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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 September 2009 (03.09.2009)

PCT

(10) International Publication Number
WO 2009/106561 A1

(51) International Patent Classification:
C07D 401/12 (2006.01) *A61P 3/00* (2006.01)
A61K 31/497 (2006.01)

(21) International Application Number:
PCT/EP2009/052268

(22) International Filing Date:
26 February 2009 (26.02.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0800458-2 27 February 2008 (27.02.2008) SE
61/067,525 27 February 2008 (27.02.2008) US

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

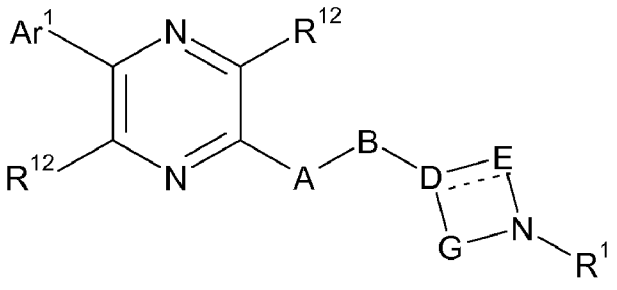
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, 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 (Art. 21(3))*

WO 2009/106561 A1

(54) **Title**: PYRAZINE COMPOUNDS FOR TREATING GPR119 RELATED DISORDERS



(Ia)

(57) **Abstract**: The application relates to compounds of Formula (Ia), and pharmaceutically acceptable salts, solvates, hydrates, geometrical isomers, tautomers, optical isomers and *N*-oxides thereof. The application also relates to pharmaceutical compositions comprising these compounds and to the use of these compounds for the prophylaxis and treatment of medical conditions relating to disorders of the G-protein-coupled receptor GPRl 19, such as diabetes, obesity and osteoporosis.

PYRAZINE COMPOUNDS FOR TREATING GPR119 RELATED DISORDERS

FIELD OF INVENTION

The present invention relates to novel pyrazine compounds, to pharmaceutical compositions comprising these compounds, and to the use of these compounds for the prophylaxis and treatment of medical conditions relating to disorders of the G-protein-coupled receptor GPR119 such as diabetes, obesity and osteoporosis.

BACKGROUND ART

Diabetes mellitus is a group of disorders characterized by abnormal glucose homeostasis resulting in high levels of blood glucose. The most common cases of diabetes mellitus are Type 1 (also referred to as insulin-dependent diabetes mellitus or IDDM) and Type 2 diabetes (also referred to as non-insulin-dependent diabetes mellitus or NIDDM). Type 2 diabetes accounts for approximately 90% of all diabetic cases. Type 2 diabetes is a serious progressive disease that results in the development of microvascular complications (e.g. retinopathy, neuropathy, nephropathy) as well as macrovascular complications (e.g. accelerated atherosclerosis, coronary heart disease, stroke). More than 75% of people with Type 2 diabetes die of cardiovascular diseases.

The increasing prevalence of obesity together with an ageing population is contributing to the predicted explosion in diabetes across the globe. Current projections suggest that 300 million people worldwide have diabetes by 2025.

The pathogenesis of Type 2 diabetes involves insulin resistance, insulin secretory dysfunction (i.e. pancreatic beta cell dysfunction) and hepatic glucose overproduction. Insulin resistance is highly correlated with obesity. Accumulating reports suggest insulin resistance to be central to a cluster of metabolic abnormalities - including dyslipidemia, hypertension, endothelial dysfunction, reduced fibrinolysis, and chronic systemic inflammation - that together are responsible for the increased cardiovascular risk.

Current antidiabetic therapy is targeting the defects mentioned above. For instance, sulphonylureas increase production of endogenous insulin. However, this enhanced insulin production is not glucose dependent and there is risk for developing hypoglycaemia. Metformin lowers hepatic glucose output. Thiazolidindiones (TZDs) reduce insulin resistance in muscle and liver and suppress inflammatory responses. A major side effect of

TZDs is weight gain due to fluid retention and increase in total body fat. An earlier drug in this class, troglitazone, was withdrawn due to rare but serious cases of hepatotoxicity. Current therapies have limited durability and/or significant side effects.

The widespread availability and increased consumption of Western diet combined with the adoption of a sedentary life-style has increased the number of obese people. Obesity is linked to a wide range of medical complications, such as diabetes, cardiovascular disease and cancer. In addition, being overweight can exacerbate the development of osteoporosis and asthma. Obesity is also proven to double the risk of hypertension. Obesity has only recently been regarded as a disease in the sense of being a specific target for medical therapy. Current therapies for obesity are based on diet and exercise and stomach surgery for extremely obese patients. Two weight loss medications are today available for long-term use. Sibutramine, a serotonin- and noradrenaline-reuptake inhibitor, controls appetite by producing a feeling of satiety. However, a prominent side effect is hypertension. Orlistat inhibits the lipase-mediated breakdown of fat in the gastrointestinal tract, thereby limiting caloric intake resulting in weight loss. However, approximately 20% of the patients using Orlistat develop faecal incontinence and urgency. Thus, there is an unmet medical need for new and novel antidiabetic and antiobesity therapies.

Osteoporosis, or porus bone, is a disabling disease characterized by low bone mass and structural deterioration of bone tissue, leading to compromised bone strength and an increased risk of fractures of the hip, spine and wrist. Anyone can develop osteoporosis, but it is common in older women. As many as half of all women and a quarter of men older than 50 will have an osteopeorosis-related fracture in their life-time. Riskfactors include getting older, gender, family history, body size, ethnicity (higher risk for Caucasians and Asians), inactive lifestyle, smoking and overconsumption of alcohol. It has recently been shown that one of the incretins, Glucose-dependent Insulinotropic Polypeptide (GIP, also known as gastric inhibitory polypeptide), promotes bone mass (Zhong et al., AM J Physiol Endocrinol Metab, 292, E543-E548, 2007).

GPR119 is a G-protein coupled receptor identified as SNORF25 in WO 00/50562. In humans, GPR119 is selectively expressed in pancreas and gastrointestinal tract. Activation of GPR119 by lysophosphatidylcholine (LPC) induces glucose-dependent insulin secretion from pancreatic beta-cells (Soga et al., Biochem. Biophys. Res. Commun. 326, 744-751,

2005). GPR119 agonists stimulate insulin secretion in rat islets and reduce blood glucose in diabetic $Lepr^{db/db}$ mice (WO 2004/065380 and Chu et al., Endocrinology 148, 2601-9, 2007). GPR119 agonists enhance the release of the incretins, GLP-1 and GIP in mice models and in GLUTag cells, which is a model used to investigate the function of intestinal L-cells (Chu et al., Endocrinology Jan 17, 2008).

Another endogenous ligand for GPR119, oleoylethanolamide (OEA), and a small molecule GPR119 agonist, PSN632408, both suppress food intake and reduce body weight gain in rat (Overton et al., Cell Metabolism 3, 167-175, 2006). Taken together, these data suggest that GPR119 is an interesting target for treating diabetes and/or obesity.

WO 2004/065380, WO 2004/076413, WO 2005/007647, WO 2005/007658 and WO 2005/121121 disclose compounds that are modulators of the Rup3 receptor, also referred to as SNORF25 (WO 00/50562) or as GPR119 (Fredriksson et al., FEBS Lett, 554, 381-388, 2003), and which *inter alia* may be used for the treatment of metabolic disorders and complications thereof, such as diabetes and obesity.

WO 2005/061489, WO 2006/067531, WO 2006/067532 and WO 2006/070208 disclose compounds that are agonists of GPR116, also referred to as SNORF25 or as GPR119 (see Overton et al, Cell Metabolism 3, 167-175, 2006), and which inter alia may be used for the treatment of metabolic disorders and complications thereof, such as diabetes and obesity.

WO 2006/076231 discloses a synergistic effect of a GPR119 agonist in combination with a DPP-IV inhibitor, in lowering elevated glucose levels in mice. Further, a synergistic effect with the said combination is shown in increasing blood GLP-1 levels after glucose challenge in mice.

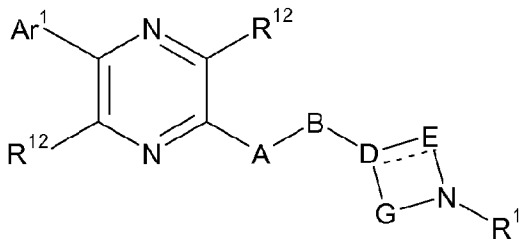
WO 2007/120689 discloses a method of using GPR119 receptor to identify compounds useful for increasing bone mass in an individual. GPR119 agonists are shown to enhance GIP in wildtype mice.

DISCLOSURE OF THE INVENTION

It has surprisingly been found that compounds of the general Formula (Ia) to (Ic) are active as agonists of GPR119 and are potentially useful in the treatment or prophylaxis of disorders relating to GPR119. Examples of such disorders include Type 1 diabetes, Type 2 diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypercholesterolemia, dyslipidemia, syndrome X, obesity, hypertension, chronic systemic

inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, reduced fibrinolysis, endothelial dysfunction and osteoporosis.

In a first aspect, the invention provides a compound of Formula (Ia),



(Ia)

or a pharmaceutically acceptable salt, solvate, hydrate, geometrical isomer, tautomer, optical isomer or *N*-oxide thereof; wherein:

A is CH_2, O, NR^{10}, C(O), S, S(O) or $S(O)_2$;

B is CH_2, O, NR^{10}, C(O), S, S(O) or $S(O)_2$, provided that when B is O, NR^{10}, C(O), S, S(O) or $S(O)_2$, then A is CH_2;

D is N, C or CR^{11}, provided that D must be CR^{11} and said R^{11} must be hydrogen or methyl when B is selected from O, NR^{10}, C(O), S, S(O) and $S(O)_2$;

---- is a single bond when D is N or CR^{11} or a double bond when D is C;

E and G are independently C_{1-3}-alkylene, each optionally substituted with a substituent independently selected from the group consisting of C_{1-3}-alkyl, C_{1-4}-alkoxy, carboxy, fluoro-C_{1-3}-alkyl, hydroxy, hydroxymethyl, and fluoro, provided that the ring formed by D, E, N and G has not more than 7 ring atoms, and further provided that the said ring has 6 or 7 ring atoms when D is N, and yet further provided that the total number of substituents on E and G independently is not more than 2;

R^1 is $C(O)OR^2$, $C(O)R^2$, $S(O)_2R^2$, $C(O)NR^2R^3$ or $-CH_2-C(O)NR^2R^3$, or a 5- or 6-membered heteroaryl group linked via a ring carbon atom, wherein the said heteroaryl group is optionally substituted with C_{1-4}-alkyl;

Ar^1 is phenyl or heteroaryl, each of which is optionally independently substituted in one or more positions with a substituent selected from:

(a) CF_3SO_3,

(b) halogen selected from chlorine, bromine and fluorine,

(c) C_{1-4}-alkylsulfoximine,

(d) $-S(O)R^4$,

(e) $-S(O)_2R^4$,

(f) $-S(O)_2NR^5R^5$,

(g) $-NR^6S(O)_2R^4$,

(h) $-CH_2-NR^6C(O)R^4$,

(i) $-NR^6C(O)R^4$,

(j) $-C(O)NR^5R^5$,

(k) $-CH_2-C(O)NR^5R^5$,

(l) $-C(O)R^4$,

(m) $H_2N-C(O)O-$,

(n) $CH_3-NH-C(O)O-$,

(o) $(CH_3)_2NC(O)O-$,

(p) $CH_3OC(O)NH-$,

(q) C-heterocyclyl, optionally substituted with C_{1-4}-alkyl,

(r) $-CN$,

(s) $-OR^8$,

(t) $-SCF_3$,

(u) $-NO_2$,

(v) C-heterocyclylsulfonyl, optionally substituted with C_{1-4}-alkyl,

(w) $-NR^5R^5$,

(x) $-C(OH)CH_3CF_3$,

(y) $[CF_3CH_3(OH)C]-C_{1-6}$-alkyl,

(z) cyano-C_{1-6}-alkyl,

(aa) guanidino,

(bb) amidino,

(cc) C_{1-6}-alkyl,

(dd) C_{1-4}-alkoxy-C_{1-4}-alkyl,

(ee) fluoro-C_{1-4}-alkyl,

(ff) C_{2-6}-alkenyl,

(gg) fluoro-C_{2-4}-alkenyl,

(hh) hydroxy-C_{1-6}-alkyl,

(ii) C_{1-4}-alkylsulfonyl-C_{1-4}-alkyl,

(jj) hydroxy-C_{2-4}-alkoxy-C_{1-4}-alkyl,

(kk) C_{2-3}-acyl-C_{1-3}-alkyl,

(ll) C_{2-6}-alkynyl,

(mm) hydroxy-C_{3-6}-cycloalkyl,

(nn) fluoro-C_{3-6}-cycloalkyl,

(oo) methyl-C_{3-6}-cycloalkyl,

(pp) C-heterocyclylcarbonyl, optionally substituted with C_{1-4}-alkyl,

(qq) C_{3-6}-cycloalkyl,

(rr) C_{3-6}-cycloalkyl-C_{1-4}-alkyl,

(ss) R^5R^5N-C_{1-2}-alkyl,

(tt) $-C(O)OR^7$,

(uu) $-CH_2C(O)OR^7$,

(vv) phenyl, and

(ww) heteroaryl,

wherein phenyl or heteroaryl as substituent on Ar^1 is optionally substituted in one or more positions with a substituent independently selected from the group Z^1 consisting of:

(a) halogen selected from chlorine and fluorine,

(b) C_{1-4}-alkyl,

(c) hydroxy,

(d) C_{1-4}-alkoxy,

(e) $-OCF_3$,

(f) $-SCF_3$,

(g) $-CN$,

(h) $-C(OH)CH_3CF_3$,

(i) hydroxy-C_{1-4}-alkyl,

(j) $-CF_3$,

(k) $-S(O)_2CH_3$,

(l) $-S(O)_2NH_2$,

(m) $-S(O)_2NHCH_3$,

(n) $-S(O)_2N(CH_3)_2$,

(o) $-N(CH_3)S(O)_2CH_3$,

(p) $-N(CH_3)C(O)CH_3$,

(q) $-C(O)NH_2$,

(r) $-C(O)NHCH_3$,

(s) $-C(O)N(CH_3)_2$,

(t) $-C(O)CH_3$,

(u) $-NH_2$,

(v) $-NHCH_3$,

(w) $-N(CH_3)_2$, and

(x) methoxycarbonyl;

R^2 is selected from:

(a) C_{1-6}-alkyl,

(b) C_{1-6}-alkoxy-C_{2-6}-alkyl,

(c) hydroxy-C_{2-6}-alkyl,

(d) fluoro-C_{2-6}-alkyl,

(e) C_{3-6}-alkynyl,

(f) C_{3-6}-alkenyl,

(g) C_{3-7}-cycloalkyl,

(h) C_{5-8}-cycloalkenyl,

(i) NR^9R^9, provided that R^1 is not selected from $C(O)OR^2$, $C(O)NR^2R^3$ and $-CH_2-C(O)NR^2R^3$,

(j) C-heterocyclyl, optionally substituted with C_{1-4}-alkyl,

(k) C_{7-8}-bicyclyl, optionally substituted with hydroxy,

(l) C_{7-8}-bicyclylmethyl,

(m) azabicyclyl, optionally substituted with hydroxy,

(n) C_{3-7}-cycloalkyl-C_{1-4}-alkyl, wherein cycloalkyl is optionally substituted with methyl,

(o) C_{1-6}-alkylsulfonyl-C_{2-6}-alkyl,

(p) C_{2-3}-acyl-C_{1-4}-alkyl,

(q) arylcarbonyl-C_{1-4}-alkyl,

(r) heteroarylcarbonyl-C_{1-4}-alkyl,

(s) $[CF_3CH_3(OH)C]$-C_{1-6}-alkyl,

(t) *N*-heterocyclylcarbonyl-C_{2-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(u) C-heterocyclylcarbonyl-C_{2-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,
(v) aminocarbonyl-C_{2-6}-alkyl,
(w) C_{1-3}-alkylaminocarbonyl-C_{2-6}-alkyl,
(x) di(C_{1-3}-alkyl)aminocarbonyl-C_{2-6}-alkyl,
(y) hydroxy-C_{2-4}-alkoxy-C_{2-4}-alkyl,
(z) hydroxy-C_{4-6}-cycloalkyl,
(aa) oxo-C_{4-6}-cycloalkyl,
(bb) fluoro-C_{4-6}-cycloalkyl,
(cc) C_{1-3}-alkoxy-C_{4-6}-cycloalkyl,
(dd) methyl-C_{3-6}-cycloalkyl,
(bb) oxo-*N*-heterocyclyl-C_{2-4}-alkyl,
(cc) fluoro-*N*-heterocyclyl-C_{2-4}-alkyl,
(dd) amino-*N*-heterocyclyl-C_{2-4}-alkyl,
(ee) hydroxy-*N*-heterocyclyl-C_{2-4}-alkyl,
(ii) *N*-heterocyclyl-C_{2-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,
(jj) C-heterocyclyl-C_{1-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,
(kk) aryl,
(ll) aryl-C_{1-4}-alkyl,
(mm) aryl-C_{3-6}-alkenyl,
(nn) aryl-C_{3-6}-alkynyl,
(oo) heteroaryl,
(pp) heteroaryl-C_{1-4}-alkyl,
(qq) heteroaryl-C_{3-6}-alkenyl, and
(rr) heteroaryl-C_{3-6}-alkynyl,

wherein any aryl or heteroaryl residue, alone or as part of another group, is optionally independently substituted in one or more position with a substituent selected from the group Z^1 as defined above;

R^3 is selected from:

(a) hydrogen,
(b) C_{1-6}-alkyl,

(c) fluoro-C_{2-6}-alkyl,

(d) hydroxy-C_{2-6}-alkyl,

(e) C_{1-6}-alkoxy-C_{2-6}-alkyl,

(f) amino-C_{2-6}-alkyl,

(g) C_{1-3}-alkylamino-C_{2-6}-alkyl,

(h) di(C_{1-3}-alkyl)amino-C_{2-6}-alkyl,

(i) cyano-C_{1-6}-alkyl, and

(j) C_{1-6}-alkylsulfonyl-C_{2-6}-alkyl;

R^4 is independently selected from:

(a) C_{1-6}-alkyl,

(b) fluoro-C_{1-6}-alkyl,

(c) hydroxy-C_{2-6}-alkyl,

(d) C_{1-4}-alkoxy-C_{2-4}-alkyl,

(e) C_{2-4}-acyl-C_{1-4}-alkyl,

(f) carboxy-C_{1-3}-alkyl,

(g) C_{3-6}-cycloalkyl,

(h) oxo-C_{4-6}-cycloalkyl,

(i) hydroxy-C_{4-6}-cycloalkyl,

(j) fluoro-C_{4-6}-cycloalkyl,

(k) methyl-C_{3-6}-cycloalkyl,

(l) *N*-heterocyclylcarbonyl-C_{2-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(m) oxo-*N*-heterocyclyl-C_{2-4}-alkyl,

(n) fluoro-*N*-heterocyclyl-C_{2-4}-alkyl,

(o) hydroxy-*N*-heterocyclyl-C_{2-4}-alkyl,

(p) amino-*N*-heterocyclyl-C_{2-4}-alkyl,

(q) aminocarbonyl-C_{2-4}-alkyl,

(r) C_{1-3}-alkylaminocarbonyl-C_{2-4}-alkyl,

(s) di(C_{1-3}-alkyl)aminocarbonyl-C_{2-4}-alkyl,

(t) C_{2-3}-acylamino-C_{2-4}-alkyl,

(u) hydroxy-C_{2-4}-alkoxy-C_{2-4}-alkyl,

(v) C-heterocyclylcarbonyl-C_{2-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(w) C_{3-6}-cycloalkyl-C_{1-2}-alkyl,

(x) amino-C_{2-4}-alkyl,

(y) C_{1-2}-alkylamino-C_{2-4}-alkyl,

(z) di(C_{1-2}-alkyl)amino-C_{2-4}-alkyl,

(aa) phenyl, and

(bb) heteroaryl,

wherein any phenyl or heteroaryl residue is optionally substituted in one or more positions with a substituent independently selected from the group Z^2 consisting of:

(a) halogen selected from chlorine and fluorine,

(b) C_{1-4}-alkoxy,

(c) hydroxymethyl,

(d) –CN,

(e) $–CF_3$,

(f) C_{1-4}-alkyl,

(g) $–OCF_3$, and

(h) $–C(O)CH_3$;

R^5 is each independently selected from:

(a) hydrogen,

(b) C_{1-6}-alkyl,

(c) C_{3-4}-cycloalkyl,

(d) fluoro-C_{2-4}-alkyl,

(e) amino-C_{2-6}-alkyl,

(f) cyano-C_{1-6}-alkyl,

(g) hydroxy-C_{2-6}-alkyl,

(h) dihydroxy-C_{2-6}-alkyl,

(i) C_{1-4}-alkoxy-C_{2-4}-alkyl,

(j) C_{1-4}-alkylamino-C_{2-4}-alkyl,

(k) di(C_{1-4}-alkyl)amino-C_{2-4}-alkyl,

(l) aminocarbonyl-C_{1-4}-alkyl,

(m) C_{2-3}-acylamino-C_{2-4}-alkyl,

(n) C_{1-4}-alkylthio-C_{2-4}-alkyl,

(o) C_{2-4}-acyl-C_{1-4}-alkyl, and

(p) C_{1-4}-alkylsulfonyl-C_{1-4}-alkyl,

or two R^5 groups together with the nitrogen to which they are attached form a heterocyclic ring, wherein said heterocyclic ring may be optionally substituted with:

i) a substituent selected from:

(aa) hydroxy,

(bb) amino,

(cc) methylamino,

(dd) dimethylamino,

(ee) hydroxymethyl, and

(ff) aminomethyl;

ii) one or two oxo groups; or

iii) one or two fluorine atoms,

provided that when the substituent is selected from fluorine, hydroxy, amino, methylamino and dimethylamino, said substituent is attached to the heterocyclic ring at a position other than alpha to a heteroatom;

and when the two R^5 groups form a piperazine ring, the nitrogen of the piperazine ring that allows the substitution is optionally substituted with C_{1-4}-alkyl;

R^6 is independently selected from:

(a) hydrogen,

(b) C_{1-4}-alkyl, and

(c) hydroxy-C_{2-4}-alkyl;

R^7 is independently selected from C_{1-4}-alkyl;

R^8 is independently selected from:

(a) hydrogen,

(b) C_{1-6}-alkyl,

(c) fluoro-C_{1-6}-alkyl,

(d) hydroxy-C_{2-6}-alkyl,

(e) amino-C_{2-5}-alkyl,

(f) C_{1-3}-alkylamino-C_{2-4}-alkyl,

(g) di(C_{1-3}-dialkyl)amino-C_{2-4}-alkyl,

(h) C_{1-4}-alkylsulfonyl-C_{2-4}-alkyl,

(i) *N*-heterocyclyl-C_{2-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(j) C-heterocyclyl, optionally substituted with methyl,

(k) C_{2-3}-acylamino-C_{2-4}-alkyl,

(l) $[CF_3CH_3(OH)C]$-C_{1-6}-alkyl,

(m) C_{3-6}-cycloalkyl,

(n) methyl-C_{3-6}-cycloalkyl,

(o) C_{3-6}-cycloalkyl-C_{1-2}-alkyl,

(p) aryl, and

(q) heteroaryl,

wherein any aryl or heteroaryl residue is optionally independently substituted in one or two positions with a substituent selected from the group Z^2 as defined above;

R^9 is each independently selected from:

(a) C_{1-4}-alkoxy-C_{2-4}-alkyl,

(b) amino-C_{2-4}-alkyl,

(c) C_{1-4}-alkylamino-C_{2-4}-alkyl,

(d) di(C_{1-4}-alkyl)amino-C_{2-4}-alkyl,

(e) C_{2-3}-acylamino-C_{2-4}-alkyl,

(f) C_{1-4}-alkylthio-C_{2-4}-alkyl, and

(g) C_{2-4}-acyl-C_{1-4}-alkyl;

or two R^9 groups together with the nitrogen to which they are attached form a heterocyclic ring, wherein said heterocyclic ring may be optionally substituted with:

i) a substituent selected from:

(aa) hydroxy,

(bb) amino,

(cc) methylamino,

(dd) dimethylamino,

(ee) hydroxymethyl, and

(ff) aminomethyl;

ii) one or two oxo groups; or

iii) one or two fluorine atoms,

provided that when the substituent is selected from fluorine, hydroxy, amino, methylamino and dimethylamino, said substituent is attached to the heterocyclic ring at a position other than alpha to a heteroatom;

and when the two R^9 groups form a piperazine ring, the nitrogen of the piperazine ring that allows the substitution is optionally substituted with C_{1-4}-alkyl;

R^{10} is independently selected from:

(a) hydrogen,

(b) C_{1-6}-alkyl,

(c) cyclopropyl,

(d) cyclobutyl,

(e) cyclopropylmethyl,

(f) fluoro-C_{2-6}-alkyl,

(g) hydroxy-C_{2-6}-alkyl,

(h) C_{1-2}-alkoxy-C_{2-6}-alkyl,

(i) amino-C_{2-6}-alkyl,

(j) di(C_{1-3}-alkyl)amino-C_{2-6}-alkyl,

(k) C_{1-3}-alkylamino-C_{2-6}-alkyl,

(l) cyano-C_{2-4}-alkyl,

(m) C_{2-6}-acyl,

(n) C_{2-6}-acyl-C_{1-6}-alkyl, and

(o) C_{1-6}-alkylsulfonyl-C_{1-6}-alkyl;

R^{11} is selected from:

(a) hydrogen,

(b) hydroxy,

(c) fluorine,

(d) C_{1-4}-alkoxy, and

(e) methyl;

R^{12} is each independently selected from:

(a) hydrogen,

(b) –CN,

(c) C_{1-4}-alkoxy,

(d) $-NR^5R^5$, wherein each R^5 is independently selected from the group consisting of hydrogen and C_{1-4}-alkyl; or two R^5 groups together with the nitrogen to which they are attached form a pyrrolidine or an azetidine ring,

(e) C_{1-3}-alkyl,

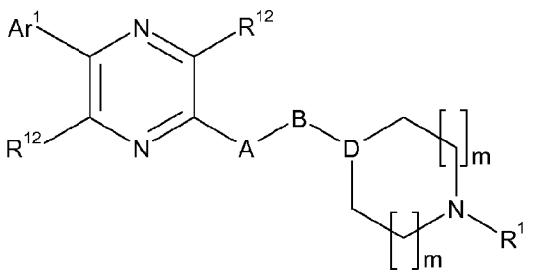
(f) C_{1-3}-alkoxy-C_{1-2}-alkyl, and

(g) hydroxy-C_{1-4}-alkyl;

and with the proviso that the compound is not selected from:

- 1-Methylethyl 4-[({5-[4-(methylsulfonyl)phenyl]-2-pyrazinyl}oxy)methyl]-1-piperidinecarboxylate;
- 2-[({1-[3-(1-Methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}methyl)oxy]-5-[4-(methylsulfonyl)phenyl]pyrazine;
- 5-Fluoro-2-{4-[({5-[4-(methylsulfonyl)phenyl]-2-pyrazinyl}oxy)methyl]-1-piperidinyl}pyrimidine;
- 2-[2-Fluoro-4-(methylsulfonyl)phenyl]-5-[({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}methyl)oxy]pyrazine;
- 1-Methylethyl 4-[({5-[2-fluoro-4-(methylsulfonyl)phenyl]-2-pyrazinyl}oxy)methyl]-1-piperidinecarboxylate; and
- 2-[({1-[3-(1-Methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}methyl)oxy]-5-[2-methyl-4-(methylsulfonyl)phenyl]pyrazine.

A preferred group of compounds of formula (Ia) are the compounds of Formula (Ib),



(Ib)

and pharmaceutically acceptable salts, solvates, hydrates, geometrical isomers, tautomers, optical isomers or *N*-oxides thereof; wherein:

A is CH_2, O, NR^{10}, C(O), S, S(O) or $S(O)_2$;

B is CH_2, O, NR^{10}, C(O), S, S(O) or $S(O)_2$, provided that when B is O, NR^{10}, C(O), S, S(O) or $S(O)_2$, then A is CH_2;

m is each independently 0 or 1;

D is N or CR^{11}, provided that D must be CR^{11} and said R^{11} must be hydrogen or methyl when B is selected from O, NR^{10}, C(O), S, S(O) and $S(O)_2$; and further provided that each m is 1 when D is N;

Ar^1, Z^1, Z^2, R^1 to R^9 and R^{12} are as defined in Formula (Ia);

R^{10} is independently selected from:

(a) hydrogen,

(b) C_{1-4}-alkyl,

(c) cyclopropyl,

(d) cyclobutyl,

(e) cyclopropylmethyl,

(f) fluoro-C_{2-4}-alkyl,

(g) C_{1-2}-alkoxy-C_{2-3}-alkyl,

(h) hydroxy-C_{2-4}-alkyl,

(i) C_{2-3}-acyl,

(j) amino-C_{2-4}-alkyl,

(k) methylamino-C_{2-4}-alkyl,

(l) dimethylamino-C_{2-4}-alkyl, and

(m) cyano-C_{2-4}-alkyl;

R^{11} is selected from:

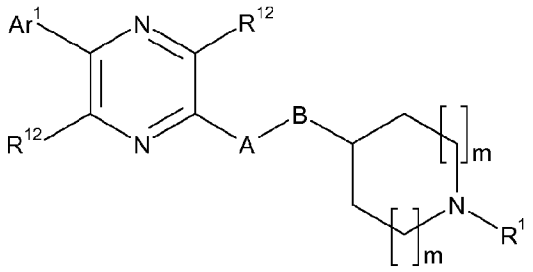
(a) hydrogen,

(b) hydroxy,

(c) fluorine, and

(d) methyl.

A further preferred group of compounds of formula (Ia) are compounds of Formula (Ic),



(Ic)

and pharmaceutically acceptable salts, solvates, hydrates, geometrical isomers, tautomers, optical isomers or *N*-oxides thereof; wherein:

A is CH_2, O or NR^{10};

B is CH_2, O or NR^{10}, provided that when B is O or NR^{10}, then A is CH_2;

m is each independently 0 or 1;

Z^1, Z^2, R^1 to R^7, R^9 and R^{12} are as defined in Formula (Ia);

R^{10} is as defined in Formula (Ib);

Ar^1 is phenyl or 5- or 6-membered heteroaryl, each of which is optionally substituted in one or two positions with a substituent independently selected from the group Z^3 consisting of:

(a) CF_3SO_3,

(b) halogen selected from bromine, chlorine and fluorine,

(c) C_{1-4}-alkylsulfoximine,

(d) $-S(O)R^4$,

(e) $-S(O)_2R^4$,

(f) $-S(O)_2NR^5R^5$,

(g) $-NR^6S(O)_2R^4$,

(h) $-NR^6C(O)R^4$,

(i) $-CH_2-NR^6C(O)R^4$,

(j) $-C(O)NR^5R^5$,

(k) $-CH_2-C(O)NR^5R^5$,

(l) $-C(O)R^4$,

(m) $H_2N-C(O)O-$,

(n) CH_3-NH-C(O)O–,

(o) $(CH_3)_2NC(O)O$–,

(p) –$NHC(O)OCH_3$,

(q) C-heterocyclyl, optionally substituted with methyl,

(r) –CN,

(s) $–OR^8$,

(t) $–SCF_3$,

(u) C-heterocyclylsulfonyl, optionally susbtituted with methyl,

(v) $–NR^5R^5$,

(w) $–C(OH)CH_3CF_3$,

(x) cyano-C_{1-6}-alkyl,

(y) C_{1-6}-alkyl,

(z) C_{1-4}-alkoxy-C_{1-4}-alkyl,

(aa) fluoro-C_{1-4}-alkyl,

(bb) C_{2-6}-alkenyl,

(cc) fluoro-C_{2-4}-alkenyl,

(dd) hydroxy-C_{1-6}-alkyl,

(ee) C_{1-4}-alkylsulfonyl-C_{1-4}-alkyl,

(ff) hydroxy-C_{2-4}-alkoxy-C_{1-4}-alkyl,

(gg) C_{2-3}-acyl-C_{1-3}-alkyl,

(hh) C_{2-6}-alkynyl,

(ii) C_{3-6}-cycloalkyl,

(jj) hydroxy-C_{3-6}-cycloalkyl,

(kk) fluoro-C_{3-6}-cycloalkyl,

(ll) methyl-C_{3-6}-cycloalkyl,

(mm) C-heterocyclylcarbonyl, optionally substituted with methyl,

(nn) C_{3-6}-cycloalkyl-C_{1-4}-alkyl,

(oo) R^5R^5N-C_{1-2}-alkyl,

(pp) $–C(O)OR^7$,

(qq) $–CH_2C(O)OR^7$, and

(rr) heteroaryl,

wherein any heteroaryl residue as substituent on Ar^1 is optionally substituted in one or more positions with a substituent independently selected from the group Z^2 as defined herein for Formula (Ia);

R^8 is independently selected from:

(a) hydrogen,

(b) C_{1-4}-alkyl,

(c) CF_3,

(d) C_{3-5}-cycloalkyl,

(e) methyl-C_{3-5}-cycloalkyl, and

(f) C-heterocyclyl, optionally substituted with methyl.

A preferred subgroup of compounds of Formula (Ic) consists of compounds wherein:

A is CH_2 and B is O or NR^{10}, or
A is O or NR^{10} and B is CH_2;
m is each 1;

Ar^1 is phenyl, pyridinyl or thienyl, each of which is optionally substituted in one or two positions with a substituent independently selected from the group Z^4 consisting of:

(a) halogen selected from chlorine and fluorine,

(b) C_{1-4}-alkylsulfoximine,

(c) C_{1-4}-alkylsulfonyl,

(d) C_{1-4}-alkylsulfinyl,

(e) hydroxy-C_{2-4}-alkylsulfonyl,

(f) C_{3-5}-cycloalkylsulfonyl,

(g) methyl-C_{3-5}-cycloalkylsulfonyl,

(h) trifluoromethylsulfonyl,

(i) $–S(O)_2NR^{5A}R^{5A}$,

(j) C_{1-4}-alkylsulfonamido,

(k) C_{2-4}-acylamino,

(l) C_{2-4}-acylaminomethyl,

(m) carboxy-C_{1-3}-alkylcarbonylamino,

(n) $–C(O)NR^{5A}R^{5A}$,

(o) $–CH_2$-$C(O)NR^{5A}R^{5A}$,

(p) $–NHC(O)OCH_3$,

(q) C_{2-4}-acyl,

(r) C_{3-5}-cycloalkylcarbonyl,

(s) C_{1-4}-alkoxy,

(t) C_{3-5}-cycloalkyloxy,

(u) C-heterocyclyl,

(v) –CN,

(w) –OH,

(x) $–OCF_3$,

(y) $–CF_3$,

(z) $–NR^{5A}R^{5A}$,

(aa) $–C(OH)CH_3CF_3$,

(bb) cyano-C_{1-2}-alkyl,

(cc) C_{1-4}-alkyl,

(dd) C_{3-5}-cycloalkyl,

(ee) C_{1-2}-alkoxy-C_{1-2}-alkyl,

(ff) vinyl,

(gg) ethynyl,

(hh) hydroxy-C_{1-2}-alkyl,

(ii) C-heterocyclyloxy, optionally substituted with methyl,

(jj) $R^{5A}R^{5A}N$-C_{1-2}-alkyl,

(kk) $–C(O)OR^{7A}$, and

(ll) $–CH_2C(O)OR^{7A}$;

R^1 is a group R^{1A} selected from $C(O)OR^{2A}$, $C(O)R^{2A}$, $S(O)_2R^{2A}$, $C(O)NR^{2A}R^{3A}$, $-CH_2-C(O)NR^{2A}R^{3A}$, or a 5- or 6-membered heteroaryl group linked via a ring carbon atom, wherein the said heteroaryl group is optionally substituted with C_{1-4}-alkyl;

R^{2A} is selected from:

(a) C_{1-6}-alkyl,

(b) C_{1-6}-alkoxy-C_{2-6}-alkyl,

(c) hydroxy-C_{2-6}-alkyl,

(d) hydroxy-C_{2-4}-alkoxy-C_{2-4}-alkyl,

(e) fluoro-C_{2-6}-alkyl,

(f) C_{3-6}-alkynyl,

(g) C_{3-7}-cycloalkyl,

(h) C_{5-8}-cycloalkenyl,

(i) $NR^{9A}R^{9A}$ provided that R^{1A} is not selected from $C(O)OR^{2A}$, $C(O)NR^{2A}R^{3A}$ and $-CH_2-C(O)NR^{2A}R^{3A}$,

(j) C-heterocyclyl, optionally substituted with methyl,

(k) C_{7-8}-bicyclyl,

(l) 2-norbornylmethyl,

(m) azabicyclyl,

(n) C_{3-6}-cycloalkyl-C_{1-4}-alkyl, wherein cycloalkyl is optionally substituted with methyl,

(o) C_{2-3}-acyl-C_{1-4}-alkyl,

(p) arylcarbonyl-C_{1-4}-alkyl,

(q) heteroarylcarbonyl-C_{1-4}-alkyl,

(r) $[CF_3CH_3(OH)C]$-C_{1-6}-alkyl,

(s) *N*-heterocyclylcarbonyl-C_{2-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(t) hydroxy-C_{4-6}-cycloalkyl,

(u) oxo-C_{4-6}-cycloalkyl,

(v) fluoro-C_{4-6}-cycloalkyl,

(w) methoxy-C_{4-6}-cycloalkyl,

(x) methyl-C_{3-6}-cycloalkyl,

(y) oxo-*N*-heterocyclyl-C_{2-4}-alkyl,

(z) hydroxy-*N*-heterocyclyl-C_{2-4}-alkyl,

(aa) fluoro-*N*-heterocyclyl-C_{2-4}-alkyl,

(bb) amino-*N*-heterocyclyl-C_{2-4}-alkyl,

(cc) *N*-heterocyclyl-C_{2-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(dd) C-heterocyclyl-C_{1-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(ee) aryl,

(ff) aryl-C_{1-4}-alkyl,

(gg) heteroaryl, and

(hh) heteroaryl-C_{1-4}-alkyl,

wherein any aryl or heteroaryl residue, alone or as a part of another group, is optionally substituted in one or more positions with a substituent independently selected from the group Z^5 consisting of:

(a) halogen selected from chlorine and fluorine,
(b) methyl,
(c) ethyl,
(d) methoxy,
(e) ethoxy,
(f) isopropoxy,
(g) hydroxy,
(h) $–OCF_3$,
(i) $–CF_3$,
(j) –CN,
(k) $–C(OH)CH_3CF_3$,
(l) dimethylamino,
(m) hydroxymethyl,
(n) $–S(O)_2CH_3$,
(o) $–C(O)CH_3$, and
(p) $–C(O)NH_2$;

R^{3A} is selected from:

(a) hydrogen,
(b) C_{1-4}-alkyl,
(c) hydroxy-C_{2-4}-alkyl, and
(d) methoxy-C_{2-4}-alkyl;

R^{5A} is each independently selected from:

(a) hydrogen,
(b) C_{1-3}-alkyl,
(c) C_{1-2}-alkoxy-C_{2-4}-alkyl,
(d) C_{3-4}-cycloalkyl,
(e) hydroxy-C_{2-4}-alkyl,
(f) cyano-C_{1-3}-alkyl,
(g) dihydroxy-C_{2-4}-alkyl,

(h) aminocarbonyl-C_{1-2}-alkyl, and

(i) di(C_{1-2}-alkyl)amino-C_{2-3}-alkyl;

or two R^{5A} groups together with the nitrogen to which they are attached form a heterocyclic ring, wherein said heterocyclic ring may be optionally substituted with:

i) a substituent selected from:

(aa) hydroxy,

(bb) amino,

(cc) methylamino,

(dd) dimethylamino,

(ee) hydroxymethyl, and

(ff) aminomethyl;

ii) one or two oxo groups; or

iii) one or two fluorine atoms, provided that when the substituent is selected from fluorine, hydroxy, amino, methylamino and dimethylamino, said substituent is attached to the heterocyclic ring at a position other than alpha to a heteroatom;

and when the two R^{5A} groups form a piperazine ring, the nitrogen of the piperazine ring that allows the substitution is optionally substituted with methyl;

R^{7A} is independently selected from C_{1-4}-alkyl;

Two groups R^{9A} together with the nitrogen to which they are attached form a heterocyclic ring, wherein said heterocyclic ring may be optionally substituted with:

i) one hydroxy or amino group;

ii) one or two fluorine atoms; or

iii) one or two oxo groups,

provided that when the substituent is selected from fluorine, hydroxy and amino, said substituent is attached to the heterocyclic ring at a position other than alpha to a heteroatom;

and when the two R^{9A} groups form a piperazine ring, the nitrogen of the piperazine ring that allows the substitution is optionally substituted with methyl;

R^{10} is independently selected from:

(a) hydrogen,

(b) C_{1-3}-alkyl,

(c) cyclopropyl, and

(d) cyclopropylmethyl;

R^{12} is each hydrogen.

