(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 October 2005 (13.10.2005)

PCT

(10) International Publication Number
WO 2005/095343 A1

(51) International Patent Classification[7]: C07D 213/40, 307/79, 261/08, 319/16, 231/12, 241/12, 311/76, 295/13, C07C 237/20, 311/13, A61K 31/4409, 31/505, 31/42, 31/415, 31/343

(21) International Application Number:
PCT/EP2005/002010

(22) International Filing Date: 25 February 2005 (25.02.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
04 005 347.2 5 March 2004 (05.03.2004) EP

(71) Applicant *(for all designated States except US)*: **GRAFFINITY PHARMACEUTICALS AG** [DE/DE]; Im Neuenheimer Feld 518-519, 62120 Heidelberg (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **EDWARDS, Paul, John** [GB/DE]; Kleinschmidtstr. 17, 69115 Heidelberg (DE). **FEURER, Achim** [DE/DE]; Erlenbrunnenweg 5, 69259 Wilhelmsfeld (DE). **CEREZO-GALVES, Silvia** [ES/DE]; Fischerstr. 29, 42287 Wuppertal (DE). **MATASSA, Victor, Giulio** [GB/DE]; Im Brambusch 20, 69493 Hirschberg (DE). **NORDHOFF, Sonja** [DE/DE]; Ruhweg 4, 69198 Schriesheim (DE). **ROSENBAUM, Claudia** [DE/DE]; Max-Reger-Strasse 16, 69121 Heidelberg (DE). **BULAT, Stephan** [DE/DE]; Kleingemünder Str. 72/II, 69118 Ziegelhausen (DE).

(74) Agent: **GOLDBACH, Klara**; Grünecker, Kinkeldey, Stockmair & Schwanhäusser, Maximilianstrasse 58, 80538 München (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *with amended claims*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DPP-IV INHIBITORS

(57) Abstract: The invention relates to compounds of formula (I), Z-C(R^1R^2)-C(R^3NH_2)-C(R^4R^5)-X-N(R^6R^7), wherein Z, R^{1-7} and X 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.

WO 2005/095343 A1

DPP-IV inhibitors

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 sulfonylureas (e.g., tolbutamide and glipizide) or meglitinide, which stimulate the pancreatic β-cells to secrete more insulin, and/or by injection of insulin when sulfonylureas or meglitinide become ineffective, can result in insulin concentrations high enough to stimulate the very insulin-resistant tissues. However, dangerously low levels of plasma glucose can result from administration of insulin or insulin secretagogues (sulfonylureas or meglitinide), and an increased level of insulin resistance, due to the even higher plasma insulin levels, can occur. The biguanides increase insulin sensitivity resulting in some correction of hyperglycemia. However, the two biguanides, phenformin and metformin, can induce lactic acidosis and nausea/diarrhoea. Metformin has fewer side effects than phenformin and is often prescribed for the treatment of Type 2 diabetes.

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

Additional methods of treating the disease are still under investigation. New

biochemical approaches that have been recently introduced or are still under development include treatment with alpha-glucosidase inhibitors (*e.g.*, acarbose) and protein tyrosine phosphatase-IB (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 and WO-A-03/181. 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):

$$Z\text{-}C(R^1R^2)\text{-}C(R^3NH_2)\text{-}C(R^4R^5)\text{-}X\text{-}N(R^6R^7) \qquad (I),$$

or a pharmaceutically acceptable salt thereof, 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^8, wherein R^8 is independently selected from the group consisting of halogen; CN; OH; NH_2; oxo (=O), where the ring is at least partially saturated; R^9; and R^{10};

R^9 is selected from the group consisting of C_{1-6} alkyl; O-C_{1-6} alkyl; and S-C_{1-6} alkyl, wherein R^9 is optionally interrupted by oxygen and wherein R^9 is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{10} is selected from the group consisting of phenyl; heterocycle; and C_{3-7} cycloalkyl, wherein R^{10} is optionally substituted with one or more R^{11}, wherein R^{11} 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^{4a};

R^2, R^5 are independently selected from the group consisting of H; F; and R^{4b};

R^{4a} is independently selected from the group consisting of C_{1-6} alkyl; and O-C_{1-6} alkyl, wherein R^{4a} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{4b} is C_{1-6} alkyl, wherein R^{4b} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

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 independently selected from the group consisting of R^1/R^2; R^2/R^3; R^3/R^4; and R^4/R^5 form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more of R^{12}, wherein R^{12} is independently selected from the group consisting of F; Cl; and OH;

X is selected from the group consisting of S(O); $S(O)_2$; C(O); and $C(R^{13}R^{14})$;

R^{13}, R^{14} are independently selected from the group consisting of H; F; C_{1-6} alkyl; R^{15}; and R^{16};

Optionally one or both pairs of R^5, R^{13}, R^{14} selected from the group consisting of R^5/R^{13}; and R^{13}/R^{14} form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more R^{17}, wherein R^{17} is independently selected from the group consisting of F; Cl; and OH;

R^{15} is selected from the group consisting of phenyl; naphthyl; and indenyl, wherein R^{15} is optionally substituted with one or more R^{18}, wherein R^{18} is independently selected from the group consisting of R^{19}; R^{20}; halogen; CN; COOH; OH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; 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; $C(O)N(R^{21})$-C_{1-6} alkyl; $S(O)_2N(R^{21})$-C_{1-6} alkyl; $S(O)N(R^{21})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{21})S(O)_2$-C_{1-6} alkyl; and $N(R^{21})S(O)$-C_{1-6} alkyl, wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{16} is selected from the group consisting of heterocycle; heterobicycle; C_{3-7} cycloalkyl; indanyl; tertralinyl; and decalinyl, wherein R^{16} is optionally substituted with one or more R^{22}, wherein R^{22} is independently selected from the group consisting of R^{19}; R^{20}; halogen; CN; OH; oxo (=O), where the ring is at least partially saturated; NH_2; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $N(R^{23})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{23})$- C_{1-6} alkyl; $N(R^{23})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{23})$-C_{1-6} alkyl; $S(O)N(R^{23})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{23})S(O)_2$-C_{1-6} alkyl; and $N(R^{23})S(O)$-C_{1-6} alkyl, wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{19} is selected from the group consisting of phenyl; and naphthyl, wherein R^{19} is optionally substituted with one or more R^{24}, wherein R^{24} is independently selected from the group consisting of halogen; CN; COOH; OH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; 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; $C(O)N(R^{25})$-C_{1-6} alkyl; $S(O)_2N(R^{25})$-C_{1-6} alkyl; $S(O)N(R^{25})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl;

$S(O)$-C_{1-6} alkyl; $N(R^{25})S(O)_2$-C_{1-6} alkyl; and $N(R^{25})S(O)$ -C_{1-6} alkyl, wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{20} is selected from the group consisting of heterocycle; heterobicycle; and C_{3-7} cycloalkyl; wherein R^{20} is optionally substituted with one or more R^{26}, wherein R^{26} is independently selected from the group consisting of halogen; CN; OH; oxo (=O), where the ring is at least partially saturated; NH_2; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $N(R^{27})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{27})$- C_{1-6} alkyl; $N(R^{27})$-$C(O)$-C_{1-6} alkyl; $S(O)_2N(R^{27})$-C_{1-6} alkyl; $S(O)N(R^{27})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; $S(O)$-C_{1-6} alkyl; $N(R^{27})S(O)_2$-C_{1-6} alkyl; and $N(R^{27})S(O)$-C_{1-6} alkyl wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{21}, R^{23}, R^{25}, R^{27} are independently selected from the group consisting of H; and C_{1-6}alkyl, which is optionally substituted with one or more of R^{28}, wherein R^{28} is independently selected from the group consisting of F; Cl and OH;

R^6, R^7 are independently selected from the group consisting of H; $(C(R^{29}R^{30}))_m$-X^1-Z^1; and $(C(R^{31}R^{32}))_n$-X^2-X^3-Z^2, provided that R^6, R^7 are selected so that not both of R^6, R^7 are independently selected from the group consisting of H; CH_3; CH_2CH_3; $CH_2CH_2CH_3$; and $CH(CH_3)_2$;

Optionally R^6, R^7 are independently C_{1-4} alkyl, which is substituted with one or more R^{29a}, wherein R^{29a} is independently selected from the group consisting of R^{29b}; and Z^1, provided that R^6, R^7 are selected so that not both of R^6, R^7 are independently selected from the group consisting of CH_3; CH_2CH_3; $CH_2CH_2CH_3$; and $CH(CH_3)_2$;

R^{29}, R^{29b}, R^{30}, R^{31}, R^{32} are independently selected from the group consisting of H; halogen; CN; OH; NH_2; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O-C_{1-6} alkyl; $N(R^{32a})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{32a})$- C_{1-6} alkyl; $N(R^{32a})$-$C(O)$-C_{1-6} alkyl; $S(O)_2N(R^{32a})$-C_{1-6} alkyl; $S(O)N(R^{32a})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; $S(O)$-C_{1-6} alkyl; $N(R^{32a})S(O)_2$-C_{1-6} alkyl; and $N(R^{32a})S(O)$-C_{1-6} alkyl wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{32a} is selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

Optionally one or more pairs of R^{29}, R^{30}, R^{31}, R^{32} independently selected from the group consisting of R^{29}/R^{30}; and R^{31}/R^{32} form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more R^{32b}, wherein R^{32b} is independently selected from the group consisting of F; Cl; and OH;

m is 0, 1, 2, 3 or 4;

n is 2, 3 or 4;

X^1 is independently selected from the group consisting of a covalent bond; -C_{1-6} alkyl-; -C_{1-6} alkyl-O-; -C_{1-6} alkyl-N(R^{33})-; -C(O)-; -C(O)-C_{1-6} alkyl-; -C(O)-C_{1-6} alkyl-O-; -C(O)-C_{1-6} alkyl-N(R^{33})-; -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^{33})-; -C(O)N(R^{33})-; -C(O)N(R^{33})-C_{1-6} alkyl-; -C(O)N(R^{33})-C_{1-6} alkyl-O-; -C(O)N(R^{33})-C_{1-6} alkyl-N(R^{34})-; -$S(O)_2$-; -S(O)-; -$S(O)_2$-C_{1-6} alkyl-; -S(O)-C_{1-6} alkyl-; -$S(O)_2$-C_{1-6} alkyl-O-; -S(O)-C_{1-6} alkyl-O-; -$S(O)_2$-C_{1-6} alkyl-N(R^{33})-; and -S(O)-C_{1-6} alkyl-N(R^{33})-; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

X^2 is selected from the group consisting of -O-; -S-; -S(O)-; $S(O)_2$-; and -N(R^{35})-;

X^3 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^{36})-; -C(O)-; -C(O)-C_{1-6} alkyl-; -C(O)-C_{1-6} alkyl-O-; -C(O)-C_{1-6} alkyl-N(R^{36})-; -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^{36})-; -C(O)N(R^{36})-; -C(O)N(R^{36})-C_{1-6} alkyl-; -C(O)N(R^{36})-C_{1-6} alkyl-O-; and -C(O)N(R^{36})-C_{1-6} alkyl-N(R^{37})-; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

Optionally X^2-X^3 are independently selected from the group consisting of -N(R^{35})-$S(O)_2$; -N(R^{35})-S(O)-; -N(R^{35})-$S(O)_2$-C_{1-6} alkyl-; -N(R^{35})-S(O)-C_{1-6} alkyl-;

-$N(R^{35})$-$S(O)_2$-C_{1-6} alkyl-O-; -$N(R^{35})$-S(O)-C_{1-6} alkyl-O-; -$N(R^{35})$-$S(O)_2$-C_{1-6} alkyl-$N(R^{36})$-; and -$N(R^{35})$-S(O)-C_{1-6} alkyl-$N(R^{36})$-; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{33}, R^{34}, R^{35}, R^{36}, R^{37} are independently selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

Z^1, Z^2 are independently selected from the group consisting of Z^3; and -$C(R^{37a})Z^{3a}Z^{3b}$;

R^{37a} is selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more F;

Z^3, Z^{3a}, Z^{3b} are independently selected from the group consisting of H; T^1; T^2; C_{1-6} alkyl; C_{1-6} alkyl-T^1; and C_{1-6} alkyl-T^2; wherein each C_{1-6} alkyl is optionally substituted with one or more R^{37b}, wherein R^{37b} is independently selected from the group consisting of halogen; CN; OH; NH_2; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O-C_{1-6} alkyl; $N(R^{37c})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{37c})$- C_{1-6} alkyl; $N(R^{37c})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{37c})$-C_{1-6} alkyl; $S(O)N(R^{37c})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{37c})S(O)_2$-C_{1-6} alkyl; and $N(R^{37c})$S(O)-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

T^1 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T^1 is optionally substituted with one or more R^{38}; wherein R^{38} is independently selected from the group consisting of halogen; CN; R^{39}; COOH; OH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; $COOT^3$; OT^3; ST^3; $C(O)N(R^{40})T^3$; $S(O)_2N(R^{40})T^3$; $S(O)N(R^{40})T^3$ 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^{41}, wherein R^{41} is independently selected from the group consisting of halogen; CN; R^{42}; 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; $C(O)N(R^{43})T^3$; $S(O)_2N(R^{43})T^3$; $S(O)N(R^{43})T^3$; $N(R^{43})T^3$; and T^3;

R^{39} 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^{44})-C_{1-6} alkyl; $S(O)_2N(R^{44})$-C_{1-6} alkyl; S(O)N(R^{44})-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; $N(R^{44})S(O)_2$-C_{1-6} alkyl; and $N(R^{44})$S(O) -C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one more R^{45}, wherein R^{45} is independently selected from the group consisting of F; $COOR^{46}$; C(O)N($R^{46}R^{47}$); $S(O)_2N(R^{46}R^{47})$; OR^{46}; N($R^{46}R^{47}$); T^3; O-T^3; and N(R^{46})-T^3;

R^{42} is selected from the group consisting of C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; N(R^{48})-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; C(O)N(R^{48})- C_{1-6} alkyl; N(R^{48})-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{48})$-C_{1-6} alkyl; S(O) N(R^{48})-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; -$N(R^{48})S(O)_2$-C_{1-6} alkyl; and -N(R^{48})S(O)-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more R^{45}, wherein R^{45} is independently selected from the group consisting of F; $COOR^{49}$; C(O)N($R^{49}R^{50}$); $S(O)_2N(R^{49}R^{50})$; S(O)N($R^{49}R^{50}$); OR^{49}; N($R^{49}R^{50}$); T^3; O-T^3; and N(R^{49})-T^3;

R^{40}, R^{43}, R^{44}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50} 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^{51}, wherein R^{51} is independently selected from the group consisting of halogen; CN; $COOR^{52}$; OR^{52}; C(O)N($R^{52}R^{53}$); $S(O)_2N(R^{52}R^{53})$; 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^{52})- C_{1-6} alkyl; $S(O)_2N(R^{52})$-C_{1-6} alkyl; S(O)N(R^{52})-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O) -C_{1-6} alkyl; $N(R^{52})S(O)_2$-C_{1-6} alkyl; and N(R^{52})S(O)-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one 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^{54}, wherein R^{54} is independently selected from the group consisting of halogen; CN; OR^{55}; oxo (=O), where the ring is at least partially saturated; N($R^{55}R^{56}$); $COOR^{55}$; C(O)N($R^{55}R^{56}$); $S(O)_2N(R^{55}R^{56})$; S(O)N($R^{55}R^{56}$); C_{1-6} alkyl; O-C_{1-6} alkyl;

S-C_{1-6} alkyl; N(R^{55})-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; C(O)N(R^{55})- C_{1-6} alkyl; N(R^{55})-C(O)-C_{1-6} alkyl; $S(O)_2$N(R^{55})-C_{1-6} alkyl; S(O)N(R^{55})-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; N(R^{55})$S(O)_2$-C_{1-6} alkyl; and N(R^{55})S(O)-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one more halogen selected from the group consisting of F; and Cl;

R^{52}, R^{53}, R^{55}, R^{56}, are independently selected from the group consisting of H; and C_{1-6} alkyl.

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≡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≡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.

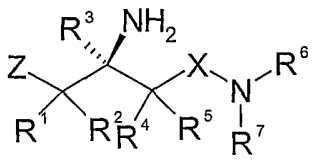
"C_{3-7} Cycloalkyl" or "C_{3-7} Cycloalkyl ring" means a cyclic alkyl chain having 3 - 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl. Each hydrogen of a cycloalkyl carbon may be replaced by a substituent.

"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 sulfur (including -S(O)-, -$S(O)_2$-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a heterocycle are furan, thiophene, pyrrole, pyrroline, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, oxazoline, isoxazole, isoxazoline, thiazole, thiazoline, isothiazole, isothiazoline, thiadiazole, thiadiazoline, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, imidazolidine, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, thiadiazolidine, sulfolane, pyran, dihydropyran, tetrahydropyran, imidazolidine, pyridine, pyridazine, pyrazine, pyrimidine, piperazine, piperidine, morpholine, tetrazole, triazole, triazolidine, tetrazolidine, azepine or homopiperazine.

"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-R^7 and X 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 substituents Z, R^1-R^7 and X of the formula (I) or (Ia) independently from each other have the following meaning. Hence, one or more of the substituents Z, R^1-R^7 and X can have the preferred or more preferred meanings given below.

Z is as defined above. Preferably, Z is phenyl or heterocycle. When Z is a heterocycle, it is preferably an aromatic heterocycle.

Preferably, Z is optionally substituted with 1, 2 or 3, in one embodiment 1 or 2, R^8, which are the same or different. Preferably, they are the same.

R^8 is as defined above. Preferably, R^8 is selected from the group consisting of Cl; F; CN; CH_3; and OCH_3, more preferably Cl, F or CN, most preferably F.

In a more preferred embodiment Z is 2-Fluoro-phenyl. In another preferred embodiment Z is 2,4,5-Trifluoro-phenyl.

R^1, R^4 are independently as defined above. Preferably, R^1, R^4 are independently selected from the group consisting of H; F; OH; CH_3; and OCH_3, more preferably H or F.

R^2, R^5 are independently as defined above. Preferably, R^2, R^5 are independently selected from the group consisting of H; F; and CH_3, more preferably H or F.

R^1, R^2, R^4, R^5 are more preferred H.

R^3 is as defined above. Preferably, R^3 is H.

X is as defined above. Preferably, X is C(O). In another embodiment, X is preferably $S(O)_2$.

R^6 is as defined above. R^6 is preferably selected from the group consisting of H, C_{1-4} alkyl and C_{3-7} cycloalkyl, more preferably H, CH_3 and cyclopropyl, most preferably H and CH_3.

In one embodiment, R^6 is preferably $CH(R^{29a})_2$; CHR^{29a}-CH_2R^{29a}; CH_2-$CH(R^{29a})_2$; CH_2-CHR^{29a}-CH_2R^{29a}; and CH_2-CH_2-$CH(R^{29a})_2$. In this embodiment, both R^{29a} are preferably different, wherein one R^{29a} is R^{29b} and the other R^{29a} is Z^1; wherein Z^1 is preferably selected from T^2. Preferred embodiments for R^{29b} and T^2 are as set forth below. Most preferably, T^2 is 5- or 6-membered heterocycle, preferably a saturated aromatic heterocycle containing preferably at least one N and optionally an O. Most preferably Z^2 is pyridyl or morpholinyl.

X^1 is as defined above. Preferably, X^1 is a covalent bond.

m is as defined above. Preferably, m is 0, 1, 2 or 3, more preferably 0 or 1.

R^7 is as defined above. Preferably, R^7 is Z^1. In this case, Z^1 is preferably T^2, wherein T^2 is as defined above, preferably selected from the group consisting of C_{3-7} cycloalkyl; indanyl; tetralinyl; decalinyl; and heterobicycle, more preferably indanyl; tetralinyl; and decalinyl; wherein T^2 is optionally substituted with one or more R^{41}. It is preferred that T^2 is unsubstituted or substituted with one R^{41}. R^{41} is as defined above, preferably halogen, methyl, O-methyl or OH, most preferred is OH.

Preferably, R^7 is C_{1-4} alkyl, substituted with 1-4, i.e. 1, 2, 3 or 4, preferably 1 or 2, R^{29a}, which are the same or different.

R^7 is more preferred selected from the group consisting of $CH(R^{29a})_2$; CHR^{29a}-CH_2R^{29a}; CH_2-$CH(R^{29a})_2$; CH_2-CHR^{29a}-CH_2R^{29a}; and CH_2-CH_2-$CH(R^{29a})_2$. In one embodiment, R^7 is selected from the group consisting of CHR^{29a}-$CH(CH_3)_2$.

In one embodiment, R^7 is $(C(R^{31}R^{32}))_n$-X^2-X^3-Z^2. In this embodiment, R^{31} and R^{32} are preferably both H. Integer n is preferably 1 or 2, more preferably 1. X^2 is preferably NH or O, more preferably O. X^3 is preferably a covalent bond, CH_2, or C(O), more preferably C(O). Z^2 is preferably T^2, more preferably a 5- or 6-membered heterocycle, preferably an aromatic heterocycle containing preferably at least one N. Most preferably Z^2 is pyridyl.

R^{29a} is as defined above. Preferably, R^{29a} is selected from the group consisting of R^{29b}; and Z^1; wherein R^{29b} is preferably selected from the group consisting of H, halogen, $N(R^{32a})$-C_{1-6} alkyl, NH_2, and C_{1-6} alkyl, more preferably H; F; Cl; NH_2; $NHCH_3$; $N(CH_3)_2$; CH_3; and C_2H_5. Most preferably, R^{29b} is selected from the group consisting of H; $N(CH_3)_2$ and CH_3.

Preferably, R^{29a} is selected from the group consisting of R^{29b}; and Z^1; wherein Z^1 is selected from the group consisting of T^1; and T^2.

In one embodiment, two R^{29a} are present and both R^{29a} are preferably different, wherein one R^{29a} is R^{29b} and the other R^{29a} is Z^1; wherein Z^1 is preferably selected from the group consisting of T^1 and T^2.

In one embodiment, two R^{29a} are present and both R^{29a} are preferably the same or different, more preferably different, and are Z^1; wherein Z^1 is selected from the group consisting of T^1 and T^2. In this embodiment, it is preferred that R^7 is selected from the group consisting of $CH(R^{29a})_2$; CHR^{29a}-CH_2R^{29a}; CH_2-CHR^{29a}-CH_2R^{29a}; and CH_2-CH_2-$CH(R^{29a})_2$, more preferably CH_2-$CH(R^{29a})_2$ and CH_2-CHR^{29a}-CH_2R^{29a}. It is particularly preferred that both of R^{29a} are selected from T^1; or that one R^{29a} is selected from T^1 and the other one R^{29a} is selected from T^2. Specifically in the case of CH_2-CHR^{29a}-CH_2R^{29a}, CH_2-CHT^1-CH_2T^2 is preferred.

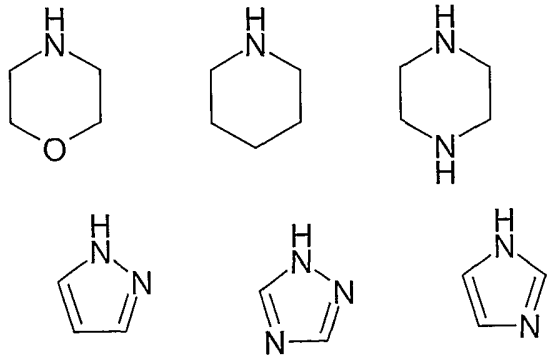
T^1 is as defined above. Preferably, T^1 is phenyl; wherein T^1 is optionally substituted with 1-3, i.e. 1, 2 or 3, more preferably 1 or 2, most preferably 1, R^{38}, which are the same or different.

R^{38} is as defined above. Preferably, R^{38} is independently selected from the group consisting of halogen, CN, SO_2NH_2, $CONH_2$, C_{1-6} alkyl optionally substituted with 1, 2

or 3 R^{45}; O-C_{1-6} alkyl optionally substituted with 1 R^{45}; S-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; S(O)$_2$-C_{1-6} alkyl; CONHT^3; CONH-C_{1-6} alkyl optionally substituted with 1 R^{45}; T^3; and O-T^3.

More preferably, R^{38} is independently selected from the group consisting of
halogen; CN; SO_2NH_2; $CONH_2$;
C_{1-4} alkyl optionally substituted with 1, 2 or 3 F;
O-C_{1-6} alkyl optionally substituted with 1 or 2 F or N($R^{49}R^{50}$);
S-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; S(O)$_2$-C_{1-6} alkyl; CONH-C_{3-7} cycloalkyl; CONH-heterocyclyl; CONH-C_{1-4} alkyl optionally substituted with 1 phenyl optionally substituted with 1 or 2 R^{51};
phenyl optionally substituted with 1 or 2 R^{51};
heterocyclyl;
O-heterocyclyl; and
O-phenyl optionally substituted with 1 or 2 R^{51}.

It is most preferred that R^{38} is independently selected from the group consisting of F; Cl; CN; CH_3; C_2H_5; $CH_2CH_2CH_3$; $CH(CH_3)_2$; CF_3; O-CH_3; O-C_2H_5; S-CH_3; S(O)-CH_3; S(O)$_2$-CH_3; SO_2NH_2; $CONH_2$;
O-ethyl substituted with 1 N(Me)$_2$;
O-methyl substituted with 2 F;
CONH-cyclopropyl; CONH-pyridyl;
CONH-C_{1-4} alkyl substituted with 1 phenyl optionally substituted with 1 or 2 F or SO_2NH_2;
phenyl;
O-pyrimidyl; O-pyrazinyl;



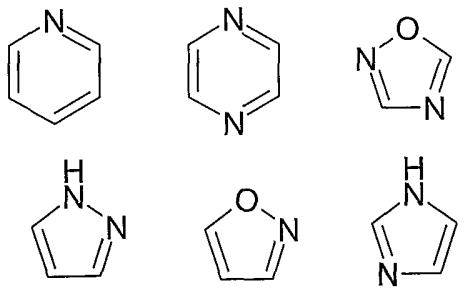
and
O-phenyl optionally substituted with 1 R^{51}.

In one embodiment, R^{38} is independently selected from the group consisting of F; Cl; CN; CH_3; C_2H_5; $CH_2CH_2CH_3$; $CH(CH_3)_2$; CF_3; O-CH_3; O-C_2H_5; S-CH_3; SO_2NH_2; T^3; and O-T^3.

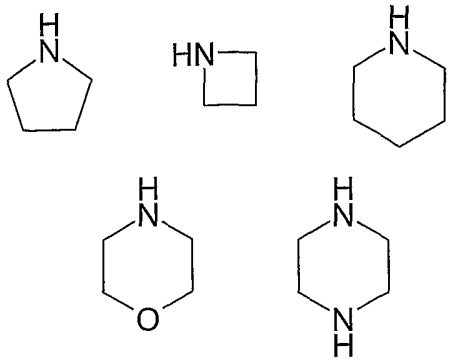
In particular in the case of the presence of two R^{29a} whereby one R^{29a} is selected from T^1 and the other one R^{29a} is selected from T^2, T^1 is preferably phenyl; wherein T^1 is unsubstituted or substituted with 1-3, i.e. 1, 2 or 3, more preferably 1 or 2, most preferably 1, R^{38} selected from F; Cl; CN; CH_3; C_2H_5; $CH_2CH_2CH_3$; $CH(CH_3)_2$; CF_3; O-CH_3; O-C_2H_5; S-CH_3; SO_2NH_2; T^3; and O-T^3, more preferably F; Cl; CN; CH_3, most preferably F or Cl.

T^2 is as defined above. Preferably, T^2 is selected from the group consisting of indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle; more preferably
- tetralinyl;
- a 4-, 5- or 6-membered, preferably a 5- or 6-membered, heterocycle containing at least one heteroatom, preferably N or O, whereby the heterocycle can be selected from the group of

(a) aromatic, preferably 5- or 6-membered ring and preferably containing at least one heteroatom selected from N, more preferably containing 1 or 2 N and optionally an O, most preferably selected from the group

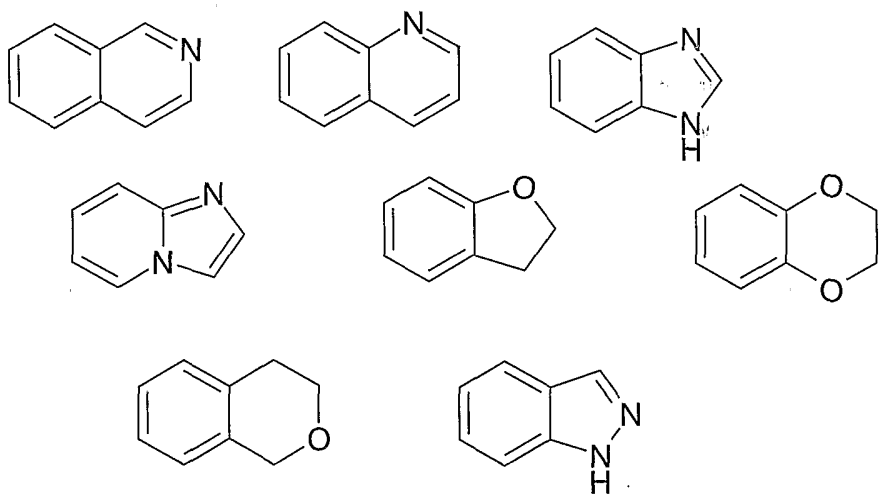


(b) saturated, preferably 4-, 5- or 6-membered ring and preferably containing at least one heteroatom selected from N, more preferably containing 1 or 2 N and optionally an O, most preferably selected from the group

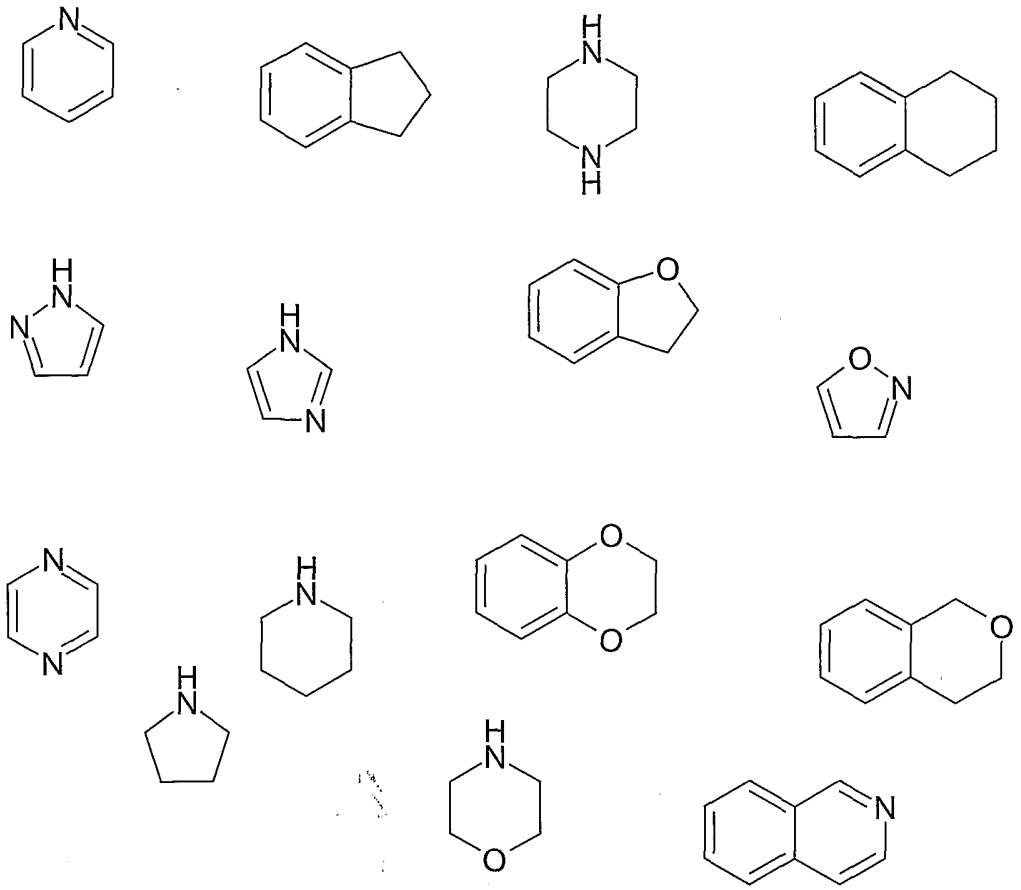


or

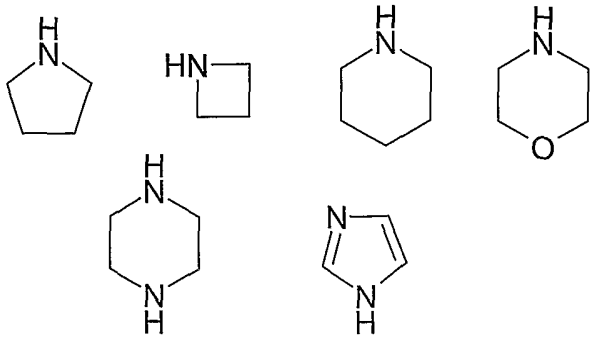
- a 9- or 10-membered heterobicycle containing at least one heteroatom, preferably N or O, and optionally a further heteroatom selected from N and O, most preferably selected from the group



In one embodiment, T^2 is selected from the group consisting of



In particular in the case of the presence of two R^{29a} whereby one R^{29a} is selected from T^1 and the other one R^{29a} is selected from T^2 or both R^{29a} are T^2, T^2 is preferably a N-containing heterocycle, preferably containing 4, 5 or 6 ring members and optionally containing a further heteroatom selected from N or O. Most preferably T^2 is selected from the group



T^2 is optionally substituted with 1, 2 or 3, preferably 1-2 R^{41}, which are the same or different. Preferably R^{41} is independently selected from the group consisting of halogen; CN; OH; C_{1-6} alkyl optionally substituted with 1, 2 or 3 F; O-C_{1-6} alkyl substituted with 1, 2 or 3 F; NH-C(O)-C_{1-6} alkyl; and T^3. More preferably R^{41} is selected from the group consisting of

F; Cl; OH;

C_{1-4} alkyl optionally substituted with 1, 2 or 3 F;

NH-C(O)-C_{1-4} alkyl;

T^4 optionally substituted with 1 or 2, more preferably 1, R^{51}, whereby R^{51} is as defined herein; or

C_{3-7} cycloalkyl.

Most preferably R^{41} is selected from the group consisting of

F; Cl;

C_{1-2} alkyl optionally substituted with 3 F;

NH-C(O)-C_{1-2} alkyl;

phenyl optionally substituted with F; Cl; CH_3; C_2H_5; O-CH_3; or O-C_2H_5, or cyclopropyl.

R^{41} is as defined above. Preferably, R^{41} is selected from the group consisting of OH; CH_3; and T^3;

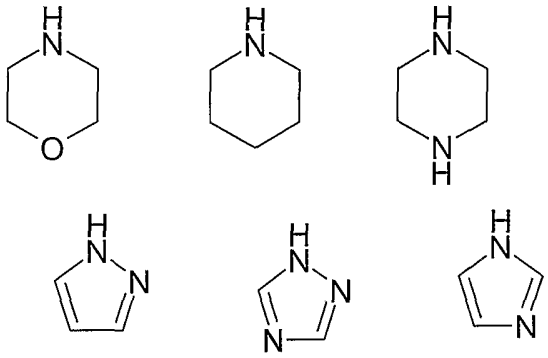
T^3 is as defined above. Preferably, T^3 is T^4.

T^4 is as defined above. Preferably, T^4 is phenyl, wherein T^4 is optionally substituted with 1-3 R^{51}, which are the same or different.

R^{51} is as defined above. Preferably, R^{51} is independently selected from the group consisting of F; Cl; CH_3; C_2H_5; $CH_2CH_2CH_3$; $CH(CH_3)_2$; CF_3; O-CH_3; O-C_2H_5; S-CH_3; and SO_2NH_2.

Preferably, T^3 is T^5.

