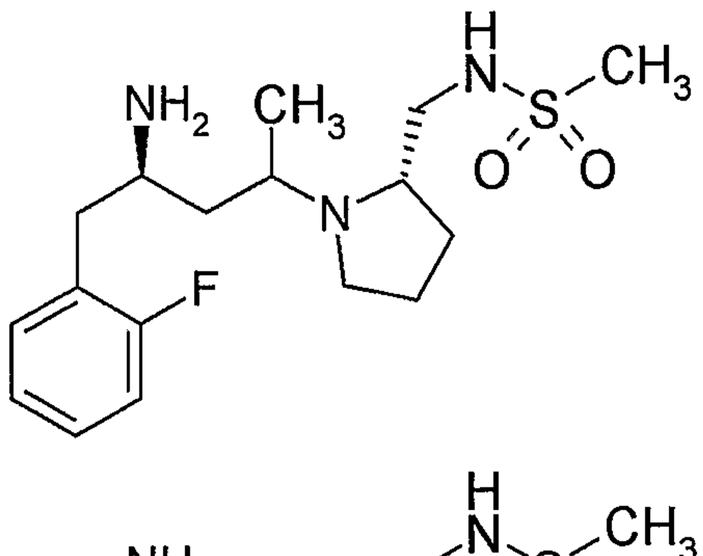
17. A compound according to claim 16, wherein Y is selected from the group consisting of -C(O)NH-CH_2-; -CH_2-NHC(O)-CH_2-; -CH_2-NHC(O)-; -CH_2-NHS$(O)_2$-CH_2-; -CH_2-O-; and -CH_2-O-CH_2-.

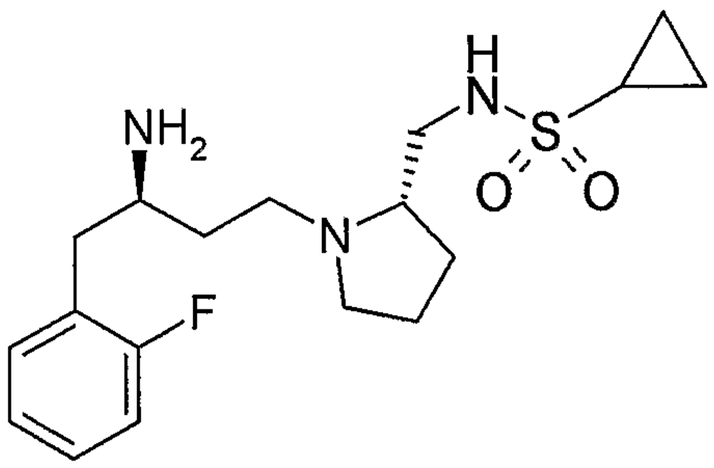
18. A compound according to claim 16, wherein T is selected from the group consisting of phenyl; C_{3-7} cycloalkyl and wherein T is optionally substituted with one or more F.

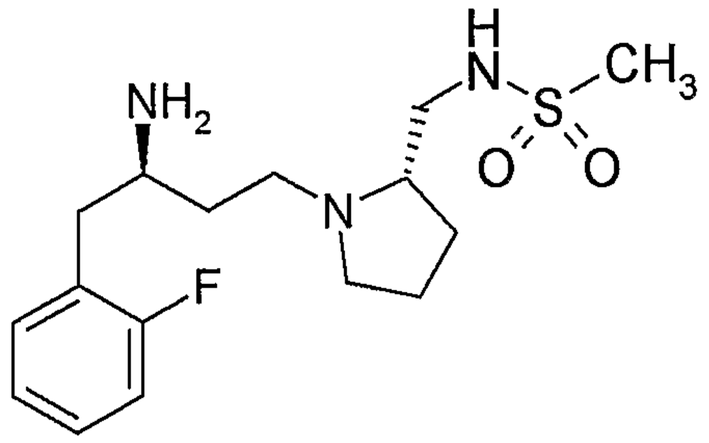
19. A compound according to claim 18, wherein C_{3-7} cylcoalkyl is cyclopropyl.

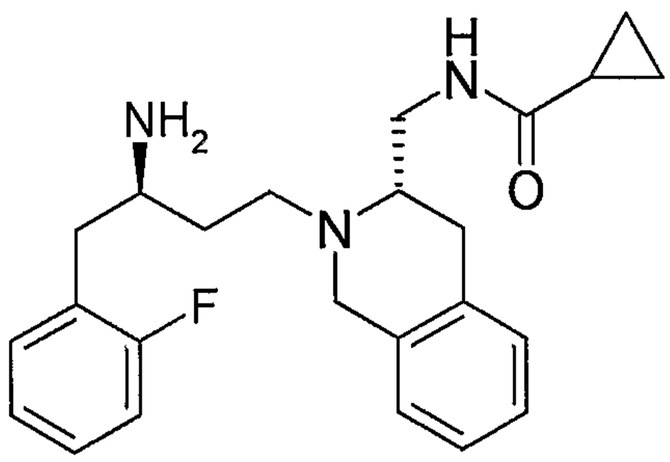
20. A compound according to claim 1 selected from the group consisting of

