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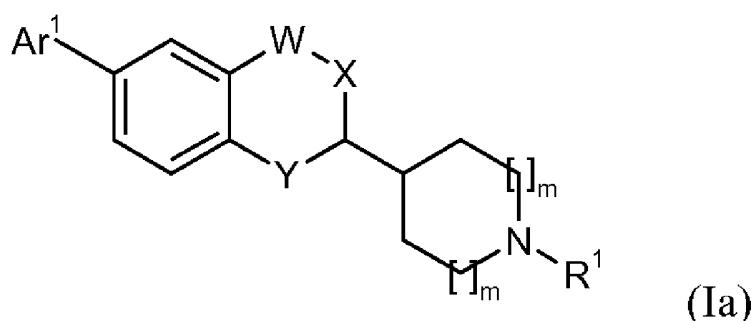
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(54) Title: NEW GPR119MODULATORS



(57) Abstract: The application relates to compounds of Formula (Ia); and pharmaceutically acceptable salts, solvates, hydrates, geometrical isomers, tautomers, optical isomers or 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 GPR119, such as diabetes, obesity and osteoporosis.

NEW GPR119MODULATORS

FIELD OF INVENTION

- 5 The present invention relates to certain novel compounds, to pharmaceutical compositions comprising these novel 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.

10 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 will 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.

30 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.

5 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
10 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. Only a few 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
15 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.

20 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 osteoporosis-related fracture in their life-time. Risk factors include
25 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).

30

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, 2601-2609, 2007). GPR119 agonists enhances 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 5 intestinal L-cells (Chu et al., Endocrinology 149, 2038-2047, 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 10 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 discloses 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 15 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.

20 WO 2008/025798, WO 2008/025799 and WO 2008/025800 disclose pyridine, pyridazine and pyrimidine compounds, respectively, as agonists of GPR119, which can 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 25 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.

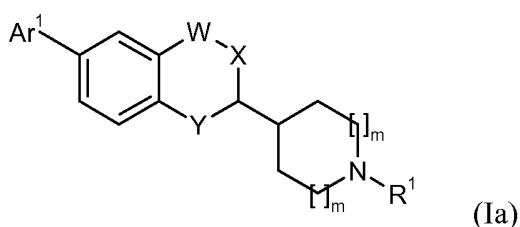
WO 2007/120689 discloses a method of using GPR119 receptor to identify compounds useful for increasing bone mass in an individual. GPR119 agonists are shown to enhance 30 GIP in wild type mice.

DISCLOSURE OF THE INVENTION

It has surprisingly been found that compounds of the general Formula (Ia) to (Id) 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.

10

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



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

W, X and Y are each independently CH₂, O, NH or N(CH₃), provided that at least one of W and X is CH₂;

20 m is each independently 0 or 1;

R¹ is -C(O)OR², -C(O)R², -C(O)NR²R³, -C(O)CH₂NR²R³, -CH₂C(O)NR²R³, -S(O)₂R², -C(O)C(O)R⁹ or a 5- or 6-membered heteroaryl group linked via a ring carbon atom, wherein said heteroaryl group is optionally substituted with C₁₋₄-alkyl;

25

Ar¹ is phenyl or heteroaryl, each of which is optionally independently substituted in one or more positions with a substituent selected from:

- (a) CF₃SO₃,
- (b) halogen selected from bromine, chlorine and fluorine,
- 30 (c) C₁₋₄-alkylsulfoximine,

- (d) $-\text{S}(\text{O})\text{R}^4$,
- (e) $-\text{S}(\text{O})_2\text{R}^4$,
- (f) $-\text{S}(\text{O})_2\text{NR}^5\text{R}^5$,
- (g) $-\text{NR}^6\text{S}(\text{O})_2\text{R}^4$,
- 5 (h) $-\text{CH}_2\text{-NR}^6\text{C}(\text{O})\text{R}^4$,
- (i) $-\text{NR}^6\text{C}(\text{O})\text{R}^4$,
- (j) $-\text{C}(\text{O})\text{NR}^5\text{R}^5$,
- (k) $-\text{CH}_2\text{-C}(\text{O})\text{NR}^5\text{R}^5$,
- 10 (l) $-\text{C}(\text{O})\text{R}^4$,
- (m) $\text{H}_2\text{N-C}(\text{O})\text{O}-$,
- (n) $\text{CH}_3\text{-NH-C}(\text{O})\text{O}-$,
- (o) $(\text{CH}_3)_2\text{NC}(\text{O})\text{O}-$,
- (p) $\text{CH}_3\text{OC}(\text{O})\text{NH}-$,
- (q) C-heterocyclyl, optionally substituted with C_{1-4} -alkyl,
- 15 (r) N-heterocyclylcarbonylvinyl, wherein N-heterocyclyl is optionally substituted with C_{1-4} -alkyl,
- (s) $-\text{CN}$,
- (t) $-\text{OR}^8$,
- (u) $-\text{SCF}_3$,
- 20 (v) $-\text{NO}_2$,
- (w) C-heterocyclsulfonyl, optionally substituted with C_{1-4} -alkyl,
- (x) $-\text{NR}^5\text{R}^5$,
- (y) $-\text{C}(\text{OH})\text{CH}_3\text{CF}_3$,
- (z) $[\text{CF}_3\text{CH}_3(\text{OH})\text{C}]\text{-C}_{1-6}\text{-alkyl}$,
- 25 (aa) cyano- C_{1-6} -alkyl,
- (bb) guanidino,
- (cc) amidino,
- (dd) C_{1-6} -alkyl,
- (ee) C_{1-6} -alkylthio,
- 30 (ff) C_{1-4} -alkoxy- C_{1-4} -alkyl,
- (gg) fluoro- C_{1-4} -alkyl,
- (hh) C_{2-6} -alkenyl,
- (ii) fluoro- C_{2-4} -alkenyl,
- (jj) hydroxy- C_{1-6} -alkyl,

- (kk) C₁₋₄-alkylsulfonyl-C₁₋₄-alkyl,
(ll) hydroxy-C₂₋₄-alkoxy-C₁₋₄-alkyl,
(mm) C₂₋₃-acyl-C₁₋₃-alkyl,
(nn) C₂₋₆-alkynyl,
5 (oo) C₃₋₆-cycloalkyl,
(pp) hydroxy-C₃₋₆-cycloalkyl,
(qq) fluoro-C₃₋₆-cycloalkyl,
(rr) methyl-C₃₋₆-cycloalkyl,
(ss) C₃₋₆-cycloalkyl-C₁₋₄-alkyl, wherein C₃₋₆-cycloalkyl is optionally substituted
10 with methyl,
(tt) C-heterocyclcarbonyl, optionally substituted with C₁₋₄-alkyl,
(uu) C₃₋₆-cycloalkylthio,
(vv) R⁵R⁵N-C₁₋₂-alkyl,
(ww) -(CH₂)_nC(O)OR⁷, wherein n is 0, 1, 2 or 3,
15 (xx) phenyl, and
(yy) heteroaryl,

wherein phenyl or heteroaryl as substituent on Ar¹ is optionally substituted in one or more positions with a substituent independently selected from the group Z¹ consisting of:

- (a) halogen selected from bromine, chlorine and fluorine,
20 (b) C₁₋₄-alkyl,
(c) hydroxy,
(d) C₁₋₄-alkoxy,
(e) -OCF₃,
(f) -SCF₃,
25 (g) -CN,
(h) -C(OH)CH₃CF₃,
(i) hydroxy-C₁₋₄-alkyl,
(j) -CF₃,
(k) -S(O)₂CH₃,
30 (l) -S(O)₂NH₂,
(m) -S(O)₂NHCH₃,
(n) -S(O)₂N(CH₃)₂,
(o) -N(CH₃)S(O)₂CH₃,
(p) -N(CH₃)C(O)CH₃,

- (q) $-\text{C}(\text{O})\text{NH}_2$,
- (r) $-\text{C}(\text{O})\text{NHCH}_3$,
- (s) $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$,
- (t) $-\text{C}(\text{O})\text{CH}_3$,
- 5 (u) N-heterocyclmethyl,
- (v) N-heterocycll, optionally substituted with methyl,
- (w) phenoxy,
- (x) $-\text{NH}_2$,
- (y) $-\text{NHCH}_3$,
- 10 (z) $-\text{N}(\text{CH}_3)_2$, and
- (aa) methoxycarbonyl;

R^2 is selected from:

- (a) C_{1-6} -alkyl,
- 15 (b) C_{1-6} -alkoxy- C_{1-6} -alkyl,
- (c) hydroxy- C_{2-6} -alkyl,
- (d) fluoro- C_{2-6} -alkyl,
- (e) amino- C_{2-6} -alkyl,
- (f) C_{1-3} -alkylamino- C_{2-6} -alkyl,
- 20 (g) di(C_{1-3} -alkyl)amino- C_{2-6} -alkyl,
- (h) cyano- C_{1-6} -alkyl,
- (i) C_{1-6} -alkylsulfonyl- C_{2-6} -alkyl,
- (j) C_{2-3} -acylamino- C_{2-4} -alkyl,
- (k) C_{1-4} -alkylthio- C_{2-4} -alkyl,
- 25 (l) C_{2-4} -acyl- C_{1-4} -alkyl,
- (m) C_{3-6} -alkynyl,
- (n) C_{3-6} -alkenyl,
- (o) C_{3-7} -cycloalkyl,
- (p) C_{5-8} -cycloalkenyl,
- 30 (q) C-heterocycll, optionally substituted with C_{1-4} -alkyl,
- (r) C_{7-8} -bicycll, optionally substituted with hydroxy,
- (s) C_{7-8} -bicyclmethyl,
- (t) azabicycll, optionally substituted with hydroxy,

- (u) C₃₋₇-cycloalkyl-C₁₋₄-alkyl, wherein cycloalkyl is optionally substituted with methyl or hydroxy,
- (v) C₁₋₆-alkylsulfonyl-C₂₋₆-alkyl,
- (w) C₂₋₃-acyl-C₁₋₄-alkyl,
- 5 (x) diphenylmethyl,
- (y) arylcarbonyl-C₁₋₄-alkyl,
- (z) heteroarylcarbonyl-C₁₋₄-alkyl,
- (aa) [CF₃CH₃(OH)C]-C₁₋₆-alkyl,
- (bb) N-heterocyclylcarbonyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- 10 (cc) C-heterocyclylcarbonyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- (dd) aminocarbonyl-C₂₋₆-alkyl,
- (ee) C₁₋₃-alkylaminocarbonyl-C₂₋₆-alkyl,
- 15 (ff) di(C₁₋₃-alkyl)aminocarbonyl-C₂₋₆-alkyl,
- (gg) hydroxy-C₂₋₄-alkoxy-C₂₋₄-alkyl,
- (hh) hydroxy-C₄₋₆-cycloalkyl,
- (ii) oxo-C₄₋₆-cycloalkyl,
- (jj) fluoro-C₄₋₆-cycloalkyl,
- 20 (kk) C₁₋₃-alkoxy-C₄₋₆-cycloalkyl,
- (ll) methyl-C₃₋₆-cycloalkyl,
- (mm) oxo-N-heterocyclyl-C₂₋₄-alkyl,
- (nn) fluoro-N-heterocyclyl-C₂₋₄-alkyl,
- (oo) amino-N-heterocyclyl-C₂₋₄-alkyl,
- 25 (pp) hydroxy-N-heterocyclyl-C₂₋₄-alkyl,
- (qq) N-heterocyclyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- (rr) C-heterocyclyl-C₁₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- 30 (ss) aryl,
- (tt) aryl-C₁₋₄-alkyl,
- (uu) aryl-C₃₋₆-alkenyl,
- (vv) aryl-C₃₋₆-alkynyl,
- (ww) aryloxymethyl,

- (xx) heteroaryl,
- (yy) heteroaryl-C₁₋₄-alkyl,
- (zz) heteroaryl-C₃₋₆-alkenyl, and
- (aaa) heteroaryl-C₃₋₆-alkynyl,

5 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 Z¹ as defined above;

R³ is selected from:

- 10 (a) hydrogen,
- (b) C₁₋₆-alkyl,
- (c) fluoro-C₂₋₆-alkyl,
- (d) hydroxy-C₂₋₆-alkyl,
- (e) C₁₋₆-alkoxy-C₂₋₆-alkyl,
- 15 (f) amino-C₂₋₆-alkyl,
- (g) C₁₋₃-alkylamino-C₂₋₆-alkyl,
- (h) di(C₁₋₃-alkyl)amino-C₂₋₆-alkyl,
- (i) cyano-C₁₋₆-alkyl,
- (j) C₁₋₆-alkylsulfonyl-C₂₋₆-alkyl,
- 20 (k) C₂₋₃-acylamino-C₂₋₄-alkyl,
- (l) C₁₋₄-alkylthio-C₂₋₄-alkyl, and
- (m) C₂₋₄-acyl-C₁₋₄-alkyl;

or R² and R³ together with the nitrogen to which they are attached form a heterocyclic ring, wherein said heterocyclic ring may be optionally substituted with:

25 i) a substituent selected from:

- (aa) hydroxy,
- (bb) C₁₋₃-alkyl,
- (cc) amino,
- (dd) methylamino,
- 30 (ee) dimethylamino,
- (ff) hydroxy-C₁₋₂-alkyl, and
- (gg) 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;

5 R⁴ is independently selected from:

- (a) C₁₋₆-alkyl,
- (b) fluoro-C₁₋₆-alkyl,
- (c) hydroxy-C₂₋₆-alkyl,
- (d) C₁₋₄-alkoxy-C₂₋₄-alkyl,
- 10 (e) C₂₋₄-acyl-C₁₋₄-alkyl,
- (f) carboxy-C₁₋₃-alkyl,
- (g) C₃₋₆-cycloalkyl,
- (h) oxo-C₄₋₆-cycloalkyl,
- (i) hydroxy-C₄₋₆-cycloalkyl,
- 15 (j) fluoro-C₄₋₆-cycloalkyl,
- (k) methyl-C₃₋₆-cycloalkyl,
- (l) N-heterocyclylcarbonyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- 20 (m) N-heterocyclyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- (n) oxo-N-heterocyclyl-C₂₋₄-alkyl,
- (o) fluoro-N-heterocyclyl-C₂₋₄-alkyl,
- (p) hydroxy-N-heterocyclyl-C₂₋₄-alkyl,
- (q) amino-N-heterocyclyl-C₂₋₄-alkyl,
- 25 (r) aminocarbonyl-C₂₋₄-alkyl,
- (s) C₁₋₃-alkylaminocarbonyl-C₂₋₄-alkyl,
- (t) di(C₁₋₃-alkyl)aminocarbonyl-C₂₋₄-alkyl,
- (u) C₂₋₃-acylamino-C₂₋₄-alkyl,
- (v) hydroxy-C₂₋₄-alkoxy-C₂₋₄-alkyl,
- 30 (w) C-heterocyclylcarbonyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- (x) C₃₋₆-cycloalkyl-C₁₋₂-alkyl, wherein cycloalkyl is optionally substituted with methyl,
- (y) amino-C₂₋₄-alkyl,

- (z) C₁₋₂-alkylamino-C₂₋₄-alkyl,
- (aa) di(C₁₋₂-alkyl)amino-C₂₋₄-alkyl,
- (bb) phenyl, and
- (cc) heteroaryl,

5 wherein any phenyl or heteroaryl residue is optionally substituted in one or more positions with a substituent independently selected from the group Z² consisting of:

- (a) halogen selected from chlorine and fluorine,
- (b) C₁₋₄-alkoxy,
- (c) hydroxymethyl,
- 10 (d) -CN,
- (e) -CF₃,
- (f) C₁₋₄-alkyl,
- (g) -OCF₃, and
- (h) -C(O)CH₃;

15

R⁵ is each independently selected from:

- (a) hydrogen,
- (b) C₁₋₆-alkyl,
- (c) C₃₋₆-alkenyl,
- 20 (d) C₃₋₆-cycloalkyl,
- (e) methyl-C₃₋₆-cycloalkyl,
- (f) C₃₋₆-cycloalkyl-C₁₋₄-alkyl, wherein cycloalkyl is optionally substituted with hydroxy or methyl,
- (g) N-heterocyclyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- 25 (h) heteroaryl-C₁₋₄-alkyl, wherein heteroaryl is optionally substituted with methyl,
- (i) carboxy-C₁₋₃-alkyl,
- (j) fluoro-C₂₋₄-alkyl,
- 30 (k) amino-C₂₋₆-alkyl,
- (l) cyano-C₁₋₆-alkyl,
- (m) hydroxy-C₂₋₆-alkyl,
- (n) dihydroxy-C₂₋₆-alkyl,
- (o) C₁₋₄-alkoxy-C₂₋₄-alkyl,

- (p) C₁₋₄-alkylamino-C₂₋₄-alkyl,
- (q) di(C₁₋₄-alkyl)amino-C₂₋₄-alkyl,
- (r) aminocarbonyl-C₁₋₄-alkyl,
- (s) C₂₋₃-acylamino-C₂₋₄-alkyl,
- 5 (t) C₁₋₄-alkylthio-C₂₋₄-alkyl,
- (u) C₂₋₄-acyl-C₁₋₄-alkyl, and
- (v) C₁₋₄-alkylsulfonyl-C₁₋₄-alkyl,

or two R⁵ groups together with the nitrogen to which they are attached form a heterocyclic ring, wherein said heterocyclic ring may be optionally substituted with:

10 i) a substituent selected from:

- (aa) hydroxy,
- (bb) C₁₋₃-alkyl,
- (cc) amino,
- (dd) methylamino,
- 15 (ee) dimethylamino,
- (ff) hydroxy-C₁₋₂-alkyl, and
- (gg) aminomethyl;

ii) one or two oxo groups; or

iii) one or two fluorine atoms,

20 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;

or two R⁵ groups together with the nitrogen to which they are attached form the group 4-(pyrimidin-2-yl)piperazin-1-yl;

25

R⁶ is independently selected from:

- (a) hydrogen,
- (b) C₁₋₄-alkyl, and
- (c) hydroxy-C₂₋₄-alkyl;

30

R⁷ is independently selected from:

- (a) hydrogen, and
- (b) C₁₋₄-alkyl;

R⁸ is independently selected from:

- (a) hydrogen,
- (b) C₁₋₆-alkyl,
- (c) fluoro-C₁₋₆-alkyl,
- 5 (d) hydroxy-C₂₋₆-alkyl,
- (e) amino-C₂₋₆-alkyl,
- (f) C₁₋₃-alkylamino-C₂₋₄-alkyl,
- (g) di(C₁₋₃-alkyl)amino-C₂₋₄-alkyl,
- (h) C₁₋₄-alkylsulfonyl-C₂₋₄-alkyl,
- 10 (i) N-heterocyclyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- (j) C-heterocyclyl, optionally substituted with methyl,
- (k) C₂₋₃-acylamino-C₂₋₄-alkyl,
- (l) [CF₃CH₃(OH)C]-C₁₋₆-alkyl,
- 15 (m) C₃₋₆-cycloalkyl,
- (n) methyl-C₃₋₆-cycloalkyl,
- (o) C₃₋₆-cycloalkyl-C₁₋₂-alkyl, wherein cycloalkyl is optionally substituted with methyl,
- (p) aryl, and
- 20 (q) heteroaryl,

wherein any aryl or heteroaryl residue is optionally independently substituted in one or two positions with a substituent selected from the group Z² as defined above; and

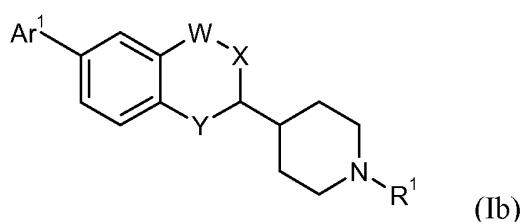
R⁹ is aryl or heteroaryl, each of which is optionally substituted in one or more positions with a substituent independently selected from the group Z² as defined above.

In a preferred embodiment of compounds of formula (Ia), W, X and Y are each independently CH₂, O or NH, provided that (i) at least one of W and X is CH₂, and (ii) no more than one of W, X and Y is NH.

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In another preferred embodiment of compounds of formula (Ia), m is each 1.

A preferred group of compounds of the invention are compounds of Formula (Ib):



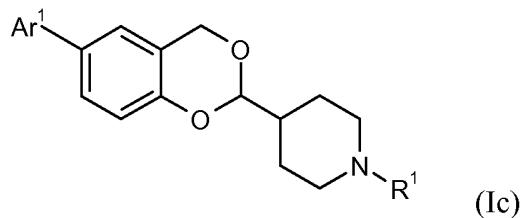
5 and pharmaceutically acceptable salts, solvates, hydrates, geometrical isomers, tautomers, optical isomers or *N*-oxides thereof; wherein:

W and X are each independently CH₂ or O, provided that at least one of W and X is CH₂;

Y is CH₂, O or NH; and

10 Ar¹, Z¹, Z², R¹ to R⁹ are as defined in Formula (Ia).

A further preferred group of compounds of the invention are compounds of Formula (Ic):



15

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

Z¹, Z², R¹ to R⁶ are as defined in Formula (Ia);

20 Ar¹ is phenyl or heteroaryl, each of which is optionally substituted in one or two positions with a substituent independently selected from the group Z³ consisting of:

- (a) CF₃SO₃,
- (b) halogen selected from bromine, chlorine and fluorine,
- (c) C₁₋₄-alkylsulfoximine,
- 25 (d) -S(O)R⁴,
- (e) -S(O)₂R⁴,
- (f) -S(O)₂NR⁵R⁵,

- (g) $-\text{NR}^6\text{S(O)}_2\text{R}^4$,
- (h) $-\text{NR}^6\text{C(O)}\text{R}^4$,
- (i) $-\text{CH}_2\text{-NR}^6\text{C(O)}\text{R}^4$,
- (j) $-\text{C(O)}\text{NR}^5\text{R}^5$,
- 5 (k) $-\text{CH}_2\text{-C(O)}\text{NR}^5\text{R}^5$,
- (l) $-\text{C(O)}\text{R}^4$,
- (m) $\text{H}_2\text{N-C(O)O-}$,
- (n) $\text{CH}_3\text{-NH-C(O)O-}$,
- (o) $(\text{CH}_3)_2\text{NC(O)O-}$,
- 10 (p) $-\text{NHC(O)OCH}_3$,
- (q) C-heterocyclyl, optionally substituted with methyl,
- (r) N-heterocyclylcarbonylvinyl, wherein N-heterocyclyl is optionally substituted with methyl,
- (s) $-\text{CN}$,
- 15 (t) $-\text{OR}^8$,
- (u) $-\text{SCF}_3$,
- (v) nitro,
- (w) C-heterocyclsulfonyl, optionally substituted with methyl,
- (x) $-\text{NR}^5\text{R}^5$,
- 20 (y) $-\text{C(OH)CH}_3\text{CF}_3$,
- (z) cyano-C₁₋₆-alkyl,
- (aa) guanidino,
- (bb) C₁₋₆-alkyl,
- (cc) C₁₋₃-alkylthio,
- 25 (dd) C₁₋₄-alkoxy-C₁₋₄-alkyl,
- (ee) fluoro-C₁₋₄-alkyl,
- (ff) C₂₋₆-alkenyl,
- (gg) fluoro-C₂₋₄-alkenyl,
- (hh) hydroxy-C₁₋₆-alkyl,
- 30 (ii) C₁₋₄-alkylsulfonyl-C₁₋₄-alkyl,
- (jj) hydroxy-C₂₋₄-alkoxy-C₁₋₄-alkyl,
- (kk) C₂₋₃-acyl-C₁₋₃-alkyl,
- (ll) C₂₋₆-alkynyl,
- (mm) C₃₋₆-cycloalkyl,

- (nn) hydroxy-C₃₋₆-cycloalkyl,
 - (oo) fluoro-C₃₋₆-cycloalkyl,
 - (pp) methyl-C₃₋₆-cycloalkyl,
 - (qq) C-heterocycl carbonyl, optionally substituted with methyl,
 - 5 (rr) C₃₋₆-cycloalkyl-C₁₋₄-alkyl,
 - (ss) R⁵R⁵N-C₁₋₂-alkyl,
 - (tt) -(CH₂)_nC(O)OH, wherein n is 1, 2 or 3, and
 - (uu) heteroaryl,
- wherein any heteroaryl residue as substituent on Ar¹ is optionally substituted in one or
10 more positions with a substituent independently selected from the group Z² as defined
herein for Formula (Ia);

R⁸ is independently selected from:

- 15 (a) hydrogen,
- (b) C₁₋₄-alkyl,
- (c) CF₃,
- (d) C₃₋₅-cycloalkyl,
- (e) methyl-C₃₋₅-cycloalkyl,
- (f) di(C₁₋₃-alkyl)amino-C₂₋₃-alkyl, and
- 20 (g) C-heterocycl, optionally substituted with methyl;

R⁹ is phenyl which is optionally substituted in one or two positions with a substituent
independently selected from the group Z² as defined herein for Formula (Ia).

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

Ar¹ is phenyl, quinolinyl, pyridinyl, thiazolyl, thieryl, furyl or isoxazolyl, each of which is
optionally substituted in one or two positions with a substituent independently selected
from the group Z⁴ consisting of:

- 30 (a) halogen selected from chlorine and fluorine,
- (b) C₁₋₄-alkylsulfoximine,
- (c) C₁₋₄-alkylsulfonyl,
- (d) C₁₋₄-alkylsulfinyl,
- (e) hydroxy-C₂₋₄-alkylsulfonyl,

- (f) amino-C₂₋₄-alkylsulfonyl,
- (g) C₃₋₅-cycloalkylsulfonyl,
- (h) methyl-C₃₋₅-cycloalkylsulfonyl,
- (i) trifluoromethylsulfonyl,
- 5 (j) methylthio,
- (k) -S(O)₂NR^{5A}R^{5A},
- (l) C₁₋₄-alkylsulfonamido,
- (m) C₂₋₄-acylamino,
- (n) C₂₋₄-acylaminomethyl,
- 10 (o) carboxy-C₁₋₃-alkylcarbonylamino,
- (p) -C(O)NR^{5A}R^{5A},
- (q) -CH₂-C(O)NR^{5A}R^{5A},
- (r) -NHC(O)OCH₃,
- (s) C₂₋₄-acyl,
- 15 (t) C₃₋₅-cycloalkylcarbonyl,
- (u) C₁₋₄-alkoxy,
- (v) C₃₋₅-cycloalkyloxy,
- (w) C-heterocyclyl,
- (x) N-heterocyclylcarbonylvinyl, wherein N-heterocyclyl is optionally substituted
20 with methyl,
- (y) -CN,
- (z) -OH,
- (aa) -OCF₃,
- (bb) nitro,
- 25 (cc) -CF₃,
- (dd) -NR^{5A}R^{5A},
- (ee) di(C₁₋₂-alkyl)amino-C₂₋₃-alkoxy,
- (ff) -C(OH)CH₃CF₃,
- (gg) cyano-C₁₋₂-alkyl,
- 30 (hh) guanidino,
- (ii) C₁₋₄-alkyl,
- (jj) C₃₋₅-cycloalkyl,
- (kk) C₁₋₂-alkoxy-C₁₋₂-alkyl,
- (ll) vinyl,

- (mm) ethynyl,
- (nn) 5-membered heteroaryl,
- (oo) hydroxy-C₁₋₂-alkyl,
- (pp) C-heterocyloxy, optionally substituted with methyl,
- 5 (qq) R^{5A}R^{5A}N-C₁₋₂-alkyl, and
- (rr) -(CH₂)_nC(O)OH, wherein n is 1, 2 or 3;

10 R¹ is a group R^{1A}, which is selected from -C(O)OR^{2A}, -C(O)R^{2A}, -C(O)NR^{2A}R^{3A}, -CH₂C(O)NR^{2A}R^{3A}, -C(O)C(O)-phenyl or a 6-membered heteroaryl group linked via a ring carbon atom, wherein the said heteroaryl group is optionally substituted with methyl;

R^{2A} is selected from:

- (a) C₁₋₆-alkyl,
- (b) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- 15 (c) hydroxy-C₂₋₆-alkyl,
- (d) hydroxy-C₂₋₄-alkoxy-C₂₋₄-alkyl,
- (e) fluoro-C₂₋₆-alkyl,
- (f) C₃₋₆-alkynyl,
- (g) C₃₋₇-cycloalkyl,
- 20 (h) C₅₋₈-cycloalkenyl,
- (i) C-heterocyclyl, optionally substituted with methyl,
- (j) C₇₋₈-bicyclyl,
- (k) 2-norbornylmethyl,
- (l) azabicyclyl,
- 25 (m) C₃₋₆-cycloalkyl-C₁₋₄-alkyl, wherein cycloalkyl is optionally substituted with methyl,
- (n) C₂₋₃-acyl-C₁₋₄-alkyl,
- (o) diphenylmethyl,
- (p) arylcarbonyl-C₁₋₄-alkyl,
- 30 (q) heteroarylcarbonyl-C₁₋₄-alkyl,
- (r) [CF₃CH₃(OH)C]-C₁₋₆-alkyl,
- (s) N-heterocyclylcarbonyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- (t) hydroxy-C₄₋₆-cycloalkyl,

- (u) oxo-C₄₋₆-cycloalkyl,
- (v) fluoro-C₄₋₆-cycloalkyl,
- (w) methoxy-C₄₋₆-cycloalkyl,
- (x) methyl-C₃₋₆-cycloalkyl,
- 5 (y) oxo-*N*-heterocyclyl-C₂₋₄-alkyl,
- (z) hydroxy-*N*-heterocyclyl-C₂₋₄-alkyl,
- (aa) fluoro-*N*-heterocyclyl-C₂₋₄-alkyl,
- (bb) amino-*N*-heterocyclyl-C₂₋₄-alkyl,
- (dd) *N*-heterocyclyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with
- 10 methyl,
- (ee) C-heterocyclyl-C₁₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- (ff) aryl,
- (gg) aryl-C₁₋₄-alkyl,
- 15 (hh) aryloxymethyl,
- (ii) heteroaryl, and
- (jj) heteroaryl-C₁₋₄-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
20 group Z⁵ consisting of:

- (a) halogen selected from bromine, chlorine and fluorine,
- (b) methyl,
- (c) ethyl,
- (d) methoxy,
- 25 (e) ethoxy,
- (f) isopropoxy,
- (g) phenoxy,
- (h) morpholin-4-ylmethyl,
- (i) 4-methylpiperazin-1-yl,
- (j) hydroxy,
- 30 (k) -OCF₃,
- (l) -CF₃,
- (m) -CN,
- (n) -C(OH)CH₃CF₃,

- (o) $-\text{N}(\text{CH}_3)_2$,
 (p) hydroxymethyl,
 (q) $-\text{S}(\text{O})_2\text{CH}_3$,
 (r) $-\text{C}(\text{O})\text{CH}_3$, and
 (s) $-\text{C}(\text{O})\text{NH}_2$;

R^{3A} is selected from:

- 10 (a) hydrogen,
(b) C₁₋₄-alkyl,
(c) hydroxy-C₂₋₄-alkyl, and
(d) methoxy-C₂₋₄-alkyl;

or R^{2A} and R^{3A} 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, amino or methyl group,

15 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;

20

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

- (a) hydrogen,
(b) C₁₋₃-alkyl,
(c) C₃₋₄-alkenyl,
25 (d) C₁₋₂-alkoxy-C₂₋₄-alkyl,
(e) C₃₋₄-cycloalkyl,
(f) C₃₋₄-cycloalkyl-C₁₋₂-alkyl, wherein cycloalkyl is optionally substituted with
hydroxy,
(g) hydroxy-C₂₋₄-alkyl,
30 (h) cyano-C₁₋₃-alkyl,
(i) N-heterocyclyl-C₂₋₄-alkyl,
(j) heteroaryl-C₁₋₂-alkyl,
(k) carboxy-C₁₋₂-alkyl,
(l) dihydroxy-C₂₋₄-alkyl,

- (m) aminocarbonyl-C₁₋₂-alkyl,
- (n) C₁₋₃-alkylamino-C₂₋₃-alkyl, and
- (o) di(C₁₋₃-alkyl)amino-C₂₋₃-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) methyl,
- (cc) amino,
- (dd) methylamino,
- (ee) dimethylamino,
- (ff) hydroxy-C₁₋₂-alkyl, and
- (gg) 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;

or two R⁵ groups together with the nitrogen to which they are attached form the group

20 4-(pyrimidin-2-yl)piperazin-1-yl.

In another more preferred subgroup of compounds of Formula (Ic), Ar¹ is selected from [(dimethylamino)carbonyl]phenyl, (methylsulfonyl)phenyl, quinolinyl, [(diethylamino)-

25 carbonyl]phenyl, [(4-methylpiperidin-1-yl)carbonyl]phenyl, [(4-oxopiperidin-1-yl)- carbonyl]phenyl, (methylsulfonyl)pyridinyl, [(methylsulfonyl)amino]phenyl, {[2-

morpholin-4-ylethyl)amino]sulfonyl}phenyl, (methylsulfonyl)nitrophenyl, (methyl- sulfonyl)aminophenyl, {[2-(dimethylamino)ethyl]amino}(methylsulfonyl)phenyl, {[2-(iso-

30 propylamino)ethyl]amino}(methylsulfonyl)phenyl, (methylsulfonyl)[(2-morpholin-4-yl- ethyl)amino]phenyl, [2-(dimethylamino)ethoxy](methylsulfonyl)phenyl, [(methylamino)- carbonyl]phenyl, [(ethylamino)carbonyl]phenyl, [(allylamino)carbonyl]phenyl, [(cyclo-

propylamino)carbonyl]phenyl, [(2-hydroxyethylamino)carbonyl]phenyl, [(3-hydroxy- propylamino)carbonyl]phenyl, [(2-methoxyethylamino)carbonyl]phenyl, {[2-hydroxy-1,1- dimethylethyl)amino]carbonyl}phenyl, [(3-hydroxyazetidin-1-yl)carbonyl]-phenyl, [(4- methylpiperazin-1-yl)carbonyl]phenyl, {[2-(furyl)ethyl]amino}carbonyl)-phenyl, (amino-

carbonyl)phenyl, (morpholin-4-ylcarbonyl)phenyl, [(2-hydroxyethyl)sulfonyl]phenyl, [(2-aminoethyl)sulfonyl]phenyl, {[[(2-methylprop-2-en-1-yl)amino]carbonyl]phenyl, [(but-3-en-1-ylamino)carbonyl]-phenyl, {[[(1-hydroxycyclopropyl)methyl]amino}carbonyl)-phenyl, {[2-(hydroxymethyl)morpholin-4-yl]carbonyl}phenyl, (2-carboxyethyl)-isoxazolyl, {[[(carboxymethyl)amino]carbonyl}furyl, (1*H*-tetrazol-5-yl)phenyl, {[amino-(imino)methyl]amino}-methyl-1,3-thiazolyl, pyridinyl, [(4-methylpiperazin-1-yl)carbonyl]furyl, [(4-methylpiperazin-1-yl)carbonyl]pyridinyl, [(1*E*)-3-(4-methylpiperazin-1-yl)-3-oxoprop-1-en-1-yl]thienyl, [(1*E*)-3-morpholin-4-yl-3-oxoprop-1-en-1-yl]thienyl, [(4-pyrimidin-2-ylpiperazin-1-yl)carbonyl]pyridinyl, {[[(2-dimethylamino)ethyl](methyl)amino]carbonyl}pyridinyl, (morpholin-4-ylcarbonyl)pyridinyl and {[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}-pyridinyl.

More preferably, Ar¹ is selected from 4-[(dimethylamino)carbonyl]phenyl, 4-(methylsulfonyl)phenyl, quinolin-5-yl, 4-[(diethylamino)carbonyl]phenyl, 4-[(4-methylpiperidin-1-yl)carbonyl]phenyl, 4-[(4-oxopiperidin-1-yl)carbonyl]phenyl, 5-(methylsulfonyl)pyridin-2-yl, 4-[(methylsulfonyl)amino]phenyl, (4-{{[(2-morpholin-4-ylethyl)amino]sulfonyl}}-phenyl, 4-(methylsulfonyl)-2-nitrophenyl, 2-amino-4-(methylsulfonyl)phenyl, 2-{{[2-(dimethylamino)ethyl]amino}-4-(methylsulfonyl)phenyl, 2-{{[2-(isopropylamino)ethyl]amino}-4-(methylsulfonyl)phenyl, 4-(methylsulfonyl)-2-[(2-morpholin-4-ylethyl)amino]}-phenyl, 2-[2-(dimethylamino)ethoxy]-4-(methylsulfonyl)phenyl, 4-[(methylamino)carbonyl]phenyl, 4-[(ethylamino)carbonyl]phenyl, 4-[(allylamino)carbonyl]phenyl, 4-[(cyclopropylamino)carbonyl]phenyl, 4-{{[(2-hydroxyethyl)amino]carbonyl}}-phenyl, 4-{{[(3-hydroxypropyl)amino]carbonyl}}-phenyl, 4-{{[(2-methoxyethyl)amino]carbonyl}}-phenyl, 4-{{[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl}}-phenyl, 4-[(3-hydroxyazetidin-1-yl)carbonyl]phenyl, 4-[(4-methylpiperazin-1-yl)carbonyl]phenyl, 4-{{[2-(2-furyl)ethyl]amino}carbonyl}phenyl, 4-(aminocarbonyl)phenyl, 4-(morpholin-4-ylcarbonyl)phenyl, 4-[(2-hydroxyethyl)sulfonyl]phenyl, 4-[(2-aminoethyl)sulfonyl]phenyl, 4-{{[(2-methylprop-2-en-1-yl)amino]carbonyl}}-phenyl, 4-{{[(but-3-en-1-ylamino)carbonyl]}-phenyl, 4-{{[(1-hydroxycyclopropyl)methyl]amino}carbonyl}phenyl, 4-{{[(2-hydroxymethyl)morpholin-4-yl]carbonyl}}-phenyl, 5-(2-carboxyethyl)isoxazol-3-yl, 5-{{[(carboxymethyl)amino]carbonyl}}-2-furyl, 6-(methylsulfonyl)pyridin-3-yl, 4-(1*H*-tetrazol-5-yl)phenyl, 2-{{[amino-(imino)methyl]amino}-4-methyl-1,3-thiazol-5-yl, 4-pyridinyl, 3-pyridinyl, 5-[(4-methylpiperazin-1-yl)carbonyl]pyridin-2-yl, 6-(morpholin-4-ylcarbonyl)pyridin-3-yl, 6-[(4-methylpiperazin-1-yl)carbonyl]pyridin-3-yl, 5-(morpholin-4-ylcarbonyl)pyridin-2-yl,

5-[(4-methylpiperazin-1-yl)carbonyl]-2-furyl, 5-[(1*E*)-3-(4-methylpiperazin-1-yl)-3-oxoprop-1-en-1-yl]-2-thienyl, 5-[(1*E*)-3-morpholin-4-yl-3-oxoprop-1-en-1-yl]-2-thienyl, 5-[(4-pyrimidin-2-yl)piperazin-1-yl]carbonyl]pyridin-2-yl, 5-{{[2-(dimethylamino)ethyl]-(methyl)amino]carbonyl}pyridin-2-yl, 5-{{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}-pyridin-2-yl and 6-{{[2-(dimethylamino)ethyl](methyl)amino]carbonyl}pyridin-3-yl.

In another more preferred subgroup of compounds of Formula (Ic), R^{1A} is selected from C(O)OR^{2A}, C(O)R^{2A}, -CH₂-C(O)NR^{2A}R^{3A}, -C(O)C(O)-phenyl or a 6-membered heteroaryl group linked via a ring carbon atom.

10

In one embodiment, R^{1A} is C(O)OR^{2A}, wherein R^{2A} is selected from benzyl, *tert*-butyl, ethyl, (1-methylcyclopropyl)methyl and isopropyl.