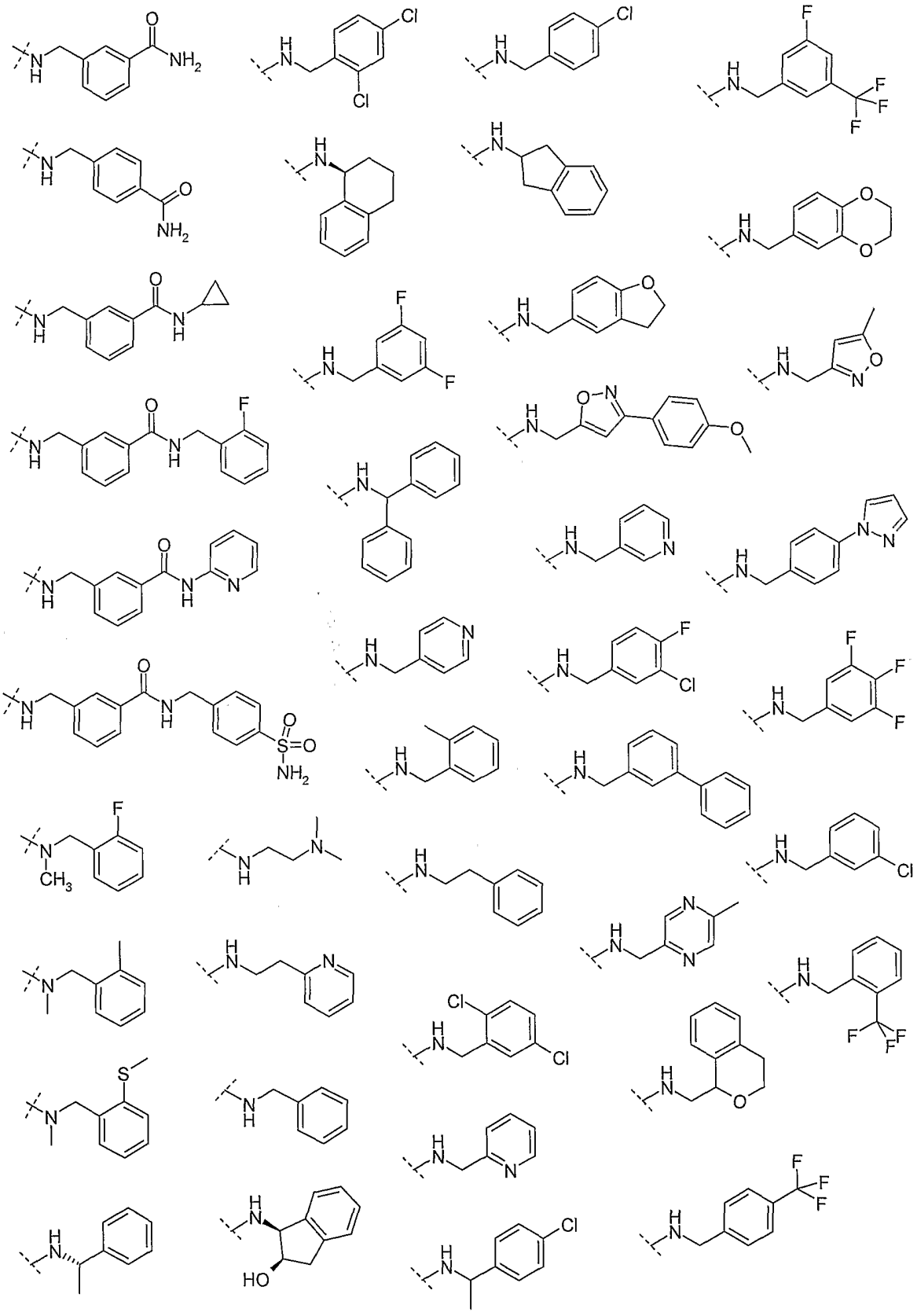
T^5 is as defined above. Preferably, T^5 is heterocycle, more preferably a 5- or 6-membered heterocycle. The heterocycle may be saturated or aromatic. The heterocycle may contain at least one N. Preferred examples of the heterocycle include:

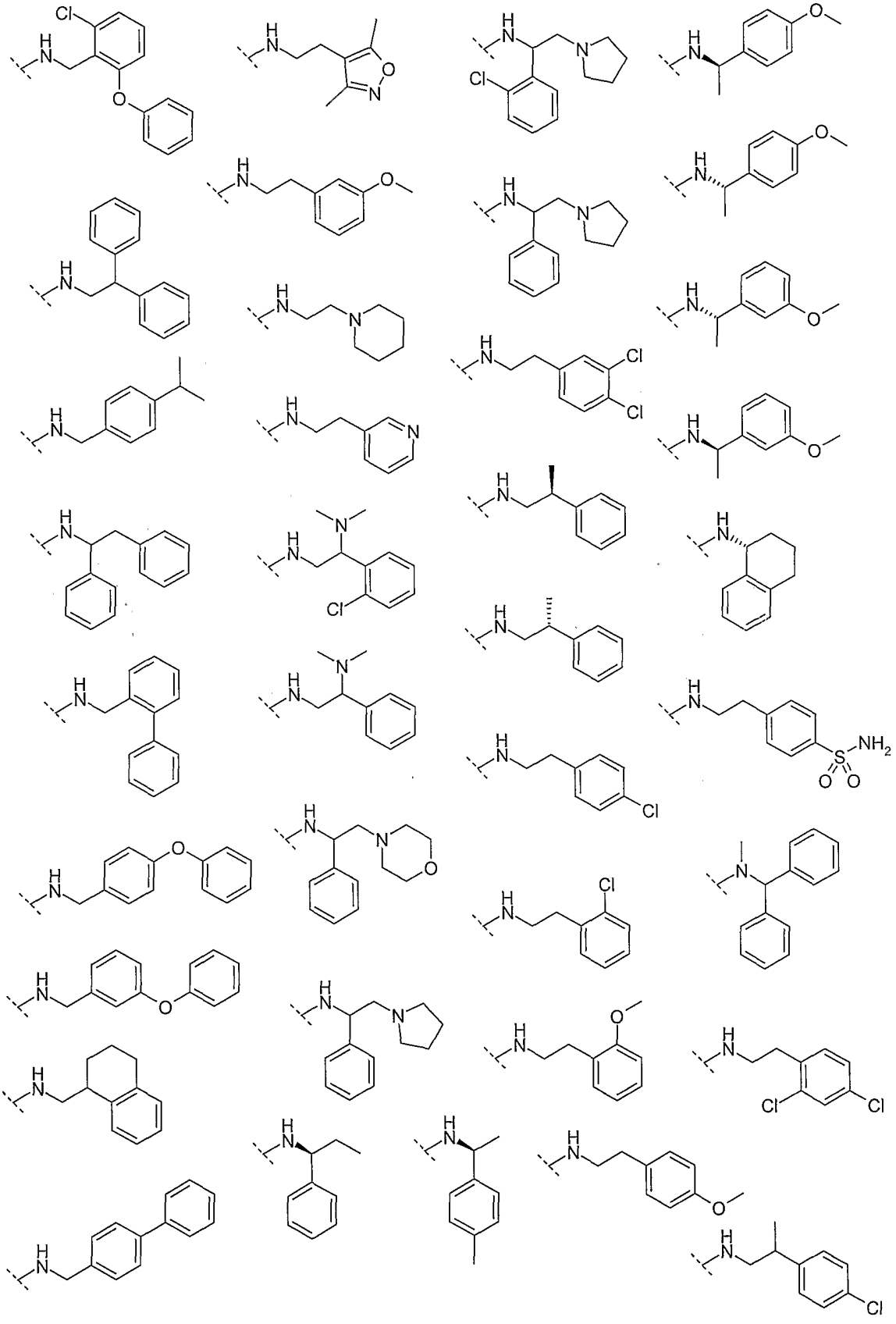


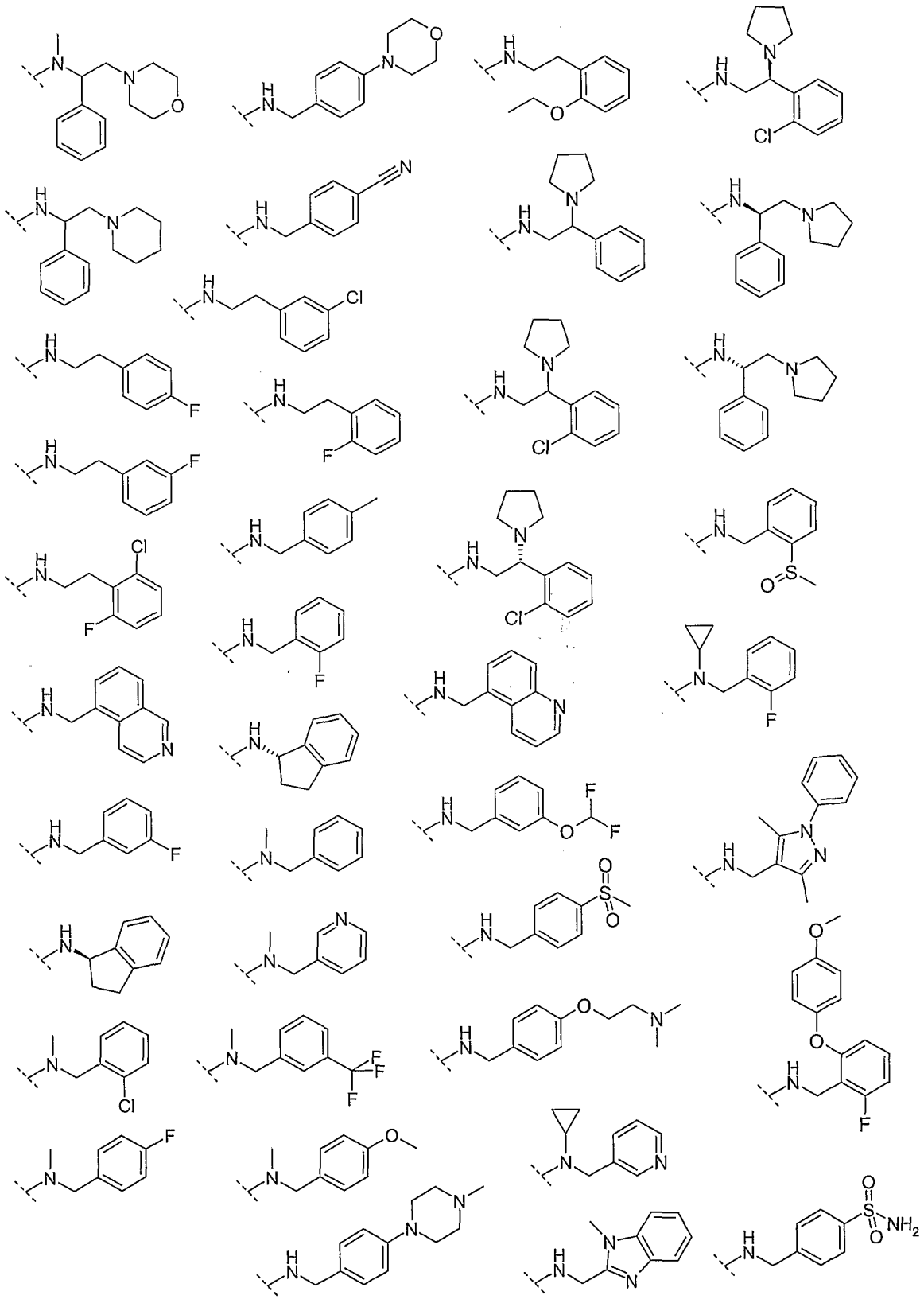
T^5 is optionally substituted with 1-2 R^{54}, which are the same or different.

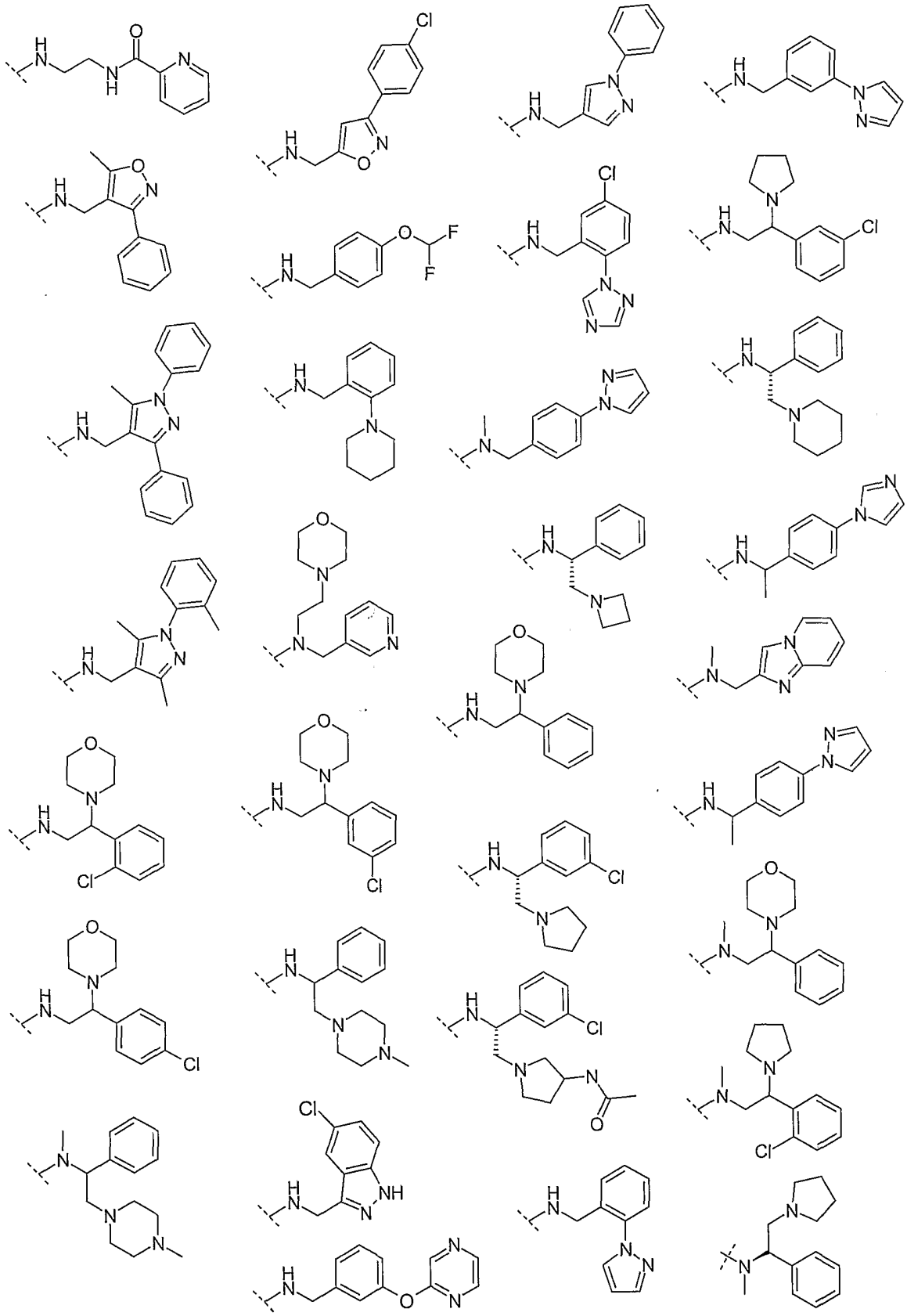
R^{54} is as defined above. Preferably, R^{54} is selected from the group consisting of OH; and CH_3.

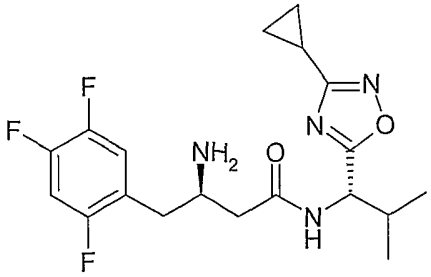
Particularly preferred definitions for $-NR^6R^7$ are as follows:

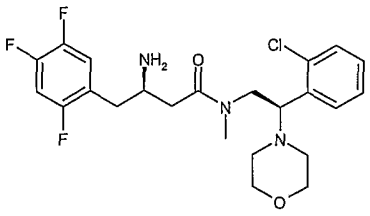


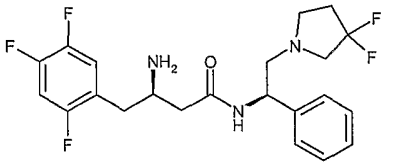


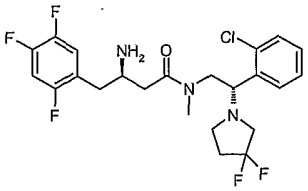


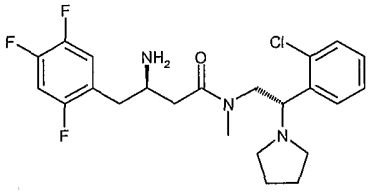


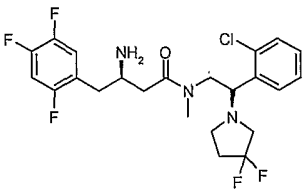


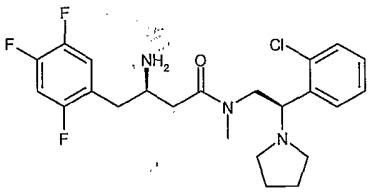


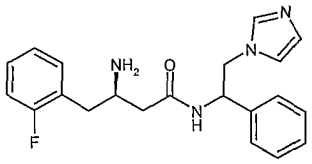


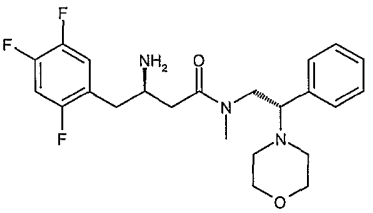


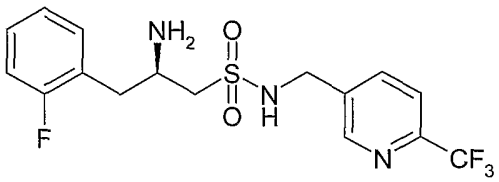


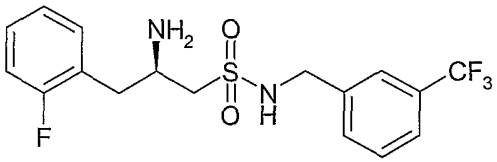


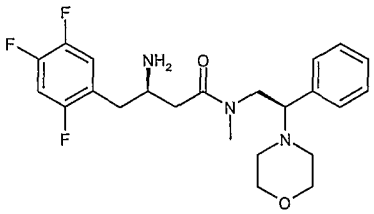


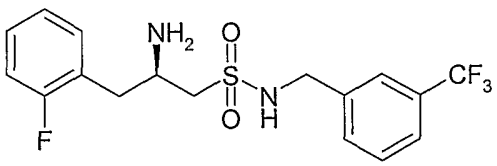


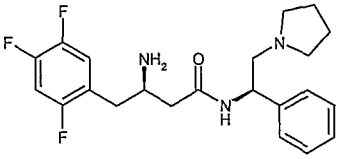


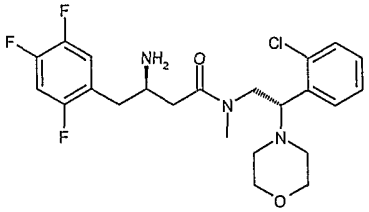












Compounds of the formula (I) or (Ia) in which some or all of the above-mentioned groups have the preferred or more preferred meanings are also an object of the present invention.

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, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the formula (I) 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; 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; anxiety; depression; 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-lB (PTP-1B) inhibitors; insulin and insulin mimetics; sulfonylureas 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; 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.

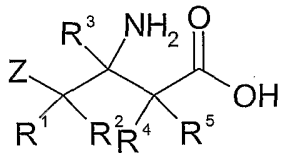
The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. 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 (II)



(II)

and substituted amine intermediates such as those of formula (III)

$HN(R^6R^7)$ (III),

using standard peptide coupling conditions.

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

ABBREVIATIONS

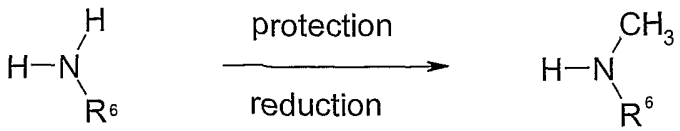
Designation	
Boc (or BOC)	*tert*-Butoxycarbonyl
DCM	Dichloromethane
DIEA	Diisopropylethylamine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
Et_3N	Triethylamine
h	Hour
HATU	O-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate

HBTU	O-(7-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HOBt	1-Hydroxybenzotriazole
HPLC	High pressure liquid chromatography
min	Minutes
MTP	Microtiter plate
PG	Protecting group
Pol	Polymeric support
rt	Retention time
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

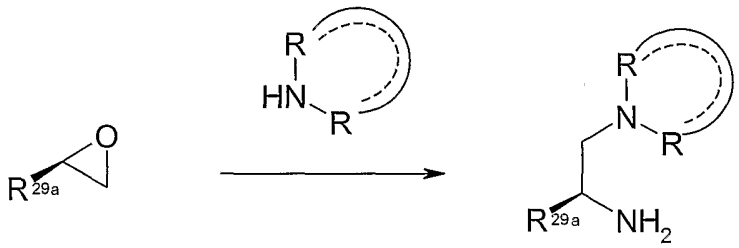
Available starting materials may be amines having the formula (III), which may be purchased from commercially available sources such as ABCR, Array, Astatech, Sigma-Aldrich, Fluka, or be synthesized by one skilled in the art. Common nucleophilic substitution reactions between compounds containing a suitable leaving group (e.g. halogenide, mesylate, tosylate, epoxides) and nucleophiles (e.g. amines) may be employed. The conversion of diverse functional groups may allow the synthesis of various amines, e.g. conversion of esters into acids, alcohols or amides intermediates; reduction of amides, nitriles or azides to amines; also novel carbon-nitrogen palladium-catalyzed coupling reactions with suitable functionalized starting materials. For the introduction of changes in the carbon chain attached to the nitrogen atom or for the synthesis of diverse (hetero)aryl derivatives, it may be possible to make use of diverse carbon-carbon coupling reactions, e.g. transition-metal catalyzed reactions, conventional techniques for ring closure, formylation of (hetero)aryls.

Schemes A through G outline general procedures for the synthesis of some compounds (III) described below. Unless otherwise indicated in the schemes, the variables have the same meaning as described above. The variable cy is selected from a group of cyclic ring systems such as aryles, heterocylces and heterobicycles.

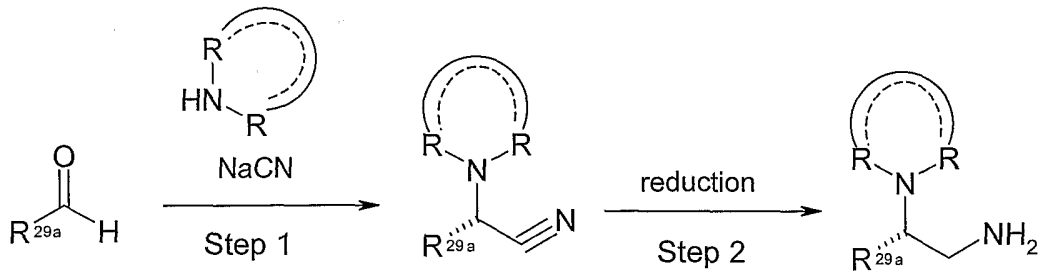
Scheme A



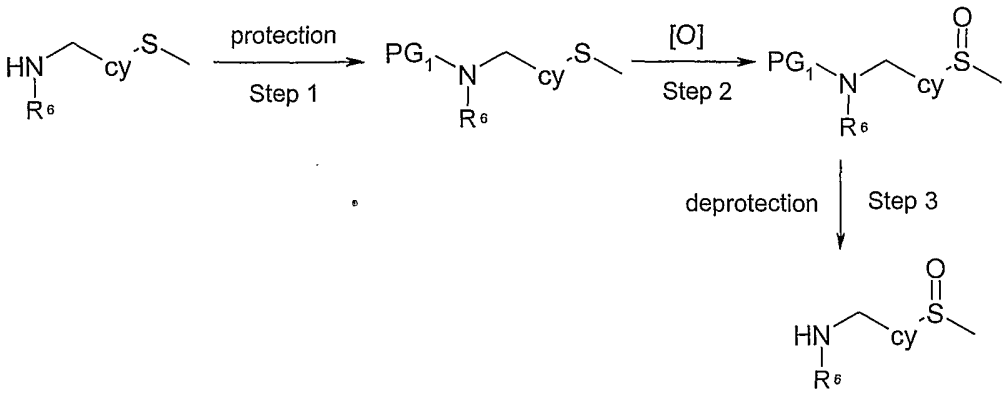
Scheme B



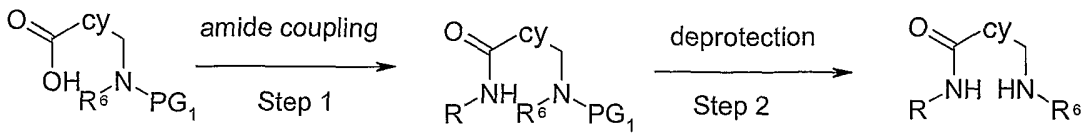
Scheme C



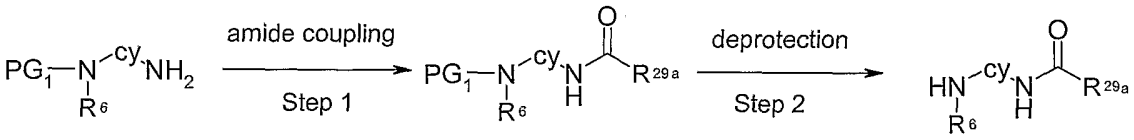
Scheme D



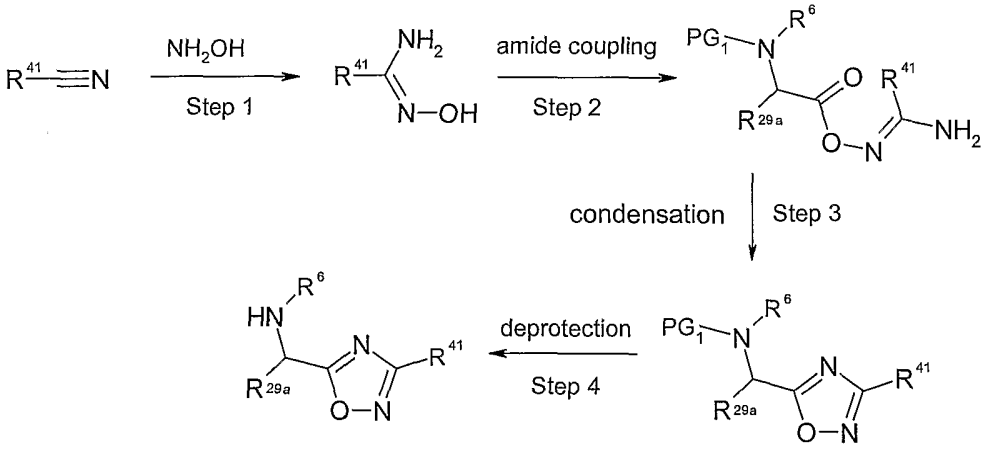
Scheme E



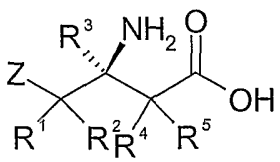
Scheme F



Scheme G



Enantiomerically pure beta amino acids having the formula (IIa)



(IIa)

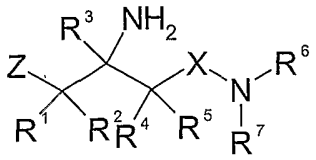
may be commercially available, known in the literature or may be conveniently synthesized using one of the methods already published and reviewed in e.g., Cole, *Tetrahedron*, 32, 9517 (1994), Juaristi et al., *Aldrichimica Acta*, 27, 3, 1994, or Juaristi, *Enantioselective Synthesis of β-Amino Acids*,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

Unless otherwise noted, all nonaqueous 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 or XTerra MS C18, 3.5 µm, 2.1 x 100 mm 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-dimethylsulfoxide as solvent; chemical shifts are reported in ppm relative to tetramethylsilane. Analytical LC/MS was performed using: a) Reprosil-Pur ODS 3.5 µM, 1 x 60 mm column with a linear gradient acetonitrile in water (0.1% TFA) at a flow rate of 250 µL/min; b) XTerra MS C18, 3.5 µm, 2.1 * 100 mm, linear gradient with acetonitrile in water (0.1% HCOOH) at a flow rate of 250 µL/min; retention times are given in minutes. Methods are:
(I) linear gradient from 5% to 95% acetonitrile in water (0.1% TFA); 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, 5 min. linear gradient; (II) idem but 3 min. linear gradient; (III) linear gradient from 5% to 95% acetonitrile in water (0.1% TFA); 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, 5 min. linear gradient; (IV) idem but 10 min. linear gradient; (V) linear gradient from 1% to 30% acetonitrile in water (0.1% TFA); (VI) linear gradient from 1% to 60% acetonitrile in water (0.1% TFA).

General procedure for making compounds of the invention

In general, compounds having the structure (I)

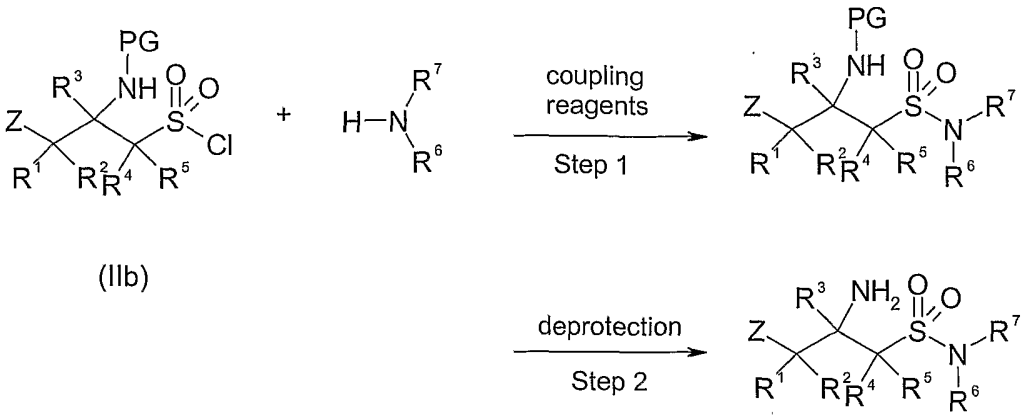


(I)

wherein the variables have the above described meanings, may be prepared in the case of X = C(O) by standard peptide coupling conditions. For example, it may be possible to use 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) hydrochloride 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) or O-(7-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) in the presence of a base, in solvents such as methylene chloride, *N,N*-dimethylformamide, or dimethylsulfoxide. In the case of X = $CR^{13}R^{14}$ by reductive amination conditions, for example, it may be possible to use sodium triacetoxyborohydride in acidic media (such as in solvents like methanol or dichloromethane containing acetic acid) in combination with a suitable amine and suitable aldehyde. In the case of X = $CR^{13}R^{14}$ by reduction of an amide carbonyl C(O) group to the corresponding carbon, the amide, prepared as described above, may be reduced with lithium aluminiumhydride in solvents such as tetrahydrofuran. In the case of X = $CR^{13}R^{14}$ by displacement of a suitable leaving group by a suitable amine, the leaving group may be a tosylate, halide, triflate or mesylate reacting with the amine in solvents such as dichloromethane, acetonitrile or *N,N*-dimethylformamide, in the presence of a base such as triethylamine or 2,6-lutidine, for example. In the case of X = $S(O)_2$ this may be prepared by coupling of a suitably prepared sulfonyl chloride with a suitable amine following standard sulfonylation conditions, in solvents such as dichloromethane in the presence of a base such as triethylamine or 2,6-lutidine. In the case of X = S(O) by coupling of a suitable amine with a suitable sulfinyl halide in solvents such as diethylether.

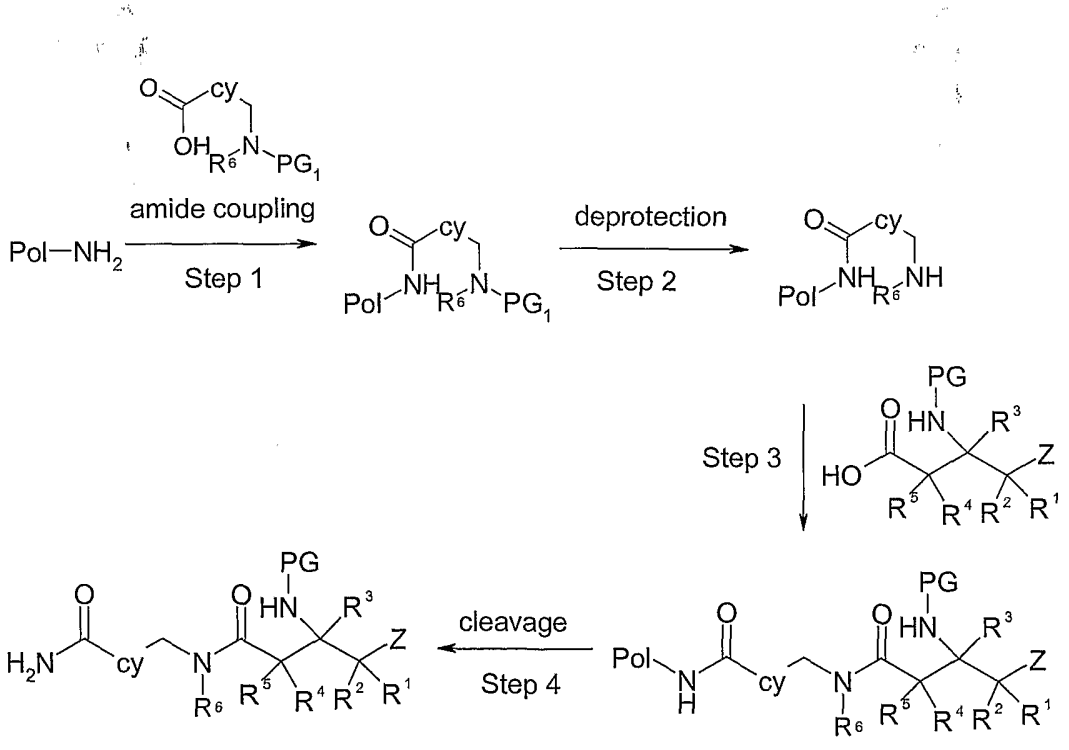
Scheme H outlines a procedure for using the amines of formula (III) and sulphonic acid chlorides of formula (IIb) to synthesize preferred compounds that are embodiments of the invention.

Scheme H



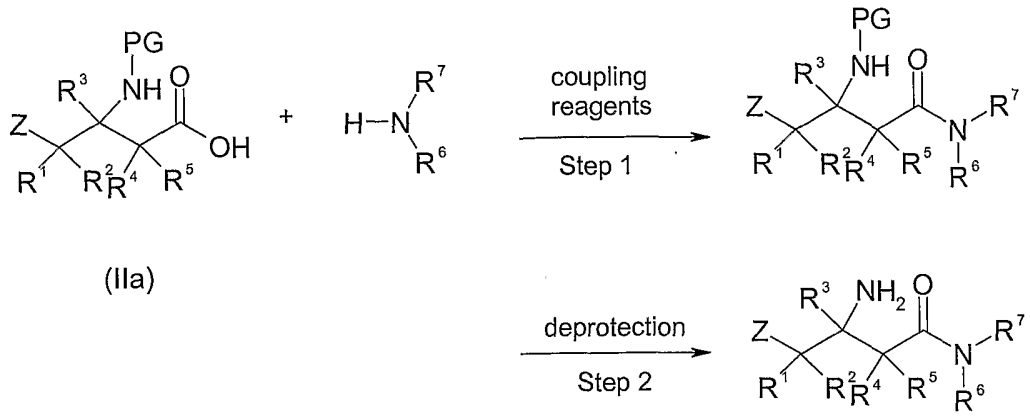
Scheme I outlines a procedure for using solid phase synthesis to synthesize preferred compounds that are embodiments of the invention.

Scheme I



Scheme J outlines a procedure for using the amines of formula (III) and acids of formula (IIa) to synthesize preferred compounds that are embodiments of the invention.

Scheme J



(IIa)

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.

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

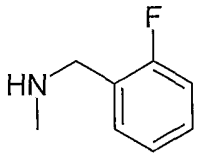
Compounds may be prepared by other means, however, and the suggested starting materials and procedures described below are exemplary only and should not be considered as limiting the scope of the invention.

EXAMPLES

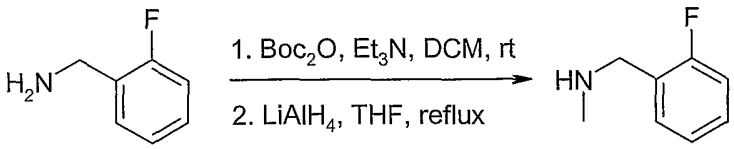
The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

PREPARATIONS

Example 1



Procedure for making an intermediate according to Scheme A.



(2-Fluoro-benzyl)-methyl amine.

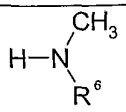
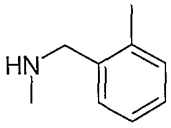
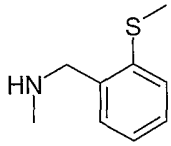
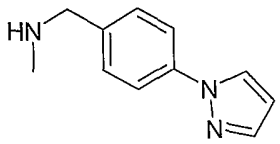
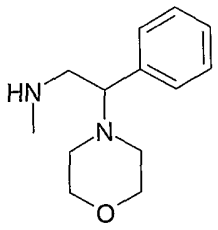
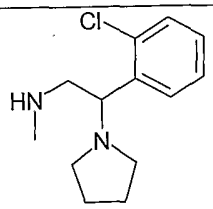
To a solution of 300 mg (2.40 mmol) of 2-fluorobenzylamine, 29.3 mg (0.24 mmol) of 4-dimethylaminopyridine and 342 µl (2.64 mmol) of triethylamine in 3 mL of dichloromethane is added 628 mg (2.88 mmol) of di(*tert*-butoxycarbonyl) in 3 mL of dichloromethane at 0 °C. The reaction is allowed to react for 72 h and solvents are removed under reduced pressure. The crude product is dissolved in 5 mL of 1N hydrochloric acid solution and extracted three times with ethyl acetate. The organic phase is separated and washed with saturated sodium bicarbonate solution and brine and dried with sodium sulphate. Removal of the solvent affords (2-fluoro-benzyl)-carbamic acid *tert*-butyl ester, which is taken directly to the next step.

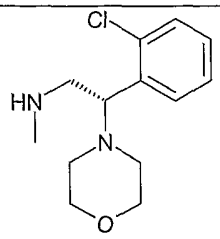
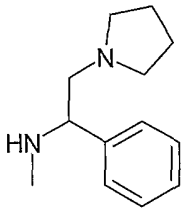
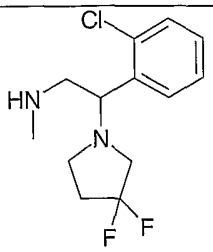
To a solution of 250 mg (1.11 mmol) of the carbamic ester dissolved in 1 mL of tetrahydrofuran is added 1.66 mL of a 1M lithium aluminiumhydride solution in tetrahydrofuran. The reaction mixture is stirred at room temperature until gas evolution has ceased and is further heated at reflux temperature for 3 h. After cooling to room temperature, 1N hydrochloric acid solution is added and the aqueous phase is extracted with dichloromethane. The aqueous phase is separated, a saturated sodium bicarbonate solution is added until pH reaches 7-8 and dichloromethane is added. The organic layer is extracted with brine and water, dried with sodium sulphate and concentrated under vacuum to obtain the title compound.

LC/MS (III) rt 1.52, m/z 140 $[M+H]^+$.

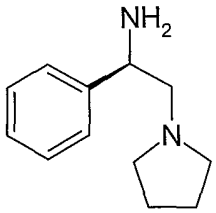
The compounds in Table 1 are synthesized according to the procedure shown for example **1**.

Table 1

Ex.		LC/MS	NMR
2		LC/MS (IIIa) rt 1.67, m/z 177 $[M+Na+H]^+$.	
3		LC/MS (Ia) rt 1.76, m/z 168 $[M+H]^+$.	
4		LC/MS (IIIa) rt 1.69, m/z 188 $[M+H]^+$.	
5		LC/MS (Ia) rt 1.78, m/z 221 $[M+H]^+$.	
6		LC/MS (IIIa) rt 1.97, m/z 239 $[M+H]^+$.	^{1}H NMR (d6-DMSO, 300 MHz) δ = 1.61 (m, 4H), 2.43-2.50 (m, 4H), 2.5 (s, 3H), 3.05 (dd, 1H, J = 5.1 Hz, J = 12.3 Hz), 3.56 (dd, 1H, J = 8.7 Hz, J = 12.6 Hz), 4.66 (m,1H), 7.34- 7.47 (m, 4H).

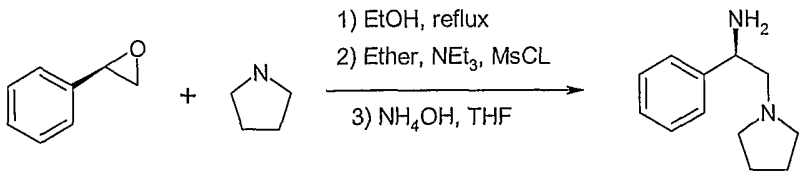
7		LC/MS (VIa) rt 3.28, m/z 255 $[M+H]^+$.	
8		LC/MS (VIa) rt 0.21, m/z 205 $[M+H]^+$.	
9		LC/MS (Va) rt 4.22, m/z 275 $[M+H]^+$.	^{1}H NMR (d6-DMSO, 300 MHz) δ = 2.12-2.22 (m, 2H), 2.55 (s, 3H), 2.61-2.70 (m, 2H), 2.75-2.88 (m, 2H), 2.92-3.00 (m, 2H), 4.05 (m,1H), 7.33-7.46 (m, 4H).