In a more preferred subgroup of compounds of Formula (Ic), A is CH_2 and B is O or NR^{10}.

In another more preferred subgroup of compounds of Formula (Ic), Ar^1 is selected from methylsulfonylphenyl, (aminocarbonyl)phenyl, [(methylamino)carbonyl]phenyl, [(dimethylamino)carbonyl]phenyl, [(4-methylpiperazin-1-yl)carbonyl]phenyl, [2-(hydroxymethyl)morpholin-4-ylcarbonyl]phenyl, (methylsulfinyl)phenyl, pyridinyl, [(3-hydroxypyrrolidin-1-yl)carbonyl]phenyl, {[(2-hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl, [(3-hydroxyazetidin-1-yl)carbonyl]phenyl, (aminocarbonyl)fluorophenyl, [(methoxycarbonyl)amino]phenyl, [(methylsulfonyl)amino]phenyl, acetylthienyl, fluoro[(propylamino)carbonyl]phenyl, (acetylamino)phenyl and fluoro(methylsulfonyl)phenyl.

More preferably, Ar^1 is selected from 4-methylsulfonylphenyl, 4-(aminocarbonyl)phenyl, 4-[(methylamino)carbonyl]phenyl, 4-[(dimethylamino)carbonyl]phenyl, 4-[(4-methylpiperazin-1-yl)carbonyl]phenyl, 4-{[2-(hydroxymethyl)morpholin-4-yl]carbonyl}phenyl, 4-(methylsulfinyl)phenyl, 4-pyridinyl, 4-[(3-hydroxypyrrolidin-1-yl)carbonyl]phenyl, 4-{[2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl, 4-[(3-hydroxyazetidin-1-yl)-carbonyl]phenyl, 4-(aminocarbonyl)-3-fluorophenyl, 4-[(methoxycarbonyl)amino]phenyl, 4-[(methylsulfonyl)amino]phenyl, 5-acetyl-2-thienyl, 3-fluoro-4-[(propylamino)carbonyl]-phenyl, 4-(acetylamino)phenyl and 2-fluoro-4-(methylsulfonyl)phenyl.

In another more preferred subgroup of compounds of Formula (Ic), R^{1A} is selected from $C(O)OR^{2A}$, $C(O)R^{2A}$ or a 6-membered heteroaryl group.

In one embodiment, R^{1A} is $C(O)OR^{2A}$, wherein R^{2A} is selected from *tert*-butyl, phenyl, benzyl, *iso*-butyl, ethyl, isopropyl, 2,2-dimethylpropyl, 1-cyclopropylethyl and (3-methyloxetan-3-yl)methyl.

In another embodiment, R^{1A} is $C(O)R^{2A}$, wherein R^{2A} is selected from phenyl, 1-methyl-1H-pyrrol-2-yl, 3,4-dichlorophenyl and 1-ethylpropyl.

In yet another embodiment, R^{1A} is 2-pyrimidinyl.

In yet another more preferred subgroup of compounds of Formula (Ic), R^{10} is independently selected from hydrogen, methyl and cyclopropyl.

Particularly preferred compounds of Formula (Ia) to (Ic) are the compounds selected from the group consisting of:

- *tert*-Butyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate;
- Isobutyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate;
- Phenyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate;
- 2,2-Dimethylpropyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]-piperidine-1-carboxylate;
- Isopropyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate;
- Benzyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate;
- *N*-({1-[(1-Methyl-1*H*-pyrrol-2-yl)carbonyl]piperidin-4-yl}methyl)-5-[4-(methylsulfonyl)phenyl]pyrazin-2-amine;
- Ethyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate;
- *N*-[(1-Benzoylpiperidin-4-yl)methyl]-5-[4-(methylsulfonyl)phenyl]pyrazin-2-amine;
- *N*-{[1-(2-Ethylbutanoyl)piperidin-4-yl]methyl}-5-[4-(methylsulfonyl)phenyl]pyrazin-2-amine;
- *tert*-Butyl 4-[({5-[4-(methylsulfinyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate;
- *tert*-Butyl 4-{[(5-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrazin-2-yl)amino]-methyl}piperidine-1-carboxylate;
- *tert*-Butyl 4-[({5-[4-(aminocarbonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate;
- *tert*-Butyl 4-{[(5-{4-[(methylamino)carbonyl]phenyl}pyrazin-2-yl)amino]methyl}-piperidine-1-carboxylate;

- *tert*-Butyl 4-{[(5-pyridin-4-ylpyrazin-2-yl)amino]methyl}piperidine-1-carboxylate;
- *tert*-Butyl 4-{[(5-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]phenyl}pyrazin-2-yl)amino]-methyl}piperidine-1-carboxylate;
- *tert*-Butyl 4-({[5-(4-{[2-(hydroxymethyl)morpholin-4-yl]carbonyl}phenyl)pyrazin-2-yl]amino}methyl)piperidine-1-carboxylate;
- *tert*-Butyl 4-({[5-(4-{[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)pyrazin-2-yl]amino}methyl)piperidine-1-carboxylate;
- *tert*-Butyl 4-({[5-(4-{[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)pyrazin-2-yl]amino}methyl)piperidine-1-carboxylate;
- *tert*-Butyl 4-{[(5-{4-[(3-hydroxyazetidin-1-yl)carbonyl]phenyl}pyrazin-2-yl)amino]-methyl}piperidine-1-carboxylate;
- *tert*-Butyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate;
- Isobutyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate;
- 1-Cyclopropylethyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]-piperidine-1-carboxylate;
- Phenyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate;
- Benzyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate;
- (3-Methyloxetan-3-yl)methyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)-methyl]piperidine-1-carboxylate;
- Ethyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate;
- 2-[(1-Benzoylpiperidin-4-yl)methoxy]-5-[4-(methylsulfonyl)phenyl]pyrazine;
- 2-{[1-(2-Ethylbutanoyl)piperidin-4-yl]methoxy}-5-[4-(methylsulfonyl)phenyl]pyrazine;
- 2,2-Dimethylpropyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]-piperidine-1-carboxylate;
- 2-({1-[(1-Methyl-1H-pyrrol-2-yl)carbonyl]piperidin-4-yl}methoxy)-5-[4-(methyl-sulfonyl)phenyl]pyrazine;
- *tert*-Butyl 4-{[(5-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]phenyl}pyrazin-2-yl)oxy]-methyl}piperidine-1-carboxylate;

- *tert*-Butyl 4-({[5-(4-{[2-(hydroxymethyl)morpholin-4-yl]carbonyl}phenyl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate;
- *tert*-Butyl 4-({[5-(4-{[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate;
- *tert*-Butyl 4-({[5-(4-{[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate;
- *tert*-Butyl 4-[({5-[4-(methylsulfinyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate;
- *tert*-Butyl 4-{[(5-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrazin-2-yl)oxy]-methyl}piperidine-1-carboxylate;
- *tert*-Butyl 4-[({5-[4-(aminocarbonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate;
- *tert*-Butyl 4-{[(5-{4-[(methylamino)carbonyl]phenyl}pyrazin-2-yl)oxy]methyl}-piperidine-1-carboxylate;
- *tert*-Butyl 4-{[(5-{4-[(3-hydroxyazetidin-1-yl)carbonyl]phenyl}pyrazin-2-yl)oxy]-methyl}piperidine-1-carboxylate;
- *tert*-Butyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate;
- 2,2-Dimethylpropyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)-amino]piperidine-1-carboxylate;
- Isobutyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate;
- Ethyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]piperidine-1-carboxylate;
- Isopropyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate;
- Phenyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]piperidine-1-carboxylate;
- 1-Cyclopropylethyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)-amino]piperidine-1-carboxylate;
- Benzyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]piperidine-1-carboxylate;
- 1-Benzoyl-N-methyl-N-({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)piperidin-4-amine;

- *tert*-Butyl 4-[[(5-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]phenyl}pyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate;
- *tert*-Butyl 4-[{[5-(4-{[2-(hydroxymethyl)morpholin-4-yl]carbonyl}phenyl)pyrazin-2-yl]methyl}(methyl)amino]piperidine-1-carboxylate;
- *tert*-Butyl 4-[{[5-(4-{[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)pyrazin-2-yl]methyl}(methyl)amino]piperidine-1-carboxylate;
- *tert*-Butyl 4-[{[5-(4-{[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)pyrazin-2-yl]methyl}(methyl)amino]piperidine-1-carboxylate;
- *tert*-Butyl 4-[methyl({5-[4-(methylsulfinyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate;
- *tert*-Butyl 4-{methyl[(5-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrazin-2-yl)-methyl]amino}piperidine-1-carboxylate;
- *tert*-Butyl 4-[({5-[4-(aminocarbonyl)phenyl]pyrazin-2-yl}methyl)(methyl)amino]-piperidine-1-carboxylate;
- *tert*-Butyl 4-{methyl[(5-{4-[(methylamino)carbonyl]phenyl}pyrazin-2-yl)methyl]-amino}piperidine-1-carboxylate;
- *tert*-Butyl 4-{methyl[(5-pyridin-4-ylpyrazin-2-yl)methyl]amino}piperidine-1-carboxylate;
- Methyl {4-[5-({cyclopropyl[1-(2-ethylbutanoyl)piperidin-4-yl]amino}methyl)pyrazin-2-yl]phenyl}carbamate;
- *N*-{4-[5-({Cyclopropyl[1-(2-ethylbutanoyl)piperidin-4-yl]amino}methyl)pyrazin-2-yl]-phenyl}methanesulfonamide;
- 4-[5-({Cyclopropyl[1-(3,4-dichlorobenzoyl)piperidin-4-yl]amino}methyl)pyrazin-2-yl]-*N*,*N*-dimethylbenzamide;
- Methyl {4-[5-({cyclopropyl[1-(3,4-dichlorobenzoyl)piperidin-4-yl]amino}methyl)-pyrazin-2-yl]phenyl}carbamate;
- *N*-{4-[5-({Cyclopropyl[1-(3,4-dichlorobenzoyl)piperidin-4-yl]amino}methyl)pyrazin-2-yl]phenyl}acetamide;
- 4-(5-{[Cyclopropyl(1-pyrimidin-2-ylpiperidin-4-yl)amino]methyl}pyrazin-2-yl)-2-fluorobenzamide;
- Methyl [4-(5-{[cyclopropyl(1-pyrimidin-2-ylpiperidin-4-yl)amino]methyl}pyrazin-2-yl)phenyl]carbamate;
- *N*-Cyclopropyl-*N*-({5-[2-fluoro-4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)-1-pyrimidin-2-ylpiperidin-4-amine;

- Methyl [4-(5-{[(1-benzoylpiperidin-4-yl)(cyclopropyl)amino]methyl}pyrazin-2-yl)-phenyl]carbamate;
- 1-Benzoyl-*N*-cyclopropyl-*N*-({5-[2-fluoro-4-(methylsulfonyl)phenyl]pyrazin-2-yl}-methyl)piperidin-4-amine;
- Isopropyl 4-[({5-[4-(aminocarbonyl)phenyl]pyrazin-2-yl}methyl)(cyclopropyl)amino]-piperidine-1-carboxylate;
- Isopropyl 4-[({5-[4-(aminocarbonyl)-3-fluorophenyl]pyrazin-2-yl}methyl)(cyclopropyl)amino]piperidine-1-carboxylate;
- Isopropyl 4-{cyclopropyl[(5-{4-[(methylamino)carbonyl]phenyl}pyrazin-2-yl)methyl]-amino}piperidine-1-carboxylate;
- Isopropyl 4-{cyclopropyl[(5-{4-[(dimethylamino)carbonyl]phenyl}pyrazin-2-yl)-methyl]amino}piperidine-1-carboxylate;
- Isopropyl 4-{cyclopropyl[(5-{3-fluoro-4-[(propylamino)carbonyl]phenyl}pyrazin-2-yl)-methyl]amino}piperidine-1-carboxylate;
- Isopropyl 4-{cyclopropyl[(5-{4-[(methoxycarbonyl)amino]phenyl}pyrazin-2-yl)-methyl]amino}piperidine-1-carboxylate;
- Isopropyl 4-[({5-[4-(acetylamino)phenyl]pyrazin-2-yl}methyl)(cyclopropyl)amino]-piperidine-1-carboxylate;
- Isopropyl 4-{cyclopropyl[(5-{4-[(methylsulfonyl)amino]phenyl}pyrazin-2-yl)methyl]-amino}piperidine-1-carboxylate;
- Isopropyl 4-[{[5-(5-acetyl-2-thienyl)pyrazin-2-yl]methyl}(cyclopropyl)amino]-piperidine-1-carboxylate;
- 4-(5-{[[1-(2-Ethylbutanoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-benzamide;
- 4-(5-{[[1-(2-Ethylbutanoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-2-fluorobenzamide;
- *N*-[4-(5-{[[1-(2-Ethylbutanoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-phenyl]acetamide;
- 4-(5-{[[1-(2-Ethylbutanoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-2-fluoro-N-propylbenzamide;
- *N*-({5-[2-Fluoro-4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)-*N*-methyl-1-pyrimidin-2-ylpiperidin-4-amine;
- 1-[5-(5-{[Methyl(1-pyrimidin-2-ylpiperidin-4-yl)amino]methyl}pyrazin-2-yl)-2-thienyl]ethanone;

- 2-Fluoro-4-(5-{[methyl(1-pyrimidin-2-ylpiperidin-4-yl)amino]methyl}pyrazin-2-yl)-*N*-propylbenzamide;
- *N*,*N*-Dimethyl-4-(5-{[methyl(1-pyrimidin-2-ylpiperidin-4-yl)amino]methyl}pyrazin-2-yl)benzamide;
- Isopropyl 4-[({5-[4-(aminocarbonyl)phenyl]pyrazin-2-yl}methyl)(methyl)amino]-piperidine-1-carboxylate;
- Isopropyl 4-[({5-[4-(aminocarbonyl)-3-fluorophenyl]pyrazin-2-yl}methyl)(methyl)-amino]piperidine-1-carboxylate;
- Isopropyl 4-{methyl[(5-{4-[(methylamino)carbonyl]phenyl}pyrazin-2-yl)methyl]-amino}piperidine-1-carboxylate;
- Isopropyl 4-[[(5-{4-[(dimethylamino)carbonyl]phenyl}pyrazin-2-yl)methyl](methyl)-amino]piperidine-1-carboxylate;
- Isopropyl 4-[[(5-{3-fluoro-4-[(propylamino)carbonyl]phenyl}pyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate;
- Isopropyl 4-[[(5-{4-[(methoxycarbonyl)amino]phenyl}pyrazin-2-yl)methyl](methyl)-amino]piperidine-1-carboxylate;
- Isopropyl 4-{methyl[(5-{4-[(methylsulfonyl)amino]phenyl}pyrazin-2-yl)methyl]-amino}piperidine-1-carboxylate;
- Isopropyl 4-[({5-[2-fluoro-4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)(methyl)-amino]piperidine-1-carboxylate;
- Isopropyl 4-[{[5-(5-acetyl-2-thienyl)pyrazin-2-yl]methyl}(methyl)amino]piperidine-1-carboxylate;
- 4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-N,N-dimethylbenzamide;
- 4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-2-fluoro-*N*-propylbenzamide;
- Methyl [4-(5-{[[1-(3,4-dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)phenyl]carbamate;
- *N*-[4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-phenyl]acetamide;
- *N*-[4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-phenyl]methanesulfonamide;
- 1-(3,4-Dichlorobenzoyl)-*N*-({5-[2-fluoro-4-(methylsulfonyl)phenyl]pyrazin-2-yl}-methyl)-*N*-methylpiperidin-4-amine;

- 1-[5-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-2-thienyl]ethanone;
- 4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-2-fluorobenzamide;
- 4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-N-methylbenzamide;
- 4-(5-{[(1-Benzoylpiperidin-4-yl)(methyl)amino]methyl}pyrazin-2-yl)-*N*-methyl-benzamide;
- 4-(5-{[(1-Benzoylpiperidin-4-yl)(methyl)amino]methyl}pyrazin-2-yl)-*N*,*N*-dimethyl-benzamide;
- *tert*-Butyl 4-({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methoxy)piperidine-1-carboxylate;
- Isobutyl 4-({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methoxy)piperidine-1-carboxylate; and
- Benzyl 4-({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methoxy)piperidine-1-carboxylate.

Another object of the invention is a compound of Formula (Ia) to (Ic) for use in therapy. The compounds can be used in the treatment or prophylaxis of disorders relating to GPR119. Examples of such disorders are Type 1 and Type 2 diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypercholesterolemia, dyslipidemia, syndrome X, obesity, hypertension, chronic systemic inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, reduced fibrinolysis, endothelial dysfunction and osteoporosis.

Another object of the invention is the use of a compound of Formula (Ia) to (Ic) in the manufacture of a medicament for use in the treatment or prophylaxis of disorders related to GPR119. The GPR119-related disorder is any disorder or symptom wherein GPR119 is involved in the process or presentation of the disorder or the symptom. The GPR119-related disorders include, but are not limited to, Type 1 and Type 2 diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypercholesterolemia, dyslipidemia, syndrome X, obesity, hypertension, chronic systemic inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, reduced fibrinolysis, endothelial dysfunction and osteoporosis.

Another object of the invention is a method for modulating the GPR119 receptor activity (e.g., agonizing human GPR119), comprising administering to a subject (e.g., mammal, human, or animal) in need thereof an effective amount of a compound of Formula (Ia) to (Ic) or a composition comprising such a compound.

Yet another object of the invention is a method for the treatment or prophylaxis of disorders related to GPR119, said method comprising administering to a subject (e.g., mammal, human, or animal) in need of such treatment an effective amount of a compound of Formula (Ia) to (Ic). The GPR119-related disorder is any disorder or symptom wherein GPR119 is involved in the process or presentation of the disorder or the symptom. The GPR119-related disorders include, but are not limited to Type 1 and Type 2 diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypercholesterolemia, dyslipidemia, syndrome X, obesity, hypertension, chronic systemic inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, reduced fibrinolysis, endothelial dysfunction and osteoporosis.

Methods delineated herein include those wherein the subject is identified as in need of a particular stated treatment. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

In other aspects, the methods herein include those further comprising monitoring subject response to the treatment administrations. Such monitoring may include periodic sampling of subject tissue, fluids, specimens, cells, proteins, chemical markers, genetic materials, etc. as markers or indicators of the treatment regimen. In other methods, the subject is prescreened or identified as in need of such treatment by assessment for a relevant marker or indicator of suitability for such treatment.

In one embodiment, the invention provides a method of monitoring treatment progress. The method includes the step of determining a level of diagnostic marker (Marker) (e.g., any target or cell type delineated herein modulated by a compound herein) or diagnostic measurement (e.g., screen, assay) in a subject suffering from or susceptible to a disorder or symptoms thereof delineated herein, in which the subject has been administered a therapeutic amount of a compound herein sufficient to treat the disease or symptoms thereof. The level of Marker determined in the method can be compared to known levels of Marker in either healthy normal controls or in other afflicted patients to establish the

subject's disease status. In preferred embodiments, a second level of Marker in the subject is determined at a time point later than the determination of the first level, and the two levels are compared to monitor the course of disease or the efficacy of the therapy. In certain preferred embodiments, a pre-treatment level of Marker in the subject is determined prior to beginning treatment according to this invention; this pre-treatment level of Marker can then be compared to the level of Marker in the subject after the treatment commences, to determine the efficacy of the treatment.

In certain method embodiments, a level of Marker or Marker activity in a subject is determined at least once. Comparison of Marker levels, e.g., to another measurement of Marker level obtained previously or subsequently from the same patient, another patient, or a normal subject, may be useful in determining whether therapy according to the invention is having the desired effect, and thereby permitting adjustment of dosage levels as appropriate. Determination of Marker levels may be performed using any suitable sampling/expression assay method known in the art or described herein. Preferably, a tissue or fluid sample is first removed from a subject. Examples of suitable samples include blood, urine, tissue, mouth or cheek cells, and hair samples containing roots. Other suitable samples would be known to the person skilled in the art. Determination of protein levels and/or mRNA levels (e.g., Marker levels) in the sample can be performed using any suitable technique known in the art, including, but not limited to, enzyme immunoassay, ELISA, radiolabelling/assay techniques, blotting/chemiluminescence methods, real-time PCR, and the like.

DEFINITIONS

The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "C_{1-6}-alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. For parts of the range "C_{1-6}-alkyl", all subgroups thereof are contemplated, such as C_{1-5}-alkyl, C_{1-4}-alkyl, C_{1-3}-alkyl, C_{1-2}-alkyl, C_{2-6}-alkyl, C_{2-5}-alkyl, C_{2-4}-alkyl, C_{2-3}-alkyl, C_{3-6}-alkyl, C_{4-5}-alkyl, etc. Examples of said C_{1-6}-alkyl include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl and straight- and branched-chain pentyl and hexyl.

Unless otherwise stated or indicated, the term "cyano-C_{1-6}-alkyl" denotes a C_{1-6}-alkyl group, as defined above, substituted with a cyano group. Exemplary cyano-C_{1-6}-alkyl groups include 2-cyanoethyl and 3-cyanopropyl.

Unless otherwise stated or indicated, the term "amino-C_{1-6}-alkyl" denotes a C_{1-6}-alkyl group, as defined above, substituted with an amino group. Exemplary amino-C_{1-6}-alkyl groups include 2-aminoethyl and 3-aminopropyl.

Unless otherwise stated or indicated, the term "hydroxy-C_{1-6}-alkyl" denotes a straight or branched alkyl group that has a hydrogen atom thereof replaced with OH. Examples of said hydroxy-C_{1-6}-alkyl include hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxybutyl and 2-hydroxy-2-methylpropyl.

Derived expressions such as "C_{1-6}-alkoxy", "C_{1-6}-alkylthio" and "C_{1-6}-alkylamino" are to be construed accordingly where an C_{1-6}-alkyl group is attached to the remainder of the molecule through an oxygen, sulfur or nitrogen atom, respectively. For parts of the range "C_{1-6}-alkoxy" all subgroups thereof are contemplated such as C_{1-5}-alkoxy, C_{1-4}-alkoxy, C_{1-3}-alkoxy, C_{1-2}-alkoxy, C_{2-6}-alkoxy, C_{2-5}-alkoxy, C_{2-4}-alkoxy, C_{2-3}-alkoxy, C_{3-6}-alkoxy, C_{4-5}-alkoxy, etc. Examples of said "C_{1-6}-alkoxy" include methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy, *t*-butoxy and straight- and branched-chain pentoxy and hexoxy etc. Subgroups of "C_{1-6}-alkylthio" and "C_{1-6}-alkylamino" are to be construed accordingly.

Unless otherwise stated or indicated, the term "C_{1-4}-alkylsulfinyl" denotes a group C_{1-4}-alkyl-S(O)—. Exemplary C_{1-4}-alkylsulfinyl groups include methylsulfinyl and ethylsulfinyl.

Unless otherwise stated or indicated, the term "dihydroxy-C_{2-6}-alkyl" denotes a C_{2-6}-alkyl group which is disubstituted with hydroxy and wherein said hydroxy groups are attached to different carbon atoms. Exemplary dihydroxy-C_{2-6}-alkyl groups include 2,3-dihydroxypropyl and 2,4-dihydroxybutyl.

Unless otherwise stated or indicated, the term "di(C_{1-4}-alkyl)amino" denotes a group $(C_{1-4}\text{-alkyl})_2N$—, wherein the two alkyl portions may be the same or different. Exemplary di(C_{1-4}-alkyl)amino groups include N,N-dimethylamino, N-ethyl-N-methylamino and N,N-diethylamino.

Unless otherwise stated or indicated, the term "di(C_{1-4}-alkyl)amino-C_{2-4}-alkyl" denotes a group di(C_{1-4}-alkyl)amino, as defined above, attached to a C_{2-4}-alkyl group. Exemplary di(C_{1-4}-alkyl)amino-C_{2-4}-alkyl groups include 2-(dimethylamino)ethyl and 3-(diethylamino)propyl.

Unless otherwise stated or indicated, the term "fluoro-C_{1-6}-alkyl" denotes a C_{1-6}-alkyl group substituted by one or more fluorine atoms. Examples of said fluoro-C_{1-6}-alkyl include 2-fluoroethyl, fluoromethyl, 2-fluoro-1-(fluoromethyl)ethyl, trifluoromethyl, 3,3,3-trifluoropropyl and 2,2,2-trifluoroethyl.

Unless otherwise stated or indicated, the term "aryl-C_{1-6}-alkyl" means a C_{1-6}-alkyl group substituted by an aryl group. Examples of said aryl-C_{1-6}-alkyl include benzyl, 2-phenylethyl, 1-phenylethyl and 2-methyl-2-phenylpropyl.

Unless otherwise stated or indicated, the term "arylcarbonyl-C_{1-4}-alkyl" denotes an arylcarbonyl group (e.g., benzoyl) that is attached through a C_{1-4}-alkyl group. Examples of said arylcarbonyl-C_{1-4}-alkyl include 3-oxo-3-phenylpropyl, 2-oxo-2-phenylethyl and 1-methyl-3-oxo-3-phenylpropyl.

Unless otherwise stated or indicated, the term "heteroarylcarbonyl-C_{1-4}-alkyl" denotes a heteroarylcarbonyl group (e.g., 3-pyridinylcarbonyl) that is attached through a C_{1-4}-alkyl group. Examples of said heteroarylcarbonyl-C_{1-4}-alkyl include 3-oxo-3-(3-pyridinyl)-propyl, 2-oxo-2-(3-pyridinyl)ethyl and 1-methyl-3-oxo-3-(3-pyridinyl)propyl.

Unless otherwise stated or indicated, the term "C_{1-6}-alkoxy-C_{2-6}-alkyl" denotes a straight or branched alkoxy group having from 1 to 6 carbon atoms connected to an alkyl group having from from 2 to 6 carbon atoms. Examples of said C_{1-5}-alkoxy-C_{2-6}-alkyl include methoxyethyl, ethoxyethyl, isopropoxyethyl, *n*-butoxyethyl, *t*-butoxyethyl and straight- and branched-chain pentoxyethyl. For parts of the range "C_{1-6}-alkoxy-C_{2-6}-alkyl" all subgroups thereof are contemplated such as C_{1-5}-alkoxy-C_{2-6}-alkyl, C_{1-4}-alkoxy-C_{2-6}-alkyl, C_{1-3}-alkoxy-C_{2-6}-alkyl, C_{1-2}-alkoxy-C_{2-6}-alkyl, C_{2-6}-alkoxy-C_{2-6}-alkyl, C_{2-5}-alkoxy-C_{2-6}-alkyl, C_{2-4}-alkoxy-C_{2-6}-alkyl, C_{2-3}-alkoxy-C_{2-6}-alkyl, C_{3-6}-alkoxy-C_{2-6}-alkyl, C_{4-5}-alkoxy-C_{2-6}-alkyl, C_{1-6}-alkoxy-C_{2-5}-alkyl, C_{1-6}-alkoxy-C_{2-4}-alkyl, etc.

Unless otherwise stated or indicated, the term "C_{2-6}-alkenyl" denotes a straight or branched hydrocarbon chain radical containing one carbon-carbon double bond and having from 2 to 6 carbon atoms. Examples of said C_{2-6}-alkenyl include vinyl, allyl, 2,3-dimethylallyl, 1-butenyl, 1-pentenyl, and 1-hexenyl. For parts of the range "C_{2-6}-alkenyl", all subgroups thereof are contemplated such as C_{2-5}-alkenyl, C_{2-4}-alkenyl, C_{2-3}-alkenyl, C_{3-6}-alkenyl, C_{4-5}-alkenyl, etc. Likewise, "aryl-C_{2-6}-alkenyl" means a C_{2-6}-alkenyl group substituted by an aryl group. Examples of said aryl-C_{2-6}-alkenyl include styryl and cinnamyl.

Unless otherwise stated or indicated, the term "C_{2-6}-alkynyl" denotes a straight or branched hydrocarbon chain radical containing one carbon-carbon triple bond and having from 2 to

6 carbon atoms. Examples of said C_{2-6}-alkynyl include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, and 1-methylprop-2-yn-1-yl.

Likewise, aryl-C_{2-6}-alkynyl means a C_{2-6}-alkynyl group substituted by an aryl group. Examples of said aryl-C_{2-6}-alkynyl include phenylethynyl, 3-phenyl-1-propyn-1-yl, 3-phenyl-2-propyn-1-yl and 4-phenyl-2-butyn-1-yl.

The term "oxo" denotes 

Unless otherwise stated or indicated, the term "C_{3-7}-cycloalkyl" denotes a cyclic alkyl group having a ring size from 3 to 7 carbon atoms and includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. For parts of the range "C_{3-7}-cycloalkyl" all subgroups thereof are contemplated such as C_{3-6}-cycloalkyl, C_{3-5}-cycloalkyl, C_{3-4}-cycloalkyl, C_{4-7}-cycloalkyl, C_{4-6}-cycloalkyl, C_{4-5}-cycloalkyl, C_{5-7}-cycloalkyl, C_{6-7}-cycloalkyl.

Unless otherwise stated or indicated, the term "C_{3-7}-cycloalkyl-C_{1-4}-alkyl" denotes a C_{3-7}-cycloalkyl group attached to a C_{1-4}-alkyl group. Exemplary C_{3-7}-cycloalkyl-C_{1-4}-alkyl groups include cyclopropylmethyl, 1-cyclopropylethyl, cyclohexylmethyl and 2-cyclohexylethyl. When the cycloalkyl portion as part of the group C_{3-7}-cycloalkyl-C_{1-4}-alkyl is substituted with methyl, examples of such groups include (1-methylcyclopropyl)methyl and 2-(4-methylcyclohexyl)ethyl.

Unless otherwise stated or indicated, the term "C_{7-8}-bicyclyl" denotes a carbobicyclic saturated aliphatic ring system in which two non-adjacent carbon atoms of a monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms. Examples of said C_{7-8}-bicyclyl include radicals obtainable from bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane (norbornane) and bicyclo[2.2.2]octane.

Unless otherwise stated or indicated, the term C_{7-8}-bicyclylalkyl means a C_{1-6}-alkyl group substituted by a C_{7-8}-bicyclyl group as defined above. An exemplary C_{7-8}-bicyclylalkyl group is bicyclo[2.2.1]hept-2-ylmethyl (2-norbonylmethyl).

Unless otherwise stated or indicated, the term "C_{5-8}-cycloalkenyl" denotes a monocyclic or bicyclic alkenyl group of 5 to 8 carbon atoms having one carbon-carbon double bond. Examples of monocyclic cycloalkenyl groups are cyclopent-3-en-1-yl and cyclohexen-1-yl. An exemplary bicyclic cycloalkenyl group is bicyclo[2.2.1]hept-5-en-2-yl (norbornen-2-yl).

Unless otherwise stated or indicated, the term "oxo-C_{4-6}-cycloalkyl" refers to a C_{4-6}-cycloalkyl wherein one of the ring carbons is a carbonyl. Examples of "oxo-C_{4-6}-

cycloalkyl" include 2-oxocyclobutyl, 3-oxocyclobutyl, 2-oxocyclopentyl and 4-oxo-cyclohexyl.

Unless otherwise stated or indicated, the term "fluoro-C_{3-6}-cycloalkyl" denotes a C_{3-6}-cycloalkyl group substituted by one or two fluorine atoms. Examples of said "fluoro-C_{3-6}-cycloalkyl" include 2,2-difluorocyclopropyl and 4-fluorocyclohexyl.

Unless otherwise stated or indicated, the term "C_{1-3}-alkoxy-C_{4-6}-cycloalkyl" denotes a C_{4-6}-cycloalkyl group substituted by a C_{1-3}-alkoxy group. Examples of said "C_{1-3}-alkoxy-C_{4-6}-cycloalkyl" include 4-methoxycyclohexyl and 2-ethoxycyclopentyl.

Unless otherwise stated or indicated, the term "methyl-C_{3-6}-cycloalkyl" denotes a C_{3-6}-cycloalkyl group substituted by one or two methyl groups. Examples of said "methyl-C_{3-6}-cycloalkyl" include 4-methylcyclohexyl and 3,3-dimethylcyclopentyl.

Unless otherwise stated or indicated, the term "acyl", which may be straight or branched, denotes a carbonyl group that is attached through its carbon atom to a hydrogen atom to form a C_1-acyl group (i.e., a formyl group) or to an alkyl group, where alkyl is defined as above. For parts of the range "C_{1-6}-acyl" all subgroups thereof are contemplated such as C_{1-5}-acyl, C_{1-4}-acyl, C_{1-3}-acyl, C_{1-2}-acyl, C_{2-6}-acyl, C_{2-5}-acyl, C_{2-4}-acyl, C_{2-3}-acyl, C_{3-6}-acyl, C_{4-5}-acyl, etc. Exemplary acyl groups include formyl, acetyl (i.e., C_2-acyl), propanoyl, butanoyl, pentanoyl, hexanoyl.

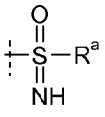
Unless otherwise stated or indicated, the term "C_{2-6}-acyl-C_{1-6}-alkyl" refers to a group C_{1-5}-alkyl-(C=O)-C_{1-6}-alkyl. Exemplary C_{2-6}-acyl-C_{1-6}-alkyl groups include 2-acetylethyl and 3-acetylpropyl.

Unless otherwise stated or indicated, the term "C_{1-6}-alkylsulfonyl", which may be straight or branched, denotes a hydrocarbon having from 1 to 6 carbon atoms with a sulfonyl group. For parts of the range "C_{1-6}-alkylsulfonyl" all subgroups thereof are contemplated such as C_{1-5}-alkylsulfonyl, C_{1-4}-alkylsulfonyl, C_{1-3}-alkylsulfonyl, C_{1-2}-alkylsulfonyl, C_{2-6}-alkylsulfonyl, C_{2-5}-alkylsulfonyl, C_{2-4}-alkylsulfonyl, C_{2-3}-alkylsulfonyl, C_{3-6}-alkylsulfonyl, C_{4-5}-alkylsulfonyl, etc. Exemplary C_{1-6}-alkylsulfonyl groups include methylsulfonyl, ethylsulfonyl, propylsulfonyl, *n*-butylsulfonyl, *sec*-butylsulfonyl, *tert*-butylsulfonyl, pentylsulfonyl and hexylsulfonyl.

Unless otherwise stated or indicated, the term "hydroxy-C_{2-4}-alkylsulfonyl" denotes a C_{2-4}-alkylsulfonyl group as defined above substituted with a hydroxy group. Examples of said hydroxy-C_{2-4}-alkylsulfonyl include hydroxymethylsulfonyl and 2-hydroxyethylsulfonyl.

Unless otherwise stated or indicated, the term "C_{1-4}-alkylsulfonamido" denotes a group C_{1-4}-alkyl-SO_2NH—. Exemplary C_{1-4}-alkylsulfonamido groups include methylsulfonyl-amino and ethylsulfonylamino.

The term "C_{1-4}-alkylsulfoximine" refers to a group with the following chemical structure:



, wherein R^a is C_{1-4}-alkyl.

Unless otherwise stated or indicated, the term "C_{1-3}-alkylene" refers to the diradicals methylene (–CH_2–), ethylene (–CH_2-CH_2–) and propylene (–CH_2-CH_2-CH_2–). In case the group denoted by E in Formula (Ia) forms a double bond with D, then E is a trivalent radical selected from (=CH_2-CH_2–) and (=CH_2-CH_2-CH_2–).

Unless otherwise stated or indicated, the term "halogen" shall mean fluorine, chlorine, bromine or iodine.

Unless otherwise stated or indicated, the term "aryl" refers to a hydrocarbon ring system having at least one aromatic ring, preferably mono- or bicyclic. Examples of aryls are phenyl, indenyl, 2,3-dihydroindenyl (indanyl), 1-naphthyl, 2-naphthyl or 1,2,3,4-tetrahydronaphthyl.

Unless otherwise stated or indicated, the term "heteroaryl" refers to a mono- or bicyclic heteroaromatic ring system having 5 to 10 ring atoms in which one or more of the ring atoms are other than carbon, such as nitrogen, sulphur or oxygen. Only one ring need be aromatic and said heteroaryl moiety can be linked to the remainder of the molecule via a carbon or nitrogen atom in any ring. Examples of heteroaryl groups include furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, quinazolinyl, indolyl, isoindolyl, 1,3-dihydro-isoindolyl, pyrazolyl, pyridazinyl, quinolinyl, quinoxalinyl, thiadiazolyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, 1,4-benzodioxinyl, 2,3-dihydro-1,4-benzodioxinyl, benzothiazolyl, benzimidazolyl, benzothiadiazolyl, benzotriazolyl, indolinyl, isoindolinyl, and chromanyl groups.

Unless otherwise stated or indicated, the term "heterocyclyl" or "heterocyclic ring" refers to a non-aromatic fully saturated or partially unsaturated monocyclic ring system having 4 to 7 ring atoms with at least one heteroatom such as O, N, or S, and the remaining ring atoms are carbon. Examples of heterocyclic groups include piperidinyl, tetrahydropyranyl, tetrahydrofuranyl, oxetanyl, azepinyl, azetidinyl, pyrrolidinyl, morpholinyl, imidazolinyl, imidazolidinyl, thiomorpholinyl, pyranyl, dioxanyl, piperazinyl and 5,6-dihydro-4H-1,3-oxazin-2-yl. When present, the sulfur atom may be in an oxidized form (i.e., S=O or

O=S=O). Exemplary heterocyclic groups containing sulfur in oxidized form are 1,1-dioxido-thiomorpholinyl and 1,1-dioxido-isothiazolidinyl.

When two groups R^5, two groups R^{5A}, two groups R^9 or two groups R^{9A} described herein form a heterocyclic ring and said heterocyclic ring is substituted with one or two oxo groups, examples of such groups include 2-pyrrolidon-1-yl, 2-piperidon-1-yl, 2-azetidinon-1-yl, 2,5-dioxopyrrolidin-1-yl and hydantoin-1-yl (i.e., 2,5-dioxoimidazolidin-1-yl).

When two groups R^5, two groups R^{5A}, two groups R^9 or two groups R^{9A} described herein form a heterocyclic ring and said heterocyclic ring is substituted with one or two fluoro atoms, examples of such groups include 4-fluoropiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 3-fluoropyrrolidin-1-yl and 3,3-difluoropyrrolin-1-yl.