15

In another embodiment, R^{1A} is C(O)R^{2A}, wherein R^{2A} is selected from 4-cyanobenzyl, 3,4-dichlorophenyl, 2,4-difluorobenzyl, 3-(trifluoromethyl)benzyl, 4-methoxybenzyl, (1*H*-indol-3-yl)methyl, (1-methyl-1*H*-indol-3-yl)methyl, cyclohexylmethyl, 2-methyl-2-phenyl-*n*-propyl, 2-(4-methoxyphenyl)ethyl, 2-(3-chloro-4-methoxyphenyl)ethyl, 2-(4-hydroxyphenyl)ethyl, 2-(1*H*-indol-3-yl)ethyl, 2-cyclohexylethyl, 3-(4-fluorophenyl)propyl, 3-oxo-butyl, 3-oxo-3-(pyrrolidin-1-yl)propyl, 2-furyl, (4-fluorophenoxy)methyl, 1*H*-pyrrol-2-yl, (1*H*-tetrazol-1-yl)methyl, 2-pyridinyl, 4-pyridinyl, 2-pyrazinyl, 6-quinoxaliny, 4-isopropoxyphenyl, 2-naphthyl, phenyl, 2-hydroxy-4-methylphenyl, 2-phenoxyypyridin-5-yl, diphenylmethyl, 5-isopropoxypyridin-2-yl, 2,2,2-trifluoroethyl, 3-hydroxypyridin-2-yl, ethyl, 7-methoxy-1-benzofuran-2-yl, 3-(*N,N*-dimethylamino)phenyl, 2-hydroxyphenyl, benzoyl, 2-(1-methylpiperazin-4-yl)ethyl, 4-(1-methylpiperazin-4-yl)phenyl, methoxymethyl, 3,5-difluoropyridin-2-yl, 4-[(morpholin-4-yl)methyl]phenyl, 6-bromo-3-hydroxypyridin-2-yl and 1-ethylpropyl.

In yet another embodiment, R^{1A} is -CH₂-C(O)NR^{2A}R^{3A}, wherein R^{2A} and R^{3A} are both ethyl.

30

In a further embodiment R^{1A} is -C(O)C(O)-phenyl.

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

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

- benzyl 4-(6-{4-[(dimethylamino)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 5 • benzyl 4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- benzyl 4-(6-quinolin-5-yl-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 4-{2-[1-(3,4-dichlorobenzoyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}-N,N-dimethylbenzamide;
- 10 • 4-(2-{1-[(2,4-difluorophenyl)acetyl]piperidin-4-yl}-4H-1,3-benzodioxin-6-yl)-N,N-dimethylbenzamide;
- N,N-dimethyl-4-[2-(1-{[3-(trifluoromethyl)phenyl]acetyl}piperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzamide;
- 4-(2-{1-[(4-methoxyphenyl)acetyl]piperidin-4-yl}-4H-1,3-benzodioxin-6-yl)-N,N-dimethylbenzamide;
- 15 • 4-(2-{1-[(4-cyanophenyl)acetyl]piperidin-4-yl}-4H-1,3-benzodioxin-6-yl)-N,N-dimethylbenzamide;
- 4-{2-[1-(1H-indol-3-ylacetyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}-N,N-dimethylbenzamide;
- 20 • N,N-dimethyl-4-(2-{1-[(1-methyl-1H-indol-3-yl)acetyl]piperidin-4-yl}-4H-1,3-benzodioxin-6-yl)benzamide;
- 4-{2-[1-(cyclohexylacetyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}-N,N-dimethylbenzamide;
- N,N-dimethyl-4-{2-[1-(3-methyl-3-phenylbutanoyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}benzamide;
- 25 • 4-(2-{1-[3-(4-methoxyphenyl)propanoyl]piperidin-4-yl}-4H-1,3-benzodioxin-6-yl)-N,N-dimethylbenzamide;
- 4-(2-{1-[3-(3-chloro-4-methoxyphenyl)propanoyl]piperidin-4-yl}-4H-1,3-benzodioxin-6-yl)-N,N-dimethylbenzamide;
- 30 • 4-(2-{1-[3-(4-hydroxyphenyl)propanoyl]piperidin-4-yl}-4H-1,3-benzodioxin-6-yl)-N,N-dimethylbenzamide;
- 4-(2-{1-[3-(1H-indol-3-yl)propanoyl]piperidin-4-yl}-4H-1,3-benzodioxin-6-yl)-N,N-dimethylbenzamide;

- 4-{2-[1-(3-cyclohexylpropanoyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-*N,N*-dimethylbenzamide;
- 4-(2-{1-[4-(4-fluorophenyl)butanoyl]piperidin-4-yl}-4*H*-1,3-benzodioxin-6-yl)-*N,N*-dimethylbenzamide;
- 5 • *N,N*-dimethyl-4-{2-[1-(4-oxopentanoyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-benzamide;
- *N,N*-dimethyl-4-{2-[1-(4-oxo-4-pyrrolidin-1-ylbutanoyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzamide;
- 10 • benzyl 4-(6-{4-[(diethylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- benzyl 4-(6-{4-[(4-methylpiperidin-1-yl)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;
- benzyl 4-(6-{4-[(4-oxopiperidin-1-yl)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;
- 15 • benzyl 4-{6-[5-(methylsulfonyl)pyridin-2-yl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- 1-(2-furoyl)-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine;
- 1-[(4-fluorophenoxy)acetyl]-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine;
- 20 • 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-1-(1*H*-pyrrol-2-yl-carbonyl)piperidine;
- 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-1-(1*H*-tetrazol-1-ylacetyl)-piperidine;
- 2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]pyridine;
- 25 • 4-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]pyridine;
- 2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]pyrazine;
- 30 • 6-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]quinoxaline;
- 1-(4-isopropoxybenzoyl)-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidine;
- 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-1-(2-naphthoyl)piperidine;

- 1-benzoyl-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine;
- 5-methyl-2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)carbonyl]phenol;
- 5-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-5
5 carbonyl]-2-phenoxyypyridine;
- 1-(diphenylacetyl)-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-10
10 piperidine;
- 5-isopropoxy-2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)carbonyl]pyridine;
- 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-1-(3,3,3-trifluoro-15
15 propanoyl)piperidine;
- 2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]pyridin-3-ol;
- 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-1-propionylpiperidine;
- 1-[(7-methoxy-1-benzofuran-2-yl)carbonyl]-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-20
20 benzodioxin-2-yl}piperidine;
- dimethyl{3-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)carbonyl]phenyl}amine;
- 2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]phenol;
- 2-(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-2-oxo-1-phenylethanone;
- 1-methyl-4-[3-(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-3-oxopropyl]piperazine;
- 1-methyl-4-{4-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)carbonyl]phenyl}piperazine;
- 1-(methoxyacetyl)-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-25
25 piperidine;
- 3,5-difluoro-2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)carbonyl]pyridine;
- 4-{4-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]benzyl}morpholine;
- 6-bromo-2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]pyridin-3-ol;

- benzyl 4-(6-{4-[(methylsulfonyl)amino]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- benzyl 4-[6-(4-[(2-morpholin-4-ylethyl)amino]sulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 5 • benzyl 4-{6-[4-(methylsulfonyl)-2-nitrophenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- benzyl 4-{6-[2-amino-4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- 10 • benzyl 4-{6-[2-[(dimethylamino)ethyl]amino}-4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- benzyl 4-{6-[2-[(isopropylamino)ethyl]amino}-4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 15 • benzyl 4-(6-{4-(methylsulfonyl)-2-[(2-morpholin-4-ylethyl)amino]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- benzyl 4-{6-[2-[2-(dimethylamino)ethoxy]-4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- 20 • *N,N*-diethyl-2-(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)acetamide;
- 1-benzoyl-4-{(2*R**)-6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine;
- 25 • 1-benzoyl-4-{(2*S**)-6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine;
- (1-methylcyclopropyl)methyl 4-(6-{4-[(methylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- (1-methylcyclopropyl)methyl 4-(6-{4-[(ethylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 30 • (1-methylcyclopropyl)methyl 4-(6-{4-[(allylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- (1-methylcyclopropyl)methyl 4-(6-{4-[(cyclopropylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- (1-methylcyclopropyl)methyl 4-[6-(4-[(2-hydroxyethyl)amino]carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 35 • (1-methylcyclopropyl)methyl 4-[6-(4-[(3-hydroxypropyl)amino]carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- (1-methylcyclopropyl)methyl 4-[6-(4-[(2-methoxyethyl)amino]carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;

- (1-methylcyclopropyl)methyl 4-[6-{[(2-hydroxy-1,1-dimethylethyl)amino]-carbonyl}phenyl]-4H-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- (1-methylcyclopropyl)methyl 4-{6-{4-[(3-hydroxyazetidin-1-yl)carbonyl]phenyl}}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 5 • (1-methylcyclopropyl)methyl 4-(6-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- (1-methylcyclopropyl)methyl 4-{6-[4-({[2-(2-furyl)ethyl]amino}carbonyl)phenyl]}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 10 • *tert*-butyl 4-{6-[4-(methylsulfonyl)phenyl]}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-{6-[4-(aminocarbonyl)phenyl]}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 15 • *tert*-butyl 4-(6-{4-[(dimethylamino)carbonyl]phenyl}}-4H-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;
- 2-({4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]phenyl}sulfonyl)ethanol;
- 2-({4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]phenyl}sulfonyl)-ethanamine;
- 20 • *tert*-butyl 4-(6-{4-[(methylamino)carbonyl]phenyl}}-4H-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{4-[(ethylamino)carbonyl]phenyl}}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{4-[(allylamino)carbonyl]phenyl}}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 25 • *tert*-butyl 4-(6-{4-[(cyclopropylamino)carbonyl]phenyl}}-4H-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;
- *tert*-butyl 4-[6-(4-{[(2-hydroxyethyl)amino]carbonyl}phenyl)}-4H-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- 30 • *tert*-butyl 4-[6-(4-{[(2-methylprop-2-en-1-yl)amino]carbonyl}phenyl)}-4H-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{4-[(but-3-en-1-ylamino)carbonyl]phenyl}}-4H-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;

- *tert*-butyl 4-[6-(4-{[(3-hydroxypropyl)amino]carbonyl}phenyl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- *tert*-butyl 4-[6-(4-{[(2-methoxyethyl)amino]carbonyl}phenyl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- 5 • *tert*-butyl 4-{6-[4-({[(1-hydroxycyclopropyl)methyl]amino}carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- *tert*-butyl 4-[6-(4-{[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl}phenyl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- 10 • *tert*-butyl 4-(6-{4-[(3-hydroxyazetidin-1-yl)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 15 • *tert*-butyl 4-{6-[4-({[2-(2-furyl)ethyl]amino}carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-methylbenzamide;
- 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-ethylbenzamide;
- *N*-allyl-4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzamide;
- 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-cyclopropylbenzamide;
- 20 • 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-(2-hydroxyethyl)-benzamide;
- 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-(2-methylprop-2-en-1-yl)-benzamide;
- 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-but-3-en-1-ylbenzamide;
- 25 • 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-(3-hydroxypropyl)-benzamide;
- 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-(2-methoxyethyl)-benzamide;
- 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-[(1-hydroxycyclopropyl)-methyl]benzamide;
- 30 • 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-(2-hydroxy-1,1-dimethyl-ethyl)benzamide;
- 1-{4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzoyl}azetidin-3-ol;
- 1-{4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzoyl}-4-methyl-piperazine;

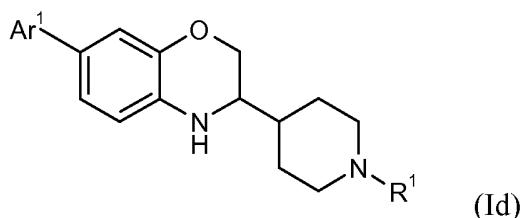
- 4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]-N-[2-(2-furyl)ethyl]-benzamide;
- ethyl 4-(6-{4-[(methylamino)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 5 • ethyl 4-(6-{4-[(ethylamino)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- ethyl 4-(6-{4-[(allylamino)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- ethyl 4-(6-{4-[(cyclopropylamino)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)-10 piperidine-1-carboxylate;
- ethyl 4-[6-(4-[(2-hydroxyethyl)amino]carbonyl)phenyl]-4H-1,3-benzodioxin-2-yl]-piperidine-1-carboxylate;
- ethyl 4-[6-(4-[(2-methylprop-2-en-1-yl)amino]carbonyl)phenyl]-4H-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- 15 • ethyl 4-(6-{4-[(but-3-en-1-ylamino)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;
- ethyl 4-[6-(4-[(3-hydroxypropyl)amino]carbonyl)phenyl]-4H-1,3-benzodioxin-2-yl]-piperidine-1-carboxylate;
- ethyl 4-[6-(4-[(2-methoxyethyl)amino]carbonyl)phenyl]-4H-1,3-benzodioxin-2-yl]-20 piperidine-1-carboxylate;
- ethyl 4-{6-[4-({[(1-hydroxycyclopropyl)methyl]amino}carbonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- ethyl 4-[6-(4-[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl)phenyl]-4H-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- 25 • ethyl 4-(6-{4-[(3-hydroxyazetidin-1-yl)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;
- ethyl 4-(6-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;
- ethyl 4-{6-[4-({[2-(2-furyl)ethyl]amino}carbonyl)phenyl]-4H-1,3-benzodioxin-2-yl}-30 piperidine-1-carboxylate;
- ethyl 4-[6-(4-{{[2-(hydroxymethyl)morpholin-4-yl]carbonyl}phenyl}-4H-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- 3-(3-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}isoxazol-5-yl)propanoic acid;

- [(5-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-2-furoyl)-amino]acetic acid;
- *tert*-butyl 4-{6-[6-(methylsulfonyl)pyridin-3-yl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- 5 • *tert*-butyl 4-{6-[5-(methylsulfonyl)pyridin-2-yl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- *tert*-butyl 4-{6-[4-(1*H*-tetrazol-5-yl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- 10 • *tert*-butyl 4-[6-(2-{{[amino(imino)methyl]amino}-4-methyl-1,3-thiazol-5-yl})-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- *tert*-butyl 4-(6-pyridin-4-yl-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-(6-pyridin-3-yl-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 15 • *tert*-butyl 4-(6-{5-[(4-methylpiperazin-1-yl)carbonyl]pyridin-2-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-{6-[6-(morpholin-4-ylcarbonyl)pyridin-3-yl]-4*H*-1,3-benzodioxin-2-yl}-piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{6-[(4-methylpiperazin-1-yl)carbonyl]pyridin-3-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 20 • *tert*-butyl 4-{6-[5-(morpholin-4-ylcarbonyl)pyridin-2-yl]-4*H*-1,3-benzodioxin-2-yl}-piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{5-[(4-methylpiperazin-1-yl)carbonyl]-2-furyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{5-[(1*E*)-3-(4-methylpiperazin-1-yl)-3-oxoprop-1-en-1-yl]-2-thienyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 25 • *tert*-butyl 4-(6-{5-[(1*E*)-3-morpholin-4-yl-3-oxoprop-1-en-1-yl]-2-thienyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{5-[(4-pyrimidin-2-yl)piperazin-1-yl)carbonyl]pyridin-2-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-[6-(5-{{[2-(dimethylamino)ethyl](methyl)amino]carbonyl}pyridin-2-yl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- 30 • *tert*-butyl 4-[6-(5-{{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}pyridin-2-yl}-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- *tert*-butyl 4-[6-(6-{{[2-(dimethylamino)ethyl](methyl)amino]carbonyl}pyridin-3-yl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;

- ethyl 4-(6-{(4-methylpiperazin-1-yl)carbonyl}pyridin-3-yl)-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- isopropyl 4-(6-{(4-methylpiperazin-1-yl)carbonyl}pyridin-3-yl)-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 5 • ethyl 4-(6-{5-{(4-methylpiperazin-1-yl)carbonyl}pyridin-2-yl})-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 1-({5-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]pyridin-2-yl}carbonyl)-4-methylpiperazine;
- 1-[(5-{2-[1-(2-ethylbutanoyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}pyridin-2-yl)-10 carbonyl]-4-methylpiperazine; and
- 2-[4-(6-{5-{(4-methylpiperazin-1-yl)carbonyl}pyridin-2-yl})-4*H*-1,3-benzodioxin-2-yl]-piperidin-1-yl]pyrimidine.

A further preferred group of compounds of the invention are compounds of Formula (Id):

15



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

20

Z^1 , Z^2 , R^1 to R^6 are as defined in Formula (Ia);

R^8 and R^9 are as defined in Formula (Ic);

Ar^1 is phenyl which is optionally substituted in one or two positions with a substituent independently selected from the group Z^3 as defined in Formula (Ic).

25

A preferred subgroup of compounds of the general Formula (Id) consists of compounds wherein:

Ar^1 is phenyl, which is optionally substituted in one or two positions with a substituent independently selected from the group Z^4 as defined in Formula (Ic);

30 R^1 is a group R^{1A} , wherein R^{1A} is as defined in Formula (Ic);

R^{2A} , R^{3A} , and R^{5A} are as defined in Formula (Ic).

In a more preferred subgroup of compounds of Formula (Id), Ar^1 is methylsulfonylphenyl.

- 5 In another more preferred subgroup of compounds of Formula (Id), R^{1A} is selected from $C(O)OR^{2A}$ and $C(O)R^{2A}$.

In one embodiment, R^{1A} is $C(O)OR^{2A}$, wherein R^{2A} is C_{1-6} alkyl. Preferably R^{2A} is *tert*-butyl.

10

In another embodiment, R^{1A} is $C(O)R^{2A}$, wherein R^{2A} is selected from C_{3-6} -cycloalkyl- C_{1-3} -alkyl and phenyl. Preferably R^{2A} is selected from cyclohexylmethyl and phenyl.

Particularly preferred compounds of Formula (Id) are the compounds selected from the group consisting of:

- *tert*-butyl 4-{7-[4-(methylsulfonyl)phenyl]-3,4-dihydro-2H-1,4-benzoxazin-3-yl}-piperidine-1-carboxylate;
- 3-[1-(cyclohexylacetyl)piperidin-4-yl]-7-[4-(methylsulfonyl)phenyl]-3,4-dihydro-2H-1,4-benzoxazine; and
- 3-(1-benzoylpiperidin-4-yl)-7-[4-(methylsulfonyl)phenyl]-3,4-dihydro-2H-1,4-benzoxazine.

Another object of the invention is a compound of Formula (Ia) to (Id) 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.

30

Another object of the invention is the use of a compound of Formula (Ia) to (Id) 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, 5 endothelial dysfunction and osteoporosis.

In one aspect, the method for preparation of a pharmaceutical composition comprises combining a compound according to any of the formulae herein with a pharmaceutically acceptable carrier. In another aspect, the method further comprises combining a compound 10 according to any of the formulae herein, an additional therapeutic agent, and a pharmaceutically acceptable carrier. The additional therapeutic agent can be, for example, a DPP-IV inhibitor.

Another object of the invention is a method for modulating the GPR119 receptor activity 15 (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 (Id) 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., 20 mammal, human, or animal) in need of such treatment an effective amount of a compound of Formula (Ia) to (Id). 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, 25 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 30 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.

- 5 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
10 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
15 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.
20 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
25 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.
30

DEFINITIONS

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

5 Unless otherwise stated or indicated, the term “C₁₋₆-alkyl” denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. For parts of the range “C₁₋₆-alkyl”, all subgroups thereof are contemplated, such as C₁₋₅-alkyl, C₁₋₄-alkyl, C₁₋₃-alkyl, C₁₋₂-alkyl, C₂₋₆-alkyl, C₂₋₅-alkyl, C₂₋₄-alkyl, C₂₋₃-alkyl, C₃₋₆-alkyl, C₄₋₅-alkyl, etc. Examples of said C₁₋₆-alkyl include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, 10 *t*-butyl and straight- and branched-chain pentyl and hexyl.

Unless otherwise stated or indicated, the term “cyano-C₁₋₆-alkyl” denotes a C₁₋₆-alkyl group, as defined above, substituted with a cyano group. Exemplary cyano-C₁₋₆-alkyl groups include 2-cyanoethyl and 3-cyanopropyl.

15 Unless otherwise stated or indicated, the term “amino-C₁₋₆-alkyl” denotes a C₁₋₆-alkyl group, as defined above, substituted with an amino group. Exemplary amino-C₁₋₆-alkyl groups include 2-aminoethyl and 3-aminopropyl.

20 Unless otherwise stated or indicated, the term “hydroxy-C₁₋₆-alkyl” denotes a straight or branched alkyl group that has a hydrogen atom thereof replaced with OH. Examples of said hydroxy-C₁₋₆-alkyl include hydroxymethyl, 2-hydroxyethyl, 2-hydroxy-1,1-dimethylethyl, 2-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxybutyl and 2-hydroxy-2-methylpropyl.

25 Derived expressions such as ”C₁₋₆-alkoxy”, ”C₁₋₆-alkylthio” and ”C₁₋₆-alkylamino” are meant to refer to an C₁₋₆-alkyl group which is attached to the remainder of the molecule through an oxygen, sulfur or nitrogen atom, respectively. For parts of the range “C₁₋₆-alkoxy” all subgroups thereof are contemplated such as C₁₋₅-alkoxy, C₁₋₄-alkoxy, C₁₋₃-alkoxy, C₁₋₂-alkoxy, C₂₋₆-alkoxy, C₂₋₅-alkoxy, C₂₋₄-alkoxy, C₂₋₃-alkoxy, C₃₋₆-alkoxy, C₄₋₅-alkoxy, etc. Examples of said “C₁₋₆-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 “C₁₋₆-alkylthio” and “C₁₋₆-alkylamino” are to be construed accordingly.

30 Unless otherwise stated or indicated, the term “C₁₋₄-alkylsulfinyl” denotes a group C₁₋₄-alkyl-S(O)–. Exemplary C₁₋₄-alkylsulfinyl groups include methylsulfinyl and ethylsulfinyl.

Unless otherwise stated or indicated, the term “dihydroxy-C₂₋₆-alkyl” denotes a C₂₋₆-alkyl group which is disubstituted with hydroxy and wherein said hydroxy groups are attached to

different carbon atoms. Exemplary dihydroxy-C₂₋₆-alkyl groups include 2,3-dihydroxypropyl and 2,4-dihydroxybutyl.

Unless otherwise stated or indicated, the term “di(C₁₋₄-alkyl)amino” denotes a group (C₁₋₄-alkyl)₂N—, wherein the two alkyl portions may be the same or different. Exemplary di(C₁₋₄-alkyl)amino groups include N,N-dimethylamino, N-ethyl-N-methylamino and N,N-diethylamino.

Unless otherwise stated or indicated, the term “di(C₁₋₄-alkyl)amino-C₂₋₄-alkyl” denotes a group di(C₁₋₄-alkyl)amino, as defined above, attached to a C₂₋₄-alkyl group. Exemplary di(C₁₋₄-alkyl)amino-C₂₋₄-alkyl groups include 2-(dimethylamino)ethyl and 3-(diethylamino)propyl.

Unless otherwise stated or indicated, the term “di(C₁₋₂-alkyl)amino-C₂₋₃-alkoxy” denotes a group di(C₁₋₂-alkyl)amino, as defined above, attached to a C₂₋₃-alkoxy group. Exemplary di(C₁₋₂-alkyl)amino-C₂₋₃-alkoxy groups include 2-(dimethylamino)ethoxy and 3-(diethylamino)propoxy.

Unless otherwise stated or indicated, the term “fluoro-C₁₋₆-alkyl” denotes a C₁₋₆-alkyl group substituted by one or more fluorine atoms. Examples of said fluoro-C₁₋₆-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-C₁₋₆-alkyl” means a C₁₋₆-alkyl group substituted by an aryl group. Examples include benzyl, 2-phenylethyl, 1-phenylethyl and 2-methyl-2-phenylpropyl.

Unless otherwise stated or indicated, the term “arylcarbonyl-C₁₋₄-alkyl” denotes an arylcarbonyl group (e.g., benzoyl) that is attached through a C₁₋₄-alkyl group. Examples of said arylcarbonyl-C₁₋₄-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-C₁₋₄-alkyl” denotes a heteroarylcarbonyl group (e.g., 3-pyridinylcarbonyl) that is attached through a C₁₋₄-alkyl group. Examples of said heteroarylcarbonyl-C₁₋₄-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 “aryloxymethyl” denotes a group aryl-O-CH₂—. An exemplary aryloxymethyl group is phenoxyethyl.

Unless otherwise stated or indicated, the term “C₁₋₆-alkoxy-C₁₋₆-alkyl” denotes a straight or branched alkoxy group having from 1 to 6 carbon atoms connected to an alkyl group having from 1 to 6 carbon atoms. Examples of said C₁₋₆-alkoxy-C₁₋₆-alkyl include

methoxymethyl, methoxyethyl, ethoxyethyl, isopropoxyethyl, *n*-butoxyethyl, *t*-butoxyethyl and straight- and branched-chain pentoxyethyl. For parts of the range “C₁₋₆-alkoxy-C₁₋₆-alkyl” all subgroups thereof are contemplated such as C₁₋₅-alkoxy-C₁₋₆-alkyl, C₁₋₄-alkoxy-C₁₋₆-alkyl, C₁₋₃-alkoxy-C₁₋₆-alkyl, C₁₋₂-alkoxy-C₁₋₆-alkyl, C₂₋₆-alkoxy-C₁₋₆-alkyl, C₂₋₅-alkoxy-C₁₋₆-alkyl, C₂₋₄-alkoxy-C₁₋₆-alkyl, C₂₋₃-alkoxy-C₁₋₆-alkyl, C₃₋₆-alkoxy-C₁₋₆-alkyl, C₄₋₅-alkoxy-C₁₋₆-alkyl, C₁₋₆-alkoxy-C₁₋₅-alkyl, C₁₋₆-alkoxy-C₁₋₄-alkyl, etc.

Unless otherwise stated or indicated, the term “C₂₋₆-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 C₂₋₆-alkenyl include vinyl, allyl, 2-methylallyl, 2,3-dimethylallyl, 1-but enyl, 1-pentenyl, and 1-hexenyl. For parts of the range “C₂₋₆-alkenyl”, all subgroups thereof are contemplated such as C₂₋₅-alkenyl, C₂₋₄-alkenyl, C₂₋₃-alkenyl, C₃₋₆-alkenyl, C₄₋₅-alkenyl, etc.

Unless otherwise stated or indicated, the term “aryl-C₂₋₆-alkenyl” means a C₂₋₆-alkenyl group substituted by an aryl group. Examples of said aryl-C₂₋₆-alkenyl include styryl and cinnamyl.

Unless otherwise stated or indicated, the term “C₂₋₆-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 C₂₋₆-alkynyl include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, and 1-methylprop-2-yn-1-yl.

Unless otherwise stated or indicated, the term “aryl-C₂₋₆-alkynyl” means a C₂₋₆-alkynyl group substituted by an aryl group. Examples of said aryl-C₂₋₆-alkynyl include phenyl-ethynyl, 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 “C₃₋₇-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 “C₃₋₇-cycloalkyl” all subgroups thereof are contemplated such as C₃₋₆-cycloalkyl, C₃₋₅-cycloalkyl, C₃₋₄-cycloalkyl, C₄₋₇-cycloalkyl, C₄₋₆-cycloalkyl, C₄₋₅-cycloalkyl, C₅₋₇-cycloalkyl and C₆₋₇-cycloalkyl.

Unless otherwise stated or indicated, the term “C₃₋₇-cycloalkyl-C₁₋₄-alkyl” denotes a C₃₋₇-cycloalkyl group attached to a C₁₋₄-alkyl group. Exemplary C₃₋₇-cycloalkyl-C₁₋₄-alkyl groups include cyclopropylmethyl, 1-cyclopropylethyl, cyclohexylmethyl and 2-cyclohexylethyl. When the cycloalkyl portion as part of the group C₃₋₇-cycloalkyl-C₁₋₄-alkyl is

substituted with methyl, examples of such groups include (1-methylcyclopropyl)methyl and 2-(4-methylcyclohexyl)ethyl.

When the cycloalkyl portion as part of the group C₃₋₆-cycloalkyl-C₁₋₄-alkyl is substituted with hydroxy, examples of such groups include (1-hydroxycyclopropyl)methyl and 4-hydroxycyclohexylmethyl.

Unless otherwise stated or indicated, the term “C₇₋₈-bicycyl” denotes a bicyclic saturated hydrocarbon ring system having 7 or 8 carbon atoms, 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 C₇₋₈-bicycyl 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 C₇₋₈-bicycyl-C₁₋₆-alkyl means a C₁₋₆-alkyl group substituted by a C₇₋₈-bicycyl group as defined above. An exemplary C₇₋₈-bicycyl-C₁₋₆-alkyl group is bicyclo[2.2.1]hept-2-ylmethyl (2-norbornylmethyl).

Unless otherwise stated or indicated, the term “C₅₋₈-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-C₄₋₆-cycloalkyl” refers to a C₄₋₆-cycloalkyl wherein two hydrogens on a cycloalkyl carbon atom are replaced by an oxo group as defined herein. Examples of “oxo-C₄₋₆-cycloalkyl” include 2-oxocyclobutyl, 3-oxocyclobutyl, 2-oxocyclopentyl and 4-oxocyclohexyl.

Unless otherwise stated or indicated, the term “fluoro-C₃₋₆-cycloalkyl” denotes a C₃₋₆-cycloalkyl group substituted by one or two fluorine atoms. Examples of said “fluoro-C₃₋₆-cycloalkyl” include 2,2-difluorocyclopropyl and 4-fluorocyclohexyl.

Unless otherwise stated or indicated, the term “C₁₋₃-alkoxy-C₄₋₆-cycloalkyl” denotes a C₄₋₆-cycloalkyl group substituted by a C₁₋₃-alkoxy group. Examples of said “C₁₋₃-alkoxy-C₄₋₆-cycloalkyl” include 4-methoxycyclohexyl and 2-ethoxycyclopentyl.

Unless otherwise stated or indicated, the term “methyl-C₃₋₆-cycloalkyl” denotes a C₃₋₆-cycloalkyl group substituted by one or two methyl groups. Examples of said “methyl-C₃₋₆-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 C₁-acyl group (i.e., a formyl group) or to an alkyl group, where alkyl is defined as

above. For parts of the range “C₁₋₆-acyl” all subgroups thereof are contemplated such as C₁₋₅-acyl, C₁₋₄-acyl, C₁₋₃-acyl, C₁₋₂-acyl, C₂₋₆-acyl, C₂₋₅-acyl, C₂₋₄-acyl, C₂₋₃-acyl, C₃₋₆-acyl, C₄₋₅-acyl, etc. Exemplary acyl groups include formyl, acetyl (i.e., C₂-acyl), propanoyl, butanoyl, pentanoyl, hexanoyl.

- 5 Unless otherwise stated or indicated, the term “C₂₋₆-acyl-C₁₋₆-alkyl” refers to a group C₁₋₅-alkyl-(C=O)-C₁₋₆-alkyl. Exemplary C₂₋₆-acyl-C₁₋₆-alkyl groups include 2-acetyleethyl and 3-acetylpropyl.

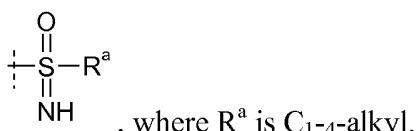
Unless otherwise stated or indicated, the term “C₁₋₆-alkylsulfonyl”, which may be straight or branched, denotes a hydrocarbon having from 1 to 6 carbon atoms attached to a sulfonyl group. For parts of the range “C₁₋₆-alkylsulfonyl” all subgroups thereof are contemplated such as C₁₋₅-alkylsulfonyl, C₁₋₄-alkylsulfonyl, C₁₋₃-alkylsulfonyl, C₁₋₂-alkylsulfonyl, C₂₋₆-alkylsulfonyl, C₂₋₅-alkylsulfonyl, C₂₋₄-alkylsulfonyl, C₂₋₃-alkylsulfonyl, C₃₋₆-alkylsulfonyl, C₄₋₅-alkylsulfonyl, etc. Exemplary C₁₋₆-alkylsulfonyl groups include methylsulfonyl, ethylsulfonyl, propylsulfonyl, n-butylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl, pentylsulfonyl and hexylsulfonyl.

Unless otherwise stated or indicated, the term “hydroxy-C₂₋₄-alkylsulfonyl” denotes a C₂₋₄-alkylsulfonyl group as defined above substituted with a hydroxy group. Examples of said hydroxy-C₂₋₄-alkylsulfonyl include 3-hydroxypropylsulfonyl and 2-hydroxyethylsulfonyl.

Unless otherwise stated or indicated, the term “amino-C₂₋₄-alkylsulfonyl” denotes a C₂₋₄-alkylsulfonyl group as defined above substituted with a amino group. Examples of said amino-C₂₋₄-alkylsulfonyl include 3-aminopropylsulfonyl and 2-aminoethylsulfonyl.

Unless otherwise stated or indicated, the term “C₁₋₄-alkylsulfonamido” denotes a group C₁₋₄-alkyl-SO₂NH—. Exemplary C₁₋₄-alkylsulfonamido groups include methylsulfonyl-amino and ethylsulfonylamino.

- 25 The term “C₁₋₄-alkylsulfoximine” refers to a group with the following chemical structure:



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, tetrazolyl, 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, preferably fully saturated, 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, tetrahydropyranly, tetrahydrofuranly, oxetanyl, azepinyl, azetidinyl, pyrrolidinyl, morpholinyl, imidazolinyl, imidazolidinyl, thiomorpholinyl, pyranly, dioxanyl, piperazinyl, homopiperazinyl 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 (i) two groups R⁵, (ii) two groups R^{5A}, (iii) R² together with R³, or (iv) R^{2A} together with R^{3A} described herein form a heterocyclic ring and said heterocyclic ring is substituted with one or two oxo groups, examples of such groups include 4-piperidon-1-yl, 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 (i) two groups R⁵, (ii) two groups R^{5A}, (iii) R² together with R³, or (iv) R^{2A} together with R^{3A} 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 (i) two groups R⁵, (ii) two groups R^{5A}, (iii) R² together with R³, or (iv) R^{2A} together with R^{3A} 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-hydroxypyrrrolidin-1-yl and 3-hydroxyazetidin-1-yl.

When (i) two groups R⁵, (ii) two groups R^{5A}, (iii) R² together with R³, or (iv) R^{2A} together with R^{3A} 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.

- 5 When (i) two groups R⁵, (ii) two groups R^{5A}, (iii) R² together with R³, or (iv) R^{2A} together with R^{3A} described herein form a heterocyclic ring and said heterocyclic ring is substituted with hydroxy-C₁₋₂-alkyl, examples of such groups include 2-(hydroxymethyl)pyrrolidin-1-yl, 2-(hydroxymethyl)morpholin-4-yl, 4-(hydroxymethyl)piperidin-1-yl and 4-(2-hydroxyethyl)piperazin-1-yl.
- 10 When (i) two groups R⁵, (ii) two groups R^{5A}, (iii) R² together with R³, or (iv) R^{2A} together with R^{3A} described herein form a heterocyclic ring and said heterocyclic ring is substituted with methylamino or dimethylamino, examples of such groups include 3-dimethylamino-pyrrolidin-1-yl and 3-methylaminopyrrolidin-1-yl.

- 15 When (i) two groups R⁵, (ii) two groups R^{5A}, (iii) R² together with R³, or (iv) R^{2A} together with R^{3A} described herein form a heterocyclic ring and said heterocyclic ring is substituted with C₁₋₃-alkyl, examples of such groups include 4-methylpiperidin-1-yl and 4-methylpiperazin-1-yl.

- 20 Unless otherwise stated or indicated, the term “heteroaryl-C₁₋₄-alkyl” denotes a heteroaryl group that is attached through a C₁₋₄-alkyl group. Examples of said heteroaryl-C₁₋₄-alkyl include 2-(pyridin-2-yl)ethyl, 1,3 benzodioxol-5-ylmethyl and 2-(2-furyl)ethyl.

- 25 ”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 C₁₋₄-alkyl, said C₁₋₄-alkyl is attached to a ring nitrogen atom or a ring carbon atom thereof. Exemplary C-heterocyclyl groups substituted by C₁₋₄-alkyl include 1-methylpiperidin-4-yl and 3-methyloxetan-3-yl. When N-heterocyclyl is substituted by methyl, said methyl is attached to a ring nitrogen atom or a ring carbon atom thereof. Exemplary N-heterocyclyl groups substituted by methyl include 4-methylpiperidin-1-yl and 4-methylpiperazin-1-yl.

30 Unless otherwise stated or indicated, the term “N-heterocyclyl-C₂₋₄-alkyl” refers to a nitrogen-containing heterocyclyl group that is directly linked to a C₂₋₄-alkyl group via a nitrogen atom of said heterocyclyl. Exemplary N-heterocyclyl-C₂₋₄-alkyl groups include 2-(pyrrolidin-1-yl)ethyl, 3-(4-morpholiny)propyl, 2-(piperazin-1-yl)ethyl and 2-(4-

morpholinyl)ethyl. Similarly, the term “N-heterocyclmethyl” means a methyl group substituted by a heterocycl group via a nitrogen atom thereof. Exemplary N-heterocyclmethyl groups include morpholin-4-ylmethyl and piperazin-1-ylmethyl.

When heterocycl as part of the group N-heterocycl-C₂₋₄-alkyl is substituted by methyl, said heterocycl 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-heterocycl-C₂₋₄-alkyl groups wherein heterocycl is substituted with methyl are 2-(4-methylpiperazin-1-yl)ethyl and 2-(4-methylhomopiperazin-1-yl)ethyl.

Unless otherwise stated or indicated, the term “C-heterocycl-C₁₋₄-alkyl” refers to a heterocycl group that is directly linked to a C₁₋₄-alkyl group via a carbon atom of said heterocycl. Exemplary C-heterocycl-C₁₋₄-alkyl groups include tetrahydropyran-4-ylmethyl, piperidin-4-ylmethyl, tetrahydrofuran-2-ylmethyl, oxetan-3-ylmethyl and 2-(piperidinyl-4-yl)ethyl.

When heterocycl as part of the group C-heterocycl-C₁₋₄-alkyl is substituted by methyl, said methyl is attached to a ring nitrogen atom or ring carbon atom thereof. Exemplary C-heterocycl-C₁₋₄-alkyl groups wherein heterocycl 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-heterocycl” denotes a nitrogen-containing heterocycl group that is substituted with one or two oxo groups.

Unless otherwise stated or indicated, the term “oxo-N-heterocycl-C₂₋₄-alkyl” refers to an oxo-N-heterocycl group that is directly linked to a C₂₋₄-alkyl group through a nitrogen atom of its heterocycl portion and where oxo-N-heterocycl is as defined above. Exemplary oxo-N-heterocycl-C₂₋₄-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-heterocycl” denotes a nitrogen-containing heterocycl 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-heterocycl-C₂₋₄-alkyl” refers to a fluoro-N-heterocycl group that is directly linked to a C₂₋₄-alkyl group through a nitrogen atom of its heterocycl portion and where fluoro-N-heterocycl is as defined above. Exemplary fluoro-N-heterocycl-C₂₋₄-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-C₂₋₄-alkyl” refers to a hydroxy-*N*-heterocyclyl group that is directly linked to a C₂₋₄-alkyl group through a nitrogen atom of its heterocyclyl portion and where hydroxy-*N*-heterocyclyl is as defined above. Exemplary hydroxy-*N*-heterocyclyl-C₂₋₄-alkyl groups include 2-(4-hydroxypiperidin-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-C₂₋₄-alkyl” refers to a amino-*N*-heterocyclyl group that is directly linked to a C₂₋₄-alkyl group through a nitrogen atom of its heterocyclyl portion and where amino-*N*-heterocyclyl is as defined above. Exemplary amino-*N*-heterocyclyl-C₂₋₄-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-heterocyclsulfonyl” refers to a heterocyclyl group that is directly bonded to SO₂ via a carbon atom. Exemplary C-heterocyclsulfonyl groups include 4-piperidinylsulfonyl and tetrahydropyran-4-ylsulfonyl.

When C-heterocyclsulfonyl is substituted by C₁₋₄-alkyl, said heterocyclyl is selected from a nitrogen-containing heterocyclyl, and said C₁₋₄-alkyl is attached to a ring nitrogen atom thereof. An exemplary C-heterocyclsulfonyl group substituted by C₁₋₄-alkyl includes 1-methylpiperidin-4-ylsulfonyl.