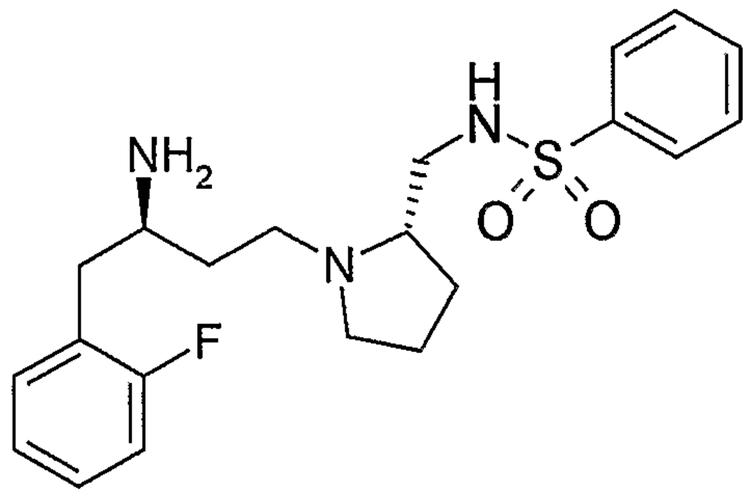


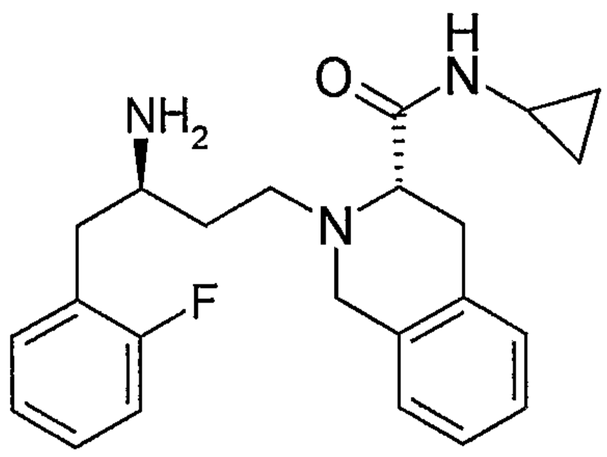


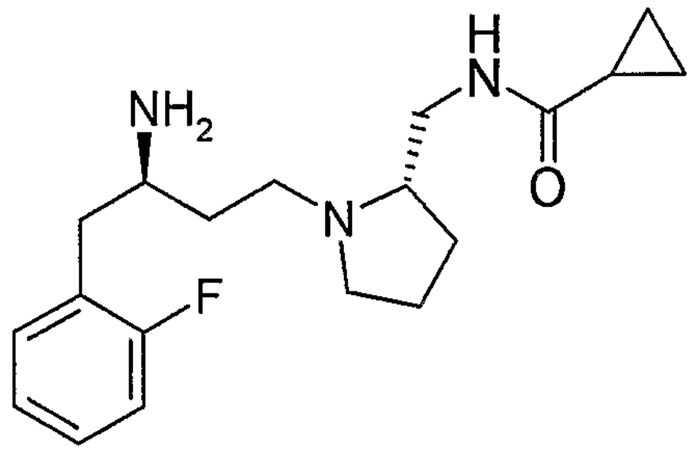


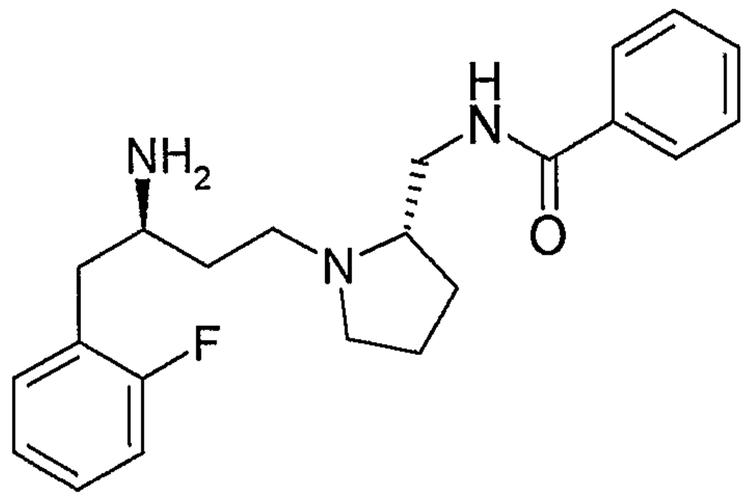