When two groups R^5, two groups R^{5A}, two groups R^9 or two groups R^{9A} described herein form a heterocyclic ring and said heterocyclic ring is substituted with hydroxy, examples of such groups include 4-hydroxypiperidin-1-yl, 3-hydroxypiperidin-1-yl, 3-hydroxy-pyrrolidin-1-yl and 3-hydroxyazetidin-1-yl.

When two groups R^5, two groups R^{5A}, two groups R^9 or two groups R^{9A} described herein form a heterocyclic ring and said heterocyclic ring is substituted with amino, examples of such groups include 4-aminopiperidin-1-yl, 3-aminopiperidin-1-yl, and 3-aminopyrrolidin-1-yl.

When two groups R^5, two groups R^{5A}, two groups R^9 or two groups R^{9A} described herein form a heterocyclic ring and said heterocyclic ring is substituted with hydroxymethyl, examples of such groups include 2-(hydroxymethyl)pyrrolidin-1-yl, 2-(hydroxymethyl)-morpholin-4-yl and 4-(hydroxymethyl)piperidin-1-yl.

When two groups R^5, two groups R^{5A}, two groups R^9 or two groups R^{9A} described herein form a heterocyclic ring and said heterocyclic ring is substituted with methylamino or dimethylamino, examples of such groups include 3-dimethylaminopyrrolidin-1-yl and 3-methylaminopyrrolidin-1-yl.

Unless otherwise stated or indicated, the term "heteroaryl-C_{1-4}-alkyl" denotes a heteroaryl group that is attached through a C_{1-4}-alkyl group. Examples of said heteroaryl-C_{1-4}-alkyl include 2-(pyridin-2-yl)ethyl and 1,3 benzodioxol-5-ylmethyl.

"C-heterocyclyl" indicates bonding via a carbon atom of said heterocyclyl, for example piperidin-4-yl, tetrahydrofuran-2-yl, oxetan-3-yl, tetrahydrofuran-3-yl and 5,6-dihydro-4H-1,3-oxazin-2-yl, while "*N*-heterocyclyl" indicates bonding through nitrogen in a nitrogen-containing heterocyclyl group, for example piperidin-1-yl and piperazin-1-yl. When C-heterocyclyl is substituted by C_{1-4}-alkyl, said C_{1-4}-alkyl is attached to a ring nitrogen

atom or a ring carbon atom thereof. Exemplary C-heterocyclyl groups substituted by C_{1-4}-alkyl include 1-methylpiperidin-4-yl and 3-methyloxetan-3-yl.

Unless otherwise stated or indicated, the term "*N*-heterocyclyl-C_{2-4}-alkyl" refers to a nitrogen-containing heterocyclyl group that is directly linked to a C_{2-4}-alkyl group via a nitrogen atom of said heterocyclyl. Exemplary *N*-heterocyclyl-C_{2-4}-alkyl groups include 2-(pyrrolidin-1-yl)ethyl, 3-(4-morpholinyl)propyl, 2-(piperazin-1-yl)ethyl and 2-(4-morpholinyl)ethyl.

When heterocyclyl as part of the group *N*-heterocyclyl-C_{2-4}-alkyl is substituted by methyl, said heterocyclyl is selected from 1-piperazinyl or 1-homopiperazinyl and said methyl is attached to the 4-position of the piperazine or homopiperazine ring. Exemplary *N*-heterocyclyl-C_{2-4}-alkyl groups wherein heterocyclyl is substituted with methyl are 2-(4-methylpiperazin-1-yl)ethyl, 2-(4-methylhomopiperazin-1-yl)ethyl.

Unless otherwise stated or indicated, the term "C-heterocyclyl-C_{1-4}-alkyl" refers to a heterocyclyl group that is directly linked to a C_{1-4}-alkyl group via a carbon atom of said heterocyclyl. Exemplary C-heterocyclyl-C_{1-4}-alkyl groups include tetrahydropyran-4-ylmethyl, piperidin-4-ylmethyl, tetrahydrofuran-2-ylmethyl, oxetan-3-ylmethyl and 2-(piperidinyl-4-yl)ethyl.

When heterocyclyl as part of the group C-heterocyclyl-C_{1-4}-alkyl is substituted by methyl, said methyl is attached to a ring nitrogen atom or ring carbon atom thereof. Exemplary C-heterocyclyl-C_{1-4}-alkyl groups wherein heterocyclyl is substituted with methyl are 2-(1-methylpiperidin-4-yl)ethyl and 3-methyloxetan-3-ylmethyl.

Unless otherwise stated or indicated, the term "oxo-*N*-heterocyclyl" denotes a nitrogen-containing heterocyclyl group that is substituted with one or two oxo groups.

Unless otherwise stated or indicated, the term "oxo-*N*-heterocyclyl-C_{2-4}-alkyl" refers to an oxo-*N*-heterocyclyl group that is directly linked to a C_{2-4}-alkyl group through a nitrogen atom of its heterocyclyl portion and where oxo-*N*-heterocyclyl is as defined above. Exemplary oxo-*N*-heterocyclyl-C_{2-4}-alkyl groups include 2-(2-pyrrolidon-1-yl)ethyl, 3-(2-pyrrolidon-1-yl)propyl and 2-(2,5-dioxoimidazolidin-1-yl)ethyl.

Unless otherwise stated or indicated, the term "fluoro-*N*-heterocyclyl" denotes a nitrogen-containing heterocyclyl group that is substituted at a position other than alpha to a ring heteroatom with one or two fluorine atoms.

Unless otherwise stated or indicated, the term "fluoro-*N*-heterocyclyl-C_{2-4}-alkyl" refers to a fluoro-*N*-heterocyclyl group that is directly linked to a C_{2-4}-alkyl group through a nitrogen atom of its heterocyclyl portion and where fluoro-*N*-heterocyclyl is as defined above.

Exemplary fluoro-*N*-heterocyclyl-C_{2-4}-alkyl groups include 2-(3-fluoropyrrolidin-1-yl)-ethyl and 3-(3-fluoropyrrolidin-1-yl)propyl.

Unless otherwise stated or indicated, the term "hydroxy-*N*-heterocyclyl" denotes a nitrogen-containing heterocyclyl group that is substituted at a position other than alpha to a ring heteroatom with a hydroxy group.

Unless otherwise stated or indicated, the term "hydroxy-*N*-heterocyclyl-C_{2-4}-alkyl" refers to a hydroxy-*N*-heterocyclyl group that is directly linked to a C_{2-4}-alkyl group through a nitrogen atom of its heterocyclyl portion and where hydroxy-*N*-heterocyclyl is as defined above. Exemplary hydroxy-*N*-heterocyclyl-C_{2-4}-alkyl groups include 2-(4-hydroxy-piperidin-1-yl)ethyl and 3-(3-hydroxypiperidin-1-yl)propyl.

Unless otherwise stated or indicated, the term "amino-*N*-heterocyclyl" denotes a nitrogen-containing heterocyclyl group that is substituted at a position other than alpha to a ring heteroatom with an amino group.

Unless otherwise stated or indicated, the term "amino-*N*-heterocyclyl-C_{2-4}-alkyl" refers to a amino-*N*-heterocyclyl group that is directly linked to a C_{2-4}-alkyl group through a nitrogen atom of its heterocyclyl portion and where amino-*N*-heterocyclyl is as defined above. Exemplary amino-*N*-heterocyclyl-C_{2-4}-alkyl groups include 2-(4-aminopiperidin-1-yl)ethyl and 3-(3-aminopiperidin-1-yl)propyl.

Unless otherwise stated or indicated, the term "azabicyclyl" denotes a bicyclic heterocyclyl group with seven or eight atoms (including bridgehead atoms), wherein at least one ring member is a nitrogen atom and the remainder ring atoms being carbon. The said azabicyclyl may optionally contain a carbon-carbon double bond. Examples of azabicyclyl groups include carbon radicals obtainable from 1-azabicyclo[2.2.2]octane, 1-aza-bicyclo[2.2.1]heptane and azabicyclo[2.2.2]oct-2-ene.

"C-heterocyclylsulfonyl" refers to a heterocyclyl group that is directly bonded to SO_2 via a carbon atom. Exemplary C-heterocyclylsulfonyl groups include 4-piperidinylsulfonyl and tetrahydropyran-4-ylsulfonyl.

When C-heterocyclylsulfonyl is substituted by C_{1-4}-alkyl, said heterocyclyl is selected from a nitrogen-containing heterocyclyl, and said C_{1-4}-alkyl is attached to a ring nitrogen atom thereof. An exemplary C-heterocyclylsulfonyl group substituted by C_{1-4}-alkyl includes 1-methylpiperidin-4-ylsulfonyl.

Unless otherwise stated or indicated, the term "C_{2-4}-acylamino" denotes a group $R^b(C=O)NH-$ wherein R^b is selected from C_{1-3}-alkyl. Exemplary C_{2-4}-acylamino groups include acetylamino and propionylamino.

Unless otherwise stated or indicated, the term "C_{2-4}-acylamino-C_{1-4}-alkyl" denotes a C_{2-4} acylamino group, as defined above, attached to a C_{1-4}-alkyl group. Examplary C_{2-4}-acylamino-C_{1-4}-alkyl groups include (acetylamino)methyl and 2-(acetylamino)ethyl.

Unless otherwise stated or indicated, the term "aminocarbonyl" refers to the radical $NH_2(C=O)$—.

Unless otherwise stated or indicated, the term "aminocarbonyl-C_{1-4}-alkyl" denotes a C_{1-4}-alkyl group, as defined above, substituted with an aminocarbonyl group. Exemplary aminocarbonyl-C_{1-4}-alkyl groups include 2-(aminocarbonyl)ethyl and 3-(aminocarbonyl)-propyl.

Unless otherwise stated or indicated, the term "carboxy" denotes a group —C(O)OH.

Unless otherwise stated or indicated, the term "carboxy-C_{1-3}-alkyl" refers to a carboxy group, as defined above, attached to a C_{1-3}-alkyl group. Exemplary carboxy-C_{1-3}-alkyl groups include 2-carboxyethyl and 3-carboxypropyl.

Unless otherwise stated or indicated, the term "carboxy-C_{1-3}-alkylcarbonylamino" refers to a carboxy-C_{1-3}-alkyl groups, as defined above, attached to the carbonyl carbon of carbonylamino (i.e., —C(O)NH—). Exemplary carboxy-C_{1-3}-alkylcarbonylamino groups include (2-carboxyethyl)carbonylamino and (3-carboxypropyl)carbonylamino.

"C-heterocyclylcarbonyl" refers to a heterocyclyl group that is directly bonded to a carbonyl group via a carbon atom while "*N*-heterocyclylcarbonyl" refers to a nitrogen-containing heterocyclyl group that is directly bonded to a carbonyl group via a nitrogen atom. Examples of *N*-heterocyclylcarbonyl groups include 1-piperidinylcarbonyl, 1-piperazinylcarbonyl and 1-pyrrolidincarbonyl. Exemplary C-heterocyclylcarbonyl groups include 3-piperidinylcarbonyl, 4-piperidinylcarbonyl and tetrahydropyranyl-4-ylcarbonyl.

When C-heterocyclylcarbonyl is substituted by C_{1-4}-alkyl, said heterocyclyl is selected from a nitrogen-containing heterocyclyl, and said C_{1-4}-alkyl is attached to a ring nitrogen atom thereof. An exemplary C-heterocyclylcarbonyl group substituted by C_{1-4}-alkyl includes 1-methylpiperidin-4-ylcarbonyl.

The term "*N*-heterocyclylcarbonyl-C_{2-4}-alkyl" refers to a *N*-heterocyclylcarbonyl group that is directly linked to a C_{2-4}-alkyl group through its carbonyl carbon atom and where *N*-heterocyclylcarbonyl is as defined above. Exemplary *N*-heterocyclylcarbonyl-C_{2-4}-alkyl groups include 2-(pyrrolidin-1-ylcarbonyl)ethyl, 2-(piperazin-1-ylcarbonyl)ethyl and 2-(piperidin-1-ylcarbonyl)ethyl.

When heterocyclyl as part of the group *N*-heterocyclylcarbonyl-C_{2-4}-alkyl is substituted by methyl, said heterocyclyl is selected from 1-piperazinyl or 1-homopiperazinyl and said methyl is attached to the 4-position of the piperazine or homopiperazine ring. Exemplary *N*-heterocyclylcarbonyl-C_{2-4}-alkyl groups wherein heterocyclyl is substituted with methyl are 2-(4-methylpiperazin-1-ylcarbonyl)ethyl, 2-(4-methylhomopiperazin-1-ylcarbonyl)-ethyl.

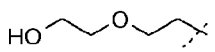
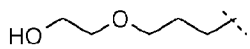
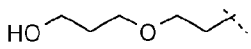
The term "C-heterocyclylcarbonyl-C_{2-4}-alkyl" refers to a C-heterocyclylcarbonyl group that is directly linked to a C_{2-4}-alkyl group through its carbonyl carbon atom and where C-heterocyclylcarbonyl is as defined above. Exemplary C-heterocyclylcarbonyl-C_{2-4}-alkyl groups include 2-(tetrahydropyran-4-ylcarbonyl)ethyl, 2-(piperidin-3-ylcarbonyl)ethyl and 2-(piperidin-4-ylcarbonyl)ethyl.

When heterocyclyl as part of the group C-heterocyclylcarbonyl-C_{2-4}-alkyl is substituted by methyl, said heterocyclyl is selected from a nitrogen-containing heterocyclyl and said methyl is attached to a ring nitrogen atom thereof. An exemplary C-heterocyclylcarbonyl-C_{2-4}-alkyl group wherein heterocyclyl is substituted with methyl is 2-(1-methylpiperidin-4-ylcarbonyl)ethyl.

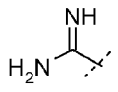
The term "C-heterocyclyloxy" refers to a heterocyclic group that is directly bonded to an oxygen atom via a carbon atom. Examples of C-heterocyclyloxy groups include 3-piperidinyloxy, 4-piperidinyloxy, 3-tetrahydrofuranyloxy, and 4-tetrahydropyranyloxy.

When C-heterocyclyloxy is substituted by C_{1-4}-alkyl, said heterocyclyl is selected from a nitrogen-containing heterocyclyl, and said C_{1-4}-alkyl is attached to a ring nitrogen atom thereof. An exemplary C-heterocyclyloxy group substituted by C_{1-4}-alkyl includes 1-methylpiperidin-4-yloxy.

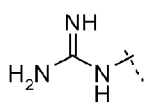
The term "hydroxy-C_{2-4}-alkoxy-C_{1-4}-alkyl" refers to a hydroxy-C_{2-4}-alkoxy group that is directly attached to a C_{1-4}-alkyl group. Representative examples of such groups include:

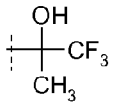
The term "amidino" refers to a group with the following chemical structure:


;

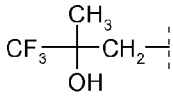
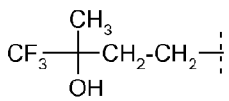
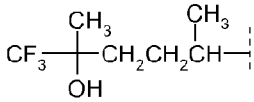
The term "guanidino" refers to a group with the following chemical structure:


;

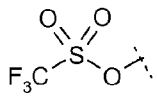
The chemical formula $-C(OH)CH_3CF_3$ refers to a group with the following chemical structure:



The term $[CF_3CH_3(OH)C]$-C_{1-6}-alkyl refers to a $CF_3CH_3(OH)C-$ group that is directly attached to a C_{1-6}-alkyl group. Representative examples of such groups include:

 ,  and 

The chemical formula CF_3SO_3 refers to a group with the following chemical structure:



The carbon-carbon double or triple bonds present in the groups C_{3-6}-alkenyl, C_{3-6}-alkynyl, aryl-C_{3-6}-alkenyl and aryl-C_{3-6}-alkynyl as values for R^2 are meant to be located at positions other than conjugated with a carbonyl group or adjacent to a nitrogen, oxygen or sulfur atom.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

The term "coupling agent" refers to a substance capable of catalyzing a coupling reaction, such as amidation or esterification. Examples of coupling agents include, but are not limited to, carbonyldiimidazole, dicyclohexylcarbodiimide, pyridine, 4-dimethylamino-pyridine, and triphenylphosphine. Another example of a coupling agent is 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC), which is used in the presence of 1-hydroxybenzotriazole (HOBT) and a base such as triethylamine.

The terms "*exo*" and "*endo*" are stereochemical prefixes that describe the relative configuration of a substituent on a bridge (not a bridgehead) of a bicyclic system such as 1-azabicyclo[2.2.1]heptane and bicyclo[2.2.1]heptane. If a substituent is oriented toward the larger of the other bridges, it is *endo*. If a substituent is oriented toward the smaller bridge it is *exo*. Both *exo* and *endo* forms and their mixtures are part of the present invention.

The term "Syndrome X" (also called metabolic syndrome) refers to a syndrome comprising some or all of the following diseases: 1) dyslipoproteinemia (combined

hypercholesterolemia-hypertriglyceridemia, low HDL-cholesterol), 2) obesity (in particular upper body obesity), 3) impaired glucose tolerance (IGT) leading to noninsulin-dependent diabetes mellitus (NIDDM), 4) essential hypertension and (5) thrombogenic/fibrinolytic defects.

"Pharmaceutically acceptable" means being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

"Treatment" as used herein includes prophylaxis of the named disorder or condition, or amelioration or elimination of the disorder once it has been established.

"An effective amount" refers to an amount of a compound that confers a therapeutic effect (e.g., treats, controls, ameliorates, prevents, delays the onset of, or reduces the risk of developing a disease, disorder, or condition or symptoms thereof) on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect).

"Prodrugs" refers to compounds that may be converted under physiological conditions or by solvolysis to a biologically active compound of the invention. A prodrug may be inactive when administered to a subject in need thereof, but is converted *in vivo* to an active compound of the invention. Prodrugs are typically rapidly transformed *in vivo* to yield the parent compound of the invention, *e.g.* by hydrolysis in the blood. The prodrug compound usually offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see Silverman, R. B., *The Organic Chemistry of Drug Design and Drug Action*, 2nd Ed., Elsevier Academic Press (2004), pp. 498-549). Prodrugs of a compound of the invention may be prepared by modifying functional groups, such as a hydroxy, amino or mercapto groups, present in a compound of the invention in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound of the invention. Examples of prodrugs include, but are not limited to, acetate, formate and succinate derivatives of hydroxy functional groups or phenyl carbamate derivatives of amino functional groups.

Throughout the specification and the appended claims, a given chemical formula or name shall also encompass all salts, hydrates, solvates, N-oxides and prodrug forms thereof. Further, a given chemical formula or name shall encompass all tautomeric and stereoisomeric forms thereof. Stereoisomers include enantiomers and diastereomers. Enantiomers can be present in their pure forms, or as racemic (equal) or unequal mixtures

of two enantiomers. Diastereomers can be present in their pure forms, or as mixtures of diastereomers. Diastereomers also include geometrical isomers, which can be present in their pure *cis* or *trans* forms or as mixtures of those.

The compounds of the Formula (Ia) to (Ic) may be used as such or, where appropriate, as pharmacologically acceptable salts (acid or base addition salts) thereof. The pharmacologically acceptable addition salts mentioned below are meant to comprise the therapeutically active non-toxic acid and base addition salt forms that the compounds are able to form. Compounds that have basic properties can be converted to their pharmaceutically acceptable acid addition salts by treating the base form with an appropriate acid. Exemplary acids include inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulphuric acid, phosphoric acid; and organic acids such as formic acid, acetic acid, propanoic acid, hydroxyacetic acid, lactic acid, pyruvic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, benzenesulphonic acid, toluenesulphonic acid, methanesulphonic acid, trifluoroacetic acid, fumaric acid, succinic acid, malic acid, tartaric acid, citric acid, salicylic acid, *p*-aminosalicylic acid, pamoic acid, benzoic acid, ascorbic acid and the like. Exemplary base addition salt forms are the sodium, potassium, calcium salts, and salts with pharmaceutically acceptable amines such as, for example, ammonia, alkylamines, benzathine, and amino acids, such as, e.g. arginine and lysine. The term addition salt as used herein also comprises solvates which the compounds and salts thereof are able to form, such as, for example, hydrates, alcoholates and the like.

COMPOSITIONS

For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. Pharmaceutical formulations are usually prepared by mixing the active substance, or a pharmaceutically acceptable salt thereof, with conventional pharmaceutical excipients. Examples of excipients are water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such formulations may also contain other pharmacologically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like. Usually, the amount of active compounds is between 0.1-95% by weight of the preparation, preferably between 0.2-20%

by weight in preparations for parenteral use and more preferably between 1-50% by weight in preparations for oral administration.

The dose level and frequency of dosage of the specific compound will vary depending on a variety of factors including the potency of the specific compound employed, the metabolic stability and length of action of that compound, the patient's age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the condition to be treated, and the patient undergoing therapy. The daily dosage may, for example, range from about 0.001 mg to about 100 mg per kilo of body weight, administered singly or multiply in doses, e.g. from about 0.01 mg to about 25 mg each. Normally, such a dosage is given orally but parenteral administration may also be chosen.

The formulations can be further prepared by known methods such as granulation, compression, microencapsulation, spray coating, etc. The formulations may be prepared by conventional methods in the dosage form of tablets, capsules, granules, powders, syrups, suspensions, suppositories or injections. Liquid formulations may be prepared by dissolving or suspending the active substance in water or other suitable vehicles. Tablets and granules may be coated in a conventional manner.

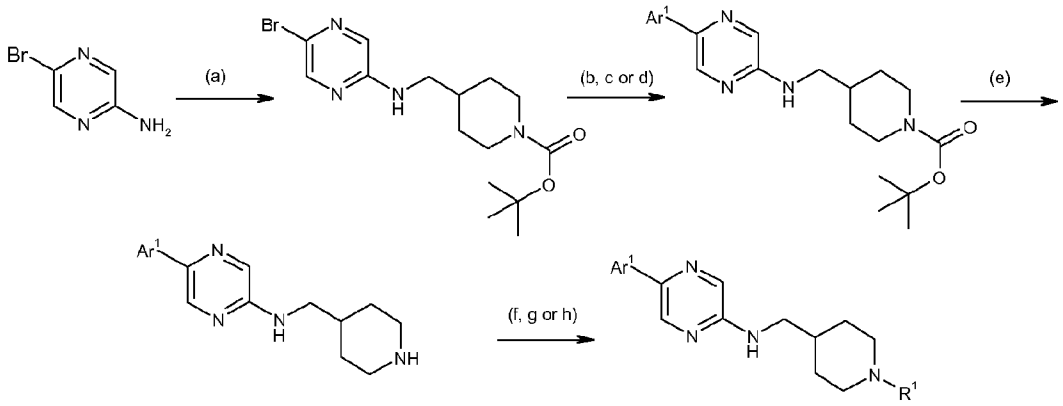
The compounds of Formula (Ia) to (Ic) may be administered with other active compounds for the treatment of diabetes and/or obesity, for example insulin and insulin analogs, DPP-IV inhibitors, sulfonyl ureas, biguanides, α2 agonists, glitazones, PPAR-γ agonists, mixed PPAR-α/γ agonists, RXR agonists, α-glucosidase inhibitors, PTP1B inhibitors, 11-β-hydroxy steroid dehydrogenase Type 1 inhibitors, phosphodiesterase inhibitors, glycogen phosphorylase inhibitors, MCH-1 antagonists, CB-1 antagonists (or inverse agonists), amylin antagonists, CCK receptor agonists, β_3-agonists, leptin and leptin mimetics, serotonergic/dopaminergic antiobesity drugs, gastric lipase inhibitors, pancreatic lipase inhibitors, fatty acid oxidation inhibitors, lipid lowering agents and thyromimetics.

It is particularly preferred that the compounds of Formula (Ia) to (Ic) are administered in combination with a DPP-IV inhibitor. The term "DPP-IV inhibitor" means a compound which inhibits, antagonizes or decreases the activity of dipeptidyl peptidase IV (EC 3.4.14.5). The said DPP-IV inhibitor can e.g. be a compound as disclosed in WO 2005/056003; WO 2005/056013; WO 2005/095343; WO 2005/113510; WO 2005/120494; WO 2005/121131; WO 2005/121089; WO 2006/013104; or WO 2006/076231, including references therein.

PREPARATION OF COMPOUNDS OF THE INVENTION

The compounds of the Formula (Ia) to (Ic) above may be prepared by, or in analogy with, conventional methods. The preparation of intermediates and compounds according to the examples of the present invention may in particular be illuminated by the following Schemes 1-6.

Scheme 1



wherein Ar^1 and R^1 are as defined in Formula (Ia);

Reagents and conditions:

(a) *tert*-butyl 4-formylpiperidine-1-carboxylate; appropriate reducing agent, such as sodium triacetoxyborohydride; in a suitable solvent such as THF or DCM; at r.t.;

(b) appropriate aryl- or heteroarylboronic acid; appropriate catalyst, such as $Pd(PPh_3)_4$; a suitable base, such as K_2CO_3 or $NaHCO_3$; in a suitable solvent mixture such as 1,4-dioxane/water or toluene/isopropyl alcohol/water; at elevated temperature, for example 90 °C;

(c) appropriate aryl- or heteroarylboronic ester; appropriate catalyst, such as $Pd(PPh_3)_4$; a suitable base, such as K_2CO_3 or $NaHCO_3$; in a suitable solvent mixture such as 1,4-dioxane/water or toluene/isopropyl alcohol/water; at elevated temperature, for example 90 °C;

(d) (i) bis(neopentylglycolato)diboron; suitable base, such as KOAc; appropriate catalyst, such as $PdCl_2(dppf)\cdot DCM$; in a suitable solvent, such as DME; at elevated temperature, for example 120 °C (microwaves); (ii) appropriate aryl halide; suitable

base, such as $NaHCO_3$; appropriate catalyst, such as $Pd(PPh_3)_4$; in a suitable solvent mixture, such as water and DME; at elevated temperature, for example 120 °C (microwaves);

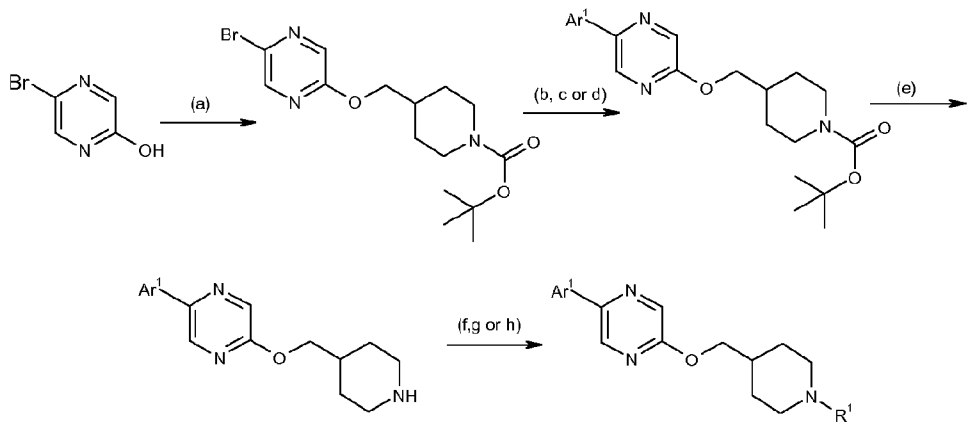
(e) suitable deprotecting agent, such as TFA, HCl (g) or aqueous concentrated HCl; in a suitable solvent, such as DCM, dioxane or ethanol; at ambient or elevated temperature;

(f) (i) appropriate carboxylic acid; suitable base, such as triethylamine; in a suitable solvent, such as THF, dioxane or DMF; (ii) appropriate coupling reagent, such as HOBT/EDC, propylphosphonic anhydride, HBTU or TBTU; at ambient temperature;

(g) appropriate acid chloride or chloroformate; suitable base, such as triethylamine; in a suitable solvent, such THF or DMF; at ambient temperature;

(h) appropriate alcohol; suitable coupling reagent, such as 1,1'-carbonylbis(1*H*-imidazole); in a suitable solvent, such DCM, acetonitrile or DCM/THF; at elevated temperature.

Scheme 2



wherein Ar^1 and R^1 are as defined in Formula (Ia);

Reagents and conditions:

(a) (i) *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate, triphenylphosphine, THF (dry) r.t. sonication (20-kHz for 1 minute) (ii) DEAD, 0 °C, sonication (20-kHz);

(b) appropriate aryl- or heteroarylboronic acid; appropriate catalyst, such as $Pd(PPh_3)_4$; a suitable base, such as K_2CO_3 or $NaHCO_3$; in a suitable solvent mixture such as 1,4-

dioxane/water or toluene/isopropyl alcohol/water; at elevated temperature, for example 90 °C;

(c) appropriate aryl- or heteroarylboronic ester; appropriate catalyst, such as $Pd(PPh_3)_4$; a suitable base, such as K_2CO_3 or $NaHCO_3$; in a suitable solvent mixture such as 1,4-dioxane/water or toluene/isopropyl alcohol/water; at elevated temperature, for example 90 °C;

(d) (i) bis(neopentylglycolato)diboron; suitable base, such as KOAc; appropriate catalyst, such as $PdCl_2(dppf)\cdot DCM$; in a suitable solvent, such as DME; at elevated temperature, for example 120 °C (microwaves); (ii) appropriate aryl halide; suitable base, such as $NaHCO_3$; appropriate catalyst, such as $Pd(PPh_3)_4$; in a suitable solvent mixture, such as water and DME; at elevated temperature, for example 120 °C (microwaves);

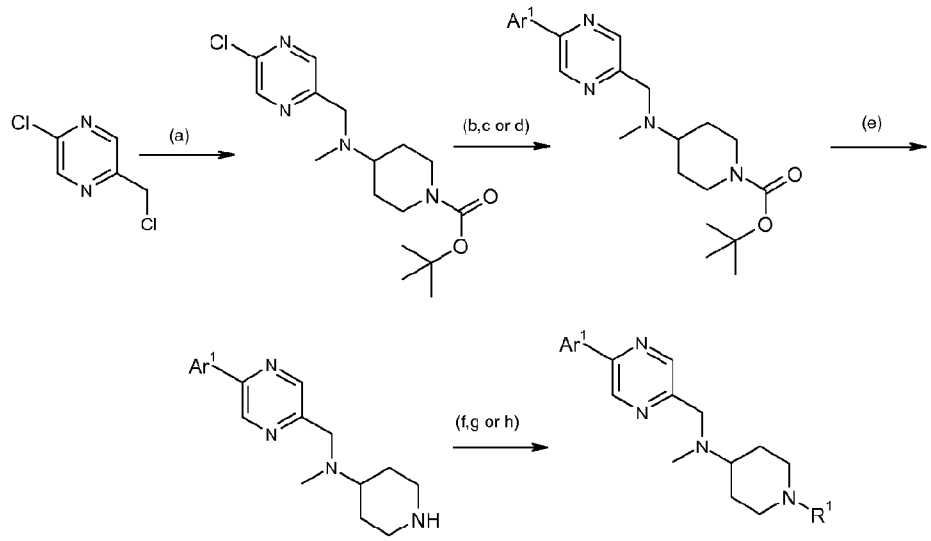
(e) suitable deprotecting agent, such as TFA, HCl (g) or aqueous concentrated HCl; in a suitable solvent, such as DCM, dioxane or ethanol; at ambient or elevated temperature;

(f) (i) appropriate carboxylic acid; suitable base, such as triethylamine; in a suitable solvent, such as THF, dioxane or DMF; (ii) appropriate coupling reagent, such as HOBT/EDC, propylphosphonic anhydride, HBTU or TBTU; at ambient temperature;

(g) appropriate acid chloride or chloroformate; suitable base, such as triethylamine; in a suitable solvent, such THF or DMF; at ambient temperature;

(h) appropriate alcohol; suitable coupling reagent, such as 1,1'-carbonylbis(1*H*-imidazole); in a suitable solvent, such DCM, acetonitrile or DCM/THF; at elevated temperature.

Scheme 3



wherein Ar^1 and R^1 are as defined in Formula (Ia);

Reagents and conditions:

(a) (i) potassium *tert*-butoxide, THF (dry), (ii) *tert*-butyl 4-(methylamino)-piperidine-1-carboxylate, reflux;

(b) appropriate aryl- or heteroarylboronic acid; appropriate catalyst, such as $Pd(PPh_3)_4$; a suitable base, such as K_2CO_3 or $NaHCO_3$; in a suitable solvent mixture such as 1,4-dioxane/water or toluene/isopropyl alcohol/water; at elevated temperature, for example 90 °C;

(c) appropriate aryl- or heteroarylboronic ester; appropriate catalyst, such as $Pd(PPh_3)_4$; a suitable base, such as K_2CO_3 or $NaHCO_3$; in a suitable solvent mixture such as 1,4-dioxane/water or toluene/isopropyl alcohol/water; at elevated temperature, for example 90 °C;

(d) (i) bis(neopentylglycolato)diboron; suitable base, such as KOAc; appropriate catalyst, such as $PdCl_2(dppf)\cdot DCM$; in a suitable solvent, such as DME; at elevated temperature, for example 120 °C (microwaves); (ii) appropriate aryl halide; suitable base, such as $NaHCO_3$; appropriate catalyst, such as $Pd(PPh_3)_4$; in a suitable solvent mixture, such as water and DME; at elevated temperature, for example 120 °C (microwaves);

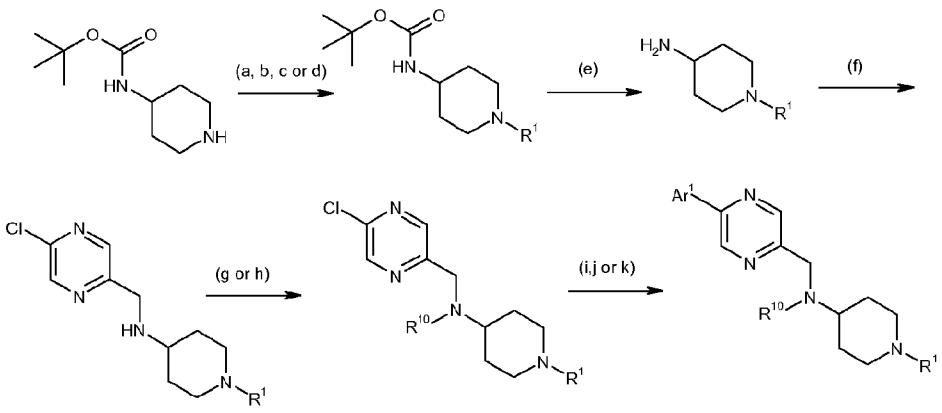
(e) suitable deprotecting agent, such as TFA, HCl (g) or aqueous concentrated HCl; in a suitable solvent, such as DCM, dioxane or ethanol; at ambient or elevated temperature;

(f) (i) appropriate carboxylic acid; suitable base, such as triethylamine; in a suitable solvent, such as THF, dioxane or DMF; (ii) appropriate coupling reagent, such as HOBT/EDC, propylphosphonic anhydride, HBTU or TBTU; at ambient temperature;

(g) appropriate acid chloride or chloroformate; suitable base, such as triethylamine; in a suitable solvent, such THF or DMF; at ambient temperature;

(h) appropriate alcohol; suitable coupling reagent, such as 1,1'-carbonylbis(1*H*-imidazole); in a suitable solvent, such DCM, acetonitrile or DCM/THF; at elevated temperature.

Scheme 4



wherein Ar^1, R^1 and R^{10} are as defined in Formula (Ia);

Reagents and conditions:

(a) appropriate acid chloride or chloroformate; suitable base, such as triethylamine; in a suitable solvent, such as THF or DMF; at ambient temperature;

(b) appropriate alcohol; suitable coupling reagent, such as 1,1'-carbonylbis(1*H*-imidazole); in a suitable solvent, such as DCM, acetonitrile or DCM/THF; at elevated temperature;

(c) appropriate halogenated heteroaromatic ring, such as 2-bromopyrimidine; in a suitable solvent, such as DMSO or acetonitrile; at elevated temperature;

(d) (i) appropriate carboxylic acid; suitable base, such as triethylamine; in a suitable solvent, such as THF, dioxane or DMF; (ii) appropriate coupling reagent, such as HOBT/EDC, propylphosphonic anhydride, HBTU or TBTU; at ambient temperature;

(e) suitable deprotecting agent, such as TFA, HCl (g) or aqueous HCl; in a suitable solvent, such as DCM, dioxane or ethanol; at ambient or elevated temperature;

(f) 2-chloro-5-chloromethylpyrazine; suitable base, such as triethylamine or *N,N*-diisopropylethyl amine in a suitable solvent, such as acetonitrile; at elevated temperature;

(g) appropriate aldehyde or ketone, or protected ketone such as [(1-ethoxycyclopropyl)oxy]trimethylsilane), corresponding to R^{10}; appropriate reducing agent, such as $NaBH(OAc)_3$ or $NaBH_3CN$; in a suitable solvent, such as MeOH, 1,2-dichloroethane, DCM, or in a solvent mixture such as methanol/water or methanol/acetic acid; at ambient or elevated temperature;

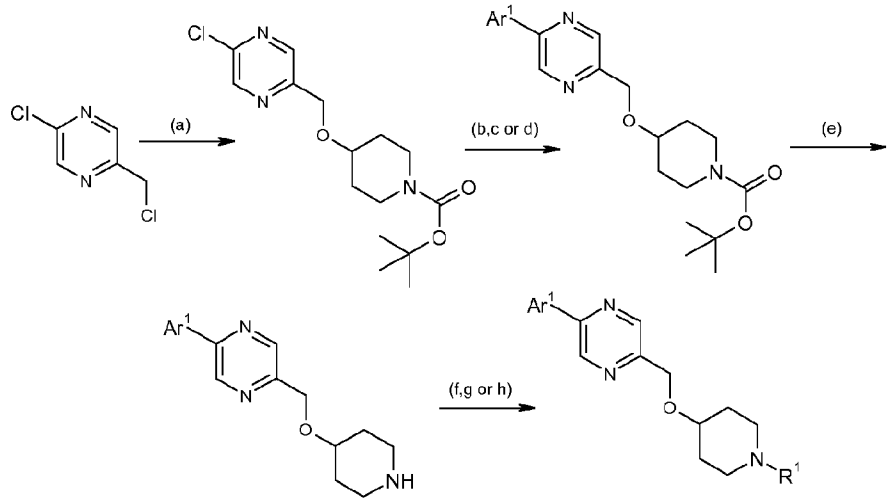
(h) appropriate alkylating agent corresponding to R^{10}, such as an alkyl halide or an alkyl triflate; suitable base, such *N,N*-diisopropylethyl amine or triethylamine; in a suitable solvent, such as THF or DMF; at elevated temperature;

(i) appropriate aryl- or heteroarylboronic acid; appropriate catalyst, such as $Pd(PPh_3)_4$; a suitable base, such as K_2CO_3 or $NaHCO_3$; in a suitable solvent mixture such as 1,4-dioxane/water or toluene/isopropyl alcohol/water; at elevated temperature, for example 90 °C;

(j) appropriate aryl- or heteroarylboronic ester; appropriate catalyst, such as $Pd(PPh_3)_4$; a suitable base, such as K_2CO_3 or $NaHCO_3$; in a suitable solvent mixture such as 1,4-dioxane/water or toluene/isopropyl alcohol/water; at elevated temperature, for example 90 °C;

(k) (i) bis(neopentylglycolato)diboron; suitable base, such as KOAc; appropriate catalyst, such as $PdCl_2(dppf)\cdot DCM$; in a suitable solvent, such as DME; at elevated temperature, for example 120 °C (microwaves); (ii) appropriate aryl halide; suitable base, such as $NaHCO_3$; appropriate catalyst, such as $Pd(PPh_3)_4$; in a suitable solvent mixture, such as water and DME; at elevated temperature, for example 120 °C (microwaves).