Unless otherwise stated or indicated, the term “C₂₋₄-acylamino” denotes a group R^b(C=O)NH— wherein R^b is selected from C₁₋₃-alkyl. Exemplary C₂₋₄-acylamino groups include acetylamino and propionylamino.

Unless otherwise stated or indicated, the term “C₂₋₄-acylamino-C₁₋₄-alkyl” denotes a C₂₋₄-acylamino group, as defined above, attached to a C₁₋₄-alkyl group. Exemplary C₂₋₄-acylamino-C₁₋₄-alkyl groups include (acetylamino)methyl and 2-(acetylamino)ethyl.

Unless otherwise stated or indicated, the term “aminocarbonyl” refers to the radical NH₂(C=O)–.

Unless otherwise stated or indicated, the term “aminocarbonyl-C₁₋₄-alkyl” denotes a C₁₋₄-alkyl group, as defined above, substituted with an aminocarbonyl group. Exemplary aminocarbonyl-C₁₋₄-alkyl groups include 2-(aminocarbonyl)ethyl and 3-(aminocarbonyl)-propyl.

Unless otherwise stated or indicated, the term “C₁₋₃-alkylaminocarbonyl” refers to the radical (C₁₋₃-alkyl)NH(C=O)–.

Unless otherwise stated or indicated, the term “C₁₋₃-alkylaminocarbonyl-C₂₋₆-alkyl” denotes a group C₁₋₃-alkylaminocarbonyl, as defined above, attached to a C₂₋₆-alkyl group. Exemplary C₁₋₃-alkylaminocarbonyl-C₂₋₆-alkyl groups include 2-(methylaminocarbonyl)-ethyl and 2-(ethylaminocarbonyl)ethyl.

Unless otherwise stated or indicated, the term “di(C₁₋₃-alkyl)aminocarbonyl” refers to the radical (C₁₋₃-alkyl)₂N(C=O)–, wherein the two alkyl portions may be the same or different.

Unless otherwise stated or indicated, the term “di(C₁₋₃-alkyl)aminocarbonyl-C₂₋₆-alkyl” denotes a group di(C₁₋₃-alkyl)aminocarbonyl, as defined above, attached to a C₂₋₆-alkyl

group. Exemplary di(C₁₋₃-alkyl)aminocarbonyl-C₂₋₆-alkyl groups include 2-(dimethylaminocarbonyl)ethyl and 2-(diethylaminocarbonyl)ethyl.

Unless otherwise stated or indicated, the term —C(O)— means a carbonyl group.

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

Unless otherwise stated or indicated, the term “carboxy-C₁₋₃-alkyl” refers to a carboxy group, as defined above, attached to a C₁₋₃-alkyl group. Exemplary carboxy-C₁₋₃-alkyl groups include 2-carboxyethyl and 3-carboxypropyl.

Unless otherwise stated or indicated, the term “carboxy-C₁₋₃-alkylcarbonylamino” refers to a carboxy-C₁₋₃-alkyl groups, as defined above, attached to the carbonyl carbon of carbonylamino (i.e., —C(O)NH—). Exemplary carboxy-C₁₋₃-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 C₁₋₄-alkyl, said heterocyclyl is selected from a nitrogen-containing heterocyclyl, and said C₁₋₄-alkyl is attached to a ring nitrogen atom thereof. An exemplary C-heterocyclylcarbonyl group substituted by C₁₋₄-alkyl includes 1-methylpiperidin-4-ylcarbonyl.

The term “N-heterocyclylcarbonyl-C₂₋₄-alkyl” refers to a N-heterocyclylcarbonyl group that is directly linked to a C₂₋₄-alkyl group through its carbonyl carbon atom and where N-heterocyclylcarbonyl is as defined above. Exemplary N-heterocyclylcarbonyl-C₂₋₄-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-C₂₋₄-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-C₂₋₄-alkyl groups wherein heterocyclyl is substituted with methyl are 2-(4-methylpiperazin-1-ylcarbonyl)ethyl, 2-(4-methylhomopiperazin-1-ylcarbonyl)ethyl.

The term “N-heterocyclylcarbonylvinyl” refers to a N-heterocyclylcarbonyl group, as defined above, that is directly linked to a vinyl group (i.e., —CH=CH₂) through its carbonyl carbon atom. Exemplary N-heterocyclylcarbonylvinyl groups include 2-(pyrrolidin-1-ylcarbonyl)vinyl, 2-(piperazin-1-ylcarbonyl)vinyl and 2-(piperidin-1-ylcarbonyl)vinyl. When the N-heterocyclyl portion as part of the group N-heterocyclylcarbonylvinyl is substituted with C₁₋₄-alkyl, an exemplary group is 2-(4-methylpiperazin-1-ylcarbonyl)vinyl.

The term “C-heterocyclylcarbonyl-C₂₋₄-alkyl” refers to a C-heterocyclylcarbonyl group that is directly linked to a C₂₋₄-alkyl group through its carbonyl carbon atom and where C-heterocyclylcarbonyl is as defined above. Exemplary C-heterocyclylcarbonyl-C₂₋₄-alkyl groups include 2-(tetrahydropyran-4-ylcarbonyl)ethyl, 2-(piperidin-3-ylcarbonyl)ethyl and 2-(piperidin-4-ylcarbonyl)ethyl.

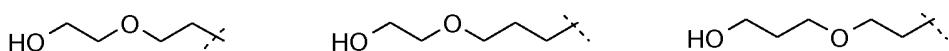
When heterocyclyl as part of the group C-heterocyclylcarbonyl-C₂₋₄-alkyl is substituted by methyl, said heterocyclyl is selected from a nitrogen-containing heterocyclyl and said methyl is attached to a ring nitrogen atom thereof. An exemplary C-heterocyclylcarbonyl-

C_{2-4} -alkyl group wherein heterocyclyl is substituted with methyl is 2-(1-methylpiperidin-4-ylcarbonyl)ethyl.

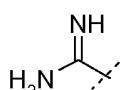
The term “C-heterocyclyloxy” refers to a heterocyclic group that is directly bonded to an oxygen atom via a carbon atom. Examples of C-heterocyclyloxy groups include
5 3-piperidinyloxy, 4-piperidinyloxy, 3-tetrahydrofuranyloxy, and 4-tetrahydropyranyloxy.

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.

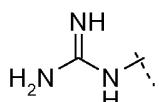
- 10 The term “hydroxy- C_{2-4} -alkoxy- C_{1-4} -alkyl” refers to a hydroxy- C_{2-4} -alkoxy group that is directly attached to a C_{1-4} -alkyl group. Representative examples of such groups include:



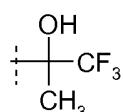
The term “amidino” refers to a group with the following chemical structure:



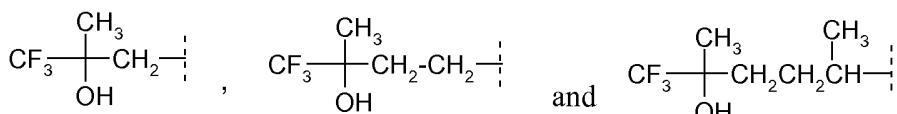
- 15 The term “guanidino” refers to a group with the following chemical structure:



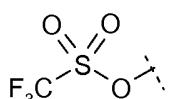
The chemical formula $-C(OH)CH_3CF_3$ refers to a group with the following chemical structure:



- 20 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:



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



- 25 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 any R^2 , R^5 or R^{5A} groups described

herein 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, which is used in the presence of 1-hydroxybenzotriazole 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 of 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.

The term "agonists" refers to compounds that have affinity for a biochemical receptor and that increase the receptor's pharmacological response upon binding. Depending on the efficacy with which they activate the receptor, agonists can be either full agonists or partial agonists. The term agonists as used herein shall include both full agonists and partial agonists.

“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 (Id) 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.

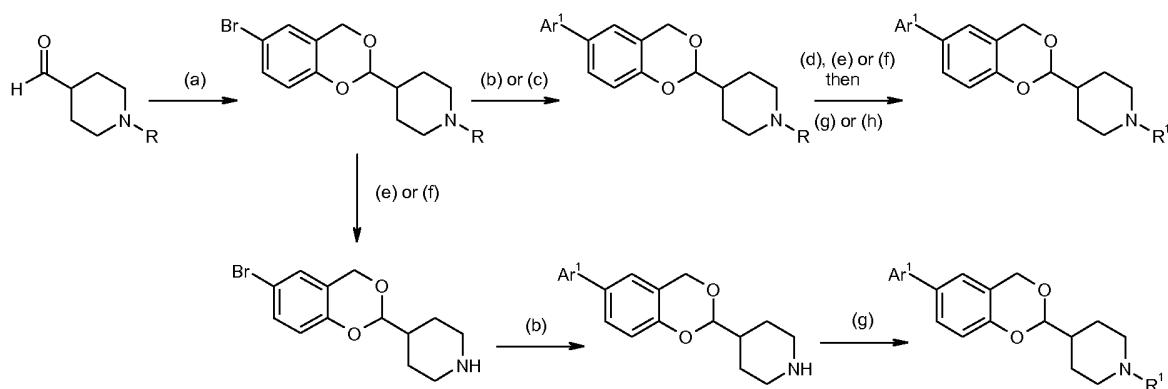
The compounds of Formula (Ia) to (Id) may be administered with other active compounds for the treatment of diabetes and/or obesity, for example insulin and insulin analogs, DPP-IV inhibitors, sulfonyl ureas, biguanides, α 2 agonists, glitazones, PPAR- γ agonists, mixed PPAR- α/γ agonists, RXR agonists, 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 (Id) 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 (Id) 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 1-4.

Scheme 1



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wherein Ar¹ and R¹ are as defined in Formula (Ia); and

R is benzyl, Boc or CBz;

15 Reagents and conditions:

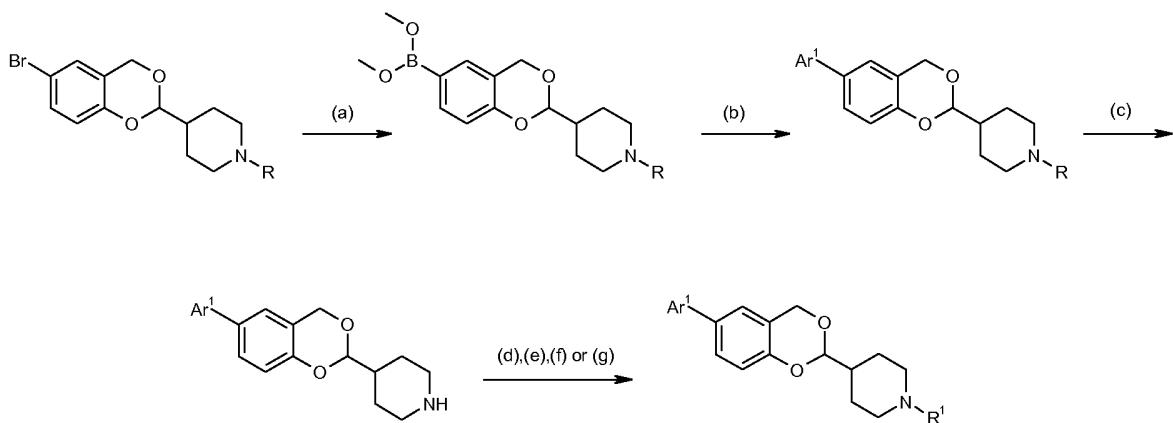
- (a) 4-bromo-2-(hydroxymethyl)phenol; a suitable acid, such as *p*-toluenesulfonic acid or sulfuric acid; in a suitable solvent, such as chloroform or benzene; at reflux temperature;
- (b) appropriate aryl- or heteroarylboronic acid; appropriate catalyst, such as Pd(PPh₃)₄ or PdCl₂(dppf)·DCM; a suitable base, such as K₂CO₃ or NaHCO₃; in a suitable solvent mixture such as 1,4-dioxane and water; at elevated temperature, for example 90 °C or 160 °C (microwaves);
- (c) (i) 5,5,5',5'-tetramethyl-2,2'-bi-1,3,2-dioxaborinane; a suitable base, such as KOAc; appropriate catalyst, such as PdCl₂(dppf)·DCM; in a suitable solvent, such as DME; at elevated temperature, for example 120 °C (microwaves); (ii) appropriate aryl or heteroaryl halide; suitable base, such as NaHCO₃; appropriate catalyst, such as

25

- Pd(PPh₃)₄; in a suitable solvent mixture, such as water and DME; at elevated temperature, for example 120 °C (microwaves);
- (d) a suitable deprotecting agent, such as TFA, HCl (g) or aqueous concentrated HCl; in a suitable solvent, such as DCM or ethanol; at ambient or elevated temperature; when R = Boc;
- (e) hydrogenolysis, a suitable catalyst, such as 10% Pd/C; a suitable hydrogen source, such as ammonium formate or H₂ (g); in a suitable solvent, such as *n*-propanol, ethanol, water, or mixtures thereof; at elevated temperature, for example 90 °C; when R = benzyl or CBz;
- (f) hydrolysis, a suitable base, such as NaOH or KOH; in a suitable solvent mixture, such as water and ethanol; at elevated temperature, for example 90 °C; when R = CBz;
- (g) (i) appropriate carboxylic acid; a suitable base, such as triethylamine or DIPEA; in a suitable solvent, such as THF, dioxane or DMF; (ii) appropriate coupling reagent, such as HOBT/EDC, propylphosphonic anhydride or TBTU;
- (h) appropriate acid chloride or chloroformate; a suitable base, such as triethylamine; in a suitable solvent, such as THF or DMF; at r.t.

Scheme 2

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wherein Ar¹ and R¹ are as defined in Formula (Ia); and
R is Boc.

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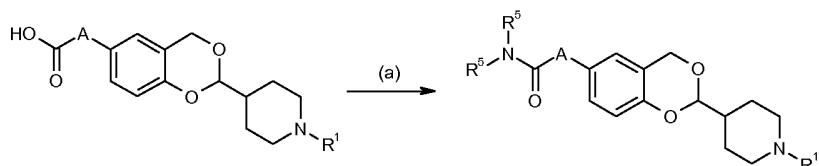
Reagents and conditions:

- (a) (i) BuLi, THF, -78 °C; (ii) B(OMe)₃;

- (b) appropriate aryl or heteroaryl halide; a suitable base, such as K_2CO_3 or $NaHCO_3$; appropriate catalyst, such as $PdCl_2dppf\cdot DCM$ or $Pd(PPh_3)_4$; in a suitable solvent mixture, such as water and DME or MeCN and water; at elevated temperature, for example 160 °C (microwaves);
- 5 (c) a suitable deprotecting agent, such as TFA, HCl (g) or aqueous HCl; in a suitable solvent, such as DCM, dioxane, methanol or ethanol; at ambient or elevated temperature;
- (d) (i) appropriate carboxylic acid; a suitable base, such as triethylamine or DIPEA; in a suitable solvent, such as THF, dioxane or DMF; (ii) appropriate coupling reagent, such as HOBT/EDC, propylphosphonic anhydride, HBTU or TBTU; at r.t.;
- 10 (e) appropriate acid chloride or chloroformate; a suitable base, such as triethylamine; in a suitable solvent, such as THF or DMF; at r.t.;
- (f) appropriate alcohol; a 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;
- 15 (g) appropriate heteroaryl halide, such as 2-bromopyrimidine; in a suitable solvent, such as DMSO or acetonitrile; at elevated temperature.

Scheme 3

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wherein A is phenyl or heteroaryl; and

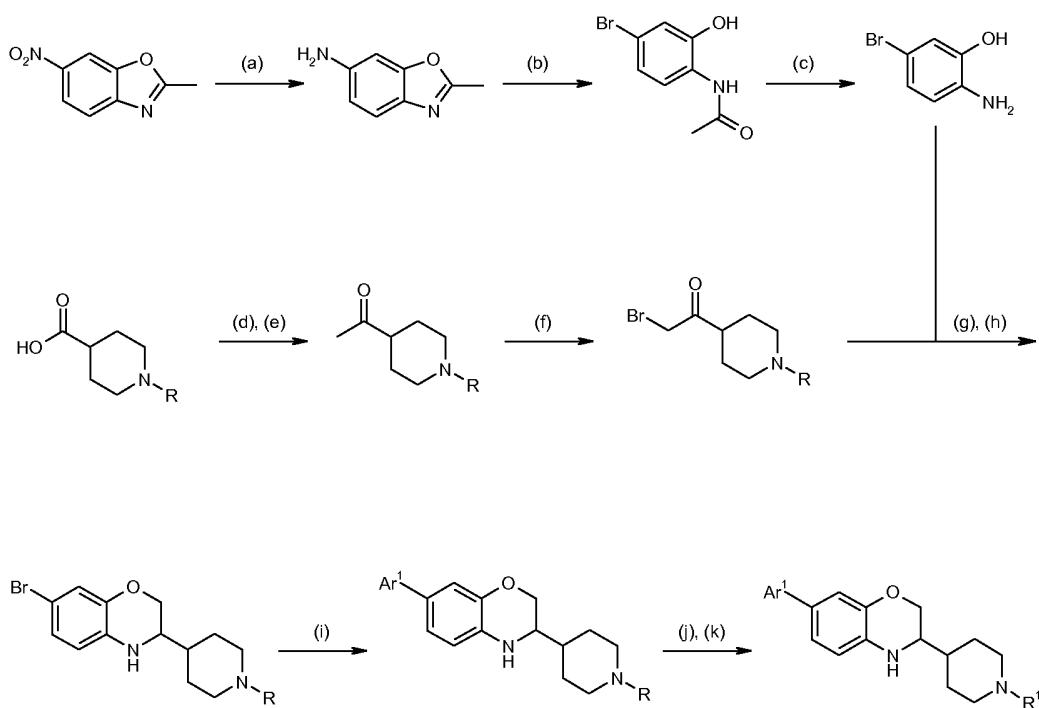
R^1 and R^5 are as defined in Formula (Ia);

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Reagents and conditions:

- (a) (i) appropriate amine; a suitable base, such as triethylamine or DIPEA; 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 at elevated temperature.

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Scheme 4

5 wherein Ar¹ and R¹ are as defined in Formula (Ia); and
R is Boc.

Reagents and conditions:

- (a) iron powder, NH₄Cl, methanol and water, 70 °C;
- 10 (b) (i) 1 M HBr, NaNO₂, water, 0 °C; (ii) CuBr, water, 0 °C → r.t.;
- (c) 3 M HCl, EtOH, 100 °C;
- (d) (i) EDC, HOBT, DMF; (ii) 1,2-dimethylhydroxylamine hydrochloride, DIEA;
- (e) bromo(methyl)magnesium, diethylether, 0 °C → r.t.;
- (f) (i) lithium bis(trimethylsilyl)amide, THF, -78 °C; (ii) trimethylsilyl chloride, -78 °C
15 → r.t. (iii) Br₂, -78 °C;
- (g) K₂CO₃, DMF, r.t.;
- (h) NaBH₄, ethanol, HOAc, r.t.;
- (i) appropriate aryl- or heteroarylboronic acid, NaHCO₃, PPh₃, Pd(OAc)₂, 80% aqueous ethanol, 80 °C;
- 20 (j) DCM, TFA, r.t.;
- (k) appropriate carboxylic acid, triethylamine, TBTU, DMF, r.t.

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

- 5 The necessary starting materials for preparing the compounds of Formula (Ia) to (Id) 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 10 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 (Id) may possess one or more chiral carbon atoms, and 15 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.

20 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 25 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. 30 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	<i>tert</i> -butyloxycarbonyl
Brine	water saturated or nearly saturated with sodium chloride
CBz	carbobenzyloxy
DCM	dichloromethane
DIEA	<i>N</i> -ethyl- <i>N,N</i> -diisopropylamine
DIPEA	<i>N,N</i> -diisopropylethyl amine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulphoxide
EDC	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide, or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ESI	electrospray ionization
EtOAc	ethyl acetate
GC	Gas Chromatography
GCMS	Gas Chromatography Mass Spectrometry
h	hour(s)
HDL	High-Density Lipoprotein
HBTU	<i>O</i> -benzotriazole- <i>N,N,N',N'</i> -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
MCPBA	3-chloroperoxybenzoic acid
MeCN	acetonitrile
MeOH	methanol
PdCl ₂ dppf·DCM	[1,1'-bis(diphenylphosphino)-ferrocene]dichloro-palladium(II) complex with DCM (1:1)
Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
Pd(OAc) ₂	palladium(II) acetate
Pd(PPh ₃) ₄	tetrakis(triphenylphosphine)palladium(0)
r.t.	room temperature

sec	second(s)
TBTU	<i>N,N,N',N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate,</i>
THF	tetrahydrofuran
Xantphos	(9,9-dimethyl-9 <i>H</i> -xanthene-4,5-diyl)bis(diphenylphosphine)
Å	Ångström

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

5 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
10 ZQ mass spectrometer. High-resolution electrospray ionization mass spectra (HRESIMS) were obtained on an 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
15 ammonium acetate; B 100 MeCN; flow rate 400 µL/min isocratic. Analytical GCMS was performed on a Hewlett-Packard 5890/6890 gas chromatograph equipped with a HP-5MS crosslinked 5% PhMe Siloxane column (30 m x 0.25 mm x 0.25 µm film thickness) with a Hewlett-Packard 5971A/5972A mass selective detector using electron impact. Flash chromatography was performed on Merck silica gel 60 (230-400 mesh). The compounds
20 were automatically named using ACD 8.0.

Analytical LCMS data were obtained with:

System A: Agilent MSD mass spectrometer; Agilent 1100 system; ACE 3 C8 column

(50x3.0 mm); Water containing 0.1% TFA and acetonitrile were used as mobile phases at a flow rate of 1 mL/min with gradient times of 3.0 min (gradient 10-97% acetonitrile); or

System B: Agilent MSD mass spectrometer; Agilent 1100 system; YMC ODS-AQ column (33x3.0 mm); Water containing 0.1% TFA and acetonitrile were used as mobile phases at a flow rate of 1 mL/min with gradient times of 3.0 min (gradient 10-97% acetonitrile); or

System C: Waters ZQ mass spectrometer; Waters 996 PDA detector (DAD 215 - 395 nm);

30 ACE C8 (3µm) column (30x3.0 mm) (from ACT); Water containing 10 mM ammonium acetate (pH=7) and acetonitrile were used as mobile phases at a flow rate of 1 mL/min with gradient times of 3.2 min (gradient 5-100% acetonitrile).

Preparative HPLC was performed on Gilson system equipped with:

System D: ACE C8 5 μ m (21.2x50mm) column. Water containing 0.1% TFA and acetonitrile were used as mobile phases at a flow rate of 25 mL/min with gradient times of 6 min.; or

- 5 System E: XTerra Prep MS C18 5 μ m (19x50 mm) column. Water containing 50mM NH₄HCO₃ (pH=10) and acetonitrile were used as mobile phases at a flow rate of 25 mL/min with gradient times of 6 min; or Xterra MS C18 5 μ m (30x100 mm) column. Water containing 50mM NH₄HCO₃ (pH=10) and acetonitrile were used as mobile phases at a flow rate of 40 mL/min with gradient times of 8.5 min.

10

General Method A1: Suzuki-type cross-coupling reaction

A suspension of benzyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate (Intermediate A1; 20 mg, 0.046 mmol), the appropriate boronic acid (0.051 mmol), K₂CO₃ (16 mg, 0.12 mmol) and Pd(PPh₃)₄ (3 mg, 0.0023 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 90 °C overnight. The solvents were removed under reduced pressure and the residue was purified by preparative HPLC (System E).

General Method A2: Suzuki-type cross-coupling reaction

Prepared from *tert*-butyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate (Intermediate A11; 20 mg, 0.05 mmol) and the appropriate boronic acid in accordance with general method A1.

General Method B: Suzuki-type cross-coupling reaction (microwave conditions)

A suspension of *tert*-butyl 4-[6-(dimethoxyboryl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate (Intermediate A19; 30 mg, 0.078 mmol), the appropriate aryl- or heteroarylboride (0.10 mmol), K₂CO₃ (26 mg, 0.19 mmol), PdCl₂dppf·DCM (6 mg, 0.0077 mmol) in MeCN/H₂O (1.5 mL; 2:1) was heated at 160 °C for 20 min in a microwave reactor. The mixture was filtered through a pad of silica, concentrated and the residue was purified by preparative HPLC (System E).

30

General Method C1: Preparation of amides from carboxylic acids using HOBT and EDC as coupling reagents

To a vial containing the appropriate carboxylic acid (0.030 mmol) was added a solution of *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3;

10 mg, 0.027 mmol) in THF (2 mL) and triethylamine (15 μ L, 0.11 mmol). HOBT (7 mg, 0.054 mmol) and EDC (10 mg, 0.054 mmol) were added and the resulting mixture was shaken overnight and then concentrated. The residue was purified by preparative HPLC (System E).

5

General Method C2: Preparation of amides from carboxylic acids using HOBT and EDC as coupling reagents

Prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine (Intermediate A4; 15 mg, 0.040 mmol) and the appropriate carboxylic acid in accordance with general method C1.

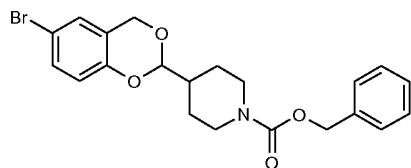
General Method D: Preparation of amides from carboxylic acids using propylphosphonic anhydride as coupling reagent

A suspension of the appropriate carboxylic acid (0.05 mmol) in dry DMSO (75 μ L) and DMF (0.75 μ L) was treated with propylphosphonic anhydride (44 μ L, 0.075 mmol; as a 50% solution in EtOAc) and stirred for 10 min. To the mixture were added a solution of the appropriate amine (0.06 mmol) and triethylamine (21 μ L, 0.20 mmol) in dry DMF (100 μ L) and the resulting mixture was shaken at r.t. overnight. Purification by preparative HPLC (System E) gave the title compound.

15

INTERMEDIATE A1

Benzyl 4-(6-bromo-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate

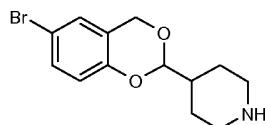


A suspension of benzyl 4-formylpiperidine-1-carboxylate (2.81 g, 11.4 mmol), 4-bromo-2-

25 (hydroxymethyl)phenol (2.31 g, 11.4 mmol) and *p*-toluenesulfonic acid and molecular sieves (4 \AA) in chloroform (100 mL) was refluxed for 3 hours using a Dean-Stark apparatus. The reaction mixture was then washed with 5% aqueous KHCO_3 (20 mL) and the water phase was extracted with chloroform (3 x 15 mL). The combined organic phases were washed with 5% aqueous KHCO_3 (20 mL) and then concentrated. Yield 4.75 g (97%). Analytical HPLC: purity 78% (System C); LRESIMS (ESI $^+$) m/z = 433 ($\text{M}+\text{H}$) $^+$.

30

INTERMEDIATE A2

4-(6-Bromo-4H-1,3-benzodioxin-2-yl)piperidine

A suspension of benzyl 4-(6-bromo-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate (Intermediate A1; 550 mg, 1.27 mmol) in 30% aqueous NaOH (10 mL) and MeOH (15 mL) was heated in a sealed tube at 90 °C for 15 h. The MeOH was removed under reduced pressure and the remaining aqueous mixture was extracted with chloroform (3 x 15 mL). The organic layers were combined, dried (MgSO_4) and concentrated. Yield 370 mg (97%). Analytical HPLC: purity 93% (System A); LRESIMS (ESI⁺) m/z = 298/300 ($\text{M}+\text{H}$)⁺.

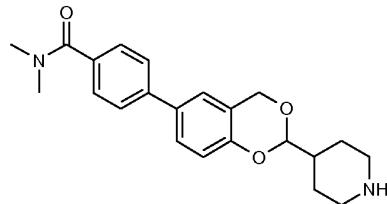
10

Alternative synthetic route:

A suspension of *tert*-butyl 4-(6-bromo-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate (Intermediate A11; 5.0 g, 0.017 mol) in TFA/DCM (50 mL; 1:4) was stirred at r.t. for 2 h. The solvents were removed under reduced pressure and the residue was partitioned between DCM and 1 M NaOH. The aqueous layer was extracted with DCM (3 x 50 mL). The organic layers were combined, washed with water and brine, dried (MgSO_4) and concentrated to give the title compound. Yield 4.7 g (94%). Analytical HPLC: purity 90% (System A); LRESIMS m/z = 298/300 ($\text{M}+\text{H}$)⁺.

20

INTERMEDIATE A3

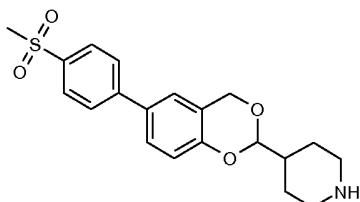
N,N-Dimethyl-4-(2-piperidin-4-yl-4H-1,3-benzodioxin-6-yl)benzamide

A suspension of 4-(6-bromo-4H-1,3-benzodioxin-2-yl)piperidine (Intermediate A2; 370 mg, 1.24 mmol), {4-[(dimethylamino)carbonyl]phenyl}boronic acid (264 mg, 1.36 mmol), Pd(PPh_3)₄ (72 mg, 0.0620 mmol) and K_2CO_3 (428 mg, 3.10 mmol) in 1,4-dioxane (10 mL) and water (3 mL) was heated at 90 °C for 15 h. The solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica using EtOAc/DCM

(1:1) followed by DCM/MeOH/25% aqueous NH₃ (90:9:1) as eluents. Yield 209 mg (46%). Analytical HPLC: purity 85% (System A); LRESIMS (ESI⁺) m/z = 367 (M+H)⁺.

INTERMEDIATE A4

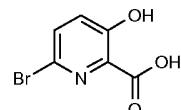
5 **4-{6-[4-(Methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine**



A suspension of benzyl 4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}-piperidine-1-carboxylate (Example A2; 1.75 g, 3.40 mmol) in 30% aqueous NaOH (10 mL) and MeOH (15 mL) was heated in a sealed tube at 90 °C for 72 h. The solvents were removed under reduced pressure and the residue was partitioned between water (75 mL) and chloroform (2 x 100 mL). The organic layers were combined, dried (MgSO₄) and concentrated. Yield 1.23 g (97%). Analytical HPLC: purity 80% (System A); LRESIMS (ESI⁺) m/z = 374 (M+H)⁺.

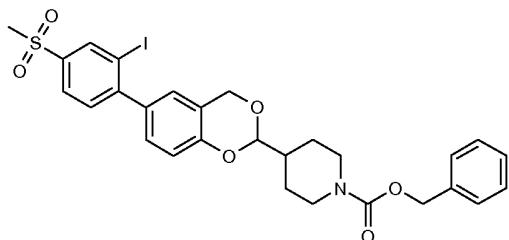
15 **INTERMEDIATE A5**

6-Bromo-3-hydroxypyridine-2-carboxylic acid



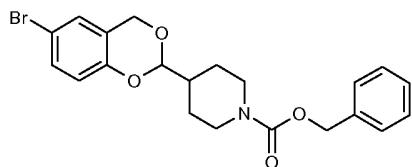
To a stirred suspension of 3-hydroxypyridine-2-carboxylic acid (2.00 g, 0.0144 mol) in DMF (30 mL) was added a solution of *N*-bromosuccinimide (2.56 g, 0.0144 mol) in DMF (30 mL). After 1 h, water (50 mL) and 1 M aqueous NaOH (25 mL) were added and the resulting mixture was extracted with chloroform (3 x 150 mL). The organic layers were combined and concentrated and the residue was purified by preparative HPLC (System D). Yield 366 mg (12%). Analytical HPLC: purity 100% (System A and B); LRESIMS (ESI⁺) m/z = 218/220 (M+H)⁺.

INTERMEDIATE A6

Benzyl 4-{6-[2-iodo-4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate

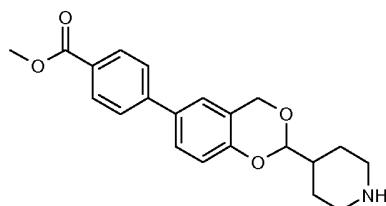
5 To a stirred and cooled (0 °C) suspension of benzyl 4-{6-[2-amino-4-(methylsulfonyl)-phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate (Example A56; 450 mg, 0.86 mmol) in acetonitrile (2 mL) and 1 M HCl (6 mL) was added a solution of sodium nitrite (89 mg, 1.3 mmol) in water (1.5 mL). The mixture was stirred at 0 °C for 20 min and then potassium iodide (214 mg, 1.29 mmol) was added. After stirring at r.t. for 2 h, water (20 mL) was added and the resulting solution was extracted with chloroform (3 x 30 mL). The organic layers were combined and concentrated. Yield 253 mg (46%). Analytical HPLC: purity 85% (System A).

INTERMEDIATE A7

Benzyl 4-(6-bromo-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate

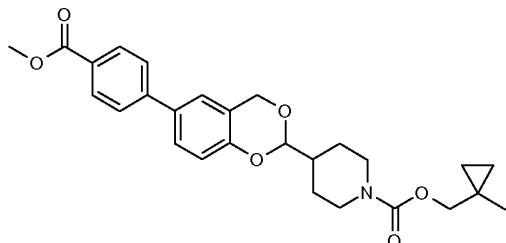
15 A mixture of 5-bromo-2-hydroxybenzyl alcohol (10.32 g, 50.85 mmol), benzyl 4-formyltetrahydro-1(2*H*)-pyridinecarboxylate (14.85 g, 60.05 mmol) and *p*-toluenesulfonic acid (0.97 g, 5.08 mmol) was stirred under reflux for 1 h in benzene (111 mL) using a Dean-Stark apparatus. The organic phase was washed with 1 M NaOH, dried (Na₂SO₄), and concentrated to give the title compound. Yield 20.94 g (95%).

INTERMEDIATE A8

Methyl 4-(2-piperidin-4-yl-4H-1,3-benzodioxin-6-yl)benzoate

A suspension of benzyl 4-(6-bromo-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate (Intermediate A7; 5.00 g, 11.6 mmol), 4-methoxycarbonyl-phenylboronic acid (2.29 g, 12.7 mmol), Pd(PPh₃)₄ (0.67 g, 0.58 mmol) and K₂CO₃ (4.00 g, 28.9 mmol) in 1,4-dioxane (40 mL) and water (10 mL) was stirred at 90 °C overnight. To the mixture was added water (50 mL) and the product was extracted with EtOAc (50 mL). The organic phase was dried (Na₂SO₄) and the solvent was removed under reduced pressure to give benzyl 4-{6-[4-(methoxycarbonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate. To a stirred suspension of this material in 1,4-dioxane (150 mL) and ethanol (100 mL) was added 10% Pd/C (0.5 g) and the mixture was heated at 60 °C under H₂ overnight. The mixture was filtered (Celite) and the filtrate was concentrated and then dissolved in 1 M HCl (100 mL) and washed with Et₂O (100 mL). The aqueous phase was collected and basified with 2 M NaOH (50 mL) and then extracted with EtOAc (100 mL). The organic phase was dried (Na₂SO₄) and concentrated to give the title compound. Yield 3.07 g (75%, over 2 steps). Analytical HPLC: purity 94% (System A); LRESIMS m/z = 354 (M+H)⁺.

INTERMEDIATE A9

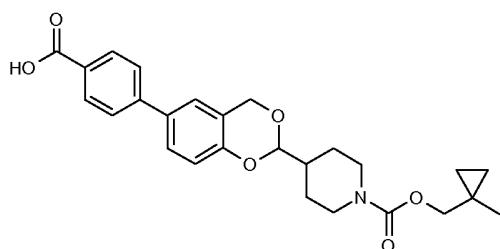
(1-Methylcyclopropyl)methyl 4-{6-[4-(methoxycarbonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate

To a suspension of 1,1'-carbonyldiimidazole (1.15 g, 7.10 mmol) in acetonitrile (2 mL) and DMF (2 mL) was added 1-methylcyclopropane methanol (0.59 g, 7.10 mmol) and the mixture was stirred for 5 minutes. A solution of methyl 4-(2-piperidin-4-yl-4H-1,3-benzodioxin-6-yl)benzoate (Intermediate A8; 0.50 g, 1.41 mmol) in DMF (2 mL) was

added and the mixture was stirred at 50 °C for 2 h. EtOAc was added and the mixture was washed with 1 M NaOH. The organic phase was dried (Na_2SO_4) and concentrated. Gradient flash chromatography on silica using EtOAc and *n*-pentane (10:90 to 50:50) as eluent gave the title compound. Yield 0.4 g (51%). Analytical HPLC: purity 100% (System A); LRESIMS m/z = 466 ($\text{M}+\text{H}$)⁺.

INTERMEDIATE A10

4-[2-(1-{[(1-Methylcyclopropyl)methoxy]carbonyl}piperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzoic acid

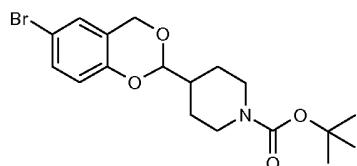


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A suspension of (1-methylcyclopropyl)methyl 4-{6-[4-(methoxycarbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate (Intermediate A9; 0.40 g, 0.86 mmol) in THF (15 mL) and MeOH (10 mL) was treated with 6 M KOH (0.86 mL, 5.16 mmol) and stirred at 50 °C for 1 h. The mixture was diluted with water, neutralized with 4 M HCl (aq) and extracted with EtOAc. The organic phase was dried (Na_2SO_4) and concentrated to give the title compound. Yield 0.38 g (99%). Analytical HPLC: purity 95% (System A); LRESIMS m/z = 452 ($\text{M}+\text{H}$)⁺.

INTERMEDIATE A11

tert-Butyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate



A suspension of *tert*-butyl 4-formylpiperidine-1-carboxylate (7.62 g, 35.7 mmol), 4-bromo-2-(hydroxymethyl)phenol (7.25 g, 35.7 mmol), *p*-toluenesulfonic acid (catalytic amount) and molecular sieves (4 Å) in benzene (100 mL) was stirred under reflux for 24 h using a Dean-Stark apparatus. The mixture was washed with 5% aqueous NaHCO_3 (50 mL) and the water phase was then extracted with chloroform (3 x 50 mL). The organic phases were combined and washed with 5% aqueous NaHCO_3 (20 mL), dried (K_2CO_3) and

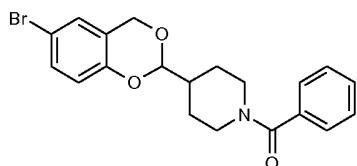
concentrated to give the title compound. Yield 14.2 g (70%). LRESIMS (ESI⁺) m/z = 298/300 (M+H-Boc)⁺.

Alternative synthetic route

- 5 To a suspension of 4-bromo-2-(hydroxymethyl)phenol (9.00 g, 44.3 mmol) in chloroform (100 mL) were added *tert*-butyl 4-formylpiperidine-1-carboxylate (9.45 g, 44.3 mmol), *p*-toluenesulfonic acid (0.38 g, 2.2 mmol) and molecular sieves (4 Å). The mixture was stirred at reflux for 12 h and then allowed to reach r.t. The solution was filtered, the filtrate was washed with saturated aqueous NaHCO₃ (3 x 30 mL) and the aqueous layer was extracted with chloroform (100 mL). The organic layer was washed with brine (50 mL), dried (Na₂SO₄) and concentrated and the residue was purified by flash chromatography on silica using 5% MeOH in DCM as eluent. Yield 14.5 g (85%). Analytical HPLC: purity 98% (System A and B); LRESIMS (ESI⁺) m/z = 298/300 (M+H-Boc)⁺.
- 10

15 INTERMEDIATE A12

1-Benzoyl-4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)piperidine

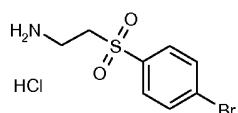


A suspension of 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)piperidine (Intermediate A2; 4.7 g, 15.8 mmol), benzoic acid (2.3 g, 18.9 mmol), *N,N*-diisopropylethylamine (11 mL, 63 mmol) and propylphosphonic anhydride (26 mL, 41 mmol; as a 50% solution in EtOAc) in dry DCM (80 mL) was stirred at r.t. for 2 h and then diluted with DCM (20 mL). The mixture was washed with 0.5 M HCl (aq), water, 5% aqueous NaHCO₃ and brine, dried (MgSO₄) and concentrated. Yield 6.3 g (100%). Analytical HPLC: purity 95% (System A and B); LRESIMS m/z = 403 (M+H)⁺.