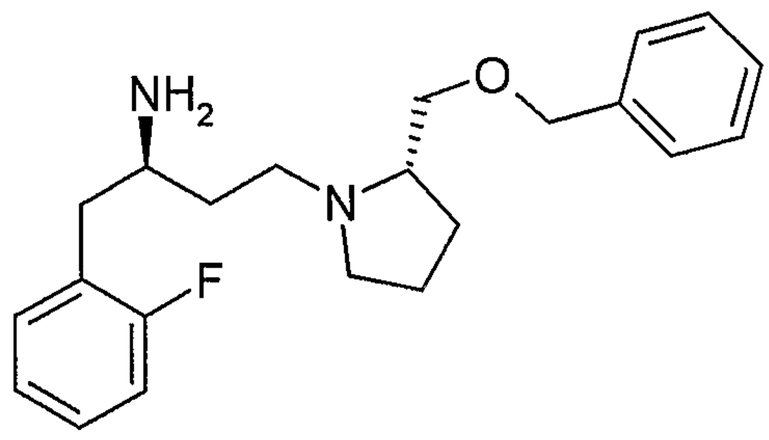




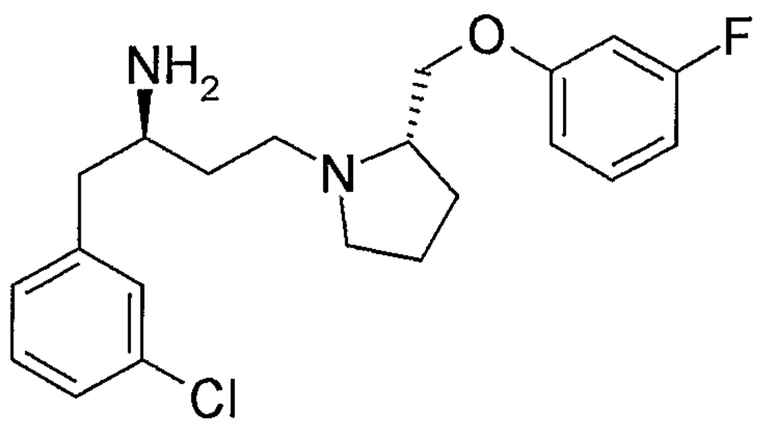


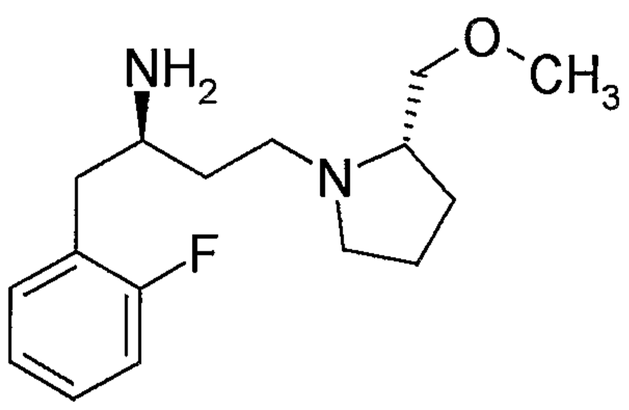


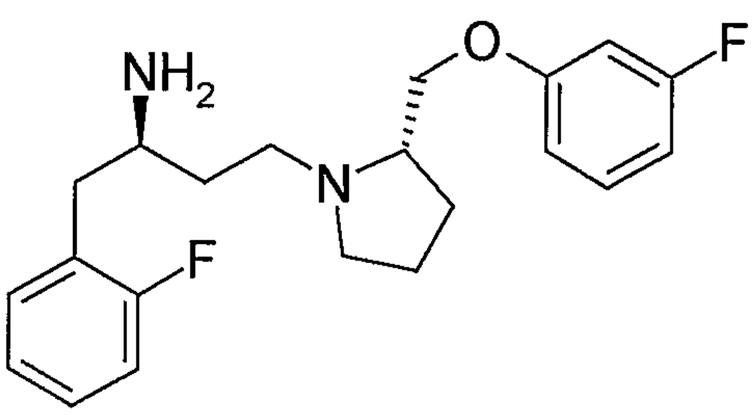