Scheme 5



wherein Ar^1 and R^1 are as defined in Formula (Ia);

Reagents and conditions:

(a) sodium hydride, THF (dry), *tert*-butyl 4-hydroxypiperidine-1-carboxylate;

(b) appropriate aryl- or heteroarylboronic acid; appropriate catalyst, such as $Pd(PPh_3)_4$; a suitable base, such as K_2CO_3 or $NaHCO_3$; in a suitable solvent mixture such as 1,4-dioxane/water or toluene/isopropyl alcohol/water; at elevated temperature, for example 90 °C;

(c) appropriate aryl- or heteroarylboronic ester; appropriate catalyst, such as $Pd(PPh_3)_4$; a suitable base, such as K_2CO_3 or $NaHCO_3$; in a suitable solvent mixture such as 1,4-dioxane/water or toluene/isopropyl alcohol/water; at elevated temperature, for example 90 °C;

(d) (i) bis(neopentylglycolato)diboron; suitable base, such as KOAc; appropriate catalyst, such as $PdCl_2(dppf)\cdot DCM$; in a suitable solvent, such as DME; at elevated temperature, for example 120 °C (microwaves); (ii) appropriate aryl halide; suitable base, such as $NaHCO_3$; appropriate catalyst, such as $Pd(PPh_3)_4$; in a suitable solvent mixture, such as water and DME; at elevated temperature, for example 120 °C (microwaves);

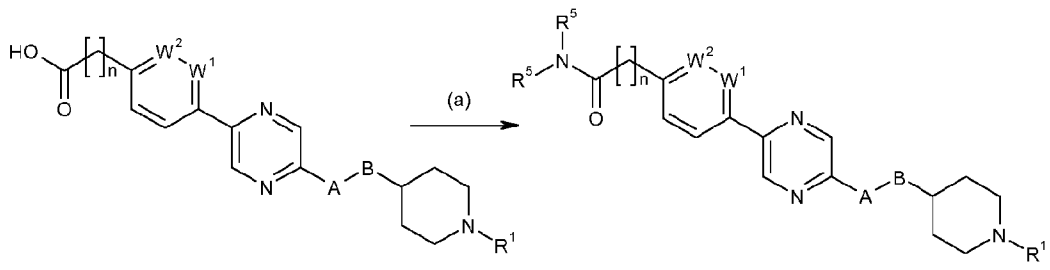
(e) suitable deprotecting agent, such as TFA, HCl (g) or aqueous concentrated HCl; in a suitable solvent, such as DCM, dioxane or ethanol; at ambient or elevated temperature;

(f) (i) appropriate carboxylic acid; suitable base, such as triethylamine; in a suitable solvent, such as THF, dioxane or DMF; (ii) appropriate coupling reagent, such as HOBT/EDC, propylphosphonic anhydride, HBTU or TBTU; at ambient temperature;

(g) appropriate acid chloride or chloroformate; suitable base, such as triethylamine; in a suitable solvent, such THF or DMF; at ambient temperature;

(h) appropriate alcohol; suitable coupling reagent, such as 1,1'-carbonylbis(1*H*-imidazole); in a suitable solvent, such DCM, acetonitrile or DCM/THF; at elevated temperature.

Scheme 6



wherein A, B, R^1 and R^5 are as defined in Formula (Ia);

W^1 and W^2 are both CH, or one of W^1 or W^2 is CH and the other of W^1 or W^2 is N; and

n = 0, 1 or 2.

Reagents and conditions:

(a) (i) appropriate amine; suitable base, such as triethylamine; in a suitable solvent, such as THF, dioxane or DMF; (ii) appropriate coupling reagent, such as HOBT/EDC, propylphosphonic anhydride, HBTU or TBTU; at 0 °C or ambient temperature.

Definitions of variables in the structures in schemes herein are commensurate with those of corresponding positions in the formulae delineated herein.

The necessary starting materials for preparing the compounds of Formula (Ia) to (Ic) and other compounds herein are either commercially available or may be prepared in analogy with the preparation of known compounds.

The processes described below in the example section may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. A pharmaceutically acceptable acid addition salt may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Examples of addition salt forming acids are mentioned above.

The compounds of Formula (Ia) to (Ic) may possess one or more chiral carbon atoms, and they may therefore be obtained in the form of optical isomers, e.g. as a pure enantiomer, or as a mixture of enantiomers (racemate) or as a mixture containing diastereomers. The separation of mixtures of optical isomers to obtain pure enantiomers is well known in the art and may, for example, be achieved by fractional crystallization of salts with optically active (chiral) acids or by chromatographic separation on chiral columns.

The chemicals used in the synthetic routes delineated herein may include, for example, solvents, reagents, catalysts, and protecting group and deprotecting group reagents. The methods described above may also additionally include steps, either before or after the steps described specifically herein, to add or remove suitable protecting groups in order to ultimately allow synthesis of the compounds. In addition, various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing applicable compounds are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

The following abbreviations have been used:

Boc	*tert*-butyloxycarbonyl
Brine	water saturated or nearly saturated with sodium chloride
$CHCl_3$	chloroform
DCM	dichloromethane
DEAD	diethyl (*Z*)-diazene-1,2-dicarboxylate
DIPEA	*N,N*-diisopropylethyl amine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulphoxide
EDC	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide, or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ESI	electrospray ionization
Et_3N	triethylamine
EtOAc	ethyl acetate
equiv.	equivalents
HDL	High-Density Lipoprotein
HBTU	O-Benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluorophosphate
HOBT	1-hydroxybenzotriazole hydrate
HPLC	High Performance Liquid Chromatography
HRESIMS	High-Resolution Electrospray Ionization Mass Spectra
LCMS	Liquid Chromatography Mass Spectrometry
LRESIMS	Low-Resolution Electrospray Ionization Mass Spectra
MeCN	acetonitrile
MeOH	methanol
$NaBH(OAc)_3$	sodium triacetoxyborohydride
$PdCl_2(dppf)\cdot DCM$	[1,1'-bis(diphenylphosphino)-ferrocene]dichloro-palladium(II) complex with DCM (1:1)
$Pd(PPh_3)_4$	tetrakis(triphenylphospine)palladium(0)
r.t.	room temperature
TBTU	*N,N,N',N'*-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatograpy

The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

The invention will now be further illustrated by the following non-limiting Examples. The specific examples below are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. All references and publications cited herein are hereby incorporated by reference in their entirety.

EXAMPLES AND INTERMEDIATE COMPOUNDS

Experimental Methods

All reagents were commercial grade and were used as received without further purification, unless otherwise specified. Commercially available anhydrous solvents were used for reactions conducted under inert atmosphere. Reagent grade solvents were used in all other cases, unless otherwise specified. Low-resolution electrospray ionization mass spectra (LRESIMS) were obtained using an Agilent MSD mass spectrometer or a Waters ZQ mass spectrometer. High-resolution electrospray ionization mass spectra (HRESIMS) were obtained on:

(a) Agilent LC/MSD TOF connected to an Agilent 1100 LC-system, Ion Source: ESI, Ion polarity: pos, Data: profile mode, Scan range: 100-1100 Da, MS parameters: Fragmentor 215V, Skimmer 560V och OCT RF (octpole rods) 250 V.; Reference Masses 121.050873 and 922.009798 (Agilent reference Mix); LC: A 15 mM ammonium acetate; B 100 MeCN; flow rate 400 µL/min isocratic.

(b) Shimadzu 2010 EV, quadruple connected to Prominence LC system. Ion Source: ESI, Ion polarity: pos, Data: scane mode, Scan range: 100-700 Da, MS parameters: CDL 5V, Q-array DC 15V, Q-array RF 150V, CDL monitor temperature 250 °C; Reference Masses PEG mixture + Raffinose (Agilent reference Mix); LC: A 0.1% ammonium acetate; B 100 MeOH; flow rate 300 µL/min isocratic.

Flash chromatography was performed on Merck silica gel 60 (230-400 mesh). The compounds were automatically named using ACD 8.0.

Analytical HPLC was performed on a Waters Alliance Separation Module 2690 system equipped with:

System A: Kromasil C18 5µm (250 x 4.6 mm), gradient 10-90% MeOH in H_2O (+ 0.1% TFA), flow rate 1 mL/min, with a gradient time of 20 min; or

System B: Zorbax C18 5µm (150 x 4.6 mm), gradient 10-90% MeOH in H_2O (+ 0.1% TFA), flow rate 1 mL/min, with a gradient time of 20 min; or

System C: Zorbax C18 5µm (150 x 4.6 mm), gradient 10-100% MeOH in H_2O, flow rate 1 mL/min, with a gradient time of 20 min; or

System D: X-bridge C18 5µm (250 x 4.6 mm), gradient 10-100% MeOH in H_2O, flow rate 1 mL/min, with a gradient time of 20 min; or

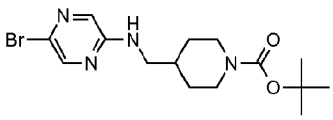
System E: Zorbax C18 5µm (150 x 4.6 mm), gradient 10-100% MeOH in H_2O (+ 0.1% TFA), flow rate 1 mL/min, with a gradient time of 26 min;

Analytical LCMS data were obtained on an Agilent 1100 system equipped with:
System F: ACE 3 C8 column (50 x 3.0 mm); gradient 10-97% H_2O (+ 0.1% TFA) in CH_3CN, flow rate 1 mL/min, with a gradient time of 3.0 min; or
System G1': YMC ODS-AQ column (33 x 3.0 mm), gradient 10-97% H_2O (+ 0.1% TFA) in CH_3CN, flow rate 1 mL/min, with a gradient time of 3.0 min; or
System G2': Xterra MSC18 column (50 x 3.0 mm), gradient 10-97% H_2O (containing 10 mM NH_4HCO_3; pH=10) in CH_3CN, flow rate 1 mL/min, with a gradient time of 3.0 min;

Preparative HPLC was performed on a Waters Delta 600 system equipped with:
System H: X-Bridge C18 5 µm (150 x 19 mm), gradient 10-90% MeOH in H_2O, flow rate 15 mL/min, with a gradient time of 10 min; or
System I: X-Bridge C18 5 µm (150 x 19 mm), gradient 10-90% MeOH in H_2O, flow rate 15 mL/min, with a gradient time of 14 min; or
System J: X-Bridge C18 5 µm (150 x 19 mm), gradient 10-90% MeOH in H_2O, flow rate 15 mL/min, with a gradient time of 9 min; or
System K: X-Bridge C18 5 µm (150 x 19 mm), gradient 10-100% MeOH in H_2O, flow rate 15 mL/min, with a gradient time of 10 min; or
System L: ACE 5 C8 (50 x 20 mm), H_2O (+ 0.1% TFA) in CH_3CN, flow rate 25 mL/min, with a gradient time of 5 min; or
System M: XTerra Prep MS C18 5 µm (19x50 mm), H_2O (containing 50 mM NH_4HCO_3; pH=10) in CH_3CN, flow rate 25 mL/min, with a gradient time of 5 min.

INTERMEDIATE 1

tert-Butyl 4-{[(5-bromopyrazin-2-yl)amino]methyl}piperidine-1-carboxylate

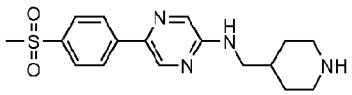


A mixture of 5-bromopyrazin-2-amine (4.9 g, 0.028 mol), prepared in accordance with the literature procedure (*Journal of Chemical Research* **2005**, *11*, 747-749), and *tert*-butyl 4-formylpiperidine-1-carboxylate (5 g, 0.023 mol) was stirred in dry THF (35 mL) at r.t.

under nitrogen atmosphere. After 10 minutes, sodium triacetoxyborohydride (8.9 g, 0.042 mol) was added in small portions within 15 minutes while maintaining the temperature at room temperature. The mixture was stirred overnight. The reaction was monitored by TLC using hexane:ethyl acetate (6:4) as mobile phase. The reaction mixture was concentrated under reduced pressure. The residue was treated with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc (3 x 100 mL). The combined organic layers were concentrated under reduced pressure to give the crude product. Column chromatography of the crude product on silica using hexane:EtOAc (6:4) as eluent gave the title compound. Yield 1.2 g (13%); LRESIMS m/z = (ESI^+) 372 $(M+H)^+$.

INTERMEDIATE 2

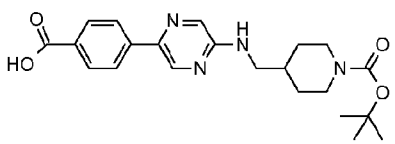
5-[4-(Methylsulfonyl)phenyl]-*N*-(piperidin-4-ylmethyl)pyrazin-2-amine



Crude *tert*-butyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate (2 g, 0.0045 mol; obtained in Example 1) was added to a 4M solution of HCl in dioxane (10 mL) at r.t. The mixture was stirred at r.t. overnight. The reaction was monitored by LCMS analysis. The reaction mixture was concentrated under reduced pressure. Water (500 mL) and EtOAc (300 mL) were added to the residue and the mixture was stirred vigorously for 10 min. The aqueous layer was basified using NaOH solution (2M; 25 mL) and the product was extracted with DCM (3 x 25 mL). The combined organic layers were washed with water (100 mL) and dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. Yield 1 g (48%). Mass m/z = (ESI^+) 347 $(M+H)^+$.

INTERMEDIATE 3

4-[5-({[1-(*tert*-butoxycarbonyl)piperidin-4-yl]methyl}amino)pyrazin-2-yl]benzoic acid

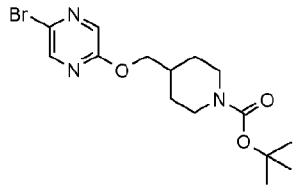


The title compound was prepared from *tert*-butyl 4-{[(5-bromopyrazin-2-yl)amino]-methyl}piperidine-1-carboxylate (2.0 g, 0.0053 mol; Intermediate 1) and 4-carboxy-benzeneboronic acid (0.98 g, 0.0059 mol) in accordance with the procedure described for

Example 1. The reaction was monitored by TLC using DCM:MeOH (8:2) as a mobile phase. The crude product was purified by column chromatography on silica using DCM:MeOH (8:2) as eluent to give the title compound. Yield 1.0 g (45%); LRESIMS (ESI^+) m/z = 311 (M^+-t-Boc-1).

INTERMEDIATE 4

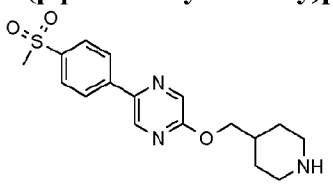
***tert*-Butyl 4-{[(5-bromopyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate**



5-Bromopyrazin-2-ol (10 g, 0.057 mol), prepared in accordance with a literature procedure (*Journal of Chemical Research* **2005**, *11*, 747-749), *tert*-butyl 4-(hydroxymethyl)-piperidine-1-carboxylate (12.2 g, 0.057 mol) and triphenylphosphine (29.9 g, 0.114 mol) were added to dry THF (75 mL) at r.t.. The reaction mixture was sonicated at 20-kHz at r.t. for 1 minute which resulted in a clear solution. The reaction mixture was cooled to 0 °C and DEAD (14.3 mL, 0.091 mol) was added dropwise to the reaction mixture at 0 °C under sonication. Overall the reaction mixture was sonicated for 7 minutes. The reaction mixture was concentrated under reduced pressure. The residue was subjected to column chromatography on silica using hexane:EtOAc (7:3) as eluent to obtain the title compound. Yield 10 g (47%). Analytical HPLC: purity 99.3% (System B); LRESIMS (ESI^+) m/z = (ESI^+) 373 $(M+H)^+$.

INTERMEDIATE 5

2-[4-(Methylsulfonyl)phenyl]-5-(piperidin-4-ylmethoxy)pyrazine

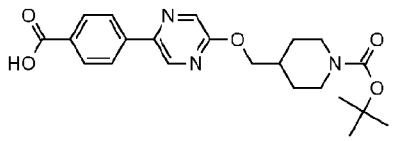


To a stirred solution of 4M HCl in dioxane (20 mL) at room temperature was added *tert*-butyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate (12 g, crude product; obtained in Example 21). The mixture was stirred at r.t. overnight and then concentrated under reduced pressure to give a crude residue. Water (100 mL) and

EtOAc (700 mL) were added to the residue and the mixture was stirred over night. The layers were separated and the aqueous layer was basified using NaOH solution (2M; 50 mL) and then extracted with DCM (3 x 100 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. Yield 4 g.

INTERMEDIATE 6

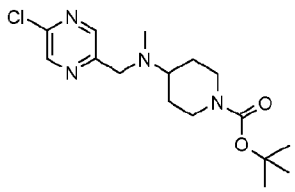
4-(5-{[1-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy}pyrazin-2-yl)benzoic acid



To a stirred mixture of *tert*-butyl 4-{[(5-bromopyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate (3.0 g, 0.0080 mol; Intermediate 4) in toluene (45 mL) at r.t. under argon atmosphere were added 4-carboxybenzeneboronic acid (1.47 g, 0.0088 mol) and isopropyl alcohol (45 mL). After 2 minutes, a 2M solution of aqueous K_2CO_3 (20.14 mL, 0.040 mol) was added dropwise to the stirred suspension. After additional 5 minutes, $Pd(PPh_3)_4$ (0.465 g, 0.0004 mol) was added and the reaction mixture was heated to reflux. The reaction was monitored by TLC using DCM:MeOH (8:2) as mobile phase. The mixture was stirred at reflux for 6 hours and then allowed to cool. The cooled mixture was poured into water (600 mL) under stirring and then left at r.t. overnight. The aqueous mixture was extracted with EtOAc (4 x 500 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by column chromatography on silica using DCM:MeOH (8:2) as eluent to give the title compound. Yield 1.5 g (45%). LRESIMS m/z = (ESI^+) 414 $(M+H)^+$.

INTERMEDIATE 7

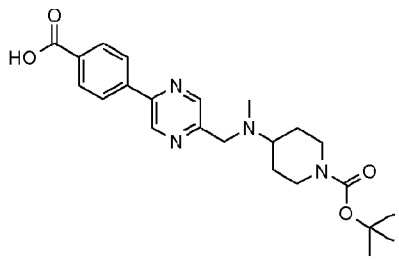
***tert*-Butyl 4-[[(5-chloropyrazin-2-yl)methyl](methyl)amino]piperidine-1-carboxylate**



To a stirred solution of 2-chloro-5-(chloromethyl)pyrazine (7.0 g, 0.0429 mol), prepared in accordance with a literature procedure (*Journal of Heterocyclic Chemistry*, **1986** *23*, 149-51), in dry THF (80 mL) under nitrogen atmosphere was added potassium *tert*-butoxide (5.29 g, 0.0471 mol). The suspension was stirred at room temperature for 10 minutes. *tert*-Butyl 4-(methylamino)piperidine-1-carboxylate (6.9 g, 0.0471 mol) was added portionwise and the resulting reaction mixture was heated at reflux for 40 hours. The reaction was monitored by TLC using EtOAc:hexane (1:1) as a mobile phase. The mixture was concentrated under reduced pressure and the residue was diluted with water (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed first with water and then with brine solution. The organic phase was concentrated under reduced pressure to give 7.8 g of a semisolid crude product. Purification of the crude product by column chromatography on silica using EtOAc:hexane (1:4) as mobile phase gave 4.0 g (27.3%) of the pure product; LRESIMS m/z = (ESI^+) 341 $(M+H)^+$.

INTERMEDIATE 8

4-(5-{[[1-(*tert*-Butoxycarbonyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-benzoic acid

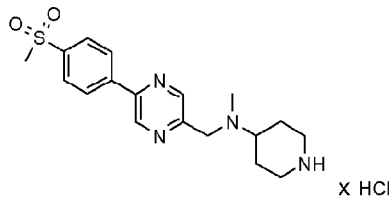


To a stirred solution of *tert*-butyl 4-[[(5-chloropyrazin-2-yl)methyl](methyl)amino]-piperidine-1-carboxylate (0.9 g, 2.64 mmol; Intermediate 7) in a dry solvent mixture of toluene (10 mL) and isopropyl alchohol (10 mL) under nitrogen atmosphere at r.t. was added 4-carboxybenzeneboronic acid (0.61 g, 3.70 mmol). After 2 minutes, a solution of K_2CO_3 (1.93 g, 13.9 mmol) in water (10 mL) was added. After additional 5 minutes, $Pd(PPh_3)_4$ (0.15 g, 0.13 mmol) was added and the reaction mixture was stirred at 120 °C for 12 hours. The reaction was monitored by TLC using DCM:MeOH (9.5:0.5) as mobile phase. The reaction mixture was concentrated under reduced pressure. The residual solid was diluted with water (100 mL) and extracted with DCM (3 x 60 mL). The organic layers were combined and concentrated under reduced pressure to afford 0.7 g of a semisolid crude product. Purification of the crude product by column chromatography on silica using

EtOAc:hexane (3:7) as eluent gave the title compound. Yield 0.6 g (53.6%). Analytical HPLC: purity 99% (System A); LRESIMS (ESI^+) for $C_{23}H_{30}N_4O_4$ m/z = 427 $(M+H)^+$.

INTERMEDIATE 9

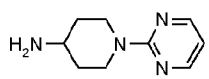
N-Methyl-N-({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)piperidin-4-amine, hydrochloride



To a stirred solution of *tert*-butyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]piperidine-1-carboxylate (4.0 g, 0.0087 mol; obtained in Example 42) in dry dioxane (50 mL) at r.t. was added dropwise a 4M HCl solution in dioxane (12 mL). The reaction mixture was allowed to stir at r.t. for 12 hours. The reaction was monitored by TLC using DCM:MeOH (8:2) + 5 drops of a 25% aqueous ammonia solution as mobile phase. The reaction mixture was concentrated under reduced pressure. The residual solid obtained was treated with MeOH and filtered. The solid was washed with MeOH and the filtrate was concentrated under reduced pressure to give the title compound as an off white solid. The off white solid obtained was used without further purification. Yield 2.5 g (83.3%); LRESIMS (ESI^+) m/z = 361 $(M+H)^+$.

INTERMEDIATE 10

1-Pyrimidin-2-ylpiperidin-4-amine

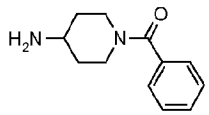


A mixture of *tert*-butyl piperidin-4-ylcarbamate (1.80 g, 9.0 mmol) and 2-bromopyrimidine (477 mg, 3.0 mmol) in DMSO (3 mL) was stirred at 55 °C for 1 hour and then added to a mixture of water (40 mL) and NH_4Cl (0.45 g). The precipitate was collected by filtration affording *tert*-butyl (1-pyrimidin-2-ylpiperidin-4-yl)carbamate (0.79 g, 95% yield). Part of this Boc-protected intermediate (695 mg, 2.5 mmol) was stirred in TFA (2.09 mL) and DCM (8.3 mL) for 2 hours at r.t. The mixture was concentrated under reduced pressure and the remaining residue dissolved in MeOH and passed through an ion-

exchange resin (Dowex 1X8, OH^-, 20 g). The eluate was concentrated under reduced pressure to give the title compound. Yield 0.43 g (97%). LRESIMS m/z = 179 $(M+H)^+$.

INTERMEDIATE 11

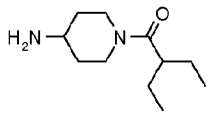
1-Benzoylpiperidin-4-amine



A stirred mixture of *tert*-butyl piperidin-4-ylcarbamate (1.0 g, 5.0 mmol), Et_3N (1.39 mL, 10 mmol) in DCM (20 mL) was cooled in an ice bath. Benzoyl chloride (0.58 mL, 5.0 mmol) was added. After 15 min, the mixture was warmed to r.t. and left for 2 h 15 min. The mixture was washed with 5% aqueous $NaHCO_3$ (20 mL), 1M HCl and brine. The organic phase was dried (Na_2SO_4) and evaporated to give *tert*-butyl (1-benzoylpiperidin-4-yl)carbamate. Yield 1.53 g (100%). Part of this Boc-protected intermediate (0.82 g) was dissolved in DCM (8 mL) and TFA (2 mL) and stirred at r.t. for 2 hours. The mixture was concentrated under reduced pressure and the remaining residue dissolved in $CHCl_3$ and washed with 1M NaOH and brine. The organic phase was concentrated under reduced pressure to give the title compound. Yield 271 mg (50%). LRESIMS m/z = 205 $(M+H)^+$.

INTERMEDIATE 12

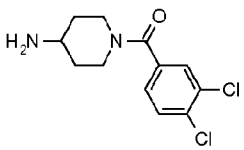
1-(2-Ethylbutanoyl)piperidin-4-amine



The title compound was prepared from *tert*-butyl piperidin-4-ylcarbamate and 2-ethylbutanoyl chloride by similar conditions as used for the synthesis of 1-benzoyl-piperidin-4-amine (Intermediate 11). Yield 523 mg (96%). LRESIMS m/z = 199 $(M+H)^+$.

INTERMEDIATE 13

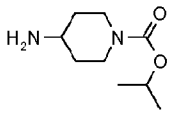
1-(3,4-Dichlorobenzoyl)piperidin-4-amine



The title compound was prepared from *tert*-butyl piperidin-4-ylcarbamate and 3,4-dichlorobenzoyl chloride by similar conditions as used for the synthesis of 1-benzoyl-piperidin-4-amine (Intermediate 11). Yield 701 mg (95%). LRESIMS m/z = 273 $(M+H)^+$.

INTERMEDIATE 14

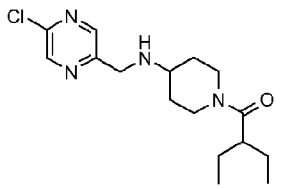
Isopropyl 4-aminopiperidine-1-carboxylate



tert-Butyl piperidin-4-ylcarbamate (750 mg, 3.75 mmol) and Et_3N (1.39 mL, 1 g, 10 mmol) were dissolved in DCM (45 mL). Isopropyl chloroformate (1M in toluene, 7.5 mL, 7.5 mmol) was added to the solution. The solution was stirred at r.t. for 2 hours and then concentrated under reduced pressure. $CHCl_3$ (90 mL) and 1M NaOH (10 mL) were added and the aqueous phase and the organic phase were allowed to separate. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give isopropyl 4-[(*tert*-butoxycarbonyl)amino]piperidine-1-carboxylate. Yield 1.072 g solid. This intermediate was stirred in a mixture of TFA (3 mL) and DCM (12 mL) at r.t. for 2 hours. The mixture was concentrated under reduced pressure and the remaining residue dissolved in $CHCl_3$ and washed with 2 M NaOH and brine. The organic phase was concentrated under reduced pressure to give the title compound. Yield 683 mg (98%); LRESIMS m/z = 187 $(M+H)^+$.

INTERMEDIATE 15

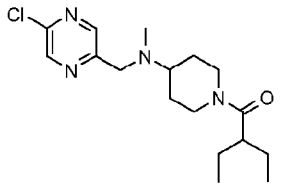
***N*-[(5-Chloropyrazin-2-yl)methyl]-1-(2-ethylbutanoyl)piperidin-4-amine**



1-(2-Ethylbutanoyl)piperidin-4-amine (0.48 g, 2.4 mmol; Intermediate 12) was dissolved in CH_3CN (6 mL) and DIPEA (0.838 mL, 4.8 mmol) and added to 2-chloro-5-chloromethylpyrazine (0.39 g, 2.4 mmol). The solution was stirred at 70 °C for 6 hours and then concentrated under reduced pressure. Flash chromatography with 2-5% 2M NH_3 in MeOH/$CHCl_3$ gave the title compound. Yield 0.50 g (64%). LRESIMS m/z = 325/327 $(M+H)^+$.

INTERMEDIATE 16

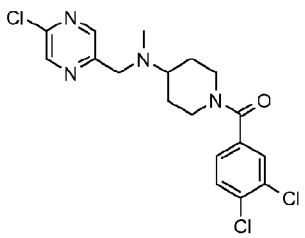
N-[(5-Chloropyrazin-2-yl)methyl]-1-(2-ethylbutanoyl)-N-methylpiperidin-4-amine



N-[(5-Chloropyrazin-2-yl)methyl]-1-(2-ethylbutanoyl)piperidin-4-amine (0.21 g, 0.65 mmol; Intermediate 15), formalin (105 mg, 1.30 mmol) and $NaBH(OAc)_3$ (551 mg, 2.60 mmol) were stirred in DCE (4 mL) at r.t. overnight. $CHCl_3$ (100 mL) and 1M NaOH (15 mL) were added to the reaction mixture and the organic phase was separated, dried (Na_2SO_4) and evaporated to give the title compound. Yield 209 mg (92%). LRMSIMS m/z = 339 $(M+H)^+$.

INTERMEDIATE 17

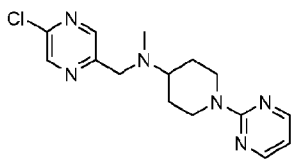
N-[(5-Chloropyrazin-2-yl)methyl]-1-(3,4-dichlorobenzoyl)-N-methylpiperidin-4-amine



The title compound was prepared starting from 2-chloro-5-chloromethylpyrazine and 1-(3,4-dichlorobenzoyl)piperidin-4-amine (Intermediate 13) in accordance with the procedures of Intermediates 15 and 16. Yield 81%. LRMSIMS m/z = 413 $(M+H)^+$.

INTERMEDIATE 18

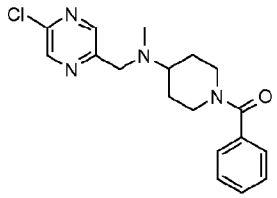
N-[(5-Chloropyrazin-2-yl)methyl]-N-methyl-1-pyrimidin-2-ylpiperidin-4-amine



The title compound was prepared starting from 2-chloro-5-chloromethylpyrazine and 1-pyrimidin-2-ylpiperidin-4-amine (Intermediate 10) in accordance with the procedures of Intermediates 15 and 16. Yield 60%. LRESIMS m/z = 319 $(M+H)^+$.

INTERMEDIATE 19

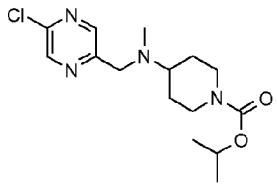
1-Benzoyl-*N*-[(5-chloropyrazin-2-yl)methyl]-*N*-methylpiperidin-4-amine



The title compound was prepared starting from 2-chloro-5-chloromethylpyrazine and 1-benzoylpiperidin-4-amine (Intermediate 11) in accordance with the procedures of Intermediates 15 and 16. LRESIMS m/z = 345 $(M+H)^+$.

INTERMEDIATE 20

Isopropyl 4-[[(5-chloropyrazin-2-yl)methyl](methyl)amino]piperidine-1-carboxylate

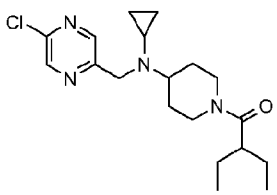


The title compound was prepared starting from 2-chloro-5-chloromethylpyrazine and isopropyl 4-aminopiperidine-1-carboxylate (Intermediate 14) in accordance with the procedures of Intermediates 15 and 16. Yield 71%. LRESIMS m/z = 327 $(M+H)^+$.

INTERMEDIATE 21

GENERAL PROCEDURE G1 FOR THE N-CYCLOPROPYLATION OF SECONDARY AMINES (compare Tetrahedron Lett. **1995**, *36*, 7399-7402).

***N*-[(5-Chloropyrazin-2-yl)methyl]-*N*-cyclopropyl-1-(2-ethylbutanoyl)piperidin-4-amine**

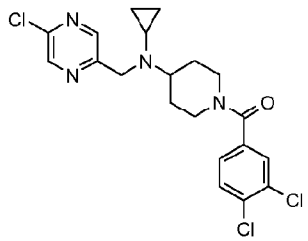


N-[(5-Chloropyrazin-2-yl)methyl]-1-(2-ethylbutanoyl)piperidin-4-amine (216 mg, 0.66 mmol; Intermediate 15) was dissolved in MeOH (4 mL) and acetic acid (0.4 mL, 10

equiv.). [(1-Ethoxycyclopropyl)oxy]trimethylsilane (0.54 g, 3.11 mmol) was added followed by $NaBH_3CN$ (167 mg, 2.66 mmol). The mixture was stirred at 62 °C overnight. The reaction mixture was concentrated under reduced pressure and the residue was acidified with 1M HCl. The mixture was made alkaline with 2M NaOH and extracted with dichloromethane. Flash chromatography on silica using MeOH/$CHCl_3$ (3:97) as eluent gave the title compound. Yield 142 mg (59%). LRESIMS m/z = 365 $(M+H)^+$.

INTERMEDIATE 22

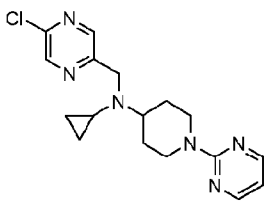
_N_-[(5-Chloropyrazin-2-yl)methyl]-_N_-cyclopropyl-1-(3,4-dichlorobenzoyl)piperidin-4-amine



2-Chloro-5-chloromethylpyrazine was reacted with 1-(3,4-dichlorobenzoyl)piperidin-4-amine (Intermediate 13) in accordance with the procedure described for Intermediate 15, and the secondary amine formed was subjected to reductive alkylation using the conditions described in General procedure G1 to afford the title compound. Yield 88%. LRESIMS m/z = 439 $(M+H)^+$.

INTERMEDIATE 23

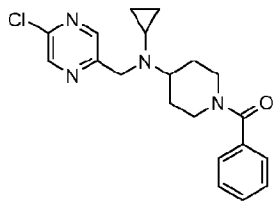
_N_-[(5-Chloropyrazin-2-yl)methyl]-_N_-cyclopropyl-1-pyrimidin-2-ylpiperidin-4-amine



2-Chloro-5-chloromethylpyrazine was reacted with 1-pyrimidin-2-ylpiperidin-4-amine (Intermediate 10) in accordance with the procedure described for Intermediate 15, and the secondary amine formed was subjected to reductive alkylation using the conditions described in General procedure G1 to afford the title compound.Yield 37%. LRESIMS m/z = 345 $(M+H)^+$.

INTERMEDIATE 24

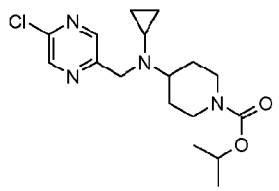
1-Benzoyl-*N*-[(5-chloropyrazin-2-yl)methyl]-*N*-cyclopropylpiperidin-4-amine



2-Chloro-5-chloromethylpyrazine was reacted with 1-benzoylpiperidin-4-amine (Intermediate 11) in accordance with the procedure described for Intermediate 15, and the secondary amine formed was subjected to reductive alkylation using the conditions described in General procedure G1 to afford the title compound. LRESIMS m/z = 371 $(M+H)^+$.

INTERMEDIATE 25

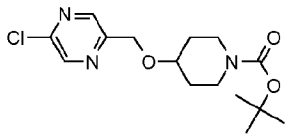
Isopropyl 4-[[(5-chloropyrazin-2-yl)methyl](cyclopropyl)amino]piperidine-1-carboxylate



2-Chloro-5-chloromethylpyrazine was reacted with isopropyl 4-aminopiperidine-1-carboxylate (Intermediate 14) in accordance with the procedure described for Intermediate 15, and the secondary amine formed was subjected to reductive alkylation using the conditions described in General Procedure G1 to afford the title compound. Yield 90%. LRESIMS m/z = 353 $(M+H)^+$.

INTERMEDIATE 26

***tert*-Butyl 4-[(5-chloropyrazin-2-yl)methoxy]piperidine-1-carboxylate**

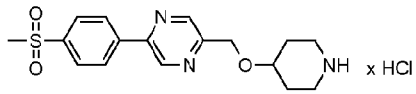


To a stirred solution of 2-chloro-5-(chloromethyl)pyrazine (10 g, 0.0613 mol), prepared in accordance with a literature procedure (*Journal of Heterocyclic Chemistry*, **1986** *23*, 149-

51), in dry THF (150 mL) at 0-5 °C under nitrogen was added NaH (4.0 g, 0.086 mol) in small portions. The resulting mixture was stirred at 0-5 °C for 1 hour, after which *tert*-butyl 4-hydroxypiperidine-1-carboxylate (12.3 g, 0.0613 mol) was added portionwise to the reaction mixture. The resulting mixture was then stirred at reflux for 18 hours. The reaction was monitored by TLC using EtOAc:hexane (2:8) as mobile phase. The mixture was diluted with water (100 mL) and extracted with EtOAc (3 x 50 mL). The combined EtOAc layers were washed with water and then with brine. The organic layer was concentrated under reduced pressure to give 8 g of a semisolid crude product. This material was purified by column chromatography on silica using EtOAc:hexane (12:88) as eluent to give the title compound. Yield 2.6 g (12.7%), LRESIMS (ESI^+) m/z = 328 $(M+H)^+$.

INTERMEDIATE 27

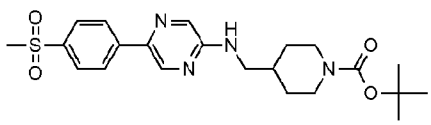
2-[4-(Methylsulfonyl)phenyl]-5-[(piperidin-4-yloxy)methyl]pyrazine, hydrochloride



To a stirred solution of *tert*-butyl 4-({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methoxy)-piperidine-1-carboxylate (1.5 g, 0.0033 mol; obtained in Example 107) in dry dioxane at room temperature under nitrogen atmosphere was added dropwise a 4 M solution of HCl in dioxane (5.0 mL). The reaction mixture was allowed to stir at room temperature for 12 hours. The reaction was monitored by TLC using DCM:MeOH (8:2) + 25% aqueous ammonia (5 drops). The reaction mixture was concentrated under reduced pressure and the residual solid obtained was treated with MeOH (10 mL) and filtered. The solid was washed with additional MeOH (10 mL) and the combined filtrate was concentrated under reduced pressure to give an off white solid. The obtained solid was used without further purification. Yield 1 g (86%); LRESIMS (ESI^+) m/z = 348 $(M+H)^+$.

EXAMPLE 1

***tert*-Butyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate**

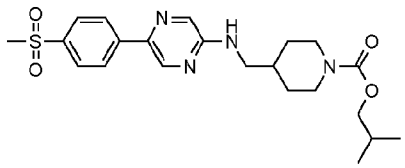


To a stirred solution of *tert*-butyl 4-{[(5-bromopyrazin-2-yl)amino]methyl}piperidine-1-carboxylate (1.5 g, 0.0040 mol; Intermediate 1) in dry toluene (22 mL) at r.t. under argon atmosphere were added 4-(methylsulfonyl)phenylboronic acid (0.89 g, 0.0044 mol) and isopropyl alcohol (22 mL). After 2 minutes, a 2M aqueous solution of K_2CO_3 (10.1 mL, 0.0202 mol) was added dropwise. After 5 minutes, $Pd(PPh_3)_4$ (0.233 g, 0.2 mmol) was added to the reaction mixture and the resulting mixture was heated to reflux. The reaction was monitored by TLC using hexane:EtOAc (2:8) as mobile phase which showed that the reaction was completed after 6 hours. The reaction mixture was added into water (250 mL) under stirring and left overnight at r.t. The aqueous mixture was extracted with EtOAc (4 x 500 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give 2 g of the crude product. This material was used in the preparation of 5-[4-(methylsulfonyl) phenyl]-*N*-(piperidin-4-ylmethyl)pyrazin-2-amine (Intermediate 2) without further purification.

A second batch of *tert*-butyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)-methyl]piperidine-1-carboxylate (0.5 g, 1.029 mmol) was synthesized using the conditions described above. The crude product was purified by column chromatography on silica using EtOAc:hexane (3:7) as mobile phase. Yield 250 mg (41%); Analytical HPLC: purity 99.3% (System A); HRESIMS (ESI^+) calcd for $C_{22}H_{30}N_4O_4S$: 446.1988, found 446.1987.