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INTERMEDIATE A13

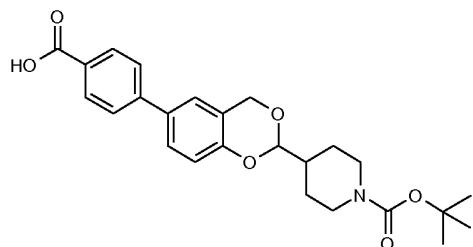
2-[(4-Bromophenyl)sulfonyl]ethanamine hydrochloride



A suspension of 4-bromothiophenol (3.52 g, 18.6 mmol), *tert*-butyl 2-bromo-ethylcarbamate (5.00 g, 22.3 mmol) and K₂CO₃ (9.25 g, 66.9 mmol) in acetone (100 mL) was

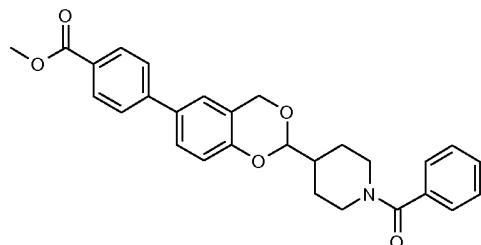
stirred at r.t. for 48 h. The mixture was filtrated and the filtrate was concentrated and dissolved in DCM (100 mL). The solution was cooled in an ice-bath and MCPBA (7.70 g, 44.6 mmol) was added. After stirring at r.t. for 48 h, additional MCPBA (3.85 g, 22.3 mmol) was added and the mixture was stirred for another 24 h. The mixture was filtrated and the solid was washed with DCM. The filtrate was washed with aqueous saturated NaHSO₃, 5% aqueous NaHCO₃ and water, dried (MgSO₄) and concentrated to give 6.4 g of *tert*-butyl 2-[(4-bromophenyl)sulfonyl]ethylcarbamate. The material was stirred in 1.25 M ethanolic HCl (100 mL) overnight. The mixture was concentrated and the residue was triturated with ethanol/Et₂O. The solid was collected by filtration and dried. Yield 4.23 g (80%). Analytical HPLC: purity 99% (System A); LRESIMS m/z = 264/266 (M+H)⁺.

INTERMEDIATE A14

4-{2-[1-(*tert*-Butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid

A suspension of *tert*-butyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate (Intermediate A11; 4.0 g, 10 mmol), 4-(dihydroxyboryl)benzoic acid (1.8 g, 11 mmol), Pd(PPh₃)₄ (577 mg, 0.05 mmol), K₂CO₃ (3.5 g, 25 mmol) in 1,4-dioxane (200 mL) and water (50 mL) was heated at 90 °C overnight. The reaction mixture was filtered and concentrated and the residue was purified by flash chromatography on silica using EtOAc/n-pentane (1:4) as eluent. Yield 2.3 g (53%). Analytical HPLC: purity 90% (System A and B); LRESIMS m/z = 440 (M+H)⁺.

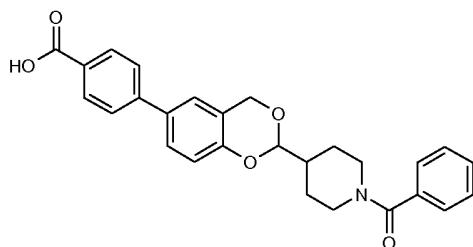
INTERMEDIATE A15

Methyl 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzoate

A suspension of methyl 4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzoate (Intermediate A8; 1.1 g, 3.0 mmol), benzoic acid (0.55 g, 4.49 mmol), triethylamine (1.8 g, 18 mmol), propylphosphonic anhydride (3 mL, 47 mmol; as a 50% solution in EtOAc) in DMF (30 mL) was stirred at r.t. for 2 h and then diluted with DCM (20 mL). The mixture 5 was extracted with 1 M NaOH (20 mL) and DCM (3 x 20 mL). The organic layers were combined, washed with water (10 mL) and brine (10 mL), dried (MgSO_4) and concentrated. The residue was purified by flash chromatography on silica using EtOAc/n-heptane (1:4) as eluent. Yield 1.2 g (90%). Analytical HPLC: purity 94% (System A and B); LRESIMS $m/z = 458 (\text{M}+\text{H})^+$.

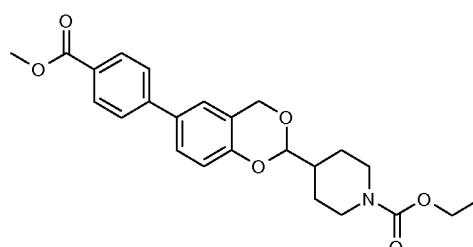
10

INTERMEDIATE A16

4-[2-(1-Benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzoic acid

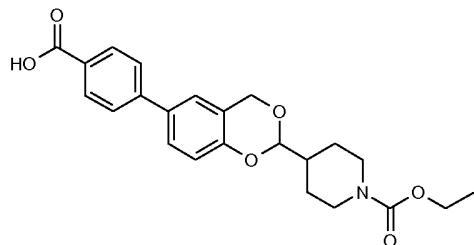
Methyl 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzoate (Intermediate 15 A15; 1.2 g, 2.6 mmol) was reacted with aqueous 6 M KOH (3 mL) in MeOH/THF (1:2, 30 mL) at 60 °C for 1 h. The solvents were removed under reduced pressure and the residue was dissolved in water (30 mL). The water solution was acidified to pH 2 with 6 M HCl and then extracted with DCM (3 x 30 mL). The organic layers were combined and washed with water (10 mL) and brine (10 mL), dried (MgSO_4) and concentrated to give the title 20 compound. Yield 0.7 g (58%). Analytical HPLC: purity 95% (System A and B); LRESIMS $m/z = 444 (\text{M}+\text{H})^+$.

INTERMEDIATE A17

Ethyl 4-{6-[4-(methoxycarbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate

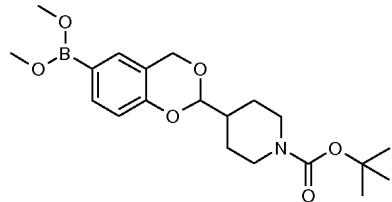
A suspension of methyl 4-(2-piperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl)benzoate (Intermediate A8; 1.4 g, 4.0 mmol), triethylamine (2.4 g, 24 mmol), ethyl chloridocarbonate (0.6 g, 5.9 mmol) in DMF (50 mL) was stirred at r.t. for 30 min. The mixture was concentrated and the residue was partitioned between 1 M NaOH (20 mL) and DCM (3 x 20 mL). The organic layers were combined, washed with water (10 mL) and brine (10 mL), dried (MgSO_4) and concentrated. The residue was purified by flash chromatography on silica using EtOAc/n-heptane (1:4) as eluent. Yield 1.1 g (65%). Analytical HPLC: purity 97% (System A and B); LRESIMS m/z = 426 ($\text{M}+\text{H}$)⁺.

10 INTERMEDIATE A18

4-{2-[1-(Ethoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid

A suspension of ethyl 4-{6-[4-(methoxycarbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidine-1-carboxylate (Intermediate A17; 1.1 g, 2.5 mmol) in 6 M aqueous KOH (3 mL) and MeOH/THF (1:2, 30 mL) was heated at 60 °C for 1 h. The solvents were removed under reduced pressure and the residue was dissolved in water (30 mL). The water solution was acidified to pH 2 using 6 M HCl and then extracted with DCM (3 x 30 mL). The organic layers were combined, washed with water (10 mL) and brine (10 mL), dried (MgSO_4) and then concentrated. Yield 0.6 g (60%). Analytical HPLC: purity 95% (System A and B); LRESIMS m/z = 412 ($\text{M}+\text{H}$)⁺.

INTERMEDIATE A19

***tert*-Butyl 4-[6-(dimethoxyboryl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate**

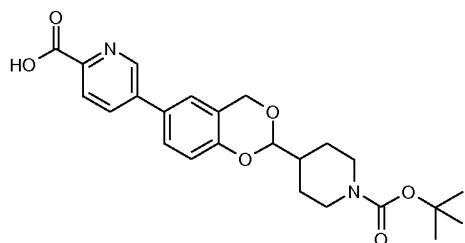
25 A stirred suspension of *tert*-butyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate (Intermediate A11; 2.5 g, 6.27 mmol) in dry THF (100 mL) under N_2 (g) was

cooled to -78 °C and *n*-BuLi (10 mL; 2 M in hexanes) was added dropwise. The mixture was stirred for 30 min at -78 °C and trimethylborate (0.84 mL, 0.78 g) was added over 10 min. Stirring was continued at -78 °C for 30 min and then at r.t. for 10 h before the reaction was quenched with saturated aqueous NaHCO₃ (10 mL). The mixture was dried (Na₂SO₄) and concentrated and the residue was purified by flash chromatography on silica using 5% MeOH in DCM as eluent. Yield 1.09 g (45%).

INTERMEDIATE A20

5-{2-[1-(*tert*-Butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}pyridine-2-

carboxylic acid

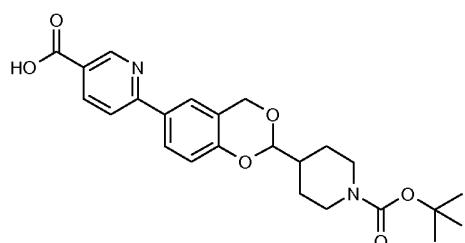


A suspension of *tert*-butyl 4-[6-(dimethoxyboryl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate (Intermediate A19; 300 mg, 0.766 mmol), 5-bromopyridine-2-carboxylic acid (201 mg, 0.996 mmol), K₂CO₃ (265 mg, 1.92 mmol), PdCl₂dppf·DCM (63 mg, 0.077 mmol) in MeCN/H₂O (5 mL; 2:1) was heated at 160 °C for 20 min in a microwave reactor.

The mixture was filtered through a pad of silica and concentrated to give the title compound. Yield 338 mg (100%). Analytical HPLC: purity 80% (System A).

INTERMEDIATE A21

6-{2-[1-(*tert*-Butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}nicotinic acid



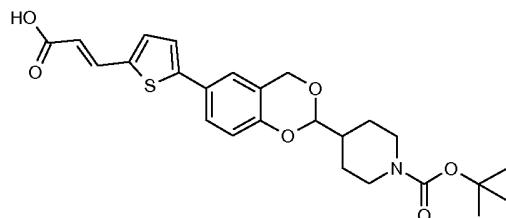
A suspension of *tert*-butyl 4-[6-(dimethoxyboryl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate (Intermediate A19; 300 mg, 0.766 mmol), 2-bromopyridine-5-carboxylic acid (201 mg, 0.996 mmol), K₂CO₃ (265 mg, 1.92 mmol), PdCl₂dppf·DCM (63 mg, 0.077 mmol) in MeCN/H₂O (5 mL; 2:1) was heated at 160 °C for 20 min in a microwave reactor.

The mixture was filtered through a pad of silica and concentrated to give the title compound. Yield 338 mg (100%). Analytical HPLC: purity 80% (System A).

The mixture was filtered through a pad of silica and concentrated to give the title compound. Yield 338 mg (100%). Analytical HPLC: purity 80% (System A).

INTERMEDIATE A22

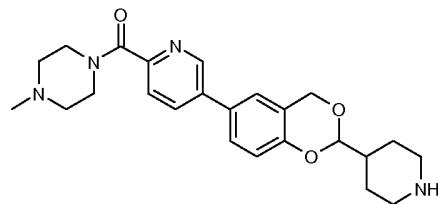
5 **(2E)-3-(5-{2-[1-(*tert*-Butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-2-thienyl)acrylic acid**



A suspension of *tert*-butyl 4-[6-(dimethoxyboryl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate (Intermediate A19; 100 mg, 0.255 mmol), (2*E*)-3-(5-bromo-2-thienyl)acrylic acid (77.4 mg, 0.332 mmol), K₂CO₃ (88 mg, 0.64 mmol), PdCl₂dppf·DCM (22 mg, 0.025 mmol) in MeCN/H₂O (4 mL; 2:1) was heated at 160 °C for 20 min in a microwave reactor. The mixture was filtered through a pad of silica and concentrated to give the title compound which was used directly in Example A137 and A138.

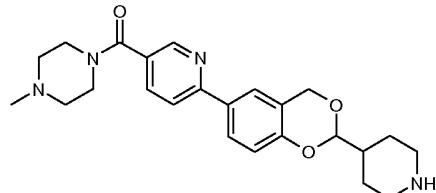
15 **INTERMEDIATE A23**

1-Methyl-4-{[5-(2-piperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]pyridin-2-yl}carbonylpiperazine



A suspension of *tert*-butyl 4-(6-{[(4-methylpiperazin-1-yl)carbonyl]pyridin-3-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate (Example A134; 122 mg, 0.234 mmol) in 1 M HCl in MeOH (20 mL) was stirred at r.t. for 80 min. The mixture was concentrated and the residue was partitioned between EtOAc and saturated aqueous Na₂CO₃. The organic phase was dried (Na₂SO₄) and concentrated to give the title compound. Yield 64 mg (64%). Analytical HPLC: purity 99% (System A); LRESIMS m/z = 423 (M+H)⁺.

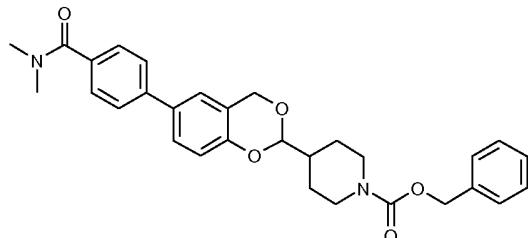
INTERMEDIATE A24

1-Methyl-4-{[6-(2-piperidin-4-yl-4H-1,3-benzodioxin-6-yl)pyridin-3-yl]carbonyl}-piperazine

5 A suspension of *tert*-butyl 4-(6-{5-[(4-methylpiperazin-1-yl)carbonyl]pyridin-2-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate (Example A132; 88 mg, 0.17 mmol) in 1 M HCl in MeOH (20 mL) was stirred at r.t. for 80 min. The mixture was concentrated and the residue was partitioned between EtOAc and saturated aqueous Na₂CO₃. The organic phase was dried (Na₂SO₄) and concentrated to give the title compound. Yield 71 mg (99%).

10 Analytical HPLC: purity 99% (System A); LRESIMS m/z = 423 (M+H)⁺.

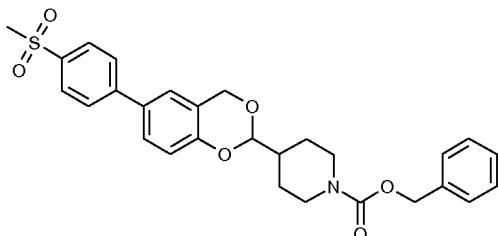
EXAMPLE A1

Benzyl 4-(6-{4-[(dimethylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate

15 The title compound was prepared from benzyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate (Intermediate A1) and {4-[(dimethylamino)carbonyl]phenyl}-boronic acid using the conditions described in general method A1. Yield 12.2 mg (53%).

20 Analytical HPLC: purity 94% (System A and B); HRESIMS (ESI⁺) calcd for C₃₀H₃₂N₂O₅ 500.2311, found 500.2315.

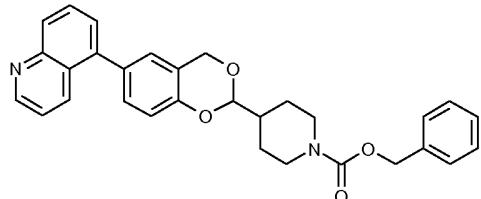
EXAMPLE A2

Benzyl 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate

5 The title compound was prepared from benzyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate (Intermediate A1) and [4-(methylsulfonyl)phenyl]boronic acid using the conditions described in general method A1. Yield 10.5 mg (45%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₈H₂₉NO₆S 507.1716, found 507.1731.

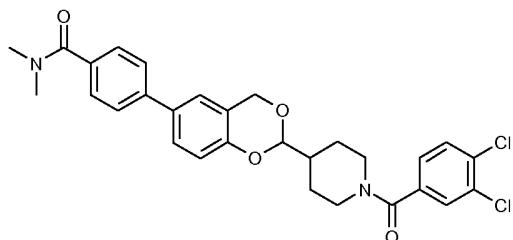
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EXAMPLE A3

Benzyl 4-(6-quinolin-5-yl-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate

15 The title compound was prepared from benzyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate (Intermediate A1) and quinolin-5-ylboronic acid using the conditions described in general method A1. Yield 8.6 mg (39%). Analytical HPLC: purity 96% (System A and B); HRESIMS (ESI⁺) calcd for C₃₀H₂₈N₂O₄ 480.2049, found 480.2055.

20 EXAMPLE A4

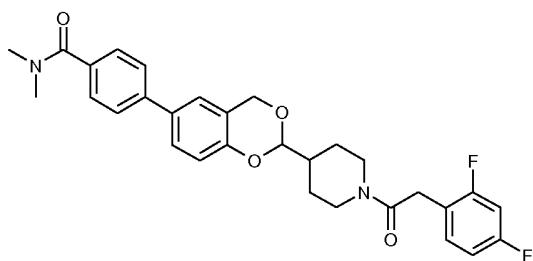
4-{2-[1-(3,4-Dichlorobenzoyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-N,N-dimethylbenzamide

The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and 3,4-dichlorobenzoic acid using the conditions described in general method C1. Yield 8.0 mg (55%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI⁺) calcd for C₂₉H₂₈Cl₂N₂O₄ 538.1426, found 538.1427.

5

EXAMPLE A5

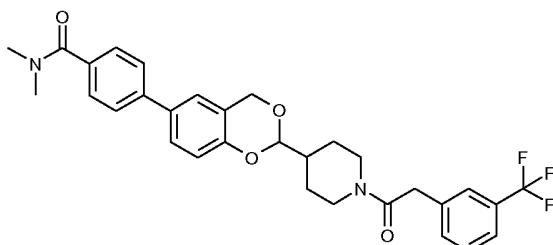
4-(2-{1-[(2,4-Difluorophenyl)acetyl]piperidin-4-yl}-4*H*-1,3-benzodioxin-6-yl)-N,N-dimethylbenzamide



10 The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and (2,4-difluorophenyl)acetic acid using the conditions described in general method C1. Yield 8.2 mg (58%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI⁺) calcd for C₃₀H₃₀F₂N₂O₄ 520.2174, found 520.2185.

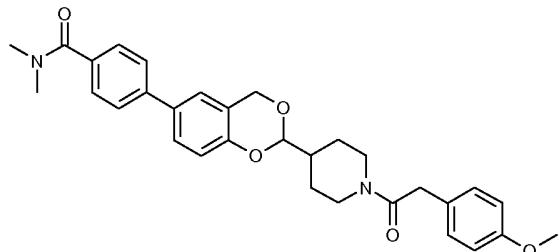
15 EXAMPLE A6

***N,N*-Dimethyl-4-[2-(1-{[3-(trifluoromethyl)phenyl]acetyl}piperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzamide**



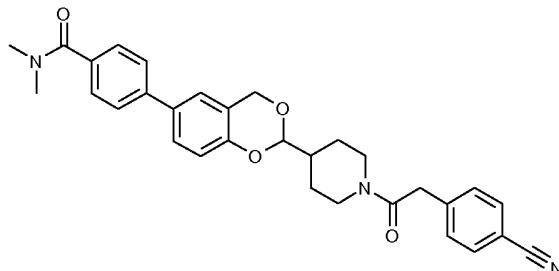
20 The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and [3-(trifluoromethyl)phenyl]acetic acid using the conditions described in general method C1. Yield 8.3 mg (56%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI⁺) calcd for C₃₁H₃₁F₃N₂O₄ 552.2236, found 552.2251.

EXAMPLE A7

4-(2-{1-[(4-Methoxyphenyl)acetyl]piperidin-4-yl}-4H-1,3-benzodioxin-6-yl)-N,N-dimethylbenzamide

5 The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and (4-methoxyphenyl)acetic acid using the conditions described in general method C1. Yield 8.4 mg (60%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI $^+$) calcd for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_5$ 514.2468, found 514.2484.

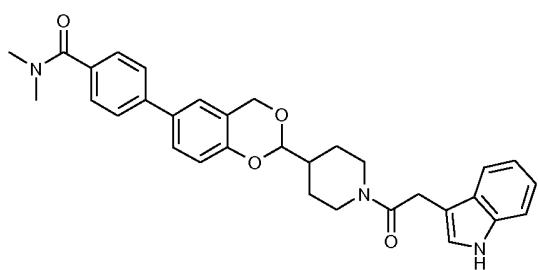
10 EXAMPLE A8

4-(2-{1-[(4-Cyanophenyl)acetyl]piperidin-4-yl}-4H-1,3-benzodioxin-6-yl)-N,N-dimethylbenzamide

15 The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and (4-cyanophenyl)acetic acid using the conditions described in general method C1. Yield 8.4 mg (61%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI $^+$) calcd for $\text{C}_{31}\text{H}_{31}\text{N}_3\text{O}_4$ 509.2315, found 509.2327.

EXAMPLE A9

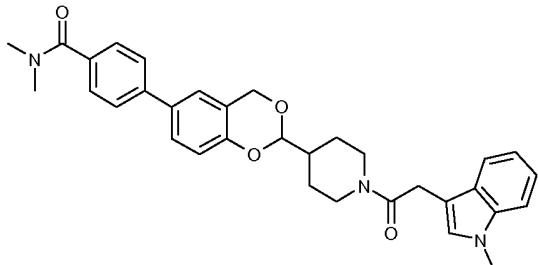
20 **4-{2-[1-(1*H*-Indol-3-ylacetyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-N,N-dimethylbenzamide**



The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and 1*H*-indol-3-ylacetic acid using the conditions described in general method C1. Yield 8.9 mg (63%). Analytical HPLC: purity 5 100% (System C); HRESIMS (ESI⁺) calcd for C₃₂H₃₃N₃O₄ 523.2471, found 523.2479.

EXAMPLE A10

***N,N*-Dimethyl-4-(2-{1-[1-methyl-1*H*-indol-3-yl]acetyl}piperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl)benzamide**

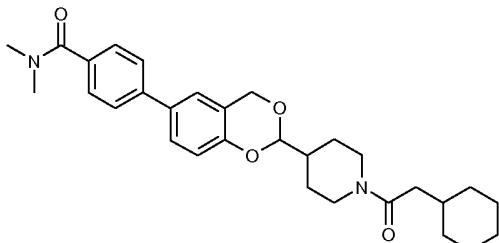


10

The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and (1-methyl-1*H*-indol-3-yl)acetic acid using the conditions described in general method C1. Yield 8.8 mg (61%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI⁺) calcd for C₃₃H₃₅N₃O₄ 537.2628, found 537.2648.

EXAMPLE A11

4-{2-[1-(Cyclohexylacetyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-*N,N*-dimethylbenzamide



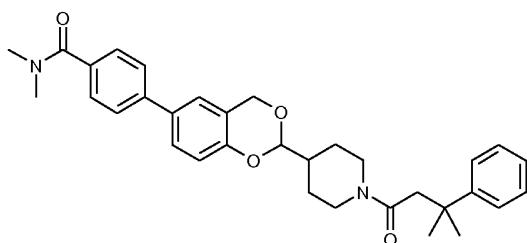
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The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and cyclohexylacetic acid using the conditions described in general method C1. Yield 7.2 mg (54%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI⁺) calcd for C₃₀H₃₈N₂O₄ 490.2832, found 490.2851.

5

EXAMPLE A12

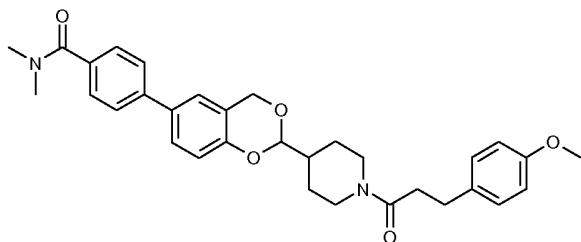
***N,N*-Dimethyl-4-{2-[1-(3-methyl-3-phenylbutanoyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzamide**



10 The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and 3-methyl-3-phenylbutanoic acid using the conditions described in general method C1. Yield 8.5 mg (60%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI⁺) calcd for C₃₃H₃₈N₂O₄ 526.2832, found 526.2852.

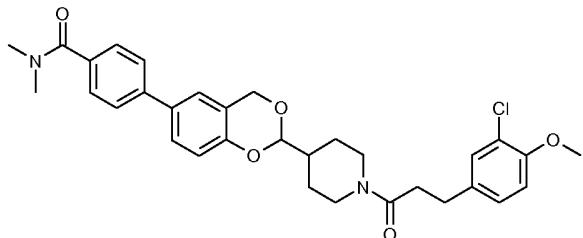
15 EXAMPLE A13

4-(2-{1-[3-(4-Methoxyphenyl)propanoyl]piperidin-4-yl}-4*H*-1,3-benzodioxin-6-yl)-*N,N*-dimethylbenzamide



20 The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and 3-(4-methoxyphenyl)propanoic acid using the conditions described in general method C1. Yield 7.9 mg (55%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI⁺) calcd for C₃₂H₃₆N₂O₅ 528.2624, found 528.2642.

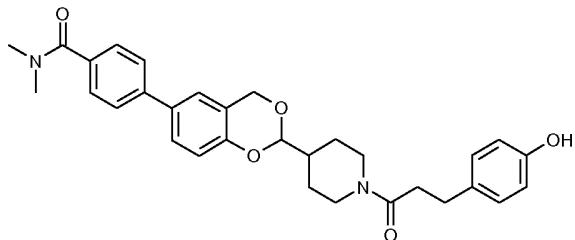
EXAMPLE A14

4-(2-{1-[3-(3-Chloro-4-methoxyphenyl)propanoyl]piperidin-4-yl}-4H-1,3-benzodioxin-6-yl)-N,N-dimethylbenzamide

5 The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and 3-(3-chloro-4-methoxyphenyl)propanoic acid using the conditions described in general method C1. Yield 9.0 mg (59%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI⁺) calcd for C₃₂H₃₅ClN₂O₅ 562.2234, found 562.2244.

10

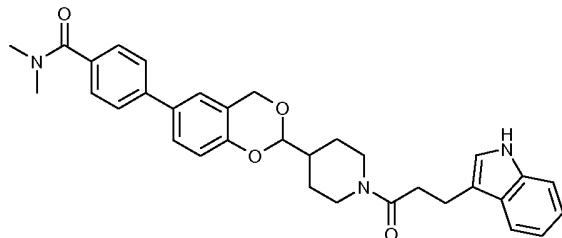
EXAMPLE A15

4-(2-{1-[3-(4-Hydroxyphenyl)propanoyl]piperidin-4-yl}-4H-1,3-benzodioxin-6-yl)-N,N-dimethylbenzamide

15 The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and 3-(4-hydroxyphenyl)propanoic acid using the conditions described in general method C1. Yield 2.8 mg (20%). Analytical HPLC: purity 98% (System C); HRESIMS (ESI⁺) calcd for C₃₁H₃₄N₂O₅ 514.2468, found 514.2472.

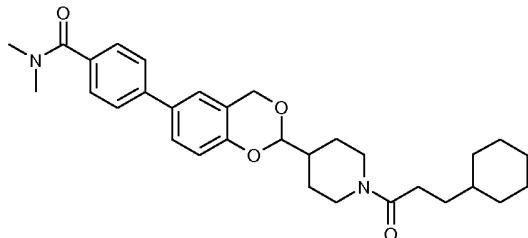
20

EXAMPLE A16

4-(2-{1-[3-(1*H*-Indol-3-yl)propanoyl]piperidin-4-yl}-4*H*-1,3-benzodioxin-6-yl)-*N,N*-dimethylbenzamide

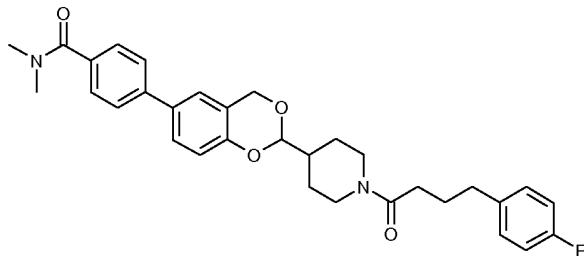
5 The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and 3-(1*H*-indol-3-yl)propanoic acid using the conditions described in general method C1. Yield 9.4 mg (65%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI⁺) calcd for C₃₃H₃₅N₃O₄ 537.2628, found 537.2632.

10 EXAMPLE A17

4-{2-[1-(3-Cyclohexylpropanoyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-*N,N*-dimethylbenzamide

15 The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and 3-cyclohexylpropanoic acid using the conditions described in general method C1. Yield 7.9 mg (58%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI⁺) calcd for C₃₁H₄₀N₂O₄ 504.2988, found 504.2991.

EXAMPLE A18

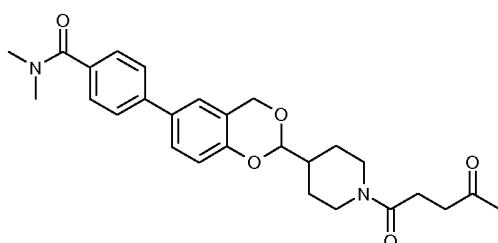
20 **4-(2-{1-[4-(4-Fluorophenyl)butanoyl]piperidin-4-yl}-4*H*-1,3-benzodioxin-6-yl)-*N,N*-dimethylbenzamide**

The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and 4-(4-fluorophenyl)butanoic acid using the conditions described in general method C1. Yield 7.6 mg (53%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI⁺) calcd for C₃₂H₃₅FN₂O₄ 530.2581, found 530.2593.

5

EXAMPLE A19

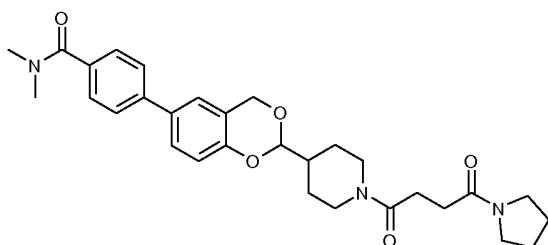
***N,N*-Dimethyl-4-{2-[1-(4-oxopentanoyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzamide**



10 The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and 4-oxopentanoic acid using the conditions described in general method C1. Yield 7.6 mg (61%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI⁺) calcd for C₂₇H₃₂N₂O₅ 464.2311, found 464.2334.

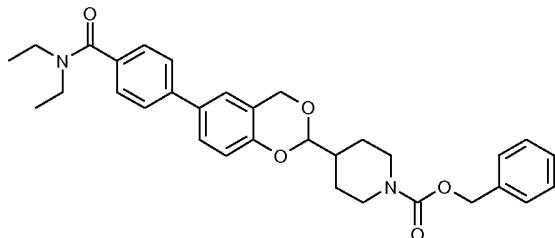
15 EXAMPLE A20

***N,N*-Dimethyl-4-{2-[1-(4-oxo-4-pyrrolidin-1-ylbutanoyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzamide**



20 The title compound was prepared from *N,N*-dimethyl-4-(2-piperidin-4-yl-4*H*-1,3-benzodioxin-6-yl)benzamide (Intermediate A3) and 4-oxo-4-pyrrolidin-1-ylbutanoic acid using the conditions described in general method C1. Yield 9.0 mg (64%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI⁺) calcd for C₃₀H₃₇N₃O₅ 519.2733, found 519.2750.

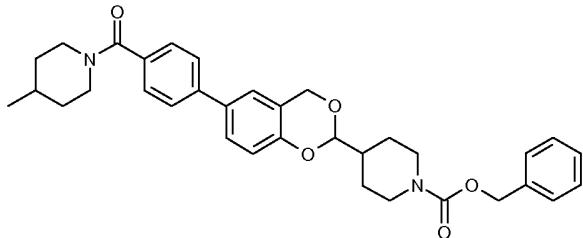
EXAMPLE A21

Benzyl 4-(6-{4-[(diethylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate

5 The title compound was prepared from benzyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate (Intermediate A1) and {4-[(diethylamino)carbonyl]phenyl}-boronic acid using the conditions described in general method A1. Yield 10.3 mg (42%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI⁺) calcd for C₃₂H₃₆N₂O₅ 528.2624, found 528.2628.

10

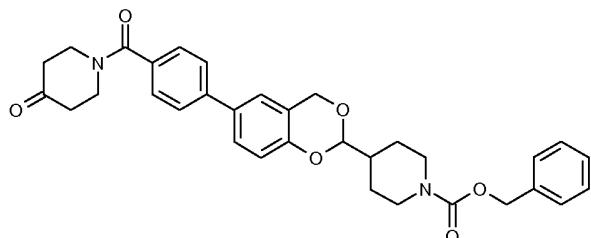
EXAMPLE A22

Benzyl 4-(6-{4-[(4-methylpiperidin-1-yl)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate

15 The title compound was prepared from benzyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate (Intermediate A1) and {4-[(4-methylpiperidin-1-yl)carbonyl]phenyl}boronic acid using the conditions described in general method A1. Yield 13.3 mg (52%). Analytical HPLC: purity 100% (System C); HRESIMS (ESI⁺) calcd for C₃₄H₃₈N₂O₅ 554.2781, found 554.2800.

20

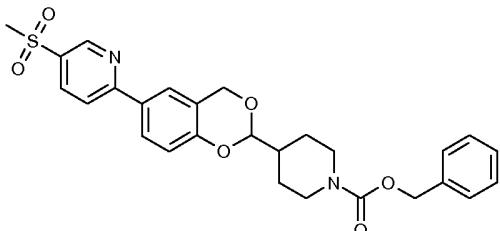
EXAMPLE A23

Benzyl 4-(6-{4-[{(4-oxopiperidin-1-yl)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl}-piperidine-1-carboxylate

5 The title compound was prepared from benzyl 4-(6-bromo-4H-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate (Intermediate A1) and {4-[{(4-oxopiperidin-1-yl)carbonyl]-phenyl}boronic acid using the conditions described in general method A1. Yield 2.9 mg (11%). Analytical HPLC: purity 90% (System C); HRESIMS (ESI⁺) calcd for C₃₃H₃₄N₂O₆ 554.2417, found 554.2395.

10

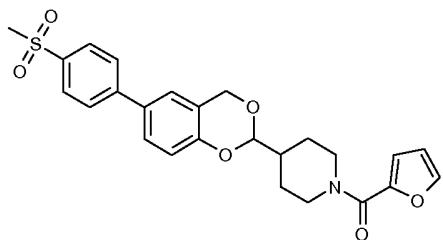
EXAMPLE A24

Benzyl 4-{6-[5-(methylsulfonyl)pyridin-2-yl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate

15 A suspension of 2-bromo-5-(methylsulfonyl)pyridine (25 mg, 0.11 mmol), 5,5,5',5'-tetramethyl-2,2'-bi-1,3,2-dioxaborinane (36 mg, 0.16 mmol), KOAc (31 mg, 0.32 mmol) and PdCl₂dppf·DCM (4 mg, 0.005 mmol) in DME (2 mL) was heated at 120 °C for 20 min in a microwave reactor. To the mixture were added benzyl 4-(6-bromo-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate (Intermediate A1; 46 mg, 0.11 mmol), NaHCO₃ (18 mg, 0.21 mmol), Pd(PPh₃)₄ (1 mg, 0.001 mmol) and water (0.5 mL). The resulting mixture was heated at 120 °C for 800 sec in a microwave reactor and then concentrated. The residue was purified by gradient flash chromatography on silica (DCM/heptane 3:1 → DCM/EtOAc 9:1). Yield 11 mg (20%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₇H₂₈N₂O₆S 508.1668, found 508.1676.

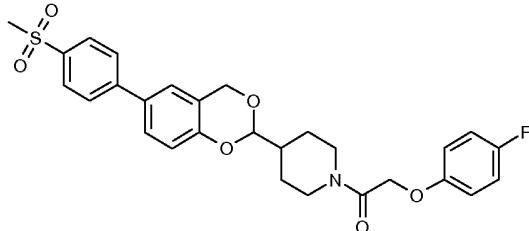
25

EXAMPLE A25

1-(2-Furoyl)-4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine

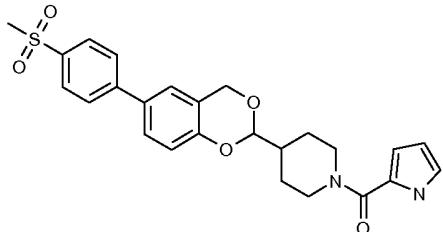
The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and 2-furoic acid using the conditions described in general method C2. Yield 3.2 mg (17%). Analytical HPLC: purity 97% (System C); HRESIMS (ESI⁺) calcd for C₂₅H₂₅NO₆S 467.1403, found 467.1409.

EXAMPLE A26

1-[(4-Fluorophenoxy)acetyl]-4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine

The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and (4-fluorophenoxy)acetic acid using the conditions described in general method C2. Yield 5.2 mg (25%). Analytical HPLC: purity 99% (System C); HRESIMS (ESI⁺) calcd for C₂₈H₂₈FNO₆S 525.1621, found 525.1622.

EXAMPLE A27

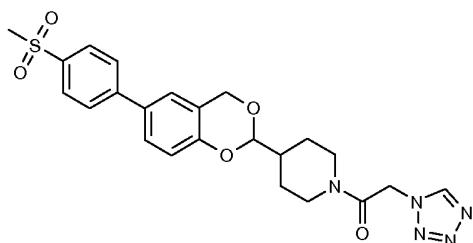
4-{6-[4-(Methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}-1-(1*H*-pyrrol-2-yl-carbonyl)piperidine

The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and 1*H*-pyrrole-2-carboxylic acid using the conditions described in general method C2. Yield 2.9 mg (16%). Analytical HPLC: purity 99% (System C); HRESIMS (ESI⁺) calcd for C₂₅H₂₆N₂O₅S 466.1562, found 466.1567.

5

EXAMPLE A28

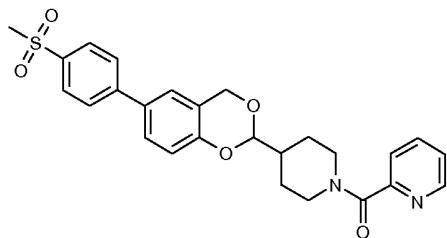
4-{6-[4-(Methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-1-(1*H*-tetrazol-1-ylacetyl)-piperidine



10 The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and 1*H*-tetrazol-1-ylacetic acid using the conditions described in general method C2. Yield 1.5 mg (8%). Analytical HPLC: purity 96% (System C); HRESIMS (ESI⁺) calcd for C₂₃H₂₅N₅O₅S 483.1576, found 483.1585.

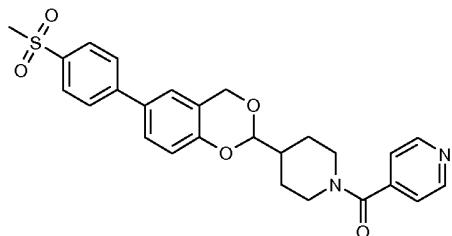
15 EXAMPLE A29

2-[(4-{6-[4-(Methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]pyridine



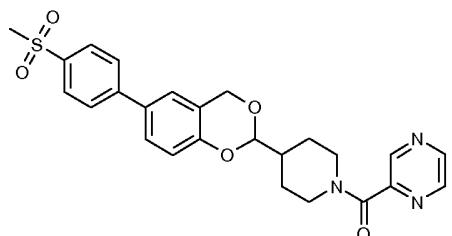
20 The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and pyridine-2-carboxylic acid using the conditions described in general method C2. Yield 4.7 mg (25%). Analytical HPLC: purity 99% (System C); HRESIMS (ESI⁺) calcd for C₂₆H₂₆N₂O₅S 478.1562, found 478.1564.