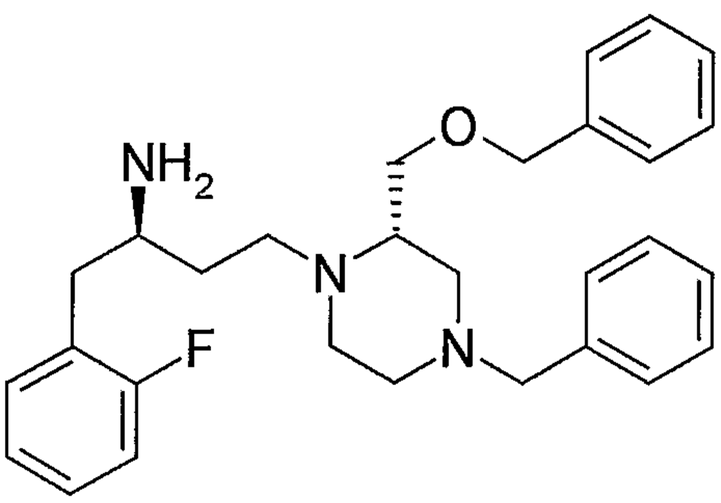


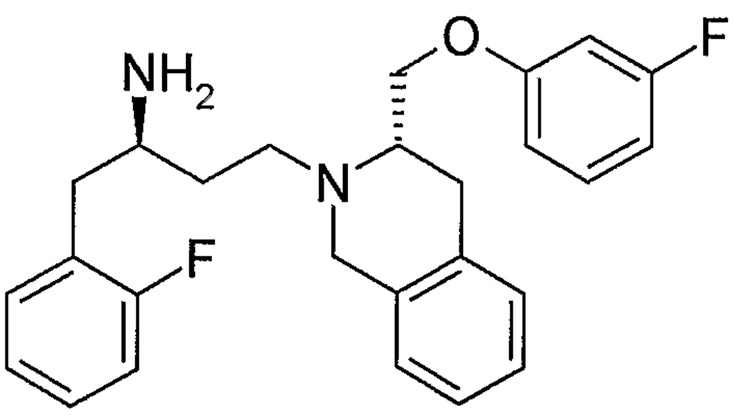
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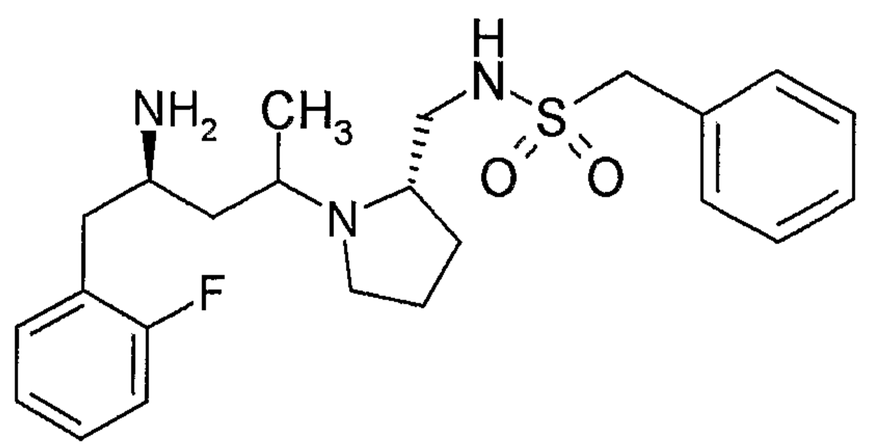