EXAMPLE 2

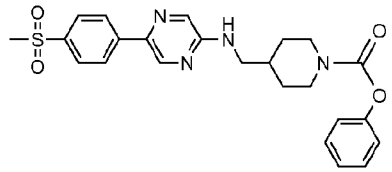
Isobutyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate



To a stirred solution of 5-[4-(methylsulfonyl)phenyl]-*N*-(piperidin-4-ylmethyl)pyrazin-2-amine (90 mg, 0.26 mmol; Intermediate 2) in dry DCM (5 mL) at room temperature was added isobutyl chloroformate (0.036 mL, 0.28 mmol). After 2 minutes, Et_3N (0.07 mL, 0.52 mmol) was added and the mixture was stirred for an additional 15 minutes at room temperature. The reaction mixture was concentrated under reduced pressure and the remaining residue was purified by preparative TLC on silica using EtOAc:hexane (9:1) as mobile phase. Yield 32 mg (27%); Analytical HPLC: purity 99.4% (System A); HRESIMS (ESI^+) calcd for $C_{22}H_{30}N_4O_4S$: 446.1988, found 446.2007.

EXAMPLE 3

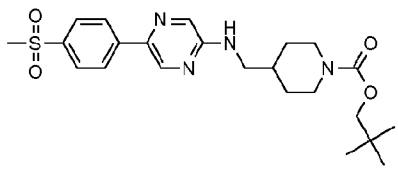
Phenyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate



The title compound was prepared from 5-[4-(methylsulfonyl)phenyl]-*N*-(piperidin-4-ylmethyl)pyrazin-2-amine (90 mg, 0.26 mmol; Intermediate 2) and phenyl chloroformate (0.036 mL, 0.28 mmol) in accordance with the procedure described for Example 2. The reaction mixture was concentrated under reduced pressure and the remaining residue was purified by preparative TLC on silica using EtOAc:acetone (8:2) as mobile phase. Yield 32 mg (26%); Analytical HPLC: purity 95.1% (System A); HRESIMS (ESI^+) calcd for $C_{24}H_{26}N_4O_4S$: 466.1675, found 466.1692.

EXAMPLE 4

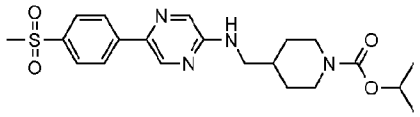
2,2-Dimethylpropyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]-piperidine-1-carboxylate



The title compound was prepared from 5-[4-(methylsulfonyl)phenyl]-*N*-(piperidin-4-ylmethyl)pyrazin-2-amine (90 mg, 0.26 mmol; Intermediate 2) and neopentyl chloroformate (0.04 mL, 0.28 mmol) in accordance with the procedure described for Example 2. The reaction mixture was concentrated under reduced pressure and the remaining residue was purified by preparative TLC on silica using EtOAc as mobile phase. Yield 32 mg (27%); Analytical HPLC: purity 99.4% (System A); HRESIMS (ESI^+) calcd for $C_{23}H_{32}N_4O_4S$: 460.2144, found 460.2163.

EXAMPLE 5

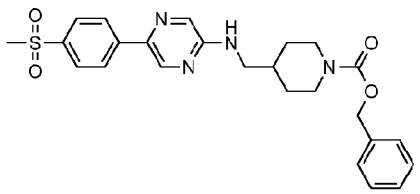
Isopropyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate



The title compound was prepared from 5-[4-(methylsulfonyl)phenyl]-*N*-(piperidin-4-ylmethyl)pyrazin-2-amine (90 mg, 0.26 mmol; Intermediate 2) and isopropyl chloroformate (0.031 mL, 0.28 mmol) in accordance with the procedure described for Example 2. The reaction mixture was concentrated under reduced pressure and the remaining residue was purified by preparative TLC on silica using EtOAc:hexane (9:1) as mobile phase. Yield 30 mg (26%); Analytical HPLC: purity 98.3% (System A); HRESIMS (ESI^+) calcd for $C_{21}H_{28}N_4O_4S$: 432.1831, found 432.1842.

EXAMPLE 6

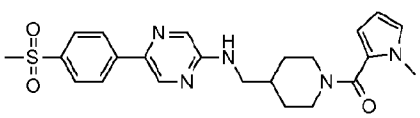
Benzyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate



The title compound was prepared from 5-[4-(methylsulfonyl)phenyl]-*N*-(piperidin-4-ylmethyl)pyrazin-2-amine (90 mg, 0.26 mmol; Intermediate 2) and benzyl chloroformate (50% solution in toluene; 0.094 mL, 0.28 mmol) in accordance with the procedure described for Example 2. The reaction mixture was concentrated under reduced pressure and the remaining residue was purified by preparative TLC on silica using EtOAc as mobile phase. Yield 30 mg (24%); Analytical HPLC: purity 99.3% (System A); HRESIMS (ESI^+) calcd for $C_{25}H_{28}N_4O_4S$: 480.1831, found 480.1845.

EXAMPLE 7

N-({1-[(1-Methyl-1H-pyrrol-2-yl)carbonyl]piperidin-4-yl}methyl)-5-[4-(methylsulfonyl)phenyl]pyrazin-2-amine

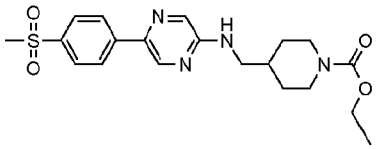


The title compound was prepared from 5-[4-(methylsulfonyl)phenyl]-*N*-(piperidin-4-ylmethyl)pyrazin-2-amine (90 mg, 0.26 mmol; Intermediate 2) and 1-methyl-1*H*-pyrrole-2-

carbonyl chloride (0.04 mL, 0.28 mmol) in accordance with the procedure described for Example 2. The reaction mixture was concentrated under reduced pressure and the remaining residue was purified by preparative TLC on silica using EtOAc:acetone (8:2) as mobile phase. Yield 33 mg (28%); Analytical HPLC: purity 99.2% (System A); HRESIMS (ESI$^+$) calcd for $C_{23}H_{27}N_5O_3S$: 453.1835, found 453.1844.

EXAMPLE 8

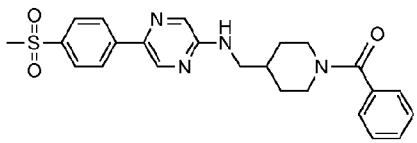
Ethyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate



The title compound was prepared from 5-[4-(methylsulfonyl)phenyl]-*N*-(piperidin-4-ylmethyl)pyrazin-2-amine (90 mg, 0.26 mmol; Intermediate 2) and ethyl chloroformate (0.026 mL, 0.28 mmol) in accordance with the procedure described for Example 2. The crude product was purified by preparative TLC using EtOAc as a mobile phase. Yield 35mg (32%); Analytical HPLC: purity 98.3% (System A); HRESIMS (ESI$^+$) calcd for $C_{20}H_{26}N_4O_4S$: 418.1675, found 418.1686.

EXAMPLE 9

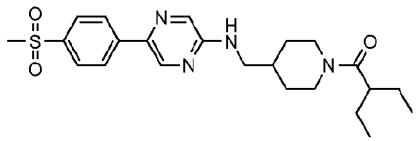
N-[(1-Benzoylpiperidin-4-yl)methyl]-5-[4-(methylsulfonyl)phenyl]pyrazin-2-amine



The title compound was prepared from 5-[4-(methylsulfonyl)phenyl]-*N*-(piperidin-4-yl methyl)pyrazin-2-amine (90 mg, 0.26 mmol; Intermediate 2) and benzoyl chloride (0.032 mL, 0.28 mmol) in accordance with the procedure described Example 2. The reaction mixture was concentrated under reduced pressure and the remaining residue was purified by preparative TLC on silica using EtOAc:acetone (8:2) as mobile phase. Yield 22 mg (19%); Analytical HPLC: purity 98.2% (System A); HRESIMS (ESI$^+$) calcd for $C_{24}H_{26}N_4O_3S$: 450.1726, found 450.1741.

EXAMPLE 10

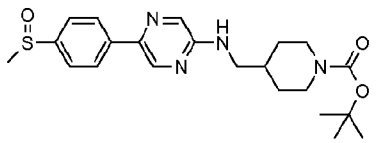
N-{[1-(2-Ethylbutanoyl)piperidin-4-yl]methyl}-5-[4-(methylsulfonyl)phenyl]pyrazin-2-amine



The title compound was prepared from 5-[4-(methylsulfonyl)phenyl]-*N*-(piperidin-4-ylmethyl)pyrazin-2-amine (90 mg, 0.26 mmol; Intermediate 2) and 2-ethylbutanoyl chloride (0.038 mL, 0.28 mmol) in accordance with the procedure described for Example 2. The crude product was purified by preparative TLC using EtOAc as a mobile phase. Yield 32 mg (27%); Analytical HPLC: purity 98.8% (System A); HRESIMS (ESI^+) calcd for $C_{23}H_{32}N_4O_3S$: 444.2195, found 444.2204.

EXAMPLE 11

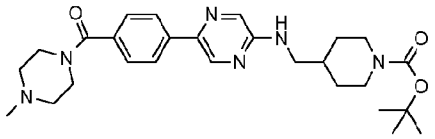
***tert*-Butyl 4-[({5-[4-(methylsulfinyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate**



The title compound was prepared from *tert*-butyl 4-{[(5-bromopyrazin-2-yl)amino]methyl}piperidine-1-carboxylate (100 mg, 0.26 mmol; Intermediate 1) and 4-methylsulfinylphenyl boronic acid (55.0 mg, 0.29 mmol) in accordance with the procedure described for Example 1. The reaction was monitored by TLC using DCM:MeOH (9.5:0.5) as a mobile phase. The crude product was purified by preparative TLC on silica using DCM:MeOH (9.5:0.5) as eluent to give the title compound. Yield 42 mg (36%); Analytical HPLC: purity 98.1% (System D); HRESIMS (ESI^+) calcd for $C_{22}H_{30}N_4O_3S$: 430.2039, found 430.2051.

EXAMPLE 12

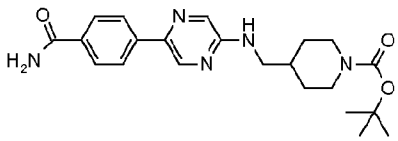
***tert*-Butyl 4-{[(5-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrazin-2-yl)amino]-methyl}piperidine-1-carboxylate**



The title compound was prepared from *tert*-butyl 4-{[(5-bromopyrazin-2-yl)amino]methyl}piperidine-1-carboxylate (100 mg, 0.26 mmol; Intermediate 1) and {4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}boronic acid (83.9 mg, 0.29 mmol) in accordance with the procedure described Example 1. The reaction was monitored by TLC using DCM:MeOH (9.5:0.5) as a mobile phase. The crude product was purified by preparative TLC on silica using DCM:MeOH (9.5:0.5) as eluent to give the title compound. Yield 24 mg (18%); Analytical HPLC: purity 99.1% (System D); HRESIMS (ESI^+) calcd for $C_{27}H_{38}N_6O_3$: 494.3005, found 494.3004.

EXAMPLE 13

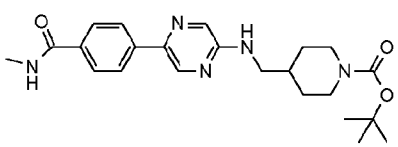
tert-Butyl 4-[({5-[4-(aminocarbonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate



The title compound was prepared from *tert*-butyl 4-{[(5-bromopyrazin-2-yl)amino]methyl}piperidine-1-carboxylate (100 mg, 0.26 mmol; Intermediate 1) and [4-(aminocarbonyl)phenyl]boronic acid (47.8 mg, 0.29 mmol) in accordance with the procedure described for Example 1. The reaction was monitored by TLC using DCM:MeOH (9.5:0.5) as a mobile phase. The crude product was purified by preparative TLC on silica using DCM:MeOH (9.5:0.5) as eluent to give the title compound. Yield 42 mg (37%); Analytical HPLC: purity 99.7% (System D); HRESIMS (ESI^+) calcd for $C_{22}H_{29}N_5O_3$: 411.2270, found 411.2268.

EXAMPLE 14

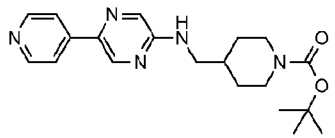
tert-Butyl 4-{[(5-{4-[(methylamino)carbonyl]phenyl}pyrazin-2-yl)amino]methyl}-piperidine-1-carboxylate



The title compound was prepared from *tert*-butyl 4-{[(5-bromopyrazin-2-yl)amino]-methyl}piperidine-1-carboxylate (100 mg, 0.26 mmol; Intermediate 1) and {4-[(methyl-amino)carbonyl]phenyl}boronic acid (51.8 mg, 0.29 mmol) in accordance with the procedure described for Example 1. The reaction was monitored by TLC using DCM:MeOH (9.5:0.5) as a mobile phase. The crude product was purified by preparative TLC on silica using DCM:MeOH (9.5:0.5) as eluent to give the title compound. Yield 50 mg (43%); Analytical HPLC: purity 99.1% (System D); HRESIMS (ESI^+) calcd for $C_{23}H_{31}N_5O_3$: 425.2427, found 425.2422.

EXAMPLE 15

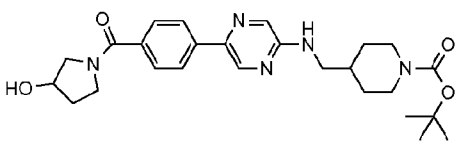
tert-Butyl 4-{[(5-pyridin-4-ylpyrazin-2-yl)amino]methyl}piperidine-1-carboxylate



The title compound was prepared from *tert*-butyl 4-{[(5-bromopyrazin-2-yl)amino]-methyl}piperidine-1-carboxylate (100 mg, 0.26 mmol; Intermediate 1) and 4-pyridyl-boronic acid (35.6 mg, 0.29 mmol) in accordance with the procedure described for Example 1. The reaction was monitored by TLC using DCM:MeOH (9.5:0.5) as a mobile phase. The crude product was purified by preparative TLC on silica using DCM:MeOH (9.5:0.5) as eluent to give the title compound. Yield 27 mg (27%); Analytical HPLC: purity 98.3% (System D); HRESIMS (ESI^+) calcd for $C_{20}H_{27}N_5O_2$: 369.2165, found 369.2178.

EXAMPLE 16

tert-Butyl 4-{[(5-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]phenyl}pyrazin-2-yl)amino]-methyl}piperidine-1-carboxylate

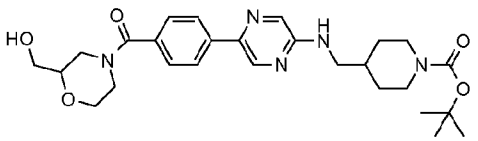


4-[5-({[1-(*tert*-Butoxycarbonyl)piperidin-4-yl]methyl}amino)pyrazin-2-yl]benzoic acid (100 mg, 0.24 mmol; Intermediate 3) and pyrrolidin-3-ol (0.02 mL, 0.26 mmol) were added to dry DMF (5.0 mL). The reaction mixture was stirred at room temperature for 2 minutes and then chilled to 0 °C. HBTU (137 mg, 0.36 mmol) was added and the resulting

reaction mixture was stirred for 2 hours at 0 °C. The mixture was concentrated under reduced pressure. The crude residue was purified by preparative TLC using DCM:MeOH (9.5:0.5) as mobile phase to give the title compound. Yield 32 mg (26%); Analytical HPLC: purity 98.7% (System D); HRESIMS (ESI^+) calcd for $C_{26}H_{35}N_5O_4$: 481.2689, found 481.2680.

EXAMPLE 17

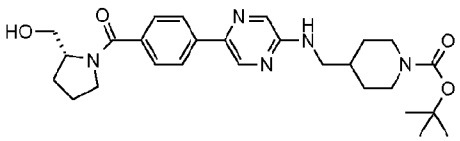
***tert*-Butyl 4-({[5-(4-{[2-(hydroxymethyl)morpholin-4-yl]carbonyl}phenyl)pyrazin-2-yl]amino}methyl)piperidine-1-carboxylate**



The title compound was prepared from 4-[5-({[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-methyl}amino)pyrazin-2-yl]benzoic acid (100 mg, 0.24 mmol; Intermediate 3) and morpholin-2-ylmethanol (0.03 mL, 0.26 mmol) in accordance with the procedure described for Example 16. The crude product was purified by preparative TLC on silica using DCM:MeOH (9.5:0.5) as eluent to give the title compound. Yield 29 mg (23%); Analytical HPLC: purity 94.0% (System D); HRESIMS (ESI^+) calcd for $C_{27}H_{37}N_5O_5$: 511.2795, found 511.2793.

EXAMPLE 18

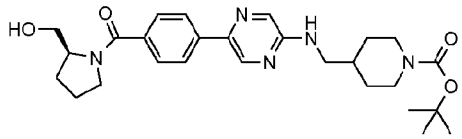
***tert*-Butyl 4-({[5-(4-{[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-pyrazin-2-yl]amino}methyl)piperidine-1-carboxylate**



The title compound was prepared from 4-[5-({[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-methyl}amino)pyrazin-2-yl]benzoic acid (100 mg, 0.24 mmol; Intermediate 3) and (2*R*)-pyrrolidin-2-ylmethanol (0.026 mL, 0.26 mmol) in accordance with the procedure described for Example 16. The crude product was purified by preparative TLC on silica using DCM:MeOH (9.5:0.5) as eluent to give the title compound. Yield 21 mg (17%); Analytical HPLC: purity 95.4% (System D); HRESIMS (ESI^+) calcd for $C_{27}H_{37}N_5O_4$: 495.2846, found 495.2851.

EXAMPLE 19

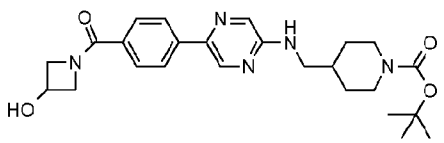
***tert*-Butyl 4-({[5-(4-{[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-pyrazin-2-yl]amino}methyl)piperidine-1-carboxylate**



The title compound was prepared from 4-[5-({[1-(*tert*-butoxycarbonyl)piperidin-4-yl]methyl}amino)pyrazin-2-yl]benzoic acid (100 mg, 0.24 mmol; Intermediate 3) and (2*S*)-pyrrolidin-2-ylmethanol (0.026 mL, 0.26 mmol) in accordance with the procedure described for Example 16. The crude product was purified by preparative TLC on silica using DCM:MeOH (9.5:0.5) as eluent to give the title compound. Yield 24 mg (20%); Analytical HPLC: purity 85.2% (System D); HRESIMS (ESI^+) calcd for $C_{27}H_{37}N_5O_4$: 495.2846, found 495.2846.

EXAMPLE 20

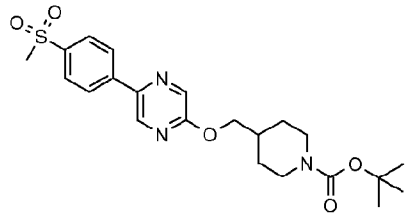
***tert*-Butyl 4-{[(5-{4-[(3-hydroxyazetidin-1-yl)carbonyl]phenyl}pyrazin-2-yl)amino]-methyl}piperidine-1-carboxylate**



The title compound was prepared from 4-[5-({[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-methyl}amino)pyrazin-2-yl]benzoic acid (100 mg, 0.24 mmol; Intermediate 3) and azetidin-3-ol (19 mg, 0.26 mmol) in accordance with the procedure described for Example 16. The crude product was purified by preparative TLC on silica using DCM:MeOH (9.5:0.5) as eluent to give the title compound. Yield 24 mg (19%); Analytical HPLC: purity 94.7% (System D); HRESIMS (ESI^+) calcd for $C_{25}H_{33}N_5O_4$: 467.2532, found 467.2531.

EXAMPLE 21

***tert*-Butyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate**

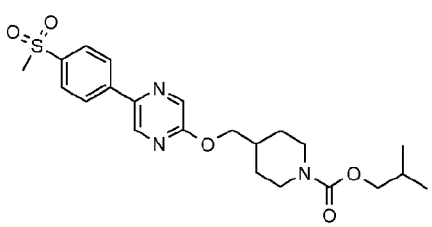


To a stirred mixture of *tert*-butyl 4-{[(5-bromopyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate (5 g, 0.0134 mol; Intermediate 4) in toluene (75 mL) at r.t. were added 4-(methylsulfonyl)phenylboronic acid (2.90 g, 0.0147 mol) and isopropyl alcohol (75 mL). After 2 minutes, a 2M K_2CO_3 solution (33.5 mL, 0.020 mol) was added dropwise to the stirred suspension. After additional 5 minutes, $Pd(PPh_3)_4$ (0.776 g, 0.6 mmol) was added and the reaction mixture was heated to reflux. The reaction was monitored by TLC using hexane:EtOAc (1:1) as mobile phase. The mixture was stirred at reflux for 6 hours and then allowed to cool. The cooled mixture was poured into water (500 mL) under stirring and then left at r.t. over night. The aqueous mixture was extracted with EtOAc (4 x 500 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product. Yield 12 g. Mass m/z = (ESI^+) 448 $(M+H)^+$. The crude product was used in the preparation of 2-[4-(methylsulfonyl)-phenyl]-5-(piperidin-4-ylmethoxy)pyrazine (Intermediate 5) without further purification.

A second batch of *tert*-butyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]-piperidine-1-carboxylate was prepared using the conditions described above. The crude product was purified by column chromatography on silica using EtOAc:hexane (4:6) as mobile phase. Yield 200 mg (33%). Analytical HPLC: purity 99.7% (System B); HRESIMS (ESI^+) calcd for $C_{22}H_{29}N_3O_5S$ 447.1828, found 447.1822.

EXAMPLE 22

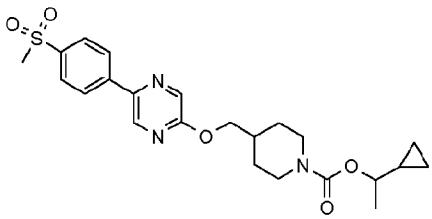
Isobutyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate



To a stirred solution of 2-[4-(methylsulfonyl)phenyl]-5-(piperidin-4-ylmethoxy)pyrazine (200 mg, 0.57 mmol; Intermediate 5) in dry DCM (10 mL) at r.t. was added isobutyl chloroformate (0.08 mL, 0.63 mmol). After 2 minutes, Et_3N (0.16 mL, 1.1 mmol) was added and the reaction mixture was stirred for 15 minutes at r.t. The reaction mixture was concentrated under reduced pressure and the crude product was purified by preparative TLC using EtOAc as mobile phase. Yield 65 mg (25%). Analytical HPLC: purity 98.1% (System A); HRESIMS (ESI^+) calcd for $C_{22}H_{29}N_3O_5S$: 447.1828, found 447.1838.

EXAMPLE 23

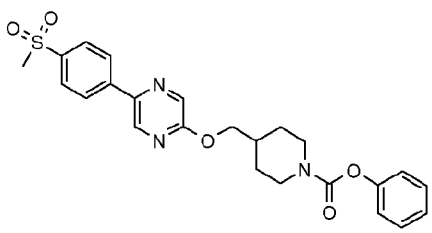
1-Cyclopropylethyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]-piperidine-1-carboxylate



To a stirred solution of 1-cyclopropylethanol (0.2 mL, 2 mmol) in dry DCM (7 mL) at r.t. under nitrogen atmosphere was added dropwise a solution of 1,1'-carbonylbis-1*H*-imidazole (CDI; 0.33 g, 2.0 mmol) in dry DCM (7 mL). The mixture was stirred at r.t. for 1.5 hours. 2-[4-(Methylsulfonyl)phenyl]-5-(piperidin-4-ylmethoxy)pyrazine (0.36 g, 0.93 mmol; Intermediate 5) was added and the mixture was stirred at r.t. overnight. The mixture was concentrated *in vacuo* and the crude product was purified by preparative TLC using EtOAc:hexane (1:1) as mobile phase. Yield 32 mg (8%). Analytical HPLC: purity 90.9% (System B); HRESIMS (ESI^+) calcd for $C_{23}H_{29}N_3O_5S$: 459.1828, found 459.1819.

EXAMPLE 24

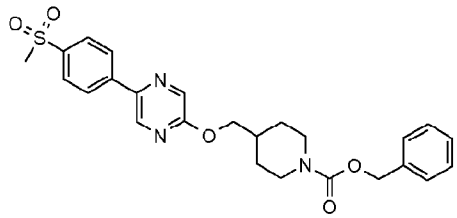
Phenyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate



The title compound was prepared from 2-[4-(methylsulfonyl)phenyl]-5-(piperidin-4-yl-methoxy)pyrazine (200 mg, 0.57 mmol; Intermediate 5) and phenyl chloroformate (0.08 mL, 0.63 mmol) in accordance with the procedure described for Example 22. The crude product was purified by preparative TLC using EtOAc:acetone (8:2) as mobile phase to give the title compound. Yield 70 mg (26%). Analytical HPLC: purity 97.4% (System A); HRESIMS (ESI^+) calcd for $C_{24}H_{25}N_3O_5S$: 467.1515, found 467.1512.

EXAMPLE 25

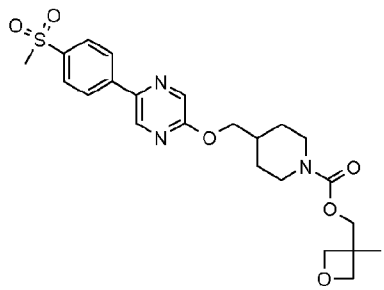
Benzyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate



The title compound was prepared from 2-[4-(methylsulfonyl)phenyl]-5-(piperidin-4-yl-methoxy)pyrazine (200 mg, 0.57 mmol; Intermediate 5) and benzyl chloroformate (50% in toluene; 0.21 mL, 0.63 mmol) in accordance with the procedure described for Example 22. The crude product was purified by preparative TLC using EtOAc as mobile phase to give the title compound. Yield 75 mg (27%). Analytical HPLC: purity 99.7% (System B); HRESIMS (ESI^+) calcd for $C_{25}H_{27}N_3O_5S$: 481.1671, found 481.1668.

EXAMPLE 27

(3-Methyloxetan-3-yl)methyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)-methyl]piperidine-1-carboxylate

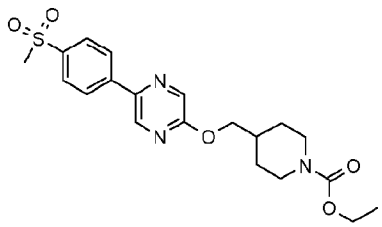


The title compound was prepared from 2-[4-(methylsulfonyl)phenyl]-5-(piperidin-4-yl-methoxy)pyrazine (0.35 g, 0.93 mmol; Intermediate 5) and (3-methyloxetan-3-yl)methanol (0.2 mL, 2.0 mmol) in accordance with the procedure described for Example 23. The crude

product was purified by preparative TLC using EtOAc as mobile phase to give the title compound. Yield 70 mg (14%). Analytical HPLC: purity 99.6% (System B); HRESIMS (ESI^+) calcd for $C_{23}H_{29}N_3O_6S$: 475.1777, found 475.1775.

EXAMPLE 28

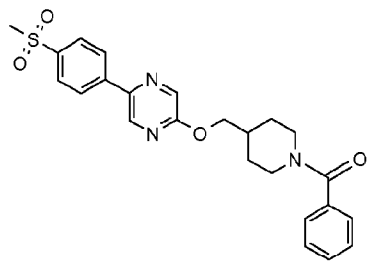
Ethyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate



The title compound was prepared from 2-[4-(methylsulfonyl)phenyl]-5-(piperidin-4-yl-methoxy)pyrazine (200 mg, 0.57 mmol; Intermediate 5) and ethyl chloroformate (0.06 mL, 0.63 mmol) in accordance with the procedure described for Example 22. The crude product was purified by preparative TLC using EtOAc as mobile phase to give the title compound. Yield 65 mg (27%). Analytical HPLC: purity 97.8% (System A); HRESIMS (ESI^+) calcd for $C_{20}H_{25}N_3O_5S$: 419.1515, found 419.1516.

EXAMPLE 29

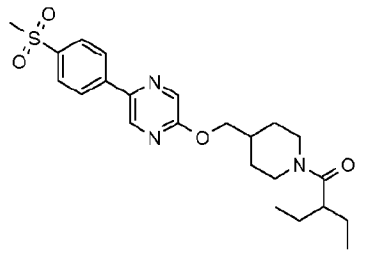
2-[(1-Benzoylpiperidin-4-yl)methoxy]-5-[4-(methylsulfonyl)phenyl]pyrazine



The title compound was prepared from 2-[4-(methylsulfonyl)phenyl]-5-(piperidin-4-yl-methoxy)pyrazine (200 mg, 0.57 mmol; Intermediate 5) and benzoyl chloride (0.07 mL, 0.63 mmol) in accordance with the procedure described for Example 22. The crude product was purified by preparative TLC using EtOAc as mobile phase to give the title compound. Yield 70 mg (27%). Analytical HPLC: purity 98.6% (System A); HRESIMS (ESI^+) calcd for $C_{24}H_{25}N_3O_4S$: 451.1566, found 451.1564.

EXAMPLE 30

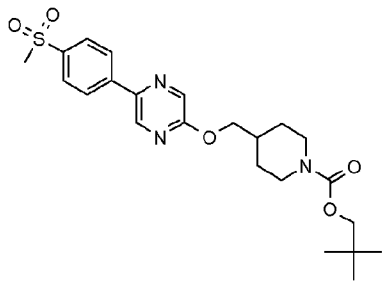
2-{[1-(2-Ethylbutanoyl)piperidin-4-yl]methoxy}-5-[4-(methylsulfonyl)phenyl]pyrazine



The title compound was prepared from 2-[4-(methylsulfonyl)phenyl]-5-(piperidin-4-yl-methoxy)pyrazine (200 mg, 0.57 mmol; Intermediate 5) and 2-ethylbutanoyl chloride (0.08 mL, 0.63 mmol) in accordance with the procedure described for Example 22. The crude product was purified by preparative TLC using EtOAc as mobile phase to give the title compound. Yield 80 mg (31%). Analytical HPLC: purity 98.1% (System A); HRESIMS (ESI^+) calcd for $C_{23}H_{31}N_3O_4S$: 445.2035, found 445.2027.

EXAMPLE 31

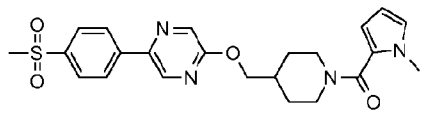
2,2-Dimethylpropyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]-piperidine-1-carboxylate



The title compound was prepared from 2-[4-(methylsulfonyl)phenyl]-5-(piperidin-4-ylmethoxy)pyrazine (200 mg, 0.57 mmol; Intermediate 5) and 2,2-dimethylpropyl chloridocarbonate (0.10 mL, 0.63 mmol) in accordance with the procedure described for Example 22. The crude product was purified by preparative TLC using EtOAc as mobile phase to give the title compound. Yield 70 mg (26%). Analytical HPLC: purity 96.9% (System A); HRESIMS (ESI^+) calcd for $C_{23}H_{31}N_3O_5S$: 461.1984, found 461.1991.

EXAMPLE 32

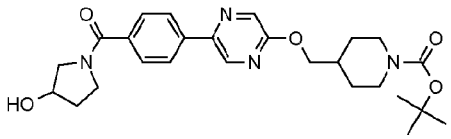
2-({1-[(1-Methyl-1H-pyrrol-2-yl)carbonyl]piperidin-4-yl}methoxy)-5-[4-(methylsulfonyl)phenyl]pyrazine



The title compound was prepared from 2-[4-(methylsulfonyl)phenyl]-5-(piperidin-4-ylmethoxy)pyrazine (200 mg, 0.57 mmol; Intermediate 5) and 1-methyl-1*H*-pyrrole-2-carbonyl chloride (0.09 mL, 0.63 mmol) in accordance with the procedure described for Example 22. The crude product was purified by preparative TLC using EtOAc as mobile phase to give the title compound. Yield 74 mg (28%). Analytical HPLC: purity 98.9% (System B); HRESIMS (ESI^+) calcd for $C_{23}H_{26}N_4O_4S$: 454.1674, found 454.1687.

EXAMPLE 33

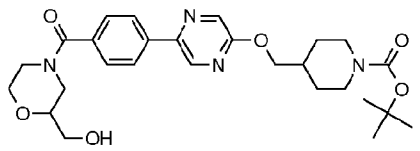
tert-Butyl 4-{[(5-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]phenyl}pyrazin-2-yl)oxy]-methyl}piperidine-1-carboxylate



4-(5-{[1-(*tert*-Butoxycarbonyl)piperidin-4-yl]methoxy}pyrazin-2-yl)benzoic acid (100 mg, 0.24 mmol; Intermediate 6) and pyrrolidin-3-ol (0.02 mL, 0.26 mmol) were added to dry DMF (5.0 mL). The reaction mixture was stirred at room temperature for 2 minutes and then chilled to 0 °C. HBTU (137 mg, 0.36 mmol) was added and the resulting reaction mixture was stirred for 2 hours at 0 °C. The mixture was concentrated under reduced pressure. The crude residue was purified by preparative TLC using EtOAc:acetone (8:2) as mobile phase to give the title compound. Yield 56 mg (48%); Analytical HPLC: purity 99.2% (System B); HRESIMS (ESI^+) calcd for $C_{26}H_{34}N_4O_5$: 482.2529, found 482.2531.

EXAMPLE 34

tert-Butyl 4-({[5-(4-{[2-(hydroxymethyl)morpholin-4-yl]carbonyl}phenyl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate

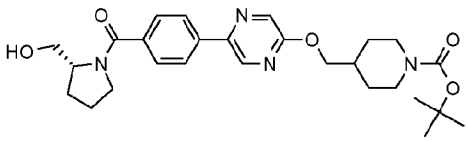


The title compound was prepared from 4-(5-{[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-methoxy}pyrazin-2-yl)benzoic acid (100 mg, 0.24 mmol; Intermediate 6) and morpholin-

2-ylmethanol (0.03 mL, 0.26 mmol) in accordance with the procedure described for Example 33. The crude product was purified by preparative TLC using EtOAc:acetone (8:2) as mobile phase to give the title compound. Yield 70 mg (56%). Analytical HPLC: purity 98.7% (System B); HRESIMS (ESI^+) calcd for $C_{27}H_{36}N_4O_6$: 512.2635, found 512.2636.

EXAMPLE 35

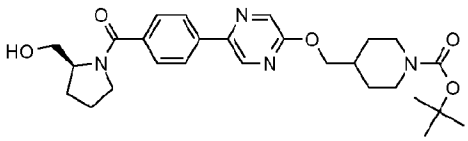
***tert*-Butyl 4-({[5-(4-{[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate**



The title compound was prepared from 4-(5-{[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-methoxy}pyrazin-2-yl)benzoic acid (100 mg, 0.24 mmol; Intermediate 6) and (2*R*)-pyrrolidin-2-ylmethanol (0.026 mL, 0.26 mmol) in accordance with the procedure described for Example 33. The crude product was purified by preparative TLC using EtOAc:acetone (8:2) as mobile phase to give the title compound. Yield 65 mg (54%). Analytical HPLC: purity 97.4% (System B); HRESIMS (ESI^+) calcd for $C_{27}H_{36}N_4O_5$: 496.2686, found 496.2694.

EXAMPLE 36

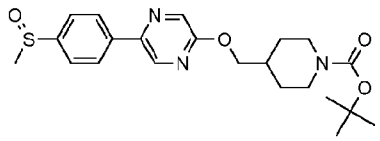
***tert*-Butyl 4-({[5-(4-{[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate**



The title compound was prepared from 4-(5-{[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-methoxy}pyrazin-2-yl)benzoic acid (100 mg, 0.24 mmol; Intermediate 6) and (2*S*)-pyrrolidin-2-ylmethanol (0.026 mL, 0.26 mmol) in accordance with the procedure described for Example 33. The crude product was purified by preparative TLC using EtOAc:acetone (8:2) as mobile phase to give the title compound. Yield 65 mg (54%). Analytical HPLC: purity 97.4% (System B); HRESIMS (ESI^+) calcd for $C_{27}H_{36}N_4O_5$: 496.2686, found 496.2696.

EXAMPLE 37

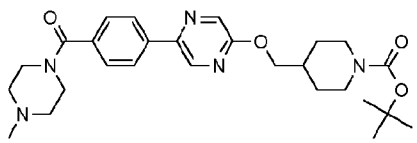
tert-Butyl 4-[({5-[4-(methylsulfinyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate



The title compound was prepared from _tert_-butyl 4-{[(5-bromopyrazin-2-yl)oxy]methyl}-piperidine-1-carboxylate (100 mg, 0.26 mmol; Intermediate 4) and 4-methylsulfinyl-phenylboronic acid (55 mg, 0.29 mmol) in accordance with the procedure described for Example 21. The crude product was purified by preparative TLC using EtOAc:hexane (8:2) as mobile phase to give the title compound. Yield 50 mg (43%). Analytical HPLC: purity 97.6% (System B); HRESIMS (ESI^+) calcd for $C_{22}H_{29}N_3O_4S$: 431.1879, found 431.1884.

EXAMPLE 38

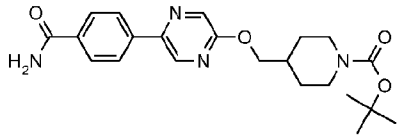
tert-Butyl 4-{[(5-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrazin-2-yl)oxy]-methyl}piperidine-1-carboxylate



The title compound was prepared from _tert_-butyl 4-{[(5-bromopyrazin-2-yl)oxy]methyl}-piperidine-1-carboxylate (100 mg, 0.26 mmol; Intermediate 4) and {4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}boronic acid (83.9 mg, 0.29 mmol) in accordance with the procedure described for Example 21. The crude product was purified by preparative TLC using DCM:MeOH (9.5:0.5) as mobile phase to give the title compound. Yield 60 mg (45%). Analytical HPLC: purity 99.4% (System B); HRESIMS (ESI^+) calcd for $C_{27}H_{37}N_5O_4$: 495.2846, found 495.2850.

EXAMPLE 39

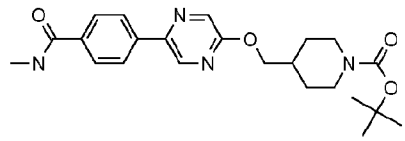
tert-Butyl 4-[({5-[4-(aminocarbonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate



The title compound was prepared from *tert*-butyl 4-{[(5-bromopyrazin-2-yl)oxy]methyl}-piperidine-1-carboxylate (100 mg, 0.26 mmol; Intermediate 4) and [4-(aminocarbonyl)-phenyl]boronic acid (47.8 mg, 0.29 mmol) in accordance with the procedure described for Example 21. The crude product was purified by preparative TLC using DCM:MeOH (9.5:0.5) as mobile phase to give the title compound. Yield 35 mg (31%). Analytical HPLC: purity 98.7% (System A); HRESIMS (ESI^+) calcd for $C_{22}H_{28}N_4O_4$: 412.2111, found 412.2127.

EXAMPLE 40

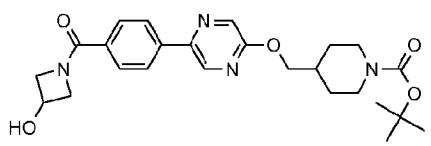
tert-Butyl 4-{[(5-{4-[(methylamino)carbonyl]phenyl}pyrazin-2-yl)oxy]methyl}-piperidine-1-carboxylate



The title compound was prepared from *tert*-butyl 4-{[(5-bromopyrazin-2-yl)oxy]methyl}-piperidine-1-carboxylate (100 mg, 0.26 mmol; Intermediate 4) and {4-[(methylamino)-carbonyl]phenyl}boronic acid (51.8 mg, 0.29 mmol) in accordance with the procedure for Example 21. The crude product was purified by preparative TLC using DCM:MeOH (9.5:0.5) to give the title compound. Yield 50 mg (43%). Analytical HPLC: purity 99.8% (System C); HRESIMS (ESI^+) calcd for $C_{23}H_{30}N_4O_4$: 426.2267, found 426.2269.