Example 10



Procedure for making an intermediate according to Scheme B.

Step 1



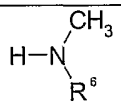
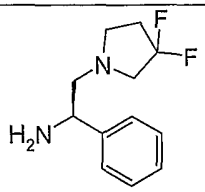
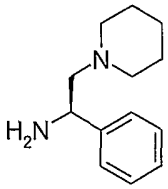
(*R*)-1-Phenyl-2-pyrrolidin-1-yl-ethylamine. (For synthesis, see *Tetrahedron Lett.* **1996**; *37*; 5619-5622.)

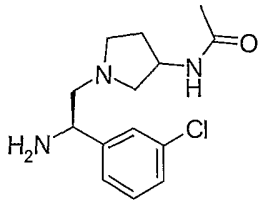
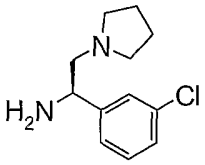
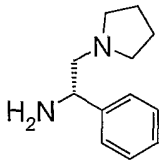
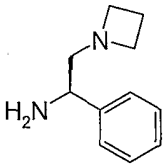
A mixture of 100.0 mg (0.83 mmol) of *(R)*-styrene oxide and 94.7 mg (1.33 mmol) of pyrrolidine are dissolved in 5 mL ethanol and heated under reflux for 3 h. After cooling, the solvent is evaporated under reduced pressure to give the crude product which is thoroughly dried for at least 1h under vacuum. Under nitrogen, this crude product is dissolved in 5 mL ether, 255 µL (2.5 mmol) triethylamine is added and the solution is cooled to 0°C. Then, 97 µL (1.25 mmol) methansulfonyl chloride is added dropwise. After being allowed to warm to room temperature, 2 mL ammonium hydroxide and 4 mL THF are added and the resulting reaction mixture is vigorously stirred for 16 h. The solvent is evaporated under reduced pressure and the crude mixture is purified by flash chromatography on silica gel with dichloromethane/methanol (10% ammonium hydroxide).

^{1}H NMR (d6-DMSO, 200 MHz) δ = 1.67 (m, 4H), 2.28- 2.60 (m, 6H), 3.93-3.97 (m,1H), 7.14-7.34 (m, 5H). LC/MS (VIa) rt 0.26, m/z 191 $[M+H]^+$.

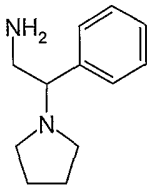
The compounds in Table 2 are synthesized according to the procedure shown for example **10**.

Table 2

Ex.		LC/MS	NMR
11		LC/MS (Ia) rt 1.87, m/z 227 $[M+H]^+$.	
12		LC/MS (Ia) rt 1.55, m/z 206 $[M+H]^+$.	^{1}H NMR (d6-DMSO, 300 MHz) δ = 1.49 (m, 4H), 1.72 (m, 8H), 3.51-3.73 (m,2H), 4.91-4.93 (m, 1H), 7.14-7.56 (m, 5H).

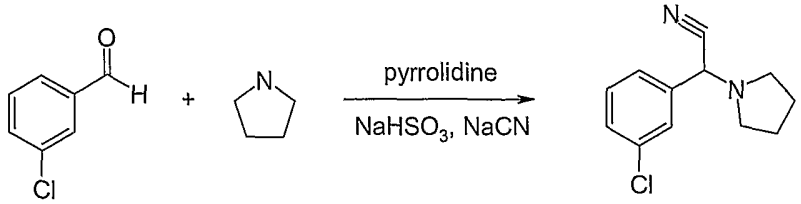
13		LC/MS (Ia) rt 1.80, m/z 283 $[M+H]^+$.	
14		LC/MS (Ia) rt 1.55, m/z 225 $[M+H]^+$.	
15		LC/MS (Va) rt 0.24, m/z 191 $[M+H]^+$.	^{1}H NMR (d6-DMSO, 200 MHz) δ = 1.67 (m, 4H), 2.28-2.60 (m, 6H), 3.93-3.97 (m,1H), 7.14-7.34 (m, 5H).
16		LC/MS (Ia) rt 0.32, m/z 177 $[M+H]^+$.	

Example 17



Procedure for making an intermediate according to Scheme C.

Step 1

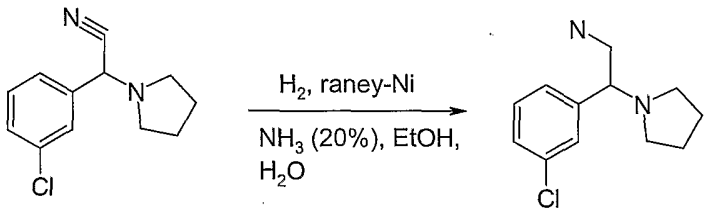


(3-Chloro-phenyl)-pyrrolidin-1-yl-acetonitrile.

202 mg (1.42 mmol) sodium sulfite and 43.6 µL (1.42 mmol) of conc. hydrochloric are dissolved in 14 mL water and 200 mg (1.42 mmol) of 3-chlorobenzaldehyde are added subsequently. After stirring for 15 min at room temperature, 130 µL (1.57 mmol) pyrrolidine are added and stirring continued for another 30 min. The reaction mixture is cooled to 0°C and 70 mg (1.42 mmol) sodium cyanate, dissolved in 7 mL water, are added dropwise. The mixture is allowed to warm up to room temperature and stirred vigorously overnight. Diethylether is added, the organic layer separated and the aqueous layer is extracted twice with diethylether. The combined extracts are dried over sodium sulphate and the solvent is evaporated under reduced pressure. The crude product is purified by flash chromatography (cyclohexane/ethylacetat 5:1), yielding the title compound as a colorless oil.

LC/MS (Va) rt 5.75, m/z 221 $[M+H]^+$.

Step 2



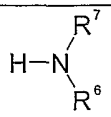
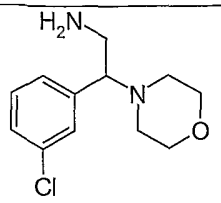
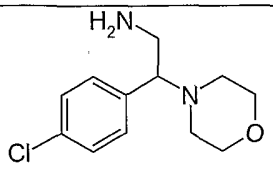
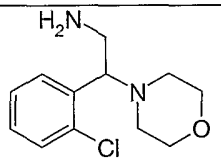
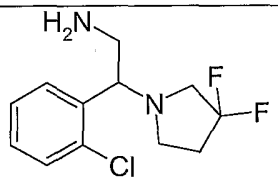
2-(3-Chloro-phenyl)-2-pyrrolidin-1-yl-ethylamine.

183 mg (0.83mmol) (3-Chloro-phenyl)-pyrrolidin-1-yl-acetonitrile are dissolved in 8 mL ethanol and 1.6 mL conc. ammonia, a slurry of Raney-Nickel in water is added and the mixture is exposed to hydrogen (1 atmosphere) for 16 h. The catalyst is removed by filtration through celite and the is evaporated under reduced pressure. Purification of the crude product by filtration through a plug of silicagel (DCM/MeOH 9:1 as eluent) yields the title compound.

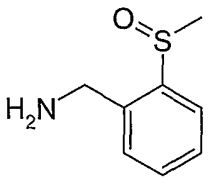
LC/MS (Va) rt 5.75, m/z 225 $[M+H]^+$.

The compounds in Table 3 are synthesized according to the procedure shown for example **17**.

Table 3

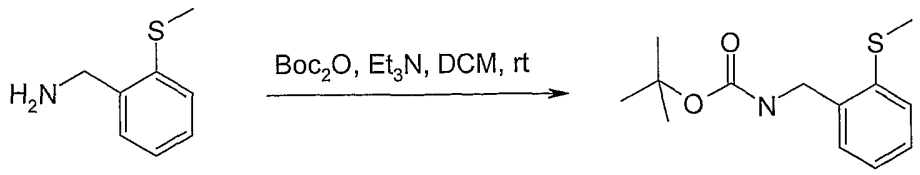
Ex.		LC/MS	NMR
18		LC/MS (IIIa) rt 1.78, m/z 241 $[M+H]^+$.	^{1}H NMR (d6-DMSO, 300 MHz) δ = 2.31 (m, 4H), 2.98 (dd, 1H, J = 6.4 Hz, J = 12.8 Hz), 2.77 (dd, 1H, J = 6.6 Hz, J = 12.8 Hz), 3.29 (t, 1H, J = 6.3 Hz), 3.52 (t, 4H, J = 4.7 Hz), 7.16 – 7.38 (m, 4H).
19		LC/MS (IVa) rt 1.78, m/z 241 $[M+H]^+$.	
20		LC/MS (Va) rt 3.42, m/z 241 $[M+H]^+$.	
21		LC/MS (Va) rt 5.20, m/z 261 $[M+H]^+$.	

Example 22



Procedure for making an intermediate according to Scheme D.

Step 1

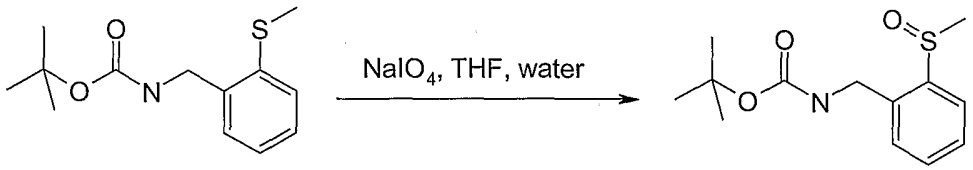


(2-Methylsulphanyl-benzyl)-carbamic acid tert-butyl ester.

To a solution of 153.0 mg (1.00 mmol) of 2-methylsulphanyl-benzylamine, 12.2 mg (0.10 mmol) of 4-dimethylaminopyridine and 11.1 mg (1.10 mmol) of triethylamine in 3 mL of dichloromethane is added 262 mg (1.20 mmol) of di(*tert*-butyloxycarbonyl) in 3 mL of dichloromethane at 0 °C. The reaction is allowed to react during 16 h and solvents are removed under reduced pressure. The crude product is dissolved in 5 mL of 1N hydrochloric acid solution and extracted three times with ethyl acetate. The organic layer is separated and washed with saturated sodium bicarbonate solution and brine and dried with sodium sulphate. Removal of the solvent affords the crude product. The residue is purified using flash chromatography (silica gel, eluent: 0% to 25% ethyl acetate in cyclohexane) to afford the title compound.

LC/MS (Ia) rt 2.97, m/z 239 $(M-(CH_3))^+$; 154 $(M\text{-boc})^+$.

Step 2



(2-Methanesulphinyl-benzyl)-carbamic acid tert-butyl ester.

To a solution of 50.0 mg (0.16 mmol) of (2-methylsulphanyl-benzyl)-carbamic acid tert-butyl ester in 1 ml THF are added dropwise 101.3 mg (0.47 mmol) of sodium periodate dissolved in 500 µL water. The reaction is allowed to react during 16 h and solvents are removed under reduced pressure. The residue is purified using flash chromatography (silica gel, eluent: 0% to 5% methanol in dichloromethane) to afford the title compound.

LC/MS (Ia) rt 2.14, m/z 270 $[M+H]^+$.

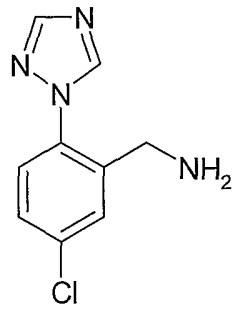
Step 3

2-Methanesulphinyl-benzylamine.

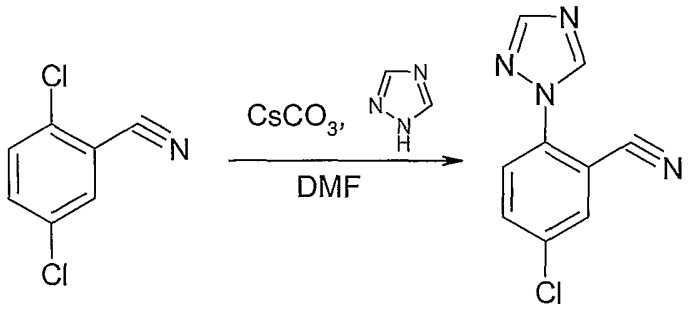
30 mg (0.06 mmol) of the product from step 3 are dissolved in 2 mL dichloromethane and 1 mL of trifluoroacetic acid is added. The mixture is stirred for 30 min. and the solvent is evaporated in vacuum. The crude product is used in the next step without further purification.

LC/MS (Ia) rt 1.82, m/z 169 $[M\text{-boc}]^+$.

Example 23



Step 1

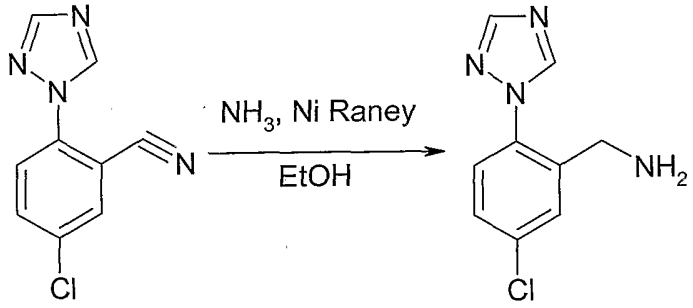


5-chloro-2-[1,2,4]triazol-1-yl-benzonitrile (For synthesis, see *J. Med. Chem.*; *47*; 2004; 2995-3008)

To a solution of 2,5-dichlorobenzonitrile (1.00 g, 5.81 mmol) in mL *N,N*-dimethylformamide (10 mL) are added cesium carbonate (2.27 g, 6.98 mmol) and 1,2,4-triazole (482 mg, 6.98 mmol). The reaction mixture is stirred at 85 °C for 16 h and at 100 °C for 8 h. The reaction mixture is diluted with water and extracted with ethyl acetate. The combined organic layers are washed with aqueous lithium chloride, dried, and concentrated to give 5-chloro-2-[1,2,4]triazol-1-yl-benzonitrile (1.12 g, 5.47 mmol). The crude product is used in the next step without further purification.

LC/MS (Ia) rt 3.00, 205 $[M+H]^+$.

Step 2



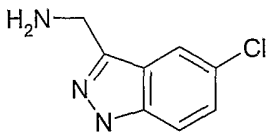
5-chloro-2-[1,2,4]triazol-1-yl-benzylamine

A suspension of 5-chloro-2-[1,2,4]triazol-1-yl-benzonitrile (500 mg, 2.42 mmol) in ethanol saturated with ammonia (20 mL) is stirred in the presence of Raney nickel (50% slurry in water, washed with ethanol, catalytic amount) under a hydrogen atmosphere for 26 h. The reaction mixture is filtered over Celite and concentrated. Purification by flash chromatography (silica gel, eluent = 2% to 10 % DCM (with 10% ammonium hydroxide) in methanol) gives 5-chloro-2-[1,2,4]triazol-1-yl-benzylamine.

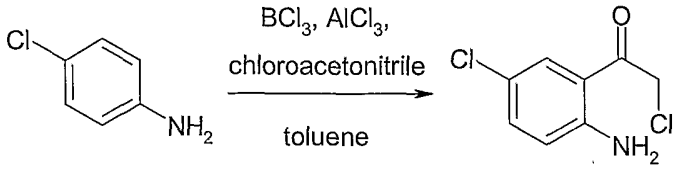
^{1}H NMR (d6-DMSO, 200 MHz) δ = 3.54 (s, 2H), 7.43 (m, 2H), 7.73 (m,1H), 8.18 (s, 1H), 8.60 (s, 1H).

LC/MS (Ia) rt 2.06, 209 (M).

Example 24



Step 1

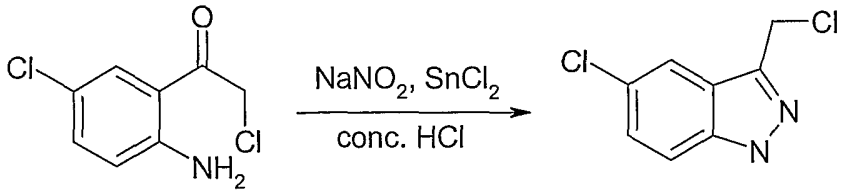


5-chloro-2-amino-α-chloroacetophenone

To a stirred solution of boron trichloride (8.62 mL of 1 M solution in heptane) in dry benzene (5 mL), a solution of 4-chloroaniline (1.00 g, 7.84 mmol) in dry benzene (15 mL) is added dropwise under icecooling. To the resulting mixture containing 4-chloroaniline borontrichloride complex, chloroacetonitrile (0.60 mL, 9.41 mmol) and aluminiumtrichloride (1.15 g, 8.62 mmol) are added successively. The mixture is then refluxed for 6 h under nitrogen, becoming a solution of two layers. The evolved hydrogen chloride is absorbed through a drying tube containing silica gel or calcium chloride to a surface of aqueous sodium hydroxide. After cooling with ice, 2 N hydrochloric acid is added and a yellow precipitate is formed. To hydrolyze the ketimine of 5-chloro-2-amino-a-chloroacetophenone, the mixture is warmed at 80 °C under stirring, until the precipitate has dissolved (ca. 30 min). The cooled mixture is extracted with chloromethane (three times) and the organic layer is washed with water, dried with sodium sulphate, and concentrated. The neutral fraction obtained (1.00 g) is recrystallized to obtain the pure 5-chloro-2-amino-α-chloroacetophenone.

LC/MS (Ia) rt 2.77, 245 $(M+H+AcCN)^+$.

Step 2

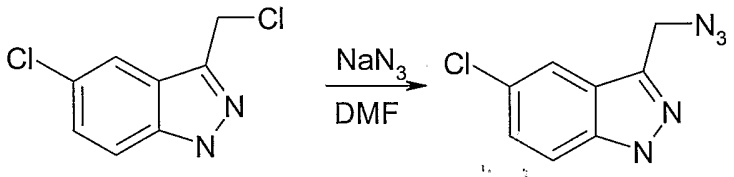


5-chloro-3-(chloromethyl)-1H-indazole

To a stirred suspension of 2-amino-5-chloro-α-chloroacetophenone (670 mg, 3.28 mmol) in conc. hydrochloric acid (10 mL) is added a solution of sodium nitrite (250 mg, 3.61 mmol) in water (2 mL) while mantaining the reaction temperature at 0 °C. After 1 h a solution of $SnCl_2 \bullet 2H_2O$ (1.78 g, 7.87 mmol) in conc. hydrochloric acid (5 mL) is added to the reaction mixture, which is then stirred at the same temperature for 1 h. Next, ice water is added to the reaction mixture. The precipitate is collected by filtration, washed with water and dried giving crude 5-chloro-3-(chloromethyl)-1H-indazole which is used in the next step without further purification.

LC/MS (Ia) 2.67, no mass peak.

Step 3

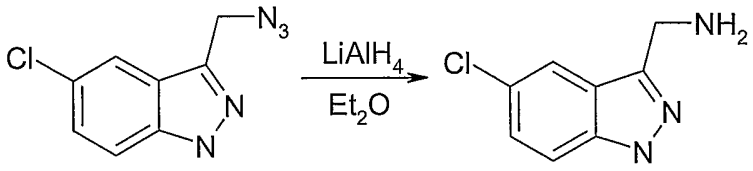


3-(Azidomethyl)-5-chloro-1H-indazole.

A stirred solution containing 5-chloro-3-(chloromethyl)-1H-indazole (370 mg, 1.84 mmol), sodium azide (156 mg, 2.40 mmol), water (0.5 mL) and *N,N*-dimethylformamide (5.00 mL) is warmed at 90 °C for 1 h and then the mixture is concentrated under reduced pressure. Ice is added and the resulting precipitate is collected by filtration and washed with water giving the 3-(azidomethyl)-5-chloro-1H-indazole.

LC/MS (Ia) rt 2.63, 249 $(M+H+AcCN)^+$.

Step 4



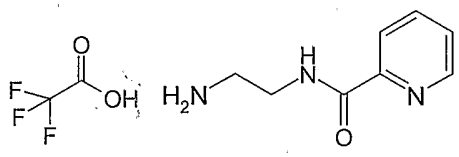
3-(aminomethyl)-5-chloro-1H-indazole

To a stirred 1M THF-solution of Lithium aluminium hydride (5.00 mL) is added a solution of 3-(azidomethyl)-5-chloro-1H-indazole (330 mg ,1.59 mmol) in Et_2O (10 mL) dropwise at room temperature, and the mixture is refluxed for 1 h. After quenching the excess of Lithium aluminium hydride with wet diethyl ether, the precipitate is filtered off and washed with dichloromethane:ethanol (9:1), giving crude 3-(aminomethyl)-5-chloro-1H-indazole. The purification by column chromatography (silica gel, eluent = 10% DCM in methanol with 0.1 % Et_3N) affords the pure material.

^1H NMR (d6-DMSO, 200 MHz) δ = 4.01 (s, 2H), 7.25-7.28 (m, 1H), 7.43-7.47 (m,1H), 7.92-7.93 (m, 1H).

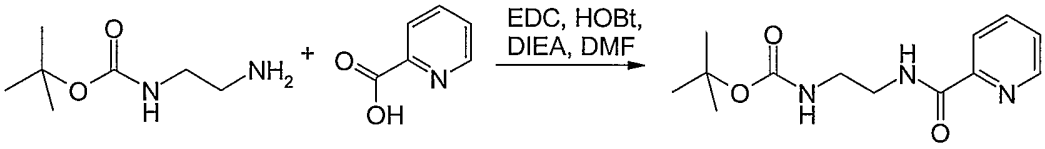
LC/MS (Ia) rt 1.59, 182 $[M+H]^+$.

Example 25



Procedure for making an intermediate according to Scheme F.

Step 1



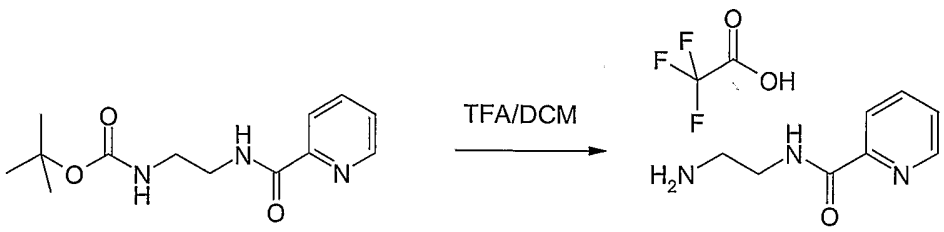
(3-Cyclopropylcarbamoyl-benzyl)-carbamic acid *tert*-butyl ester

To a solution of 77 mg (0.62 mmol) pyridine-2-carboxylic acid in 2 mL *N,N*-dimethylformamide are added 156 mg (0.81 mmol) 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC), 110 mg (0.81 mmol) 1-hydroxybenzotriazole (HOBt) and 155 µL (0.94 mmol) diisopropylethylamine (DIEA) and after 10 min 100 mg (0.62 mmol) (2-amino-ethyl)-carbamic acid *tert*-butyl ester. The mixture is stirred overnight at ambient temperature and diluted with ethyl acetate. The organic phase is washed sequentially with 5 % citric acid, saturated aqueous sodium bicarbonate solution, and

brine, dried over sodium sulphate and concentrated under vacuum to yield the title compound.

LCMS (Ia) rt 3.51, m/z 266 $[M+H]^+$.

Step 2

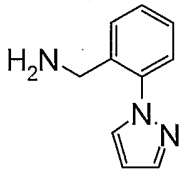


3-Aminomethyl-N-cyclopropyl-benzamide

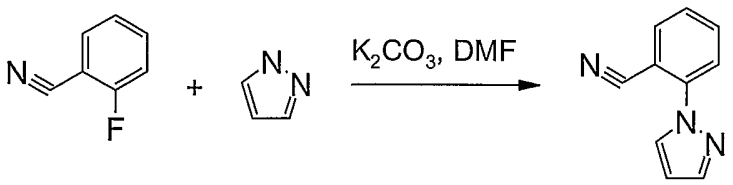
30 mg (0.10 mmol) of the product from step 1 are dissolved in 2 mL dichloromethane and 1 mL of trifluoroacetic acid is added. The mixture is stirred for 30 min and the solvent is evaporated under vacuum. The title compound is taken directly to the next step.

^{1}H NMR (d6-DMSO, 300 MHz) δ = 2.71 (m, 2H), 3.31 (m, 2H), 7.52-7.56 (m, 1H), 7.91-8.00 (m, 2H), 8.58-8.59 (m, 1H).

Example 26



Step 1



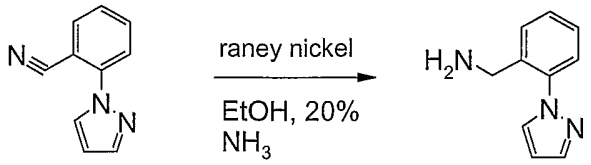
2-Pyrazol-1-yl-benzonitrile.

To a solution of 200 mg (1.65 mmol) 2-fluoro-benzonitrile and 135 mg (1.98 mmol) pyrazole dissolved in 2 mL *N,N*-dimethylformamide is added 274 mg (1.98 mmol) potassium carbonate. The mixture is stirred overnight under argon at 120°C and diluted

with ethyl acetate. The organic phase is washed sequentially with water and brine, dried over sodium sulphate and concentrated under vacuum to yield the title compound.

LCMS (IVa) rt 3.31, m/z 170 $[M+H]^+$.

Step 2

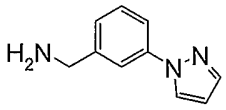


2-Pyrazol-1-yl-benzylamine.

A suspension of 2-pyrazol-1-yl-benzonitrile (126 mg, 0.74 mmol) in ethanol saturated with ammonia (5 mL) is stirred in the presence of Raney nickel (50% slurry in water, washed with ethanol, catalytic amount) under a hydrogen atmosphere for 66 h. The reaction mixture is filtered over Celite and concentrated. Purification of the crude product by filtration through a plug of silicagel (dichloromethane:methanol 9:1 as eluent) yields the title compound.

LC/MS (Ia) rt 1.77, 174 $[M+H]^+$.

Example 27

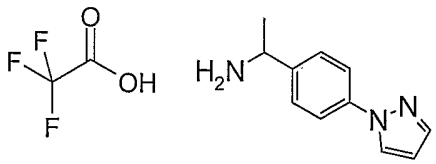


3-Pyrazol-1-yl-benzylamine.

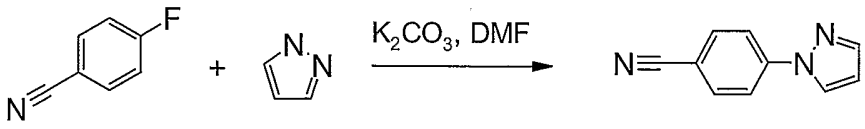
The title compound was prepared according the procedure from example **26**.

LCMS (Va) rt 4.49, m/z 174 $[M+H]^+$.

Example 28



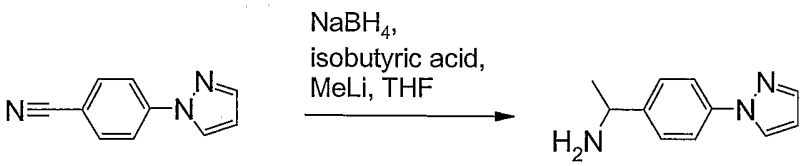
Step 1



4-Pyrazol-1-yl-benzonitrile.

The title compound was prepared according the procedure from step 1 example **26**. LCMS (IVa) rt 3.78, m/z 170 $[M+H]^+$.

Step 2



1-(4-Pyrazol-1-yl-phenyl)-ethylamine.

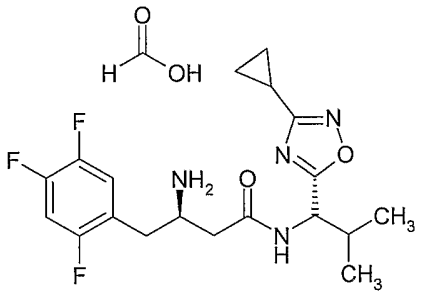
A suspension of sodium borohydride (22.3 mg, 0.59 mmol) in tetrahydrofuran (5 mL) is stirred at room temperature. Isobutyric acid (54.8 µL, 0.59 mmol) and 4-pyrazol-1-yl-benzonitrile (100 mg, 0.591 mmol), dissolved in 3 mL tetrahydrofuran, are added. The reaction mixture is stirred at 70°C for 6 h and then cooled to –80°C. Methyllithium (739 µL, 1.18 mmol, 1.6 M in diethyl ether) is added and the reaction mixture is allowed to warm to room temperature over night. The reaction is quenched by addition of 1 mL water and 2 mL 1 M HCl. The organic solvent is evaporated under reduced pressure and the remaining aqueous phase is adjusted with ammonium hydroxide to pH = 7 and extracted with ethylacetate (three times) and the combined organic layer is washed

with water, dried with sodium sulphate, and concentrated in vacuum. Purification of the crude product by preparative HPLC yields the title compound.

^{1}H NMR (d6-DMSO, 300 MHz) δ = 1.52 (d, 3H, J = 6.9 Hz), 4.43 (m, 1H), 6.51 (m,1H), 7.56 (d, 2H, J = 9.0 Hz), 7.70 (s, 1H), 7.85 (d, 2H, J = 9.0 Hz), 8.46 (d, 1H, J = 2.7 Hz).

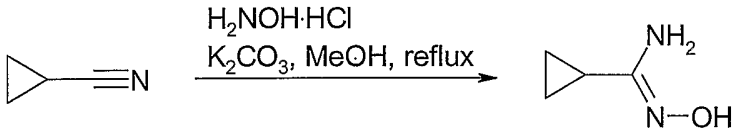
LC/MS (VIa) rt 3.63, 187 (M).

Example 29



Procedure for making an intermediate according to Scheme G and a compound of the invention according to Scheme J.

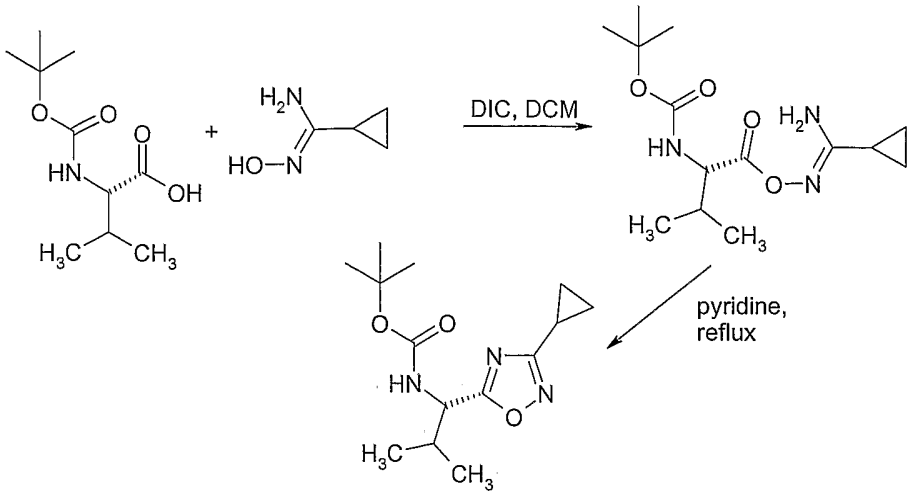
Step 1



N-Hydroxy-cyclopropanecarboxamidine

1.00 g (14.9 mmol) of cyclopropanecarbonitrile is dissolved in 20 mL of methanol, 3.09 g (22.4 mmol) of powdered potassium carbonate is added and 2.07 g (29.8 mmol) of hydroxylamine hydrochloride is added subsequently in small portions. The reaction mixture is refluxed for 5 h, then the solvent is evaporated and the residue is taken up in a 1:4 mixture of water and chloroform. The organic layer is separated, washed twice with water, dried with magnesium sulphate, filtered and evaporated to dryness. The residue is recrystallized from ether/hexane to afford the desired product.

Steps 2 and 3



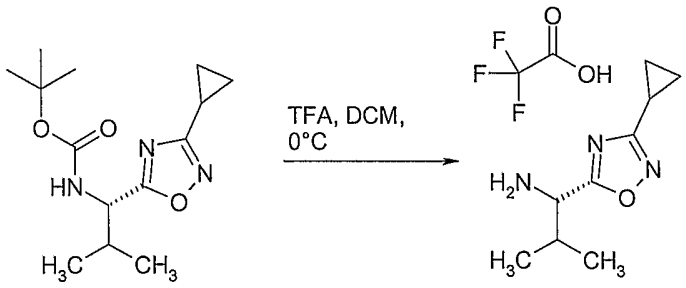
[(*S*)-1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-2-methyl-propyl]-carbamic acid *tert*-butyl ester

To a solution of 50.0 mg (0.50 mmol) *N*-hydroxy-cyclopropylcarboxamidine, 109 mg (0.50 mmole) Boc-(*S*)-valine in 2 mL dichloromethane, 75.5 mg (0.60 mmol) 1,3-di-*iso*-propylcarbodiimide is added, and the mixture is stirred at room temperature. After 12 h the solvent is evaporated and the residue is dissolved in 10 mL of pyridine and refluxed for 4 h. Then the pyridine is evaporated and the residue is taken up in a 2:1 mixture of dichloromethane and water. The aqueous phase is extracted with dichloromethane, and the combined organic layers are washed with 3 % hydrochloric acid solution, saturated sodium bicarbonate solution, water and brine, dried with sodium sulphate, filtered and concentrated in vacuo. The residue is subjected to column chromatography (silica gel, eluent: *c*-hexane:ethyl acetate = 50:50) to afford the title compound.

1H-NMR (300 MHz, DMSO-d6) δ = 0.78-0.91 (m, 8H), 1.04-1.07 (m, 2H), 1.22-1.37 (d, 9H), 2.08-2.12 (m, 2H), 4.52 (m, 1H), 7.65-7.67 (d, 1H, NH).

LCMS (Ia) rt 4.21, 226, 267, 282.

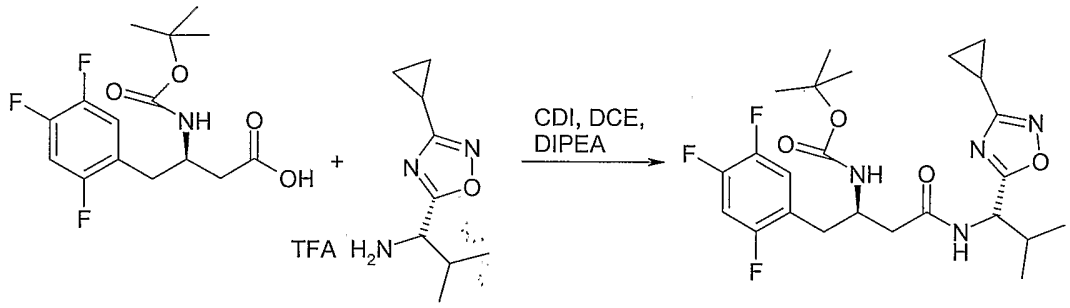
Step 4



(*S*)-1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-2-methyl-propylamine trifluoroacetic acid salt

85.0 mg (0.30 mmol) of [(*S*)-1-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-2-methyl-propyl]-carbamic acid *tert*-butyl ester from step 3 is dissolved in 2 mL dichloromethane and the mixture is cooled to 0°C. Then 1 mL of trifluoroacetic acid is added and the reaction solution is allowed to warm to room temperature. After complete conversion of the starting material, as monitored by TLC the solvent is evaporated and the residue is dried in vacuo to yield the title compound.

Step 5

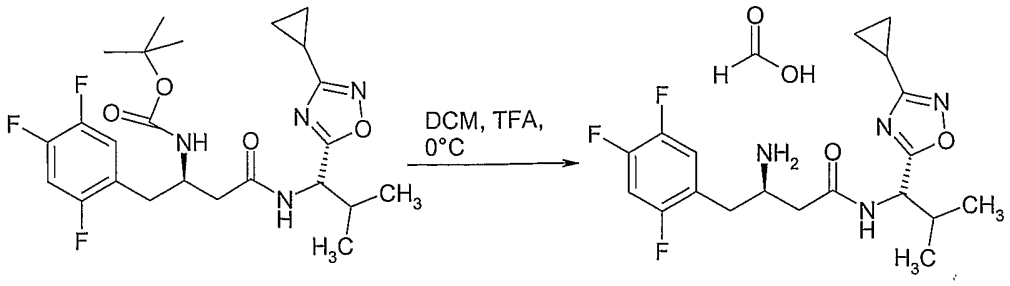


[(*R*)-1-{[(*S*)-1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-2-methyl-propylcarbamoyl]-methyl}-2-(2,4,5-trifluoro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester

A mixture of 99.0 mg (0.30 mmol) Boc-(*R*)-3-amino-4-(2,4,5-trifluoro-phenyl)-butyric acid, 60.0 mg (0.45 mmol) 1-hydroxybenzotriazole, 183 µL (1.31 mmol) triethylamine and 86.0 mg (0.45 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride in 4 mL of *N*,*N*-dimethylformamide is stirred for 10 min. Then 89.0 mg (0.30 mmol) of the trifluoroacetic acid salt of (*S*)-1-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-2-methyl-propylamine is added to the reaction mixture. After stirring over night the solution is poured into 15 mL of brine and the resulting mixture is extracted 3 times with ethyl acetate. The combined organic layers are washed with saturated sodium bicarbonate solution, water and brine, dried with sodium sulphate, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel (*c*-hexane:ethyl acetate 50:50) affords the title compound.

LCMS (Ia) rt 4.55, 397 $(M\text{-boc})^+$, 438 $(M\text{-boc}+CH_3CN)^+$, 497 $(M+H)^+$.

Step 6



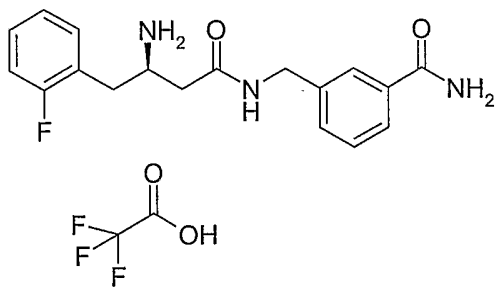
(*R*)-3-Amino-*N*-[(*S*)-1-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-2-methyl-propyl]-4-(2,4,5-trifluoro-phenyl)-butyramide. formic acid salt

108 mg (0.22 mmol) of [(*R*)-1-{[(*S*)-1-(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-2-methyl-propylcarbamoyl]-methyl}-2-(2,4,5-trifluoro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester is dissolved in 1 mL dichloromethane and cooled to 0°C. Then 0.5 mL of trifluoroacetic acid is added and the reaction mixture is allowed to warm to room temperature over the course of the reaction. Stirring is continued until complete conversion is observed by TLC analysis. The solvents are evaporated under vacuo and the residue is subjected to purification by preparative HPLC affording the title compound.