EXAMPLE A30

4-[(4-{6-[4-(Methylsulfonyl)phenyl]phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]pyridine

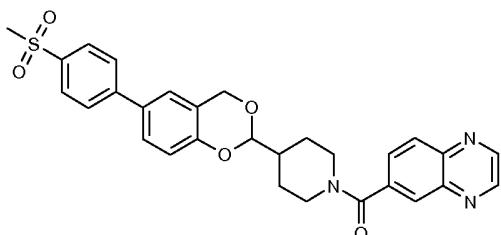
- 5 The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and isonicotinic acid using the conditions described in general method C2. Yield 4.1 mg (21%). Analytical HPLC: purity 98% (System C); HRESIMS (ESI⁺) calcd for C₂₆H₂₆N₂O₅S 478.1562, found 478.1568.

10 EXAMPLE A31

2-[(4-{6-[4-(Methylsulfonyl)phenyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidin-1-yl]-carbonyl]pyrazine

- 15 The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and pyrazine-2-carboxylic acid using the conditions described in general method C2. Yield 3.2 mg (17%). Analytical HPLC: purity 98% (System C); HRESIMS (ESI⁺) calcd for C₂₅H₂₅N₃O₅S 479.1515, found 479.1516.

EXAMPLE A32

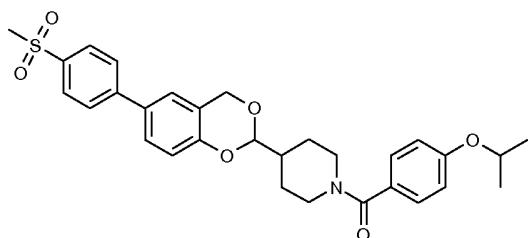
20 **6-[(4-{6-[4-(Methylsulfonyl)phenyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidin-1-yl]-carbonyl]quinoxaline**

The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and quinoxaline-6-carboxylic acid using the conditions described in general method C2. Yield 4.5 mg (21%). Analytical HPLC: purity 98% (System C); HRESIMS (ESI⁺) calcd for C₂₉H₂₇N₃O₅S 529.1671, found 529.1665.

5

EXAMPLE A33

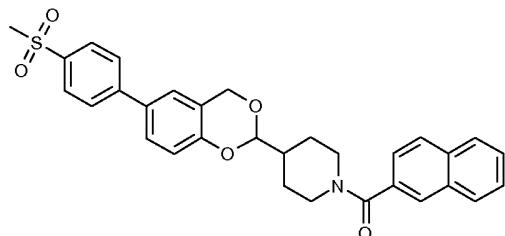
1-(4-Isopropoxybenzoyl)-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidine



10 The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and 4-isopropoxybenzoic acid using the conditions described in general method C2. Yield 4.9 mg (23%). Analytical HPLC: purity 99% (System C); HRESIMS (ESI⁺) calcd for C₃₀H₃₃NO₆S 535.2029, found 535.2039.

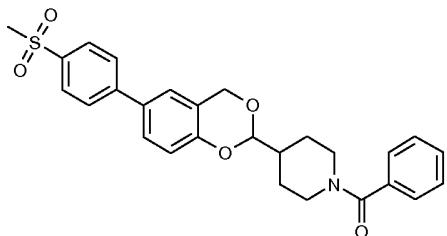
15 EXAMPLE A34

4-{6-[4-(Methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-1-(2-naphthoyl)piperidine



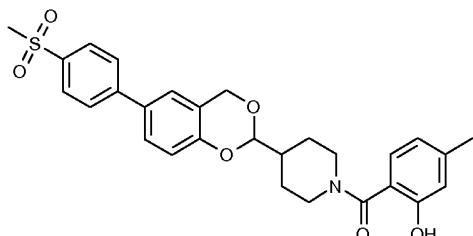
20 The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and 2-naphthoic acid using the conditions described in general method C2. Yield 5.0 mg (24%). Analytical HPLC: purity 99% (System C); HRESIMS (ESI⁺) calcd for C₃₁H₂₉NO₅S 527.1766, found 527.1771.

EXAMPLE A35

1-Benzoyl-4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine

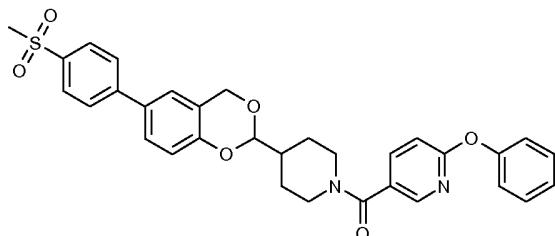
The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and benzoic acid using the conditions described in general method C2. Yield 4.4 mg (23%). Analytical HPLC: purity 98% (System C); HRESIMS (ESI⁺) calcd for C₂₇H₂₇NO₅S 477.1610, found 477.1615.

EXAMPLE A36

10 **5-Methyl-2-[(4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidin-1-yl)carbonyl]phenol**

The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and 2-hydroxy-4-methylbenzoic acid using the conditions described in general method C2. Yield 0.7 mg (3%). Analytical HPLC: purity 90% (System C); HRESIMS (ESI⁺) calcd for C₂₈H₂₉NO₆S 507.1716, found 507.1716.

EXAMPLE A37

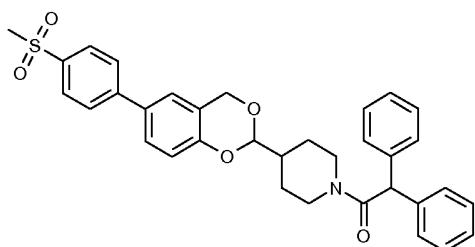
20 **5-[(4-{6-[4-(Methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]-2-phenoxyypyridine**

The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and 6-phenoxy nicotinic acid using the conditions described in general method C2. Yield 4.7 mg (21%). Analytical HPLC: purity 90% (System C); HRESIMS (ESI⁺) calcd for C₃₂H₃₀N₂O₆S 570.1825, found 570.1826.

5

EXAMPLE A38

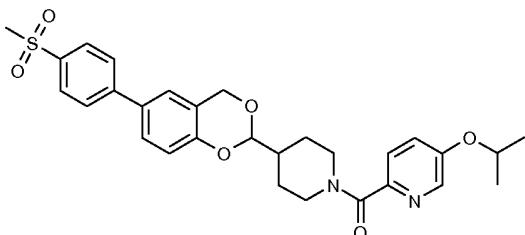
1-(Diphenylacetyl)-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidine



10 The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and diphenylacetic acid using the conditions described in general method C2. Yield 4.5 mg (20%). Analytical HPLC: purity 99% (System C); HRESIMS (ESI⁺) calcd for C₃₄H₃₃NO₅S 567.2079, found 567.2088.

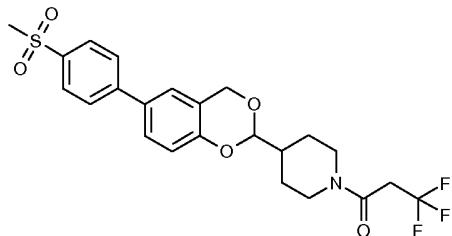
15 EXAMPLE A39

5-Isopropoxy-2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)carbonyl]pyridine



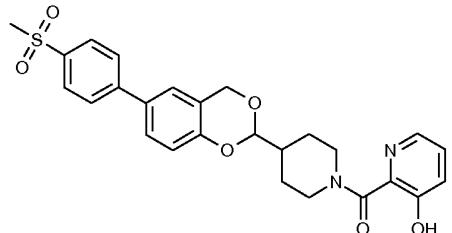
20 The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and 5-isopropoxypyridine-2-carboxylic acid using the conditions described in general method C2. Yield 1.9 mg (9%). Analytical HPLC: purity 96% (System C); HRESIMS (ESI⁺) calcd for C₂₉H₃₂N₂O₆S 536.1981, found 536.1990.

EXAMPLE A40

4-{6-[4-(Methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}-1-(3,3,3-trifluoropropanoyl)piperidine

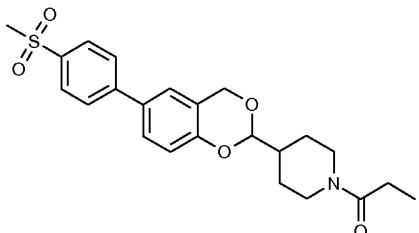
5 The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and 3,3,3-trifluoropropanoic acid using the conditions described in general method C2. Yield 3.6 mg (19%). Analytical HPLC: purity 94% (System C); HRESIMS (ESI⁺) calcd for C₂₃H₂₄F₃NO₅S 483.1327, found 483.1332.

10 EXAMPLE A41

2-[(4-{6-[4-(Methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]pyridin-3-ol

15 The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and 3-hydroxypyridine-2-carboxylic acid using the conditions described in general method C2. Yield 2.5 mg (13%). Analytical HPLC: purity 97% (System C); LRESIMS m/z = 495 (M+H)⁺.

EXAMPLE A42

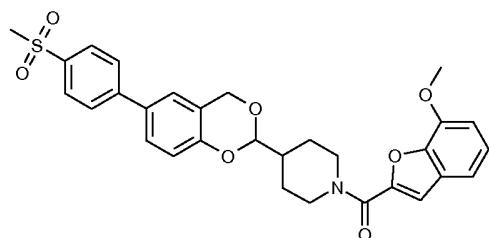
20 **4-{6-[4-(Methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}-1-propionylpiperidine**

The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and propionic acid using the conditions described in general method C2. Yield 5.1 mg (30%). Analytical HPLC: purity 98% (System C); HRESIMS (ESI⁺) calcd for C₂₃H₂₇NO₅S 429.1610, found 429.1614.

5

EXAMPLE A43

1-[(7-Methoxy-1-benzofuran-2-yl)carbonyl]-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine

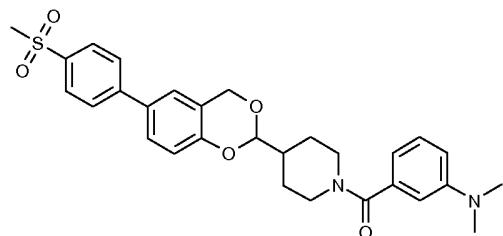


- 10 The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and 7-methoxy-1-benzofuran-2-carboxylic acid using the conditions described in general method C2. Yield 5.1 mg (23%). Analytical HPLC: purity 99% (System C); HRESIMS (ESI⁺) calcd for C₃₀H₂₉NO₇S 547.1665, found 547.1674.

15

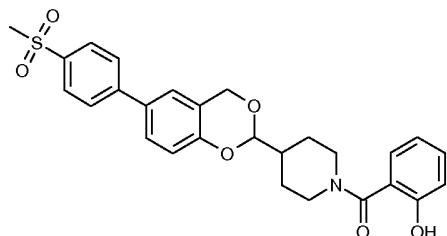
EXAMPLE A44

Dimethyl{3-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)carbonyl]phenyl}amine



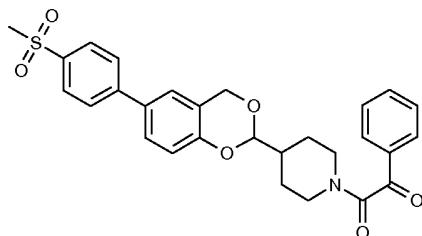
- 20 The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and 3-(dimethylamino)benzoic acid using the conditions described in general method C2. Yield 4.9 mg (24%). Analytical HPLC: purity 98% (System C); HRESIMS (ESI⁺) calcd for C₂₉H₃₂N₂O₅S 520.2032, found 520.2047.

EXAMPLE A45

2-[(4-{6-[4-(Methylsulfonyl)phenyl]phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]phenol

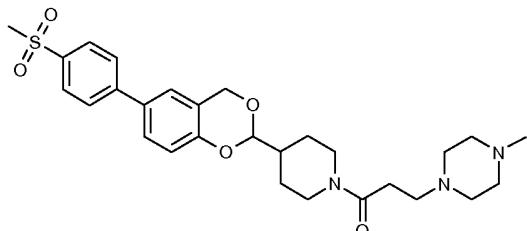
5 The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and salicylic acid using the conditions described in general method C2. Yield 3.6 mg (18%). Analytical HPLC: purity 95% (System C); HRESIMS (ESI⁺) calcd for C₂₇H₂₇NO₆S 493.1559, found 493.1560.

10 EXAMPLE A46

2-(4-{6-[4-(Methylsulfonyl)phenyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidin-1-yl)-2-oxo-1-phenylethanone

15 The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and oxo(phenyl)acetic acid using the conditions described in general method C2. Yield 3.8 mg (19%). Analytical HPLC: purity 98% (System C); HRESIMS (ESI⁺) calcd for C₂₈H₂₇NO₆S 505.1559, found 505.1564.

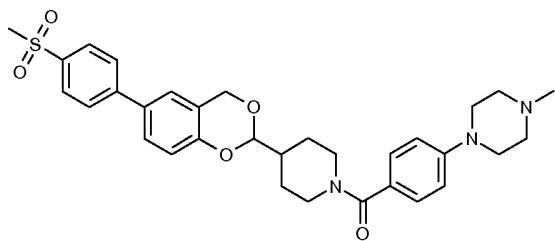
EXAMPLE A47

20 **1-Methyl-4-[3-(4-{6-[4-(methylsulfonyl)phenyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidin-1-yl]-3-oxopropyl]piperazine**

The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and 3-(4-methylpiperazin-1-yl)propanoic acid using the conditions described in general method C2. Yield 3.7 mg (18%). Analytical HPLC: purity 99% (System C); HRESIMS (ESI⁺) calcd for C₂₈H₃₇N₃O₅S 527.2454, found 527.2465.

EXAMPLE A48

1-Methyl-4-{4-[{(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)carbonyl]phenyl}piperazine

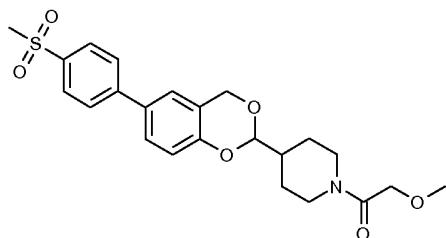


10

The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and 4-(4-methylpiperazin-1-yl)benzoic acid using the conditions described in general method C2. Yield 4.3 mg (19%). Analytical HPLC: purity 97% (System C); HRESIMS (ESI⁺) calcd for C₃₂H₃₇N₃O₅S 575.2454, found 575.2470.

EXAMPLE A49

1-(Methoxyacetyl)-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidine

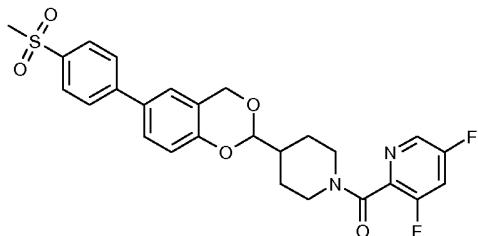


20

The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and methoxyacetic acid using the conditions described in general method C2. Yield 4.0 mg (22%). Analytical HPLC: purity 98% (System C); HRESIMS (ESI⁺) calcd for C₂₃H₂₇NO₆S 445.1559, found 445.1560.

25

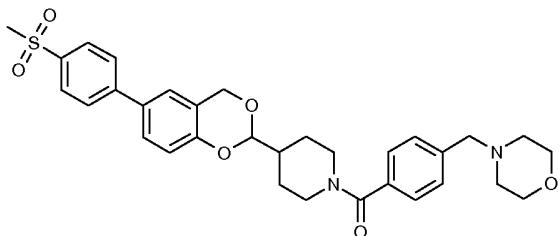
EXAMPLE A50

3,5-Difluoro-2-[(4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidin-1-yl)carbonyl]pyridine

- 5 The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and 3,5-difluoropyridine-2-carboxylic acid using the conditions described in general method C2. Yield 4.7 mg (23%). Analytical HPLC: purity 99% (System C); HRESIMS (ESI⁺) calcd for C₂₆H₂₄F₂N₂O₅S 514.1374, found 514.1372.

10

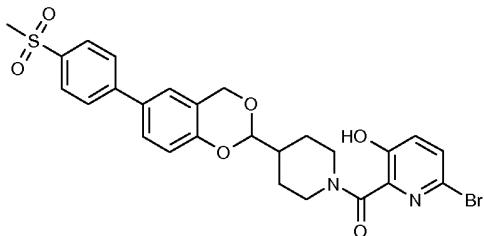
EXAMPLE A51

4-{4-[(4-{6-[4-(Methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidin-1-yl)carbonyl]benzyl}morpholine

- 15 The title compound was prepared from 4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine (Intermediate A4) and 4-(morpholin-4-ylmethyl)benzoic acid using the conditions described in general method C2. Yield 4.3 mg (28%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₃₂H₃₆N₂O₆S 576.2294, found 576.2296.

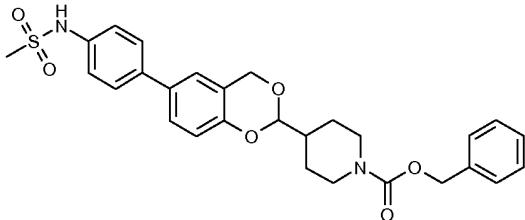
20

EXAMPLE A52

6-Bromo-2-[(4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidin-1-yl)carbonyl]pyridin-3-ol

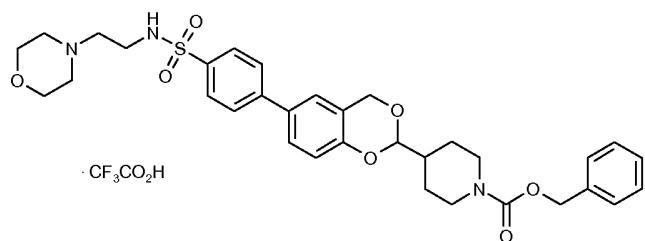
5 To a vial containing 6-bromo-3-hydroxypyridine-2-carboxylic acid (Intermediate A5; 61 mg, 0.28 mmol) was added a solution of 4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine (Intermediate A4; 95 mg, 0.25 mmol) in THF (5 mL) and triethylamine (140 μ L, 1.0 mmol) followed by HOBT (69 mg, 0.51 mmol) and EDC (97 mg, 0.51 mmol). The resulting mixture was stirred overnight. The solvent was removed
10 under reduced pressure and the residue was purified by preparative HPLC (System D). Yield 20 mg (14%). Analytical HPLC: purity 91% (System A and B); HRESIMS (ESI $^+$) calcd for C₂₆H₂₅BrN₂O₆S 572.0618, found 572.0613.

EXAMPLE A53

Benzyl 4-(6-{4-[(methylsulfonyl)amino]phenyl}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate

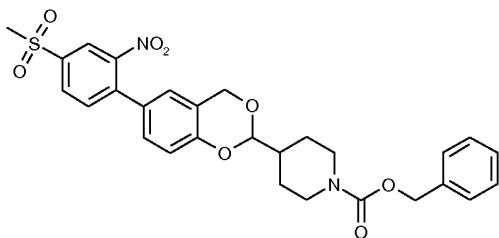
A suspension of benzyl 4-(6-bromo-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate (Intermediate A1; 10 mg, 0.023 mmol), 4-(methanesulfonylamino)phenylboronic acid (5.4 mg, 0.025 mmol), Pd(OAc)₂ (2 mg, 0.009 mmol), K₂CO₃ (8.0 mg, 0.058 mmol) in MeCN (2 mL) and water (0.5 mL) was heated at 90 °C for 1.5 h. The mixture was filtered and then purified by preparative HPLC (System D). Yield 3.0 mg (25%). Analytical GC: purity 99%; HRESIMS (ESI $^+$) calcd for C₂₈H₃₀N₂O₆S 522.1825, found 522.1824.

EXAMPLE A54

Benzyl 4-[6-{[(2-morpholin-4-ylethyl)amino]sulfonyl}phenyl]-4H-1,3-benzodioxin-2-yl]piperidine-1-carboxylate trifluoroacetate

5 A suspension of benzyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate (Intermediate A1; 100 mg, 0.23 mmol), 5,5,5',5'-tetramethyl-2,2'-bi-1,3,2-dioxaborinane (78 mg, 0.35 mmol), KOAc (68 mg, 0.69 mmol) and PdCl₂dppf·DCM (10 mg, 0.012 mmol) in DME (3 mL) was heated at 90 °C for 1 h. To the mixture was then added 4-iodo-*N*-(2-morpholin-4-yl-ethyl)benzene-sulfonamide (91 mg, 0.23 mmol) followed by
10 NaHCO₃ (39 mg, 0.46 mmol), Pd(PPh₃)₄ (27 mg, 0.023 mmol) and water (1 mL). The resulting mixture was heated at 90 °C overnight and then concentrated. The residue was purified by preparative HPLC (System D). Yield 4.2 mg (2%). Analytical HPLC: purity 99% (System A and B); LRESIMS (ESI⁺) m/z = 622 (M+H)⁺.

15 EXAMPLE A55

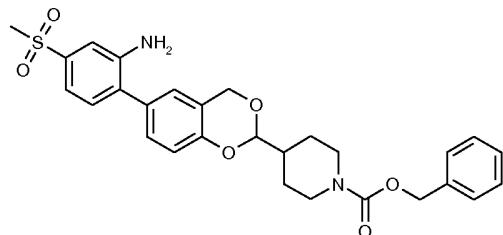
Benzyl 4-{6-[4-(methylsulfonyl)-2-nitrophenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate

20 A suspension of benzyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate (Intermediate A1; 2.0 g, 0.0046 mol), 5,5,5',5'-tetramethyl-2,2'-bi-1,3,2-dioxaborinane (1.6 g, 0.0069 mol), potassium acetate (1.4 g, 0.014 mol) and PdCl₂dppf·DCM (190 mg, 0.23 mmol) in DME (20 mL) was heated at 90 °C for 1 h. To the mixture were then added NaHCO₃ (0.77 g, 0.0092 mol), Pd(PPh₃)₄ (53 mg, 0.046 mmol), 2-bromo-5-methylsulfonylnitrobenzene (1.29 g, 0.0046 mol) and water (5 mL). The mixture was heated at 90 °C for 15 h. The solvents were removed under reduced pressure and the residue was partitioned between water (50 mL) and chloroform (3 x 75 mL). The organic

layers were combined and concentrated. The residue was purified by flash chromatography on silica using heptane/EtOAc (1:1). Yield 1.89 g (74%). Analytical HPLC: purity 98% (System A and B); HRESIMS (ESI⁺) calcd for C₂₈H₂₈N₂O₈S 552.1566, found 552.1579.

5 EXAMPLE A56

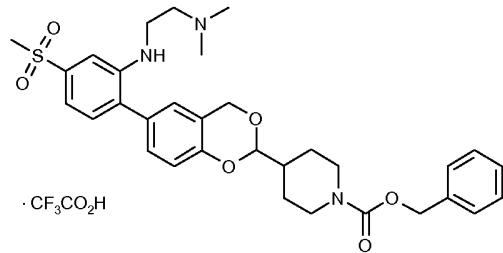
Benzyl 4-{6-[2-amino-4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate



A suspension of benzyl 4-{6-[4-(methylsulfonyl)-2-nitrophenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate (Example A55; 675 mg, 1.22 mmol) and indium powder (560 mg, 4.89 mmol) in saturated NH₄Cl (8 mL) and MeOH (10 mL) was heated in a sealed tube at 85 °C for 15 h. The mixture was filtered and concentrated. The residue was partitioned between water (75 mL) and chloroform (2 x 100 mL) and the organic layers were combined and concentrated. Purification by flash chromatography on silica using EtOAc/DCM (1:3) gave an off-white solid. Yield 515 mg (81%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₂₈H₃₀N₂O₆S 522.1825, found 522.1825.

EXAMPLE A57

Benzyl 4-{6-[2-{[2-(dimethylamino)ethyl]amino}-4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate trifluoroacetate

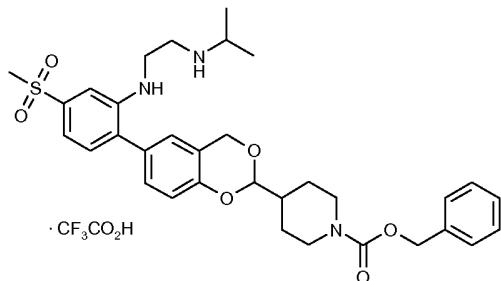


A suspension of benzyl 4-{6-[2-iodo-4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate (Intermediate A6; 50 mg, 0.079 mmol), N,N-dimethylethane-1,2-diamine (8 mg, 0.095 mmol), Pd₂(dba)₃ (2 mg, 0.002 mmol), Xantphos (5 mg, 0.008 mmol) and potassium *tert*-butoxide (12 mg, 0.11 mmol) in toluene (4 mL) was heated at

110 °C overnight. The reaction mixture was concentrated and the residue was purified by preparative HPLC (System D). Yield 12 mg (21%). Analytical HPLC: purity 90% (System A and B); HRESIMS (ESI⁺) calcd for C₃₂H₃₉N₃O₆S 593.2560, found 593.2572.

5 EXAMPLE A58

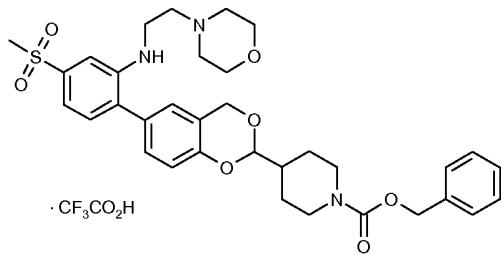
Benzyl 4-{6-[2-{[2-(isopropylamino)ethyl]amino}-4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate trifluoroacetate



The title compound was prepared from benzyl 4-{6-[2-iodo-4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate (Intermediate A6; 50 mg, 0.079 mmol) and N-isopropylethane-1,2-diamine (10 mg, 0.095 mmol) using the conditions described for Example A57. Yield 6 mg (11%). Analytical HPLC: purity 98% (System A and B); HRESIMS (ESI⁺) calcd for C₃₃H₄₁N₃O₆S 607.2716, found 607.2728.

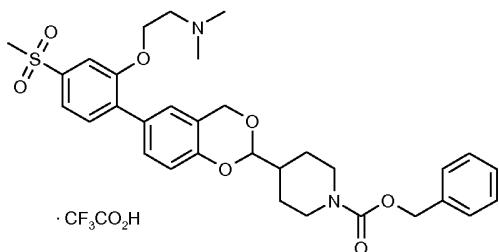
15 EXAMPLE A59

Benzyl 4-(6-{4-(methylsulfonyl)-2-[(2-morpholin-4-ylethyl)amino]phenyl}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate trifluoroacetate



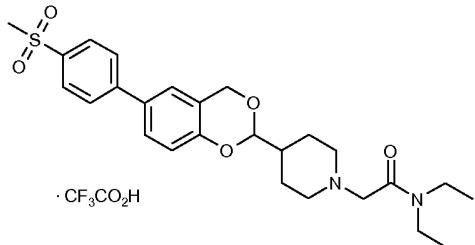
The title compound was prepared from benzyl 4-{6-[2-iodo-4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate (Intermediate A6; 50 mg, 0.079 mmol) and (2-morpholin-4-ylethyl)amine (12 mg, 0.095 mmol) using the conditions described for Example A57. Yield 19 mg (32%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₃₄H₄₁N₃O₇S 635.2665, found 635.2679.

EXAMPLE A60

Benzyl 4-{6-[2-[2-(dimethylamino)ethoxy]-4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate trifluoroacetate

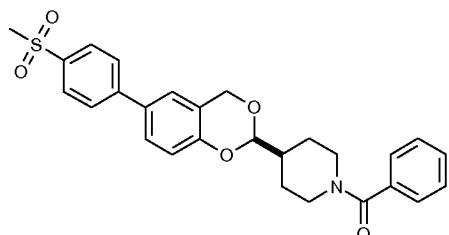
- 5 A suspension of benzyl 4-{6-[2-iodo-4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate (Intermediate A6; 50 mg, 0.079 mmol), CuI (3 mg, 0.016 mmol), 1,10-phenanthroline monohydrate (6 mg, 0.032 mmol) and Cs₂CO₃ (64 mg, 0.20 mmol) in *N,N*-dimethylethanamine (1 mL) was heated at 110 °C for 15 h. The reaction mixture was purified by preparative HPLC (System D). Yield 7 mg (13%). Analytical HPLC: purity 97% (System A and B); HRESIMS (ESI⁺) calcd for C₃₂H₃₈N₂O₇S 594.2400, found 594.2411.
- 10

EXAMPLE A61

***N,N*-Diethyl-2-(4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidin-1-yl)acetamide trifluoroacetate**

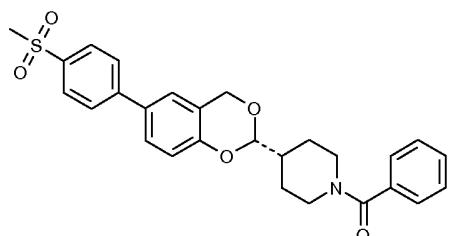
- A suspension of 4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine (Intermediate A4; 10 mg, 0.054 mmol), 2-chloro-*N,N*-diethylacetamide (9 mg, 0.059 mmol) and K₂CO₃ (30 mg, 0.22 mmol) in MeCN (2 mL) was heated at 90 °C overnight.
- 20 The reaction mixture was filtered and purified by preparative HPLC (System D). Yield 5.6 mg (17%). Analytical HPLC: purity 96% (System A and B); HRESIMS (ESI⁺) calcd for C₂₆H₃₄N₂O₅S 486.2188, found 486.2204.

EXAMPLE A62

1-Benzoyl-4-{(2*R*^{*})-6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine

The racemic 1-benzoyl-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidine (Example A35; 60 mg, 0.13 mmol) was separated by Chiral Technologies Europe using the following conditions: Column: CHIRALPAK[®] IA 5 µm, 250 x 21 mm; Mobile phase: *n*-heptane/ethanol/diethylamine 40/60/0.1 (v/v/v); Flow rate: 15 mL/min; Detection: UV 220 nm; Temperature: 25 °C. The retention times of the first eluting enantiomer (the title compound) and the second eluting enantiomer (Example A63) were 10 26.8 min and 32.4 min, respectively. Yield 23 mg (38%). Analytical HPLC: purity 97% (System A and B); HRESIMS (ESI⁺) calcd for C₂₇H₂₇NO₅S 477.1610, found 477.1613.

EXAMPLE A63

1-benzoyl-4-{(2*S*^{*})-6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine

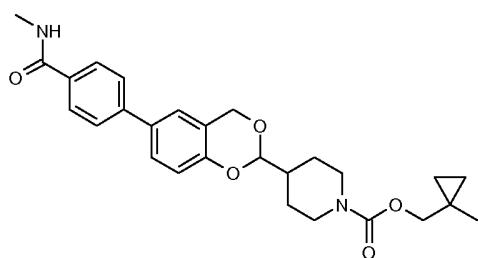
15

The title compound was prepared from 1-benzoyl-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine (Example A35) in accordance with the method described for Example A62. Yield 29 mg (48%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₇H₂₇NO₅S 477.1610, found 477.1634.

20

EXAMPLE A64

(1-Methylcyclopropyl)methyl 4-(6-{4-[(methylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate

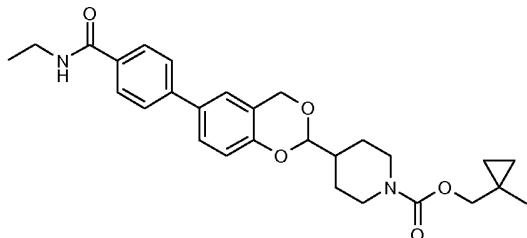


The title compound was prepared from 4-[2-(1-[(1-methylcyclopropyl)methoxy]-carbonyl)piperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A10) and methylamine using the conditions described in general method D. Yield 1.3 mg (6%).
5 Analytical HPLC: purity 95% (System A); HRESIMS (ESI⁺) calcd for C₂₇H₃₂N₂O₅ 464.2311, found 464.2303.

EXAMPLE A65

(1-Methylcyclopropyl)methyl 4-(6-{4-[(ethylamino)carbonyl]phenyl}-4H-1,3-benzo-

dioxin-2-yl)piperidine-1-carboxylate

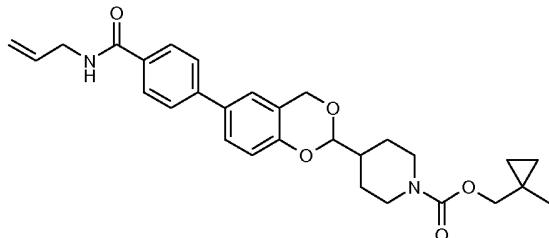


The title compound was prepared from 4-[2-(1-[(1-methylcyclopropyl)methoxy]-carbonyl)piperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A10) and ethylamine using the conditions described in general method D. Yield 4.4 mg (18%).
15 Analytical HPLC: purity 94% (System A); HRESIMS (ESI⁺) calcd for C₂₈H₃₄N₂O₅ 478.2468, found 478.2458.

EXAMPLE A66

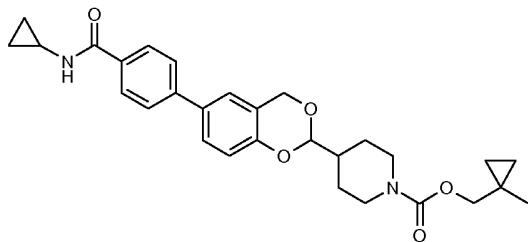
(1-Methylcyclopropyl)methyl 4-(6-{4-[(allylamino)carbonyl]phenyl}-4H-1,3-benzo-

dioxin-2-yl)piperidine-1-carboxylate



The title compound was prepared from 4-[2-(1-[(1-methylcyclopropyl)methoxy]-carbonyl)-piperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A10) and allylamine using the conditions described in general method D. Yield 0.6 mg (2%). Analytical HPLC: purity 98% (System A); HRESIMS (ESI⁺) calcd for C₂₉H₃₄N₂O₅ 490.2468, found 490.2469.

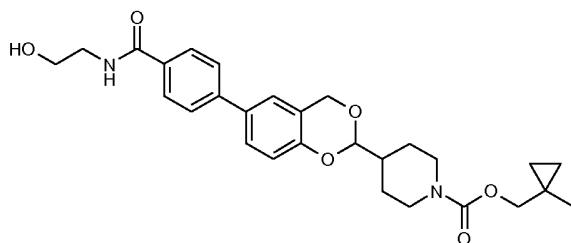
EXAMPLE A67

(1-Methylcyclopropyl)methyl 4-(6-{4-[(cyclopropylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate

10

The title compound was prepared from 4-[2-(1-[(1-methylcyclopropyl)methoxy]-carbonyl)-piperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A10) and cyclopropylamine using the conditions described in general method D. Yield 1.9 mg (8%). Analytical HPLC: purity 100% (System A); HRESIMS (ESI⁺) calcd for C₂₉H₃₄N₂O₅ 490.2468, found 490.2459.

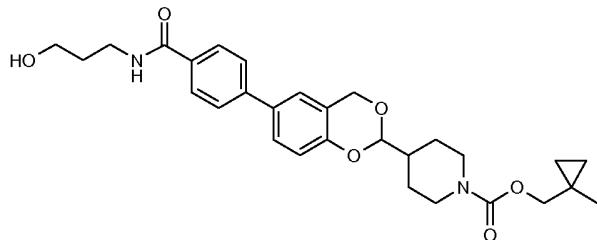
EXAMPLE A68

(1-Methylcyclopropyl)methyl 4-[6-(4-[(2-hydroxyethyl)amino]carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate

20

The title compound was prepared from 4-[2-(1-[(1-methylcyclopropyl)methoxy]-carbonyl)-piperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A10) and ethanolamine using the conditions described in general method D. Yield 0.6 mg (2%). Analytical HPLC: purity 99% (System A); HRESIMS (ESI⁺) calcd for C₂₈H₃₄N₂O₆ 494.2417, found 494.2395.

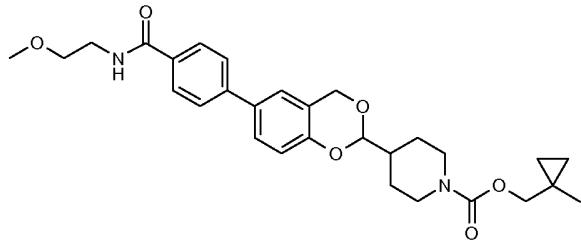
EXAMPLE A69

(1-Methylcyclopropyl)methyl 4-[6-{[(3-hydroxypropyl)amino]carbonyl}phenyl]-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate

5 The title compound was prepared from 4-[2-(1-[(1-methylcyclopropyl)methoxy]-carbonyl)piperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A10) and 3-amino-1-propanol using the conditions described in general method D. Yield 1.2 mg (5%). Analytical HPLC: purity 100% (System A); HRESIMS (ESI⁺) calcd for C₂₉H₃₆N₂O₆ 508.2573, found 508.2561.

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EXAMPLE A70

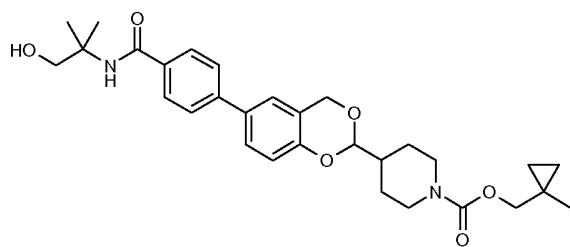
(1-Methylcyclopropyl)methyl 4-[6-{[(2-methoxyethyl)amino]carbonyl}phenyl]-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate

15 The title compound was prepared from 4-[2-(1-[(1-methylcyclopropyl)methoxy]-carbonyl)piperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A10) and 2-methoxyethylamine using the conditions described in general method D. Yield 1.2 mg (5%). Analytical HPLC: purity 100% (System A); HRESIMS (ESI⁺) calcd for C₂₉H₃₆N₂O₆ 508.2573, found 508.2575.

20

EXAMPLE A71

(1-Methylcyclopropyl)methyl 4-[6-{[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl}phenyl]-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate

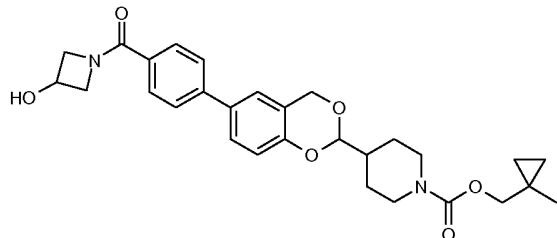


The title compound was prepared from 4-[2-(1-[(1-methylcyclopropyl)methoxy]carbonyl)piperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A10) and 2-amino-2-methyl-1-propanol using the conditions described in general method D. Yield 2.0 mg (8%). Analytical HPLC: purity 100% (System A); HRESIMS (ESI⁺) calcd for C₃₀H₃₈N₂O₆ 522.273, found 522.2736.

EXAMPLE A72

(1-Methylcyclopropyl)methyl 4-(6-{4-[3-hydroxyazetidin-1-yl]carbonyl}phenyl)-4H-

10 1,3-benzodioxin-2-yl)piperidine-1-carboxylate

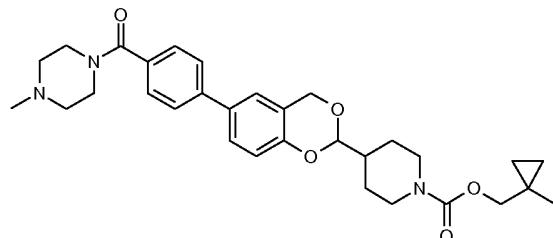


The title compound was prepared from 4-[2-(1-[(1-methylcyclopropyl)methoxy]carbonyl)piperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A10) and 3-hydroxazetidine hydrochloride using the conditions described in general method D. Yield 0.8 mg (3%). Analytical HPLC: purity 100% (System A); HRESIMS (ESI⁺) calcd for C₂₉H₃₄N₂O₆ 506.2417, found 506.2398.

