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References cited:
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Remarks:
The file contains technical information submitted after the application was filed and not included in this specification.

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FIELD OF THE INVENTION

Description

[0001] The present invention relates to novel phenoxy-acetic acids, pharmaceuticals comprising the same, and methods of using the same. The phenoxy-acetic acids are activators of peroxisome proliferator-activated receptors (PPAR-δ).

BACKGROUND OF THE INVENTION

[0002] Coronary artery disease (CAD) is the major cause of death in Type 2 diabetic and metabolic syndrome patients (i.e., patients that fall within the ‘deadly quartet’ category of impaired glucose tolerance, insulin resistance, hypertriglyceridemia and/or obesity).

[0003] The hypolipidaemic fibrates and antidiabetic thiazolidinediones separately display moderately effective triglyceride-lowering activities, although they are neither potent nor efficacious enough to be a single therapy of choice for the dyslipidaemia often observed in Type 2 diabetic or metabolic syndrome patients. The thiazolidinediones also potently lower circulating glucose levels of Type 2 diabetic animal models and humans. However, the fibrate class of compounds are without beneficial effects on glycaemia. Studies on the molecular actions of these compounds indicate that thiazolidinediones and fibrates exert their action by activating distinct transcription factors of the peroxisome proliferator activated receptor (PPAR) family, resulting in increased and decreased expression of specific enzymes and apolipoproteins respectively, both key-players in regulation of plasma triglyceride content.

[0004] PPAR-δ activation was initially reported not to be involved in modulation of glucose or triglyceride levels. (Berger et al., J. Biol. Chem. 1999, 274, 6718-6725). Later it was shown that PPAR-δ activation leads to increased levels of HDL cholesterol in db/db mice (Leibowitz et al., FEBS letters 2000, 473, 333-336). Further, a PPAR-δ agonist when dosed to insulin-resistant middle-aged obese rhesus monkeys caused a dramatic dose-dependent rise in serum HDL cholesterol while lowering the levels of small dense LDL, fasting triglycerides and fasting insulin (Oliver et al., PNAS 2001, 98, 5306-5311). The same paper also reported that PPAR-δ activation increased the reverse cholesterol transporter ATP-binding cassette A1 and induced apolipoprotein A1-specific cholesterol efflux. The involvement of PPAR-δ in fatty acid oxidation in muscles was further substantiated in PPAR-α knock-out mice. Muoio et al. (J. Biol. Chem. 2002, 277, 26089-26097) showed that the high levels of PPAR-δ in skeletal muscle can compensate for deficiency in PPAR-α. In addition to the effects on cholesterol homeostasis, PPARδ treatment was observed to lower plasma glucose and insulin and improve insulin sensitivity in diabetic ob/ob and db/db mice and high fat diet induced insulin resistant mice (PNAS 2003, 100, 15924-15929; PNAS 2006, 103, 3444-3449). Taken together these observations suggest that PPAR-δ activation is useful in the treatment and prevention of Type 2 diabetes, cardiovascular diseases and conditions including atherosclerosis, hypertriglyceridemia, and mixed dyslipidemia (WO 01/00603).


[0006] Glucose lowering as a single approach does not overcome the macrovascular complications associated with Type 2 diabetes and metabolic syndrome. Novel treatments of Type 2 diabetes and metabolic syndrome must therefore aim at lowering both the overt hypertriglyceridaemia associated with these syndromes as well as alleviation of hyperglycaemia. This indicates that research for compounds displaying various degree of PPAR-δ activation should lead to the discovery of efficacious triglyceride and/or cholesterol and/or glucose lowering drugs that have great potential in the treatment of diseases such as type 2 diabetes, dyslipidemia, syndrome X (including the metabolic syndrome, i.e., impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity), cardiovascular diseases (including atherosclerosis) and hypercholesteremia.

SUMMARY OF THE INVENTION

[0007] In an aspect, the present invention provides novel phenoxy-acetic acids or pharmaceutically acceptable salts thereof that are useful as PPAR-δ activators.

[0008] In another aspect, the present invention provides novel pharmaceutical compositions comprising a pharma-
ceuatically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt thereof.

[0009] In another aspect, the present invention provides the compounds of the invention for use in a novel method of treating type 2 diabetes comprising administering to a patient in need thereof a therapeutically effective amount of at least one compound of the present invention or a pharmaceutically acceptable salt thereof.

[0010] In another aspect, the present invention provides the compounds of the invention for use in a novel method of treating a disease comprising administering to a patient in need thereof a therapeutically effective amount of at least one compound of the present invention or a pharmaceutically acceptable salt thereof, wherein the disease is selected from dyslipidemia, syndrome X (including the metabolic syndrome, e.g., hypertension, impaired glucose tolerance (IGT), insulin resistance, hypertriglyceridaemia, and obesity), cardiovascular diseases (e.g., atherosclerosis, coronary artery disease, and myocardial ischemia), hyperglycemia, hyperlipidemia, and hypercholesterolemia.