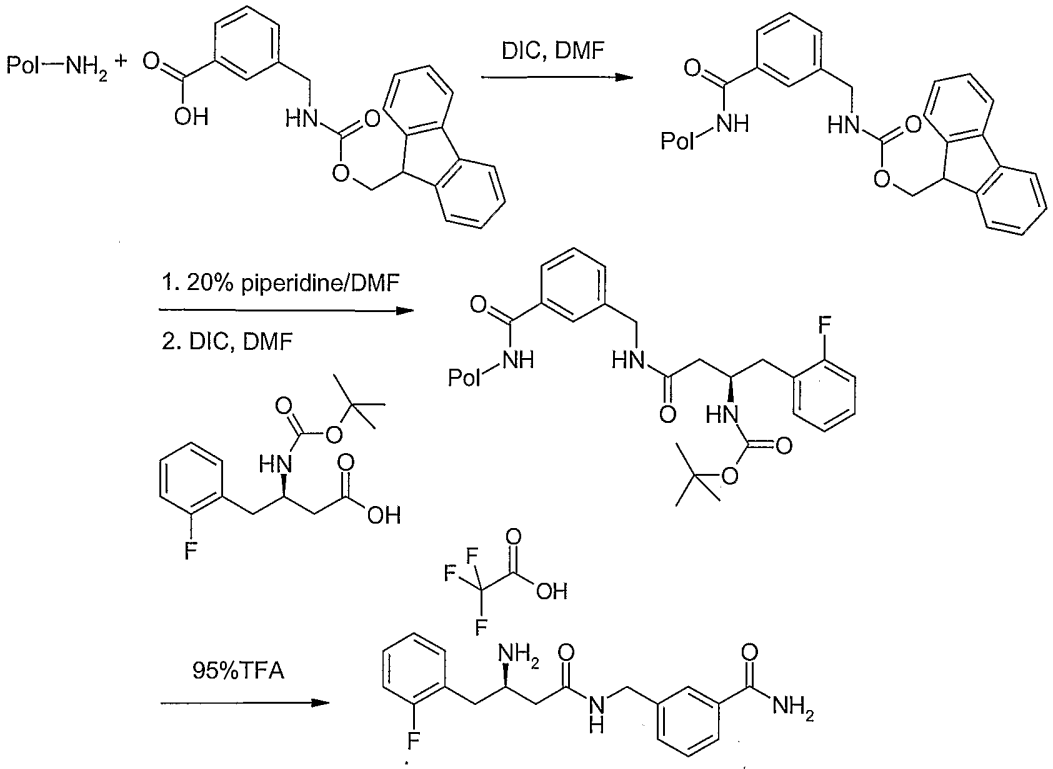
^{1}H-NMR (300 MHz, DMSO-d_6) δ = 0.80-0.82 (d, 5H), 0.90-0.92 (d, 3H), 1.04-1.06 (m, 2H), 2.07-2.12 (m, 2H), 2.83-2.87 (m, 2H), 3.63-3.65 (m, 1H), 4.83-4.86 (m, 1H), 7.43-7.47 (t, 1H), 7.50-7.57 (t, 1H), 8.14 (s, 1H), 8.84-8.86 (d, 1H, NH).

LCMS (Ia) rt 2.54, 397 $(M+H)^+$, 438 $(M+CH_3CN)^+$.

Example 30



Procedure for making a compound of the invention according to Scheme I.

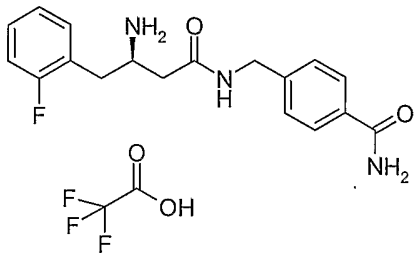


3-{[(3*R*)-3-Amino-4-(2-fluoro-phenyl)-butyrylamino]-methyl}-benzamide.trifluoroacetate salt

40 mg Rink Amide Novagel (loading 0.6 mmol/g – 0.024 mmol) are briefly swollen in *N,N*-dimethylformamide and drained. A solution of 45 mg (0.11 mmol) Fmoc-(3-aminomethyl)-benzoic acid and 21 µL (0.15 mmol) diisopropylcarbodiimide (DIC) in 0.5 mL *N,N*-dimethylformamide is added and the reaction is shaken at ambient temperature for 5 hours. The solution is drained and the resin is washed with *N,N*-dimethylformamide (3x), dichloromethane (2x), methanol (2x), dichloromethane (2x) and diethylether (2x). The fluorenylmethoxycarbonyl (Fmoc) group is then removed by treatment with 20% piperidine in *N,N*-dimethylformamide, shaken for 30 min, followed by washing with *N,N*-dimethylformamide (3x). A solution of 15 mg (0.052 mmol) Boc-(*R*)-3-amino-4-(2-fluoro-phenyl)-butyric acid, 9 µL (0.057 mmol) diisopropylcarbodiimide (DIC), 7.5 mg (0.057 mmol) 1-hydroxybenzotriazole (HOBt) and 15 µL (0.092 mmol) diisopropylethylamine (DIEA) in 0.5 mL DMF is added and the mixture is shaken overnight. The resin is then washed with *N,N*-dimethylformamide (3x), dichloromethane (2x), methanol (2x), dichloromethane (2x) and diethylether (2x) and dried. Cleavage from the resin is performed by treatment with 95% trifluoroacetic acid in DCM for 90 min, followed by washing of the resin with 95% trifluoroacetic acid in

DCM (2x). Evaporation of the solvent gives crude material that is purified by reversed phase HPLC yielding the title compound.
LCMS (IIIa) rt 2.07, m/z 330 $(M+H)^+$.

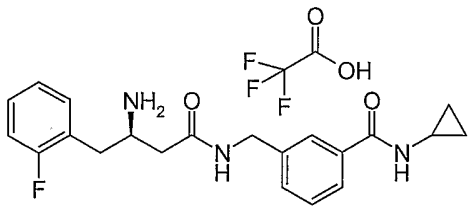
Example 31



4-{[(3*R*)-3-Amino-4-(2-fluoro-phenyl)-butyrylamino]-methyl}-benzamide.trifluoroacetate salt

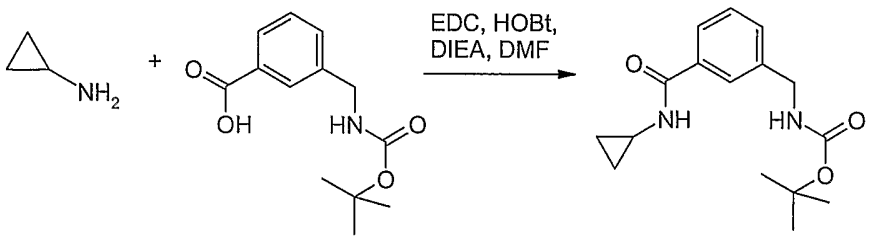
The title compound was prepared according to the procedure from example **30**.
LCMS (IIIa) rt 2.08, m/z 330 $(M+H)^+$.

Example 32



Procedure for making an intermediate according to Scheme E and a compound of the invention according to Scheme J.

Step 1

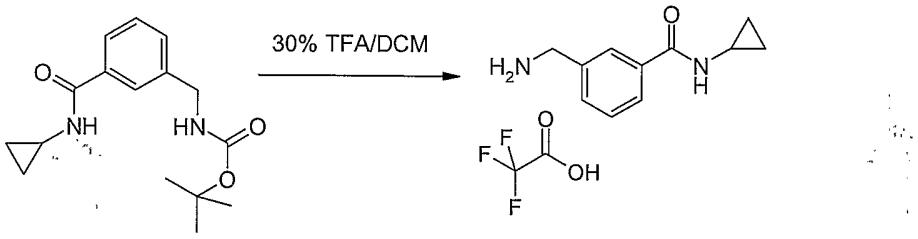


(3-Cyclopropylcarbamoyl-benzyl)-carbamic acid *tert*-butyl ester

To a solution of 30 mg (0.12 mmol) Boc-(3-aminomethyl)-benzoic acid in 3 mL *N,N*-dimethylformamide is added 25 mg (0.13 mmol) 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC), 18 mg (0.13 mmol) 1-hydroxybenzotriazole (HOBt) and 49 µL (0.29 mmol) diisopropylethylamine (DIEA) and after 10 min 8 mg (0.14 mmol) cyclopropylamine. The mixture is stirred overnight at ambient temperature and diluted with ethyl acetate. The organic layer is washed sequentially with 5 % citric acid, saturated aqueous sodium bicarbonate solution and brine, dried over sodium sulphate and concentrated under vacuum to yield the title compound.

LCMS (Ia) rt 2.31, m/z 313 $(M+Na)^+$.

Step 2

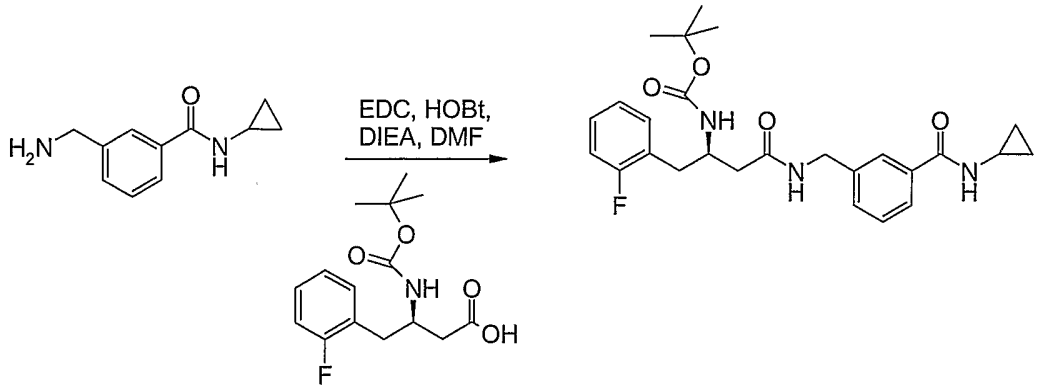


3-Aminomethyl-*N*-cyclopropyl-benzamide. trifluoroacetate salt

30 mg (0.10 mmol) of the product from step 1 are dissolved in 2 mL dichloromethane and 1 mL of trifluoroacetic acid is added. The mixture is stirred for 30 min and the solvent is evaporated in vacuum. The title compound is directly taken to the next step.

LCMS (Ia) rt 1.52, m/z 191 $(M+H)^+$.

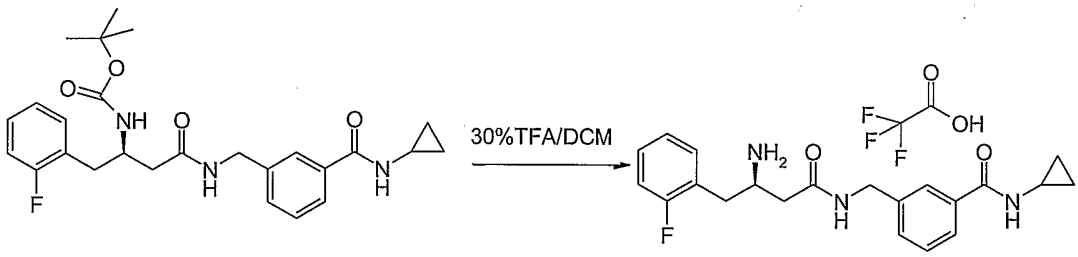
Step 3



[(*R*)-1-[(3-Cyclopropylcarbamoyl-benzylcarbamoyl)-methyl]-2-(2-fluoro-phenyl)-ethyl]-carbamic acid tert-butyl ester

To a solution of 55 mg (0.19 mmol) Boc-(*R*)-3-amino-4-(2-fluoro-phenyl)-butyric acid in 2 mL *N,N*-dimethylformamide is added 39 mg (0.20 mmol) 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC), 33 mg (0.24 mmol) 1-hydroxybenzotriazole (HOBt) and 75 µL (0.44 mmol) diisopropylethylamine (DIEA). After 10 min the crude material from step 2 (0.10 mmol) is dissolved in 1 mL *N,N*-dimethylformamide and added to the reaction mixture. The mixture is stirred overnight at ambient temperature and diluted with ethyl acetate. The organic phase is washed sequentially with 5 % citric acid, saturated aqueous sodium bicarbonate solution and brine, dried over sodium sulphate and concentrated under vacuum. Purification by flash chromatography (silica gel, cyclohexane to ethyl acetate) affords the title compound.
LCMS (IIIa) rt 2.65, m/z 492 $(M+Na)^+$.

Step 4

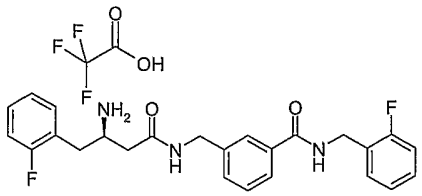
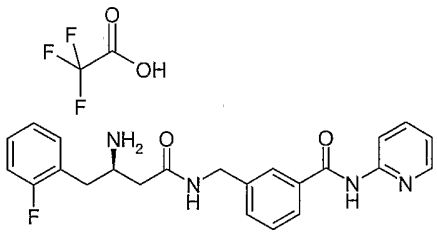
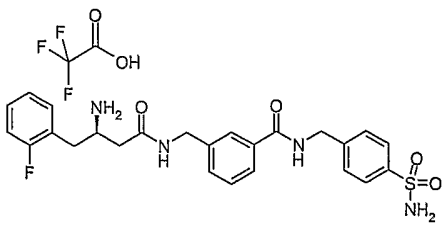


3-{[(3*R*)-3-Amino-4-(2-fluoro-phenyl)-butyrylamino]-methyl}-*N*-cyclopropyl-benzamide. trifluoroacetate salt

30 mg (0.06 mmol) of the product from step 3 are dissolved in 2 mL dichloromethane and 1 mL of trifluoroacetic acid is added. The mixture is stirred for 30 min and the solvent is evaporated in vacuum. The crude material is purified by reversed phase HPLC to yield the title compound. ^{1}H-NMR (300 MHz, DMSO-d_6) δ = 0.57 (m, 2H), 0.70 (m, 2H), 2.50 (m, 2H covered by dmso signal), 2.81 – 2.90 (m, 2H), 3.00 (dd, 1H, J = 13.1 Hz, J = 5.1 Hz), 3.69 (m, 1H), 4.27 (m, 2H), 7.13 - 7.33 (m, 6H), 7.66 (m, 2H), 7.96 (bs, 3H), 8.30 (d, 1H, J = 3.8Hz), 8.58 (t, 1H, J = 5.1 Hz).
LCMS (Ia) rt 2.02, m/z 370 $(M+H)^+$.

The compounds in Table 4 are synthesized according to the procedure shown for example **32**.

Table 4

Ex.		LC/MS	NMR
33		(Ia) rt 2.31, m/z 438 $(M+H)^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 2.50 (m, 2H covered by dmso signal), 2.87 (dd, 1H, J = 13.9 Hz, J = 8.8 Hz), 3.00 (dd, 1H, J = 13.3 Hz, J = 5.8 Hz), 3.69 (m, 1H), 4.27 (m, 2H), 4.49 (m, 2H), 7.06 - 7.41 (m, 10H), 7.74 (m, 2H), 7.98 (bs, 3H), 8.60 (t, 1H, J = 6.0 Hz), 8.90 (t, 1H, J = 6.0 Hz).
34		(Ia) rt 1.88, m/z 407 $(M+H)^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 2.50 (m, 2H covered by dmso signal), 2.87 (dd, 1H, J = 13.5 Hz, J = 8.3 Hz), 3.00 (dd, 1H, J = 14.0 Hz, J = 5.7 Hz), 3.70 (m, 1H), 4.28 (m, 2H), 7.13 (m, 3H), 7.28 (m, 2H), 7.43 (m, 2H), 7.79 – 7.86 (m, 3H), 7.97 (bs, 3H), 8.12 (d, 1H, J = 8.8Hz), 8.34 (d, 1H, J = 6.0 Hz), 8.61 (t, 1H, J = 6.0 Hz), 10.63 (s, 1H).
35		(Ia) rt 2.01, m/z 499 $(M+H)^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 2.50 (m, 2H covered by dmso signal), 2.87 (dd, 1H, J = 13.5 Hz, J = 8.3

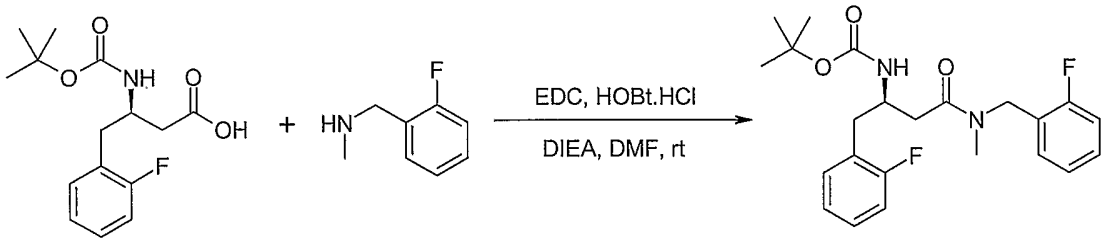
			Hz), 3.00 (dd, 1H, J = 14.0 Hz, J = 5.7 Hz), 3.70 (m, 1H), 4.28 (m, 2H), 4.50 (d, 2H, J = 5.9 Hz), 7.11 - 7.45 (m, 8H), 7.73 (m, 4H), 7.98 (bs, 3H), 8.60 (t, 1H, J = 5.8Hz), 9.02 (t, 1H, J = 6.2 Hz).

The following examples deal with compounds of the invention synthesized according to Scheme J.

A description of the general procedures used for Steps 1 and 2 follows.

Example 36

Step 1

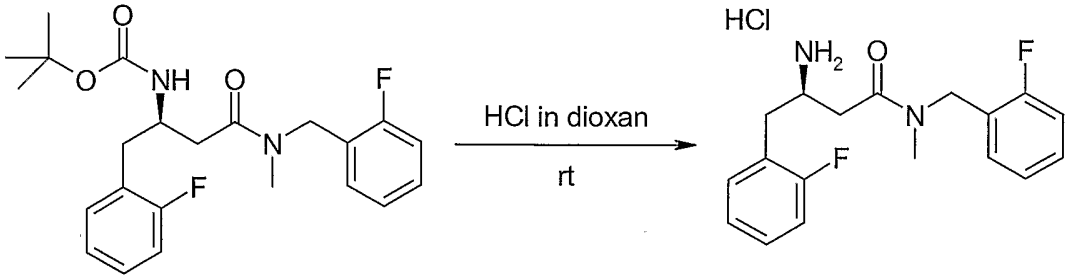


[1-(*R*)-{[(2-Fluoro-benzyl)-methyl-carbamoyl]-methyl}-2-(2-fluoro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester.

A mixture of 20.0 mg (0.07 mmol) of *(3R)-tert*-butoxycarbonylamino-4-[2-fluoro-phenyl]-butyric acid, 12.8 mg (0.09 mmol) of 1-hydroxybenzotriazole, 18.1 mg (0.09 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 38 µL (0.29 mmol) of diisopropylethylamine in 1.5 mL of *N,N*-dimethylformamide is stirred for 5 min. After addition of 11.8 mg (0.08 mmol) of (2-fluoro-benzyl)-methyl amine (Example 1) 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, eluent: 0% to 20% ethyl acetate in cyclohexane) to afford the title compound.
LC/MS (Ia) rt 3.24, m/z 419 $[M+H]^+$.

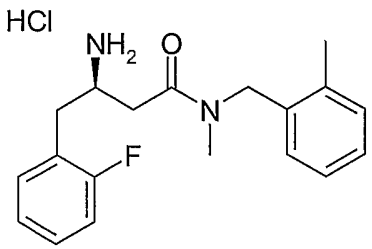
Step 2



(3R)-Amino-*N*-(2-fluoro-benzyl)-4-(2-fluoro-phenyl)-*N*-methyl-butyramide hydrochloride.

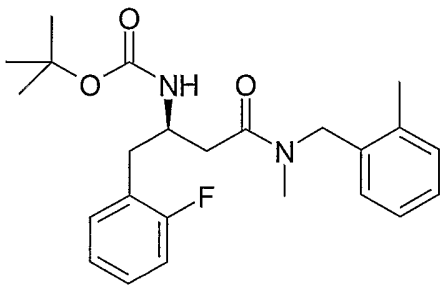
A solution of 20.0 mg (0.04 mmol) of [1-(*R*)-{[(2-fluoro-benzyl)-methyl-carbamoyl]-methyl}-2-(2-fluoro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester in 1.0 mL of 4N hydrochloric acid solution in 1,4-dioxan is stirred for 2 h and then evaporated under reduced pressure. The crude mixture is diluted in methanol and again evaporated under vacuum to afford the title compound.
^{1}H-NMR δ (ppm) = 2.65-2.88 (m, 5H), 2.95-3.15 (m, 2H), 3.67 (m, 2H), 4.27-4.53 (2m, 1H), 7.10-7.33 (m, 8H), 8.28 (bs, 2H).
LC/MS (Ia) rt 2,13, m/z 319 $[M+H]^+$.

Example 37



Example **37** prepared following the procedure above outlined for Example **36** according to Scheme J.

Step 1

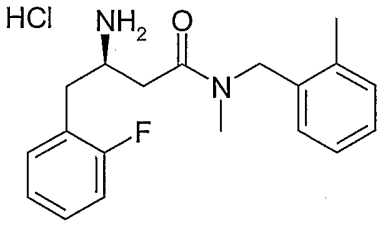


(2-(2-Fluoro-phenyl)-1-{[methyl-(2-methyl-benzyl)-carbamoyl]-methyl}-ethyl)-carbamic acid *tert*-butyl ester.

Obtained from *(3R)-tert*-butoxycarbonylamino-4-[2-fluoro-phenyl]-butyric acid and methyl-(2-methyl-benzyl)-amine.

LC/MS (Ia) rt 3.37, m/z 415 $[M+H]^+$.

Step 2

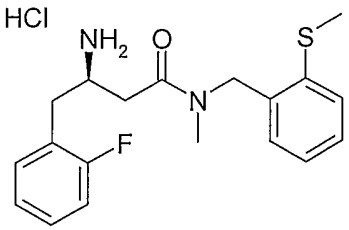


3-Amino-4-(2-fluoro-phenyl)-*N*-methyl-*N*-(2-methyl-benzyl)-butyramide hydrochloride.

Obtained from (2-(2-fluoro-phenyl)-1-{[methyl-(2-methyl-benzyl)-carbamoyl]-methyl}-ethyl)-carbamic acid tert-butyl ester according to Step 2 in the procedure described for Example **36**.

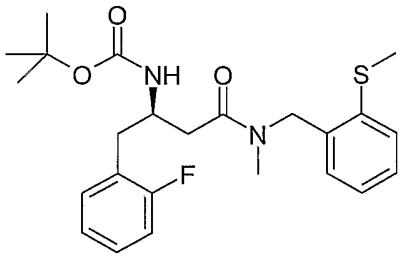
LC/MS (Ia) rt 2.30, m/z 315 $[M+H]^+$.

Example 38



Example **38** prepared following the procedure outlined for Example **36** according to Scheme J.

Step 1

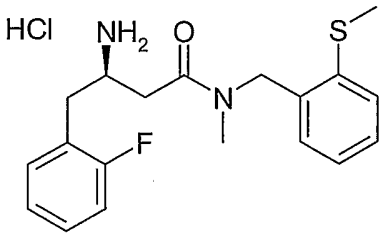


(2-(2-Fluoro-phenyl)-1-{[methyl-(2-methylsulfanyl-benzyl)-carbamoyl]-methyl}-ethyl)-carbamic acid tert-butyl ester.

Obtained from *(3R)-tert*-butoxycarbonylamino-4-[2-fluoro-phenyl]-butyric acid and methyl-(2-methylsulfanyl-benzyl)-amine.

LC/MS (Ia) rt 3.31 , m/z 415 $[M+H]^+$.

Step 2

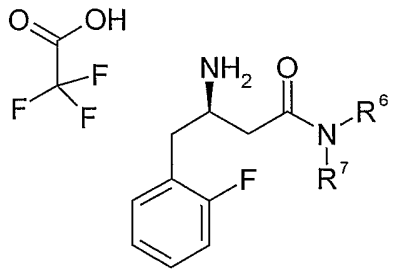


3-Amino-4-(2-fluoro-phenyl)-*N*-methyl-*N*-(2-methylsulfanyl-benzyl)-butyramide hydrochloride.

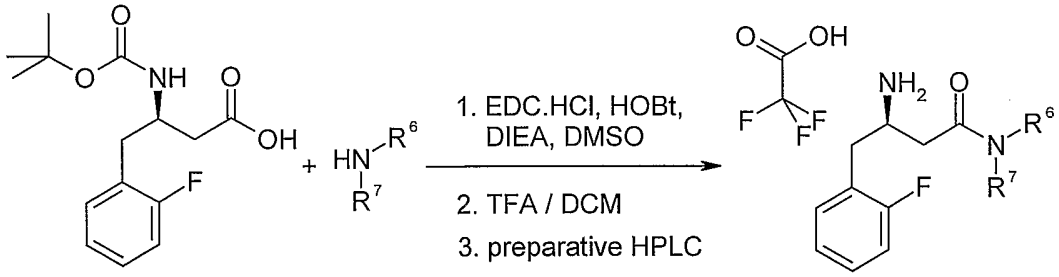
Obtained from (2-(2-fluoro-phenyl)-1-{[methyl-(2-methylsulfanyl-benzyl)-carbamoyl]-methyl}-ethyl)-carbamic acid *tert*-butyl ester according to Step 2 in the procedure described for Example **36**.

LC/MS (Ia) rt 2.30, m/z 315 $[M+H]^+$.

Compounds listed in Table 5 with the formula



are prepared according to the following experimental procedure:

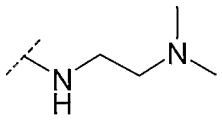
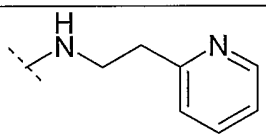
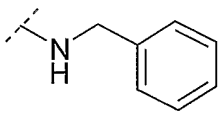
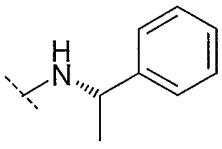
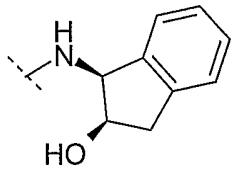
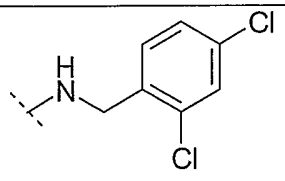


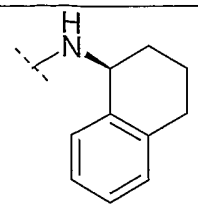
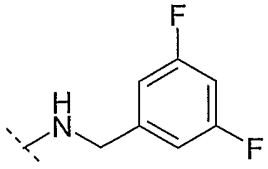
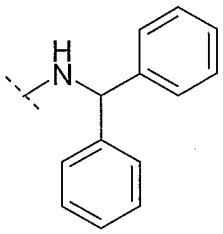
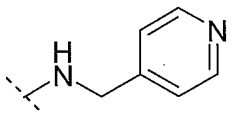
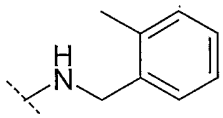
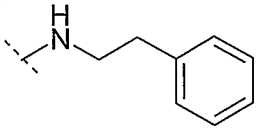
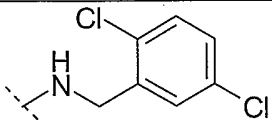
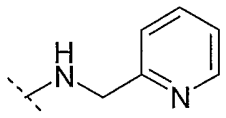
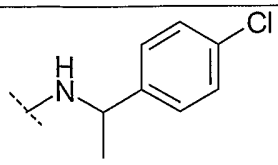
To 100 µL of a 0.5M dimethylsulphoxide solution of *(3R)-tert*-butoxycarbonylamino-4-[2-fluoro-phenyl]-butyric acid in a well of a 96-MTP are added sequentially 140 µL of a 0.5M dimethylsulfoxide solution of 1-hydroxybenzotriazole, 140 µL of a 0.5M dimethylsulfoxide solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 20 µL (0.15 mmol) of diisopropylethylamine. After 15 min stirring at room temperature 0.06 mmol of the corresponding amine dissolved in 100 µL of dimethylsulfoxide is added and the reaction mixture is stirred overnight at room temperature. Solvents are removed under vacuum, 500 µL of a solution of trifluoroacetic acid in dichloromethane (33% v/v) is added and the reaction mixture is

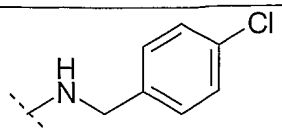
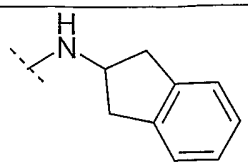
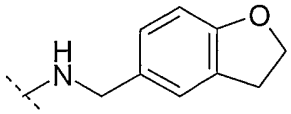
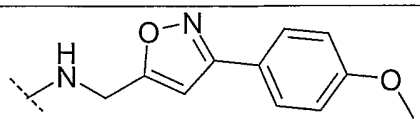
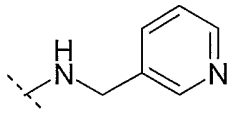
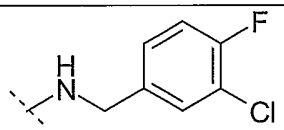
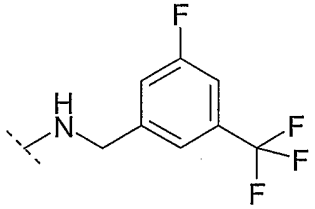
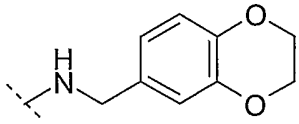
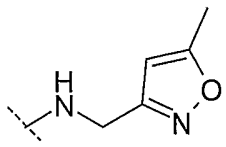
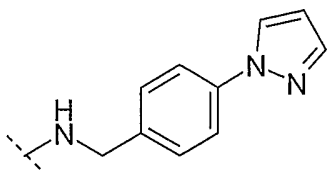
stirred for 2 h at room temperature. After removal of the solvents under reduced pressure, 500 µL of methanol are added and the crude material is purified using preparative HPLC with a 10 min linear gradient from 5% to 95% acetonitrile in water (0.1% TFA) to afford the title compounds.

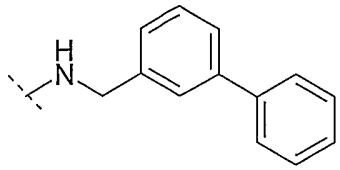
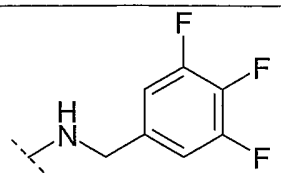
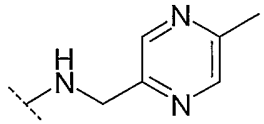
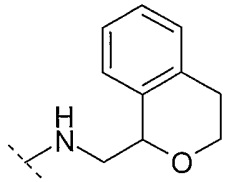
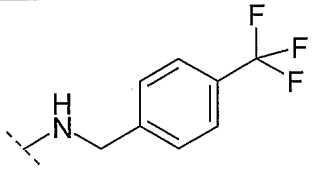
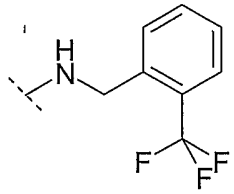
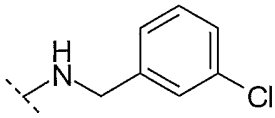
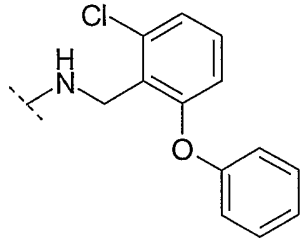
Diastereoisomeric compounds generated from racemic amines are separated via reversed phase HPLC. The absolute configuration for these diastereoisomeres is not assigned.

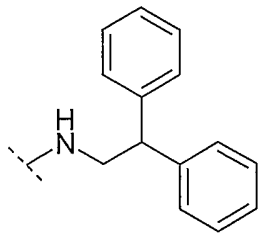
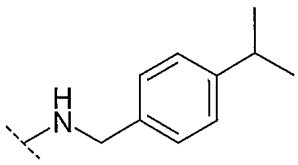
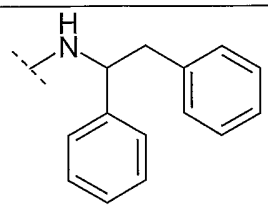
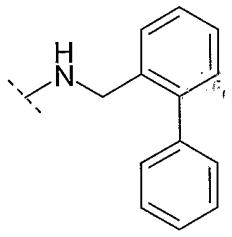
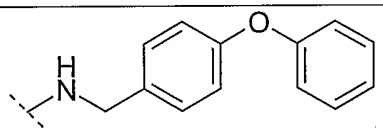
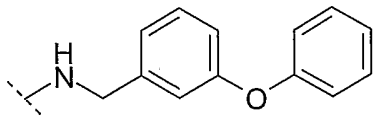
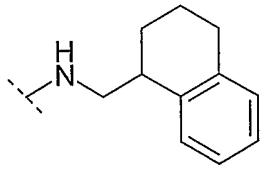
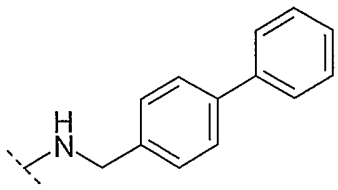
TABLE 5

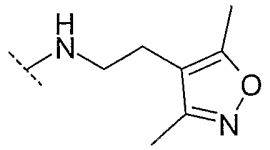
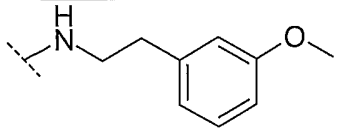
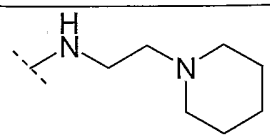
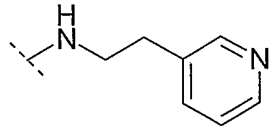
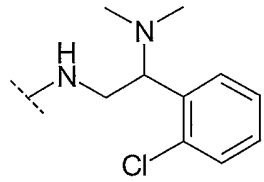
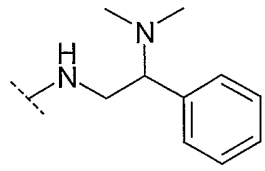
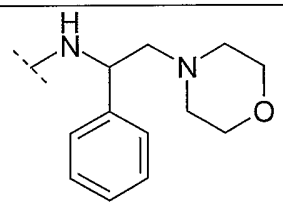
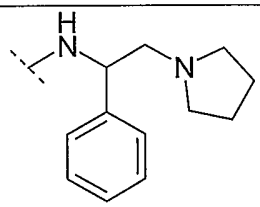
Ex.	R^6R^7N-	LC/MS data m/z	LC/MS data rt (min) Method IVa
39		268 $[M+H]^+$	1.76
40		302 $[M+H]^+$	2.08
41		287 $[M+H]^+$	2.08 (Method IIIa)
42		301 $[M+H]^+$	4.94
43		329 $[M+H]^+$	4.24
44		355 $[M+H]^+$	5.72

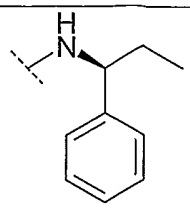
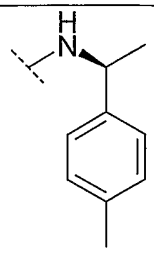
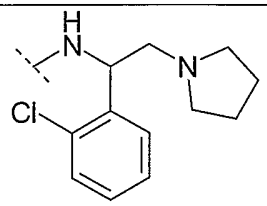
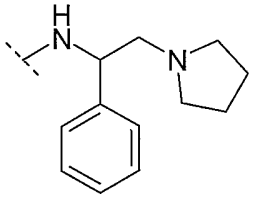
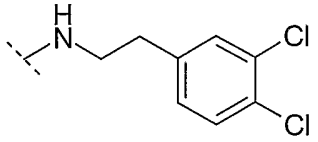
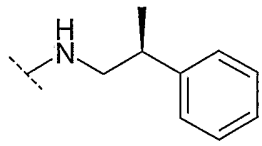
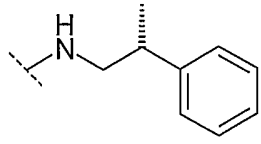
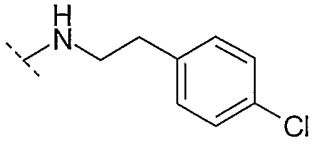
45		327 $[M+H]^+$	5.56
46		323 $[M+H]^+$	5.08
47		363 $[M+H]^+$	6.18
48		288 $[M+H]^+$	1.87
49		301 $[M+H]^+$	5.04
50		301 $[M+H]^+$	4.97
51		355 $[M+H]^+$	5.67
52		288 $[M+H]^+$	1.99
53		376 $[M+CH_3CN+H]^+$	5.63

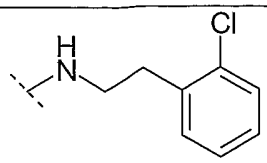
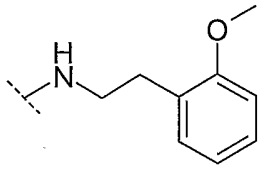
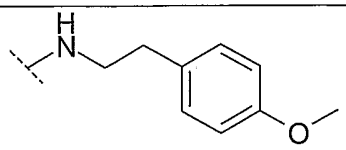
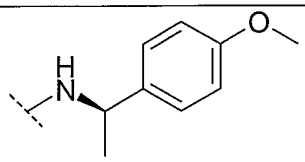
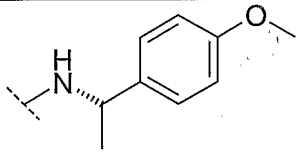
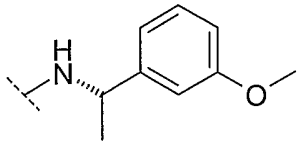
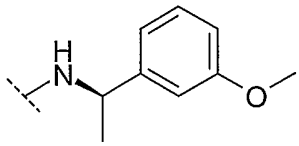
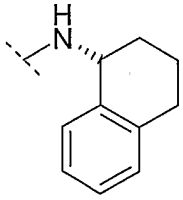
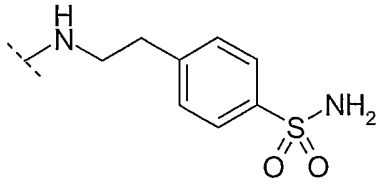
54		321 $[M+H]^+$	3.34
55		313 $[M+H]^+$	5.22
56		329 $[M+H]^+$	4.73
57		384 $[M+H]^+$	5.37
58		288 $[M+H]^+$	1.59
59		341 $[M+H]^+$	5.48
60		373 $[M+H]^+$	5.84
61		345 $[M+H]^+$	4.75
62		292 $[M+H]^+$	3.60
63		353 $[M+H]^+$	4.83