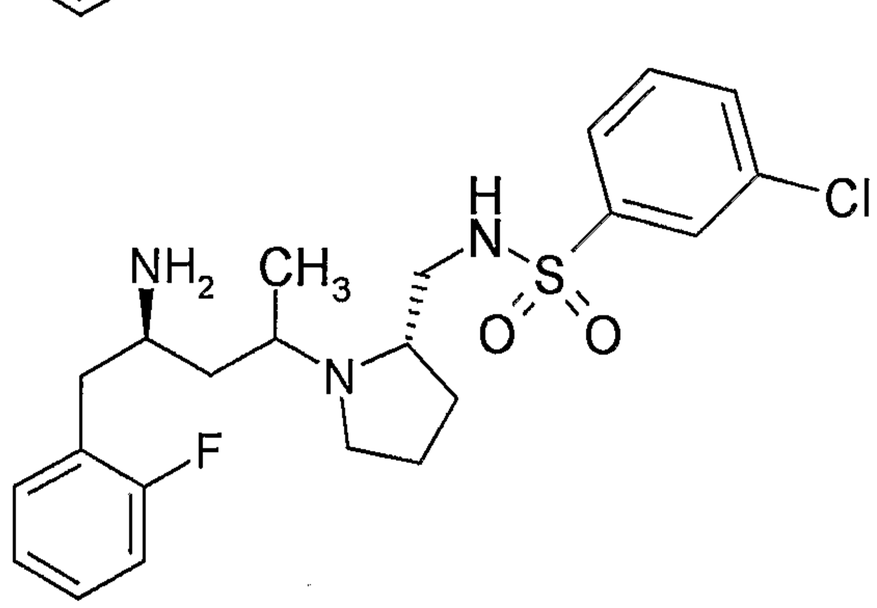


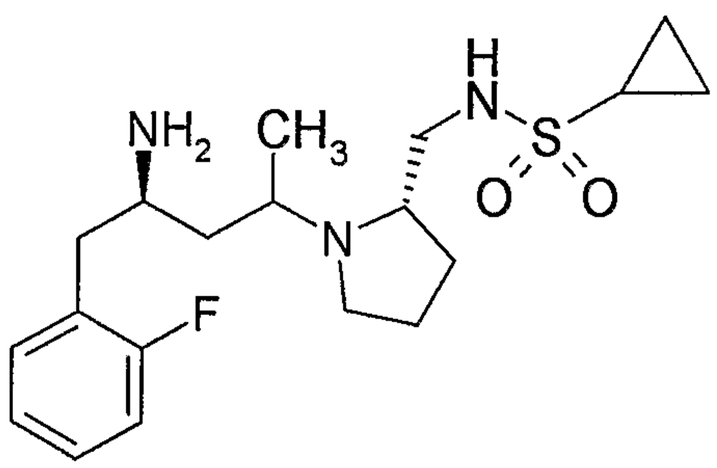


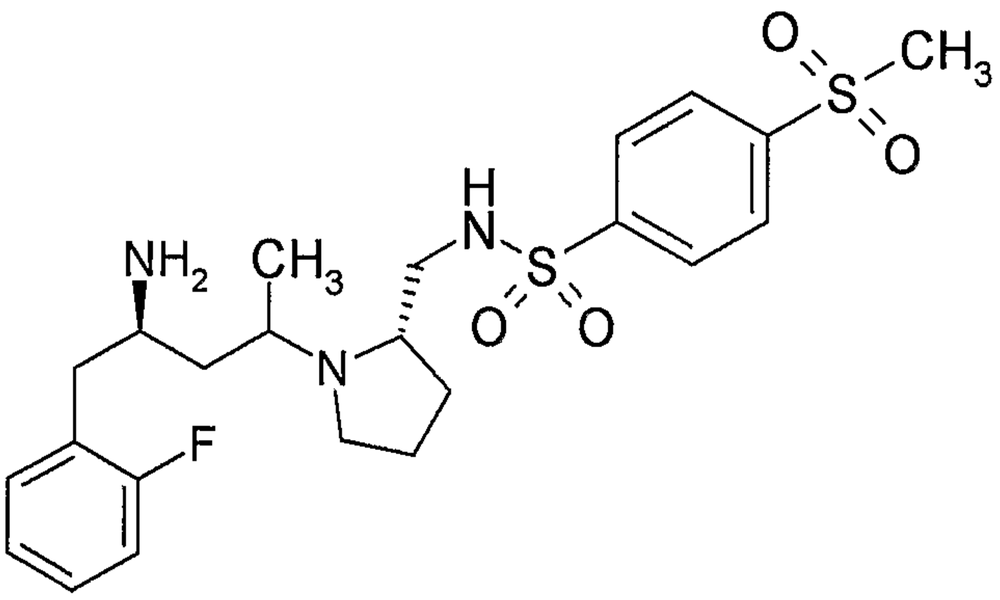




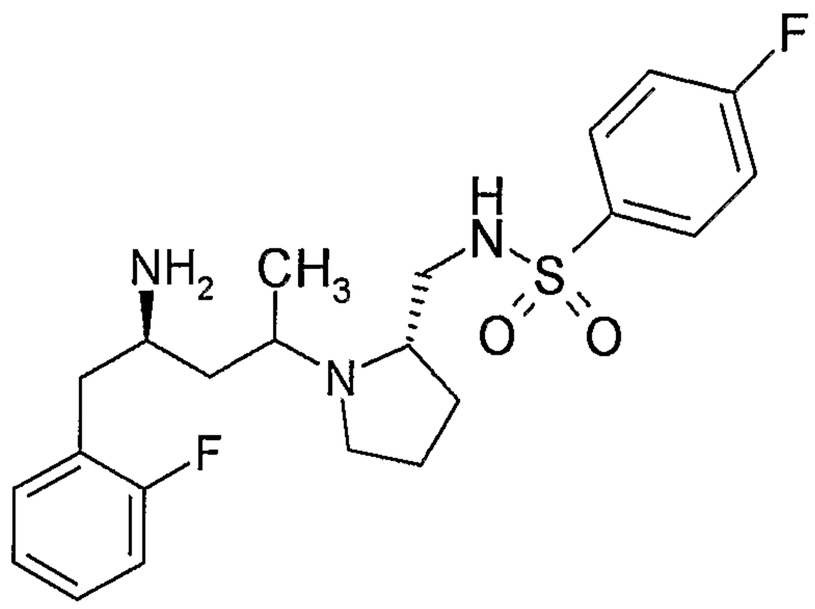