EXAMPLE A73

(1-Methylcyclopropyl)methyl 4-(6-{4-[4-methylpiperazin-1-yl]carbonyl}phenyl)-4H-

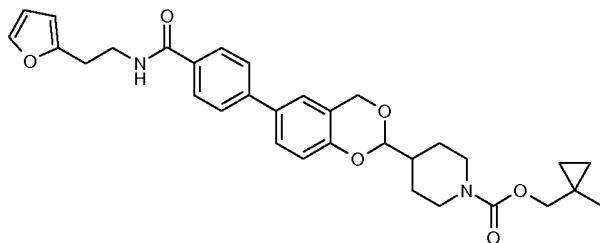
20 1,3-benzodioxin-2-yl)piperidine-1-carboxylate



The title compound was prepared from 4-[2-(1-{[(1-methylcyclopropyl)methoxy]-carbonyl}piperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A10) and 1-methylpiperazine using the conditions described in general method D. Yield 1.5 mg (6%). Analytical HPLC: purity 99% (System A); HRESIMS (ESI⁺) calcd for C₃₁H₃₉N₃O₅ 533.2890, found 533.2896.

EXAMPLE A74

(1-Methylcyclopropyl)methyl 4-{6-[4-({[2-(2-furyl)ethyl]amino}carbonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate

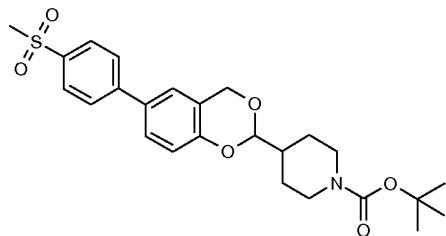


10

The title compound was prepared from 4-[2-(1-{[(1-methylcyclopropyl)methoxy]-carbonyl}piperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A10) and 2-furan-2-yl-ethylamine using the conditions described in general method D. Yield 1.2 mg (4%). Analytical HPLC: purity 98% (System A); HRESIMS (ESI⁺) calcd for C₃₂H₃₆N₂O₆ 544.2573, found 544.2568.

EXAMPLE A75

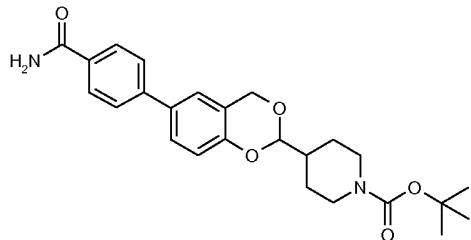
tert-Butyl 4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate



20

The title compound was prepared from *tert*-butyl 4-(6-bromo-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate (Intermediate A11; 20 mg, 0.05 mmol), and [4-(methylsulfonyl)phenyl]boronic acid (11 mg, 0.055 mmol) using the conditions described in general method A2. Yield 7 mg (42%). Analytical HPLC: purity 90% (System A and B); HRESIMS (ESI⁺) calcd for C₂₅H₃₁NO₆S 473.1872, found 473.1872.

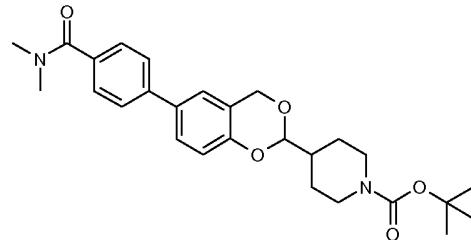
EXAMPLE A76

***tert*-Butyl 4-{6-[4-(aminocarbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate**

- 5 The title compound was prepared from *tert*-butyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate (Intermediate A11; 20 mg, 0.05 mmol), and [4-(aminocarbonyl)-phenyl]boronic acid (9 mg, 0.055 mmol) using the conditions described in general method A2. Yield 6.6 mg (30%). Analytical HPLC: purity 94% (System A and B); HRESIMS (ESI⁺) calcd for C₂₅H₃₀N₂O₅ 438.2155, found 438.2152.

10

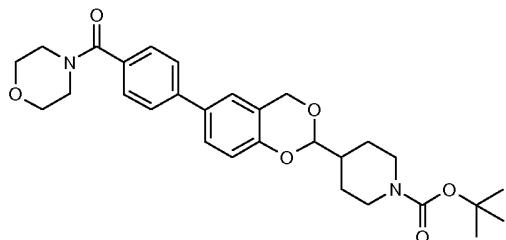
EXAMPLE A77

***tert*-Butyl 4-{6-[4-[(dimethylamino)carbonyl]phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidine-1-carboxylate**

- 15 The title compound was prepared from *tert*-butyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate (Intermediate A11; 20 mg, 0.05 mmol) and {4-[(dimethylamino)-carbonyl]phenyl}boronic acid (11 mg, 0.055 mmol) using the conditions described in general method A2. Yield 10.5 mg (46%). Analytical HPLC: purity 90% (System A and B); HRESIMS (ESI⁺) calcd for C₂₇H₃₄N₂O₅ 466.2468, found 466.2469.

20

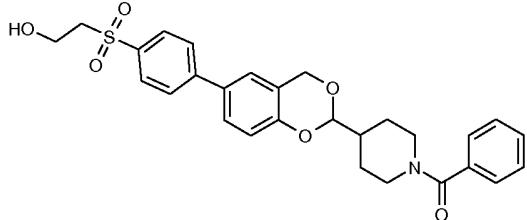
EXAMPLE A78

***tert*-Butyl 4-{6-[4-(morpholin-4-ylcarbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidine-1-carboxylate**

5 The title compound was prepared from *tert*-butyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate (Intermediate A11; 20 mg, 0.05 mmol) and [4-(morpholin-4-ylcarbonyl)phenyl]boronic acid (13 mg, 0.055 mmol) using the conditions described in general method A2. Yield 8.5 mg (34%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₂₉H₃₆N₂O₆ 508.2573, found 508.2573.

10

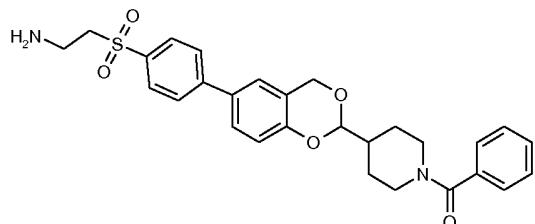
EXAMPLE A79

2-({4-[2-(1-Benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]phenyl}sulfonyl)ethanol

A mixture of 2-[(4-bromophenyl)sulfonyl]ethanol (prepared using similar conditions as 15 described in Verhart, C. G. J *et al.*, Rec. Trav. Chim. Pays-Bas. **1988**, 107(11), 621-626) (66 mg, 0.25 mmol), 5,5,5',5'-tetramethyl-2,2'-bi-1,3,2-dioxaborinane (84 mg, 0.37 mmol), K₂CO₃ (73 mg, 0.75 mmol), PdCl₂dppf·DCM (10 mg, 0.01 mmol) and DME (2 mL) was heated at 120 °C for 20 min in a microwave reactor. To the same tube were then added NaHCO₃ (42 mg, 0.5 mmol), Pd(PPh₃)₄ (9 mg, 0.01 mmol), 1-benzoyl-4-(6-bromo-4*H*-1,3-20 benzodioxin-2-yl)piperidine (Intermediate A12; 100 mg, 0.25 mmol) and water (0.5 mL). The reaction mixture was heated at 120 °C for 800 sec in a microwave reactor and then filtered through Celite. The filtrate was concentrated and the crude material was purified by preparative HPLC (System E). Yield 30 mg (24%). Analytical HPLC: purity 95% (System A and B); HRESIMS (ESI⁺) calcd for C₂₈H₂₉NO₆S 507.1716, found 507.1733.

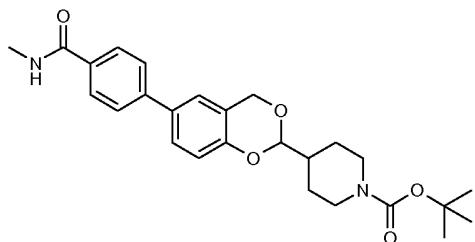
25

EXAMPLE A80

2-(*{*4-[2-(1-Benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]phenyl*}sulfonyl}-ethanamine*

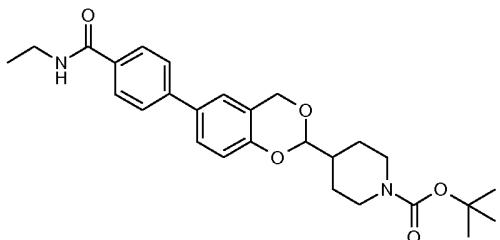
5 A mixture of 1-benzoyl-4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)piperidine (Intermediate
A12; 100 mg, 0.25 mmol), 5,5,5',5'-tetramethyl-2,2'-bi-1,3,2-dioxaborinane (84 mg, 0.37
mmol), potassium acetate (73 mg, 0.75 mmol), PdCl₂dppf·DCM (10 mg, 0.01 mmol) and
DME (2 mL) was heated at 120 °C for 20 min in a microwave reactor. To the same tube
were added NaHCO₃ (42 mg, 0.5 mmol), Pd(PPh₃)₄ (9.0 mg, 0.01 mmol), 2-[*(*4-
10 bromophenyl)sulfonyl]ethanamine hydrochloride (Intermediate A13; 75 mg, 0.25 mmol)
and water (0.5 mL). The reaction mixture was heated at 120 °C for 800 sec in a microwave
reactor and then filtered through Celite. The filtrate was concentrated and the residue was
purified by preparative HPLC (System E). Yield 30 mg (24%). Analytical HPLC: purity
93% (System A and B); HRESIMS (ESI⁺) calcd for C₂₈H₃₀N₂O₅S 506.1875, found
15 506.1882.

EXAMPLE A81

***tert*-Butyl 4-*{*4-[*(*methylamino)carbonyl]phenyl*}-*4*H*-1,3-benzodioxin-2-yl*-*piperidine-1-carboxylate**

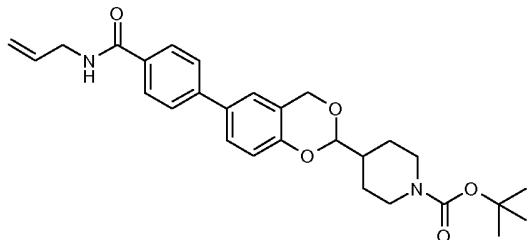
20 The title compound was prepared from 4-*{*2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-
1,3-benzodioxin-6-yl*}benzoic acid (Intermediate A14) and methylamine using the
conditions described in general method D. Yield 2.1 mg (9%). Analytical HPLC: purity
100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₆H₃₂N₂O₅ 452.2311, found
25 452.2305.*

EXAMPLE A82

***tert*-Butyl 4-(6-{4-[(ethylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate**

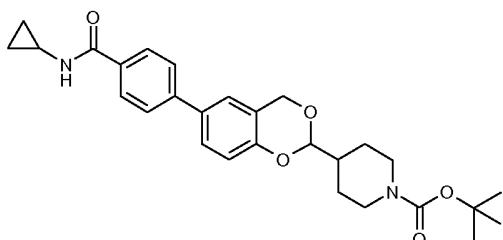
5 The title compound was prepared from 4-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A14) and ethylamine using the conditions described in general method D. Yield 2.5 mg (11%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₇H₃₄N₂O₅ 466.2468, found 466.2471.

10 EXAMPLE A83

***tert*-Butyl 4-(6-{4-[(allylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate**

15 The title compound was prepared from 4-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A14) and allylamine using the conditions described in general method D. Yield 0.7 mg (3%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₈H₃₄N₂O₅ 478.2468, found 478.2466.

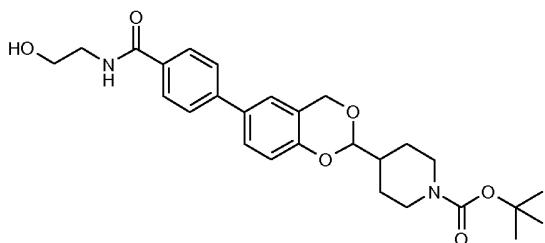
EXAMPLE A84

20 ***tert*-Butyl 4-(6-{4-[(cyclopropylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate**

The title compound was prepared from 4-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A14) and cyclopropylamine using the conditions described in general method D. Yield 3.6 mg (15%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₈H₃₄N₂O₅ 478.2468, found 478.2469.

EXAMPLE A85

***tert*-Butyl 4-[6-{[(2-hydroxyethyl)amino]carbonyl}phenyl]-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate**

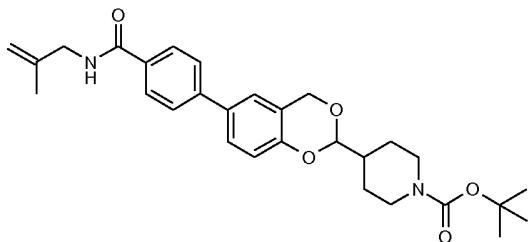


10

The title compound was prepared from 4-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A14) and ethanolamine using the conditions described in general method D. Yield 2.8 mg (12%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₇H₃₄N₂O₆ 482.2417, found 482.2418.

EXAMPLE A86

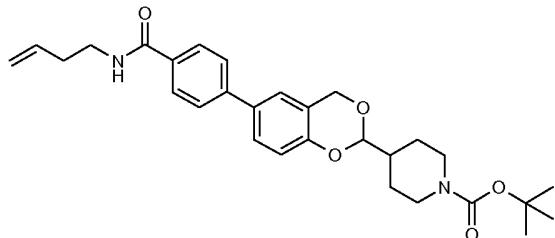
***tert*-Butyl 4-[6-{[(2-methylprop-2-en-1-yl)amino]carbonyl}phenyl]-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate**



20

The title compound was prepared from 4-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A14) and (2-methylprop-2-en-1-yl)amine using the conditions described in general method D. Yield 0.3 mg (1%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₉H₃₆N₂O₅ 492.2624, found 492.2617.

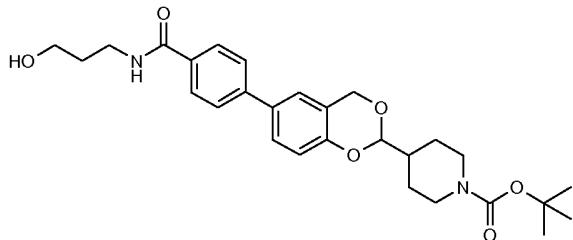
EXAMPLE A87

***tert*-Butyl 4-(6-{4-[(but-3-en-1-ylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate**

5 The title compound was prepared from 4-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A14) and but-3-en-1-amine using the conditions described in general method D. Yield 1.2 mg (5%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₉H₃₆N₂O₅ 492.2624, found 492.2622.

10

EXAMPLE A88

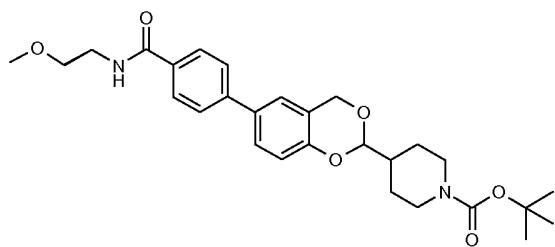
***tert*-Butyl 4-[6-(4-[(3-hydroxypropyl)amino]carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate**

15 The title compound was prepared from 4-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A14) and 3-amino-1-propanol using the conditions described in general method D. Yield 3.8 mg (15%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₈H₃₆N₂O₆ 496.2573, found 496.2580.

20

EXAMPLE A89

***tert*-Butyl 4-[6-(4-[(2-methoxyethyl)amino]carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate**

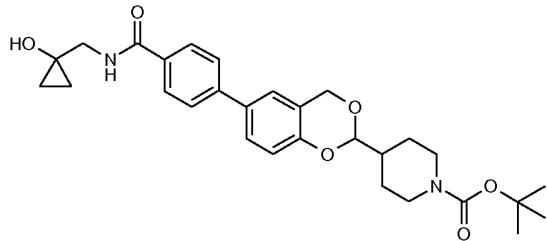


The title compound was prepared from 4-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A14) and 2-methoxyethylamine using the conditions described in general method D. Yield 3.8 mg (15%). Analytical HPLC: purity 5 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₈H₃₆N₂O₆ 496.2573, found 496.2580.

EXAMPLE A90

tert-Butyl 4-{6-[4-({[(1-hydroxycyclopropyl)methyl]amino}carbonyl)phenyl]-4*H*-1,3-

10 benzodioxin-2-yl}piperidine-1-carboxylate

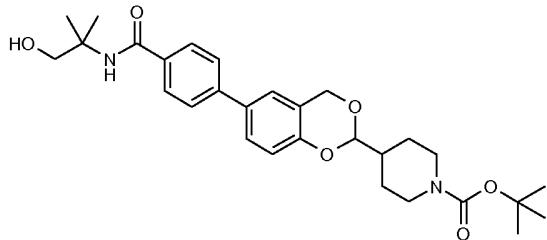


The title compound was prepared from 4-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A14) and 1-(aminomethyl)cyclopropanol using the conditions described in general method D. Yield 3.9 mg (16%). Analytical 15 HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₉H₃₆N₂O₆ 508.2573, found 508.2581.

EXAMPLE A91

tert-Butyl 4-[6-(4-[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl)phenyl]-4*H*-1,3-

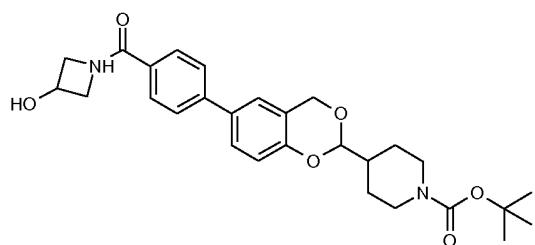
20 benzodioxin-2-yl]piperidine-1-carboxylate



The title compound was prepared from 4-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A14) and 2-amino-2-methyl-1-propanol using the conditions described in general method D. Yield 3.6 mg (14%). Analytical HPLC: purity 97% (System A and B); HRESIMS (ESI⁺) calcd for C₂₉H₃₈N₂O₆ 510.2730, found 510.2748.

EXAMPLE A92

***tert*-Butyl 4-(6-{4-[(3-hydroxyazetidin-1-yl)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate**

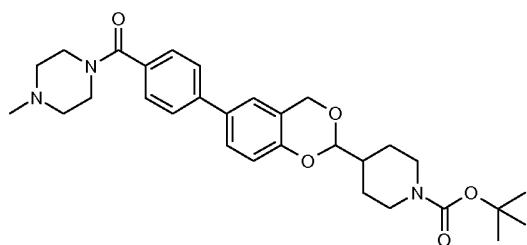


10

The title compound was prepared from 4-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A14) and 3-hydroxazetidine hydrochloride using the conditions general method D. Yield 3.8 mg (15%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₈H₃₄N₂O₆ 494.2417, found 494.2345.

EXAMPLE A93

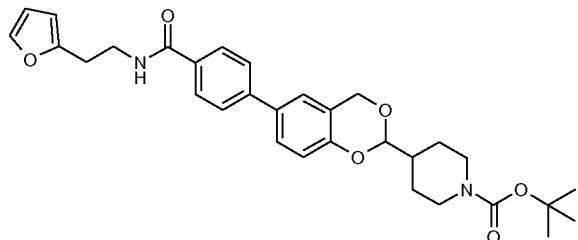
***tert*-Butyl 4-(6-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate**



20

The title compound was prepared from 4-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A14) and 1-methylpiperazine using the conditions described in general method D. Yield 4.0 mg (15%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₃₀H₃₉N₃O₅ 521.289, found 521.2906.

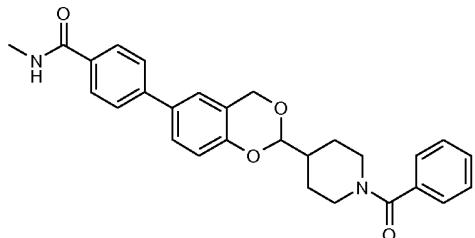
EXAMPLE A94

***tert*-Butyl 4-{6-[4-({[2-(2-furyl)ethyl]amino}carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate**

5 The title compound was prepared from 4-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A14) and 2-furan-2-yl-ethylamine using the conditions described in general method D. Yield 3.9 mg (14%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₃₁H₃₆N₂O₆ 532.2573, found 532.2567.

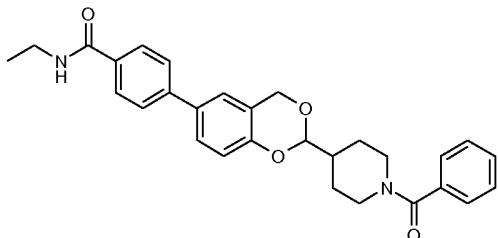
10

EXAMPLE A95

4-[2-(1-Benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-N-methylbenzamide

15 The title compound was prepared from 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A16) and methylamine using the conditions described in general method D. Yield 2.9 mg (13%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₈H₂₈N₂O₄ 456.2049, found 456.2058.

EXAMPLE A96

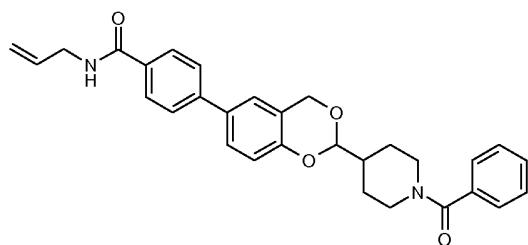
4-[2-(1-Benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-N-ethylbenzamide

The title compound was prepared from 4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A16) and ethylamine using the conditions described in general method D. Yield 7.6 mg (32%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₉H₃₀N₂O₄ 470.2206, found 470.2202.

5

EXAMPLE A97

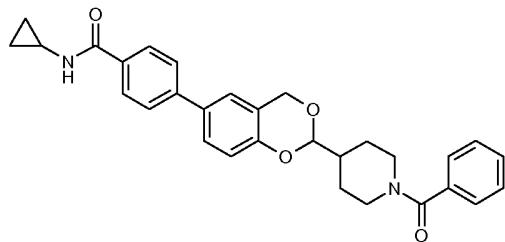
N-Allyl-4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzamide



The title compound was prepared from 4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A16) and allylamine using the conditions described in general method D. Yield 5.5 mg (23%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₃₀H₃₀N₂O₄ 482.2206, found 482.2200.

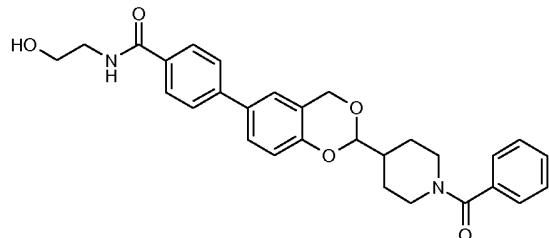
EXAMPLE A98

4-[2-(1-Benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]-*N*-cyclopropylbenzamide



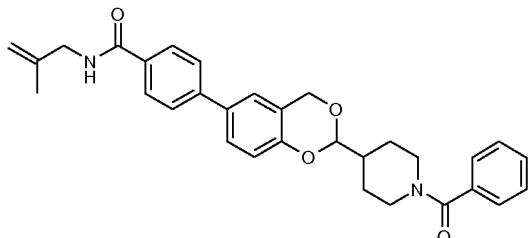
The title compound was prepared from 4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A16) and cyclopropylamine using the conditions described in general method D. Yield 8.7 mg (36%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₃₀H₃₀N₂O₄ 482.2206, found 482.2200.

EXAMPLE A99

4-[2-(1-Benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]-N-(2-hydroxyethyl)-benzamide

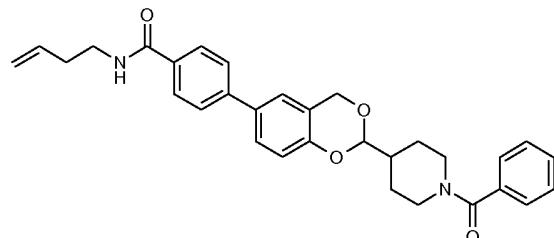
5 The title compound was prepared from 4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A16) and ethanolamine using the conditions described in general method D. Yield 8.7 mg (36%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₉H₃₀N₂O₅ 486.2155, found 486.2164.

10 EXAMPLE A100

4-[2-(1-Benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]-N-(2-methylprop-2-en-1-yl)-benzamide

15 The title compound was prepared from 4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A16) and 2-methylprop-2-en-1-amine using the conditions described in general method D. Yield 6.0 mg (24%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₃₁H₃₂N₂O₄ 496.2362, found 496.2356.

20 EXAMPLE A101

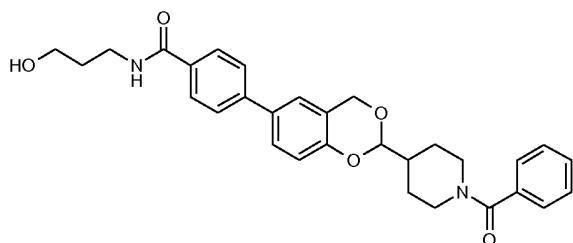
4-[2-(1-Benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]-N-but-3-en-1-ylbenzamide

The title compound was prepared from 4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A16) and but-3-en-1-amine using the conditions described in general method D. Yield 9.2 mg (37%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₃₁H₃₂N₂O₄ 496.2362, found 496.2352.

5

EXAMPLE A102

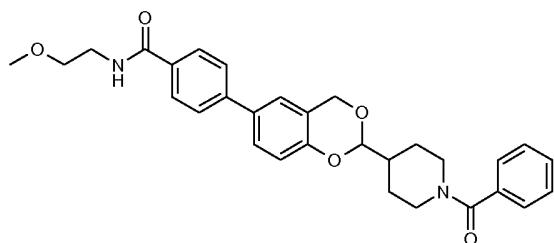
4-[2-(1-Benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]-N-(3-hydroxypropyl)-benzamide



- 10 The title compound was prepared from 4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A16) and 3-amino-1-propanol using the conditions described in general method D. Yield 9.2 mg (37%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₃₀H₃₂N₂O₅ 500.2311, found 500.2310.

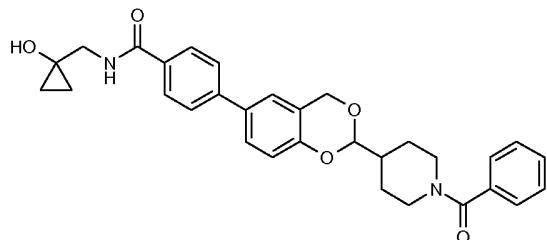
15 EXAMPLE A103

4-[2-(1-Benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]-N-(2-methoxyethyl)-benzamide



- 20 The title compound was prepared from 4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A16) and 2-methoxyethylamine using the conditions described in general method D. Yield 6.0 mg (24%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₃₀H₃₂N₂O₅ 500.2311, found 500.2317.

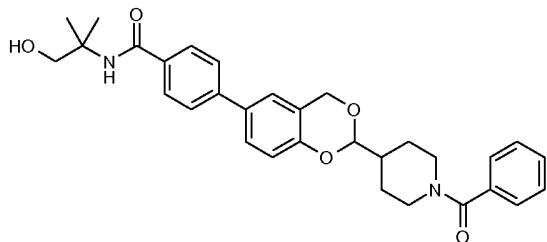
EXAMPLE A104

4-[2-(1-Benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]-N-[(1-hydroxycyclopropyl)methyl]benzamide

5 The title compound was prepared from 4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A16) and 1-(aminomethyl)cyclopropanol using the conditions described in general method D. Yield 7.9 mg (30%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₃₁H₃₂N₂O₅ 512.2311, found 512.2311.

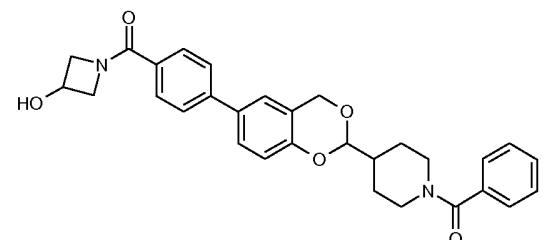
10

EXAMPLE A105

4-[2-(1-Benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]-N-(2-hydroxy-1,1-dimethylethyl)benzamide

15 The title compound was prepared from 4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A16) and 2-amino-2-methyl-1-propanol according to general method D. Yield 5.6 mg (22%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₃₁H₃₄N₂O₅ 514.2468, found 514.2464.

20 EXAMPLE A106

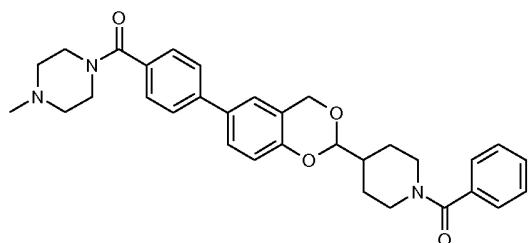
1-{4-[2-(1-Benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoyl}azetidin-3-ol

The title compound was prepared from 4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A16) and 3-hydroxazetidine hydrochloride using the conditions described in general method D. Yield 11.7 mg (47%). Analytical HPLC: purity 100% (System A and B); LRESIMS m/z = 499 ($M+H$)⁺.

5

EXAMPLE A107

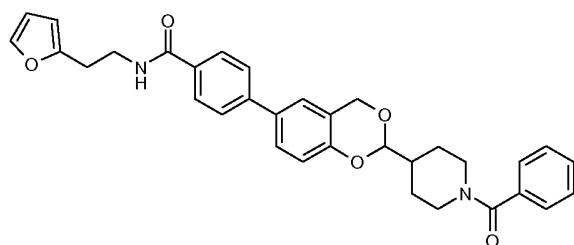
1-{4-[2-(1-Benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoyl}-4-methyl-piperazine



- 10 The title compound was prepared from 4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A16) and 1-methylpiperazine using the conditions described in general method D. Yield 10 mg (38%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₃₂H₃₅N₃O₄ 525.2628, found 525.2627.

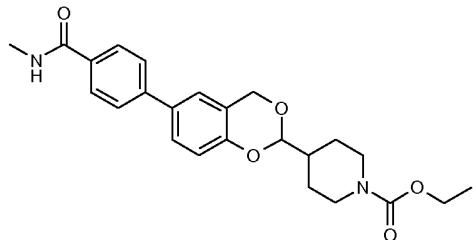
15 EXAMPLE A108

4-[2-(1-Benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]-N-[2-(2-furyl)ethyl]-benzamide



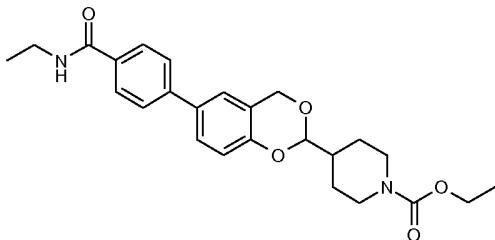
- 20 The title compound was prepared from 4-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzoic acid (Intermediate A16) and 2-furan-2-yl-ethylamine using the conditions described in general method D. Yield 3.7 mg (14%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₃₃H₃₂N₂O₅ 536.2311, found 536.2291.

EXAMPLE A109

Ethyl 4-(6-{4-[(methylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate

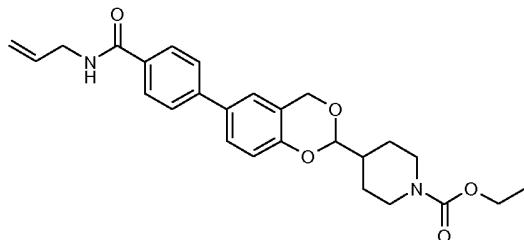
5 The title compound was prepared from 4-{2-[1-(ethoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A18) and methylamine using the conditions described in general method D. Yield 3.0 mg (14%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₄H₂₈N₂O₅ 424.1998, found 424.1980.

10 EXAMPLE A110

Ethyl 4-(6-{4-[(ethylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate

15 The title compound was prepared from 4-{2-[1-(ethoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A18) and ethylamine using the conditions described in general method D. Yield 3.8 mg (17%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₅H₃₀N₂O₅ 438.2155, found 438.2142.

EXAMPLE A111

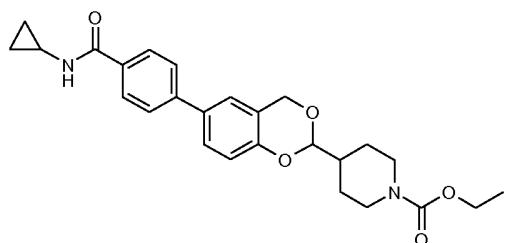
20 **Ethyl 4-(6-{4-[(allylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate**

The title compound was prepared from 4-{2-[1-(ethoxycarbonyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A18) and allylamine using the conditions described in general method D. Yield 4.8 mg (22%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₆H₃₀N₂O₅ 450.2155, found 450.2142.

5

EXAMPLE A112

Ethyl 4-(6-{4-[(cyclopropylamino)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate

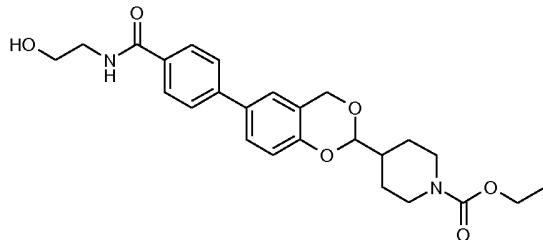


- 10 The title compound was prepared from 4-{2-[1-(ethoxycarbonyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A18) and cyclopropylamine using the conditions described in general method D. Yield 3.5 mg (16%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₆H₃₀N₂O₅ 450.2155, found 450.2142.

15

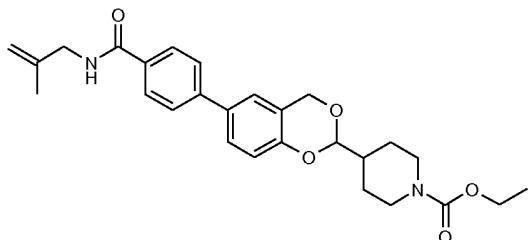
EXAMPLE A113

Ethyl 4-[6-(4-[(2-hydroxyethyl)amino]carbonyl)phenyl]-4H-1,3-benzodioxin-2-yl]-piperidine-1-carboxylate



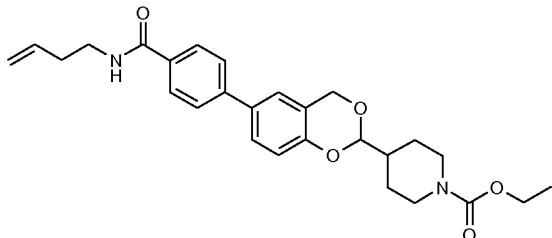
- 20 The title compound was prepared from 4-{2-[1-(ethoxycarbonyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A18) and ethanolamine using the conditions described in general method D. Yield 8.6 mg (39%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₅H₃₀N₂O₆ 454.2104, found 454.2107.

EXAMPLE A114

Ethyl 4-[6-{4-[(2-methylprop-2-en-1-yl)amino]carbonyl}phenyl]-4H-1,3-benzodioxin-2-yl]piperidine-1-carboxylate

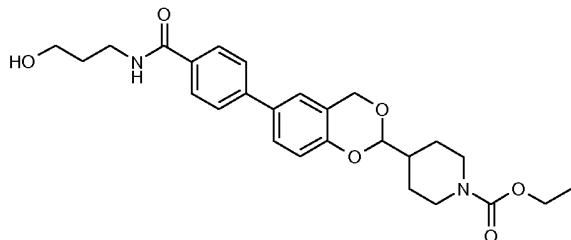
5 The title compound was prepared from 4-{2-[1-(ethoxycarbonyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A18) and 2-methylprop-2-en-1-amine according to general method D. Yield 8.1 mg (35%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₇H₃₂N₂O₅ 464.2311, found 464.2314.

10 EXAMPLE A115

Ethyl 4-(6-{4-[(but-3-en-1-yl)amino]carbonyl}phenyl)-4H-1,3-benzodioxin-2-yl]piperidine-1-carboxylate

15 The title compound was prepared from 4-{2-[1-(ethoxycarbonyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A18) and but-3-en-1-amine according to general method D. Yield 6.4 mg (28%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₇H₃₂N₂O₅ 464.2311, found 464.2308.

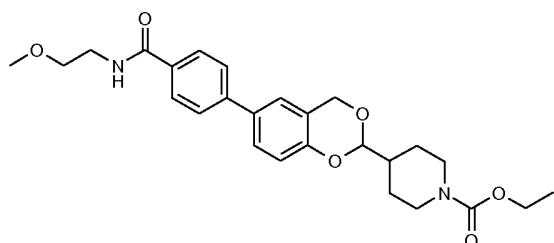
EXAMPLE A116

20 **Ethyl 4-[6-{4-[(3-hydroxypropyl)amino]carbonyl}phenyl]-4H-1,3-benzodioxin-2-yl]piperidine-1-carboxylate**

The title compound was prepared from 4-{2-[1-(ethoxycarbonyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A18) and 3-amino-1-propanol using the conditions described in general method D. Yield 6.8 mg (30%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₆H₃₂N₂O₆ 468.2260, found 468.2248.

EXAMPLE A117

Ethyl 4-[6-(4-[(2-methoxyethyl)amino]carbonyl)phenyl]-4H-1,3-benzodioxin-2-yl]-piperidine-1-carboxylate

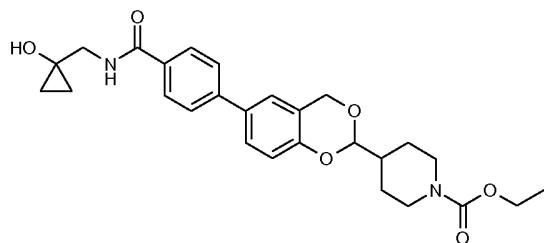


10

The title compound was prepared from 4-{2-[1-(ethoxycarbonyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A18) and 2-methoxyethylamine using the conditions described in general method D. Yield 8.3 mg (36%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₆H₃₂N₂O₆ 468.2260, found 468.2255.

EXAMPLE A118

Ethyl 4-[6-[4-({[(1-hydroxycyclopropyl)methyl]amino}carbonyl)phenyl]-4H-1,3-benzodioxin-2-yl]-piperidine-1-carboxylate

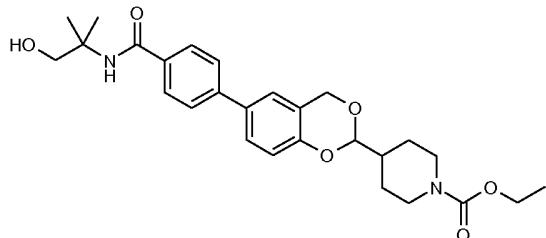


20

The title compound was prepared from 4-{2-[1-(ethoxycarbonyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A18) and 1-(aminomethyl)cyclopropanol using the conditions described in general method D. Yield 8.4 mg (35%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₇H₃₂N₂O₆ 480.2260, found 480.2242.

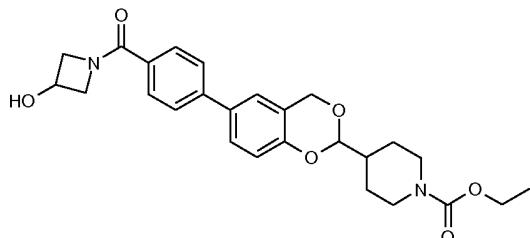
25

EXAMPLE A119

Ethyl 4-[6-{4-[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl}phenyl]-4H-1,3-benzodioxin-2-yl]piperidine-1-carboxylate

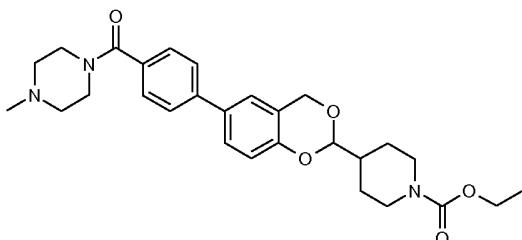
5 The title compound was prepared from 4-{2-[1-(ethoxycarbonyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A18) and 2-amino-2-methyl-1-propanol according to general method D. Yield 4.4 mg (18%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₇H₃₄N₂O₆ 482.2417, found 482.2408.

10 EXAMPLE A120

Ethyl 4-(6-{4-[(3-hydroxyazetidin-1-yl)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate

15 The title compound was prepared from 4-{2-[1-(ethoxycarbonyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A18) and 3-hydroxazetidine hydrochloride according to general method D. Yield 8.2 mg (36%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₆H₃₀N₂O₆ 466.2104, found 466.2101.