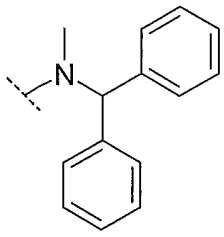
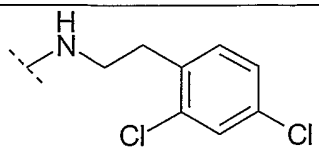
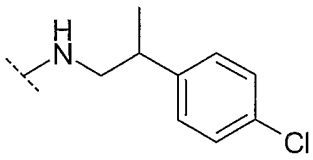
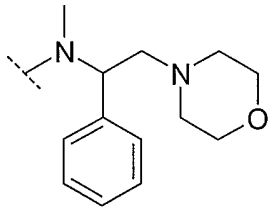
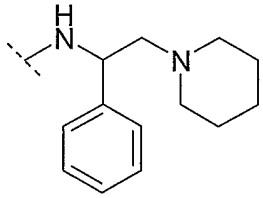
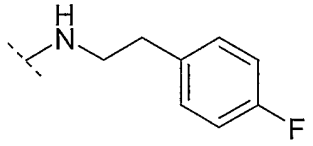
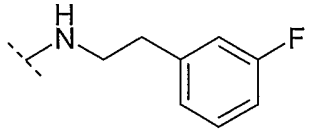
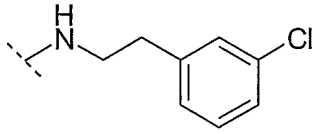
64		363 $[M+H]^+$	6.32
65		341 $[M+H]^+$	5.36
66		303 $[M+H]^+$	3.09
67		343 $[M+H]^+$	4.99
68		355 $[M+H]^+$	5.75
69		355 $[M+H]^+$	5.52
70		321 $[M+H]^+$	5.34
71		413 $[M+H]^+$	6.59

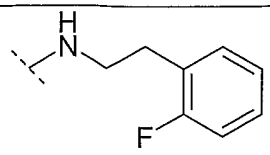
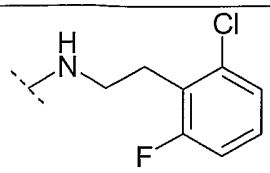
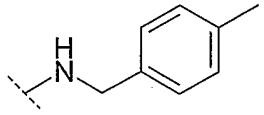
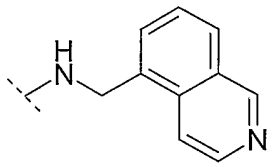
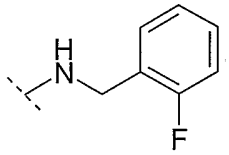
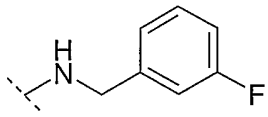
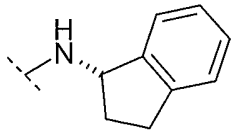
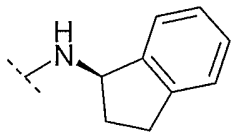
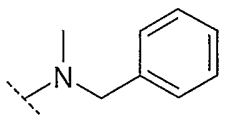
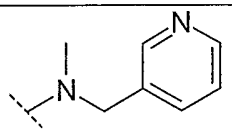
72		377 $[M+H]^+$	6.34
73		329 $[M+H]^+$	6.02
74		377 $[M+H]^+$	2.55 (Method Ia)
75		363 $[M+H]^+$	6.25
76		379 $[M+H]^+$	6.42
77		379 $[M+H]^+$	6.39
78		341 $[M+H]^+$	5.98
79		363 $[M+H]^+$	6.42

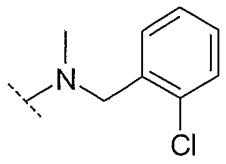
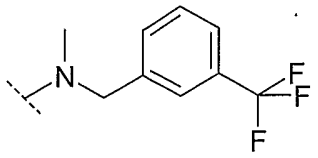
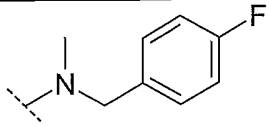
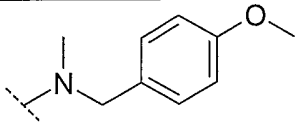
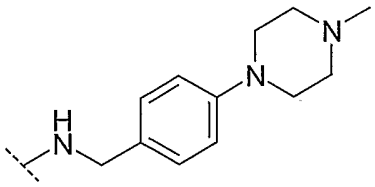
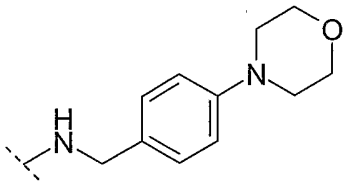
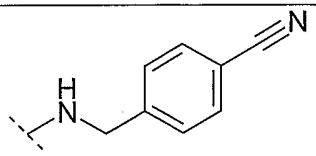
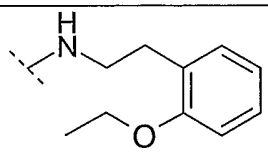
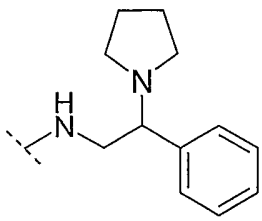
80		320 $[M+H]^+$	4.04
81		331 $[M+H]^+$	5.01
82		308 $[M+H]^+$	2.42
83		302 $[M+H]^+$	2.18
84		378 $[M+H]^+$	1.54 (Method IIa)
85		344 $[M+H]^+$	3.28
86		386 $[M+H]^+$	1.52 (Method IIa)
87		370 $[M+H]^+$	1.52 (Method IIa)

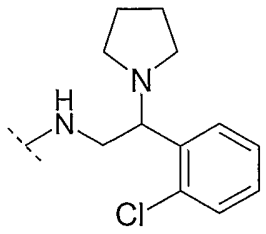
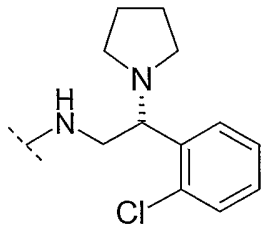
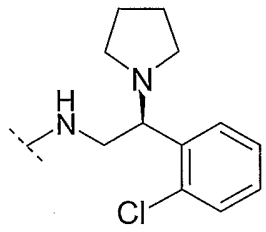
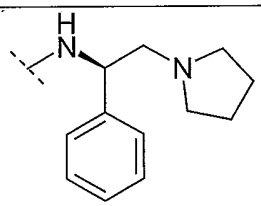
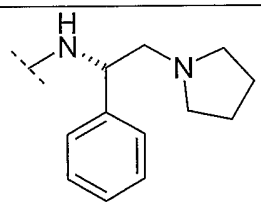
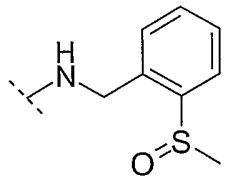
88		315 $[M+H]^+$	5.38
89		315 $[M+H]^+$	5.57
90		404 $[M+H]^+$	1.55 (Method IIa)
91		370 $[M+H]^+$	1.54 (Method IIa)
92		369 $[M+H]^+$	6.15
93		315 $[M+H]^+$	5.48
94		315 $[M+H]^+$	5.46
95		335 $[M+H]^+$	5.77

96		335 $[M+H]^+$	5.65
97		331 $[M+H]^+$	5.44
98		331 $[M+H]^+$	4.95
99		331 $[M+H]^+$	5.82
100		331 $[M+H]^+$	4.99
101		331 $[M+H]^+$	5.30
102		331 $[M+H]^+$	5.30
103		327 $[M+H]^+$	5.82
104		380 $[M+H]^+$	3.97

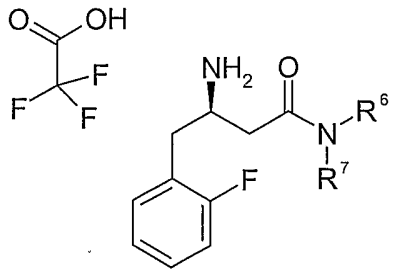
105		377 $[M+H]^+$	6.88
106		371 $[M+H]^+$	6.26
107		349 $[M+H]^+$	5.91
108		400 $[M+H]^+$	2.02 (Method Ia)
109		384 $[M+H]^+$	1.52 (Method IIa)
110		319 $[M+H]^+$	5.49
111		319 $[M+H]^+$	5.50
112		335 $[M+H]^+$	5.92

113		319 $[M+H]^+$	5.46
114		353 $[M+H]^+$	5.45
115		301 $[M+H]^+$	5.44
116		338 $[M+H]^+$	3.14
117		305 $[M+H]^+$	2.01 (Method Ia)
118		305 $[M+H]^+$	2.11 (Method Ia)
119		313 $[M+H]^+$	2.20 (Method Ia)
120		313 $[M+H]^+$	2.18 (Method Ia)
121		301 $[M+H]^+$	2.16 (Method Ia)
122		302 $[M+H]^+$	1.42

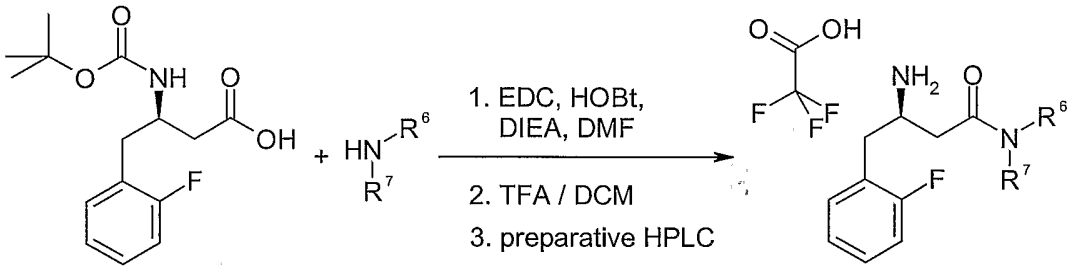
123		335 $[M+H]^+$	3.42
124		369 $[M+H]^+$	3.55
125		319 $[M+H]^+$	3.13
126		331 $[M+H]^+$	3.19
127		385 $[M+H]^+$	2.47
128		372 $[M+H]^+$	2.61
129		312 $[M+H]^+$	2.93
130		345 $[M+H]^+$	2.42 (Method Ia)
131		370 $[M+H]^+$	1.54 (Method IIa)

132		404/406 $[M+H]^+$	2.21 (Method IIa)
133		404/406 $[M+H]^+$	5.74 (Method Va)
134		404/406 $[M+H]^+$	5.94 (Method Va)
135		370 $[M+H]^+$	6.18 (Method Va)
136		370 $[M+H]^+$	5.73 (Method Va)
137		349 $[M+H]^+$	1.91 (Method Va)

Compounds listed in Table 6 with the formula

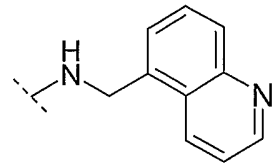
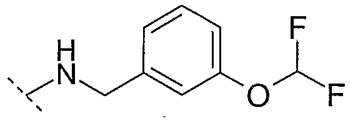
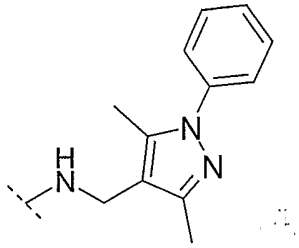
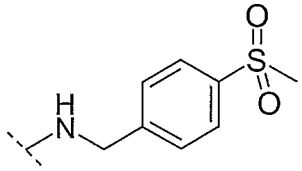
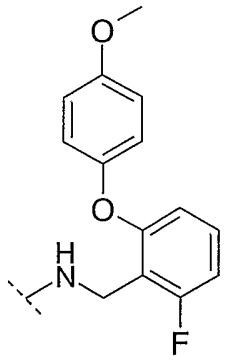
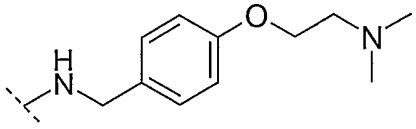


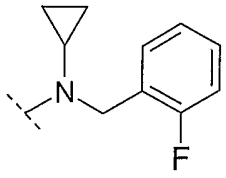
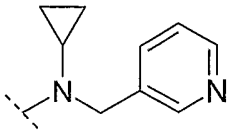
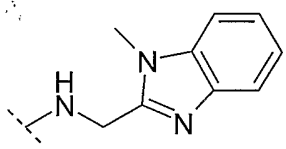
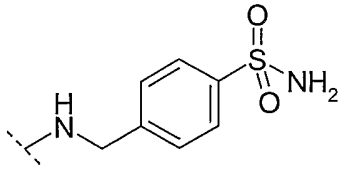
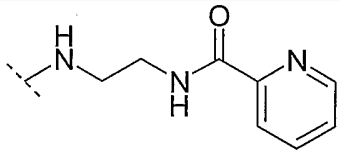
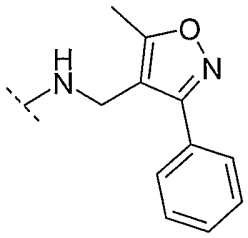
are prepared according to the following experimental procedure described in Scheme J:

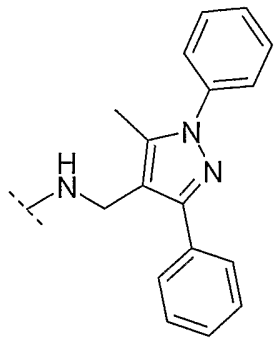
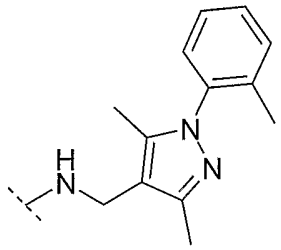
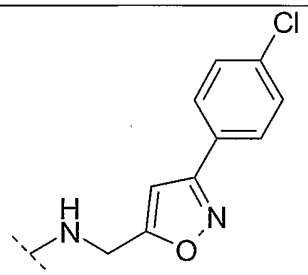
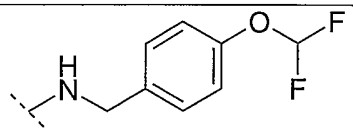
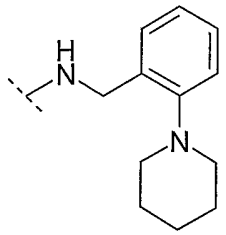
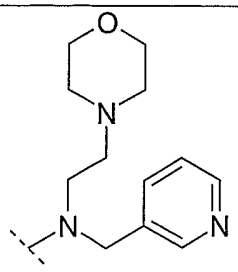


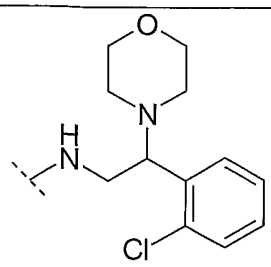
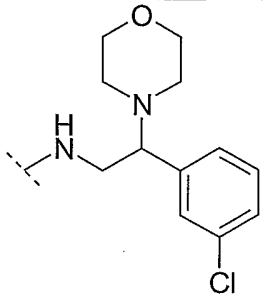
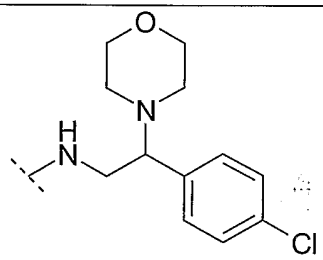
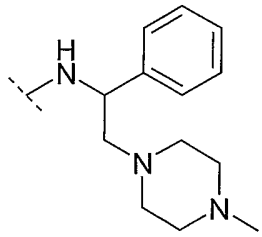
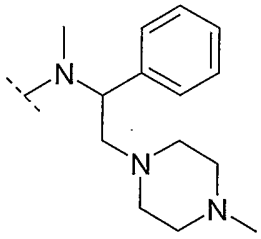
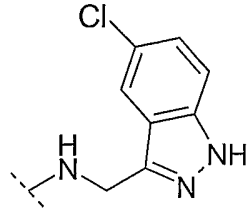
To 100 µL of a 0.5M *N,N*-Dimethylformamide solution of *(3R)-tert*-butoxycarbonylamino-4-[2-fluoro-phenyl]-butyric acid in a well of a 96-MTP are added sequentially 140 µL of a 0.5M *N,N*-Dimethylformamide solution of 1-hydroxybenzotriazole, 140 µL of a 0.5M *N,N*-Dimethylformamide solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 20 µL (0.15 mmol) of diisopropylethylamine. After 15 min at room temperature 0.06 mmol of the corresponding amine dissolved in 100 µL of *N,N*-Dimethylformamide is added and the reaction mixture is stirred overnight at room temperature. Solvents are removed under vacuum, 500 µL of a solution of trifluoroacetic acid in dichloromethane (33% v/v) is added and the reaction mixture is stirred for 2 h at room temperature. After removal of the solvents under reduced pressure, 500 µL of methanol are added and the crude material is purified using preparative HPLC with a 10 min linear gradient from 5% to 95% acetonitrile in water (0.1% TFA) to afford the title compounds.

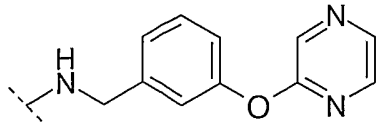
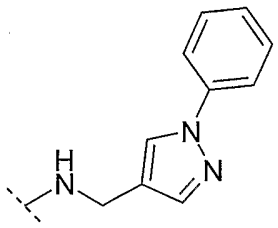
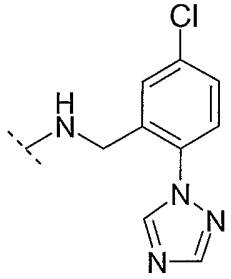
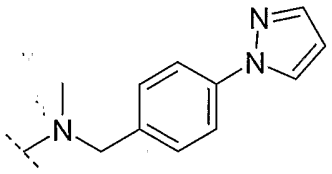
TABLE 6

Ex.	R^6R^7N-	LC/MS data m/z	NMR
138		LC/MS (Va) rt 4.70, m/z 338 $[M+H]^+$.	
139		LC/MS (Ia) rt 2.19, m/z 353 $[M+H]^+$.	
140		LC/MS (Ia) rt 2.05, m/z 381 $[M+H]^+$.	
141		LC/MS (Ia) rt 1.77, m/z 365 $[M+H]^+$.	
142		LC/MS (IVa) rt 3.86, m/z 427 $[M+H]^+$.	
143		LC/MS (IVa) rt 2.17, m/z 374 $[M+H]^+$.	

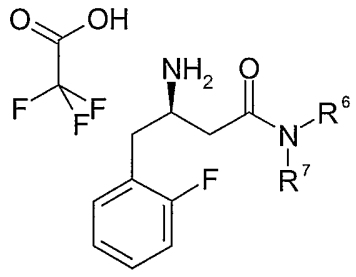
144		LC/MS (Ia) rt 2.24, m/z 345 $[M+H]^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 0.70 (m, 4H), 2.56 (m, 2H), 2.79-3.09 (m, 4H), 4.52 (s, 2H), 7.09-7.29 (m, 8H), 7.99 (s, 2H, NH).
145		LC/MS (IVa) rt 4.65, m/z 328 $[M+H]^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 0.75 (m, 3H), 1.26 (m, 1H), 2.58 (m, 2H), 2.79-3.16 (m, 4H), 4.55 (s, 2H), 7.12-7.19 (m, 2H), 7.27-7.31 (m, 1H), 7.46-7.50 (m, 1H), 7.93 (m, 1H), 8.51 (s, 2H, NH).
146		LC/MS (IVa) rt 2.31, m/z 341 $[M+H]^+$.	
147		LC/MS (IVa) rt 2.35, m/z 366 $[M+H]^+$.	
148		LC/MS (IVa) rt 1.94, m/z 345 $[M+H]^+$.	
149		LC/MS (Ia) rt 2.18, m/z 368 $[M+H]^+$.	

150		LC/MS (IVa) rt 3.98, m/z 429 $[M+H]^+$.	
151		LC/MS (Ia) rt 2.11, m/z 395 $[M+H]^+$.	
152		LC/MS (Ia) rt 2.40, m/z 388 $[M+H]^+$.	
153		LC/MS (Ia) rt 2.27, m/z 353 $[M+H]^+$.	
154		LC/MS (IVa) rt 2.45, m/z 370 $[M+H]^+$.	
155		LC/MS (IVa) rt 3.89, m/z 401 $[M+H]^+$.	

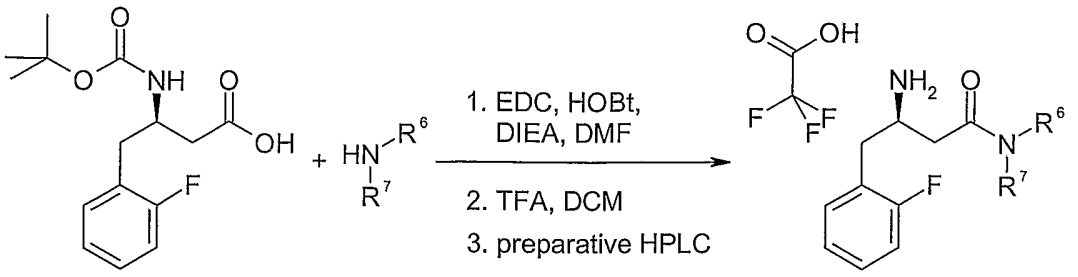
156		LC/MS (VIa) rt 3.12, m/z 420 $[M+H]^+$.	
157		LC/MS (VIa) rt 3.31, m/z 420 $[M+H]^+$.	
158		LC/MS (VIa) rt 3.42, m/z 420 $[M+H]^+$.	
159		LC/MS (VIa) rt 3.09, m/z 399 $[M+H]^+$.	
160		LC/MS (VIa) rt 3.58, m/z 413 $[M+H]^+$.	
161		LC/MS (VIa) rt 4.15, m/z 361 $[M+H]^+$.	

162		LC/MS (VIa) rt 3.77, m/z 381 $[M+H]^+$.	
163		LC/MS (VIa) rt 3.95, m/z 353 $[M+H]^+$.	
164		LC/MS (VIa) rt 3.72, m/z 388 $[M+H]^+$.	
165		LC/MS (VIa) rt 4.25, m/z 367 $[M+H]^+$.	

Compounds listed in Table 7 with the formula

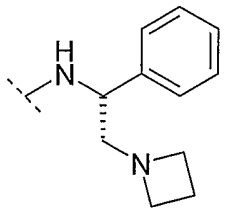
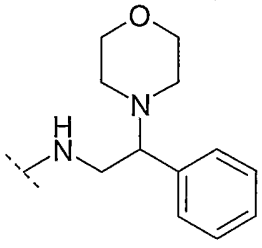


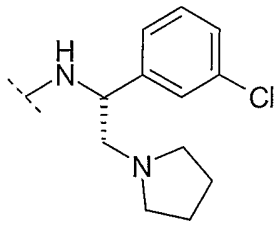
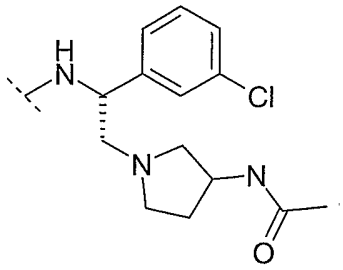
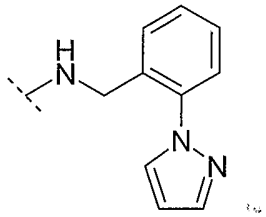
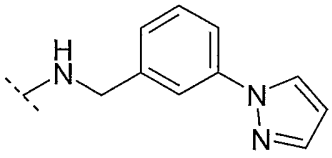
are prepared according to the following experimental procedure described in Scheme J:

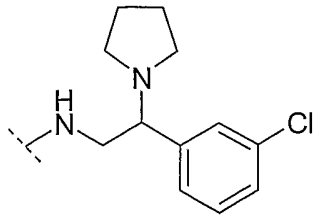
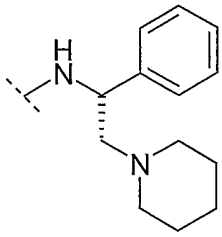
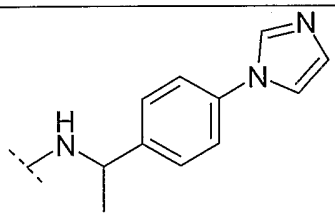
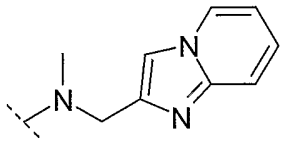
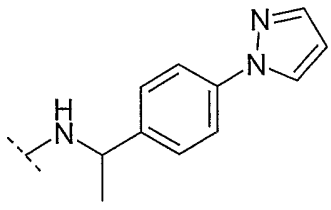


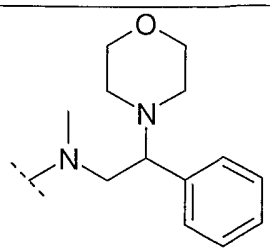
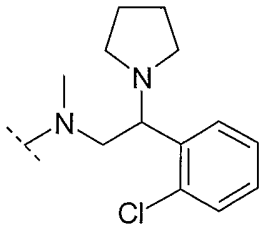
To 26.4 mg (0.089 mmol) of *(3R)-tert*-butoxycarbonylamino-4-[2-fluoro-phenyl]-butyric acid dissolved in 1 mL *N,N*-Dimethylformamide are added 16.8 mg (0.124 mmol) of 1-hydroxybenzotriazole, 23.9 mg (0.124 mmol) 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride and 22 µL (0.124 mmol) of diisopropylethylamine. After 15 min stirring at room temperature 0.107 mmol of the corresponding amine are added and the reaction mixture is stirred overnight at room temperature. Solvents are removed in vacuum, 500 µL of a solution of trifluoroacetic acid in dichloromethane (33% v/v) are added and the reaction mixture is stirred for 2 h at room temperature. After removal of the solvents under reduced pressure, 500 µL of methanol are added and the crude material is purified using preparative HPLC with a 10 min linear gradient from 5% to 95% acetonitrile in water (0.1% TFA) to afford the title compounds.

TABLE 7

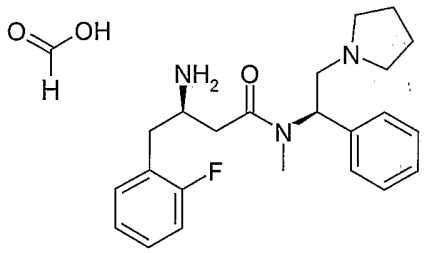
Ex.	R^6R^7N-	LC/MS data m/z	NMR
166		LC/MS (Va) rt 5.73, m/z 356 $[M+H]^+$.	
167		LC/MS (Va) rt 5.41, m/z 386 $[M+H]^+$.	

168		LC/MS (Va) rt 7.24, m/z 404 $[M+H]^+$.	
169		LC/MS (VIa) rt 3.45, m/z 462 $[M+H]^+$.	
170		LC/MS (VIa) rt 3.07, m/z 354 $[M+H]^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 2.44 (m, 2H), 2.82 (dd, 1H, J = 13.5 Hz, J = 8.3 Hz), 2.95 (dd, 1H, J = 14.0 Hz, J = 5.7 Hz), 3.66 (m, 1H), 4.18 (d, 2H, J = 5.1 Hz), 6.44 (m, 1H), 7.13 - 7.38 (m, 8H), 7.66 (m, 1H), 7.94 (bs, 2H), 7.97 (m, 1H), 8.44 (t, 1H, J = 5.4 Hz).
171		LC/MS (VIa) rt 3.23, m/z 353 $[M+H]^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 2.5 (m, 2H, covered by DMSO), 2.87 (dd, 1H, J = 13.5 Hz, J = 8.3 Hz), 2.99 (dd, 1H, J = 14.0 Hz, J = 5.7 Hz), 3.69 (m, 1H), 4.30 (m, 2H), 6.49 (m, 1H), 7.13 - 7.69 (m, 9H), 7.98 (bs, 2H), 8.37 (m, 1H), 8.60 (t, 1H, J = 5.4 Hz).

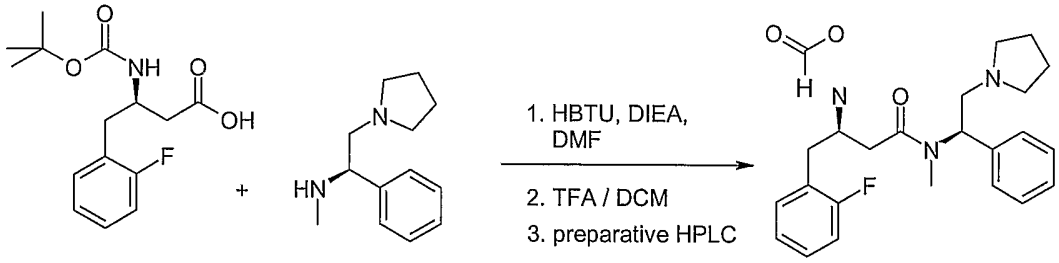
172		LC/MS (Va) rt 6.43, m/z 404 $[M+H]^+$.	
173		LC/MS (Va) rt 6.58, m/z 384 $[M+H]^+$.	
174		LC/MS (Va) rt 5.25, m/z 367 $[M+H]^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 1.35 (dd, 3H, J = 9.6 Hz, J = 7.2 Hz), 2.5 (m, 2H, covered by DMSO), 2.87 (dd, 1H, J = 13.5 Hz, J = 8.3 Hz), 2.95 (m, 2H), 3.69 (m, 1H), 4.91 (m, 1H), 6.49 (m, 1H), 7.13 - 7.26 (m, 3H), 7.44-7.50 (m, 2H), 7.67-7.71 (m, 2H), 7.82 (s, 1H), 8.06 (bs, 2H), 8.63 (t, 1H, J = 5.4 Hz)), 9.53 (m, 1H).
175		LC/MS (Va) rt 5.34, m/z 341 $[M+H]^+$.	^{1}H-NMR (300 MHz, DMSO-d_6) δ = 2.67-2.78 (m, 2H), 2.91-3.09 (m, 6H), 3.69 (m, 1H), 4.91 (m, 1H), 4.76 (m, 1H), 7.02-7.42 (m, 5H), 7.73-7.86 (m, 2H), 8.08 (bs, 2H), 8.18 (s, 1H), 8.78 (m, 1H).
176		LC/MS (VIa) rt 3.91, m/z 488 $[M+Na+H]^+$.	

177		LC/MS (Va) rt 6.14, m/z 400 $[M+H]^+$.	
178		LC/MS (Va) rt 6.36, m/z 418 $[M+H]^+$.	

Example 179



step 1



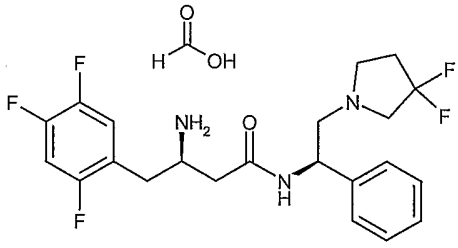
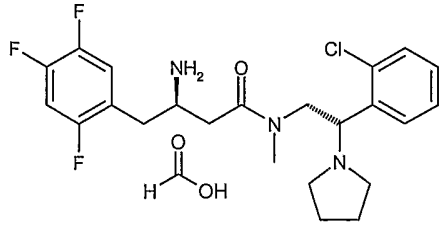
(*R*)-3-Amino-4-(2-fluoro-phenyl)-*N*-methyl-N-(1-phenyl-2-pyrrolidin-1-yl-ethyl)-butyramide formic acid.

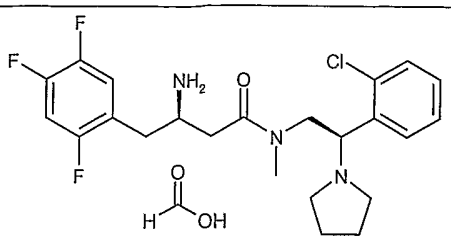
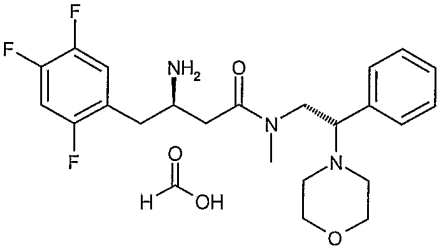
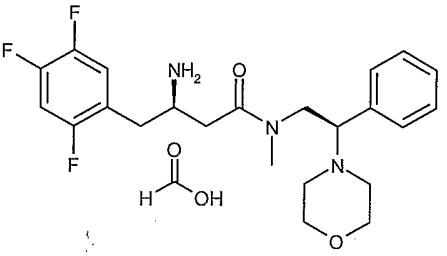
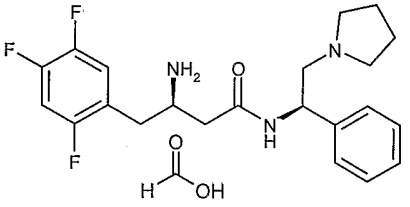
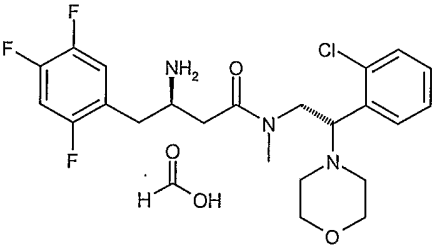
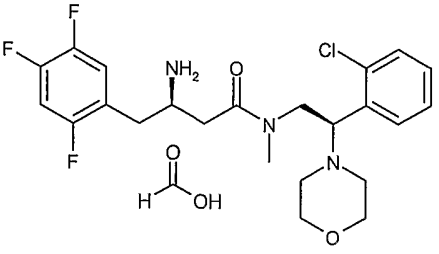
To 40.0 mg (0.13 mmol) of *(3R)-tert*-butoxycarbonylamino-4-[2-fluoro-phenyl]-butyric acid dissolved in 3 mL *N,N*-Dimethylformamid including 1.0 eq of triethylamine are

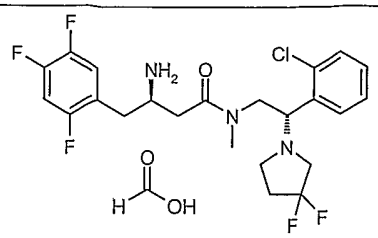
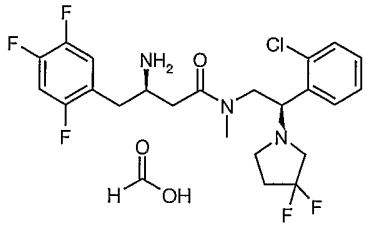
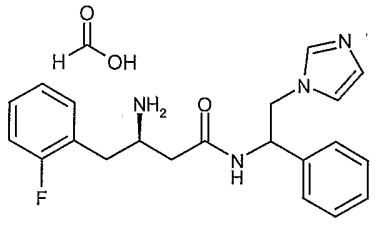
added 51.2 mg (0.13 mmol) of O-(benzotrialzol-1-YL)-*N*-*N*-*N*-*N*–tetramethyluronium hexafluoro phosphate (HBTU). After 15 min. at room temperature 35.7 mg (0.176 mmol) of (*R*)-methyl-(1-phenyl-2-pyrrolidin-1-yl-ethyl)-amine and 37.2 µL (0.338 mmol) of *N*-methylmorpholine are added and the reaction mixture is stirred overnight at 50°C. Solvents are removed under vacuum, 500 µL of a solution of trifluoroacetic acid in dichloromethane (33% v/v) is added and the reaction mixture is stirred for 2 h at room temperature. After removal of the solvents under reduced pressure, 500 µL of methanol are added and the crude material is purified using preparative HPLC with a 10 min linear gradient from 5% to 95% acetonitrile in water (0.1% TFA) to afford the title compound. Diastereomeres generated from racemic amines are separated via reversed phase HPLC. The absolute configuration for these diastereomeres is not assigned.

The compounds listed in Table 8 are prepared according to the experimental procedure outlined for Example **179**:

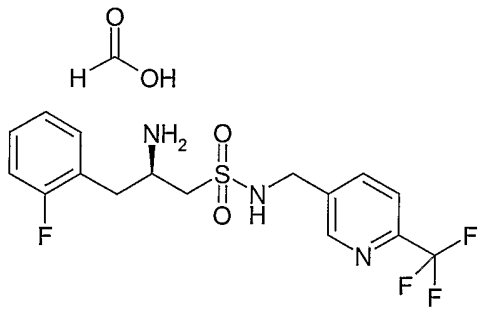
TABLE 8

Ex.	R^6R^7N-	LC/MS data m/z	NMR
180		LC/MS (VIa) rt 2.92, m/z 442 $[M+H]^+$.	^{1}H-NMR (300 MHz, MeOD) δ = 2.17-2.31 (m, 2H), 2.54-2.59 (m, 3H), 2.88-3.19 (m, 7H), 3.71 (m, 1H), 5.10 (m, 1H), 7.33 - 7.45 (m, 7H).
181		LC/MS (Va) rt 4.25, m/z 454 $[M+H]^+$.	

182		LC/MS (Va) rt 5.04, m/z 454 $[M+H]^+$.	
183		LC/MS (Va) rt 4.40, m/z 436 $[M+H]^+$.	
184		LC/MS (Va) rt 4.38, m/z 436 $[M+H]^+$.	
185		LC/MS (Va) rt 5.89, m/z 406 $[M+H]^+$.	
186		LC/MS (Va) rt 5.94, m/z 470 $[M+H]^+$.	
187		LC/MS (Va) rt 5.94, m/z 470 $[M+H]^+$.	

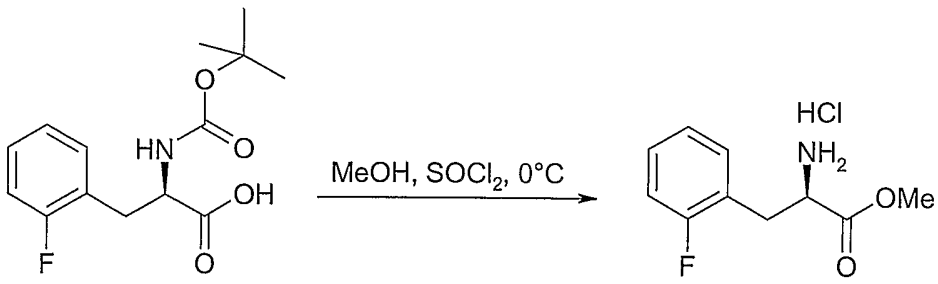
188		LC/MS (Vb) rt 4.37, m/z 490 $[M+H]^+$.	
189		LC/MS (Vb) rt 4.43, m/z 490 $[M+H]^+$.	
190		LC/MS (Vb) rt 4.27, m/z 367 $[M+H]^+$.	

Example 191



Procedure for making a compound of the invention according to Scheme H.