EXAMPLE 41

tert-Butyl 4-{[(5-{4-[(3-hydroxyazetidin-1-yl)carbonyl]phenyl}pyrazin-2-yl)oxy]-methyl}piperidine-1-carboxylate

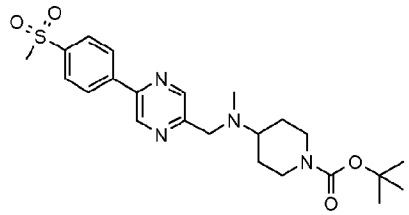


The title compound was prepared from 4-(5-{[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-methoxy}pyrazin-2-yl)benzoic acid (100 mg, 0.26 mmol; Intermediate 6) and azetidin-3-ol (35.6 mg, 0.29 mmol) in accordance with the procedure described for Example 33. The

crude product was purified by preparative TLC using DCM:MeOH (9.5:0.5) as mobile phase to give the title compound. Yield 40 mg (35%). Analytical HPLC: purity 99.5% (System C); HRESIMS (ESI+) calcd for $C_{25}H_{32}N_4O_5$: 468.2373, found 468.2372.

EXAMPLE 42

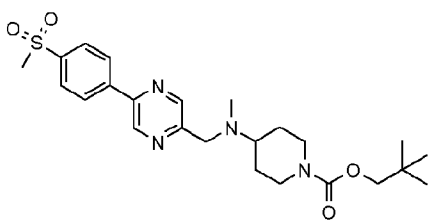
tert-Butyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate



To a stirred solution of dry toluene (60 mL) and isopropyl alcohol (60 mL) at r.t. under nitrogen atmosphere were added _tert_-butyl 4-[[(5-chloropyrazin-2-yl)methyl](methyl)-amino]piperidine-1-carboxylate (6 g, 0.0176 mol; Intermediate 7) and (4-methylsulfonyl-phenyl)boronic acid (4.5 g, 0.0229 mol). After 2 minutes, a solution of K_2CO_3 (12.89 g, 0.0932 mol) was added. After additional 5 minutes, $Pd(PPh_3)_4$ (1 g, 0.0008 mol) was added and the reaction mixture was allowed to stir at 120 °C for 12 hours. The reaction was monitored by TLC using DCM:MeOH (9.5:0.5) as mobile phase. The reaction mixture was concentrated under reduced pressure and to the residual solid was added water (100 mL). The aqueous mixture was extracted with DCM (3 x 60 mL). The combined organic layers were concentrated under reduced pressure to give 7 g of a semi-solid product. The crude product was purified by column chromatography on silica using EtOAc:hexane (7:3) as eluent to give the title compound. Yield 4.5 g (55.6%). Analytical HPLC: purity 99% (System B); HRESIMS (ESI^+) calcd for $C_{23}H_{32}N_4O_4S$: 460.2144, found 460.2144.

EXAMPLE 43

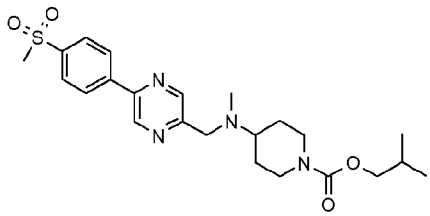
2,2-Dimethylpropyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)-amino]piperidine-1-carboxylate



To a stirred mixture of crude *N*-methyl-*N*-({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}-methyl)piperidin-4-amine, hydrochloride (200 mg, 0.55 mmol; Intermediate 9) in dry DCM (10 mL) at r.t. was added 2,2-dimethylpropyl chloridocarbonate (0.09 mL, 0.66 mmol). After 2 min, Et_3N (0.156 mL, 1.11 mmol) was added and the reaction mixture was stirred at r.t. for 3 h and 15 min. The reaction was monitored by TLC using DCM:MeOH (9:1) as mobile phase. The reaction mixture was concentrated under reduced pressure. The residual crude product was purified by preparative TLC using DCM:MeOH (95:5) as mobile phase to give the title compound. Yield 85 mg (32.3%). Analytical HPLC: purity 97.0% (System E); HRESIMS (ESI^+) calcd for $C_{24}H_{34}N_4O_4S$: 474.2301, found 474.2297.

EXAMPLE 44

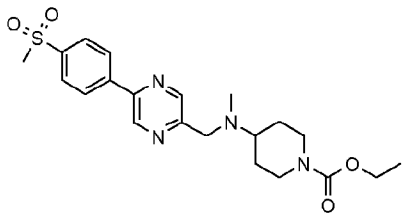
Isobutyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate



The title compound was prepared from crude *N*-methyl-*N*-({5-[4-(methylsulfonyl)phenyl]-pyrazin-2-yl}methyl)piperidin-4-amine, hydrochloride (200 mg, 0.55 mmol; Intermediate 9) and isobutyl chloroformate (0.09 mL, 0.66 mmol) in accordance with the procedure described for Example 43. The crude product was purified by preparative TLC using DCM:MeOH (95:5) to give the title compound. Yield 74 mg (29%). Analytical HPLC: purity 99.9% (System B); HRESIMS (ESI^+) calcd for $C_{23}H_{32}N_4O_4S$: 460.2144, found 460.2143.

EXAMPLE 45

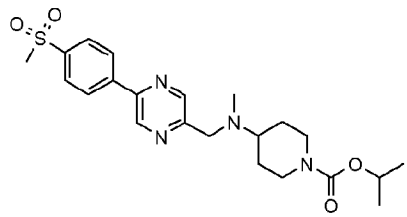
Ethyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]piperidine-1-carboxylate



The title compound was prepared from crude *N*-methyl-*N*-({5-[4-(methylsulfonyl)phenyl]-pyrazin-2-yl}methyl)piperidin-4-amine, hydrochloride (200 mg, 0.55 mmol; Intermediate 9) and ethyl chloroformate (0.06 mL, 0.66 mmol) in accordance with the procedure described for Example 43. The crude product was purified by preparative TLC using DCM:MeOH (95:5) as mobile phase to give the title compound. Yield 78 mg (32.5%). Analytical HPLC: purity 99.6% (System B); HRESIMS (ESI^+) calcd for $C_{21}H_{28}N_4O_4S$: 432.1831, found 432.1832.

EXAMPLE 46

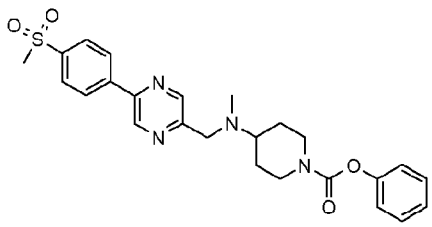
Isopropyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate



The title compound was prepared from crude *N*-methyl-*N*-({5-[4-(methylsulfonyl)phenyl]-pyrazin-2-yl}methyl)piperidin-4-amine, hydrochloride (200 mg, 0.55 mmol; Intermediate 9) and isopropyl chloroformate (0.88 mL, 0.66 mmol) in accordance with the procedure described for Example 43. The crude product was purified by preparative TLC using DCM:MeOH (95:5) as mobile phase to give the title compound. Yield 70 mg (28%). Analytical HPLC: purity 99% (System B); HRESIMS (ESI^+) calcd for $C_{22}H_{30}N_4O_4S$: 446.1988, found 446.1986.

EXAMPLE 47

Phenyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate

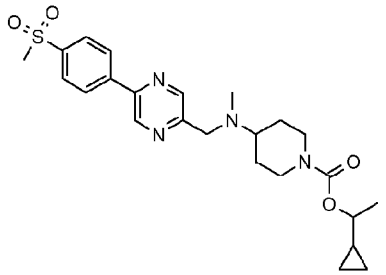


The title compound was prepared from crude *N*-methyl-*N*-({5-[4-(methylsulfonyl)phenyl]-pyrazin-2-yl}methyl)piperidin-4-amine, hydrochloride (180 mg, 0.50 mmol; Intermediate

9) and phenyl chloroformate (0.07 mL, 0.60 mmol) in accordance with the procedure described for Example 43. The crude product was purified by preparative TLC using DCM:MeOH (95:5) as mobile phase to give the title compound. Yield 72 mg (30%). Analytical HPLC: purity 99.2% (System B); HRESIMS (ESI^+) calcd for $C_{25}H_{28}N_4O_4S$: 480.1831, found 480.1851.

EXAMPLE 48

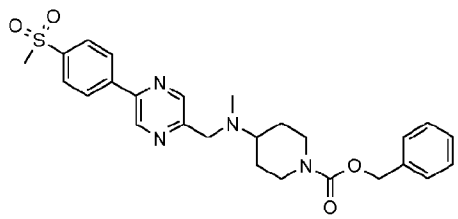
1-Cyclopropylethyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)-amino]piperidine-1-carboxylate



To a stirred solution of 1-cyclopropylethanol (0.1 mL, 1.1 mmol) in dry DCM (7.0 mL) at room temperature under nitrogen atmosphere was added dropwise a solution of 1,1'-carbonylbis-1*H*-imidazole (CDI; 0.17 g, 1.1 mmol) in dry DCM (7.0 mL). The mixture was stirred at room temperature for 1.5 hours. *N*-Methyl-*N*-({5-[4-(methylsulfonyl)-phenyl]pyrazin-2-yl}methyl)piperidin-4-amine, hydrochloride (0.2 g, 0.55 mmol; Intermediate 9) was added and the mixture was stirred at r.t. overnight. The mixture was concentrated under reduced pressure and the crude product was purified by TLC using DCM:MeOH (9.5:0.5) as mobile phase. Yield 84 mg (32.1%). Analytical HPLC: purity 99.8% (System C); HRESIMS (ESI^+) calcd for $C_{24}H_{32}N_4O_4S$: 472.2144, found 472.2143.

EXAMPLE 49

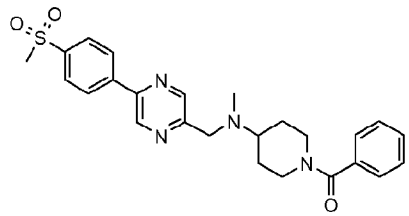
Benzyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate



The title compound was prepared from crude *N*-methyl-*N*-({5-[4-(methylsulfonyl)phenyl]-pyrazin-2-yl}methyl)piperidin-4-amine hydrochloride (150 mg, 0.40 mmol; Intermediate 9) and benzyl chloroformate (0.08 mL, 0.50 mmol) in accordance with the procedure for Example 43. The crude product was purified by preparative TLC using DCM:MeOH (95:5) to give the title compound. Yield 62 mg (30%). Analytical HPLC: purity 99.5% (System E); HRESIMS (ESI^+) calcd for $C_{26}H_{30}N_4O_4S$: 494.1988, found 494.1999.

EXAMPLE 50

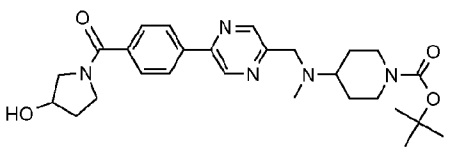
1-Benzoyl-N-methyl-N-({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)piperidin-4-amine



The title compound was prepared from crude *N*-methyl-*N*-({5-[4-(methylsulfonyl)phenyl]-pyrazin-2-yl}methyl)piperidin-4-amine hydrochloride (180 mg, 0.50 mmol; Intermediate 9) and benzoyl chloride (0.07 mL, 0.60 mmol) in accordance with the procedure described for Example 43. The crude product was purified by preparative TLC using DCM:MeOH (95:5) as mobile phase to give the title compound. Yield 55 mg (24%). Analytical HPLC: purity 99.5% (System E); HRESIMS (ESI^+) calcd for $C_{25}H_{28}N_4O_3S$: 464.1882, found 464.1902.

EXAMPLE 51

***tert*-Butyl 4-[[(5-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]phenyl}pyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate**

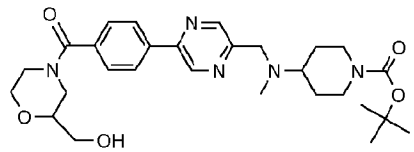


4-(5-{[[1-(*tert*-Butoxycarbonyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-benzoic acid (0.2 g, 0.46 mmol; Intermediate 8) was dissolved in dry DMF (5 mL) at room temperature. The solution was cooled to 0-5 °C and pyrrolidin-3-ol (0.04 mL, 0.51 mmol) followed by HBTU (0.26 g, 0.70 mmol) were added and the reaction mixture was stirred

for 1 hour at this temperature. The cooling bath was removed and the reaction mixture was stirred at r.t. for 12 hours. The reaction was monitored by TLC using DCM:MeOH (9:1) as mobile phase. DMF was removed under reduced pressure and the crude compound isolated was purified by preparative TLC on silica using DCM:MeOH (95:5) as mobile phase. The isolated semi-pure compound was subjected to preparative HPLC purification (System K) to give the pure title compound. Yield 38 mg (16.5%); Analytical HPLC: purity 99.8% (System D); HRESIMS (ESI^+) calcd for $C_{27}H_{37}N_5O_4$: 495.2846, found 495.2867.

EXAMPLE 52

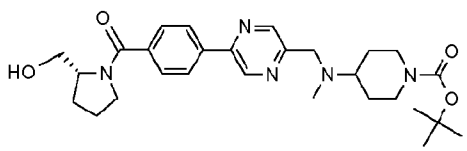
tert-Butyl 4-[{[5-(4-{[2-(hydroxymethyl)morpholin-4-yl]carbonyl}phenyl)pyrazin-2-yl]methyl}(methyl)amino]piperidine-1-carboxylate



The title compound was prepared from 4-(5-{[[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-(methyl)amino]methyl}pyrazin-2-yl)benzoic acid (0.2 g, 0.46 mmol; Intermediate 8) and morpholin-2-ylmethanol (0.06 mL, 0.51 mmol) in accordance with the procedure described for Example 51. The crude product was purified by preparative HPLC (System J). Yield 40 mg (16.7%); Analytical HPLC: purity 96.7% (System D); HRESIMS (ESI^+) calcd for $C_{28}H_{39}N_5O_5$: 525.2951, found 525.2971.

EXAMPLE 53

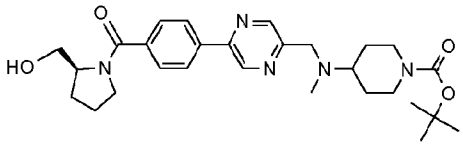
tert-Butyl 4-[{[5-(4-{[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-pyrazin-2-yl]methyl}(methyl)amino]piperidine-1-carboxylate



The title compound was prepared from 4-(5-{[[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-(methyl)amino]methyl}pyrazin-2-yl)benzoic acid (0.2 g, 0.46 mmol; Intermediate 8) and (2*R*)-pyrrolidin-2-ylmethanol (0.05 mL, 0.51 mmol) in accordance with the procedure described for Example 51. The crude product was purified by preparative HPLC (System I). Yield 26 mg (11.3%); Analytical HPLC: purity 95.7% (System D); HRESIMS (ESI^+) calcd for $C_{28}H_{39}N_5O_4$: 509.3002, found 509.3014.

EXAMPLE 54

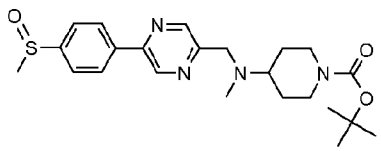
tert-Butyl 4-[{[5-(4-{[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-pyrazin-2-yl]methyl}(methyl)amino]piperidine-1-carboxylate



The title compound was prepared from 4-(5-{[[1-(_tert_-butoxycarbonyl)piperidin-4-yl]-(methyl)amino]methyl}pyrazin-2-yl)benzoic acid (0.2 g, 0.46 mmol; Intermediate 8) and (2_S_)-pyrrolidin-2-ylmethanol (0.05 mL, 0.51 mmol) in accordance with the procedure described for Example 51. The crude product was purified by preparative HPLC (System H). Yield 48 mg (20.8%); Analytical HPLC: purity 98.5% (System D); HRESIMS (ESI^+) calcd for $C_{28}H_{39}N_5O_4$: 509.3002, found 509.3008.

EXAMPLE 55

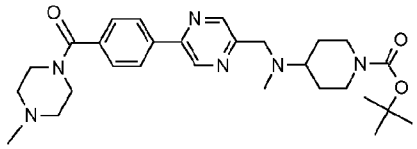
tert-Butyl 4-[methyl({5-[4-(methylsulfinyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate



The title compound was prepared from _tert_-butyl 4-[[(5-chloropyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate (0.2 g, 0.58 mmol; Intermediate 7) and 4-(methylsulfinylpheny)lboronic acid (0.1 g, 0.56 mmol) in accordance with the procedure described for Example 42 to give the title compound. The crude product was purified by preparative TLC using DCM:MeOH (95:5) as mobile phase. Yield 72 mg (27.7%); Analytical HPLC: purity 97.2% (System A); HRESIMS (ESI^+) calcd for $C_{23}H_{32}N_4O_3S$: 444.2195, found 444.2216.

EXAMPLE 56

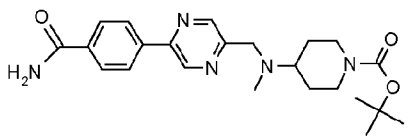
tert-Butyl 4-{methyl[(5-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrazin-2-yl)-methyl]amino}piperidine-1-carboxylate



The title compound was prepared from *tert*-butyl 4-[[(5-chloropyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate (0.2 g, 0.58 mmol; Intermediate 7) and [4-[(4-methyl-1-piperazinyl)carbonyl]phenyl]-boronic acid (0.2 g, 0.70 mmol) in accordance with the procedure described for Example 42 to give the title compound. The crude product was purified by preparative TLC using DCM:MeOH (95:5) as mobile phase. Yield 75 mg (25.9%); Analytical HPLC: purity 99.7% (System B); HRESIMS (ESI^+) calcd for $C_{28}H_{40}N_6O_3$: 508.3162, found 508.3164.

EXAMPLE 57

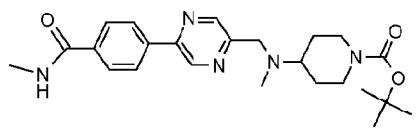
tert-Butyl 4-[({5-[4-(aminocarbonyl)phenyl]pyrazin-2-yl}methyl)(methyl)amino]-piperidine-1-carboxylate



The title compound was prepared from *tert*-butyl 4-[[(5-chloropyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate (0.15 g, 0.44 mmol; Intermediate 7) and 4-aminocarbonylphenylboronic acid (0.087 g, 0.53 mmol) in accordance with the procedure described for Example 42 to give the title compound. The crude product was purified by preparative TLC using DCM:MeOH (95:5) as mobile phase. Yield 32 mg (17.1%); Analytical HPLC: purity 98.2% (System B); HRESIMS (ESI^+) calcd for $C_{23}H_{31}N_5O_3$: 425.2427, found 425.2439.

EXAMPLE 58

tert-Butyl 4-{methyl[(5-{4-[(methylamino)carbonyl]phenyl}pyrazin-2-yl)methyl]-amino}piperidine-1-carboxylate

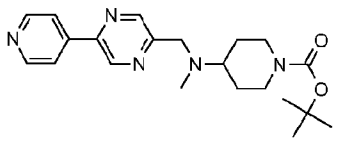


The title compound was prepared from *tert*-butyl 4-[[(5-chloropyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate (0.15 g, 0.44 mmol; Intermediate 7) and 4-(N-

methylaminocarbonyl)phenylboronic acid (0.094 g, 0.53 mmol) in accordance with the procedure described for Example 42 to give the title compound. The crude product was purified by preparative TLC using DCM:MeOH (95:5) as mobile phase. Yield 64 mg (33.2%); Analytical HPLC: purity 98.8% (System B); HRESIMS (ESI^+) calcd for $C_{24}H_{33}N_5O_3$: 439.2583, found 439.2604.

EXAMPLE 59

***tert*-Butyl 4-{methyl[(5-pyridin-4-ylpyrazin-2-yl)methyl]amino}piperidine-1-carboxylate**

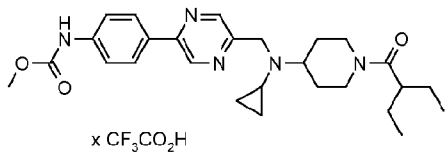


The title compound was prepared from *tert*-butyl 4-[[(5-chloropyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate (0.20 g, 0.58 mmol; Intermediate 7) and pyridine-4-boronic acid (0.086 g, 0.70 mmol) in accordance with the procedure described for Example 42 to give the title compound. The crude product was purified by preparative TLC using DCM:MeOH (95:5). Yield 50 mg (22.2%); Analytical HPLC: purity 98.2% (System B); HRESIMS (ESI^+) calcd for $C_{21}H_{29}N_5O_2$: 383.2321, found 383.2333.

EXAMPLE 60

GENERAL PROCEDURE G2 FOR SUZUKI-TYPE CROSS-COUPLING REACTIONS.

Methyl {4-[5-({cyclopropyl[1-(2-ethylbutanoyl)piperidin-4-yl]amino}methyl)pyrazin-2-yl]phenyl}carbamate, trifluoroacetate

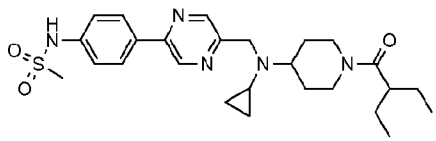


N-[(5-Chloropyrazin-2-yl)methyl]-*N*-cyclopropyl-1-(2-ethylbutanoyl)piperidin-4-amine (0.06 mmol; Intermediate 21) was dissolved in dioxane (0.48 mL) in a test tube. 4-(Methoxycarbonylamino)phenylboronic acid (0.072 mmol), aqueous K_2CO_3 (0.12 mL, 1.25 M, 0.15 mmol) and $Pd(PPh_3)_4$ (3 mg, 0.003 mmol, 0.05 equiv.) were added to the tube. The mixture was stirred at 80-85 °C overnight. The mixture was then concentrated under reduced pressure and the residue mixed with 10% aqueous Na_2CO_3 (0.8 mL) and EtOAc (7 mL). The organic phase was separated and concentrated *in vacuo*. The crude

product was purified by preparative HPLC (System M followed by System L) to give the title compound as the TFA-salt. Yield 5.1 mg (18%). Analytical HPLC: purity 99% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{27}H_{37}N_5O_3$: 479.2896, found 479.2919.

EXAMPLE 61

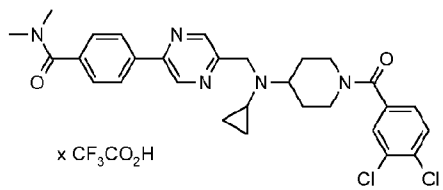
N-{4-[5-({Cyclopropyl[1-(2-ethylbutanoyl)piperidin-4-yl]amino}methyl)pyrazin-2-yl]-phenyl}methanesulfonamide



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-*N*-cyclopropyl-1-(2-ethylbutanoyl)piperidin-4-amine (Intermediate 21) and (4-methylsulfonylamino-phenyl)boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 7.8 mg (26%). Analytical HPLC: purity 95% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{26}H_{37}N_5O_3S$: 499.2617, found 499.2634.

EXAMPLE 62

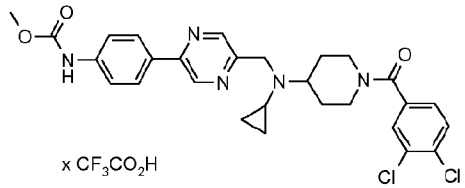
4-[5-({Cyclopropyl[1-(3,4-dichlorobenzoyl)piperidin-4-yl]amino}methyl)pyrazin-2-yl]-*N*,*N*-dimethylbenzamide, trifluoroacetate



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-*N*-cyclopropyl-1-(3,4-dichlorobenzoyl)piperidin-4-amine (Intermediate 22) and [4-(*N*,*N*-dimethylamino-carbonyl)phenyl]boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M followed by System L). Yield 4.2 mg (13%). Analytical HPLC: purity 100% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{29}H_{31}Cl_2N_5O_2$: 551.1855, found 551.1855.

EXAMPLE 63

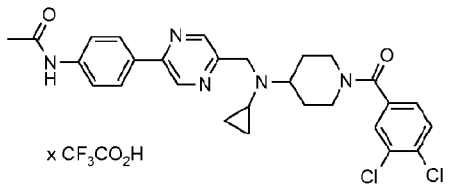
Methyl {4-[5-({cyclopropyl[1-(3,4-dichlorobenzoyl)piperidin-4-yl]amino}methyl)-pyrazin-2-yl]phenyl}carbamate, trifluoroacetate



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-*N*-cyclopropyl-1-(3,4-dichlorobenzoyl)piperidin-4-amine (Intermediate 22) and 4-(methoxycarbonylamino)-phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M followed by System L). Yield 3.6 mg (11%). Analytical HPLC: purity 99% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{28}H_{29}Cl_2N_5O_3$: 553.1647, found 553.1655.

EXAMPLE 64

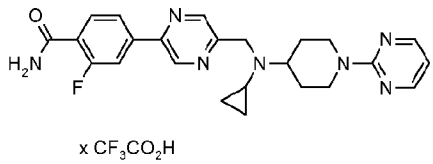
N-{4-[5-({Cyclopropyl[1-(3,4-dichlorobenzoyl)piperidin-4-yl]amino}methyl)pyrazin-2-yl]phenyl}acetamide, trifluoroacetate



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-*N*-cyclopropyl-1-(3,4-dichlorobenzoyl)piperidin-4-amine (Intermediate 22) and 4-acetamidophenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M followed by System L). Yield 4.4 mg (14%). Analytical HPLC: purity 99% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{28}H_{29}Cl_2N_5O_2$: 537.1698, found 537.1704.

EXAMPLE 65

4-(5-{[Cyclopropyl(1-pyrimidin-2-ylpiperidin-4-yl)amino]methyl}pyrazin-2-yl)-2-fluorobenzamide, trifluoroacetate

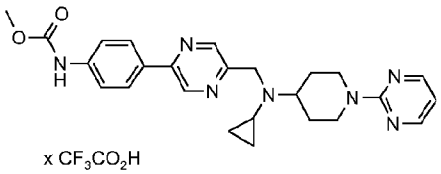


The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-*N*-cyclopropyl-1-pyrimidin-2-ylpiperidin-4-amine (Intermediate 23) and 4-carbamoyl-3-fluorophenyl-

boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M followed by System L). Yield 1.7 mg (6%). Analytical HPLC: purity 99% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{24}H_{26}FN_7O$: 447.2183, found 447.2193.

EXAMPLE 66

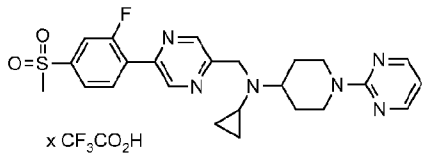
Methyl [4-(5-{[cyclopropyl(1-pyrimidin-2-ylpiperidin-4-yl)amino]methyl}pyrazin-2-yl)phenyl]carbamate, trifluoroacetate



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-*N*-cyclopropyl-1-pyrimidin-2-ylpiperidin-4-amine (Intermediate 23) and 4-(methoxycarbonylamino)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M followed by System L). Yield 2.9 mg (11%). Analytical HPLC: purity 98% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{25}H_{29}N_7O_2$: 459.2383, found 459.2392.

EXAMPLE 67

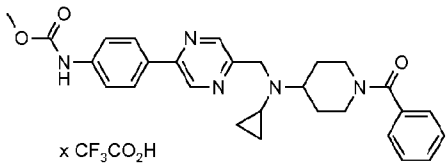
***N*-Cyclopropyl-*N*-({5-[2-fluoro-4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)-1-pyrimidin-2-ylpiperidin-4-amine, trifluoroacetate**



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-*N*-cyclopropyl-1-pyrimidin-2-ylpiperidin-4-amine (Intermediate 23) and 2-fluoro-4-(methylsulfonyl)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M followed by System L). Yield 3.9 mg (13%). Analytical HPLC: purity 99% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{24}H_{27}FN_6O_2S$: 482.1900, found 482.1904.

EXAMPLE 68

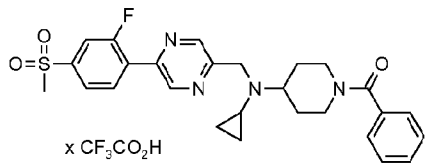
Methyl [4-(5-{[(1-benzoylpiperidin-4-yl)(cyclopropyl)amino]methyl}pyrazin-2-yl)-phenyl]carbamate, trifluoroacetate



The title compound was prepared from 1-benzoyl-*N*-[(5-chloropyrazin-2-yl)methyl]-*N*-cyclopropylpiperidin-4-amine (Intermediate 24) and 4-(methoxycarbonylamino)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M followed by System L). Yield 2.8 mg (10%). Analytical HPLC: purity 100% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{28}H_{31}N_5O_3$: 485.2427, found 485.2445.

EXAMPLE 69

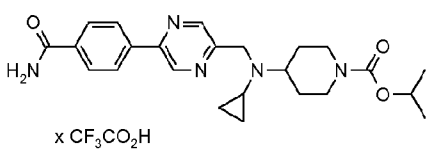
1-Benzoyl-*N*-cyclopropyl-*N*-({5-[2-fluoro-4-(methylsulfonyl)phenyl]pyrazin-2-yl}-methyl)piperidin-4-amine, trifluoroacetate



The title compound was prepared from 1-benzoyl-*N*-[(5-chloropyrazin-2-yl)methyl]-*N*-cyclopropylpiperidin-4-amine (Intermediate 24) and 2-fluoro-4-(methylsulfonyl)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M followed by System L). Yield 5.6 mg (18%). Analytical HPLC: purity 99% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{27}H_{29}FN_4O_3S$: 508.1944, found 508.1959.

EXAMPLE 70

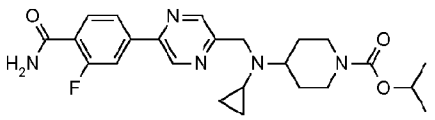
Isopropyl 4-[({5-[4-(aminocarbonyl)phenyl]pyrazin-2-yl}methyl)(cyclopropyl)amino]-piperidine-1-carboxylate, trifluoroacetate



The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl](cyclopropyl)amino]piperidine-1-carboxylate (Intermediate 25) and (4-aminocarbonylphenyl)boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M followed by System L). Yield 1.3 mg (5%). Analytical HPLC: purity 100% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{24}H_{31}N_5O_3$: 437.2427, found 437.2447.

EXAMPLE 71

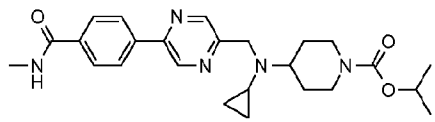
Isopropyl 4-[({5-[4-(aminocarbonyl)-3-fluorophenyl]pyrazin-2-yl}methyl)-(cyclopropyl)amino]piperidine-1-carboxylate



The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl](cyclopropyl)amino]piperidine-1-carboxylate (Intermediate 25) and 4-carbamoyl-3-fluorophenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 5.0 mg (18%). Analytical HPLC: purity 99% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{24}H_{30}FN_5O_3$: 455.2333, found 455.2345.

EXAMPLE 72

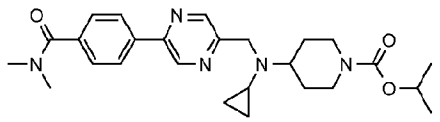
Isopropyl 4-{cyclopropyl[(5-{4-[(methylamino)carbonyl]phenyl}pyrazin-2-yl)methyl]-amino}piperidine-1-carboxylate



The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl](cyclopropyl)amino]piperidine-1-carboxylate (Intermediate 25) and 4-(*N*-methylaminocarbonyl)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 3.1 mg (11%). Analytical HPLC: purity 99% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{25}H_{33}N_5O_3$: 451.2583, found 451.2599.

EXAMPLE 73

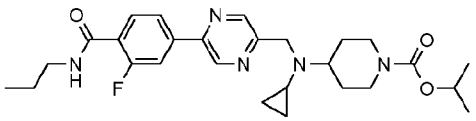
Isopropyl 4-{cyclopropyl[(5-{4-[(dimethylamino)carbonyl]phenyl}pyrazin-2-yl)-methyl]amino}piperidine-1-carboxylate



The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl]-(cyclopropyl)amino]piperidine-1-carboxylate (Intermediate 25) and [4-(*N*,*N*-dimethyl-aminocarbonyl)phenyl]boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 3.5 mg (13%). Analytical HPLC: purity 100% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{26}H_{35}N_5O_3$: 465.2740, found 465.2762.

EXAMPLE 74

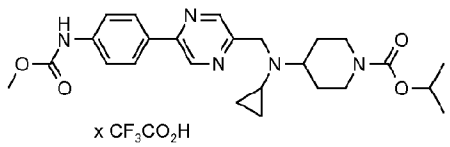
Isopropyl 4-{cyclopropyl[(5-{3-fluoro-4-[(propylamino)carbonyl]phenyl}pyrazin-2-yl)methyl]amino}piperidine-1-carboxylate



The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl]-(cyclopropyl)amino]piperidine-1-carboxylate (Intermediate 25) and 3-fluoro-4-(propyl-carbamoyl)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 1.2 mg (4%). Analytical HPLC: purity 100% (System F and G1'); HRESIMS m/z = (ESI^+) calcd for $C_{27}H_{36}FN_5O_3$: 497.2802, found 497.2826.

EXAMPLE 75

Isopropyl 4-{cyclopropyl[(5-{4-[(methoxycarbonyl)amino]phenyl}pyrazin-2-yl)-methyl]amino}piperidine-1-carboxylate, trifluoroacetate

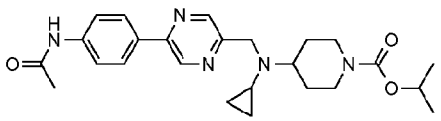


x CF_3CO_2H

The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl]-(cyclopropyl)amino]piperidine-1-carboxylate (Intermediate 25) and 4-(methoxycarbonyl-amino)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M followed by System L). Yield 3.4 mg (12%). Analytical HPLC: purity 100% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{25}H_{33}N_5O_4$: 467.2533, found 467.2541.

EXAMPLE 76

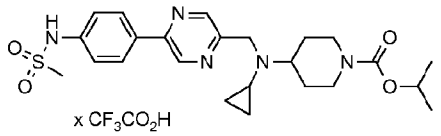
Isopropyl 4-[({5-[4-(acetylamino)phenyl]pyrazin-2-yl}methyl)(cyclopropyl)amino]-piperidine-1-carboxylate



The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl]-(cyclopropyl)amino]piperidine-1-carboxylate (Intermediate 25) and 4-acetamidophenyl-boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 2.9 mg (11%). Analytical HPLC: purity 98% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{25}H_{33}N_5O_3$: 451.2583, found 451.2597.

EXAMPLE 77

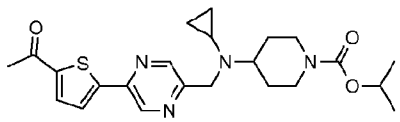
Isopropyl 4-{cyclopropyl[(5-{4-[(methylsulfonyl)amino]phenyl}pyrazin-2-yl)methyl]-amino}piperidine-1-carboxylate, trifluoroacetate



The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl]-(cyclopropyl)amino]piperidine-1-carboxylate (Intermediate 25) and (4-methylsulfonyl-aminophenyl)boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M followed by System L). Yield 9.8 mg (33%). Analytical HPLC: purity 99% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{24}H_{33}N_5O_4S$: 487.2253, found 487.2270.

EXAMPLE 78

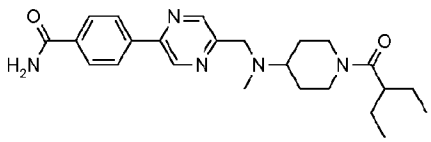
Isopropyl 4-[{[5-(5-acetyl-2-thienyl)pyrazin-2-yl]methyl}(cyclopropyl)amino]-piperidine-1-carboxylate



The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl]-(cyclopropyl)amino]piperidine-1-carboxylate (Intermediate 25) and 5-acetyl-2-thiopheneboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 6.1 mg (23%). Analytical HPLC: purity 100% (System F and G1'); HRESIMS (ESI^+) calcd for $C_{23}H_{30}N_4O_3S$: 442.2039, found 442.2059.

EXAMPLE 79

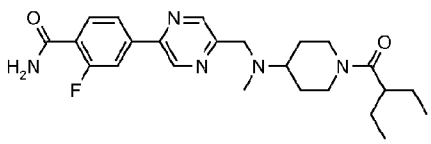
4-(5-{[[1-(2-Ethylbutanoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-benzamide



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-1-(2-ethylbutanoyl)-*N*-methylpiperidin-4-amine (Intermediate 16) and (4-aminocarbonylphenyl)boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 4.0 mg (16%). Analytical HPLC: purity 92% (System F), 96% (System G2'); HRESIMS (ESI^+) calcd for $C_{24}H_{33}N_5O_2$: 423.2634, found 423.2647.

EXAMPLE 80

4-(5-{[[1-(2-Ethylbutanoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-2-fluorobenzamide

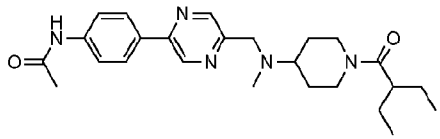


The compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-1-(2-ethylbutanoyl)-*N*-methylpiperidin-4-amine (Intermediate 16) and 4-carbamoyl-3-fluorophenylboronic acid

in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 9.0 mg (34%). Analytical HPLC: purity 100% (System F), 96% (System G2'); HRESIMS (ESI^+) calcd for $C_{24}H_{32}FN_5O_2$: 441.2540, found 441.2552.

EXAMPLE 81

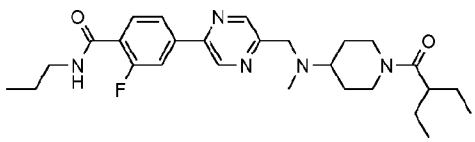
***N*-[4-(5-{[[1-(2-Ethylbutanoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-phenyl]acetamide**



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-1-(2-ethylbutanoyl)-*N*-methylpiperidin-4-amine (Intermediate 16) and 4-acetamidophenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 7.4 mg (28%). Analytical HPLC: purity 97% (System F), 97% (System G2'); HRESIMS (ESI^+) calcd for $C_{25}H_{35}N_5O_2$: 437.2791, found 437.2805.

EXAMPLE 82

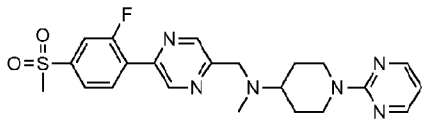
4-(5-{[[1-(2-Ethylbutanoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-2-fluoro-N-propylbenzamide



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-1-(2-ethylbutanoyl)-*N*-methylpiperidin-4-amine (Intermediate 16) and 3-fluoro-4-(propylcarbamoyl)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 8.3 mg (29%). Analytical HPLC: purity 100% (System F), 98% (System G2'); HRESIMS (ESI^+) calcd for $C_{27}H_{38}FN_5O_2$: 483.3010, found 483.3024.

EXAMPLE 83

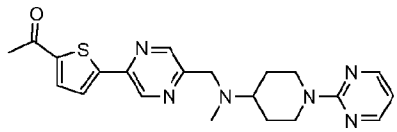
***N*-({5-[2-Fluoro-4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)-*N*-methyl-1-pyrimidin-2-ylpiperidin-4-amine**



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-*N*-methyl-1-pyrimidin-2-ylpiperidin-4-amine (Intermediate 18) and 2-fluoro-4-(methylsulfonyl)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 4.5 mg (16%). Analytical HPLC: purity 94% (System F) 94% (System G2'); HRESIMS (ESI^+) calcd for $C_{22}H_{25}FN_6O_2S$: 456.1744, found 456.1758.