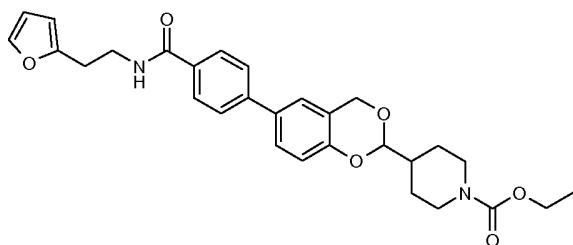
EXAMPLE A121

20 **Ethyl 4-(6-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate**

The title compound was prepared from 4-{2-[1-(ethoxycarbonyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A18) and 1-methylpiperazine using the conditions described in general method D. Yield 8.6 mg (34%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₈H₃₅N₃O₅ 493.2577, found 493.2576.

EXAMPLE A122

Ethyl 4-{6-[4-({[2-(2-furyl)ethyl]amino}carbonyl)phenyl]-4H-1,3-benzodioxin-2-yl}-piperidine-1-carboxylate

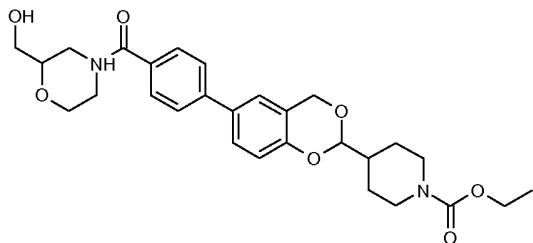


10

The title compound was prepared from 4-{2-[1-(ethoxycarbonyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A18) and 2-furan-2-yl-ethylamine using the conditions described in general method D. Yield 8.6 mg (34%). Analytical HPLC: purity 100% (System A and B); HRESIMS (ESI⁺) calcd for C₂₉H₃₂N₂O₆ 504.2260, found 504.2256.

EXAMPLE A123

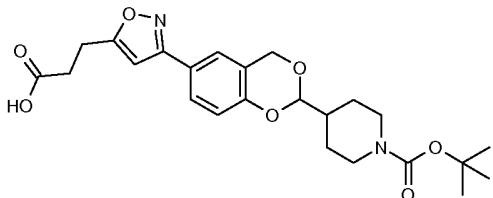
Ethyl 4-[6-(4-{{[2-(hydroxymethyl)morpholin-4-yl]carbonyl}phenyl}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate



20

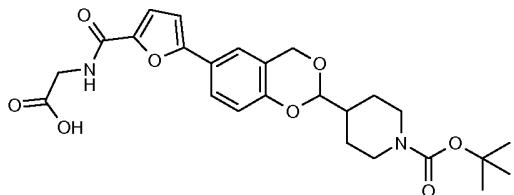
The title compound was prepared from 4-{2-[1-(ethoxycarbonyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}benzoic acid (Intermediate A18) and 2-morpholinemethanol using the conditions described in general method D. Yield 9.9 mg (38%). Analytical HPLC: purity 95% (System A and B); HRESIMS (ESI⁺) calcd for C₂₈H₃₄N₂O₇ 510.2366, found 510.2367.

EXAMPLE A124

3-(3-{2-[1-(*tert*-Butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}isoxazol-5-yl)propanoic acid

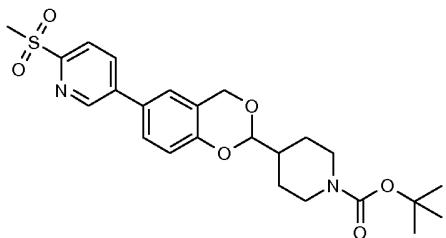
5 The title compound was prepared from *tert*-butyl 4-[6-(dimethoxyboryl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate (Intermediate A19) and 3-(3-bromoisoaxazol-5-yl)-propanoic acid according to general method B. Yield 3 mg (9%). Analytical HPLC: purity 92% (System A and B); LRESIMS (ESI⁺) m/z = 358 (M+H-Boc)⁺.

10 EXAMPLE A125

[(5-{2-[1-(*tert*-Butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-2-furoyl)-amino]acetic acid

15 The title compound was prepared from *tert*-butyl 4-[6-(dimethoxyboryl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate (Intermediate A19) and *N*-(5-bromo-2-furoyl)glycine using the conditions described in general method B. Yield 4.4 mg (12%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₂₅H₃₀N₂O₈ 486.2002, found 486.1992.

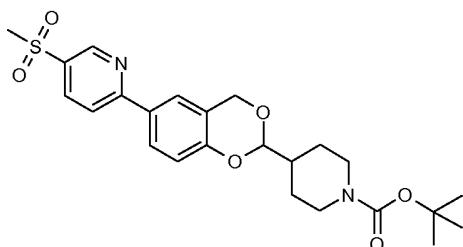
20 EXAMPLE A126

***tert*-Butyl 4-{6-[6-(methylsulfonyl)pyridin-3-yl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate**

The title compound was prepared from *tert*-butyl 4-[6-(dimethoxyboryl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate (Intermediate A19) and 5-bromo-2-(methylsulfonyl)-pyridine using the conditions described in general method B. Yield 3.2 mg (9%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₂₄H₃₀N₂O₆S 474.1825, found 474.1826.

EXAMPLE A127

***tert*-Butyl 4-{6-[5-(methylsulfonyl)pyridin-2-yl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate**



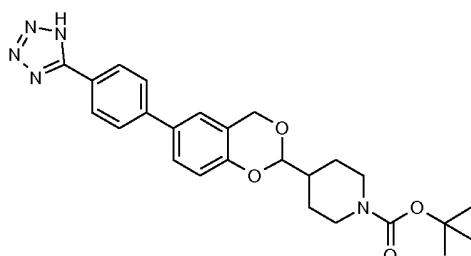
10

The title compound was prepared from *tert*-butyl 4-[6-(dimethoxyboryl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate (Intermediate A19) and 2-bromo-5-(methylsulfonyl)-pyridine according to general method B. Yield 4.9 mg (13%). Analytical HPLC: purity 99% (System A and B); LRESIMS (ESI⁺) m/z = 419 (M+H-*t*Bu)⁺.

15

EXAMPLE A128

***tert*-Butyl 4-{6-[4-(1*H*-tetrazol-5-yl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate**

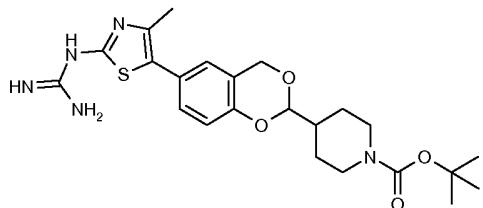


20

The title compound was prepared from *tert*-butyl 4-[6-(dimethoxyboryl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate (Intermediate A19) and 5-(4-bromophenyl)-1*H*-tetrazole using the conditions described in general method B. Yield 2.8 mg (8%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₂₅H₂₉N₅O₄ 463.2220, found 463.2240.

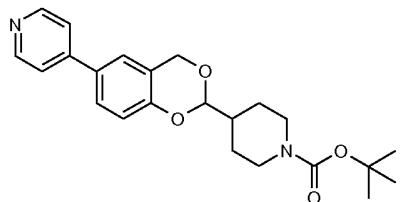
25

EXAMPLE A129

***tert*-Butyl 4-[6-(2-{{[amino(imino)methyl]amino}-4-methyl-1,3-thiazol-5-yl)-4H-1,3-benzodioxin-2-yl]piperidine-1-carboxylate**

5 The title compound was prepared from *tert*-butyl 4-[6-(dimethoxyboryl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate (Intermediate A19) and *N*-(5-bromo-4-methyl-1,3-thiazol-2-yl)guanidine according to general method B. Yield 1.5 mg (4%). Analytical HPLC: purity 93% (System A and B); LRESIMS (ESI⁺) m/z = 474 (M+H)⁺.

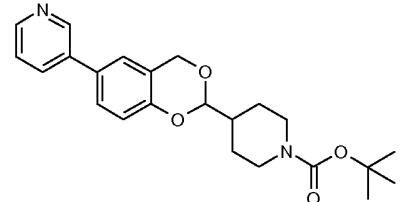
10 EXAMPLE A130

***tert*-Butyl 4-(6-pyridin-4-yl-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate**

A suspension of *tert*-butyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate (Intermediate A11; 100 mg, 0.251 mmol), pyridin-4-ylboronic acid (37 mg, 0.301 mmol), 15 K₂CO₃ (87 mg, 0.63 mmol), PdCl₂dppf·DCM (21 mg, 0.025 mmol) in MeCN/H₂O (3 mL; 2:1) was heated at 160 °C for 20 min in a microwave reactor. The mixture was filtered through a pad of silica, concentrated and the residue was purified by preparative HPLC (System E). Yield 45 mg (45%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₂₃H₂₈N₂O₄ 396.2049, found 396.2068.

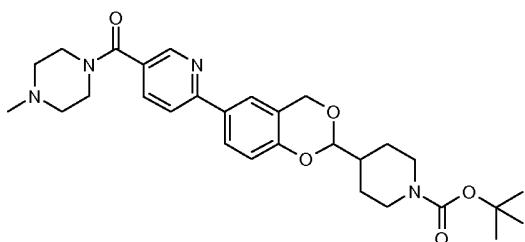
20

EXAMPLE A131

***tert*-Butyl 4-(6-pyridin-3-yl-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate**

The title compound was prepared from *tert*-butyl 4-(6-bromo-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate (Intermediate A11; 70 mg, 0.18 mmol) and pyridin-3-ylboronic acid (26 mg, 0.21 mmol) using the conditions described for Example A130. Yield 29 mg (42%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₂₃H₂₈N₂O₄ 396.2049, found 396.2061.

EXAMPLE A132

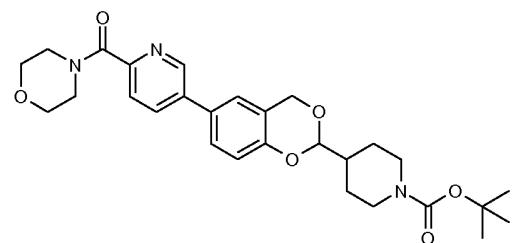
***tert*-Butyl 4-(6-{5-[(4-methylpiperazin-1-yl)carbonyl]pyridin-2-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate**

10

To a suspension of 6-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}nicotinic acid (Intermediate A21; 50 mg, 0.11 mmol), HOBT (31 mg, 0.23 mmol), EDC (44 mg, 0.23 mmol) and triethylamine (46 mg, 0.45 mmol) in DMF (3 mL) was added 1-methylpiperazine (17 mg, 0.17 mmol). The mixture was stirred at r.t. for 12 h and then at 15 100 °C for 24 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (System E). Yield 10.3 mg (17%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₂₉H₃₈N₄O₅ 522.2842, found 522.2853.

20

EXAMPLE A133

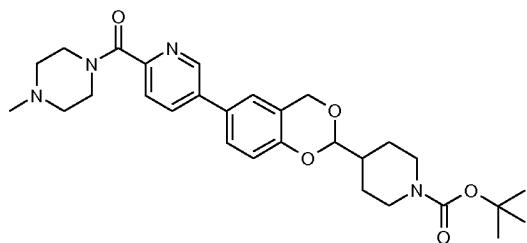
***tert*-Butyl 4-{6-[6-(morpholin-4-ylcarbonyl)pyridin-3-yl]-4*H*-1,3-benzodioxin-2-yl}-piperidine-1-carboxylate**

The title compound was prepared from 5-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}pyridine-2-carboxylic acid (Intermediate A20; 50 mg, 0.11 mmol) and morpholine (15 mg, 0.17 mmol) using the conditions described for Example A132.

Yield 1.4 mg (2%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₂₈H₃₅N₃O₆ 509.2526, found 509.2540.

EXAMPLE A134

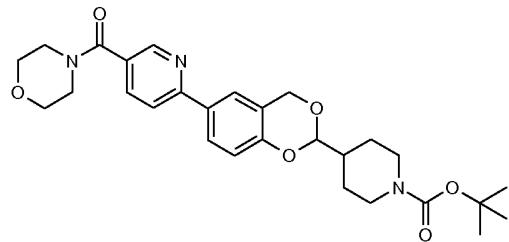
- 5 ***tert*-Butyl 4-{6-[{(4-methylpiperazin-1-yl)carbonyl]pyridin-3-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate**



The title compound was prepared from 5-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}pyridine-2-carboxylic acid (Intermediate A20; 50 mg, 0.11 mmol) and 1-methylpiperazine (17 mg, 0.17 mmol) using the conditions described for Example A132. Yield 1.7 mg (3%). Analytical HPLC: purity 96% (System A and B); HRESIMS (ESI⁺) calcd for C₂₉H₃₈N₄O₅ 522.2842, found 522.2854.

EXAMPLE A135

- 15 ***tert*-Butyl 4-{6-[5-(morpholin-4-ylcarbonyl)pyridin-2-yl]-4*H*-1,3-benzodioxin-2-yl}-piperidine-1-carboxylate**



The title compound was prepared from 6-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}nicotinic acid (Intermediate A21; 50 mg, 0.11 mmol) and morpholine (15 mg, 0.17 mmol) using the conditions described for Example A132. Yield 7.7 mg (17%). Analytical HPLC: purity 96% (System B and C); HRESIMS (ESI⁺) calcd for C₂₈H₃₅N₃O₆ 509.2526, found 509.2529.

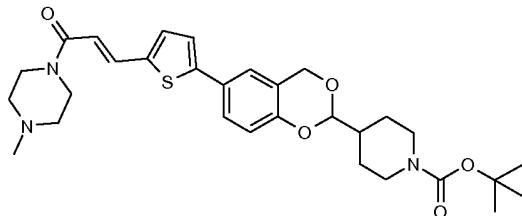
EXAMPLE A136

***tert*-Butyl 4-(6-{5-[(4-methylpiperazin-1-yl)carbonyl]-2-furyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate**

5 A suspension of *tert*-butyl 4-[6-(dimethoxyboryl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate (Intermediate A19; 100 mg, 0.254 mmol), 5-bromo-2-furoic acid (58 mg, 0.31 mmol), K₂CO₃ (88 mg, 0.64 mmol), PdCl₂dppfDCM (22 mg, 0.025 mmol) in MeCN/H₂O (4 mL; 2:1) was heated at 160 °C for 20 min in a microwave reactor. The mixture was filtered through a pad of silica and concentrated to give 5-{2-[1-(*tert*-butoxycarbonyl)-piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-2-furoic acid.

10 Part of this material (50 mg, 0.116 mmol), HOBT (32 mg, 0.23 mmol), EDC (45 mg, 0.23 mmol), triethylamine (47 mg, 0.47 mmol) and 1-methylpiperazine (35 mg, 0.35 mmol) was dissolved in DMF (4 mL) and stirred at r.t. for 24 h. The mixture was concentrated and the residue was purified by preparative HPLC (System E). Yield 17 mg (29%). Analytical
15 HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₂₈H₃₇N₃O₆ 511.2682, found 511.2683.

EXAMPLE A137

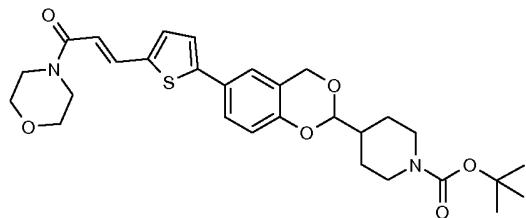
***tert*-Butyl 4-(6-{5-[(1*E*)-3-(4-methylpiperazin-1-yl)-3-oxoprop-1-en-1-yl]-2-thienyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate**

20 A suspension of (2*E*)-3-(5-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-2-thienyl)acrylic acid (Intermediate A22; 50 mg, 0.116 mmol) HOBT (29 mg, 0.21 mmol), EDC (41 mg, 0.21 mmol), triethylamine (43 mg, 0.42 mmol) and 1-methyl-piperazine (32 mg, 0.32 mmol) in DMF (3 mL) was stirred at r.t. for 24 h. The mixture was concentrated and the residue was purified by preparative HPLC (System E). Yield 12 mg

(20%). Analytical HPLC: purity 90% (System A and B); HRESIMS (ESI⁺) calcd for C₃₀H₃₉N₃O₅S 553.2610, found 553.2623.

EXAMPLE A138

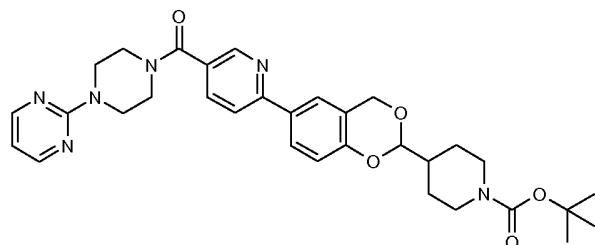
5 ***tert*-Butyl 4-(6-{5-[(1*E*)-3-morpholin-4-yl-3-oxoprop-1-en-1-yl]-2-thienyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate**



The title compound was prepared from (2*E*)-3-(5-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-2-thienyl)acrylic acid (Intermediate A22; 50 mg, 0.12 mmol) and morpholine (27 mg, 0.32 mmol) using the conditions described for Example A137. Yield 14 mg (25%). Analytical HPLC: purity 93% (System A and B); HRESIMS (ESI⁺) calcd for C₂₉H₃₆N₂O₆S 540.2294, found 540.2299.

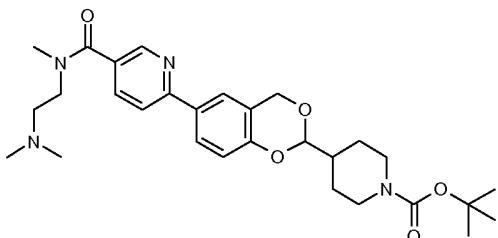
EXAMPLE A139

15 ***tert*-Butyl 4-(6-{5-[(4-pyrimidin-2-ylpiperazin-1-yl)carbonyl]pyridin-2-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate**



The title compound was prepared from 6-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}nicotinic acid (Intermediate A21; 50 mg, 0.11 mmol) and 2-(1-piperazinyl)pyrimidine (28 mg, 0.17 mmol) using the conditions described for Example A137. Yield 9 mg (13%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₃₂H₃₈N₆O₅ 586.2904, found 586.2913.

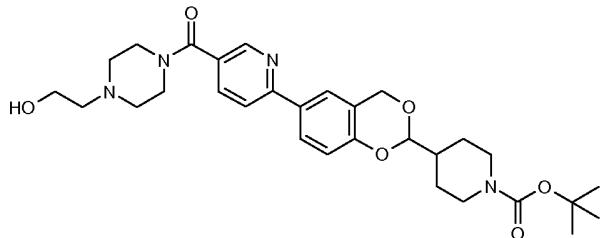
EXAMPLE A140

***tert*-Butyl 4-[6-{[2-(dimethylamino)ethyl](methyl)amino]carbonyl}pyridin-2-yl]-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate**

- 5 The title compound was prepared from 6-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}nicotinic acid (Intermediate A21; 50 mg, 0.12 mmol) and *N,N,N'*-trimethylethane-1,2-diamine (17 mg, 0.17 mmol) using the conditions described for Example A137. Yield 9 mg (15%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₂₉H₄₀N₄O₅ 524.2999, found 524.3005.

10

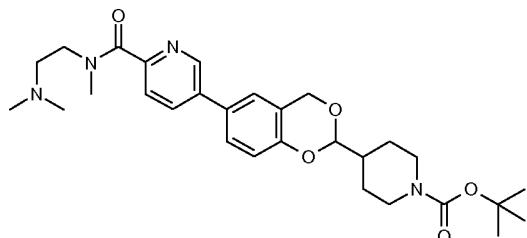
EXAMPLE A141

***tert*-Butyl 4-[6-{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}pyridin-2-yl]-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate**

- 15 The title compound was prepared from 6-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}nicotinic acid (Intermediate A21; 50 mg, 0.11 mmol) and *N*-(2-hydroxyethyl)piperazine (22 mg, 0.17 mmol) using the conditions described for Example A137. Yield 17 mg (17%). Analytical HPLC: purity 99% (System A and B); MS (ESI+) calcd for C₃₀H₄₀N₄O₆ 552.2948, found 552.2958.

20

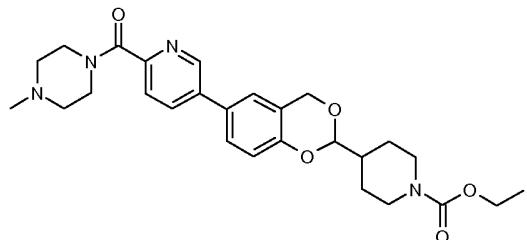
EXAMPLE A142

***tert*-Butyl 4-[6-{[2-(dimethylamino)ethyl](methyl)amino]carbonyl}pyridin-3-yl]-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate**

- 5 The title compound was prepared from 5-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}pyridine-2-carboxylic acid (Intermediate A20; 50 mg, 0.11 mmol;) and *N,N,N'*-trimethylethane-1,2-diamine (17 mg, 0.17 mmol) using the conditions described for Example A137. Yield 1.5 mg (3%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₂₉H₄₀N₄O₅ 524.2999, found 524.3010.

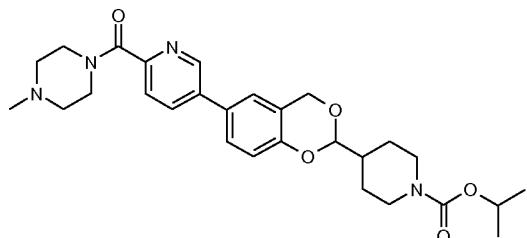
10

EXAMPLE A143

Ethyl 4-(6-{[(4-methylpiperazin-1-yl)carbonyl]pyridin-3-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate

- 15 A suspension of 1,1'-carbonyldiimidazole (24 mg, 0.14 mmol), ethanol (7 mg, 0.14 mmol) and DCM (0.5 mL) under N₂ (g) was treated with a solution of 1-methyl-4-{[5-(2-piperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]pyridin-2-yl]carbonyl}piperazine (Intermediate A23; 30 mg, 0.071 mmol;) in DCM (0.5 mL) and stirred at r.t. for 24 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (System E). Yield 5.2 mg (15%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₂₇H₃₄N₄O₅ 494.2529, found 494.2543.
- 20

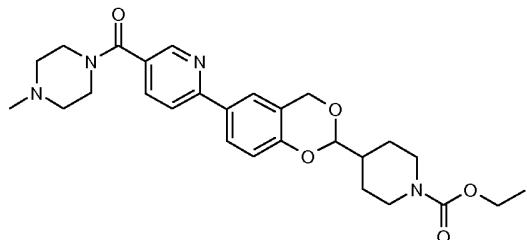
EXAMPLE A144

Isopropyl 4-(6-{[(4-methylpiperazin-1-yl)carbonyl]pyridin-3-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate

- 5 The title compound was prepared from 1-methyl-4-{{[5-(2-piperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]pyridin-2-yl}carbonyl}piperazine (Intermediate A23; 30 mg, 0.071 mmol) and 2-propanol (9 mg, 0.14 mmol) using the conditions described for Example A143. Yield 6.9 mg (19%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₂₈H₃₆N₄O₅ 508.2686, found 508.2700.

10

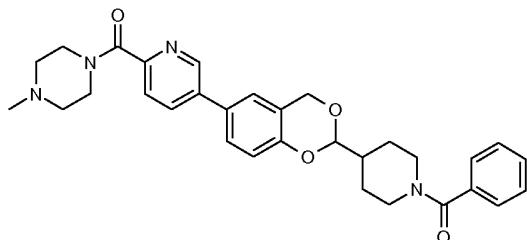
EXAMPLE A145

Ethyl 4-(6-{5-[(4-methylpiperazin-1-yl)carbonyl]pyridin-2-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate

- 15 The title compound was prepared from 1-methyl-4-{{[6-(2-piperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]pyridin-3-yl}carbonyl}piperazine (Intermediate A24; 22 mg, 0.052 mmol) and ethanol (5 mg, 0.1 mmol) using the conditions described for Example A143. Yield 2.3 mg (9%). Analytical HPLC: purity 96% (System A and B); HRESIMS (ESI⁺) calcd for C₂₇H₃₄N₄O₅ 494.2529, found 494.2529.

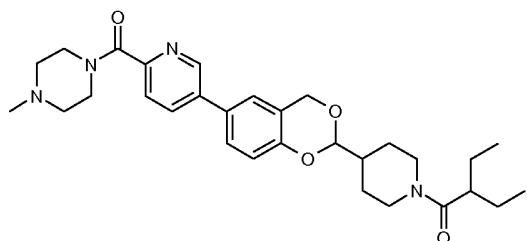
20

EXAMPLE A146

1-({5-[2-(1-Benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]pyridin-2-yl}carbonyl)-4-methylpiperazine

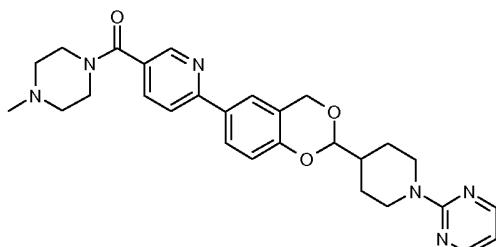
5 A cooled (5 °C) suspension of 1-methyl-4-{[5-(2-piperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-pyridin-2-yl}piperazine (Intermediate A23; 30 mg, 0.071 mmol) in dry pyridine (2 mL) was stirred under N₂ for 10 min. To the mixture was then added benzoyl chloride (12 mg, 0.071 mmol) and the resulting mixture was stirred for 1 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC
10 (System E). Yield 6.3 mg (17%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₃₁H₃₄N₄O₄ 526.2580, found 526.2601.

EXAMPLE A147

1-[(5-{2-[1-(2-Ethylbutanoyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}pyridin-2-yl)-carbonyl]-4-methylpiperazine

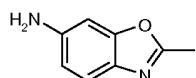
The title compound was prepared from 1-methyl-4-{[5-(2-piperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]pyridin-2-yl}piperazine (Intermediate A23; 30 mg, 0.071 mmol) and 2-ethylbutanoyl chloride (12 mg, 0.071 mmol) using the conditions described for Example
20 A146. Yield 5.6 mg (15%). Analytical HPLC: purity 99% (System A and B); HRESIMS (ESI⁺) calcd for C₃₀H₄₀N₄O₄ 520.3050, found 520.3068.

EXAMPLE A148

2-[4-(6-{[4-Methylpiperazin-1-yl]carbonyl}pyridin-2-yl)-4H-1,3-benzodioxin-2-yl]piperidin-1-yl]pyrimidine

5 A suspension of 2-bromopyrimidine (6 mg, 0.037 mmol) and 1-methyl-4-{{[6-(2-piperidin-4-yl)-4H-1,3-benzodioxin-6-yl]pyridin-3-yl]carbonyl}piperazine (Intermediate A24; 14 mg, 0.033 mmol) in dry DMSO (1 mL) under N₂ (g) was stirred at 50 °C for 12 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (System E). Yield 2.1 mg (13%). Analytical HPLC: purity 99% (System A and B);
10 HRESIMS (ESI⁺) calcd for C₂₈H₃₂N₆O₃ 500.2536, found 500.2551.

INTERMEDIATE B1

2-Methyl-1,3-benzoxazol-6-amine

15 To a heated suspension (70 °C) of 6-nitro-2-methyl-benzoxazole (4.00 g, 22.4 mmol) in MeOH (60 mL) was added a solution of ammonium chloride (12.1 g, 0.227 mol) in water (40 mL) followed by iron powder (4.52 g, 80.1 mmol). The mixture was stirred for 2 h at 70 °C and then filtered through Celite and washed with MeOH. The filtrate was concentrated and the residue was partitioned between water and EtOAc. The organic layers
20 were combined and the solvent was removed under reduced pressure to give the title compound. Yield 2.83 g (85%). Analytical HPLC: purity 100% (System A); LRESIMS (ESI⁺) m/z = 149 (M+H)⁺.

INTERMEDIATE B2

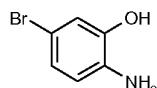
N-(4-Bromo-2-hydroxyphenyl)acetamide

To a cooled (0 °C) suspension of 2-methyl-1,3-benzoxazol-6-amine (Intermediate B1; 1.96 g, 13.2 mmol) in 1 M HBr (40 mL) was carefully added NaNO₂ (1.38 g, 20 mmol). After stirring for 10 min, a solution of CuBr (2.92 g, 20 mmol) in water (14 mL) was added and the mixture was stirred at 0 °C for 5 min. The ice-bath was removed and the mixture was 5 stirred overnight and then 25% aqueous ammonia (5 mL) was added. The mixture was extracted with EtOAc (500 mL) and the organic layer was concentrated. The residue was purified by flash chromatography on silica using MeOH/CHCl₃ (0.05:1) as eluent. Yield 1.47 g (32%). Analytical HPLC: purity 100% (System A); LRESIMS (ESI⁺) m/z = 230/232 (M+H)⁺.

10

INTERMEDIATE B3

2-Amino-5-bromophenol

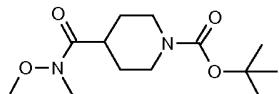


A suspension of *N*-(4-bromo-2-hydroxyphenyl)acetamide (Intermediate B2; 1.35 g, 5.87 15 mmol) in EtOH (30 mL) and 3 M HCl (30 mL) was heated to 100 °C (reflux) for 3 h. To the mixture was then added 1 M Na₂CO₃ (45 mL) and the ethanol was removed under reduced pressure. The residue was extracted with DCM (3 x 250 mL), dried and concentrated. Yield 988 mg (89%). Analytical HPLC: purity 100% (System A); LRESIMS (ESI⁺) m/z = 188/190 (M+H)⁺.

20

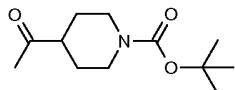
INTERMEDIATE B4

tert-Butyl 4-{[methoxy(methyl)amino]carbonyl}piperidine-1-carboxylate



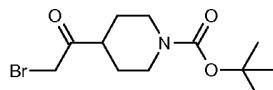
A suspension of 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (5.0 g, 21.8 mmol), 25 EDC (6.27 g, 32.7 mmol) and HOBT (2.95 g, 21.8 mmol) in DMF (10 mL) was stirred for 20 min. To the mixture were then added 1,2-dimethylhydroxylamine hydrochloride (3.19 g, 32.7 mmol) and DIEA (13 mL, 76.3 mmol) and the stirring continued overnight. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was concentrated and the residue was purified by flash chromatography on silica using EtOAc 30 as eluent. Yield 5.22 g (88%). Analytical HPLC: purity 100% (System A and B); LRESIMS (ESI⁺) m/z = 217 (M+H-*t*Bu)⁺.

INTERMEDIATE B5

***tert*-Butyl 4-acetyl**

5 A 3 M solution of bromo(methyl)magnesium in diethylether (13.8 mL, 41.4 mmol) was cooled in an ice-bath and a solution of *tert*-butyl 4-{[methoxy(methyl)amino]carbonyl}-
10 piperidine-1-carboxylate (Intermediate B4; 5.2 g 19.2 mmol) in Et₂O (25 mL) was added dropwise. The ice-bath was removed and the mixture was stirred at r.t. for 2 h. The excess bromo(methyl)magnesium was quenched by dropwise addition of water, and the water phase was then extracted with ether. Yield 3.35 g (77%). Analytical HPLC: purity 95%
15 (System A); LRESIMS (ESI⁺) m/z = 172 (M+H-*t*Bu)⁺.

INTERMEDIATE B6

***tert*-Butyl 4-(bromoacetyl)piperidine-1-carboxylate**

15 To a cooled (-78 °C) suspension of *tert*-butyl 4-acetyl (Intermediate B5; 2.87 g, 12.6 mmol) in THF (30 mL) was added 1 M lithium bis(trimethylsilyl)amide in THF (13.3 mL) over 20 min. The mixture was stirred for 1 h before the addition of trimethylsilyl chloride (1.74 mL, 13.7 mmol). After stirring at 0 °C
20 for 30 min, the solution was cooled to -78 °C and bromine (0.645 mL, 12.6 mmol) was added. The mixture was allowed to reach r.t. and then poured into a solution of 10% Na₂S₂O₃ (20 mL) and saturated NH₄Cl (20 mL). Extraction with EtOAc (2 x 80 mL) gave the title compound. Yield 3.69 g (96%).

25 INTERMEDIATE B7

***tert*-Butyl 4-(7-bromo-2*H*-1,4-benzoxazin-3-yl)piperidine-1-carboxylate**

To a stirred solution of 2-amino-5-bromophenol (Intermediate B3; 898 mg, 4.78 mmol) in DMF (10 mL) was added K₂CO₃ (660 mg, 4.78 mmol). After 45 min, a solution of *tert*-

butyl 4-(bromoacetyl)piperidine-1-carboxylate (Intermediate B6; 1.53 g, ca 5 mmol) in DMF (2 mL) was added and the mixture was stirred at r.t. overnight. Water was added and the product was extracted with toluene. The organic phase was washed with water and brine, dried and evaporated to give 952 mg of crude title compound (used in Intermediate 5 B8). The aqueous layer was extracted with CHCl₃ and the organic layer was concentrated. The residue was purified by flash chromatography on silica using 1% MeOH/CHCl₃ as eluent to give an additional 628 mg of the title compound. Total yield 1.58 g (84%). Analytical HPLC: purity 83% (System A); LRESIMS (ESI⁺) m/z = 339/341 (M+H-*t*Bu)⁺.

10 INTERMEDIATE B8

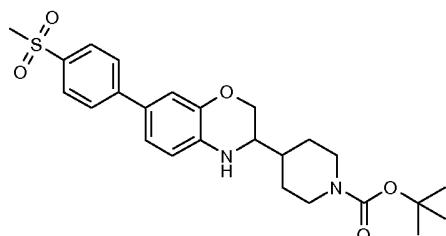
tert-Butyl 4-(7-bromo-3,4-dihydro-2*H*-1,4-benzoxazin-3-yl)piperidine-1-carboxylate



A suspension of *tert*-butyl 4-(7-bromo-2*H*-1,4-benzoxazin-3-yl)piperidine-1-carboxylate (crude Intermediate B7; 952 mg, 2.4 mmol) in ethanol (25 mL) was treated with NaBH₄ (200 mg, 5.26 mmol) and stirred for 6 h. To the reaction mixture was then added HOAc (1.5 mL) followed by 2 M NaOH (13 mL). The ethanol was removed under reduced pressure and the residue was extracted with DCM. The organic layer was concentrated and the residue was purified by flash chromatography on silica using EtOAc/*n*-hexane (1:2) as eluent. Yield 306 mg. Analytical HPLC: purity 100% (System A); LRESIMS (ESI⁺) m/z = 20 341/343 (M+H-*t*Bu)⁺.

EXAMPLE B1

tert-Butyl 4-{7-[4-(methylsulfonyl)phenyl]-3,4-dihydro-2*H*-1,4-benzoxazin-3-yl}-piperidine-1-carboxylate



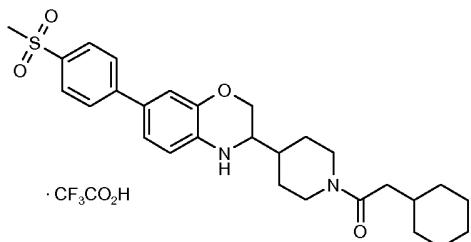
25

A suspension of *tert*-butyl 4-(7-bromo-3,4-dihydro-2*H*-1,4-benzoxazin-3-yl)piperidine-1-carboxylate (Intermediate B8; 200 mg, 0.50 mmol), (4-methylsulfonylphenyl)boronic acid

(120 mg, 0.6 mmol), NaHCO₃ (126 mg, 1.5 mmol), PPh₃ (20 mg, 0.075 mmol) and Pd(OAc)₂ (6 mg, 0.025 mmol) in 80% EtOH (4 mL) was heated at 80 °C overnight. The reaction mixture was filtered through Celite and the filtrate was concentrated. The residue was dissolved in DCM and washed with 5% NaHCO₃ and brine. Flash chromatography 5 using gradient elution (45 → 60% EtOAc in *n*-hexane) gave the title compound. Yield 30 mg (13%). Analytical HPLC: purity 98% (System A); HRESIMS (ESI+) calcd for C₂₅H₃₂N₂O₅S 472.2032, found 472.2039.

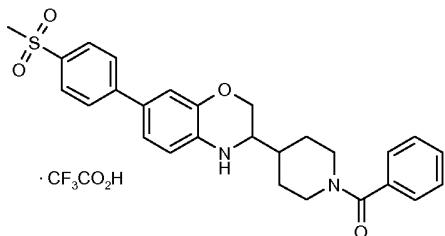
EXAMPLE B2

10 **3-[1-(Cyclohexylacetyl)piperidin-4-yl]-7-[4-(methylsulfonyl)phenyl]-3,4-dihydro-2*H*-1,4-benzoxazine trifluoroacetate**



A suspension of *tert*-butyl 4-{7-[4-(methylsulfonyl)phenyl]-3,4-dihydro-2*H*-1,4-benzoxazin-3-yl}piperidine-1-carboxylate (Example B1; 63 mg, 0.13 mmol) in DCM (0.8 mL) and TFA (0.2 mL) was stirred for 30 min and then concentrated. The residue was partitioned between CHCl₃ (20 + 10 mL) and 1 M Na₂CO₃ (2 mL) and the combined organic layers were concentrated to give 7-[4-(methylsulfonyl)phenyl]-3-piperidin-4-yl-15 3,4-dihydro-2*H*-1,4-benzoxazine. The deprotected material was then treated with DMF (0.8 mL), triethylamine (0.031 mL, 23 mg, 0.226 mmol) and cyclohexylacetic acid (816 mg, 0.113 mmol) followed by the addition of TBTU (43 mg, 0.135 mmol). The mixture 20 was stirred at r.t. overnight. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (System D). Yield 16 mg (20%). Analytical HPLC: purity 100% (System A); HRESIMS (ESI+) calcd for C₂₈H₃₆N₂O₄S 496.2396, found 496.2407.

EXAMPLE B3

3-(1-Benzoylpiperidin-4-yl)-7-[4-(methylsulfonyl)phenyl]-3,4-dihydro-2*H*-1,4-benzoxazine trifluoroacetate

5 The title compound was prepared from *tert*-butyl 4-{7-[4-(methylsulfonyl)phenyl]-3,4-dihydro-2*H*-1,4-benzoxazin-3-yl}piperidine-1-carboxylate (Example B1; 42 mg, 0.089 mmol) and benzoic acid (14 mg, 0.113 mmol) using the conditions described for Example B2. Yield 15 mg (28%). Analytical HPLC: purity 100% (System A); HRESIMS (ESI+) calcd for C₂₇H₂₈N₂O₄S 476.1770, found 476.1763.

10

BIOLOGICAL TESTS

Human GPR119 Activity Assay

15 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

20 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% confluence, cells were detached using Trypsine and aliquoted at a density of 5x10⁶ 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 thawed and diluted to 0.4x10⁶ 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 25 incubated 1 hour, followed by measuring the fluorescence ratio at 665 nm / 620 nm. Test 30

substances was diluted in compound buffer (1x HBSS (Gibco Cat. no. 14025-049), 20 mM Hepes (Gibco Cat. no. 15630-056), 0.1% BSA, 2 mM IBMX (Sigma-Aldrich Cat. No. I7018, pH 7.4). The potency of the agonist was quantified by determining the concentration that caused 50% activation of hGPR119 evoked increase in cAMP, EC₅₀.

5 Compounds of the invention showed a concentration-dependant increase in intracellular cAMP level and generally had an EC₅₀ value of <10 µM.

Hamster GPR119 Activity Assay

10 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
15 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,
20 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).

25 *Effects of GPR119 Agonists on Glucose-Stimulated Insulin Release*

In vitro experiments

The effect of GPR119 agonists on glucose-stimulated insulin release is determined in isolated pancreatic islets from Wistar rats and diabetic rat models, e.g. GK rat. Briefly,
30 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 60min at 37 °C. Aliquots of the medium will be frozen for measurement of insulin using a radioimmunoassay with rabbit ant-porcine insulin antibodies.

5 *In vivo experiments*

The effects of GPR119 agonists 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 10 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 heparinized tubes and centrifugation.

15 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).