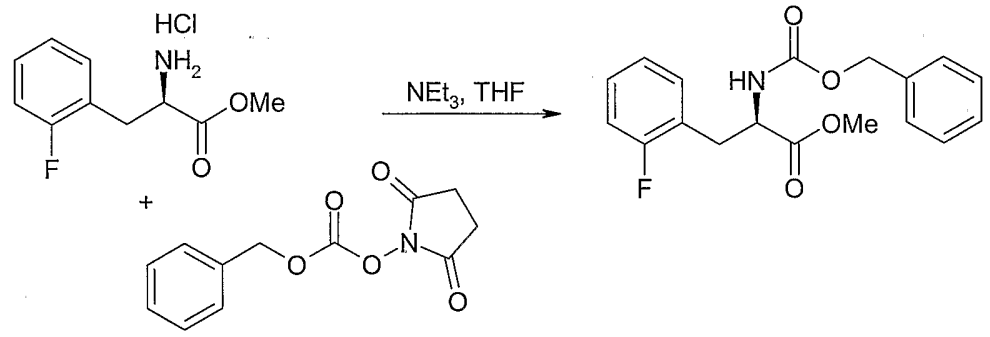
Step 1



(*R*)-2-Amino-3-(2-fluoro-phenyl)-propionic acid methyl ester hydrochloride

1.50 g (5.11 mmol) of (*R*)-2-*tert*-butoxycarbonylamino-3-(2-fluoro-phenyl)-propionic acid are dissolved in 10 mL of methanol. The solution is cooled to 0°C and 450 µL (6.14 mmol) of thionylchloride are added dropwise via a syringe. Then the mixture is allowed to warm to room temperature and stirred for 12 h. The solvent is removed under reduced pressure and the crude product is used in the next step without further purification.

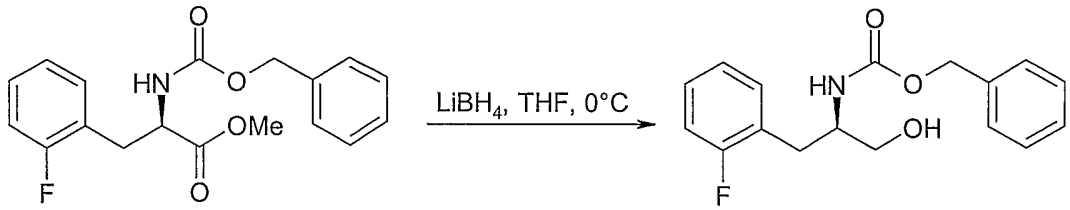
Step 2



(*R*)-2-Benzyloxycarbonylamino-3-(2-fluoro-phenyl)-propionic acid methyl ester

1.22 g (5.2 mmol) of crude (*R*)-2-amino-3-(2-fluoro-phenyl)-propionic acid methyl ester hydrochloride from step 1 are suspended in 10 mL of tetrahydrofuran. Then 1.81 mL (13.1 mmol) of triethylamine and 1.56 g (6.26 mmol) of *N*-(benzyl-oxycarbonyloxy)succinimide are added, followed by enough water to completely dissolve the mixture. The resulting solution is stirred for 12 h at room temperature and the organic solvent is removed under reduced pressure. The residue is diluted with 10 mL of saturated sodium bicarbonate solution and extracted 3 times with ethyl acetate. The combined organic layers are washed with brine, dried with sodium sulphate and the solvent is evaporated. The crude product is used in step 3 without any further purification.

Step 3

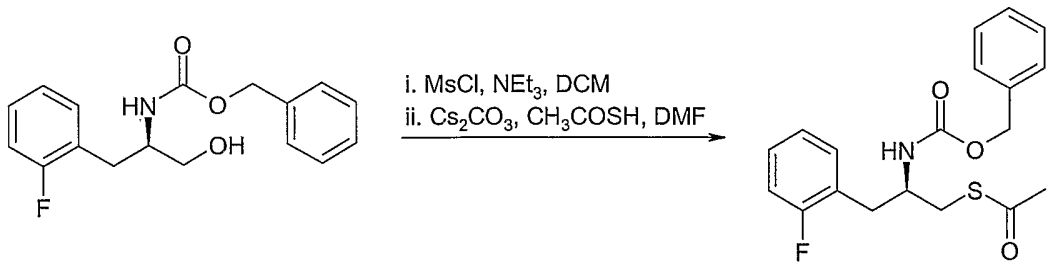


[(*R*)-2-(2-Fluoro-phenyl)-1-hydroxymethyl-ethyl]-carbamic acid benzyl ester

1.60 g (4.82 mmol) of (*R*)-2-benzyloxycarbonylamino-3-(2-fluoro-phenyl)-propionic acid methyl ester from step 2 is dissolved in 10 mL of tetrahydrofuran and the solution is cooled to 0°C. Then 2.8 mL (5.78 mmol) of a 2 M solution of lithium borohydride in tetrahydrofuran are added dropwise and the mixture is allowed to warm to room temperature. After 2 h stirring at room temperature, methanol is added and the mixture is stirred for another 30 min. The solvent is evaporated and the residue is taken up in dichloromethane. The solution is washed with 1 M aqueous hydrochloric acid solution, saturated sodium bicarbonate solution, water and brine, dried with sodium sulphate and evaporated to dryness.

LCMS (Ia) rt 2.28 min, 260, 304 $(M+H)^+$, 345 $(M+CH_3CN)^+$.

Step 4



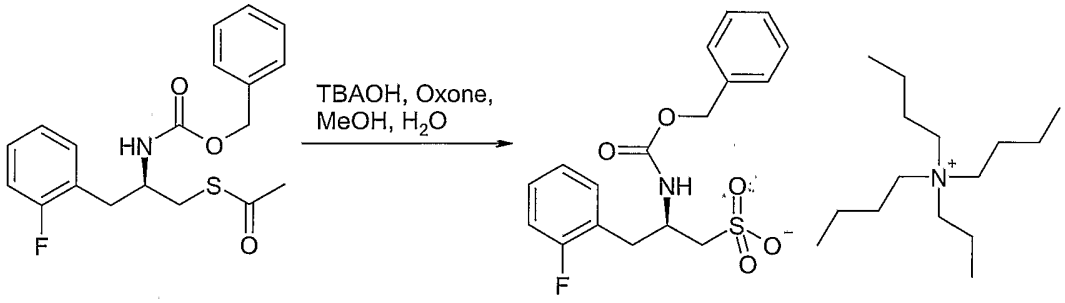
Thioacetic acid *S*-[(*R*)-2-benzyloxycarbonylamino-3-(2-fluoro-phenyl)-propyl] ester

1.27 g (4.19 mmol) of [(*R*)-2-(2-fluoro-phenyl)-1-hydroxymethyl-ethyl]-carbamic acid benzyl ester from step 3 are dissolved in 20 mL of dichloromethane and the solution is cooled to 0°C. Then 1.28 mL (9.21 mmol) of triethylamine followed by 0.49 mL (6.28 mmol) methanesulfonylchlorid in 10 mL dichloromethane are added. The resulting mixture is stirred for 1 h at 0°C, washed with water, dried with sodium sulphate, and the solvent is removed under reduced pressure. The crude mesylate is dissolved in 10 mL *N*,*N*-dimethyl formamide and transfered into a flask, wrapped in aluminium foil, that had

been charged with 0.89 g (2.73 mmol) cesium carbonate, 10 mL *N,N*-dimethyl formamide and 0.36 mL (5.03 mmol) thioacetic acid. The reaction mixture is stirred for 12 h at room temperature. Afterwards the solution is poured into 50 mL of brine and the mixture is extracted 3 times with ethyl acetate. The combined organic layers are washed with saturated sodium bicarbonate solution and brine, and is dried over sodium sulphate. Then the solvent is evaporated and the crude product is purified by column chromatography on silica gel with cyclohexane:ethyl acetate (80:20) as eluent. The product is further recrystalized from cyclohexane.

LCMS (Ia) rt 3.20 min, 302, 318, 363 $(M+H)^+$, 384 $(M-H+Na)^+$, 403 $(M+CH_3CN)^+$, 425 $(M+CH_3CN+Na)^+$.

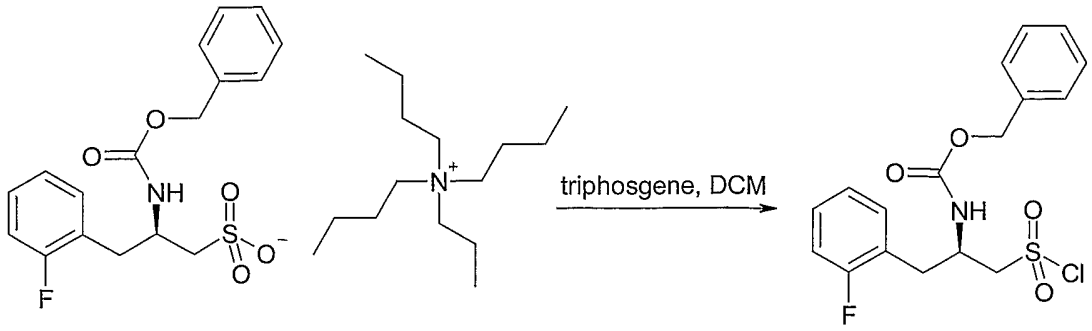
Step 5



(*R*)-2-Benzyloxycarbonylamino-3-(2-fluoro-phenyl)-propane-1-sulphonate tetra-*n*-butyl ammonium salt

942 mg (2.61 mmol) of thioacetic acid *S*-[(*R*)-2-benzyloxycarbonylamino-3-(2-fluoro-phenyl)-propyl] ester from step 4 are dissolved in 80 mL of methanol and a solution of 4.00 g (6.50 mmolq) oxone in 80 mL of water is added. After stirring for 30 min at room temperature a solution of 4.00 mL of aqueous tetra-*n*-butyl ammonium hydroxide solution (40 %) in 20 mL of water is added and the resulting mixture is stirred for 12 h at room temperature. Then most of the methanol is evaporated and the residue is diluted with 80 mL of water and extracted 3 times with dichloromethane. The combined organic layers are dried with sodium sulphate and the solvent is evaporated.

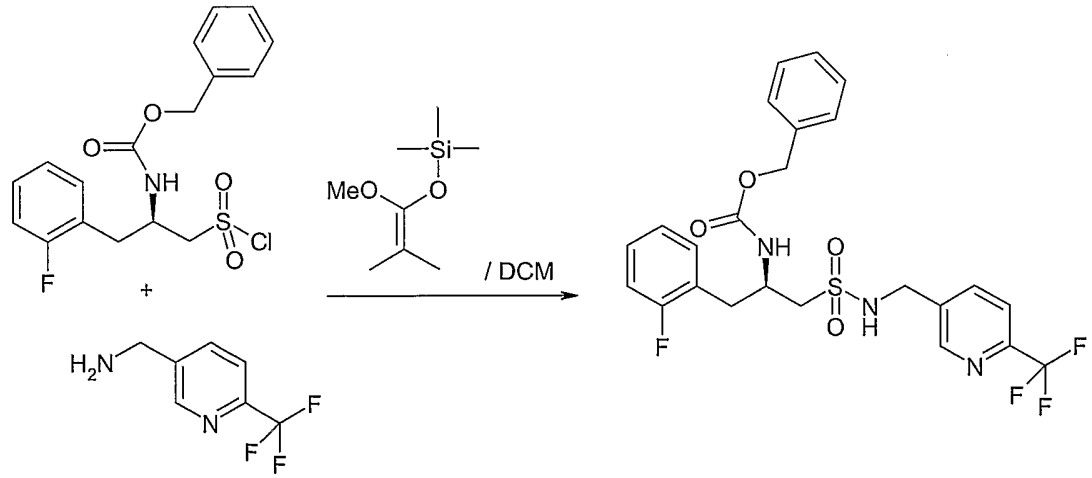
Step 6



[(*R*)-1-Chlorosulphonylmethyl-2-(2-fluoro-phenyl)-ethyl]-carbamic acid benzyl ester

441 mg (0.72 mmol) of the tetra-*n*-butyl ammonium salt of (*R*)-2-benzyloxycarbonyl-amino-3-(2-fluoro-phenyl)-propane-1-sulphonic acid from step 5 are dissolved in 4.5 mL of dichloromethane. To this mixture a solution of 144 mg (0.49 mmol) of triphosgene in 1 mL of dichloromethane is added and the reaction mixture is stirred for 2 h at room temperature. The solvent is removed under reduced pressure and the crude product is purified by column chromatography on silica gel with cyclo-hexane:ethyl acetate (70:30) as eluent.

Step 7

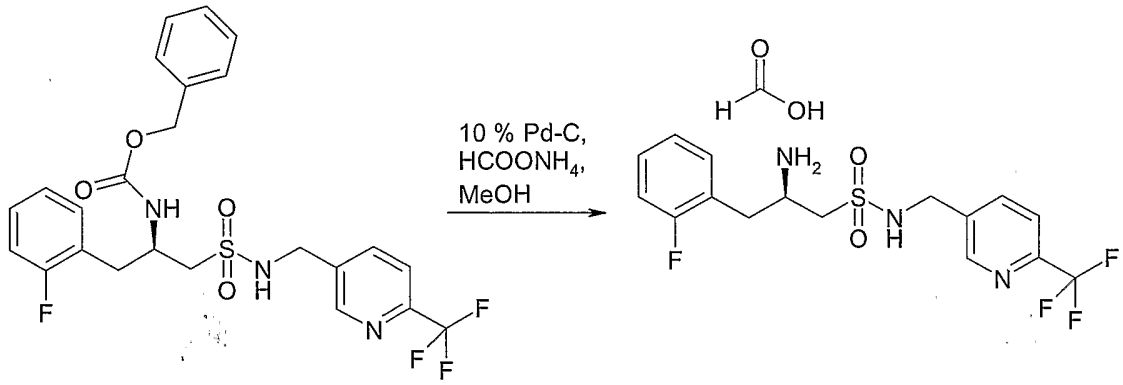


((*R*)-2-(2-Fluoro-phenyl)-1-{[(6-trifluoromethyl-pyridin-3-ylmethyl)-sulphamoyl]-methyl}-ethyl)-carbamic acid benzyl ester

16.4 mg (0.09 mmol) of 3-aminomethyl-6-(trifluoromethyl)pyridine are dissolved in 500 µL dichloromethane and 20.3 mg (0.12 mmol) of 1-methoxy-1-(trimethylsiloxy)-2-methyl-1-propane dissolved in 500 µL dichloromethane are added. This mixture is aged

for 5 min at room temperature and added to a solution of 30.0 mg (0.08 mmol) of [(*R*)-1-chlorosulphonylmethyl-2-(2-fluoro-phenyl)-ethyl]-carbamic acid benzyl ester from step 6 in 2 mL of dichloromethane. After stirring the solution for 48 h at room temperature the solvent is evaporated and the residue is purified by column chromatography on silica gel with cyclohexane:ethyl acetate (70:30) as eluent.
LCMS (Ia) rt 4.33 min, 526 $(M+H)^+$, 548 $(M+Na)^+$, 589 $(M+Na+CH_3CN)^+$.

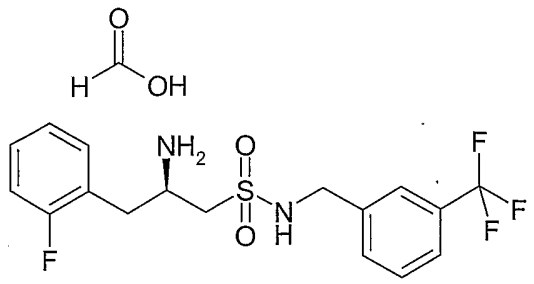
Step 8



(*R*)-2-Amino-3-(2-fluoro-phenyl)-propane-1-sulphonic acid (6-trifluoromethyl-pyridin-3-ylmethyl)-amide

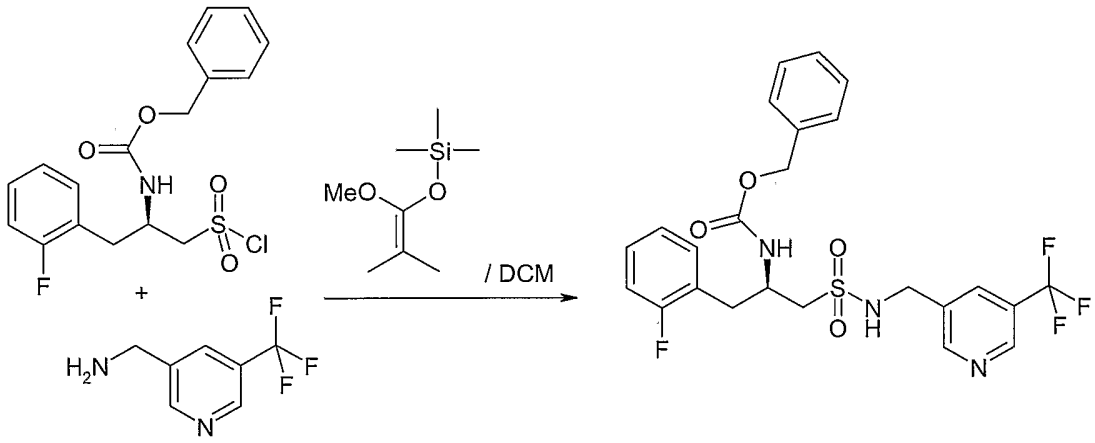
15.5 mg (0.03 mmol) of ((*R*)-2-(2-fluoro-phenyl)-1-{[(6-trifluoromethyl-pyridin-3-ylmethyl)-sulphamoyl]-methyl}-ethyl)-carbamic acid benzyl ester from step 7 are dissolved in 2 mL of methanol. Then 5.6 mg (0.09 mmol) of ammonium formate and 15 mg of 10 % palladium on charcoal is added and the reaction mixture is heated to reflux for 45 min. The mixture is filtered through celite and the filtrate is evaporated to dryness and purified by preparative HPLC.
^{1}H-NMR (300 MHz, DMSO-d_6) δ = 2.66-2.71 (m, 2H), 3.02-3.08 (m, 2H), 3.37-3.38 (m, 1H), 4.19-4.30 (m, 2H), 7.14-7.32 (m, 5H), 7.90 (d, 1H), 8.00 (d, 1H), 8.70 (s, 1H).
LCMS (Va) rt 6.82 min, 374, 392 $(M+H)^+$, 415 $(M+Na)^+$, 433 $(M+CH_3CN)^+$.

Example 192



Steps 1- 6 are carried out according to example **191**.

Step 7

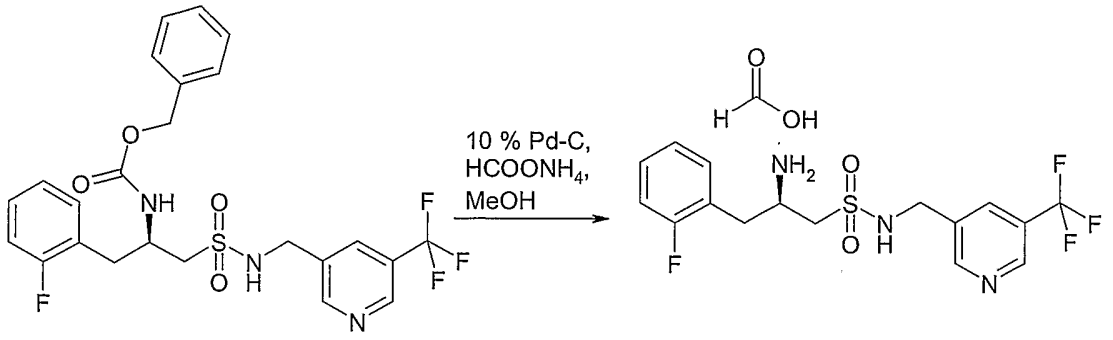


{(*R*)-2-(2-Fluoro-phenyl)-1-[(3-trifluoromethyl-benzylsulphamoyl)-methyl]-ethyl} carbamic acid benzyl ester

16.3 mg (0.09 mmol) of 3-(trifluoromethyl)benzyl amine are dissolved in 500 µL dichloromethane and 20.3 mg (0.12 mmol) of 1-methoxy-1-(trimethylsiloxy)-2-methyl-1-propane dissolved in 500 µL dichloromethane are added. This mixture is aged for 5 min at room temperature and added to a solution of 30.0 mg (0.08 mmol) of [(*R*)-1-chlorosulfonylmethyl-2-(2-fluoro-phenyl)-ethyl]-carbamic acid benzyl ester in 2 mL of dichloromethane. After stirring the solution for 48 h at room temperature the solvent is evaporated and the residue is purified by column chromatography on silica gel with cyclohexane:ethyl acetate (70:30) as eluent.

LCMS (Ia) rt 4.65 min, 481, 525 $(M+H)^+$, 547 $(M+Na)^+$, 588 $(M+Na+CH_3CN)^+$.

Step 8



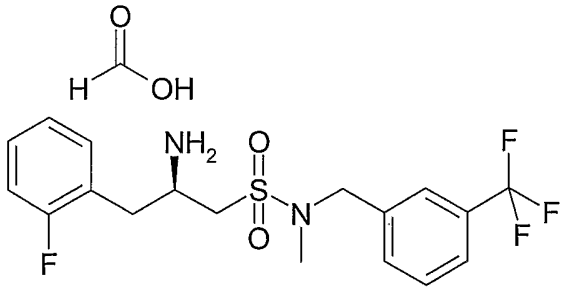
(*R*)-2-Amino-3-(2-fluoro-phenyl)-propane-1-sulphonic acid 3-trifluoromethyl-benzyl-amide

18.0 mg (0.03 mmol) of {(*R*)-2-(2-fluoro-phenyl)-1-[(3-trifluoromethyl-benzylsulphamoyl)- methyl]-ethyl}-carbamic acid benzyl ester from step 7 are dissolved in 2 mL of methanol. Then 6.5 mg (0.10 mmol) of ammonium formate and 18 mg of 10 % palladium on charcoal is added and the reaction mixture is heated to reflux for 45 min. The mixture is filtered through celite and the filtrate is evaporated to dryness and purified by preparative HPLC.

^{1}H-NMR (300 MHz, DMSO-d_6) δ = 2.65-2.70 (m, 2H), 3.01-3.08 (m, 2H), 3.38-3.40 (m, 1H), 4.12-4.24 (m, 2H), 7.14-7.32 (m, 5H), 7.58-7.68 (m, 4H).

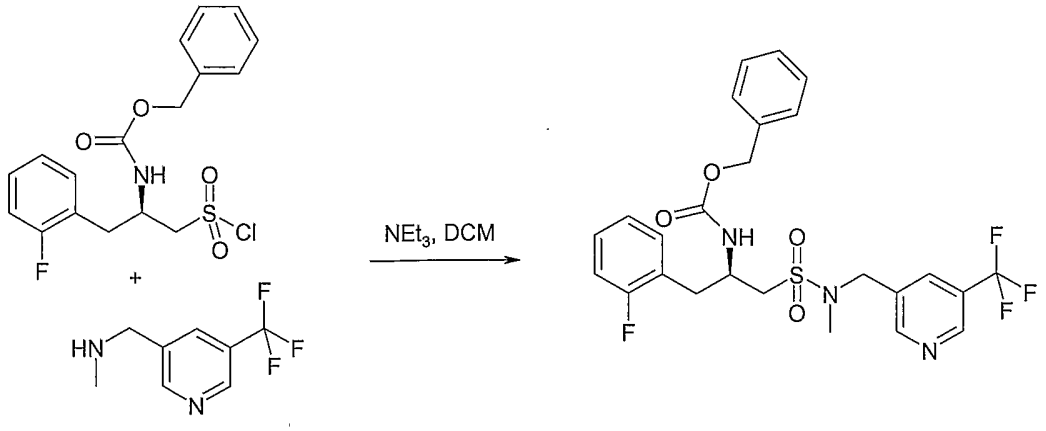
LCMS (Va) rt 8.86 min, 373, 391 $(M+H)^+$, 414 $(M+Na)^+$, 432 $(M+ CH_3CN)^+$.

Example 193



Steps 1- 6 are carried out according to example **191**.

Step 7

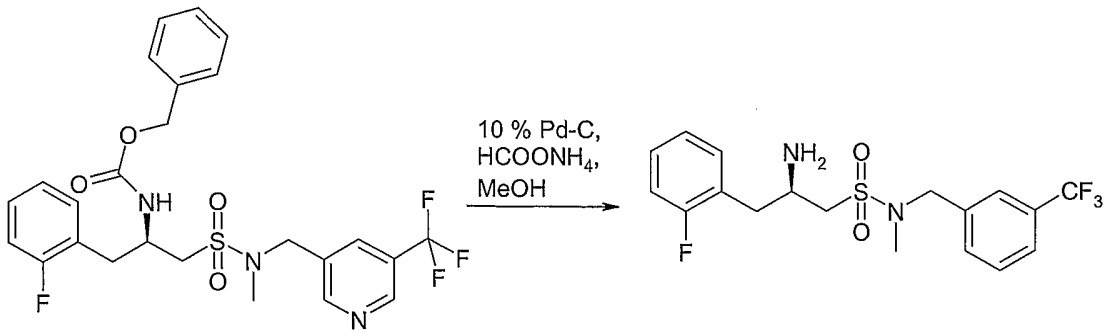


((*R*)-2-(2-Fluoro-phenyl)-1-{[methyl-(3-trifluoromethyl-benzyl)-sulphamoyl]-methyl}-ethyl)-carbamic acid benzyl ester

30.0 mg (0.08 mmol) of [(*R*)-1-chlorosulphonylmethyl-2-(2-fluoro-phenyl)-ethyl]-carbamic acid benzyl ester are dissolved in 2 mL of dichloromethane. Then 12.8 µL (0.09 mmol) of triethylamine and 14.6 mg (0.08 mmol) of *N*-methyl-*N*-[3-trifluoromethyl)benzyl]amine are added and the resulting mixture is stirred for 12 h at room temperature.

LCMS (Ia) rt 4.89 min, 539 $(M+H)^+$, 561 $(M+Na)^+$, 602 $(M+Na+CH_3CN)^+$.

Step 8



(R)-2-Amino-3-(2-fluoro-phenyl)-propane-1-sulphonic acid methyl-(3-trifluoromethyl-benzyl)-amide

17.7 mg (0.03 mmol) of ((*R*)-2-(2-Fluoro-phenyl)-1-{[methyl-(3-trifluoromethyl-benzyl)-sulphamoyl]-methyl}-ethyl)-carbamic acid benzyl ester from step 7 are dissolved in 2 mL of methanol. Then 6.2 mg (0.09 mmol) of ammonium formate and 18 mg of 10 % palladium on charcoal is added and the reaction mixture is heated to reflux for 45 min.

The mixture is filtered through celite and the filtrate is evaporated to dryness and purified by preparative HPLC.
^{1}H-NMR (300 MHz, DMSO-d_6) δ = 2.68 (s, 3H), 2.68-2.93 (m, 2H), 3.45-3.46 (m, 1H), 4.38 (s, 2H), 7.15-7.20 (m, 2H), 7.29-7.36 (m, 2H), 7.64-7.69 (m, 4H).
LCMS (Va) rt 9.52 min, 405 $(M+H)^+$, 446 $(M+CH_3CN)^+$.

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.

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).

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 $\leq$ 100 nM; b $\geq$101 nM and $\leq$ 1001 nM ; c $\geq$1001 nM $\leq$ 2000 nM.

Example	IC_{50}	Example	IC_{50}	Example	IC_{50}	Example	IC_{50}
29	a	53	b	77	b	101	b
30	b	54	b	78	b	102	c
31	b	55	b	79	b	103	b
32	b	56	b	80	b	104	b
33	b	57	b	81	c	105	b
34	b	58	b	82	b	106	b
35	b	59	b	83	b	107	b
36	b	60	b	84	b	108	b
37	b	61	b	85	b	109	b
38	b	62	b	86	b	110	c
39	b	63	a	87	a	111	c
40	b	64	c	88	b	112	b
41	c	65	b	89	b	113	b
42	b	66	b	90	a	114	b
43	c	67	b	91	b	115	b
44	b	68	b	92	b	116	c
45	b	69	c	93	c	117	b
46	b	70	b	94	b	118	b
47	b	71	b	95	b	119	b
48	b	72	b	96	b	120	c
49	b	73	b	97	c	121	b
50	b	74	b	98	c	122	b
51	b	75	b	99	c	123	b
52	b	76	b	100	b	124	b

Example	IC_{50}
125	b
126	b
127	b
128	b
129	b
130	b
131	b
132	b
133	b
134	a
135	a
136	b
137	b
138	b
139	b
140	b
141	b
142	b
143	c
144	b
145	b
146	b
147	b
148	b
149	b

Example	IC_{50}
150	b
151	b
152	b
153	c
154	b
155	b
156	b
157	b
158	b
159	b
160	c
161	b
162	c
163	b
164	b
165	b
166	b
167	b
168	b
169	c
170	b
171	b
172	b
173	b
174	b

Example	IC_{50}
175	c
176	b
177	a
178	a
179	b
180	a
181	a
182	a
183	a
184	a
185	a
186	a
187	a
188	a
189	a
190	b
191	b
192	b
193	b

Claims

1. A compound of the formula (I)

$$Z\text{-}C(R^1R^2)\text{-}C(R^3NH_2)\text{-}C(R^4R^5)\text{-}X\text{-}N(R^6R^7) \qquad (I),$$

or a pharmaceutically acceptable salt thereof, 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^8, wherein R^8 is independently selected from the group consisting of halogen; CN; OH; NH_2; oxo (=O), where the ring is at least partially saturated; R^9; and R^{10};

R^9 is selected from the group consisting of C_{1-6} alkyl; O-C_{1-6} alkyl; and S-C_{1-6} alkyl, wherein R^9 is optionally interrupted by oxygen and wherein R^9 is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{10} is selected from the group consisting of phenyl; heterocycle; and C_{3-7} cycloalkyl, wherein R^{10} is optionally substituted with one or more R^{11}, wherein R^{11} 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^{4a};

R^2, R^5 are independently selected from the group consisting of H; F; and R^{4b};

R^{4a} is independently selected from the group consisting of C_{1-6} alkyl; and O-C_{1-6} alkyl, wherein R^{4a} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{4b} is C_{1-6} alkyl, wherein R^{4b} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

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 independently selected from the group consisting of R^1/R^2; R^2/R^3; R^3/R^4; and R^4/R^5 form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more of R^{12}, wherein R^{12} is independently selected from the group consisting of F; Cl; and OH;

X is selected from the group consisting of S(O); $S(O)_2$; C(O); and $C(R^{13}R^{14})$;

R^{13}, R^{14} are independently selected from the group consisting of H; F; C_{1-6} alkyl; R^{15}; and R^{16};

Optionally one or both pairs of R^5, R^{13}, R^{14} selected from the group consisting of R^5/R^{13}; and R^{13}/R^{14} form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more R^{17}, wherein R^{17} is independently selected from the group consisting of F; Cl; and OH;

R^{15} is selected from the group consisting of phenyl; naphthyl; and indenyl, wherein R^{15} is optionally substituted with one or more R^{18}, wherein R^{18} is independently selected from the group consisting of R^{19}; R^{20}; halogen; CN; COOH; OH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; 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; $C(O)N(R^{21})$-C_{1-6} alkyl; $S(O)_2N(R^{21})$-C_{1-6} alkyl; $S(O)N(R^{21})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{21})S(O)_2$-C_{1-6} alkyl; and $N(R^{21})S(O)$-C_{1-6} alkyl, wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{16} is selected from the group consisting of heterocycle; heterobicycle; C_{3-7} cycloalkyl; indanyl; tertralinyl; and decalinyl, wherein R^{16} is optionally substituted with one or more R^{22}, wherein R^{22} is independently selected from the group consisting of R^{19}; R^{20}; halogen; CN; OH; oxo (=O), where the ring is at least partially saturated; NH_2; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $N(R^{23})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{23})$- C_{1-6} alkyl; $N(R^{23})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{23})$-C_{1-6} alkyl; $S(O)N(R^{23})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{23})S(O)_2$-C_{1-6} alkyl; and $N(R^{23})S(O)$-C_{1-6} alkyl, wherein each C_{1-6} alkyl is optionally

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

R^{19} is selected from the group consisting of phenyl; and naphthyl, wherein R^{19} is optionally substituted with one or more R^{24}, wherein R^{24} is independently selected from the group consisting of halogen; CN; COOH; OH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; 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; $C(O)N(R^{25})$-C_{1-6} alkyl; $S(O)_2N(R^{25})$-C_{1-6} alkyl; $S(O)N(R^{25})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{25})S(O)_2$-C_{1-6} alkyl; and $N(R^{25})S(O)$ -C_{1-6} alkyl, wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{20} is selected from the group consisting of heterocycle; heterobicycle; and C_{3-7} cycloalkyl; wherein R^{20} is optionally substituted with one or more R^{26}, wherein R^{26} is independently selected from the group consisting of halogen; CN; OH; oxo (=O), where the ring is at least partially saturated; NH_2; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $N(R^{27})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{27})$- C_{1-6} alkyl; $N(R^{27})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{27})$-C_{1-6} alkyl; $S(O)N(R^{27})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{27})S(O)_2$-C_{1-6} alkyl; and $N(R^{27})S(O)$-C_{1-6} alkyl wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{21}, R^{23}, R^{25}, R^{27} are independently selected from the group consisting of H; and C_{1-6}alkyl, which is optionally substituted with one or more of R^{28}, wherein R^{28} is independently selected from the group consisting of F; Cl and OH;

R^6, R^7 are independently selected from the group consisting of H; $(C(R^{29}R^{30}))_m$-X^1-Z^1; and $(C(R^{31}R^{32}))_n$-X^2-X^3-Z^2, provided that R^6, R^7 are selected so that not both of R^6, R^7 are independently selected from the group consisting of H; CH_3; CH_2CH_3; $CH_2CH_2CH_3$; and $CH(CH_3)_2$;

Optionally R^6, R^7 are independently C_{1-4} alkyl, which is substituted with one or more R^{29a}, wherein R^{29a} is independently selected from the group consisting of R^{29b}; and Z^1, provided that R^6, R^7 are selected so that not both of R^6, R^7 are independently selected from the group consisting of CH_3; CH_2CH_3; $CH_2CH_2CH_3$; and $CH(CH_3)_2$;

R^{29}, R^{29b}, R^{30}, R^{31}, R^{32} are independently selected from the group consisting of H; halogen; CN; OH; NH_2; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O-C_{1-6} alkyl; $N(R^{32a})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{32a})$- C_{1-6} alkyl; $N(R^{32a})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{32a})$-C_{1-6} alkyl; $S(O)N(R^{32a})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{32a})S(O)_2$-C_{1-6} alkyl; and $N(R^{32a})$S(O)-C_{1-6} alkyl wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{32a} is selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

Optionally one or more pairs of R^{29}, R^{30}, R^{31}, R^{32} independently selected from the group consisting of R^{29}/R^{30}; and R^{31}/R^{32} form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more R^{32b}, wherein R^{32b} is independently selected from the group consisting of F; Cl; and OH;

m is 0, 1, 2, 3 or 4;

n is 2, 3 or 4;

X^1 is independently selected from the group consisting of a covalent bond; -C_{1-6} alkyl-; -C_{1-6} alkyl-O-; -C_{1-6} alkyl-$N(R^{33})$-; -C(O)-; -C(O)-C_{1-6} alkyl-; -C(O)-C_{1-6} alkyl-O-; -C(O)-C_{1-6} alkyl-$N(R^{33})$-; -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-$N(R^{33})$-; -$C(O)N(R^{33})$-; -$C(O)N(R^{33})$-C_{1-6} alkyl-; -$C(O)N(R^{33})$-C_{1-6} alkyl-O-; -$C(O)N(R^{33})$-C_{1-6} alkyl-$N(R^{34})$-; -$S(O)_2$-; -S(O)-; -$S(O)_2$-C_{1-6} alkyl-; -S(O)-C_{1-6} alkyl-; -$S(O)_2$-C_{1-6} alkyl-O-; -S(O)-C_{1-6} alkyl-O-; -$S(O)_2$-C_{1-6} alkyl-$N(R^{33})$-; and -S(O)-C_{1-6} alkyl-$N(R^{33})$-; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

X^2 is selected from the group consisting of -O-; -S-; -S(O)-; $S(O)_2$-; and -$N(R^{35})$-;

X^3 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^{36})-; -C(O)-; -C(O)-C_{1-6} alkyl-; -C(O)-C_{1-6} alkyl-O-; -C(O)-C_{1-6} alkyl-N(R^{36})-; -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^{36})-; -C(O)N(R^{36})-; -C(O)N(R^{36})-C_{1-6} alkyl-; -C(O)N(R^{36})-C_{1-6} alkyl-O-; and -C(O)N(R^{36})-C_{1-6} alkyl-N(R^{37})-; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

Optionally X^2-X^3 are independently selected from the group consisting of -N(R^{35})-$S(O)_2$; -N(R^{35})-S(O)-; -N(R^{35})-$S(O)_2$-C_{1-6} alkyl-; -N(R^{35})-S(O)-C_{1-6} alkyl-; -N(R^{35})-$S(O)_2$-C_{1-6} alkyl-O-; -N(R^{35})-S(O)-C_{1-6} alkyl-O-; -N(R^{35})-$S(O)_2$-C_{1-6} alkyl-N(R^{36})-; and -N(R^{35})-S(O)-C_{1-6} alkyl-N(R^{36})-; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{33}, R^{34}, R^{35}, R^{36}, R^{37} are independently selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

Z^1, Z^2 are independently selected from the group consisting of Z^3; and -C(R^{37a})$Z^{3a}Z^{3b}$;

R^{37a} is selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more F;

Z^3, Z^{3a}, Z^{3b} are independently selected from the group consisting of H; T^1; T^2; C_{1-6} alkyl; C_{1-6} alkyl-T^1; and C_{1-6} alkyl-T^2; wherein each C_{1-6} alkyl is optionally substituted with one or more R^{37b}, wherein R^{37b} is independently selected from the group consisting of halogen; CN; OH; NH_2; COOH; C(O)NH_2; $S(O)_2NH_2$; S(O)NH_2; C_{1-6} alkyl; O-C_{1-6} alkyl; N(R^{37c})-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; C(O)N(R^{37c})- C_{1-6} alkyl; N(R^{37c})-C(O)-C_{1-6} alkyl; $S(O)_2$N(R^{37c})-C_{1-6} alkyl; S(O)N(R^{37c})-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; N(R^{37c})$S(O)_2$-C_{1-6} alkyl; and N(R^{37c})S(O)-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

T^1 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T^1 is optionally substituted with one or more R^{38}; wherein R^{38} is independently selected from the group consisting of halogen; CN; R^{39}; COOH; OH; C(O)NH_2;

$S(O)_2NH_2$; $S(O)NH_2$; $COOT^3$; OT^3; ST^3; $C(O)N(R^{40})T^3$; $S(O)_2N(R^{40})T^3$; $S(O)N(R^{40})T^3$ 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^{41}, wherein R^{41} is independently selected from the group consisting of halogen; CN; R^{42}; 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; $C(O)N(R^{43})T^3$; $S(O)_2N(R^{43})T^3$; $S(O)N(R^{43})T^3$; $N(R^{43})T^3$; and T^3;

R^{39} 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; $C(O)N(R^{44})$-C_{1-6} alkyl; $S(O)_2N(R^{44})$-C_{1-6} alkyl; $S(O)N(R^{44})$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; $N(R^{44})S(O)_2$-C_{1-6} alkyl; and $N(R^{44})S(O)$ -C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one more R^{45}, wherein R^{45} is independently selected from the group consisting of F; $COOR^{46}$; $C(O)N(R^{46}R^{47})$; $S(O)_2N(R^{46}R^{47})$; OR^{46}; $N(R^{46}R^{47})$; T^3; O-T^3; and $N(R^{46})$-T^3;

R^{42} is selected from the group consisting of C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $N(R^{48})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{48})$- C_{1-6} alkyl; $N(R^{48})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{48})$-C_{1-6} alkyl; $S(O)$ $N(R^{48})$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; $-N(R^{48})S(O)_2$-C_{1-6} alkyl; and $-N(R^{48})S(O)$-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more R^{45}, wherein R^{45} is independently selected from the group consisting of F; $COOR^{49}$; $C(O)N(R^{49}R^{50})$; $S(O)_2N(R^{49}R^{50})$; $S(O)N(R^{49}R^{50})$; OR^{49}; $N(R^{49}R^{50})$; T^3; O-T^3; and $N(R^{49})$-T^3;

R^{40}, R^{43}, R^{44}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50} 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;

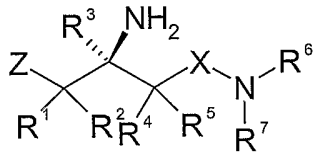
T^4 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T^4 is optionally substituted with one or more R^{51}, wherein R^{51} is independently selected from the group consisting of halogen; CN; $COOR^{52}$; OR^{52}; $C(O)N(R^{52}R^{53})$; $S(O)_2N(R^{52}R^{53})$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{52})$- C_{1-6} alkyl; $S(O)_2N(R^{52})$-C_{1-6} alkyl; $S(O)N(R^{52})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl;

S(O) -C_{1-6} alkyl; $N(R^{52})S(O)_2$-C_{1-6} alkyl; and $N(R^{52})S(O)$-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one 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^{54}, wherein R^{54} is independently selected from the group consisting of halogen; CN; OR^{55}; oxo (=O), where the ring is at least partially saturated; $N(R^{55}R^{56})$; $COOR^{55}$; $C(O)N(R^{55}R^{56})$; $S(O)_2N(R^{55}R^{56})$; $S(O)N(R^{55}R^{56})$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $N(R^{55})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{55})$- C_{1-6} alkyl; $N(R^{55})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{55})$-C_{1-6} alkyl; $S(O)N(R^{55})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{55})S(O)_2$-C_{1-6} alkyl; and $N(R^{55})S(O)$-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one more halogen selected from the group consisting of F; and Cl;

R^{52}, R^{53}, R^{55}, R^{56}, are independently selected from the group consisting of H; and C_{1-6} alkyl.