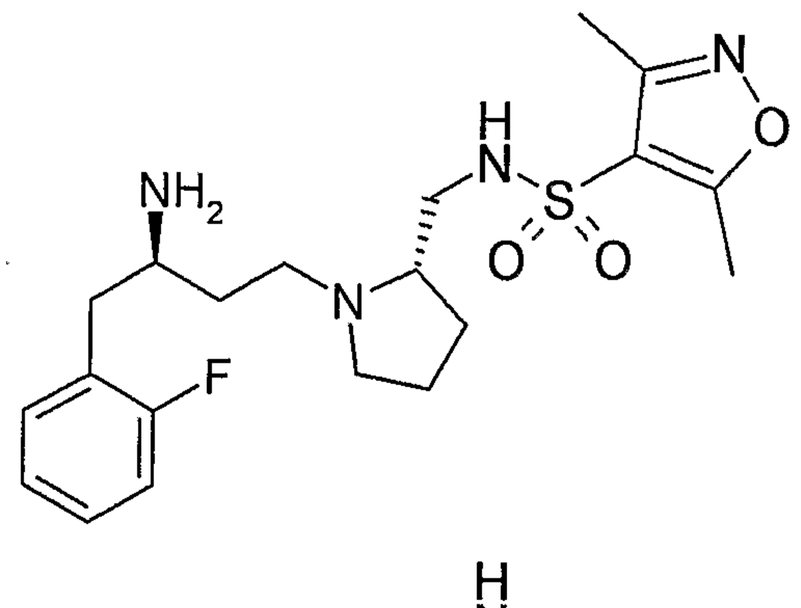


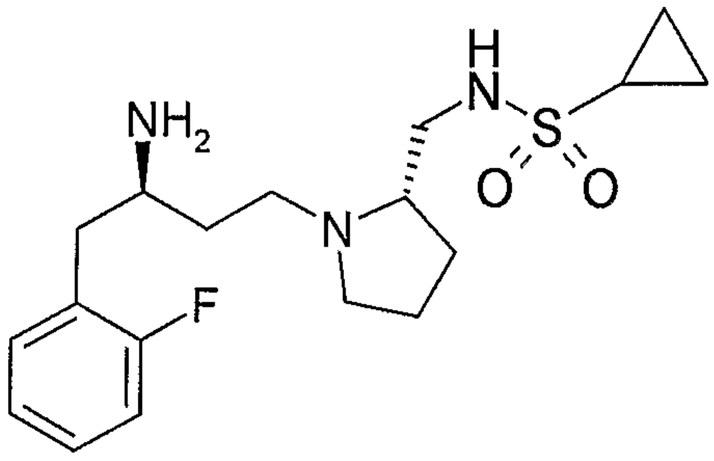


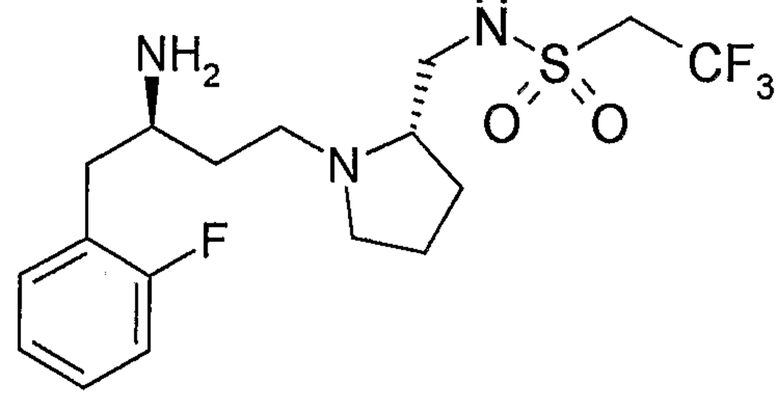


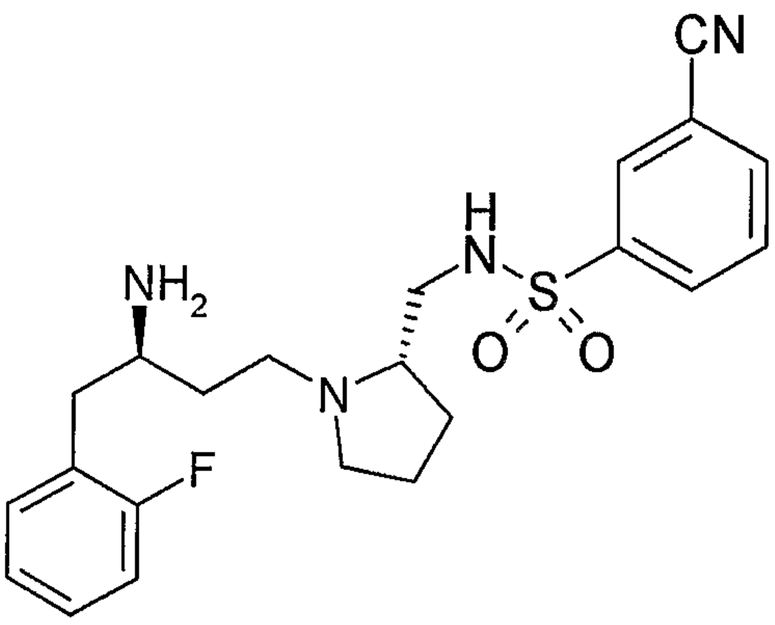
AMENDED SHEET (ARTICLE 19)