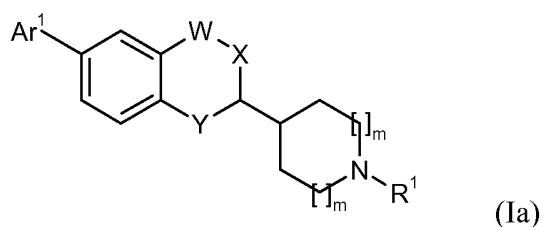
20 *Effects of GPR119 Agonists on Incretin Secretion and Body Weight*

In vivo experiments

The effect of GPR119 agonists 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 25 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)



5

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

10 W, X and Y are each independently CH₂, O, NH or N(CH₃), provided that at least one of W and X is CH₂;

m is each independently 0 or 1;

15 R¹ is -C(O)OR², -C(O)R², -C(O)NR²R³, -C(O)CH₂NR²R³, -CH₂C(O)NR²R³, -S(O)₂R², -C(O)C(O)R⁹ or a 5- or 6-membered heteroaryl group linked via a ring carbon atom, wherein said heteroaryl group is optionally substituted with C₁₋₄-alkyl;

20 Ar¹ is phenyl or heteroaryl, each of which is optionally independently substituted in one or more positions with a substituent selected from:

- (a) CF₃SO₃,
- (b) halogen selected from bromine, chlorine and fluorine,
- (c) C₁₋₄-alkylsulfoximine,
- (d) -S(O)R⁴,
- (e) -S(O)₂R⁴,
- 25 (f) -S(O)₂NR⁵R⁵,
- (g) -NR⁶S(O)₂R⁴,
- (h) -CH₂-NR⁶C(O)R⁴,
- (i) -NR⁶C(O)R⁴,
- (j) -C(O)NR⁵R⁵,
- 30 (k) -CH₂-C(O)NR⁵R⁵,

- (l) $-C(O)R^4$,
- (m) $H_2N-C(O)O-$,
- (n) $CH_3-NH-C(O)O-$,
- (o) $(CH_3)_2NC(O)O-$,
- 5 (p) $CH_3OC(O)NH-$,
- (q) C-heterocyclyl, optionally substituted with C_{1-4} -alkyl,
- (r) N-heterocyclylcarbonylvinyl, wherein N-heterocyclyl is optionally substituted with C_{1-4} -alkyl,
- (s) $-CN$,
- 10 (t) $-OR^8$,
- (u) $-SCF_3$,
- (v) $-NO_2$,
- (w) C-heterocyclylsulfonyl, optionally substituted with C_{1-4} -alkyl,
- (x) $-NR^5R^5$,
- 15 (y) $-C(OH)CH_3CF_3$,
- (z) $[CF_3CH_3(OH)C]-C_{1-6}$ -alkyl,
- (aa) cyano- C_{1-6} -alkyl,
- (bb) guanidino,
- (cc) amidino,
- 20 (dd) C_{1-6} -alkyl,
- (ee) C_{1-6} -alkylthio,
- (ff) C_{1-4} -alkoxy- C_{1-4} -alkyl,
- (gg) fluoro- C_{1-4} -alkyl,
- (hh) C_{2-6} -alkenyl,
- 25 (ii) fluoro- C_{2-4} -alkenyl,
- (jj) hydroxy- C_{1-6} -alkyl,
- (kk) C_{1-4} -alkylsulfonyl- C_{1-4} -alkyl,
- (ll) hydroxy- C_{2-4} -alkoxy- C_{1-4} -alkyl,
- (mm) C_{2-3} -acyl- C_{1-3} -alkyl,
- 30 (nn) C_{2-6} -alkynyl,
- (oo) C_{3-6} -cycloalkyl,
- (pp) hydroxy- C_{3-6} -cycloalkyl,
- (qq) fluoro- C_{3-6} -cycloalkyl,
- (rr) methyl- C_{3-6} -cycloalkyl,

(ss) C₃₋₆-cycloalkyl-C₁₋₄-alkyl, wherein C₃₋₆-cycloalkyl is optionally substituted with methyl,

(tt) C-heterocyclylcarbonyl, optionally substituted with C₁₋₄-alkyl,

(uu) C₃₋₆-cycloalkylthio,

5 (vv) R⁵R⁵N-C₁₋₂-alkyl,

(ww) -(CH₂)_nC(O)OR⁷, wherein n is 0, 1, 2 or 3,

(xx) phenyl, and

(yy) heteroaryl,

10 wherein phenyl or heteroaryl as substituent on Ar¹ is optionally substituted in one or more positions with a substituent independently selected from the group Z¹ consisting of:

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

(b) C₁₋₄-alkyl,

(c) hydroxy,

15 (d) C₁₋₄-alkoxy,

(e) -OCF₃,

(f) -SCF₃,

(g) -CN,

(h) -C(OH)CH₃CF₃,

20 (i) hydroxy-C₁₋₄-alkyl,

(j) -CF₃,

(k) -S(O)₂CH₃,

(l) -S(O)₂NH₂,

(m) -S(O)₂NHCH₃,

25 (n) -S(O)₂N(CH₃)₂,

(o) -N(CH₃)S(O)₂CH₃,

(p) -N(CH₃)C(O)CH₃,

(q) -C(O)NH₂,

(r) -C(O)NHCH₃,

30 (s) -C(O)N(CH₃)₂,

(t) -C(O)CH₃,

(u) N-heterocyclylmethyl,

(v) N-heterocyclyl, optionally substituted with methyl,

(w) phenoxy,

- (x) $-\text{NH}_2$,
- (y) $-\text{NHCH}_3$,
- (z) $-\text{N}(\text{CH}_3)_2$, and
- (aa) methoxycarbonyl;

5

R^2 is selected from:

- (a) $\text{C}_{1\text{-}6}$ -alkyl,
- (b) $\text{C}_{1\text{-}6}$ -alkoxy- $\text{C}_{1\text{-}6}$ -alkyl,
- (c) hydroxy- $\text{C}_{2\text{-}6}$ -alkyl,
- 10 (d) fluoro- $\text{C}_{2\text{-}6}$ -alkyl,
- (e) amino- $\text{C}_{2\text{-}6}$ -alkyl,
- (f) $\text{C}_{1\text{-}3}$ -alkylamino- $\text{C}_{2\text{-}6}$ -alkyl,
- (g) di($\text{C}_{1\text{-}3}$ -alkyl)amino- $\text{C}_{2\text{-}6}$ -alkyl,
- (h) cyano- $\text{C}_{1\text{-}6}$ -alkyl,
- 15 (i) $\text{C}_{1\text{-}6}$ -alkylsulfonyl- $\text{C}_{2\text{-}6}$ -alkyl,
- (j) $\text{C}_{2\text{-}3}$ -acylamino- $\text{C}_{2\text{-}4}$ -alkyl,
- (k) $\text{C}_{1\text{-}4}$ -alkylthio- $\text{C}_{2\text{-}4}$ -alkyl,
- (l) $\text{C}_{2\text{-}4}$ -acyl- $\text{C}_{1\text{-}4}$ -alkyl,
- (m) $\text{C}_{3\text{-}6}$ -alkynyl,
- 20 (n) $\text{C}_{3\text{-}6}$ -alkenyl,
- (o) $\text{C}_{3\text{-}7}$ -cycloalkyl,
- (p) $\text{C}_{5\text{-}8}$ -cycloalkenyl,
- (q) C-heterocyclyl, optionally substituted with $\text{C}_{1\text{-}4}$ -alkyl,
- (r) $\text{C}_{7\text{-}8}$ -bicyclyl, optionally substituted with hydroxy,
- 25 (s) $\text{C}_{7\text{-}8}$ -bicycylmethyl,
- (t) azabicyclyl, optionally substituted with hydroxy,
- (u) $\text{C}_{3\text{-}7}$ -cycloalkyl- $\text{C}_{1\text{-}4}$ -alkyl, wherein cycloalkyl is optionally substituted with methyl or hydroxy,
- (v) $\text{C}_{1\text{-}6}$ -alkylsulfonyl- $\text{C}_{2\text{-}6}$ -alkyl,
- 30 (w) $\text{C}_{2\text{-}3}$ -acyl- $\text{C}_{1\text{-}4}$ -alkyl,
- (x) diphenylmethyl,
- (y) arylcarbonyl- $\text{C}_{1\text{-}4}$ -alkyl,
- (z) heteroarylcarbonyl- $\text{C}_{1\text{-}4}$ -alkyl,
- (aa) $[\text{CF}_3\text{CH}_3(\text{OH})\text{C}]\text{-C}_{1\text{-}6}$ -alkyl,

- (bb) *N*-heterocyclylcarbonyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- (cc) C-heterocyclylcarbonyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- 5 (dd) aminocarbonyl-C₂₋₆-alkyl,
- (ee) C₁₋₃-alkylaminocarbonyl-C₂₋₆-alkyl,
- (ff) di(C₁₋₃-alkyl)aminocarbonyl-C₂₋₆-alkyl,
- (gg) hydroxy-C₂₋₄-alkoxy-C₂₋₄-alkyl,
- (hh) hydroxy-C₄₋₆-cycloalkyl,
- 10 (ii) oxo-C₄₋₆-cycloalkyl,
- (jj) fluoro-C₄₋₆-cycloalkyl,
- (kk) C₁₋₃-alkoxy-C₄₋₆-cycloalkyl,
- (ll) methyl-C₃₋₆-cycloalkyl,
- (mm) oxo-*N*-heterocyclyl-C₂₋₄-alkyl,
- 15 (nn) fluoro-*N*-heterocyclyl-C₂₋₄-alkyl,
- (oo) amino-*N*-heterocyclyl-C₂₋₄-alkyl,
- (pp) hydroxy-*N*-heterocyclyl-C₂₋₄-alkyl,
- (qq) *N*-heterocyclyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- 20 (rr) C-heterocyclyl-C₁₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- (ss) aryl,
- (tt) aryl-C₁₋₄-alkyl,
- (uu) aryl-C₃₋₆-alkenyl,
- 25 (vv) aryl-C₃₋₆-alkynyl,
- (ww) aryloxymethyl,
- (xx) heteroaryl,
- (yy) heteroaryl-C₁₋₄-alkyl,
- (zz) heteroaryl-C₃₋₆-alkenyl, and
- 30 (aaa) heteroaryl-C₃₋₆-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 Z¹ as defined above;

R³ is selected from:

- (a) hydrogen,
- (b) C₁₋₆-alkyl,
- (c) fluoro-C₂₋₆-alkyl,
- 5 (d) hydroxy-C₂₋₆-alkyl,
- (e) C₁₋₆-alkoxy-C₂₋₆-alkyl,
- (f) amino-C₂₋₆-alkyl,
- (g) C₁₋₃-alkylamino-C₂₋₆-alkyl,
- (h) di(C₁₋₃-alkyl)amino-C₂₋₆-alkyl,
- 10 (i) cyano-C₁₋₆-alkyl,
- (j) C₁₋₆-alkylsulfonyl-C₂₋₆-alkyl,
- (k) C₂₋₃-acylamino-C₂₋₄-alkyl,
- (l) C₁₋₄-alkylthio-C₂₋₄-alkyl, and
- (m) C₂₋₄-acyl-C₁₋₄-alkyl;

15 or R² and R³ 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) C₁₋₃-alkyl,
- 20 (cc) amino,
- (dd) methylamino,
- (ee) dimethylamino,
- (ff) hydroxy-C₁₋₂-alkyl, and
- (gg) aminomethyl;

25 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;

30

R⁴ is independently selected from:

- (a) C₁₋₆-alkyl,
- (b) fluoro-C₁₋₆-alkyl,
- (c) hydroxy-C₂₋₆-alkyl,

- (d) C₁₋₄-alkoxy-C₂₋₄-alkyl,
- (e) C₂₋₄-acyl-C₁₋₄-alkyl,
- (f) carboxy-C₁₋₃-alkyl,
- (g) C₃₋₆-cycloalkyl,
- 5 (h) oxo-C₄₋₆-cycloalkyl,
- (i) hydroxy-C₄₋₆-cycloalkyl,
- (j) fluoro-C₄₋₆-cycloalkyl,
- (k) methyl-C₃₋₆-cycloalkyl,
- (l) N-heterocyclylcarbonyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- 10 (m) N-heterocyclyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- (n) oxo-N-heterocyclyl-C₂₋₄-alkyl,
- (o) fluoro-N-heterocyclyl-C₂₋₄-alkyl,
- 15 (p) hydroxy-N-heterocyclyl-C₂₋₄-alkyl,
- (q) amino-N-heterocyclyl-C₂₋₄-alkyl,
- (r) aminocarbonyl-C₂₋₄-alkyl,
- (s) C₁₋₃-alkylaminocarbonyl-C₂₋₄-alkyl,
- (t) di(C₁₋₃-alkyl)aminocarbonyl-C₂₋₄-alkyl,
- 20 (u) C₂₋₃-acylamino-C₂₋₄-alkyl,
- (v) hydroxy-C₂₋₄-alkoxy-C₂₋₄-alkyl,
- (w) C-heterocyclylcarbonyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- (x) C₃₋₆-cycloalkyl-C₁₋₂-alkyl, wherein cycloalkyl is optionally substituted with methyl,
- 25 (y) amino-C₂₋₄-alkyl,
- (z) C₁₋₂-alkylamino-C₂₋₄-alkyl,
- (aa) di(C₁₋₂-alkyl)amino-C₂₋₄-alkyl,
- (bb) phenyl, and
- (cc) heteroaryl,

wherein any phenyl or heteroaryl residue is optionally substituted in one or more positions with a substituent independently selected from the group Z² consisting of:

- (a) halogen selected from chlorine and fluorine,
- (b) C₁₋₄-alkoxy,

- 5
- (c) hydroxymethyl,
 - (d) $-\text{CN}$,
 - (e) $-\text{CF}_3$,
 - (f) $\text{C}_{1-4}\text{-alkyl}$,
 - (g) $-\text{OCF}_3$, and
 - (h) $-\text{C}(\text{O})\text{CH}_3$;

R^5 is each independently selected from:

- 10
- (a) hydrogen,
 - (b) $\text{C}_{1-6}\text{-alkyl}$,
 - (c) $\text{C}_{3-6}\text{-alkenyl}$,
 - (d) $\text{C}_{3-6}\text{-cycloalkyl}$,
 - (e) methyl- $\text{C}_{3-6}\text{-cycloalkyl}$,
 - (f) $\text{C}_{3-6}\text{-cycloalkyl-C}_{1-4}\text{-alkyl}$, wherein cycloalkyl is optionally substituted
15 with hydroxy or methyl,
 - (g) N-heterocyclyl- $\text{C}_{2-4}\text{-alkyl}$, wherein heterocyclyl is optionally substituted with methyl,
 - (h) heteroaryl- $\text{C}_{1-4}\text{-alkyl}$, wherein heteroaryl is optionally substituted with methyl,

20

 - (i) carboxy- $\text{C}_{1-3}\text{-alkyl}$,
 - (j) fluoro- $\text{C}_{2-4}\text{-alkyl}$,
 - (k) amino- $\text{C}_{2-6}\text{-alkyl}$,
 - (l) cyano- $\text{C}_{1-6}\text{-alkyl}$,
 - (m) hydroxy- $\text{C}_{2-6}\text{-alkyl}$,

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 - (n) dihydroxy- $\text{C}_{2-6}\text{-alkyl}$,
 - (o) $\text{C}_{1-4}\text{-alkoxy-C}_{2-4}\text{-alkyl}$,
 - (p) $\text{C}_{1-4}\text{-alkylamino-C}_{2-4}\text{-alkyl}$,
 - (q) di($\text{C}_{1-4}\text{-alkyl}$)amino- $\text{C}_{2-4}\text{-alkyl}$,
 - (r) aminocarbonyl- $\text{C}_{1-4}\text{-alkyl}$,

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 - (s) $\text{C}_{2-3}\text{-acylamino-C}_{2-4}\text{-alkyl}$,
 - (t) $\text{C}_{1-4}\text{-alkylthio-C}_{2-4}\text{-alkyl}$,
 - (u) $\text{C}_{2-4}\text{-acyl-C}_{1-4}\text{-alkyl}$, and
 - (v) $\text{C}_{1-4}\text{-alkylsulfonyl-C}_{1-4}\text{-alkyl}$,

or two R⁵ 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:

- (a) hydroxy,
- (b) C₁₋₃-alkyl,
- (c) amino,
- (d) methylamino,
- (e) dimethylamino,
- (f) hydroxy-C₁₋₂-alkyl, and
- (g) 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;

or two R⁵ groups together with the nitrogen to which they are attached form the group 4-(pyrimidin-2-yl)piperazin-1-yl;

R⁶ is independently selected from:

- (a) hydrogen,
- (b) C₁₋₄-alkyl, and
- (c) hydroxy-C₂₋₄-alkyl;

R⁷ is independently selected from:

- (a) hydrogen, and
- (b) C₁₋₄-alkyl;

R⁸ is independently selected from:

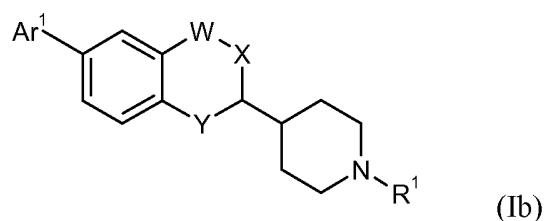
- (a) hydrogen,
- (b) C₁₋₆-alkyl,
- (c) fluoro-C₁₋₆-alkyl,
- (d) hydroxy-C₂₋₆-alkyl,
- (e) amino-C₂₋₆-alkyl,
- (f) C₁₋₃-alkylamino-C₂₋₄-alkyl,

- (g) di(C₁₋₃-alkyl)amino-C₂₋₄-alkyl,
- (h) C₁₋₄-alkylsulfonyl-C₂₋₄-alkyl,
- (i) N-heterocyclyl-C₂₋₄-alkyl, wherein heterocyclyl is optionally substituted with methyl,
- 5 (j) C-heterocyclyl, optionally substituted with methyl,
- (k) C₂₋₃-acylamino-C₂₋₄-alkyl,
- (l) [CF₃CH₃(OH)C]-C₁₋₆-alkyl,
- (m) C₃₋₆-cycloalkyl,
- (n) methyl-C₃₋₆-cycloalkyl,
- 10 (o) C₃₋₆-cycloalkyl-C₁₋₂-alkyl, wherein cycloalkyl is optionally substituted with methyl,
- (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 Z² as defined above; and

20 R⁹ is aryl or heteroaryl, each of which is optionally substituted in one or more positions with a substituent independently selected from the group Z² as defined above.

2. A compound according to claim 1 having Formula (Ib):

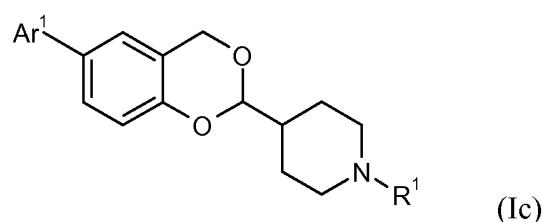


25 wherein W and X are each independently CH₂ or O, provided that at least one of W and X is CH₂;

Y is CH₂, O or NH; and

Ar¹, Z¹, Z², R¹ to R⁹ are as defined in claim 1.

3. A compound according to claim 1 or 2 having Formula (Ic):



5 wherein Z¹, Z², R¹ to R⁶ are as defined in claim 1;

Ar¹ is phenyl or heteroaryl, each of which is optionally substituted in one or two positions with a substituent independently selected from the group Z³ consisting of:

- (a) CF₃SO₃,
- (b) halogen selected from bromine, chlorine and fluorine,
- 10 (c) C₁₋₄-alkylsulfoximine,
- (d) -S(O)R⁴,
- (e) -S(O)₂R⁴,
- (f) -S(O)₂NR⁵R⁵,
- (g) -NR⁶S(O)₂R⁴,
- 15 (h) -NR⁶C(O)R⁴,
- (i) -CH₂-NR⁶C(O)R⁴,
- (j) -C(O)NR⁵R⁵,
- (k) -CH₂-C(O)NR⁵R⁵,
- (l) -C(O)R⁴,
- 20 (m) H₂N-C(O)O-,
- (n) CH₃-NH-C(O)O-,
- (o) (CH₃)₂NC(O)O-,
- (p) -NHC(O)OCH₃,
- (q) C-heterocyclyl, optionally substituted with methyl,
- 25 (r) N-heterocyclylcarbonylvinyl, wherein N-heterocyclyl is optionally substituted with methyl,
- (s) -CN,
- (t) -OR⁸,
- (u) -SCF₃,
- 30 (v) nitro,

- (w) C-heterocyclsulfonyl, optionally substituted with methyl,
(x) $-NR^5R^5$,
(y) $-C(OH)CH_3CF_3$,
(z) cyano-C₁₋₆-alkyl,
5 (aa) guanidino,
(bb) C₁₋₆-alkyl,
(cc) C₁₋₃-alkylthio,
(dd) C₁₋₄-alkoxy-C₁₋₄-alkyl,
(ee) fluoro-C₁₋₄-alkyl,
10 (ff) C₂₋₆-alkenyl,
(gg) fluoro-C₂₋₄-alkenyl,
(hh) hydroxy-C₁₋₆-alkyl,
(ii) C₁₋₄-alkylsulfonyl-C₁₋₄-alkyl,
(jj) hydroxy-C₂₋₄-alkoxy-C₁₋₄-alkyl,
15 (kk) C₂₋₃-acyl-C₁₋₃-alkyl,
(ll) C₂₋₆-alkynyl,
(mm) C₃₋₆-cycloalkyl,
(nn) hydroxy-C₃₋₆-cycloalkyl,
(oo) fluoro-C₃₋₆-cycloalkyl,
20 (pp) methyl-C₃₋₆-cycloalkyl,
(qq) C-heterocyclcarbonyl, optionally substituted with methyl,
(rr) C₃₋₆-cycloalkyl-C₁₋₄-alkyl,
(ss) R⁵R⁵N-C₁₋₂-alkyl,
(tt) $-(CH_2)_nC(O)OH$, wherein n is 1, 2 or 3, and
25 (uu) heteroaryl,

wherein any heteroaryl residue as substituent on Ar¹ is optionally substituted in one or more positions with a substituent independently selected from the group Z² as defined in claim 1;

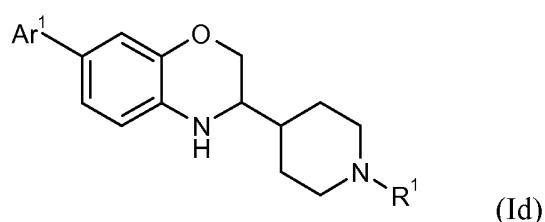
30 R⁸ is independently selected from:

- (a) hydrogen,
(b) C₁₋₄-alkyl,
(c) CF₃,
(d) C₃₋₅-cycloalkyl,

- (e) methyl-C₃₋₅-cycloalkyl,
- (f) di(C₁₋₃-alkyl)amino-C₂₋₃-alkyl, and
- (g) C-heterocyclyl, optionally substituted with methyl;

5 R⁹ is phenyl which is optionally substituted in one or two positions with a substituent independently selected from the group Z² as defined in claim 1.

4. A compound according to claim 1 or 2 having Formula (Id):



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wherein Z¹, Z², R¹ to R⁶ are as defined in claim 1;

R⁸ and R⁹ are as defined in claim 3;

Ar¹ is phenyl which is optionally substituted in one or two positions with a substituent independently selected from the group Z³ as defined in claim 3.

5. A compound according to any one of claims 1 to 4, which is selected from:

- benzyl 4-(6-{4-[(dimethylamino)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;
- benzyl 4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- benzyl 4-(6-quinolin-5-yl-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 4-{2-[1-(3,4-dichlorobenzoyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}-N,N-dimethylbenzamide;
- 4-(2-{1-[(2,4-difluorophenyl)acetyl]piperidin-4-yl}-4H-1,3-benzodioxin-6-yl)-N,N-dimethylbenzamide;
- N,N-dimethyl-4-[2-(1-{[3-(trifluoromethyl)phenyl]acetyl}piperidin-4-yl)-4H-1,3-benzodioxin-6-yl]benzamide;
- 4-(2-{1-[(4-methoxyphenyl)acetyl]piperidin-4-yl}-4H-1,3-benzodioxin-6-yl)-N,N-dimethylbenzamide;

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- 4-(2-{1-[(4-cyanophenyl)acetyl]piperidin-4-yl}-4*H*-1,3-benzodioxin-6-yl)-*N,N*-dimethylbenzamide;
- 4-{2-[1-(1*H*-indol-3-ylacetyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-*N,N*-dimethylbenzamide;
- 5 • *N,N*-dimethyl-4-(2-{1-[(1-methyl-1*H*-indol-3-yl)acetyl]piperidin-4-yl}-4*H*-1,3-benzodioxin-6-yl)benzamide;
- 4-{2-[1-(cyclohexylacetyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-*N,N*-dimethylbenzamide;
- 10 • *N,N*-dimethyl-4-{2-[1-(3-methyl-3-phenylbutanoyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzamide;
- 4-(2-{1-[3-(4-methoxyphenyl)propanoyl]piperidin-4-yl}-4*H*-1,3-benzodioxin-6-yl)-*N,N*-dimethylbenzamide;
- 15 • 4-(2-{1-[3-(3-chloro-4-methoxyphenyl)propanoyl]piperidin-4-yl}-4*H*-1,3-benzodioxin-6-yl)-*N,N*-dimethylbenzamide;
- 4-(2-{1-[3-(4-hydroxyphenyl)propanoyl]piperidin-4-yl}-4*H*-1,3-benzodioxin-6-yl)-*N,N*-dimethylbenzamide;
- 20 • 4-(2-{1-[3-(1*H*-indol-3-yl)propanoyl]piperidin-4-yl}-4*H*-1,3-benzodioxin-6-yl)-*N,N*-dimethylbenzamide;
- 4-{2-[1-(3-cyclohexylpropanoyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-*N,N*-dimethylbenzamide;
- 4-(2-{1-[4-(4-fluorophenyl)butanoyl]piperidin-4-yl}-4*H*-1,3-benzodioxin-6-yl)-*N,N*-dimethylbenzamide;
- 25 • *N,N*-dimethyl-4-{2-[1-(4-oxopentanoyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzamide;
- *N,N*-dimethyl-4-{2-[1-(4-oxo-4-pyrrolidin-1-ylbutanoyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}benzamide;
- benzyl 4-(6-{4-[(diethylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;
- 30 • benzyl 4-(6-{4-[(4-methylpiperidin-1-yl)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- benzyl 4-(6-{4-[(4-oxopiperidin-1-yl)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- benzyl 4-{6-[5-(methylsulfonyl)pyridin-2-yl]-4*H*-1,3-benzodioxin-2-yl}-piperidine-1-carboxylate;

- 1-(2-furoyl)-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidine;
- 1-[(4-fluorophenoxy)acetyl]-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine;
- 5 • 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-1-(1*H*-pyrrol-2-yl)-carbonylpiperidine;
- 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-1-(1*H*-tetrazol-1-yl)-acetyl)piperidine;
- 10 • 2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]pyridine;
- 4-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]pyridine;
- 2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]pyrazine;
- 15 • 6-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]quinoxaline;
- 1-(4-isopropoxybenzoyl)-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine;
- 20 • 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-1-(2-naphthoyl)-piperidine;
- 1-benzoyl-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine;
- 5-methyl-2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidin-1-yl)carbonyl]phenol;
- 25 • 5-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]-2-phenoxyypyridine;
- 1-(diphenylacetyl)-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidine;
- 5-isopropoxy-2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidin-1-yl)carbonyl]pyridine;
- 30 • 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-1-(3,3,3-trifluoro-propanoyl)piperidine;
- 2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]pyridin-3-ol;

- 4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-1-propionyl-piperidine;
- 1-[(7-methoxy-1-benzofuran-2-yl)carbonyl]-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine;
- 5 • dimethyl{3-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidin-1-yl)carbonyl]phenyl}amine;
- 2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]phenol;
- 2-(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-2-oxo-1-phenylethanone;
- 10 • 1-methyl-4-[3-(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidin-1-yl)-3-oxopropyl]piperazine;
- 1-methyl-4-{4-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidin-1-yl)carbonyl]phenyl}piperazine;
- 15 • 1-(methoxyacetyl)-4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidine;
- 3,5-difluoro-2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidin-1-yl)carbonyl]pyridine;
- 4-{4-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidin-1-yl)-carbonyl]benzyl}morpholine;
- 20 • 6-bromo-2-[(4-{6-[4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidin-1-yl)carbonyl]pyridin-3-ol;
- benzyl 4-(6-{4-[(methylsulfonyl)amino]phenyl}-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;
- benzyl 4-[6-(4-{{(2-morpholin-4-ylethyl)amino}sulfonyl}phenyl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- 25 • benzyl 4-{6-[4-(methylsulfonyl)-2-nitrophenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidine-1-carboxylate;
- benzyl 4-{6-[2-amino-4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidine-1-carboxylate;
- 30 • benzyl 4-{6-[2-{{(2-dimethylamino)ethyl}amino}-4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- benzyl 4-{6-[2-{{(2-isopropylamino)ethyl}amino}-4-(methylsulfonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;

- benzyl 4-(6-{4-(methylsulfonyl)-2-[(2-morpholin-4-ylethyl)amino]phenyl}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- benzyl 4-{6-[2-[2-(dimethylamino)ethoxy]-4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- 5 • *N,N*-diethyl-2-(4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}-piperidin-1-yl)acetamide;
- 1-benzoyl-4-{(2*R**)-6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}-piperidine;
- 10 • 1-benzoyl-4-{(2*S**)-6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}-piperidine;
- (1-methylcyclopropyl)methyl 4-(6-{4-[(methylamino)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 15 • (1-methylcyclopropyl)methyl 4-(6-{4-[(ethylamino)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- (1-methylcyclopropyl)methyl 4-(6-{4-[(allylamino)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 20 • (1-methylcyclopropyl)methyl 4-(6-{4-[(cyclopropylamino)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- (1-methylcyclopropyl)methyl 4-[6-(4-[(2-hydroxyethyl)amino]carbonyl)-phenyl]-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 25 • (1-methylcyclopropyl)methyl 4-[6-(4-[(3-hydroxypropyl)amino]carbonyl)-phenyl]-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- (1-methylcyclopropyl)methyl 4-[6-(4-[(2-methoxyethyl)amino]carbonyl)-phenyl]-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 30 • (1-methylcyclopropyl)methyl 4-[6-(4-[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl)-phenyl]-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- (1-methylcyclopropyl)methyl 4-(6-{4-[(3-hydroxyazetidin-1-yl)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- (1-methylcyclopropyl)methyl 4-(6-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4H-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 35 • (1-methylcyclopropyl)methyl 4-{6-[4-({[2-(2-furyl)ethyl]amino} carbonyl)-phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- *tert*-butyl 4-{6-[4-(methylsulfonyl)phenyl]-4H-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;

- *tert*-butyl 4-{6-[4-(aminocarbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{4-[(dimethylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;
- 5 • *tert*-butyl 4-{6-[4-(morpholin-4-ylcarbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}-piperidine-1-carboxylate;
- 2-({4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]phenyl}sulfonyl)-ethanol;
- 10 • 2-({4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]phenyl}sulfonyl)-ethanamine;
- *tert*-butyl 4-(6-{4-[(methylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{4-[(ethylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;
- 15 • *tert*-butyl 4-(6-{4-[(allylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{4-[(cyclopropylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-[6-(4-{[(2-hydroxyethyl)amino]carbonyl}phenyl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- 20 • *tert*-butyl 4-[6-(4-{[(2-methylprop-2-en-1-yl)amino]carbonyl}phenyl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{4-[(but-3-en-1-ylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 25 • *tert*-butyl 4-[6-(4-{[(3-hydroxypropyl)amino]carbonyl}phenyl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- *tert*-butyl 4-[6-(4-{[(2-methoxyethyl)amino]carbonyl}phenyl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- *tert*-butyl 4-{6-[4-({[(1-hydroxycyclopropyl)methyl]amino}carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- 30 • *tert*-butyl 4-[6-(4-{[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl}phenyl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{4-[(3-hydroxyazetidin-1-yl)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;

- *tert*-butyl 4-(6-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-[6-{4-([2-(2-furyl)ethyl]amino)carbonyl}phenyl]-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 5 • 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-methylbenzamide;
- 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-ethylbenzamide;
- *N*-allyl-4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzamide;
- 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-cyclopropylbenzamide;
- 10 • 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-(2-hydroxyethyl)benzamide;
- 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-(2-methylprop-2-en-1-yl)benzamide;
- 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-but-3-en-1-ylbenzamide;
- 15 • 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-(3-hydroxypropyl)benzamide;
- 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-(2-methoxyethyl)benzamide;
- 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*[(1-hydroxycyclopropyl)methyl]benzamide;
- 20 • 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-(2-hydroxy-1,1-dimethylethyl)benzamide;
- 1-{4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzoyl}azetidin-3-ol;
- 25 • 1-{4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]benzoyl}-4-methylpiperazine;
- 4-[2-(1-benzoylpiperidin-4-yl)-4*H*-1,3-benzodioxin-6-yl]-*N*-[2-(2-furyl)ethyl]benzamide;
- 30 • ethyl 4-(6-{4-[(methylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- ethyl 4-(6-{4-[(ethylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;

- ethyl 4-(6-{4-[(allylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- ethyl 4-(6-{4-[(cyclopropylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;
- 5 • ethyl 4-[6-(4-[(2-hydroxyethyl)amino]carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- ethyl 4-[6-(4-[(2-methylprop-2-en-1-yl)amino]carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- 10 • ethyl 4-(6-{4-[(but-3-en-1-ylamino)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)-piperidine-1-carboxylate;
- ethyl 4-[6-(4-[(3-hydroxypropyl)amino]carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- ethyl 4-[6-(4-[(2-methoxyethyl)amino]carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- 15 • ethyl 4-{6-[4-([(1-hydroxycyclopropyl)methyl]amino]carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- ethyl 4-[6-(4-[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- ethyl 4-(6-{4-[(3-hydroxyazetidin-1-yl)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 20 • ethyl 4-(6-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- ethyl 4-{6-[4-([(2-(2-furyl)ethyl)amino]carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- ethyl 4-[6-(4-[[2-(hydroxymethyl)morpholin-4-yl]carbonyl)phenyl]-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- 25 • 3-(3-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-isoxazol-5-yl)propanoic acid;
- [(5-{2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-4*H*-1,3-benzodioxin-6-yl}-2-furoyl)amino]acetic acid;
- *tert*-butyl 4-{6-[6-(methylsulfonyl)pyridin-3-yl]-4*H*-1,3-benzodioxin-2-yl}-piperidine-1-carboxylate;
- 30 • *tert*-butyl 4-{6-[5-(methylsulfonyl)pyridin-2-yl]-4*H*-1,3-benzodioxin-2-yl}-piperidine-1-carboxylate;

- *tert*-butyl 4-{6-[4-(1*H*-tetrazol-5-yl)phenyl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- *tert*-butyl 4-[6-(2-{[amino(imino)methyl]amino}-4-methyl-1,3-thiazol-5-yl)-4*H*-1,3-benzodioxin-2-yl]piperidine-1-carboxylate;
- 5 • *tert*-butyl 4-(6-pyridin-4-yl-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-(6-pyridin-3-yl-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{5-[(4-methylpiperazin-1-yl)carbonyl]pyridin-2-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 10 • *tert*-butyl 4-{6-[6-(morpholin-4-ylcarbonyl)pyridin-3-yl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{6-[(4-methylpiperazin-1-yl)carbonyl]pyridin-3-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-{6-[5-(morpholin-4-ylcarbonyl)pyridin-2-yl]-4*H*-1,3-benzodioxin-2-yl}piperidine-1-carboxylate;
- 15 • *tert*-butyl 4-(6-{5-[(4-methylpiperazin-1-yl)carbonyl]-2-furyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{5-[(1*E*)-3-(4-methylpiperazin-1-yl)-3-oxoprop-1-en-1-yl]-2-thienyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 20 • *tert*-butyl 4-(6-{5-[(1*E*)-3-morpholin-4-yl-3-oxoprop-1-en-1-yl]-2-thienyl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-(6-{5-[(4-pyrimidin-2-yl)piperazin-1-yl)carbonyl]pyridin-2-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 25 • *tert*-butyl 4-[6-(5-{{[2-(dimethylamino)ethyl](methyl)amino]carbonyl}pyridin-2-yl)-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-[6-(5-{{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}pyridin-2-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- *tert*-butyl 4-[6-(6-{{[2-(dimethylamino)ethyl](methyl)amino]carbonyl}pyridin-3-yl)-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- 30 • ethyl 4-(6-{6-[(4-methylpiperazin-1-yl)carbonyl]pyridin-3-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- isopropyl 4-(6-{6-[(4-methylpiperazin-1-yl)carbonyl]pyridin-3-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;
- ethyl 4-(6-{5-[(4-methylpiperazin-1-yl)carbonyl]pyridin-2-yl}-4*H*-1,3-benzodioxin-2-yl)piperidine-1-carboxylate;

- 1-({5-[2-(1-benzoylpiperidin-4-yl)-4H-1,3-benzodioxin-6-yl]pyridin-2-yl}-carbonyl)-4-methylpiperazine;
- 1-[(5-{2-[1-(2-ethylbutanoyl)piperidin-4-yl]-4H-1,3-benzodioxin-6-yl}pyridin-2-yl)carbonyl]-4-methylpiperazine;
- 5 • 2-[4-(6-{5-[(4-methylpiperazin-1-yl)carbonyl]pyridin-2-yl}-4H-1,3-benzodioxin-2-yl)piperidin-1-yl]pyrimidine;
- *tert*-butyl 4-{7-[4-(methylsulfonyl)phenyl]-3,4-dihydro-2H-1,4-benzoxazin-3-yl}-piperidine-1-carboxylate;
- 10 • 3-[1-(cyclohexylacetyl)piperidin-4-yl]-7-[4-(methylsulfonyl)phenyl]-3,4-dihydro-2H-1,4-benzoxazine; and
- 3-(1-benzoylpiperidin-4-yl)-7-[4-(methylsulfonyl)phenyl]-3,4-dihydro-2H-1,4-benzoxazine.

6. A compound according to any one of claims 1 to 5 for use in therapy.

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7. A compound according to any one of claims 1 to 5 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, 20 hypercholesterolemia, dyslipidemia, syndrome X, obesity, hypertension, chronic systemic inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, reduced fibrinolysis, endothelial dysfunction and osteoporosis.

25 8. Use of a compound according to any one of claims 1 to 5 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, 30 reduced fibrinolysis, endothelial dysfunction and osteoporosis.

9. 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 5, 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.

10. A pharmaceutical formulation containing a compound according to any one of claims 1 to 5 as active ingredient in combination with a pharmaceutically acceptable diluent or carrier.

15. The pharmaceutical formulation according to claim 10 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.

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25. Use of a compound according to any one of claims 1 to 5, 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.

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13. 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 5 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.

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14. The pharmaceutical formulation according to claim 10 which in addition comprises a DPP-IV inhibitor.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2009/057074

A. CLASSIFICATION OF SUBJECT MATTER

INV.	A61K31/453	A61K31/454	A61K31/4545	A61K31/496	A61K31/497
	A61K31/5377	A61K31/538	C07D405/04	C07D405/14	C07D413/04
	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 A61K A61P

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, BIOSIS, EMBASE, 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.
A	WO 2006/067532 A (PROSIDION LTD [GB]; FYFE MATTHEW COLIN THOR [GB]; THOMAS GERARD HUGH []) 29 June 2006 (2006-06-29) cited in the application the whole document -----	1-14
A	WO 2008/008895 A (SMITHKLINE BEECHAM CORP [US]; AMMALA CARINA [US]; BRISCOE CELIA [US]) 17 January 2008 (2008-01-17) the whole document -----	1-14

Further documents are listed in the continuation of Box C.

See patent family annex

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

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

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

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

& document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 August 2009	02/09/2009
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Lécaillon, Jennifer

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2009/057074

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006067532 A	29-06-2006	EP 1838706 A1 JP 2008525417 T US 2009099227 A1	03-10-2007 17-07-2008 16-04-2009
WO 2008008895 A	17-01-2008	EP 2043744 A2 WO 2008008887 A2	08-04-2009 17-01-2008