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



(Ia)

or a pharmaceutically acceptable salt thereof, wherein Z, R^1-R^7 and X have the meaning as indicated in claim 1.

3. A compound according to claim 1 or 2, wherein Z is phenyl or heterocycle.

4. A compound according to any one of the preceding claims, wherein Z is optionally substituted with 1 or 2 R^8, which are the same or different.

5. A compound according to any one of the preceding claims, wherein R^8 is selected from the group consisting of Cl; F; CN; CH_3; and OCH_3.

6. A compound according to any one of the preceding claims, wherein Z is 2-Fluoro-phenyl.

7. A compound according to any one of the preceding claims, wherein R^1, R^4 are independently selected from the group consisting of H; F; OH; CH_3; and OCH_3.

8. A compound according to any one of the preceding claims, wherein R^2, R^5 are independently selected from the group consisting of H; F; and CH_3.

9. A compound according to any one of the preceding claims, wherein R^1, R^2, R^4, R^5 are H.

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

11. A compound according to any one of the preceding claims, wherein X is C(O) or $S(O)_2$.

12. A compound according to any one of the preceding claims, wherein R^6 is selected from the group consisting of H; and CH_3.

13. A compound according to any one of the preceding claims, wherein X^1 is a covalent bond.

14. A compound according to any one of the preceding claims, wherein m is 0, 1, 2 or 3.

15. A compound according to any one of the preceding claims, wherein R^7 is Z^1.

16. A compound according to any one of the preceding claims, wherein R^7 is C_{1-4} alkyl, substituted with 1-4 R^{29a}, which are the same or different.

17. A compound according to claim 16, wherein R^7 is selected from the group consisting of $CH(R^{29a})_2$; CHR^{29a}-CH_2R^{29a}; CH_2-$CH(R^{29a})_2$; CH_2-CHR^{29a}-CH_2R^{29a}; and CH_2-CH_2-$CH(R^{29a})_2$.

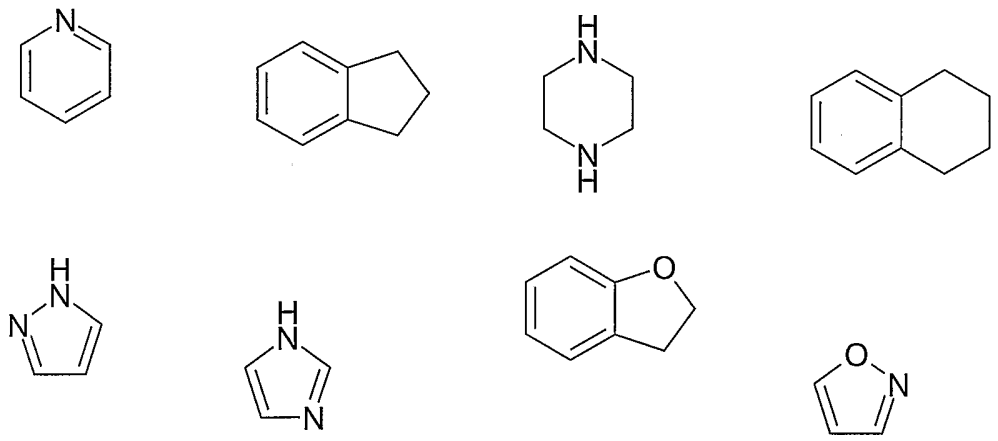
18. A compound according to any one of the preceding claims, wherein R^{29a} is selected from the group consisting of R^{29b}; and Z^1; and wherein R^{29b} is selected from the group consisting of H; F; Cl; NH_2; $NHCH_3$; $N(CH_3)_2$; CH_3; and C_2H_5.

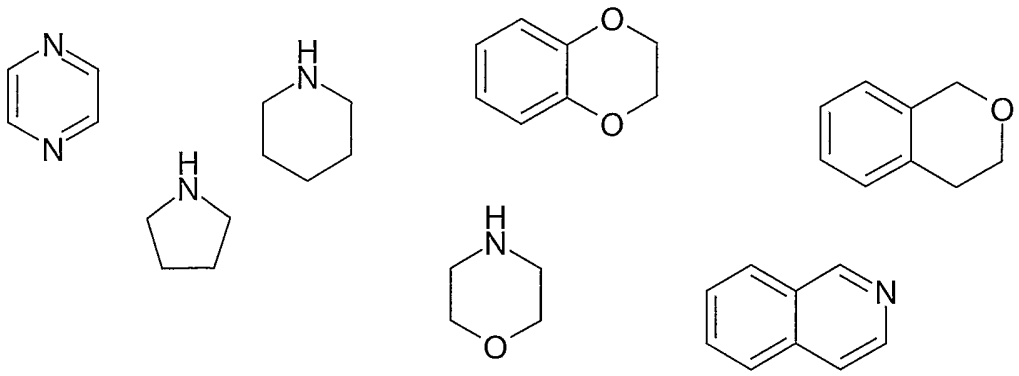
19. A compound according to any one of the preceding claims, wherein R^{29a} is selected from the group consisting of R^{29b}; and Z^1; and wherein Z^1 is selected from the group consisting of T^1; and T^2.

20. A compound according to any one of the preceding claims, wherein T^1 is phenyl; and wherein T^1 is optionally substituted with 1-3 R^{38}, which are the same or different.

21. A compound according to any one of the preceding claims, wherein R^{38} is independently selected from the group consisting of F; Cl; CN; CH_3; C_2H_5; $CH_2CH_2CH_3$; $CH(CH_3)_2$; CF_3; O-CH_3; O-C_2H_5; S-CH_3; SO_2NH_2; T^3; and O-T^3.

22. A compound according to any one of the preceding claims, wherein T^2 is selected from the group consisting of





and wherein T^2 is optionally substituted with 1-2 R^{41}, which are the same or different.

23. A compound according to any one of the preceding claims, wherein R^{41} is selected from the group consisting of OH; CH_3; and T^3;

24. A compound according to any one of the preceding claims, wherein T^3 is T^4.

25. A compound according to any one of the preceding claims, wherein T^4 is phenyl, wherein T^4 is optionally substituted with 1-3 R^{51}, which are the same or different.

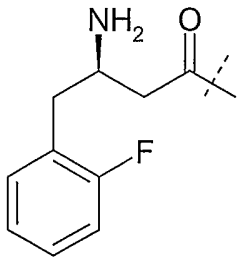
26. A compound according to any one of the preceding claims, wherein R^{51} is independently selected from the group consisting of F; Cl; CH_3; C_2H_5; $CH_2CH_2CH_3$; $CH(CH_3)_2$; CF_3; O-CH_3; O-C_2H_5; S-CH_3; and SO_2NH_2.

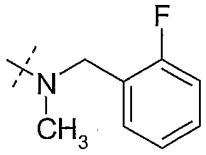
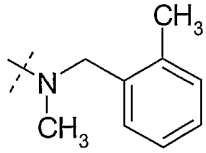
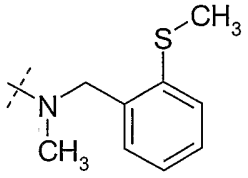
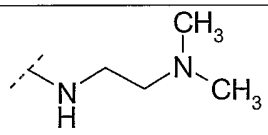
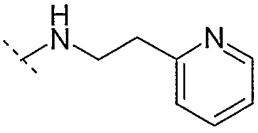
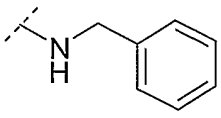
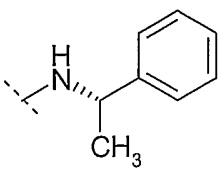
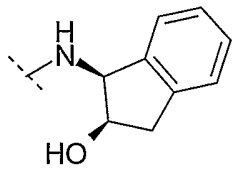
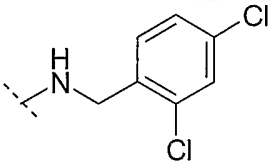
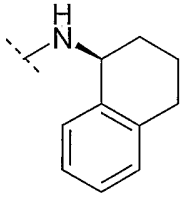
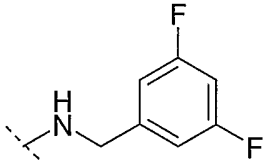
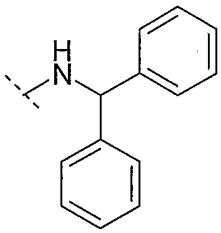
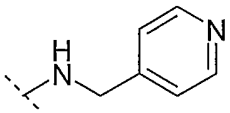
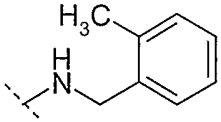
27. A compound according to any one of the preceding claims, wherein T^3 is T^5.

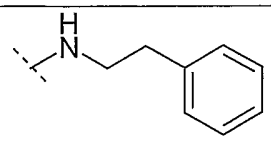
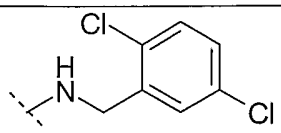
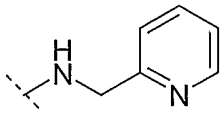
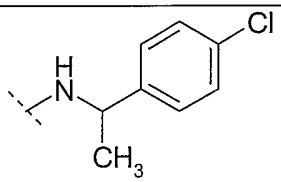
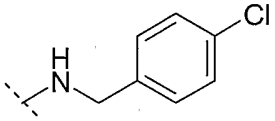
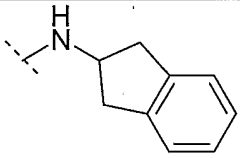
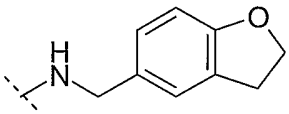
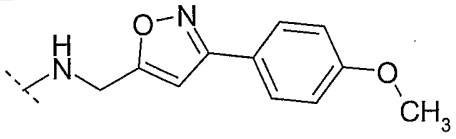
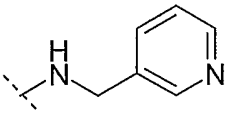
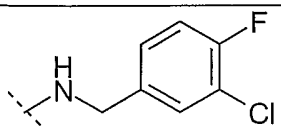
28. A compound according to any one of the preceding claims, wherein T^5 is heterocycle, wherein T^5 is optionally substituted with 1-2 R^{54}, which are the same or different.

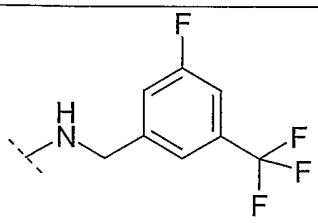
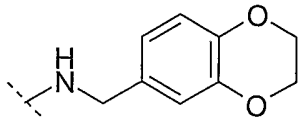
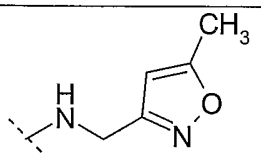
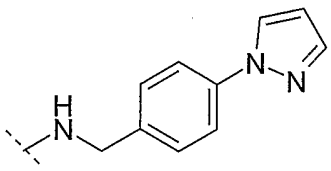
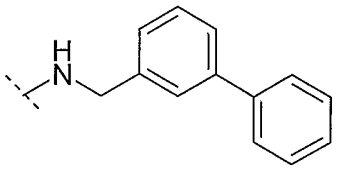
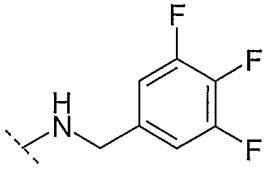
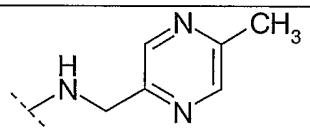
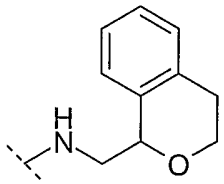
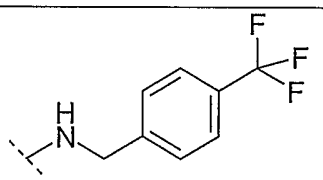
29. A compound according to any one of the preceding claims, wherein R^{54} is selected from the group consisting of OH; and CH_3.

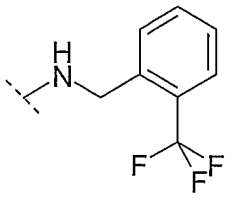
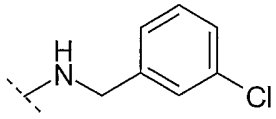
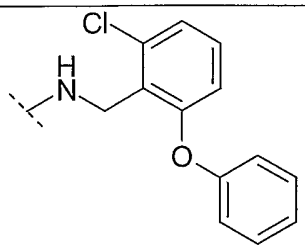
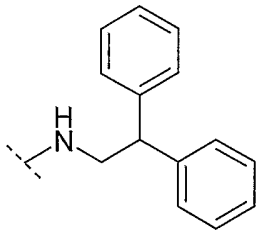
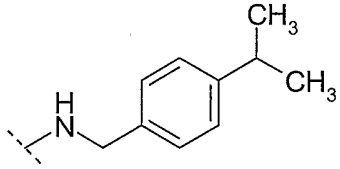
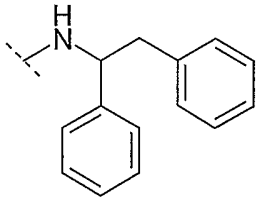
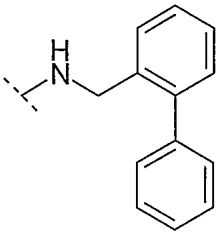
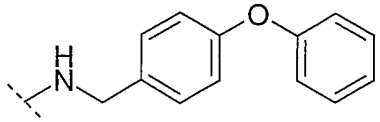
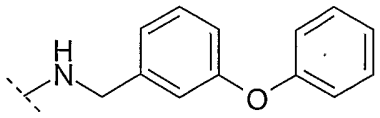
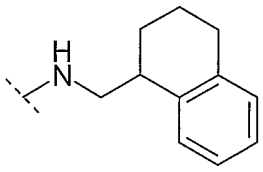
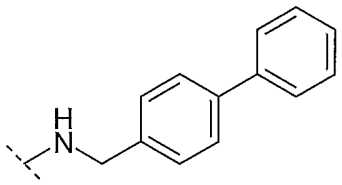
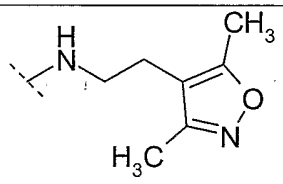
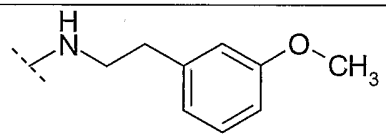
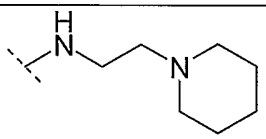
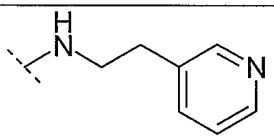
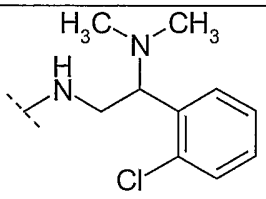
30. A compound according to claim 1 selected from the group consisting of

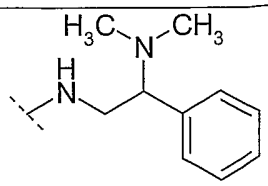
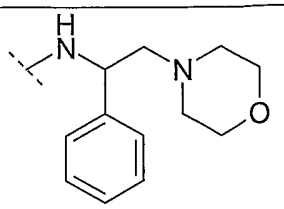
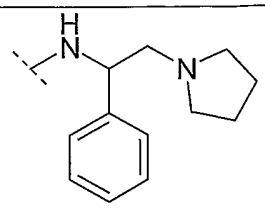
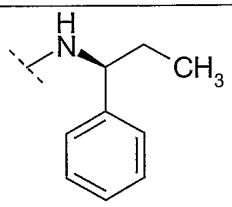
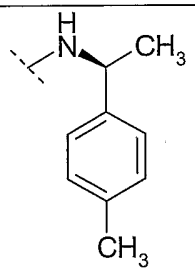
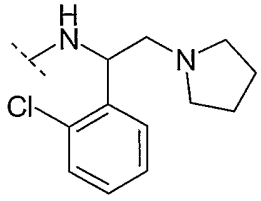
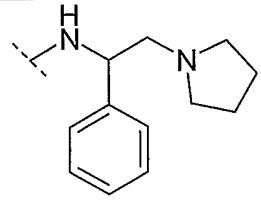


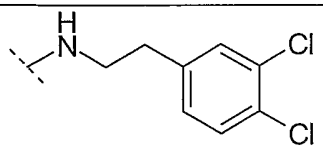
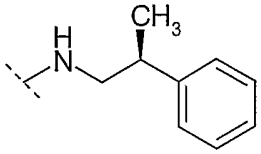
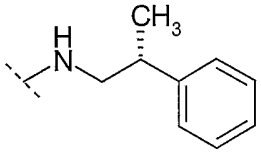
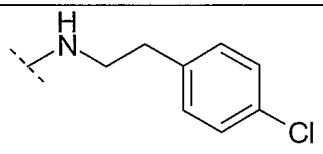
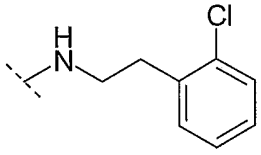
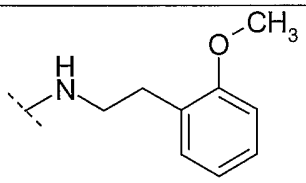
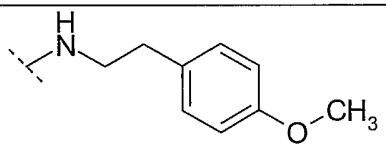
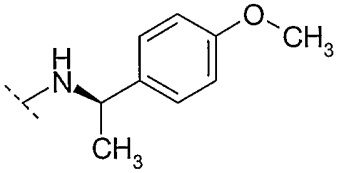
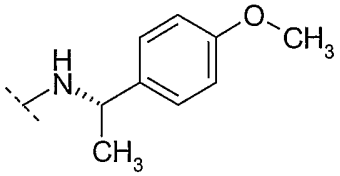
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	

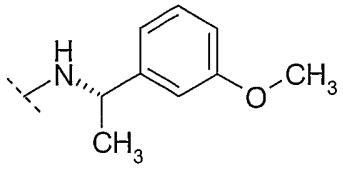
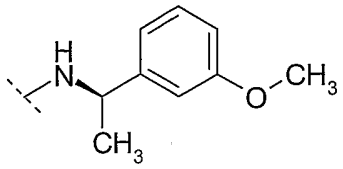
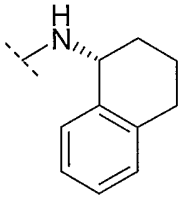
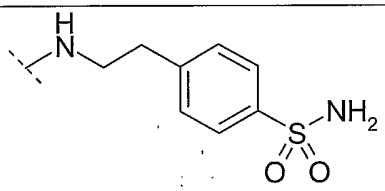
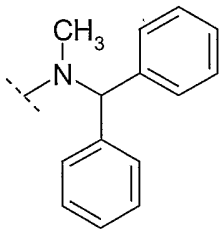
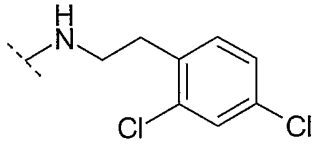
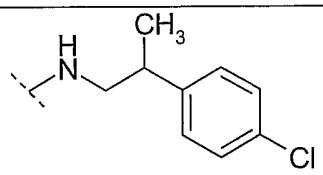
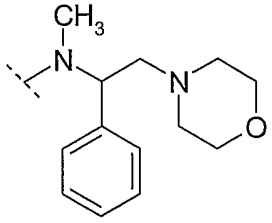
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	

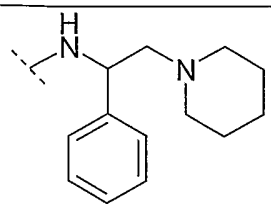
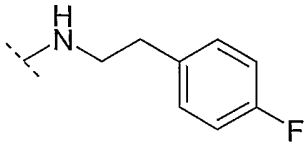
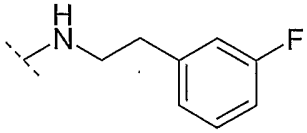
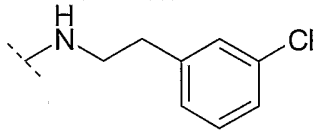
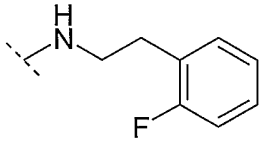
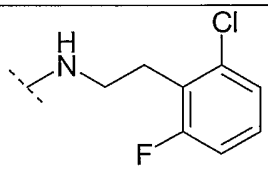
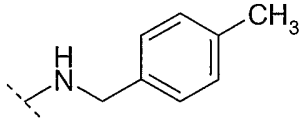
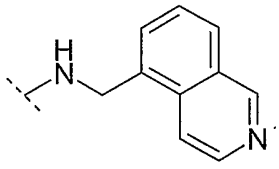
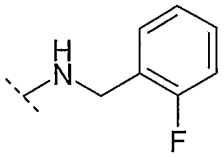
28	
29	
30	
31	
32	
33	
34	
35	
36	

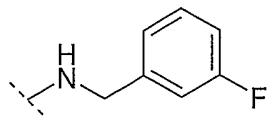
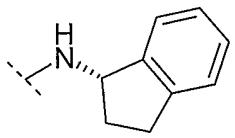
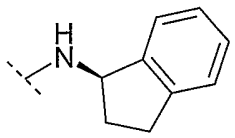
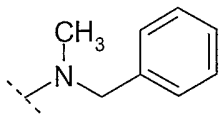
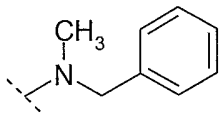
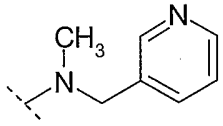
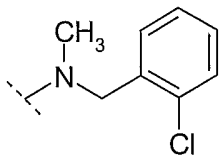
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	

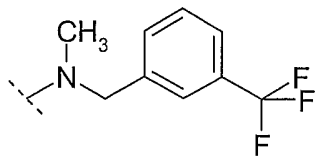
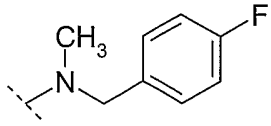
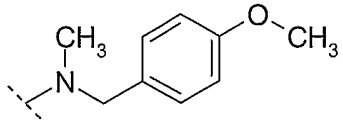
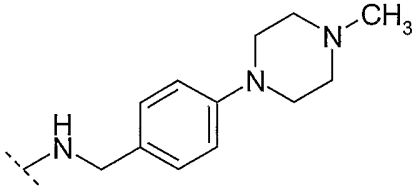
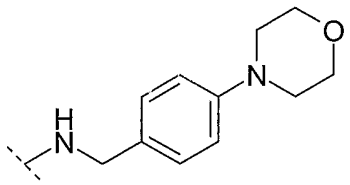
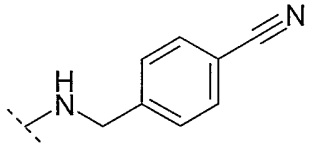
53	
54	
55	
56	
57	
58	
59	

60	
61	
62	
63	
64	
65	
66	
67	
68	

69	
70	
71	
72	
73	
74	
75	
76	

77	
78	
79	
80	
81	
82	
83	
84	
85	

86	
87	
88	
89	
90	
91	
92	

93	
94	
95	
96	
97	
98	

31. A prodrug compound of a compound according to any one of the claims 1 to 30.

32. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof according to any one of the claims 1 to 31 together with a pharmaceutically acceptable carrier.

33. A pharmaceutical composition according to claim 32, 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 27; another DPP-IV inhibitor; insulin sensitizers; PPAR agonists; biguanides;

protein tyrosinephosphatase-IB (PTP-1B) inhibitors; insulin and insulin mimetics; sulfonylureas 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.

34. A compound or a pharmaceutically acceptable salt thereof of any one of the claims 1 to 31 for use as a medicament.

35. Use of a compound or a pharmaceutically acceptable salt thereof of any of the claims 1 to 31 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; anxiety; depression; retinopathy; nephropathy; neuropathy; Syndrome X; ovarian hyperandrogenism (polycystic ovarian syndrome; Type n diabetes; or growth hormone deficiency.

36. Use of a compound according to any one of the claims 1 to 31 as DPP-IV inhibitor.

AMENDED CLAIMS

[received by the International Bureau on 08 August 2005 (08.08.2005); original claim 1 amended]

1. A compound of the formula (I)

$$Z\text{-}C(R^1R^2)\text{-}C(R^3NH_2)\text{-}C(R^4R^5)\text{-}X\text{-}N(R^6R^7) \qquad (I),$$

or a pharmaceutically acceptable salt thereof, wherein

Z is selected from the group consisting of phenyl; naphthyl; indenyl; $C_{3\text{-}7}$ cycloalkyl; indanyl; tetralinyl; decalinyl; heterocycle; and heterobicycle, wherein Z is optionally substituted with one or more R^8, wherein R^8 is independently selected from the group consisting of halogen; CN; OH; NH_2; oxo (=O), where the ring is at least partially saturated; R^9; and R^{10};

R^9 is selected from the group consisting of $C_{1\text{-}6}$ alkyl; O-$C_{1\text{-}6}$ alkyl; and S-$C_{1\text{-}6}$ alkyl, wherein R^9 is optionally interrupted by oxygen and wherein R^9 is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{10} is selected from the group consisting of phenyl; heterocycle; and $C_{3\text{-}7}$ cycloalkyl, wherein R^{10} is optionally substituted with one or more R^{11}, wherein R^{11} is independently selected from the group consisting of halogen; CN; OH; NH_2; oxo (=O), where the ring is at least partially saturated; $C_{1\text{-}6}$ alkyl; O-$C_{1\text{-}6}$ alkyl; and S-$C_{1\text{-}6}$ alkyl;

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

R^2, R^5 are independently selected from the group consisting of H; F; and R^{4b};

R^{4a} is independently selected from the group consisting of C_{1-6} alkyl; and O-C_{1-6} alkyl, wherein R^{4a} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{4b} is C_{1-6} alkyl, wherein R^{4b} is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

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 independently selected from the group consisting of R^1/R^2; R^2/R^3; R^3/R^4; and R^4/R^5 form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more of R^{12}, wherein R^{12} is independently selected from the group consisting of F; Cl; and OH;

X is selected from the group consisting of S(O); $S(O)_2$; C(O); and $C(R^{13}R^{14})$;

R^{13}, R^{14} are independently selected from the group consisting of H; F; C_{1-6} alkyl; R^{15}; and R^{16};

Optionally one or both pairs of R^5, R^{13}, R^{14} selected from the group consisting of R^5/R^{13}; and R^{13}/R^{14} form a C_{3-7} cycloalkyl ring, which is optionally substituted with one or more R^{17}, wherein R^{17} is independently selected from the group consisting of F; Cl; and OH;

R^{15} is selected from the group consisting of phenyl; naphthyl; and indenyl, wherein R^{15} is optionally substituted with one or more R^{18}, wherein R^{18} is independently selected from the group consisting of R^{19}; R^{20}; halogen; CN; COOH; OH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; 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; $C(O)N(R^{21})$-C_{1-6} alkyl; $S(O)_2N(R^{21})$-C_{1-6} alkyl; $S(O)N(R^{21})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{21})S(O)_2$-C_{1-6} alkyl; and $N(R^{21})S(O)$-C_{1-6} alkyl, wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{16} is selected from the group consisting of heterocycle; heterobicycle; C_{3-7} cycloalkyl; indanyl; tertralinyl; and decalinyl, wherein R^{16} is optionally substituted with one or more R^{22}, wherein R^{22} is independently selected from the group consisting of R^{19}; R^{20}; halogen; CN; OH; oxo (=O), where the ring is at least partially saturated; NH_2; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $N(R^{23})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{23})$-C_{1-6} alkyl; $N(R^{23})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{23})$-C_{1-6} alkyl; $S(O)N(R^{23})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{23})S(O)_2$-C_{1-6} alkyl; and $N(R^{23})S(O)$-C_{1-6} alkyl, wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{19} is selected from the group consisting of phenyl; and naphthyl, wherein R^{19} is optionally substituted with one or more R^{24}, wherein R^{24} is independently selected from the group consisting of halogen; CN; COOH; OH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; 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; $C(O)N(R^{25})$-C_{1-6} alkyl; $S(O)_2N(R^{25})$-C_{1-6} alkyl; $S(O)N(R^{25})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{25})S(O)_2$-C_{1-6} alkyl; and $N(R^{25})S(O)$ -C_{1-6} alkyl, wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{20} is selected from the group consisting of heterocycle; heterobicycle; and C_{3-7} cycloalkyl; wherein R^{20} is optionally substituted with one or more R^{26}, wherein R^{26} is independently selected from the group consisting of halogen; CN; OH; oxo

(=O), where the ring is at least partially saturated; NH_2; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; $O\text{-}C_{1-6}$ alkyl; $S\text{-}C_{1-6}$ alkyl; $N(R^{27})\text{-}C_{1-6}$ alkyl; $COO\text{-}C_{1-6}$ alkyl; $OC(O)\text{-}C_{1-6}$ alkyl; $C(O)N(R^{27})\text{-}C_{1-6}$ alkyl; $N(R^{27})\text{-}C(O)\text{-}C_{1-6}$ alkyl; $S(O)_2N(R^{27})\text{-}C_{1-6}$ alkyl; $S(O)N(R^{27})\text{-}C_{1-6}$ alkyl; $S(O)_2\text{-}C_{1-6}$ alkyl; $S(O)\text{-}C_{1-6}$ alkyl; $N(R^{27})S(O)_2\text{-}C_{1-6}$ alkyl; and $N(R^{27})S(O)\text{-}C_{1-6}$ alkyl wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{21}, R^{23}, R^{25}, R^{27} are independently selected from the group consisting of H; and C_{1-6}alkyl, which is optionally substituted with one or more of R^{28}, wherein R^{28} is independently selected from the group consisting of F; Cl and OH;

R^6, R^7 are independently selected from the group consisting of H; $(C(R^{29}R^{30}))_m\text{-}X^1\text{-}Z^1$; $(C(R^{31}R^{32}))_n\text{-}X^2\text{-}X^3\text{-}Z^2$; and C_{1-4} alkyl, which is substituted with one or more R^{29a}, wherein R^{29a} is independently selected from the group consisting of R^{29b}; and Z^1, provided that R^6, R^7 are selected so that not both of R^6, R^7 are independently selected from the group consisting of H; CH_3; CH_2CH_3; $CH_2CH_2CH_3$; and $CH(CH_3)_2$;

R^{29}, R^{29b}, R^{30}, R^{31}, R^{32} are independently selected from the group consisting of H; halogen; CN; OH; NH_2; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; $O\text{-}C_{1-6}$ alkyl; $N(R^{32a})\text{-}C_{1-6}$ alkyl; $COO\text{-}C_{1-6}$ alkyl; $OC(O)\text{-}C_{1-6}$ alkyl; $C(O)N(R^{32a})\text{-}C_{1-6}$ alkyl; $N(R^{32a})\text{-}C(O)\text{-}C_{1-6}$ alkyl; $S(O)_2N(R^{32a})\text{-}C_{1-6}$ alkyl; $S(O)N(R^{32a})\text{-}C_{1-6}$ alkyl; $S(O)_2\text{-}C_{1-6}$ alkyl; $S(O)\text{-}C_{1-6}$ alkyl; $N(R^{32a})S(O)_2\text{-}C_{1-6}$ alkyl; and $N(R^{32a})S(O)\text{-}C_{1-6}$ alkyl wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{32a} is selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

Optionally one or more pairs of R^{29}, R^{30}, R^{31}, R^{32} independently selected from the group consisting of R^{29}/R^{30}; and R^{31}/R^{32} form a C_{3-7} cycloalkyl ring, which is option-

ally substituted with one or more R^{32b}, wherein R^{32b} is independently selected from the group consisting of F; Cl; and OH;

m is 0, 1, 2, 3 or 4;

n is 2, 3 or 4;

X^1 is independently selected from the group consisting of a covalent bond; -C_{1-6} alkyl-; -C_{1-6} alkyl-O-; -C_{1-6} alkyl-N(R^{33})-; -C(O)-; -C(O)-C_{1-6} alkyl-; -C(O)-C_{1-6} alkyl-O-; -C(O)-C_{1-6} alkyl-N(R^{33})-; -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^{33})-; -C(O)N(R^{33})-; -C(O)N(R^{33})-C_{1-6} alkyl-; -C(O)N(R^{33})-C_{1-6} alkyl-O-; -C(O)N(R^{33})-C_{1-6} alkyl-N(R^{34})-; -$S(O)_2$-; -S(O)-; -$S(O)_2$-C_{1-6} alkyl-; -S(O)-C_{1-6} alkyl-; -$S(O)_2$-C_{1-6} alkyl-O-; -S(O)-C_{1-6} alkyl-O-; -$S(O)_2$-C_{1-6} alkyl-N(R^{33})-; and -S(O)-C_{1-6} alkyl-N(R^{33})-; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

X^2 is selected from the group consisting of -O-; -S-; -S(O)-; $S(O)_2$-; and -N(R^{35})-;

X^3 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^{36})-; -C(O)-; -C(O)-C_{1-6} alkyl-; -C(O)-C_{1-6} alkyl-O-; -C(O)-C_{1-6} alkyl-N(R^{36})-; -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^{36})-; -C(O)N(R^{36})-; -C(O)N(R^{36})-C_{1-6} alkyl-; -C(O)N(R^{36})-C_{1-6} alkyl-O-; and -C(O)N(R^{36})-C_{1-6} alkyl-N(R^{37})-; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

Optionally X^2-X^3 are independently selected from the group consisting of -N(R^{35})-$S(O)_2$; -N(R^{35})-S(O)-; -N(R^{35})-$S(O)_2$-C_{1-6} alkyl-; -N(R^{35})-S(O)-C_{1-6} alkyl-; -N(R^{35})-$S(O)_2$-C_{1-6} alkyl-O-; -N(R^{35})-S(O)-C_{1-6} alkyl-O-; -N(R^{35})-$S(O)_2$-C_{1-6} alkyl-

$N(R^{36})$-; and $-N(R^{35})$-S(O)-C_{1-6} alkyl-$N(R^{36})$-; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

R^{33}, R^{34}, R^{35}, R^{36}, R^{37} are independently selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

Z^1, Z^2 are independently selected from the group consisting of Z^3; and $-C(R^{37a})Z^{3a}Z^{3b}$;

R^{37a} is selected from the group consisting of H; and C_{1-6} alkyl, which is optionally substituted with one or more F;

Z^3, Z^{3a}, Z^{3b} are independently selected from the group consisting of H; T^1; T^2; C_{1-6} alkyl; C_{1-6} alkyl-T^1; and C_{1-6} alkyl-T^2; wherein each C_{1-6} alkyl is optionally substituted with one or more R^{37b}, wherein R^{37b} is independently selected from the group consisting of halogen; CN; OH; NH_2; COOH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; C_{1-6} alkyl; O-C_{1-6} alkyl; $N(R^{37c})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)-C_{1-6} alkyl; $C(O)N(R^{37c})$-C_{1-6} alkyl; $N(R^{37c})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{37c})$-C_{1-6} alkyl; $S(O)N(R^{37c})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{37c})S(O)_2$-C_{1-6} alkyl; and $N(R^{37c})$S(O)-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more halogen independently selected from the group consisting of F; and Cl;

T^1 is selected from the group consisting of phenyl; naphthyl; and indenyl; wherein T^1 is optionally substituted with one or more R^{38}; wherein R^{38} is independently selected from the group consisting of halogen; CN; R^{39}; COOH; OH; $C(O)NH_2$; $S(O)_2NH_2$; $S(O)NH_2$; $COOT^3$; OT^3; ST^3; $C(O)N(R^{40})T^3$; $S(O)_2N(R^{40})T^3$; $S(O)N(R^{40})T^3$ and T^3;