EXAMPLE 84

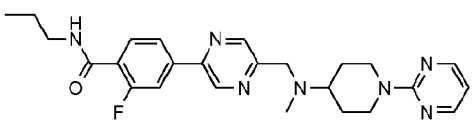
1-[5-(5-{[Methyl(1-pyrimidin-2-ylpiperidin-4-yl)amino]methyl}pyrazin-2-yl)-2-thienyl]ethanone



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-*N*-methyl-1-pyrimidin-2-ylpiperidin-4-amine (Intermediate 18) and 5-acetyl-2-thiophene-boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 5.9 mg (24%). Analytical HPLC: purity 95% (System F) 99% (System G2'); HRESIMS (ESI^+) calcd for $C_{21}H_{24}N_6OS$: 408.1732, found 408.1739.

EXAMPLE 85

2-Fluoro-4-(5-{[methyl(1-pyrimidin-2-ylpiperidin-4-yl)amino]methyl}pyrazin-2-yl)-*N*-propylbenzamide

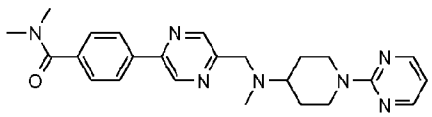


The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-*N*-methyl-1-pyrimidin-2-ylpiperidin-4-amine (Intermediate 18) and 3-fluoro-4-(propylcarbamoyl)-phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 6.9 mg (25%). Analytical HPLC: purity 91%

(System F), 90% (System G2'); HRESIMS (ESI^+) calcd for $C_{25}H_{30}FN_7O$: 463.2496, found 463.2517.

EXAMPLE 86

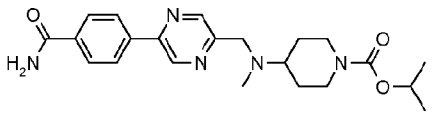
_N_,_N_-Dimethyl-4-(5-{[methyl(1-pyrimidin-2-ylpiperidin-4-yl)amino]methyl}pyrazin-2-yl)benzamide



The title compound was prepared from _N_-[(5-chloropyrazin-2-yl)methyl]-_N_-methyl-1-pyrimidin-2-ylpiperidin-4-amine (Intermediate 18) and [4-(_N_,_N_-dimethylaminocarbonyl)-phenyl]boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 6.2 mg (24%). Analytical HPLC: purity 99% (System F). 96% (System G2'); HRESIMS (ESI^+) calcd for $C_{24}H_{29}N_7O$: 431.2434, found 431.2427.

EXAMPLE 87

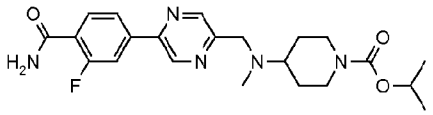
Isopropyl 4-[({5-[4-(aminocarbonyl)phenyl]pyrazin-2-yl}methyl)(methyl)amino]-piperidine-1-carboxylate



The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate (Intermediate 20) and (4-aminocarbonylphenyl)-boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 6.6 mg (27%). Analytical HPLC: purity 98% (System F), 100% System G2'); HRESIMS (ESI^+) calcd for $C_{22}H_{29}N_5O_3$: 411.2270, found 411.2290.

EXAMPLE 88

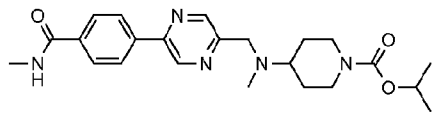
Isopropyl 4-[({5-[4-(aminocarbonyl)-3-fluorophenyl]pyrazin-2-yl}methyl)(methyl)-amino]piperidine-1-carboxylate



The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate (Intermediate 20) and 4-carbamoyl-3-fluoro-phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 6.6 mg (26%). Analytical HPLC: purity 95% (System F), 95% (System G2'); HRESIMS (ESI^+) calcd for $C_{22}H_{28}FN_5O_3$: 429.2176, found 429.2187.

EXAMPLE 89

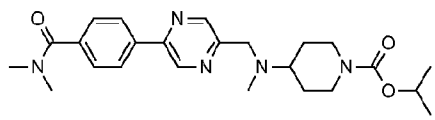
Isopropyl 4-{methyl[(5-{4-[(methylamino)carbonyl]phenyl}pyrazin-2-yl)methyl]-amino}piperidine-1-carboxylate



The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate (Intermediate 20) and 4-(*N*-methylamino-carbonyl)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 7.3 mg (29%). Analytical HPLC: purity 95% (System F), 97% (System G2'); HRESIMS (ESI^+) calcd for $C_{23}H_{31}N_5O_3$: 425.2427, found 425.2432.

EXAMPLE 90

Isopropyl 4-[[(5-{4-[(dimethylamino)carbonyl]phenyl}pyrazin-2-yl)methyl](methyl)-amino]piperidine-1-carboxylate

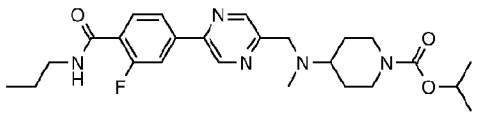


The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate (Intermediate 20) and [4-(*N*,*N*-dimethylamino-carbonyl)phenyl]boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 10.5 mg (40%). Analytical HPLC: purity

93% (System F), 97% (System G2'); HRESIMS (ESI^+) calcd for $C_{24}H_{33}N_5O_3$: 439.2583, found 439.2599.

EXAMPLE 91

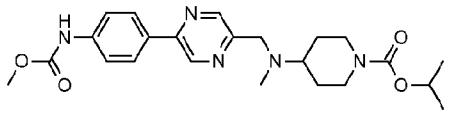
Isopropyl 4-[[(5-{3-fluoro-4-[(propylamino)carbonyl]phenyl}pyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate



The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate (Intermediate 20) and 3-fluoro-4-(propyl-carbamoyl)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 9.6 mg (34%). Analytical HPLC: purity 98% (System F), 95% (System G2'); HRESIMS (ESI^+) calcd for $C_{25}H_{34}FN_5O_3$: 471.2646, found 471.2636.

EXAMPLE 92

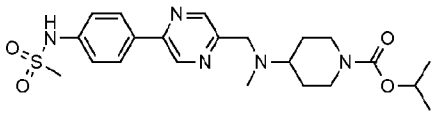
Isopropyl 4-[[(5-{4-[(methoxycarbonyl)amino]phenyl}pyrazin-2-yl)methyl](methyl)-amino]piperidine-1-carboxylate



The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate (Intermediate 20) and 4-(methoxycarbonyl-amino)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 8.8 mg (33%). Analytical HPLC: purity 92% (System F), 100% (System G2'); HRESIMS (ESI^+) calcd for $C_{23}H_{31}N_5O_4$: 441.2376, found 441.2386.

EXAMPLE 93

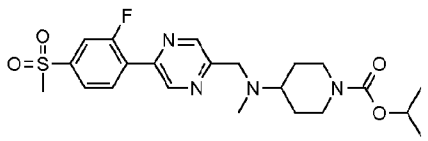
Isopropyl 4-{methyl[(5-{4-[(methylsulfonyl)amino]phenyl}pyrazin-2-yl)methyl]-amino}piperidine-1-carboxylate



The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate (Intermediate 20) and (4-methylsulfonylamino-phenyl)boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 14.9 mg (54%). Analytical HPLC: purity 97% (System F), 98% (System G2'); HRESIMS (ESI^+) calcd for $C_{22}H_{31}N_5O_4S$: 461.2097, found 461.2110.

EXAMPLE 94

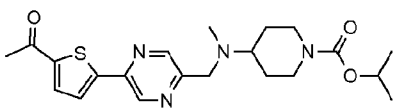
Isopropyl 4-[({5-[2-fluoro-4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)(methyl)-amino]piperidine-1-carboxylate



The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate (Intermediate 20) and 2-fluoro-4-(methyl-sulfonyl)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 4.3 mg (15%). Analytical HPLC: purity 95% (System F), 95% (System G2'); HRESIMS (ESI^+) calcd for $C_{22}H_{29}FN_4O_4S$: 464.1894, found 464.1912.

EXAMPLE 95

Isopropyl 4-[{[5-(5-acetyl-2-thienyl)pyrazin-2-yl]methyl}(methyl)amino]piperidine-1-carboxylate

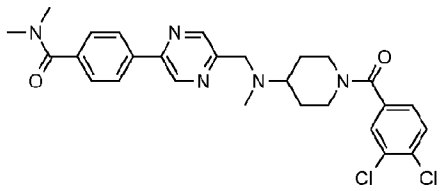


The title compound was prepared from isopropyl 4-[[(5-chloropyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate (Intermediate 20) and 5-acetyl-2-thiophene-boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 4.0 mg (16%). Analytical HPLC: purity 95%

(System F), 95% (System G2'); HRESIMS (ESI^+) calcd for $C_{21}H_{28}N_4O_3S$: 416.1882, found 416.1900.

EXAMPLE 96

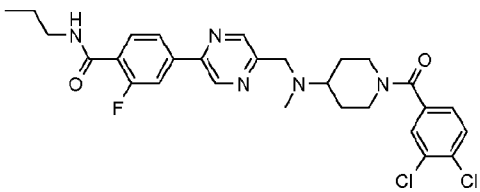
4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-N,N-dimethylbenzamide



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-1-(3,4-dichlorobenzoyl)-N-methylpiperidin-4-amine (Intermediate 17) and [4-(*N*,*N*-dimethylaminocarbonyl)phenyl]boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 8.0 mg (25%). Analytical HPLC: purity 99% (System F), 94% (System G2'); HRESIMS (ESI^+) calcd for $C_{27}H_{29}Cl_2N_5O_2$: 525.1698, found 525.17098.

EXAMPLE 97

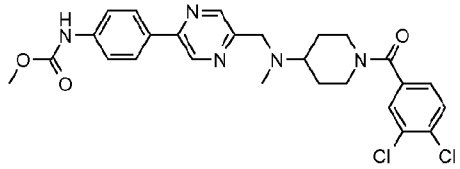
4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-2-fluoro-*N*-propylbenzamide



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-1-(3,4-dichlorobenzoyl)-N-methylpiperidin-4-amine (Intermediate 17) and 3-fluoro-4-(propylcarbamoyl)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 7.7 mg (23%). Analytical HPLC: purity 100% (System F), 93% (System G2'); HRESIMS (ESI^+) calcd for $C_{28}H_{30}Cl_2FN_5O_2$: 557.1761, found 557.1776.

EXAMPLE 98

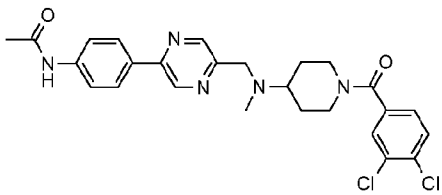
Methyl [4-(5-{[[1-(3,4-dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)phenyl]carbamate



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-1-(3,4-dichlorobenzoyl)-N-methylpiperidin-4-amine (Intermediate 17) and 4-(methoxycarbonylamino)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 3.2 mg (10%). Analytical HPLC: purity 97% (System F), 95% (System G2'); HRESIMS (ESI^+) calcd for $C_{26}H_{27}Cl_2N_5O_3$: 527.1491, found 527.1504.

EXAMPLE 99

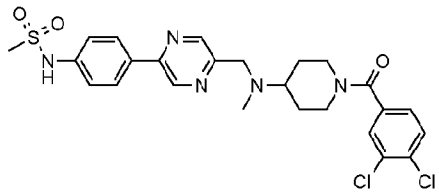
***N*-[4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-phenyl]acetamide**



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-1-(3,4-dichlorobenzoyl)-N-methylpiperidin-4-amine (Intermediate 17) and 4-acetamidophenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 6.6 mg (21%). Analytical HPLC: purity 100% (System F) 93% (System G2'); HRESIMS (ESI^+) calcd for $C_{26}H_{27}Cl_2N_5O_2$: 511.1542, found 511.1549.

EXAMPLE 100

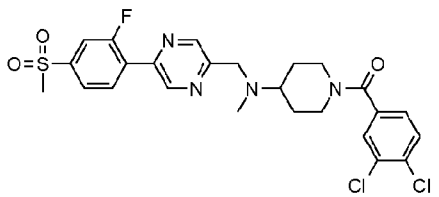
***N*-[4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-phenyl]methanesulfonamide**



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-1-(3,4-dichlorobenzoyl)-N-methylpiperidin-4-amine (Intermediate 17) and (4-methylsulfonyl-aminophenyl)boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 9.0 mg (27%). Analytical HPLC: purity 99% (System F), 96% (System G2'); HRESIMS (ESI^+) calcd for $C_{25}H_{27}Cl_2N_5O_3S$: 547.1212, found 547.1217.

EXAMPLE 101

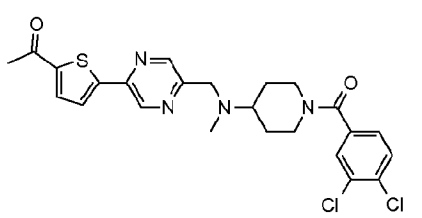
1-(3,4-Dichlorobenzoyl)-*N*-({5-[2-fluoro-4-(methylsulfonyl)phenyl]pyrazin-2-yl}-methyl)-*N*-methylpiperidin-4-amine



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-1-(3,4-dichlorobenzoyl)-N-methylpiperidin-4-amine (Intermediate 17) and 2-fluoro-4-(methyl-sulfonyl)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 9.8 mg (30%). Analytical HPLC: purity 99% (System F), 100% (System G2'); HRESIMS (ESI^+) calcd for $C_{25}H_{25}Cl_2FN_4O_3S$: 550.1008, found 550.1020.

EXAMPLE 102

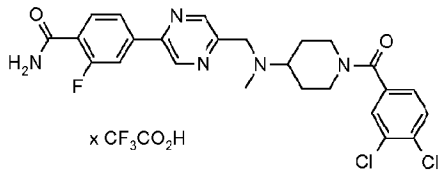
1-[5-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-2-thienyl]ethanone



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-1-(3,4-dichlorobenzoyl)-N-methylpiperidin-4-amine (Intermediate 17) and 5-acetyl-2-thiopheneboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 3.6 mg (12%). Analytical HPLC: purity 95% (System F), 94% (System G2'); HRESIMS (ESI^+) calcd for $C_{24}H_{24}Cl_2N_4O_2S$: 502.0997, found 502.1008.

EXAMPLE 103

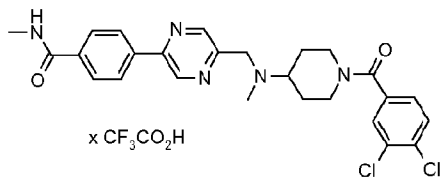
4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-2-fluorobenzamide, trifluoroacetate



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-1-(3,4-dichlorobenzoyl)-N-methylpiperidin-4-amine (Intermediate 17) and 4-carbamoyl-3-fluorophenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System L). Yield 3.5 mg (9%). Analytical HPLC: purity 100% (System F) and 92% (System G2'); HRESIMS (ESI^+) calcd for $C_{25}H_{24}Cl_2FN_5O_2$ 515.1291, found 515.1298.

EXAMPLE 104

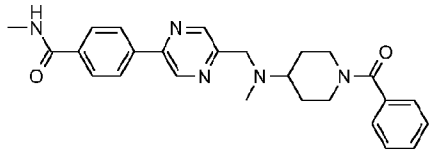
4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-N-methylbenzamide, trifluoroacetate



The title compound was prepared from *N*-[(5-chloropyrazin-2-yl)methyl]-1-(3,4-dichlorobenzoyl)-N-methylpiperidin-4-amine (Intermediate 17) and 4-(*N*-methylaminocarbonyl)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System L). Yield 9.3 mg (25%). Analytical HPLC: purity 96% (System F) and 94% (System G2'); HRESIMS (ESI^+) calcd for $C_{26}H_{27}Cl_2N_5O_2$ 511.1542, found 511.1549.

EXAMPLE 105

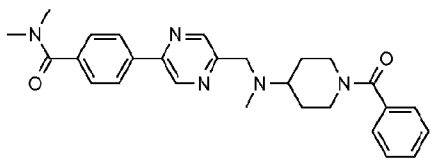
4-(5-{[(1-Benzoylpiperidin-4-yl)(methyl)amino]methyl}pyrazin-2-yl)-*N*-methyl-benzamide



The title compound was prepared from 1-benzoyl-*N*-[(5-chloropyrazin-2-yl)methyl]-*N*-methylpiperidin-4-amine (Intermediate 19) and 4-(*N*-methylaminocarbonyl)phenylboronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 5.0 mg (19%). Analytical HPLC: purity 92% (System F), 94% (System G2'); HRESIMS (ESI^+) calcd for $C_{26}H_{29}N_5O_2$: 443.2321, found 443.2336.

EXAMPLE 106

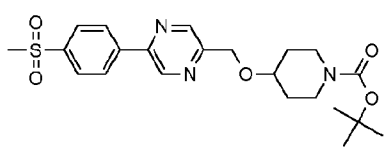
4-(5-{[(1-Benzoylpiperidin-4-yl)(methyl)amino]methyl}pyrazin-2-yl)-*N*,*N*-dimethyl-benzamide



The title compound was prepared from 1-benzoyl-*N*-[(5-chloropyrazin-2-yl)methyl]-*N*-methylpiperidin-4-amine (Intermediate 19) and [4-(*N*,*N*-dimethylaminocarbonyl)phenyl]-boronic acid in accordance with General procedure G2. The residue was purified by preparative HPLC (System M). Yield 6.2 mg (23%). Analytical HPLC: purity 97% (System F), 94% (System G2'); HRESIMS (ESI^+) calcd for $C_{27}H_{31}N_5O_2$: 457.2478, found 457.2500.

EXAMPLE 107

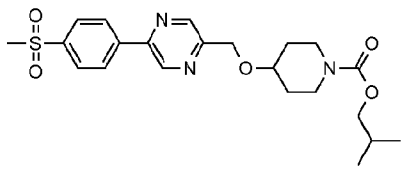
***tert*-Butyl 4-({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methoxy)piperidine-1-carboxylate**



To stirred solution of *tert*-butyl 4-[(5-chloropyrazin-2-yl)methoxy]piperidine-1-carboxylate (2.5 g, 0.0076 mol; Intermediate 26) in dry toluene (30 mL) and dry isopropyl alcohol (30 mL) at r.t. under nitrogen atmosphere was added 4-(methylsulfonyl) phenylboronic acid (1.98 g, 0.0099 mol). After 2 minutes, a 2M solution of aqueous K_2CO_3 (3.2 g, 0.023 mol) was added portionwise to the reaction. After additional 5 minutes, $Pd(PPh_3)_4$ (0.25 g, 0.0002 mol) was added and the reaction mixture was heated to 120 °C and stirred at this temperature for 12 hours. The reaction was monitored by TLC using DCM:MeOH (9.5:0.5) as mobile phase. The mixture was allowed to cool and then concentrated under reduced pressure. The residue was diluted with water (100 mL) and extracted with DCM (3 x 60 mL). The combined organic layers were concentrated under reduced pressure to give 3.5 g of a semi-solid residue. The crude product was purified using column chromatography on silica using EtOAc:hexane (2:8) as eluent to give the title compound. Yield 1.5 g (44%). Analytical HPLC: purity 98% (System A); HRESIMS (ESI^+) calcd for $C_{22}H_{29}N_3O_5S$: 447.1828, found 447.1808.

EXAMPLE 108

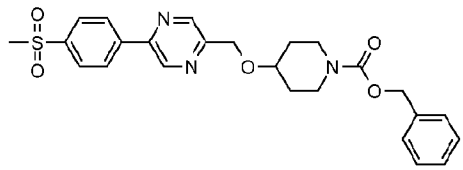
Isobutyl 4-({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methoxy)piperidine-1-carboxylate



To a stirred mixture of crude 2-[4-(methylsulfonyl)phenyl]-5-[(piperidin-4-yloxy)methyl]-pyrazine, hydrochloride (70 mg, 0.20 mmol; Intermediate 27) in dry DCM (5 mL) at r.t. was added isobutyl chloroformate (0.031 mL, 0.24 mmol). After 2 minutes, Et_3N (0.056 mL, 0.46 mmol) was added and the mixture was stirred at r.t. for 3 hours and 15 minutes. The reaction was monitored by TLC using DCM:MeOH (9.5:0.5) as mobile phase. The reaction mixture was concentrated under reduced pressure. The residual crude product was purified by preparative TLC using DCM:MeOH (95:5) as mobile phase to give the title compound. Yield 54 mg (60%). Analytical HPLC: purity 92.6% (System A); HRESIMS (ESI^+) calcd for $C_{22}H_{29}N_3O_5S$: 447.1828, found 447.1812.

EXAMPLE 109

Benzyl 4-({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methoxy)piperidine-1-carboxylate



The title compound was prepared from crude 2-[4-(methylsulfonyl)phenyl]-5-[(piperidin-4-yloxy)methyl]pyrazine hydrochloride (50 mg, 0.14 mmol; Intermediate 27) and benzyl chloroformate (0.03 mL, 0.17 mmol) in accordance with the procedure described for Example 108. The crude product was purified by preparative TLC using DCM:MeOH (95:5) as mobile phase to give the title compound. Yield 40 mg (57.7%). Analytical HPLC: purity 98% (System B); HRESIMS (ESI^+) calcd for $C_{25}H_{27}N_3O_5S$: 481.1671, found 481.1673.

BIOLOGICAL TESTS

Human GPR119 Activity Assay

Agonists to the human GPR119 receptor were characterized by measuring human GPR119 receptor-mediated stimulation of cyclic AMP (cAMP) in HEK 293 cells expressing the human GPR119 receptor.

Briefly, cAMP content was determined using a cAMP kit based on HTRF technology (Homogeneous Time-Resolved Fluorescence, Cisbio Cat. no. 62AM2PEC). HEK293 cells stably expressing the human GPR119 receptor (HEK293-hGPR119 cells) were cultured in DMEM (Gibco # 31966-021) supplemented with 10% Bovine Calf Serum (Hyclone # SH30072.03), and 500 µg/mL Hygromycin B (Roche Diagnostics 843555). At 80% confluency, cells were detached using Trypsine and aliquoted at a density of $5x10^6$ cells/mL in freezing medium (DMEM (Gibco # 31966-021), 20% BCS (Hyclone # SH30072.03), 10% DMSO (Sigma #D2650) and stored at -135 °C. On the experimental day, HEK293-hGPR119 cells were thawn and diluted to $0.4x10^6$ cells/mL in assay buffer (1x HBSS (Gibco Cat. no. 14025-049), 20 mM Hepes (Gibco Cat. no.15630-056), 0.1% BSA, pH 7.4) and incubated with test substances for 20 min at room temperature. After addition of HTRF reagents diluted in lysis buffer, the 96- or 384-well plates were

incubated 1 hour, followed by measuring the fluorescence ratio at 665 nm / 620 nm. Test substances was diluted in compound buffer (1x HBSS (Gibco Cat. no. 14025-049), 20 mM Hepes (Gibco Cat. no.15630-056), 0.1% BSA, 2mM IBMX (Sigma-Aldrich Cat. No. I7018, pH 7.4). The potency of the agonist was quantified by determine the concentration that cause 50% activation of hGPR119 evoked increase in cAMP, EC_{50}.

Compounds of the invention showed a concentration-dependant increase in intracellular cAMP level and generally had an EC_{50} value of <10 μM.

Hamster GPR119 Activity Assay

Agonists to the GPR119 receptor are characterized by measuring receptor-mediated stimulation of cyclic AMP in HIT-T15 cells (Hamster beta-cell line, American Type Culture Collection) endogenously expressing the hamster GPR119. HIT-T15 cells are grown in suitable media (typically F12 Kaighn´s Nutrient Mixture Kaighn´s modification supplemented with 10% Horse serum, 1.5 g/L sodium bicarbonate, 2.5% dialyzed and heat-inactivated Fetal Bovine Serum) as recommended by the provider. Cells are trypsinated, resuspended in growth media supplemented with 10 % DMSO, aliquoted and frozen as ready-to-use vials. For potency analyses, frozen cells are thawed, spun and resuspended in HTRF assay buffer at a suitable cell density. Cells are treated with various concentrations of test compounds, a reference compound to define 100% response, forskolin or buffer containing the same DMSO concentration as the compound solutions to define base line. Typically, stimulation proceeds for 15 to 30 minutes and thereafter the cAMP levels are determined using the HTRF® kit (Homogenous Time-Resolved FRET, CisBio).

Effects of GPR119 Modulators on Glucose-Stimulated Insulin Release

In vitro experiments

The effect of GPR119 modulators on glucose-stimulated insulin release is determined in isolated pancreatic islets from Wistar rats and diabetic rat models, e.g. GK rat. Briefly, islets are isolated from the rats by digestion with collagenase according to standard protocol. The islets are cultured for 24 h in RPMI-1640 medium supplemented with 11.1 mM glucose and 10 % (vol/vol) fetal calf serum. On the experimental day, batches of three islets are preincubated in KRB (Krebs-Ringer bicarbonate) buffer and 3.3 mM glucose for

30 min, 37 °C. Thereafter the batches with islets are incubated in 16.7 mM glucose and KRB buffer supplemented with vehicle or test compounds for 60 min at 37 °C. Aliquots of the medium will be frozen for measurement of insulin using a radioimmunoassay with rabbit ant-porcine insulin antibodies.

In vivo experiments

The effects of GPR119 modulators on glucose stimulated insulin release is determined in diabetic mice models (eg. $Lep^{ob/ob}$ or diet-induced obese (DIO) mice) undergoing an oral glucose tolerance test. Briefly, overnight fasted mice is given either vehicle or test compound at desired doses via oral gavage. Based on the pharmacokinetic of the test compounds, a glucose boluse dose is delivered via oral gavage 30min-2hrs following the test compound. Plasma glucose and insulin levels are determined at desired time points over a 2 hour period using blood collection from tail nick. Plasma glucose is determined using a Glucometer and plasma insulin is determined using an insulin ELISA following blood collection in heparinated tubes and centrifugation.

For GLP-1 and GIP pharmacodynamic studies, vehicle or test compounds are administered orally prior to glucose bolus dose. Blood is collected in tubes containing EDTA and a DPPIV inhibitor at desired time points. After centrifugation, plasma is collected and analysed for active GLP-1 and GIP (using ELISA kit).

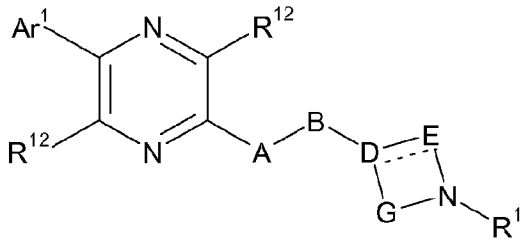
Effects of GPR119 Modulators on Incretin Secretion and Body Weight

In vivo experiments

The effect of GPR119 modulators on body weight is determined in diabetic and obese mice models, eg. $Lep^{ob/ob}$ or diet-induced obese (DIO) mice. The food intake and body weight gain is measured during subchronic treatment with vehicle or test compound via oral gavage. At the end of the experiment, vena cava blood is collected and e.g. HbA1c, GLP-1, insulin, ALAT, ASAT are measured.

CLAIMS

1. A compound of Formula (Ia),



(Ia)

or a pharmaceutically acceptable salt, solvate, hydrate, geometrical isomer, tautomer, optical isomer or *N*-oxide thereof; wherein:

A is CH_2, O, NR^{10}, C(O), S, S(O) or $S(O)_2$;
B is CH_2, O, NR^{10}, C(O), S, S(O) or $S(O)_2$, provided that when B is O, NR^{10}, C(O), S, S(O) or $S(O)_2$, then A is CH_2;
D is N, C or CR^{11}, provided that D must be CR^{11} and said R^{11} must be hydrogen or methyl when B is selected from O, NR^{10}, C(O), S, S(O) and $S(O)_2$;
---- is a single bond when D is N or CR^{11} or a double bond when D is C;

E and G are independently C_{1-3}-alkylene, each optionally substituted with a substituent independently selected from the group consisting of C_{1-3}-alkyl, C_{1-4}-alkoxy, carboxy, fluoro-C_{1-3}-alkyl, hydroxy, hydroxymethyl, and fluoro, provided that the ring formed by D, E, N and G has not more than 7 ring atoms, and further provided that the said ring has 6 or 7 ring atoms when D is N, and yet further provided that the total number of substituents on E and G independently is not more than 2;

R^1 is $C(O)OR^2$, $C(O)R^2$, $S(O)_2R^2$, $C(O)NR^2R^3$ or $-CH_2-C(O)NR^2R^3$, or a 5- or 6-membered heteroaryl group linked via a ring carbon atom, wherein the said heteroaryl group is optionally substituted with C_{1-4}-alkyl;

Ar^1 is phenyl or heteroaryl, each of which is optionally independently substituted in one or more positions with a substituent selected from:

(a) CF_3SO_3,

(b) halogen selected from chlorine, bromine and fluorine,

(c) C_{1-4}-alkylsulfoximine,

(d) $-S(O)R^4$,

(e) $-S(O)_2R^4$,

(f) $-S(O)_2NR^5R^5$,

(g) $-NR^6S(O)_2R^4$,

(h) $-CH_2-NR^6C(O)R^4$,

(i) $-NR^6C(O)R^4$,

(j) $-C(O)NR^5R^5$,

(k) $-CH_2-C(O)NR^5R^5$,

(l) $-C(O)R^4$,

(m) $H_2N-C(O)O-$,

(n) $CH_3-NH-C(O)O-$,

(o) $(CH_3)_2NC(O)O-$,

(p) $CH_3OC(O)NH-$,

(q) C-heterocyclyl, optionally substituted with C_{1-4}-alkyl,

(r) $-CN$,

(s) $-OR^8$,

(t) $-SCF_3$,

(u) $-NO_2$,

(v) C-heterocyclylsulfonyl, optionally substituted with C_{1-4}-alkyl,

(w) $-NR^5R^5$,

(x) $-C(OH)CH_3CF_3$,

(y) $[CF_3CH_3(OH)C]-C_{1-6}$-alkyl,

(z) cyano-C_{1-6}-alkyl,

(aa) guanidino,

(bb) amidino,

(cc) C_{1-6}-alkyl,

(dd) C_{1-4}-alkoxy-C_{1-4}-alkyl,

(ee) fluoro-C_{1-4}-alkyl,

(ff) C_{2-6}-alkenyl,

(gg) fluoro-C_{2-4}-alkenyl,

(hh) hydroxy-C_{1-6}-alkyl,

(ii) C_{1-4}-alkylsulfonyl-C_{1-4}-alkyl,

(jj) hydroxy-C_{2-4}-alkoxy-C_{1-4}-alkyl,

(kk) C_{2-3}-acyl-C_{1-3}-alkyl,

(ll) C_{2-6}-alkynyl,

(mm) hydroxy-C_{3-6}-cycloalkyl,

(nn) fluoro-C_{3-6}-cycloalkyl,

(oo) methyl-C_{3-6}-cycloalkyl,

(pp) C-heterocyclylcarbonyl, optionally substituted with C_{1-4}-alkyl,

(qq) C_{3-6}-cycloalkyl,

(rr) C_{3-6}-cycloalkyl-C_{1-4}-alkyl,

(ss) R^5R^5N-C_{1-2}-alkyl,

(tt) $-C(O)OR^7$,

(uu) $-CH_2C(O)OR^7$,

(vv) phenyl, and

(ww) heteroaryl,

wherein phenyl or heteroaryl as substituent on Ar^1 is optionally substituted in one or more positions with a substituent independently selected from the group Z^1 consisting of:

(a) halogen selected from chlorine and fluorine,

(b) C_{1-4}-alkyl,

(c) hydroxy,

(d) C_{1-4}-alkoxy,

(e) $-OCF_3$,

(f) $-SCF_3$,

(g) $-CN$,

(h) $-C(OH)CH_3CF_3$,

(i) hydroxy-C_{1-4}-alkyl,

(j) $-CF_3$,

(k) $-S(O)_2CH_3$,

(l) $-S(O)_2NH_2$,

(m) $-S(O)_2NHCH_3$,

(n) $-S(O)_2N(CH_3)_2$,

(o) $-N(CH_3)S(O)_2CH_3$,

(p) $-N(CH_3)C(O)CH_3$,

(q) $-C(O)NH_2$,

(r) $-C(O)NHCH_3$,

(s) $-C(O)N(CH_3)_2$,

(t) $-C(O)CH_3$,

(u) $-NH_2$,

(v) $-NHCH_3$,

(w) $-N(CH_3)_2$, and

(x) methoxycarbonyl;

R^2 is selected from:

(a) C_{1-6}-alkyl,

(b) C_{1-6}-alkoxy-C_{2-6}-alkyl,

(c) hydroxy-C_{2-6}-alkyl,

(d) fluoro-C_{2-6}-alkyl,

(e) C_{3-6}-alkynyl,

(f) C_{3-6}-alkenyl,

(g) C_{3-7}-cycloalkyl,

(h) C_{5-8}-cycloalkenyl,

(i) NR^9R^9, provided that R^1 is not selected from $C(O)OR^2$, $C(O)NR^2R^3$ and $-CH_2-C(O)NR^2R^3$,

(j) C-heterocyclyl, optionally substituted with C_{1-4}-alkyl,

(k) C_{7-8}-bicyclyl, optionally substituted with hydroxy,

(l) C_{7-8}-bicyclylmethyl,

(m) azabicyclyl, optionally substituted with hydroxy,

(n) C_{3-7}-cycloalkyl-C_{1-4}-alkyl, wherein cycloalkyl is optionally substituted with methyl,

(o) C_{1-6}-alkylsulfonyl-C_{2-6}-alkyl,

(p) C_{2-3}-acyl-C_{1-4}-alkyl,

(q) arylcarbonyl-C_{1-4}-alkyl,

(r) heteroarylcarbonyl-C_{1-4}-alkyl,

(s) $[CF_3CH_3(OH)C]$-C_{1-6}-alkyl,

(t) *N*-heterocyclylcarbonyl-C_{2-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(u) C-heterocyclylcarbonyl-C_{2-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(v) aminocarbonyl-C_{2-6}-alkyl,

(w) C_{1-3}-alkylaminocarbonyl-C_{2-6}-alkyl,

(x) di(C_{1-3}-alkyl)aminocarbonyl-C_{2-6}-alkyl,

(y) hydroxy-C_{2-4}-alkoxy-C_{2-4}-alkyl,

(z) hydroxy-C_{4-6}-cycloalkyl,

(aa) oxo-C_{4-6}-cycloalkyl,

(bb) fluoro-C_{4-6}-cycloalkyl,

(cc) C_{1-3}-alkoxy-C_{4-6}-cycloalkyl,

(dd) methyl-C_{3-6}-cycloalkyl,

(bb) oxo-*N*-heterocyclyl-C_{2-4}-alkyl,

(cc) fluoro-*N*-heterocyclyl-C_{2-4}-alkyl,

(dd) amino-*N*-heterocyclyl-C_{2-4}-alkyl,

(ee) hydroxy-*N*-heterocyclyl-C_{2-4}-alkyl,

(ii) *N*-heterocyclyl-C_{2-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(jj) C-heterocyclyl-C_{1-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(kk) aryl,

(ll) aryl-C_{1-4}-alkyl,

(mm) aryl-C_{3-6}-alkenyl,

(nn) aryl-C_{3-6}-alkynyl,

(oo) heteroaryl,

(pp) heteroaryl-C_{1-4}-alkyl,

(qq) heteroaryl-C_{3-6}-alkenyl, and

(rr) heteroaryl-C_{3-6}-alkynyl,

wherein any aryl or heteroaryl residue, alone or as part of another group, is optionally independently substituted in one or more position with a substituent selected from the group Z^1;

R^3 is selected from:

(a) hydrogen,

(b) C_{1-6}-alkyl,

(c) fluoro-C_{2-6}-alkyl,

(d) hydroxy-C_{2-6}-alkyl,

(e) C_{1-6}-alkoxy-C_{2-6}-alkyl,

(f) amino-C_{2-6}-alkyl,

(g) C_{1-3}-alkylamino-C_{2-6}-alkyl,

(h) di(C_{1-3}-alkyl)amino-C_{2-6}-alkyl,

(i) cyano-C_{1-6}-alkyl, and

(j) C_{1-6}-alkylsulfonyl-C_{2-6}-alkyl;

R^4 is independently selected from:

(a) C_{1-6}-alkyl,

(b) fluoro-C_{1-6}-alkyl,

(c) hydroxy-C_{2-6}-alkyl,

(d) C_{1-4}-alkoxy-C_{2-4}-alkyl,

(e) C_{2-4}-acyl-C_{1-4}-alkyl,

(f) carboxy-C_{1-3}-alkyl,

(g) C_{3-6}-cycloalkyl,

(h) oxo-C_{4-6}-cycloalkyl,

(i) hydroxy-C_{4-6}-cycloalkyl,

(j) fluoro-C_{4-6}-cycloalkyl,

(k) methyl-C_{3-6}-cycloalkyl,

(l) *N*-heterocyclylcarbonyl-C_{2-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(m) oxo-*N*-heterocyclyl-C_{2-4}-alkyl,

(n) fluoro-*N*-heterocyclyl-C_{2-4}-alkyl,

(o) hydroxy-*N*-heterocyclyl-C_{2-4}-alkyl,

(p) amino-*N*-heterocyclyl-C_{2-4}-alkyl,

(q) aminocarbonyl-C_{2-4}-alkyl,

(r) C_{1-3}-alkylaminocarbonyl-C_{2-4}-alkyl,

(s) di(C_{1-3}-alkyl)aminocarbonyl-C_{2-4}-alkyl,

(t) C_{2-3}-acylamino-C_{2-4}-alkyl,

(u) hydroxy-C_{2-4}-alkoxy-C_{2-4}-alkyl,

(v) C-heterocyclylcarbonyl-C_{2-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(w) C_{3-6}-cycloalkyl-C_{1-2}-alkyl,

(x) amino-C_{2-4}-alkyl,

(y) C_{1-2}-alkylamino-C_{2-4}-alkyl,

(z) di(C_{1-2}-alkyl)amino-C_{2-4}-alkyl,

(aa) phenyl, and

(bb) heteroaryl,

wherein any phenyl or heteroaryl residue is optionally substituted in one or more positions with a substituent independently selected from the group Z^2 consisting of:

(a) halogen selected from chlorine and fluorine,

(b) C_{1-4}-alkoxy,

(c) hydroxymethyl,

(d) –CN,

(e) $–CF_3$,

(f) C_{1-4}-alkyl,

(g) $–OCF_3$, and

(h) $–C(O)CH_3$;

R^5 is each independently selected from:

(a) hydrogen,

(b) C_{1-6}-alkyl,

(c) C_{3-4}-cycloalkyl,

(d) fluoro-C_{2-4}-alkyl,

(e) amino-C_{2-6}-alkyl,

(f) cyano-C_{1-6}-alkyl,

(g) hydroxy-C_{2-6}-alkyl,

(h) dihydroxy-C_{2-6}-alkyl,

(i) C_{1-4}-alkoxy-C_{2-4}-alkyl,

(j) C_{1-4}-alkylamino-C_{2-4}-alkyl,

(k) di(C_{1-4}-alkyl)amino-C_{2-4}-alkyl,

(l) aminocarbonyl-C_{1-4}-alkyl,

(m) C_{2-3}-acylamino-C_{2-4}-alkyl,

(n) C_{1-4}-alkylthio-C_{2-4}-alkyl,

(o) C_{2-4}-acyl-C_{1-4}-alkyl, and

(p) C_{1-4}-alkylsulfonyl-C_{1-4}-alkyl,

or two R^5 groups together with the nitrogen to which they are attached form a heterocyclic ring, wherein said heterocyclic ring may be optionally substituted with:

i) a substituent selected from:

(aa) hydroxy,

(bb) amino,

(cc) methylamino,

(dd) dimethylamino,

(ee) hydroxymethyl, and

(ff) aminomethyl;

ii) one or two oxo groups; or

iii) one or two fluorine atoms,

provided that when the substituent is selected from fluorine, hydroxy, amino, methylamino and dimethylamino, said substituent is attached to the heterocyclic ring at a position other than alpha to a heteroatom;

and when the two R^5 groups form a piperazine ring, the nitrogen of the piperazine ring that allows the substitution is optionally substituted with C_{1-4}-alkyl;

R^6 is independently selected from:

(a) hydrogen,

(b) C_{1-4}-alkyl, and

(c) hydroxy-C_{2-4}-alkyl;

R^7 is independently selected from C_{1-4}-alkyl;

R^8 is independently selected from:

(a) hydrogen,

(b) C_{1-6}-alkyl,

(c) fluoro-C_{1-6}-alkyl,

(d) hydroxy-C_{2-6}-alkyl,

(e) amino-C_{2-6}-alkyl,

(f) C_{1-3}-alkylamino-C_{2-4}-alkyl,

(g) di(C_{1-3}-dialkyl)amino-C_{2-4}-alkyl,

(h) C_{1-4}-alkylsulfonyl-C_{2-4}-alkyl,

(i) *N*-heterocyclyl-C_{2-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(j) C-heterocyclyl, optionally substituted with methyl,

(k) C_{2-3}-acylamino-C_{2-4}-alkyl,

(l) [CF_3CH_3(OH)C]-C_{1-6}-alkyl,

(m) C_{3-6}-cycloalkyl,

(n) methyl-C_{3-6}-cycloalkyl,

(o) C_{3-6}-cycloalkyl-C_{1-2}-alkyl,

(p) aryl, and

(q) heteroaryl,

wherein any aryl or heteroaryl residue is optionally independently substituted in one or two positions with a substituent selected from the group Z^2;

R^9 is each independently selected from:

(a) C_{1-4}-alkoxy-C_{2-4}-alkyl,

(b) amino-C_{2-4}-alkyl,

(c) C_{1-4}-alkylamino-C_{2-4}-alkyl,

(d) di(C_{1-4}-alkyl)amino-C_{2-4}-alkyl,

(e) C_{2-3}-acylamino-C_{2-4}-alkyl,

(f) C_{1-4}-alkylthio-C_{2-4}-alkyl, and

(g) C_{2-4}-acyl-C_{1-4}-alkyl;

or two R^9 groups together with the nitrogen to which they are attached form a heterocyclic ring, wherein said heterocyclic ring may be optionally substituted with:

i) a substituent selected from:

(aa) hydroxy,

(bb) amino,

(cc) methylamino,

(dd) dimethylamino,

(ee) hydroxymethyl, and

(ff) aminomethyl;

ii) one or two oxo groups; or

iii) one or two fluorine atoms,

provided that when the substituent is selected from fluorine, hydroxy, amino, methylamino and dimethylamino, said substituent is attached to the heterocyclic ring at a position other than alpha to a heteroatom;

and when the two R^9 groups form a piperazine ring, the nitrogen of the piperazine ring that allows the substitution is optionally substituted with C_{1-4}-alkyl;

R^{10} is independently selected from:

(a) hydrogen,

(b) C_{1-6}-alkyl,

(c) cyclopropyl,

(d) cyclobutyl,

(e) cyclopropylmethyl,

(f) fluoro-C_{2-6}-alkyl,

(g) hydroxy-C_{2-6}-alkyl,

(h) C_{1-2}-alkoxy-C_{2-6}-alkyl,

(i) amino-C_{2-6}-alkyl,

(j) di(C_{1-3}-alkyl)amino-C_{2-6}-alkyl,

(k) C_{1-3}-alkylamino-C_{2-6}-alkyl,

(l) cyano-C_{2-4}-alkyl,

(m) C_{2-6}-acyl,

(n) C_{2-6}-acyl-C_{1-6}-alkyl, and

(o) C_{1-6}-alkylsulfonyl-C_{1-6}-alkyl;

R^{11} is selected from:

(a) hydrogen,

(b) hydroxy,

(c) fluorine,

(d) C_{1-4}-alkoxy, and

(e) methyl;

R^{12} is each independently selected from:

(a) hydrogen,

(b) –CN,

(c) C_{1-4}-alkoxy,

(d) $-NR^5R^5$, wherein each R^5 is independently selected from the group consisting of hydrogen and C_{1-4}-alkyl; or two R^5 groups together with the nitrogen to which they are attached form a pyrrolidine or an azetidine ring,

(e) C_{1-3}-alkyl,

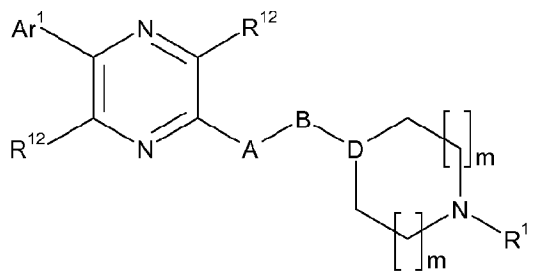
(f) C_{1-3}-alkoxy-C_{1-2}-alkyl, and

(g) hydroxy-C_{1-4}-alkyl;

with the proviso that the compound is not selected from:

- 1-Methylethyl 4-[({5-[4-(methylsulfonyl)phenyl]-2-pyrazinyl}oxy)methyl]-1-piperidinecarboxylate;
- 2-[({1-[3-(1-Methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}methyl)oxy]-5-[4-(methylsulfonyl)phenyl]pyrazine;
- 5-Fluoro-2-{4-[({5-[4-(methylsulfonyl)phenyl]-2-pyrazinyl}oxy)methyl]-1-piperidinyl}pyrimidine;
- 2-[2-Fluoro-4-(methylsulfonyl)phenyl]-5-[({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}methyl)oxy]pyrazine;
- 1-Methylethyl 4-[({5-[2-fluoro-4-(methylsulfonyl)phenyl]-2-pyrazinyl}oxy)-methyl]-1-piperidinecarboxylate; and
- 2-[({1-[3-(1-Methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}methyl)oxy]-5-[2-methyl-4-(methylsulfonyl)phenyl]pyrazine.

2. A compound according to claim 1 having Formula (Ib),



(Ib)

wherein:

A is CH_2, O, NR^{10}, C(O), S, S(O) or $S(O)_2$;

B is CH_2, O, NR^{10}, C(O), S, S(O) or $S(O)_2$, provided that when B is O, NR^{10}, C(O), S, S(O) or $S(O)_2$, then A is CH_2;

m is each independently 0 or 1;

D is N or CR^{11}, provided that D must be CR^{11} and said R^{11} must be hydrogen or methyl when B is selected from O, NR^{10}, C(O), S, S(O) and $S(O)_2$; and further provided that each m is 1 when D is N;

Ar^1, Z^1, Z^2, R^1 to R^9 and R^{12} are as defined in claim 1;

R^{10} is independently selected from:

(a) hydrogen,

(b) C_{1-4}-alkyl,

(c) cyclopropyl,

(d) cyclobutyl,

(e) cyclopropylmethyl,

(f) fluoro-C_{2-4}-alkyl,

(g) C_{1-2}-alkoxy-C_{2-3}-alkyl,

(h) hydroxy-C_{2-4}-alkyl,

(i) C_{2-3}-acyl,

(j) amino-C_{2-4}-alkyl,

(k) methylamino-C_{2-4}-alkyl,

(l) dimethylamino-C_{2-4}-alkyl, and

(m) cyano-C_{2-4}-alkyl;

R^{11} is selected from:

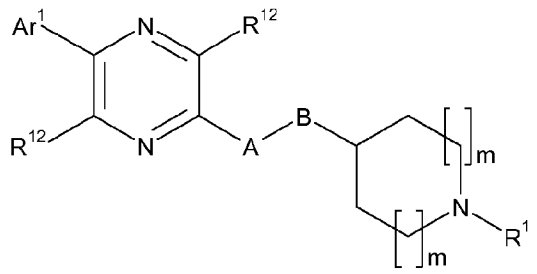
(a) hydrogen,

(b) hydroxy,

(c) fluorine, and

(d) methyl.

3. A compound according to claim 1 or 2 having Formula (Ic),



(Ic)

wherein:

A is CH_2, O or NR^{10};

B is CH_2, O or NR^{10}, provided that when B is O or NR^{10}, then A is CH_2;

m is each independently 0 or 1;

Z^1, Z^2, R^1 to R^7, R^9 and R^{12} are as defined in claim 1;

R^{10} is as defined in claim 2;

Ar^1 is phenyl or 5- or 6-membered heteroaryl, each of which is optionally substituted in one or two positions with a substituent independently selected from the group Z^3 consisting of:

(a) CF_3SO_3,

(b) halogen selected from bromine, chlorine and fluorine,

(c) C_{1-4}-alkylsulfoximine,

(d) $–S(O)R^4$,

(e) $–S(O)_2R^4$,

(f) $–S(O)_2NR^5R^5$,

(g) $–NR^6S(O)_2R^4$,

(h) $–NR^6C(O)R^4$,

(i) $–CH_2-NR^6C(O)R^4$,

(j) $–C(O)NR^5R^5$,

(k) $–CH_2-C(O)NR^5R^5$,

(l) $–C(O)R^4$,

(m) $H_2N-C(O)O–$,

(n) $CH_3-NH-C(O)O–$,

(o) $(CH_3)_2NC(O)O$–,

(p) –$NHC(O)OCH_3$,

(q) C-heterocyclyl, optionally substituted with methyl,

(r) –CN,

(s) $-OR^8$,

(t) $-SCF_3$,

(u) C-heterocyclylsulfonyl, optionally susbtituted with methyl,

(v) $-NR^5R^5$,

(w) $-C(OH)CH_3CF_3$,

(x) cyano-C_{1-6}-alkyl,

(y) C_{1-6}-alkyl,

(z) C_{1-4}-alkoxy-C_{1-4}-alkyl,

(aa) fluoro-C_{1-4}-alkyl,

(bb) C_{2-6}-alkenyl,

(cc) fluoro-C_{2-4}-alkenyl,

(dd) hydroxy-C_{1-6}-alkyl,

(ee) C_{1-4}-alkylsulfonyl-C_{1-4}-alkyl,

(ff) hydroxy-C_{2-4}-alkoxy-C_{1-4}-alkyl,

(gg) C_{2-3}-acyl-C_{1-3}-alkyl,

(hh) C_{2-6}-alkynyl,

(ii) C_{3-6}-cycloalkyl,

(jj) hydroxy-C_{3-6}-cycloalkyl,

(kk) fluoro-C_{3-6}-cycloalkyl,

(ll) methyl-C_{3-6}-cycloalkyl,

(mm) C-heterocyclylcarbonyl, optionally substituted with methyl,

(nn) C_{3-6}-cycloalkyl-C_{1-4}-alkyl,

(oo) R^5R^5N-C_{1-2}-alkyl,

(pp) $-C(O)OR^7$,

(qq) $-CH_2C(O)OR^7$, and

(rr) heteroaryl,

wherein any heteroaryl residue as substituent on Ar^1 is optionally substituted in one or more positions with a substituent independently selected from the group Z^2 as defined herein for claim 1;

R^8 is independently selected from:

(a) hydrogen,

(b) C_{1-4}-alkyl,

(c) CF_3,

(d) C_{3-5}-cycloalkyl,

(e) methyl-C_{3-5}-cycloalkyl, and

(f) C-heterocyclyl, optionally substituted with methyl.

4. A compound according to any one of claims 1 to 3, wherein A is CH_2 and B is O or NR^{10}; and m is each 1.

5. A compound according to any one of claims 1 to 3, wherein A is O or NR^{10} and B is CH_2; and m is each 1.

6. A compound according to any one of claims 1 to 5, wherein Ar^1 is phenyl, pyridinyl or thienyl, each of which is optionally substituted in one or two positions with a substituent independently selected from the group Z^4 consisting of:

(a) halogen selected from chlorine and fluorine,

(b) C_{1-4}-alkylsulfoximine,

(c) C_{1-4}-alkylsulfonyl,

(d) C_{1-4}-alkylsulfinyl,

(e) hydroxy-C_{2-4}-alkylsulfonyl,

(f) C_{3-5}-cycloalkylsulfonyl,

(g) methyl-C_{3-5}-cycloalkylsulfonyl,

(h) trifluoromethylsulfonyl,

(i) $–S(O)_2NR^{5A}R^{5A}$,

(j) C_{1-4}-alkylsulfonamido,

(k) C_{2-4}-acylamino,

(l) C_{2-4}-acylaminomethyl,

(m) carboxy-C_{1-3}-alkylcarbonylamino,

(n) $–C(O)NR^{5A}R^{5A}$,

(o) $–CH_2$-$C(O)NR^{5A}R^{5A}$,

(p) $–NHC(O)OCH_3$,

(q) C_{2-4}-acyl,

(r) C_{3-5}-cycloalkylcarbonyl,

(s) C_{1-4}-alkoxy,

(t) C_{3-5}-cycloalkyloxy,

(u) C-heterocyclyl,

(v) –CN,

(w) –OH,

(x) $–OCF_3$,

(y) $–CF_3$,

(z) $–NR^{5A}R^{5A}$,

(aa) $–C(OH)CH_3CF_3$,

(bb) cyano-C_{1-2}-alkyl,

(cc) C_{1-4}-alkyl,

(dd) C_{3-5}-cycloalkyl,

(ee) C_{1-2}-alkoxy-C_{1-2}-alkyl,

(ff) vinyl,

(gg) ethynyl,

(hh) hydroxy-C_{1-2}-alkyl,

(ii) C-heterocyclyloxy, optionally substituted with methyl,

(jj) $R^{5A}R^{5A}N$-C_{1-2}-alkyl,

(kk) $–C(O)OR^{7A}$, and

(ll) $–CH_2C(O)OR^{7A}$;

R^1 is a group R^{1A} selected from $C(O)OR^{2A}$, $C(O)R^{2A}$, $S(O)_2R^{2A}$, $C(O)NR^{2A}R^{3A}$, $-CH_2-C(O)NR^{2A}R^{3A}$, or a 5- or 6-membered heteroaryl group linked via a ring carbon atom, wherein the said heteroaryl group is optionally substituted with C_{1-4}-alkyl;

R^{2A} is selected from:

(a) C_{1-6}-alkyl,

(b) C_{1-6}-alkoxy-C_{2-6}-alkyl,

(c) hydroxy-C_{2-6}-alkyl,

(d) hydroxy-C_{2-4}-alkoxy-C_{2-4}-alkyl,

(e) fluoro-C_{2-6}-alkyl,

(f) C_{3-6}-alkynyl,

(g) C_{3-7}-cycloalkyl,

(h) C_{5-8}-cycloalkenyl,

(i) $NR^{9A}R^{9A}$ provided that R^{1A} is not selected from $C(O)OR^{2A}$, $C(O)NR^{2A}R^{3A}$ and $-CH_2-C(O)NR^{2A}R^{3A}$,

(j) C-heterocyclyl, optionally substituted with methyl,

(k) C_{7-8}-bicyclyl,

(l) 2-norbornylmethyl,

(m) azabicyclyl,

(n) C_{3-6}-cycloalkyl-C_{1-4}-alkyl, wherein cycloalkyl is optionally substituted with methyl,

(o) C_{2-3}-acyl-C_{1-4}-alkyl,

(p) arylcarbonyl-C_{1-4}-alkyl,

(q) heteroarylcarbonyl-C_{1-4}-alkyl,

(r) $[CF_3CH_3(OH)C]$-C_{1-6}-alkyl,

(s) *N*-heterocyclylcarbonyl-C_{2-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(t) hydroxy-C_{4-6}-cycloalkyl,

(u) oxo-C_{4-6}-cycloalkyl,

(v) fluoro-C_{4-6}-cycloalkyl,

(w) methoxy-C_{4-6}-cycloalkyl,

(x) methyl-C_{3-6}-cycloalkyl,

(y) oxo-*N*-heterocyclyl-C_{2-4}-alkyl,

(z) hydroxy-*N*-heterocyclyl-C_{2-4}-alkyl,

(aa) fluoro-*N*-heterocyclyl-C_{2-4}-alkyl,

(bb) amino-*N*-heterocyclyl-C_{2-4}-alkyl,

(cc) *N*-heterocyclyl-C_{2-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(dd) C-heterocyclyl-C_{1-4}-alkyl, wherein heterocyclyl is optionally substituted with methyl,

(ee) aryl,

(ff) aryl-C_{1-4}-alkyl,

(gg) heteroaryl, and

(hh) heteroaryl-C_{1-4}-alkyl,

wherein any aryl or heteroaryl residue, alone or as a part of another group, is optionally substituted in one or more positions with a substituent independently selected from the group Z^5 consisting of:

(a) halogen selected from chlorine and fluorine,
(b) methyl,
(c) ethyl,
(d) methoxy,
(e) ethoxy,
(f) isopropoxy,
(g) hydroxy,
(h) $-OCF_3$,
(i) $-CF_3$,
(j) –CN,
(k) $-C(OH)CH_3CF_3$,
(l) dimethylamino,
(m) hydroxymethyl,
(n) $-S(O)_2CH_3$,
(o) $-C(O)CH_3$, and
(p) $-C(O)NH_2$;

R^{3A} is selected from:

(a) hydrogen,
(b) C_{1-4}-alkyl,
(c) hydroxy-C_{2-4}-alkyl, and
(d) methoxy-C_{2-4}-alkyl;

R^{5A} is each independently selected from:

(a) hydrogen,
(b) C_{1-3}-alkyl,
(c) C_{1-2}-alkoxy-C_{2-4}-alkyl,
(d) C_{3-4}-cycloalkyl,
(e) hydroxy-C_{2-4}-alkyl,
(f) cyano-C_{1-3}-alkyl,
(g) dihydroxy-C_{2-4}-alkyl,

(h) aminocarbonyl-C_{1-2}-alkyl, and

(i) di(C_{1-2}-alkyl)amino-C_{2-3}-alkyl;

or two R^{5A} groups together with the nitrogen to which they are attached form a heterocyclic ring, wherein said heterocyclic ring may be optionally substituted with:

i) a substituent selected from:

(aa) hydroxy,

(bb) amino,

(cc) methylamino,

(dd) dimethylamino,

(ee) hydroxymethyl, and

(ff) aminomethyl;

ii) one or two oxo groups; or

iii) one or two fluorine atoms, provided that when the substituent is selected from fluorine, hydroxy, amino, methylamino and dimethylamino, said substituent is attached to the heterocyclic ring at a position other than alpha to a heteroatom; and

when the two R^{5A} groups form a piperazine ring, the nitrogen of the piperazine ring that allows the substitution is optionally substituted with methyl;

R^{7A} is independently selected from C_{1-4}-alkyl;

Two groups R^{9A} together with the nitrogen to which they are attached form a heterocyclic ring, wherein said heterocyclic ring may be optionally substituted with:

i) one hydroxy or amino group;

ii) one or two fluorine atoms; or

iii) one or two oxo groups,

provided that when the substituent is selected from fluorine, hydroxy and amino, said substituent is attached to the heterocyclic ring at a position other than alpha to a heteroatom;

and when the two R^{9A} groups form a piperazine ring, the nitrogen of the piperazine ring that allows the substitution is optionally substituted with methyl;

R^{10} is independently selected from:

(a) hydrogen,

(b) C_{1-3}-alkyl,

(c) cyclopropyl, and

(d) cyclopropylmethyl;

R^{12} is each hydrogen.

7. A compound according to claim 6, wherein Ar^1 is selected from methylsulfonylphenyl, (aminocarbonyl)phenyl, [(methylamino)carbonyl]phenyl, [(dimethylamino)carbonyl]phenyl, [(4-methylpiperazin-1-yl)carbonyl]phenyl, [2-(hydroxymethyl)morpholin-4-ylcarbonyl]phenyl, (methylsulfinyl)phenyl, pyridinyl, [(3-hydroxypyrrolidin-1-yl)carbonyl]phenyl, {[(2-hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl, [(3-hydroxyazetidin-1-yl)carbonyl]phenyl, (aminocarbonyl)fluorophenyl, [(methoxycarbonyl)amino]phenyl, [(methylsulfonyl)amino]phenyl, acetylthienyl, fluoro[(propylamino)carbonyl]phenyl, fluoro(methylsulfonyl)phenyl and (acetylamino)phenyl.

8. A compound according to claim 6 or 7, wherein R^{1A} is selected from $C(O)OR^{2A}$, $C(O)R^{2A}$ or a 6-membered heteroaryl group.

9. A compound according to any one of claims 6 to 8, wherein R^{1A} is $C(O)OR^{2A}$ and wherein R^{2A} is selected from *tert*-butyl, phenyl, benzyl, *iso*-butyl, ethyl, isopropyl, 2,2-dimethylpropyl, 1-cyclopropylethyl and (3-methyloxetan-3-yl)methyl.

10. A compound according to any one of claims 6 to 8, wherein R^{1A} is $C(O)R^{2A}$ and wherein R^{2A} is selected from phenyl, 1-methyl-1H-pyrrol-2-yl, 3,4-dichlorophenyl and 1-ethylpropyl.

11. A compound according to any one of claims 6 to 8, wherein R^{1A} is 2-pyrimidinyl.

12. A compound according to any one of claims 6 to 11, wherein R^{10} is independently selected from hydrogen, methyl and cyclopropyl.

13. A compound according to any one of claims 1 to 12, which is selected from:

- *tert*-Butyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]-piperidine-1-carboxylate;

- Isobutyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate;
- Phenyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate;
- 2,2-Dimethylpropyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)-methyl]piperidine-1-carboxylate;
- Isopropyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]-piperidine-1-carboxylate;
- Benzyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate;
- *N*-({1-[(1-Methyl-1*H*-pyrrol-2-yl)carbonyl]piperidin-4-yl}methyl)-5-[4-(methylsulfonyl)phenyl]pyrazin-2-amine;
- Ethyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}amino)methyl]piperidine-1-carboxylate;
- *N*-[(1-Benzoylpiperidin-4-yl)methyl]-5-[4-(methylsulfonyl)phenyl]pyrazin-2-amine;
- *N*-{[1-(2-Ethylbutanoyl)piperidin-4-yl]methyl}-5-[4-(methylsulfonyl)phenyl]-pyrazin-2-amine;
- *tert*-Butyl 4-[({5-[4-(methylsulfinyl)phenyl]pyrazin-2-yl}amino)methyl]-piperidine-1-carboxylate;
- *tert*-Butyl 4-{[(5-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrazin-2-yl)-amino]methyl}piperidine-1-carboxylate;
- *tert*-Butyl 4-[({5-[4-(aminocarbonyl)phenyl]pyrazin-2-yl}amino)methyl]-piperidine-1-carboxylate;
- *tert*-Butyl 4-{[(5-{4-[(methylamino)carbonyl]phenyl}pyrazin-2-yl)amino]-methyl}piperidine-1-carboxylate;
- *tert*-Butyl 4-{[(5-pyridin-4-ylpyrazin-2-yl)amino]methyl}piperidine-1-carboxylate;
- *tert*-Butyl 4-{[(5-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]phenyl}pyrazin-2-yl)-amino]methyl}piperidine-1-carboxylate;
- *tert*-Butyl 4-({[5-(4-{[2-(hydroxymethyl)morpholin-4-yl]carbonyl}phenyl)-pyrazin-2-yl]amino}methyl)piperidine-1-carboxylate;
- *tert*-Butyl 4-({[5-(4-{[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-pyrazin-2-yl]amino}methyl)piperidine-1-carboxylate;

- *tert*-Butyl 4-({[5-(4-{[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-pyrazin-2-yl]amino}methyl)piperidine-1-carboxylate;
- *tert*-Butyl 4-{[(5-{4-[(3-hydroxyazetidin-1-yl)carbonyl]phenyl}pyrazin-2-yl)-amino]methyl}piperidine-1-carboxylate;
- *tert*-Butyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate;
- Isobutyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate;
- 1-Cyclopropylethyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]-piperidine-1-carboxylate;
- Phenyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate;
- Benzyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate;
- (3-Methyloxetan-3-yl)methyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}-oxy)methyl]piperidine-1-carboxylate;
- Ethyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate;
- 2-[(1-Benzoylpiperidin-4-yl)methoxy]-5-[4-(methylsulfonyl)phenyl]pyrazine;
- 2-{[1-(2-Ethylbutanoyl)piperidin-4-yl]methoxy}-5-[4-(methylsulfonyl)phenyl]-pyrazine;
- 2,2-Dimethylpropyl 4-[({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}oxy)methyl]-piperidine-1-carboxylate;
- 2-({1-[(1-Methyl-1H-pyrrol-2-yl)carbonyl]piperidin-4-yl}methoxy)-5-[4-(methyl-sulfonyl)phenyl]pyrazine;
- *tert*-Butyl 4-{[(5-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]phenyl}pyrazin-2-yl)-oxy]methyl}piperidine-1-carboxylate;
- *tert*-Butyl 4-({[5-(4-{[2-(hydroxymethyl)morpholin-4-yl]carbonyl}phenyl)-pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate;
- *tert*-Butyl 4-({[5-(4-{[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate;
- *tert*-Butyl 4-({[5-(4-{[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate;

- *tert*-Butyl 4-[({5-[4-(methylsulfinyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate;
- *tert*-Butyl 4-{[(5-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrazin-2-yl)-oxy]methyl}piperidine-1-carboxylate;
- *tert*-Butyl 4-[({5-[4-(aminocarbonyl)phenyl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate;
- *tert*-Butyl 4-{[(5-{4-[(methylamino)carbonyl]phenyl}pyrazin-2-yl)oxy]methyl}-piperidine-1-carboxylate;
- *tert*-Butyl 4-{[(5-{4-[(3-hydroxyazetidin-1-yl)carbonyl]phenyl}pyrazin-2-yl)-oxy]methyl}piperidine-1-carboxylate;
- *tert*-Butyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate;
- 2,2-Dimethylpropyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}-methyl)amino]piperidine-1-carboxylate;
- Isobutyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate;
- Ethyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate;
- Isopropyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate;
- Phenyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate;
- 1-Cyclopropylethyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}-methyl)amino]piperidine-1-carboxylate;
- Benzyl 4-[methyl({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate;
- 1-Benzoyl-N-methyl-N-({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)-piperidin-4-amine;
- *tert*-Butyl 4-[[(5-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]phenyl}pyrazin-2-yl)-methyl](methyl)amino]piperidine-1-carboxylate;
- *tert*-Butyl 4-[{[5-(4-{[2-(hydroxymethyl)morpholin-4-yl]carbonyl}phenyl)-pyrazin-2-yl]methyl}(methyl)amino]piperidine-1-carboxylate;
- *tert*-Butyl 4-[{[5-(4-{[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-pyrazin-2-yl]methyl}(methyl)amino]piperidine-1-carboxylate;

- *tert*-Butyl 4-[{[5-(4-{[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}phenyl)-pyrazin-2-yl]methyl}(methyl)amino]piperidine-1-carboxylate;
- *tert*-Butyl 4-[methyl({5-[4-(methylsulfinyl)phenyl]pyrazin-2-yl}methyl)amino]-piperidine-1-carboxylate;
- *tert*-Butyl 4-{methyl[(5-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrazin-2-yl)methyl]amino}piperidine-1-carboxylate;
- *tert*-Butyl 4-[({5-[4-(aminocarbonyl)phenyl]pyrazin-2-yl}methyl)(methyl)amino]-piperidine-1-carboxylate;
- *tert*-Butyl 4-{methyl[(5-{4-[(methylamino)carbonyl]phenyl}pyrazin-2-yl)-methyl]amino}piperidine-1-carboxylate;
- *tert*-Butyl 4-{methyl[(5-pyridin-4-ylpyrazin-2-yl)methyl]amino}piperidine-1-carboxylate;
- Methyl {4-[5-({cyclopropyl[1-(2-ethylbutanoyl)piperidin-4-yl]amino}methyl)-pyrazin-2-yl]phenyl}carbamate;
- *N*-{4-[5-({Cyclopropyl[1-(2-ethylbutanoyl)piperidin-4-yl]amino}methyl)pyrazin-2-yl]phenyl}methanesulfonamide;
- 4-[5-({Cyclopropyl[1-(3,4-dichlorobenzoyl)piperidin-4-yl]amino}methyl)-pyrazin-2-yl]-*N*,*N*-dimethylbenzamide;
- Methyl {4-[5-({cyclopropyl[1-(3,4-dichlorobenzoyl)piperidin-4-yl]amino}-methyl)pyrazin-2-yl]phenyl}carbamate;
- *N*-{4-[5-({Cyclopropyl[1-(3,4-dichlorobenzoyl)piperidin-4-yl]amino}methyl)-pyrazin-2-yl]phenyl}acetamide;
- 4-(5-{[Cyclopropyl(1-pyrimidin-2-ylpiperidin-4-yl)amino]methyl}pyrazin-2-yl)-2-fluorobenzamide;
- Methyl [4-(5-{[cyclopropyl(1-pyrimidin-2-ylpiperidin-4-yl)amino]methyl}-pyrazin-2-yl)phenyl]carbamate;
- *N*-Cyclopropyl-*N*-({5-[2-fluoro-4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)-1-pyrimidin-2-ylpiperidin-4-amine;
- Methyl [4-(5-{[(1-benzoylpiperidin-4-yl)(cyclopropyl)amino]methyl}pyrazin-2-yl)phenyl]carbamate;
- 1-Benzoyl-*N*-cyclopropyl-*N*-({5-[2-fluoro-4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)piperidin-4-amine;
- Isopropyl 4-[({5-[4-(aminocarbonyl)phenyl]pyrazin-2-yl}methyl)(cyclopropyl)-amino]piperidine-1-carboxylate;

- Isopropyl 4-[({5-[4-(aminocarbonyl)-3-fluorophenyl]pyrazin-2-yl}methyl)(cyclopropyl)amino]piperidine-1-carboxylate;
- Isopropyl 4-{cyclopropyl[(5-{4-[(methylamino)carbonyl]phenyl}pyrazin-2-yl)methyl]amino}piperidine-1-carboxylate;
- Isopropyl 4-{cyclopropyl[(5-{4-[(dimethylamino)carbonyl]phenyl}pyrazin-2-yl)methyl]amino}piperidine-1-carboxylate;
- Isopropyl 4-{cyclopropyl[(5-{3-fluoro-4-[(propylamino)carbonyl]phenyl}pyrazin-2-yl)methyl]amino}piperidine-1-carboxylate;
- Isopropyl 4-{cyclopropyl[(5-{4-[(methoxycarbonyl)amino]phenyl}pyrazin-2-yl)methyl]amino}piperidine-1-carboxylate;
- Isopropyl 4-[({5-[4-(acetylamino)phenyl]pyrazin-2-yl}methyl)(cyclopropyl)amino]piperidine-1-carboxylate;
- Isopropyl 4-{cyclopropyl[(5-{4-[(methylsulfonyl)amino]phenyl}pyrazin-2-yl)methyl]amino}piperidine-1-carboxylate;
- Isopropyl 4-[{[5-(5-acetyl-2-thienyl)pyrazin-2-yl]methyl}(cyclopropyl)amino]piperidine-1-carboxylate;
- 4-(5-{[[1-(2-Ethylbutanoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)benzamide;
- 4-(5-{[[1-(2-Ethylbutanoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-2-fluorobenzamide;
- *N*-[4-(5-{[[1-(2-Ethylbutanoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)phenyl]acetamide;
- 4-(5-{[[1-(2-Ethylbutanoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-2-fluoro-N-propylbenzamide;
- *N*-({5-[2-Fluoro-4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)-*N*-methyl-1-pyrimidin-2-ylpiperidin-4-amine;
- 1-[5-(5-{[Methyl(1-pyrimidin-2-ylpiperidin-4-yl)amino]methyl}pyrazin-2-yl)-2-thienyl]ethanone;
- 2-Fluoro-4-(5-{[methyl(1-pyrimidin-2-ylpiperidin-4-yl)amino]methyl}pyrazin-2-yl)-*N*-propylbenzamide;
- *N*,*N*-Dimethyl-4-(5-{[methyl(1-pyrimidin-2-ylpiperidin-4-yl)amino]methyl}-pyrazin-2-yl)benzamide;
- Isopropyl 4-[({5-[4-(aminocarbonyl)phenyl]pyrazin-2-yl}methyl)(methyl)amino]-piperidine-1-carboxylate;

- Isopropyl 4-[({5-[4-(aminocarbonyl)-3-fluorophenyl]pyrazin-2-yl}methyl)-(methyl)amino]piperidine-1-carboxylate;
- Isopropyl 4-{methyl[(5-{4-[(methylamino)carbonyl]phenyl}pyrazin-2-yl)methyl]-amino}piperidine-1-carboxylate;
- Isopropyl 4-[[(5-{4-[(dimethylamino)carbonyl]phenyl}pyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate;
- Isopropyl 4-[[(5-{3-fluoro-4-[(propylamino)carbonyl]phenyl}pyrazin-2-yl)-methyl](methyl)amino]piperidine-1-carboxylate;
- Isopropyl 4-[[(5-{4-[(methoxycarbonyl)amino]phenyl}pyrazin-2-yl)methyl]-(methyl)amino]piperidine-1-carboxylate;
- Isopropyl 4-{methyl[(5-{4-[(methylsulfonyl)amino]phenyl}pyrazin-2-yl)methyl]-amino}piperidine-1-carboxylate;
- Isopropyl 4-[({5-[2-fluoro-4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)-(methyl)amino]piperidine-1-carboxylate;
- Isopropyl 4-[{[5-(5-acetyl-2-thienyl)pyrazin-2-yl]methyl}(methyl)amino]-piperidine-1-carboxylate;
- 4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-N,N-dimethylbenzamide;
- 4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-2-fluoro-*N*-propylbenzamide;
- Methyl [4-(5-{[[1-(3,4-dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}-pyrazin-2-yl)phenyl]carbamate;
- *N*-[4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)phenyl]acetamide;
- *N*-[4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)phenyl]methanesulfonamide;
- 1-(3,4-Dichlorobenzoyl)-*N*-({5-[2-fluoro-4-(methylsulfonyl)phenyl]pyrazin-2-yl}methyl)-*N*-methylpiperidin-4-amine;
- 1-[5-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-2-thienyl]ethanone;
- 4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-2-fluorobenzamide;
- 4-(5-{[[1-(3,4-Dichlorobenzoyl)piperidin-4-yl](methyl)amino]methyl}pyrazin-2-yl)-N-methylbenzamide;

- 4-(5-{[(1-Benzoylpiperidin-4-yl)(methyl)amino]methyl}pyrazin-2-yl)-*N*-methylbenzamide;
- 4-(5-{[(1-Benzoylpiperidin-4-yl)(methyl)amino]methyl}pyrazin-2-yl)-*N*,*N*-dimethylbenzamide;
- *tert*-Butyl 4-({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methoxy)piperidine-1-carboxylate;
- Isobutyl 4-({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methoxy)piperidine-1-carboxylate; and
- Benzyl 4-({5-[4-(methylsulfonyl)phenyl]pyrazin-2-yl}methoxy)piperidine-1-carboxylate.

14. A compound according to any one of claims 1 to 13 for use in therapy.

15. A compound according to any one of claims 1 to 13 for use in the treatment or prophylaxis of disorders relating to GPR119 activity, wherein said disorders are selected from the group consisting of Type 1 diabetes, Type 2 diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypercholesterolemia, dyslipidemia, syndrome X, obesity, hypertension, chronic systemic inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, reduced fibrinolysis, endothelial dysfunction and osteoporosis.

16. Use of a compound according to any one of claims 1 to 13 in the manufacture of a medicament for the treatment or prophylaxis of disorders relating to GPR119 activity, wherein said disorders are selected from the group consisting of Type 1 diabetes, Type 2 diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypercholesterolemia, dyslipidemia, syndrome X, obesity, hypertension, chronic systemic inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, reduced fibrinolysis, endothelial dysfunction and osteoporosis.

17. A method for the treatment or prophylaxis of disorders relating to GPR119 activity which comprises administering to a mammal, including man, in need of such treatment an effective amount of a compound according to any one of claims 1 to 13, wherein said disorders relating to GPR119 activity are selected from the group

consisting of Type 1 diabetes, Type 2 diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypercholesterolemia, dyslipidemia, syndrome X, obesity, hypertension, chronic systemic inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, reduced fibrinolysis, endothelial dysfunction and osteoporosis.

18. A pharmaceutical formulation comprising a compound according to any one of claims 1 to 13 as active ingredient in combination with a pharmaceutically acceptable diluent or carrier.

19. The pharmaceutical formulation according to claim 18 for use in the treatment or prophylaxis of disorders relating to GPR119 activity, wherein said disorders are selected from the group consisting of Type 1 diabetes, Type 2 diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypercholesterolemia, dyslipidemia, syndrome X, obesity, hypertension, chronic systemic inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, reduced fibrinolysis, endothelial dysfunction and osteoporosis.

20. Use of a compound according to any one of claims 1 to 13, in combination with a DPP-IV inhibitor, in the manufacture of a medicament for the treatment or prophylaxis of disorders relating to GPR119 activity, wherein said disorders are selected from the group consisting of Type 1 diabetes, Type 2 diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypercholesterolemia, dyslipidemia, syndrome X, obesity, hypertension, chronic systemic inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, reduced fibrinolysis, endothelial dysfunction and osteoporosis.

21. A method for the treatment or prophylaxis of disorders relating to GPR119 activity which comprises administering to a mammal, including man, in need of such treatment an effective amount of a compound according to any one of claims 1 to 13 in combination with a DPP-IV inhibitor, wherein said disorders relating to GPR119 activity are selected from the group consisting of Type 1 diabetes, Type 2 diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypercholesterolemia, dyslipidemia, syndrome X, obesity, hypertension, chronic

systemic inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, reduced fibrinolysis, endothelial dysfunction and osteoporosis.

22. The pharmaceutical formulation according to claim 18 which in addition comprises a DPP-IV inhibitor.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/052268

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 A61K31/497 A61P3/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/070208 A (PROSIDION LTD [GB]; BRADLEY STUART EDWARD [GB]; FYFE MATTHEW COLIN THO) 6 July 2006 (2006-07-06) page 3, line 26; claims 1,3-5,8,17,19-21; examples 1-3	1-22
P,Y	WO 2008/025800 A (BIOVITRUM AB PUBL [SE]; BRANDT PETER [SE]; JOHANSSON GARY [SE]; JOHANS) 6 March 2008 (2008-03-06) the whole document	1-22
P,X	WO 2008/070692 A (SMITHKINE BEECHAM CORP [US]; FANG JING [US]; TANG JUN [US]; CARPENTER) 12 June 2008 (2008-06-12) claims 1,11,14,15,20,24-27; examples 134,145,152,161,165,188	1-22

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 June 2009	17/06/2009

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1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/052268

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006070208 A	06-07-2006	EP 1838698 A1	03-10-2007
		JP 2008526724 T	24-07-2008
WO 2008025800 A	06-03-2008	AU 2007291252 A1	06-03-2008
		AU 2007291254 A1	06-03-2008
		CA 2660699 A1	06-03-2008
		CA 2661371 A1	06-03-2008
		EP 2059516 A1	20-05-2009
		EP 2059517 A1	20-05-2009
		WO 2008025798 A1	06-03-2008
		WO 2008025799 A1	06-03-2008
		US 2008058339 A1	06-03-2008
		US 2008103141 A1	01-05-2008
		US 2008103123 A1	01-05-2008
WO 2008070692 A	12-06-2008	NONE	