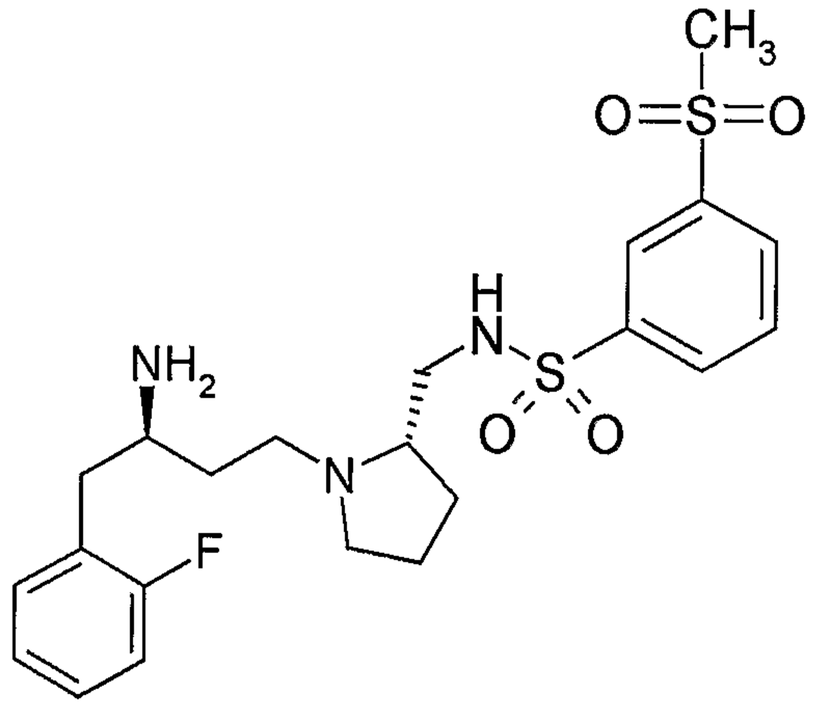


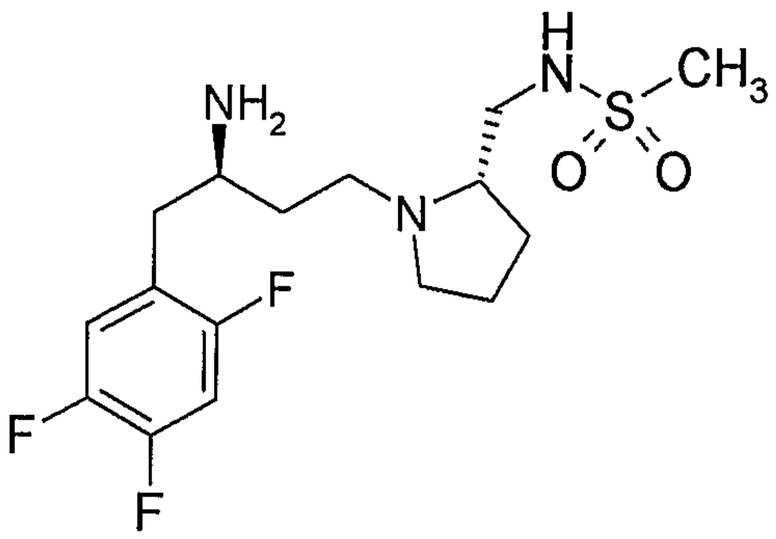


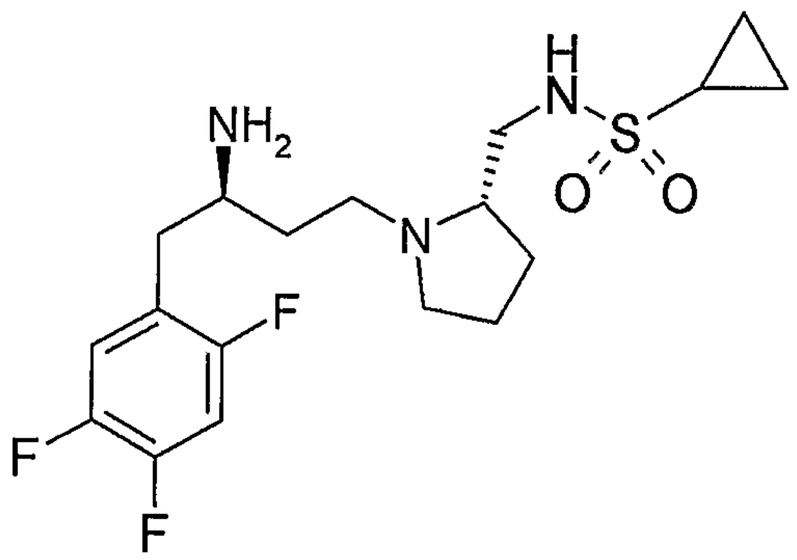


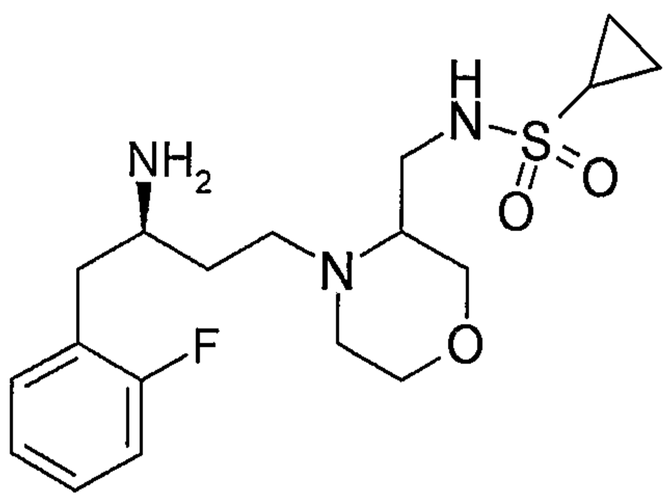












21. A prodrug compound of a compound according to any one of the claims 1 to 20.

22. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof according to any one of the claims 1 to 21 together with a pharmaceutically acceptable carrier.

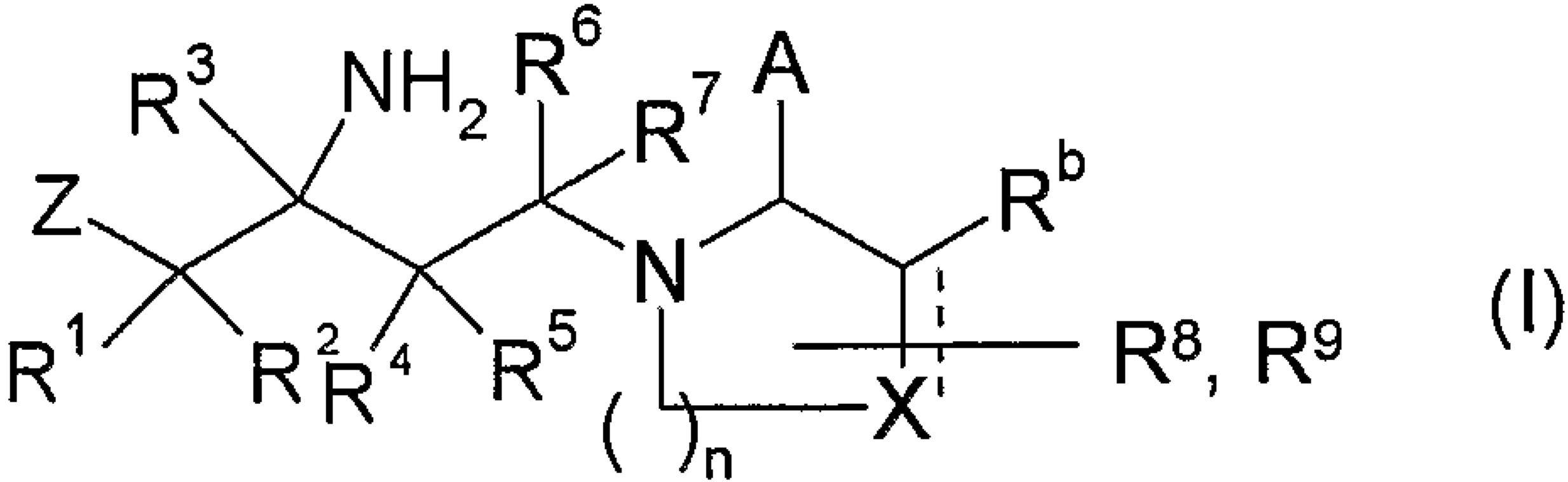
23. A pharmaceutical composition according to claim 22, comprising one or more additional compounds or pharmaceutically acceptable salts thereof selected from the group consisting of another compound according to any one of the claims 1 to 21; another DPP-IV inhibitor; insulin sensitizers; PPAR agonists; biguanides; protein tyrosinephosphatase-IB (PTP-1B) inhibitors; insulin and insulin mimetics; sulphonylureas and other insulin secretagogues; a-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; PPARa agonists; PPARoly dual agonists; inhibitors of cholesterol absorption; acyl CoA : cholesterol acyltransferase inhibitors; anti-oxidants; PPARo agonists; antiobesity compounds; an ileal bile acid transporter inhibitor; and anti-inflammatory agents.

24. A compound or a pharmaceutically acceptable salt thereof of any one of the claims 1 to 21 for use as a medicament.

25. Use of a compound or a pharmaceutically acceptable salt thereof of any of the claims 1 to 21 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; hypercholestrerolemia; 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; ist 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.

26. Use of a compound according to any one of the claims 1 to 21 as a DPP-IV inhibitor.



(I)