AMENDED SHEET (ARTICLE 19)

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^{41}, wherein R^{41} is independently selected from the group consisting of halogen; CN; R^{42}; 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; $C(O)N(R^{43})T^3$; $S(O)_2N(R^{43})T^3$; $S(O)N(R^{43})T^3$; $N(R^{43})T^3$; and T^3;

R^{39} 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; $C(O)N(R^{44})$-C_{1-6} alkyl; $S(O)_2N(R^{44})$-C_{1-6} alkyl; $S(O)N(R^{44})$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; $N(R^{44})S(O)_2$-C_{1-6} alkyl; and $N(R^{44})S(O)$ -C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one more R^{45}, wherein R^{45} is independently selected from the group consisting of F; $COOR^{46}$; $C(O)N(R^{46}R^{47})$; $S(O)_2N(R^{46}R^{47})$; OR^{46}; $N(R^{46}R^{47})$; T^3; O-T^3; and $N(R^{46})$-T^3;

R^{42} is selected from the group consisting of C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $N(R^{48})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{48})$- C_{1-6} alkyl; $N(R^{48})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{48})$-C_{1-6} alkyl; S(O) $N(R^{48})$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; $-N(R^{48})S(O)_2$-C_{1-6} alkyl; and $-N(R^{48})S(O)$-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one or more R^{45}, wherein R^{45} is independently selected from the group consisting of F; $COOR^{49}$; $C(O)N(R^{49}R^{50})$; $S(O)_2N(R^{49}R^{50})$; $S(O)N(R^{49}R^{50})$; OR^{49}; $N(R^{49}R^{50})$; T^3; O-T^3; and $N(R^{49})$-T^3;

R^{40}, R^{43}, R^{44}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50} 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^{51}, wherein R^{51} is independently selected from the group consisting of halogen; CN; $COOR^{52}$; OR^{52}; $C(O)N(R^{52}R^{53})$; $S(O)_2N(R^{52}R^{53})$; 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;
$C(O)N(R^{52})$- C_{1-6} alkyl; $S(O)_2N(R^{52})$-C_{1-6} alkyl; $S(O)N(R^{52})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O) -C_{1-6} alkyl; $N(R^{52})S(O)_2$-C_{1-6} alkyl; and $N(R^{52})S(O)$-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one more halogen selected from the group consisting of F; and Cl;

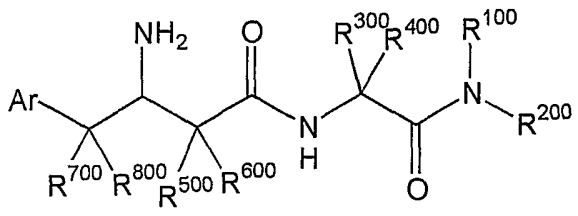
T^5 is selected from the group consisting of heterocycle; heterobicycle; C_{3-7} cycloalkyl; indanyl; tetralinyl; and decalinyl; wherein T^5 is optionally substituted with one or more R^{54}, wherein R^{54} is independently selected from the group consisting of halogen; CN; OR^{55}; oxo (=O), where the ring is at least partially saturated; $N(R^{55}R^{56})$; $COOR^{55}$; $C(O)N(R^{55}R^{56})$; $S(O)_2N(R^{55}R^{56})$; $S(O)N(R^{55}R^{56})$; C_{1-6} alkyl; O-C_{1-6} alkyl; S-C_{1-6} alkyl; $N(R^{55})$-C_{1-6} alkyl; COO-C_{1-6} alkyl; OC(O)- C_{1-6} alkyl; $C(O)N(R^{55})$- C_{1-6} alkyl; $N(R^{55})$-C(O)-C_{1-6} alkyl; $S(O)_2N(R^{55})$-C_{1-6} alkyl; $S(O)N(R^{55})$-C_{1-6} alkyl; $S(O)_2$-C_{1-6} alkyl; S(O)-C_{1-6} alkyl; $N(R^{55})S(O)_2$-C_{1-6} alkyl; and $N(R^{55})S(O)$-C_{1-6} alkyl; wherein each C_{1-6} alkyl is optionally substituted with one more halogen selected from the group consisting of F; and Cl;

R^{52}, R^{53}, R^{55}, R^{56}, are independently selected from the group consisting of H; and C_{1-6} alkyl;

with the proviso that the following compounds are excluded:

3-amino-N-cyclohexyl-4-phenyl-butyramide,
(S)-3-amino-N-[5-(6-dimethylamino-purin-9-yl)-4-hydroxy-2-hydroxymethyl-tetrahydrofuran-3-yl]-4-p-tolyl-butyramide,
(S)-2-((S)-2-amino-3-phenyl-propane-1-sulfonylamino)-3-phenyl-propionic acid,
(S)-3-amino-4,N-diphenyl-butyramide;

and with the further proviso that compounds according to the following formula are excluded:



wherein

Ar is phenyl optionally substituted with 1, 2, 3, 4, or 5 groups independently selected from halogen; C_{1-6} alkyl optionally substituted with 1 to 5 halogens; O-C_{1-6} alkyl optionally substituted with 1 to 5 halogens; and cyano,

R^{500}, R^{600}, R^{700}, R^{800} are independently selected from H; and C_{1-6} alkyl, optionally substituted by 1 or 2 F,

R^{300} and R^{400} are independently selected from hydrogen; C_{1-6} alkyl, which is optionally substituted by 1 or 2 F; and C_{3-7} cycloalkyl, optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halogen and hydroxy,

R^{100} is selected from hydrogen; and C_{1-6} alkyl, optionally substituted by 1 or 2 F,

R^{200} is selected from hydrogen; C_{1-6} alkyl; C_{3-7} cycloalkyl; phenyl; HET1; C_{1-6} alkylphenyl; -C_{1-6} alkylAR2; -C_{1-6} alkyl-C_{3-7} cycloalkyl; -C_{1-6} alkyl-HET1; -C_{1-6} alkyl-HET2; -C_{1-6} alkyl-CO_2C_{1-6} alkyl; -C_{1-6} alkylOCO-C_{1-6} alkyl;-C_{1-6} alkylCO-C_{1-6} alkyl; -C_{1-6} alkylNHCO-C_{1-6} alkyl; -C_{1-6} alkylCONH-alkyl; -C_{1-6} alkylCON-di-C_{1-6} alkyl; -C_{1-6} alkylNH-C_{1-6} alkyl; -C_{1-6} alkylN-di-C_{1-6} alkyl; -C_{1-6} alkylNHSO$_2$-C_{1-6} alkyl; -C_{1-6} alkylSO$_2$NH-C_{1-6} alkyl; -C_{1-6} alkylSO$_2$-C_{1-6} alkyl; and -C_{1-6} alkylSO$_2$N-di(C_{1-6}) alkyl;

wherein each C_{1-6} alkyl is optionally substituted by 1 or 2 F; and

wherein phenyl, AR2, HET1, HET2 and C_{3-7} cycloalkyl are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from phenyl (optionally substituted with halogen, trifluoromethyl, C_{1-4} alkyl or O-C_{1-4} alkyl), halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, dihaloC_{1-6} alkyl, trifluoromethyl, O-C_{1-6} alkyl, carboxy-C_{1-6} alkyl, carboxy-C_{1-6} alkyoxy, hydroxy, amino, C_{1-6} alkylamino, diC_{1-6} alkylamino, -$CONH_2$, - CONH-C_{1-6} alkyl, CON-di(C_{1-6})alkyl, -NHCO-C_{1-6} alkyl, -SO_2-C_{1-6} alkyl, SO_2NH_2, -SO_2NH-C_{1-6} alkyl, SO_2N-diC_{1-6} alkyl and –$NHSO_2$-C_{1-6} alkyl,

further

R^{100} and R^{200} may together with the nitrogen to which they are attached form a ring defined by HET1 or HET3,

wherein a ring comprising R^{100} and R^{200} is optionally substituted by 1 or 2 substituents independently selected from halogen, C_{1-6} alkyl, O-C_{1-6} alkyl, cyano, carboxy, carboxy-C_{1-6} alkyl, -CO_2-C_{1-6} alkyl, C_{1-6} alkylamino, di-(C_{1-6}) alkylamino, -NHCO-C_{1-6} alkyl, -CONH-C_{1-6} alkyl, -CON-di-C_{1-6} alkyl and HET1, wherein each C_{1-6} alkyl group is optionally substituted by 1 or 2 substituents independently selected from hydroxy and fluoro;

and

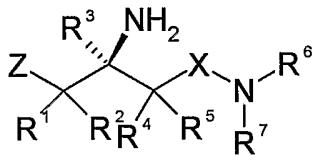
AR2 is a 8-, 9- or 10-membered unsaturated, partially or fully saturated bicyclic carbocylic ring;

HET1 is a 3-, 4-, 5- or 6-membered, unsaturated, partially or fully saturated monocyclic heterocyclyl ring containing up to four heteroatoms independently selected from O, N, and S (but not containing any O-O, O-S or S-S bonds) linked via a ring carbon atom or a ring nitrogen atom if the ring is not thereby quaternised, and wherein an available carbon, sulfur or nitrogen atom may be oxidized;

HET2 is a 8-, 9- or 10-membered, unsaturated, partially or fully saturated bicyclic heterocyclyl ring containing up to four heteroatoms independently selected from O, N, and S (but not containing any O-O, O-S or S-S bonds) and linked via a ring carbon atom in either of the rings comprising the bicyclic system; and

HET3 is a N-linked saturated bicyclic ring system containing up to 12 ring atoms including the linking nitrogen atom.

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



(Ia)

or a pharmaceutically acceptable salt thereof, wherein Z, R^1-R^7 and X have the meaning as indicated in claim 1.

3. A compound according to claim 1 or 2, wherein Z is phenyl or heterocycle.

4. A compound according to any one of the preceding claims, wherein Z is optionally substituted with 1 or 2 R^8, which are the same or different.

5. A compound according to any one of the preceding claims, wherein R^8 is selected from the group consisting of Cl; F; CN; CH_3; and OCH_3.

6. A compound according to any one of the preceding claims, wherein Z is 2-Fluoro-phenyl.

7. A compound according to any one of the preceding claims, wherein R^1, R^4 are independently selected from the group consisting of H; F; OH; CH_3; and OCH_3.

8. A compound according to any one of the preceding claims, wherein R^2, R^5 are independently selected from the group consisting of H; F; and CH_3.

9. A compound according to any one of the preceding claims, wherein R^1, R^2, R^4, R^5 are H.

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

11. A compound according to any one of the preceding claims, wherein X is C(O) or $S(O)_2$.

12. A compound according to any one of the preceding claims, wherein R^6 is selected from the group consisting of H; and CH_3.

13. A compound according to any one of the preceding claims, wherein X^1 is a covalent bond.

14. A compound according to any one of the preceding claims, wherein m is 0, 1, 2 or 3.

15. A compound according to any one of the preceding claims, wherein R^7 is Z^1.

16. A compound according to any one of the preceding claims, wherein R^7 is C_{1-4} alkyl, substituted with 1-4 R^{29a}, which are the same or different.

17. A compound according to claim 16, wherein R^7 is selected from the group consisting of $CH(R^{29a})_2$; CHR^{29a}-CH_2R^{29a}; CH_2-$CH(R^{29a})_2$; CH_2-CHR^{29a}-CH_2R^{29a}; and CH_2-CH_2-$CH(R^{29a})_2$.

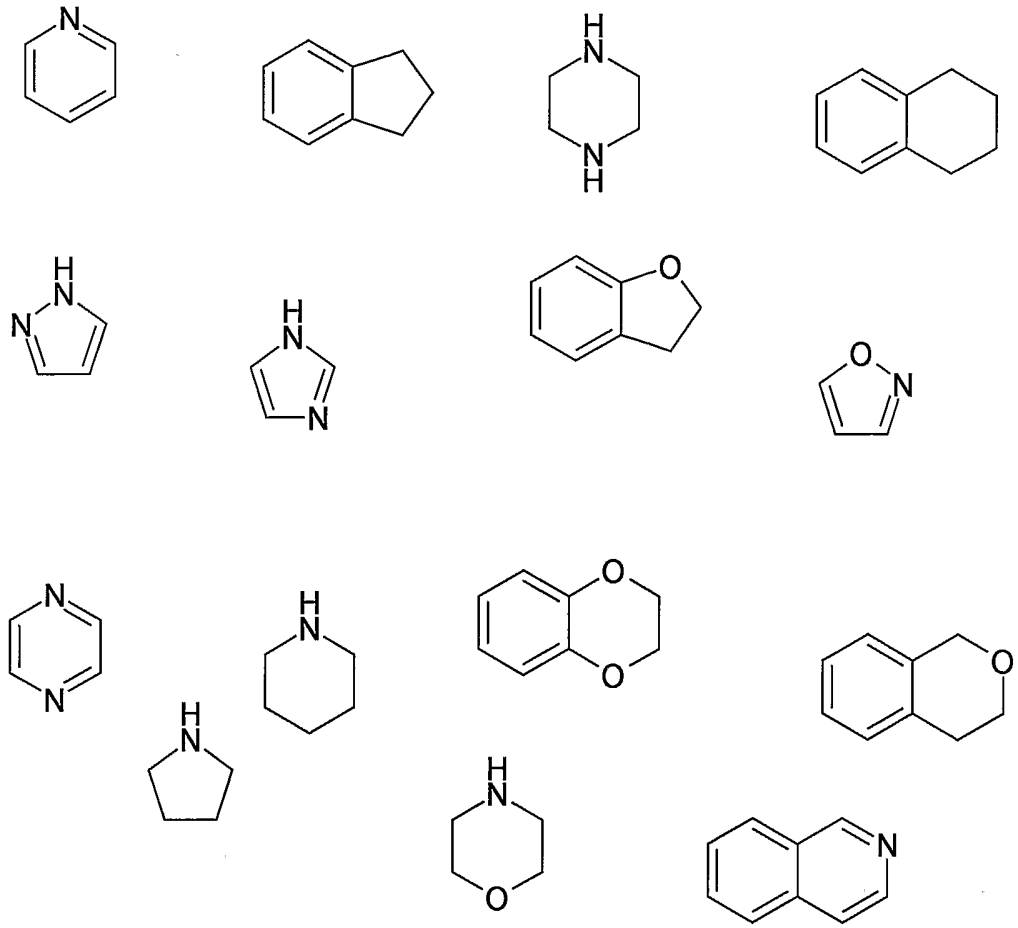
18. A compound according to any one of the preceding claims, wherein R^{29a} is selected from the group consisting of R^{29b}; and Z^1; and wherein R^{29b} is selected from the group consisting of H; F; Cl; NH_2; $NHCH_3$; $N(CH_3)_2$; CH_3; and C_2H_5.

19. A compound according to any one of the preceding claims, wherein R^{29a} is selected from the group consisting of R^{29b}; and Z^1; and wherein Z^1 is selected from the group consisting of T^1; and T^2.

20. A compound according to any one of the preceding claims, wherein T^1 is phenyl; and wherein T^1 is optionally substituted with 1-3 R^{38}, which are the same or different.

21. A compound according to any one of the preceding claims, wherein R^{38} is independently selected from the group consisting of F; Cl; CN; CH_3; C_2H_5; $CH_2CH_2CH_3$; $CH(CH_3)_2$; CF_3; O-CH_3; O-C_2H_5; S-CH_3; SO_2NH_2; T^3; and O-T^3.

22. A compound according to any one of the preceding claims, wherein T^2 is selected from the group consisting of



and wherein T^2 is optionally substituted with 1-2 R^{41}, which are the same or different.

23. A compound according to any one of the preceding claims, wherein R^{41} is selected from the group consisting of OH; CH_3; and T^3;

24. A compound according to any one of the preceding claims, wherein T^3 is T^4.

25. A compound according to any one of the preceding claims, wherein T^4 is phenyl, wherein T^4 is optionally substituted with 1-3 R^{51}, which are the same or different.

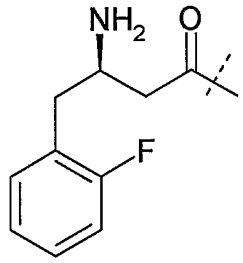
26. A compound according to any one of the preceding claims, wherein R^{51} is independently selected from the group consisting of F; Cl; CH_3; C_2H_5; $CH_2CH_2CH_3$; $CH(CH_3)_2$; CF_3; O-CH_3; O-C_2H_5; S-CH_3; and SO_2NH_2.

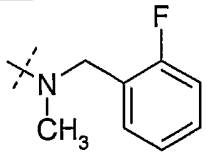
27. A compound according to any one of the preceding claims, wherein T^3 is T^5.

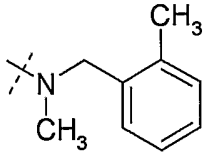
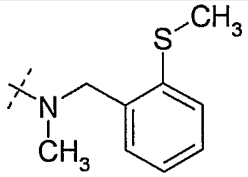
28. A compound according to any one of the preceding claims, wherein T^5 is heterocycle, wherein T^5 is optionally substituted with 1-2 R^{54}, which are the same or different.

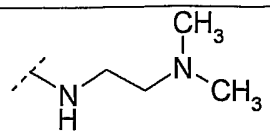
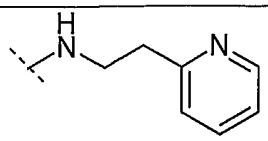
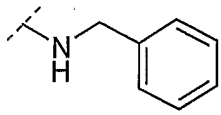
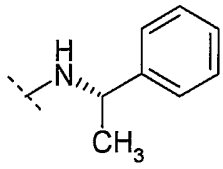
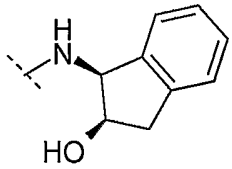
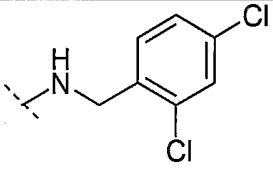
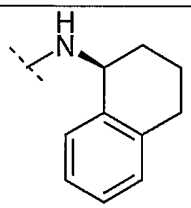
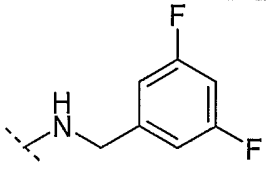
29. A compound according to any one of the preceding claims, wherein R^{54} is selected from the group consisting of OH; and CH_3.

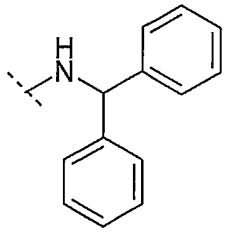
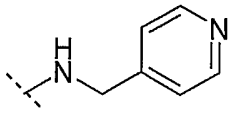
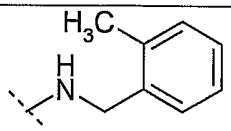
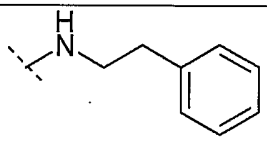
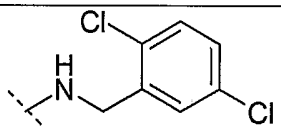
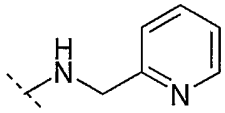
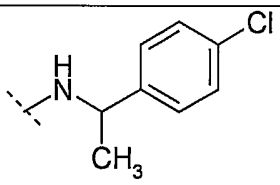
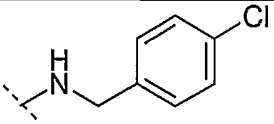
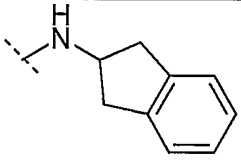
30. A compound according to claim 1 selected from the group consisting of

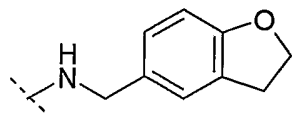
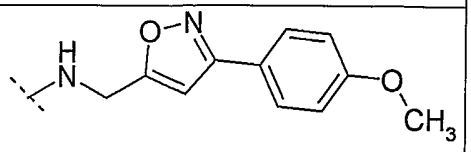
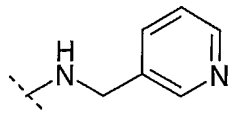
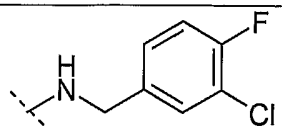
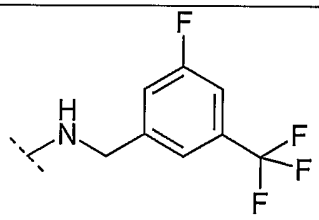
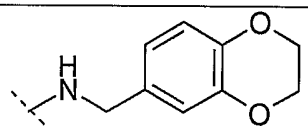
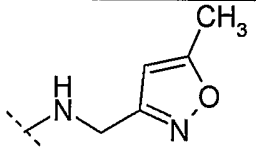
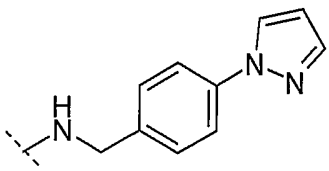


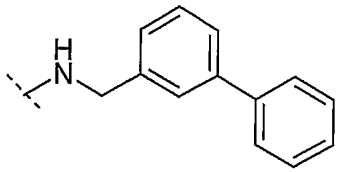
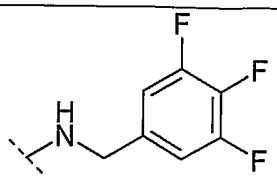
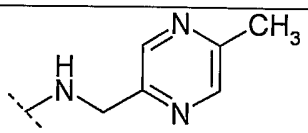
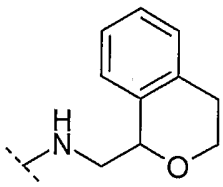
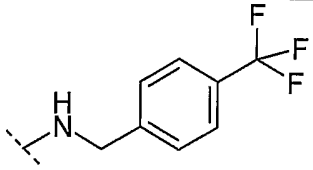
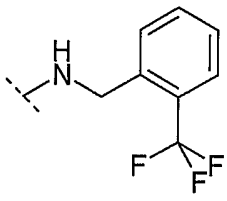
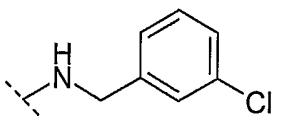
4	

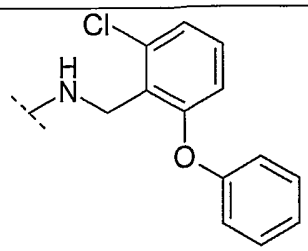
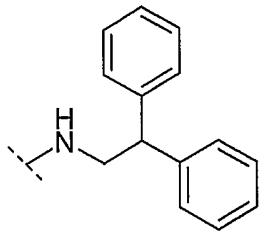
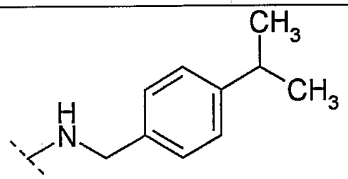
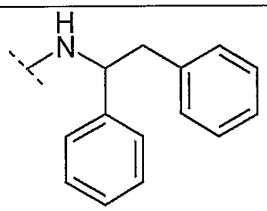
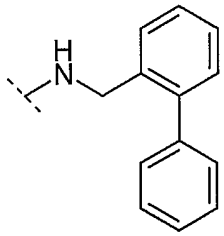
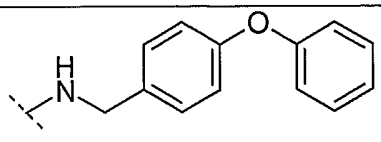
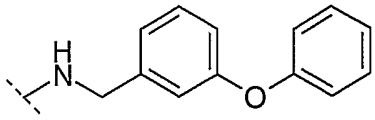
5	
6	

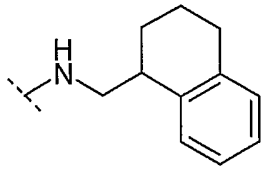
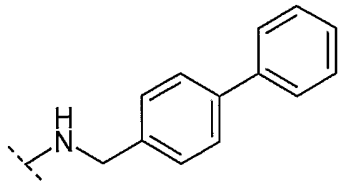
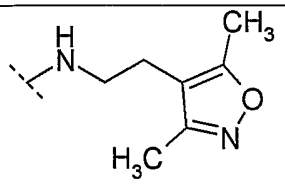
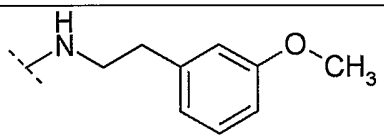
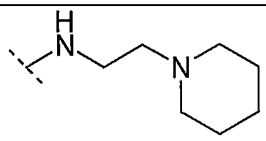
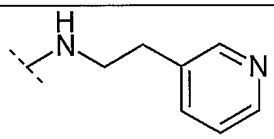
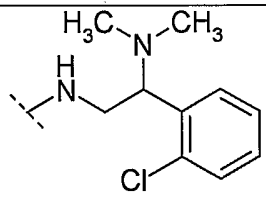
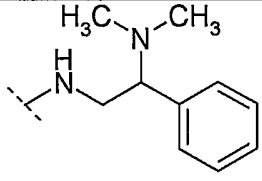
7	
8	
9	
10	
11	
12	
13	
14	

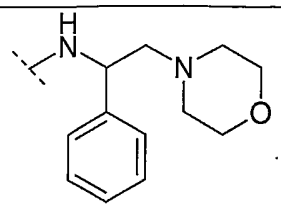
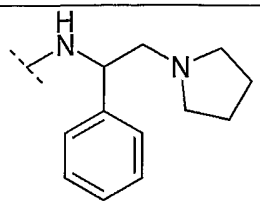
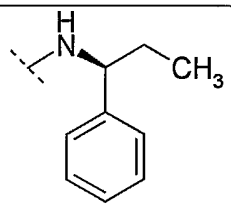
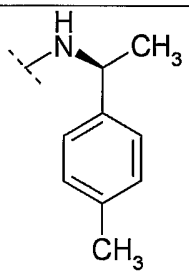
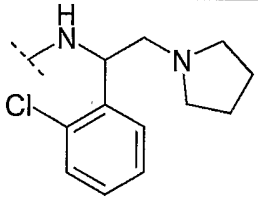
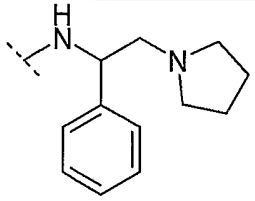
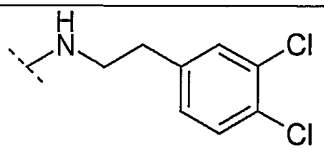
15	
16	
17	
18	
19	
20	
21	
22	
23	

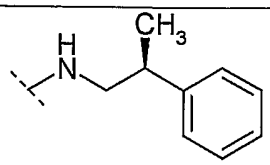
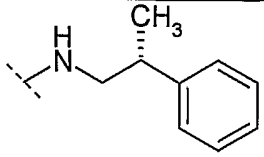
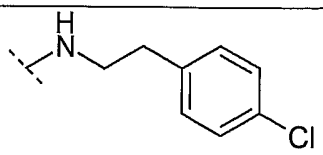
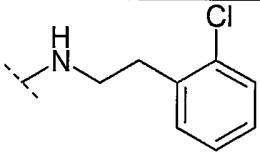
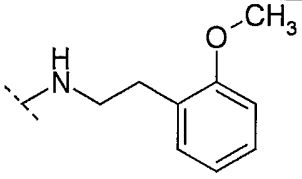
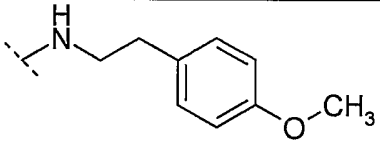
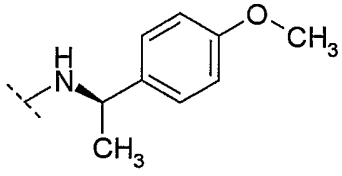
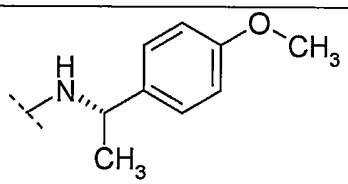
24	
25	
26	
27	
28	
29	
30	
31	

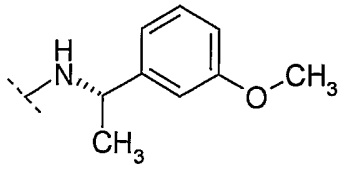
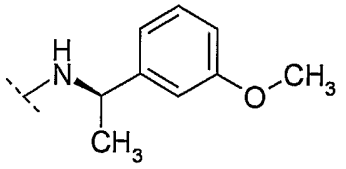
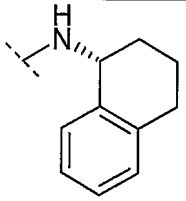
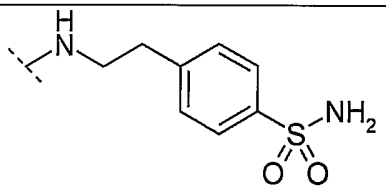
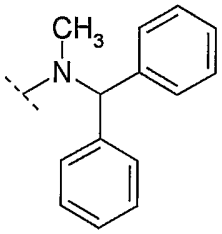
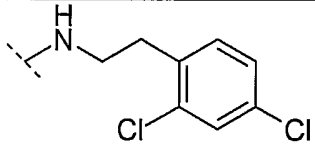
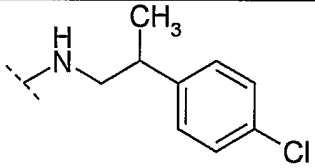
32	
33	
34	
35	
36	
37	
38	

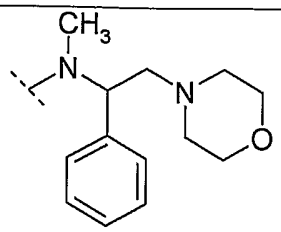
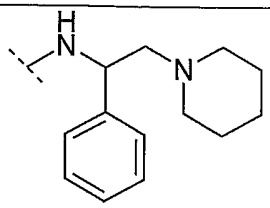
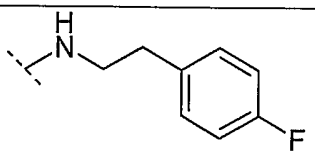
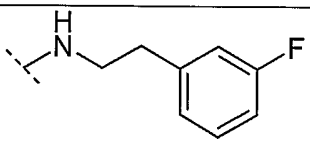
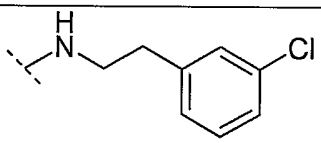
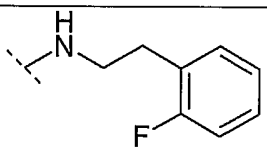
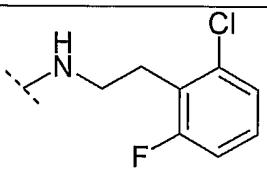
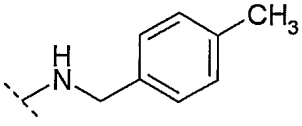
39	
40	
41	
42	
43	
44	
45	

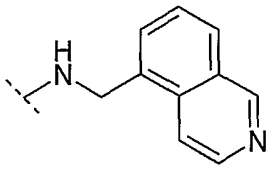
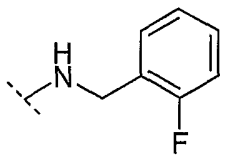
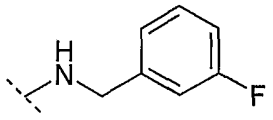
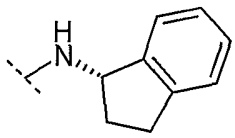
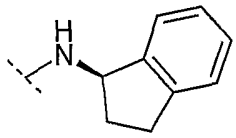
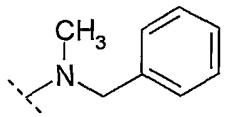
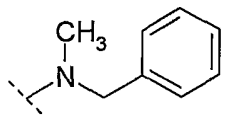
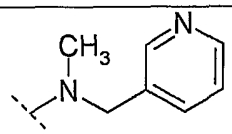
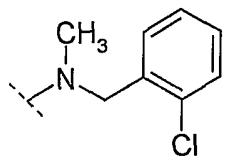
46	
47	
48	
49	
50	
51	
52	
53	

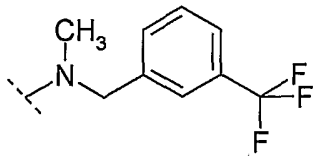
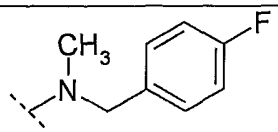
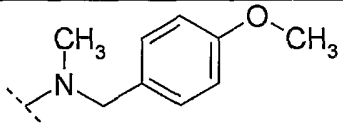
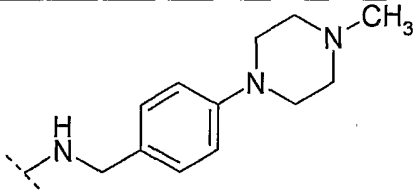
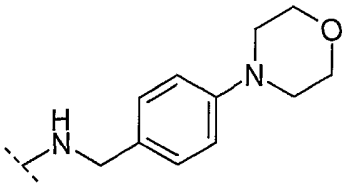
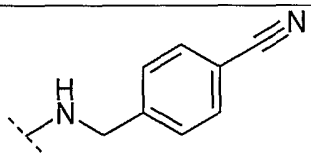
54	
55	
56	
57	
58	
59	
60	

61	
62	
63	
64	
65	
66	
67	
68	

69	
70	
71	
72	
73	
74	
75	

76	
77	
78	
79	
80	
81	
82	
83	

84	
85	
86	
87	
88	
89	
90	
91	
92	

93	
94	
95	
96	
97	
98	

31. A prodrug compound of a compound according to any one of the claims 1 to 30.

32. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof according to any one of the claims 1 to 31 together with a pharmaceutically acceptable carrier.

33. A pharmaceutical composition according to claim 32, 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 27; another DPP-IV inhibitor; insulin sensitizers; PPAR agonists; biguanides; protein tyrosinephosphatase-IB (PTP-1B) inhibitors; insulin and insulin mimetics; sulfonylureas 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.

34. A compound or a pharmaceutically acceptable salt thereof of any one of the claims 1 to 31 for use as a medicament.

35. Use of a compound or a pharmaceutically acceptable salt thereof of any of the claims 1 to 31 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; anxiety; depression; retinopathy; nephropathy; neuropathy; Syndrome X; ovarian hyperandrogenism (polycystic ovarian syndrome; Type n diabetes; or growth hormone deficiency.

36. Use of a compound according to any one of the claims 1 to 31 as DPP-IV inhibitor.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/002010

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/40 C07D307/79 C07D261/08 C07D319/16 C07D231/12
C07D241/12 C07D311/76 C07D295/13 C07C237/20 C07C311/13
A61K31/4409 A61K31/505 A61K31/42 A61K31/415 A61K31/343

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARUGG J L ET AL: "Selective catch and release of a synthetically useful phosphine ligand" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 44, no. 40, 29 September 2003 (2003-09-29), pages 7537-7540, XP004453464 ISSN: 0040-4039 see compound 2, Table 2 ----- -/--	1,3,4, 7-15

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 2005	08/06/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP2005/002010

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S.R.STARCK ET AL: "The puromycin route to assess stereo- and regiochemical constraints on peptide bond formation in eukaryotic ribosomes" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 125, no. 27, 6 November 2003 (2003-11-06), pages 8090-8091, XP002284840 see compound 2c	1-5,7-15
Y	WO 03/000180 A (EDMONDSON SCOTT D ; PARMEE EMMA (US); WEBER ANN E (US); XU JINYOU (US)) 3 January 2003 (2003-01-03) cited in the application the whole document	1-36
Y	WO 03/000181 A (PARMEE EMMA ; WEBER ANN E (US); MERCK & CO INC (US); BROCKUNIER LINDA) 3 January 2003 (2003-01-03) cited in the application the whole document	1-36
P,X	SAVIANO, GABRIELLA ET AL: "Influence of conformational flexibility on biological activity in cyclic astin analogues" BIOPOLYMERS , 76(6), 477-484 CODEN: BIPMAA; ISSN: 0006-3525, 15 September 2004 (2004-09-15), XP002328124 see compound butanoic acid, 2'''(2S)-2-amino-3-phenylpropyl!sulfonyl!amino-methylester(2S), RN842170-15-4	1-4,6-14
P,X	WO 2004/085378 A (MERCK & CO. INC; XIAO, YI; ARMSTRONG, JOSEPH, D., III; KRSKA, SHANE, W) 7 October 2004 (2004-10-07) se example 6, page 19	1-4,7-15
P,X	RAJU, B. ET AL: "Conformationally restricted analogs of deoxynegamycin" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS , 14(12), 3103-3107 CODEN: BMCLE8; ISSN: 0960-894X, 2004, XP004841352 see compound 1k, scheme 7	1
X	GUDE, MARKUS ET AL: "A new method for the solution and solid phase synthesis of chiral .beta.-sulfonopeptides under mild conditions" TETRAHEDRON LETTERS , 37(47), 8589-8592 CODEN: TELEAY; ISSN: 0040-4039, 1996, XP004068724 see 6, RN 185548-36-1, benzenepropanesulfonamide, beta amino-N-phenylmethylmonoHCl	1,11

-/--

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/002010

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MOREE, WILNA J. ET AL: "Synthesis of Peptidosulfinamides and Peptidosulfonamides: Peptidomimetics Containing the Sulfinamide or Sulfonamide Transition-State Isostere" JOURNAL OF ORGANIC CHEMISTRY , 60(16), 5157-69 CODEN: JOCEAH; ISSN: 0022-3263, 1995, XP002953415 see RN167867-34-7, L-phenylalanine,N'(2-amino-3-phenylpropyl) sulfonyl!(S), compound 38	1,11
P,X	CANTEL, SONIA ET AL: "Synthesis of chiral .alpha.-amino-diazoketones on solid support: an access to .beta.-homologated amino acid derivatives" SYNLETT , (15), 2791-2793 CODEN: SYNLES; ISSN: 0936-5214, 8 November 2004 (2004-11-08), XP001206415 see compound 1 and table 2, RNs 839730-21-1,839730-20-0,839730-17-5 and 839730-16-4	1-5,7-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/002010

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03000180 A	03-01-2003	CA 2450579 A1	03-01-2003
		EP 1406872 A2	14-04-2004
		JP 2004535433 T	25-11-2004
		WO 03000180 A2	03-01-2003
		US 2004176428 A1	09-09-2004
WO 03000181 A	03-01-2003	CA 2450475 A1	03-01-2003
		EP 1406622 A2	14-04-2004
		JP 2005500308 T	06-01-2005
		WO 03000181 A2	03-01-2003
		US 2004236102 A1	25-11-2004
WO 2004085378 A	07-10-2004	WO 2004085378 A1	07-10-2004