[0011] In another aspect, the present invention provides the compounds of the invention for use in a novel method of treating a disease comprising administering to a patient in need thereof a therapeutically effective amount of at least one compound of the present invention or a pharmaceutically acceptable salt thereof, wherein the disease is selected from dyslipidemia, syndrome X (including the metabolic syndrome, e.g., hypertension, impaired glucose tolerance (IGT), insulin resistance, hypertriglyceridaemia, and obesity), cardiovascular diseases (e.g., atherosclerosis, coronary artery disease, and myocardial ischemia), hyperglycemia, hyperlipidemia, and hypercholesterolemia.

[0012] In another aspect, the present invention provides novel compounds for use in therapy.

[0013] In another aspect, the present invention provides the use of novel compounds for the manufacture of a medicament for the treatment of type 2 diabetes.

[0014] These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors’ discovery that compounds of formula I:

\[
\text{IIb}
\]

[0015] or pharmaceutically acceptable salts thereof, are PPAR-δ activators.

DESCRIPTION OF THE INVENTION

[0016] The present invention provides a novel compound of formula IIb

\[
\text{IIb}
\]

or a pharmaceutically acceptable salt thereof, wherein

\[
X = \text{SCH}_2; \\
X^1 = \text{O or S};
\]
R¹ is H, C₁₋₈ alkyl, heteroaryl, or C₃₋₁₀ cycloalkyl, wherein each R¹ group is substituted with 0-4 R¹a;

R¹a, at each occurrence, is selected from C₁₋₆ alkyl substituted with 0-3 R¹b; C₂₋₆ alkenyl substituted with 0-2 R¹b; aryl substituted with 0-2 R¹b; heteroaryl substituted with 0-2 R¹b, C₃₋₁₀ cycloalkyl substituted with 0-2 R¹b; and a heterocycle substituted with 0-2 R¹b;

R¹b, at each occurrence, is selected from OH substituted with 0-1 R¹c; SH substituted with 0-1 R¹c; Cl, F, NH₂ substituted with 0-3 R¹c, -CN, NO₂, methanesulfonyl, C₃₋₄ alkyl substituted with 0-3 R¹c, C₂₋₄ alkenyl substituted with 0-2 R¹c, aryl substituted with 0-2 R¹c, heteroaryl substituted with 0-2 R¹c, C₃₋₆ cycloalkyl substituted with 0-2 R¹c, and a heterocycle substituted with 0-2 R¹c;

R¹c, at each occurrence, is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₃₋₄ alkyl, and C₂₋₄ alkenyl, aryl substituted with 0-2 R¹d, heteroaryl substituted with 0-2 R¹d, C₃₋₆ cycloalkyl substituted with 0-2 R¹d, and a heterocycle substituted with 0-2 R¹d;

R¹d, at each occurrence, is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₃₋₄ alkyl, and C₂₋₄ alkenyl;

R²a is selected from C₁₋₉ alkyl substituted with 0-2 R²b; aryl substituted with 0-2 R²b; and heteroaryl substituted with 0-2 R²b;

R²b, at each occurrence, is selected from OH substituted with 0-1 R²c; SH substituted with 0-1 R²c; Cl, F, NH₂ substituted with 0-2 R²c, -CN, NO₂, methanesulfonyl, C₃₋₄ alkyl substituted with 0-2 R²c, C₂₋₄ alkenyl substituted with 0-2 R²c, aryl substituted with 0-2 R²c, heteroaryl substituted with 0-2 R²c, C₃₋₆ cycloalkyl substituted with 0-2 R²c, and a heterocycle substituted with 0-2 R²c;

R²c, at each occurrence, is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₃₋₄ alkyl, and C₂₋₄ alkenyl, aryl substituted with 0-2 R²d; and heteroaryl substituted with 0-2 R²d;

R²d, at each occurrence, is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₃₋₄ alkyl, and C₂₋₄ alkenyl; and

R³ is selected from Cl, F, CH₃, and CH₂CH₃.

[0017] In another embodiment, the present invention provides a novel compound of formula IIb, wherein R¹ is C₁₋₆ alkyl substituted with a heterocycle.

[0018] In another embodiment, the present invention provides a novel compound of formula IIb, wherein R²a is C₁₋₄ alkyl substituted with morpholinyl.

[0019] In another embodiment, the present invention provides a novel compound of formula IIb, wherein R²a is C₁₋₄ alkyl substituted with a heterocycle.

[0020] In another embodiment, the present invention provides a novel compound of formula IIb, wherein R³ is selected from C₁₋₄ alkyl substitutted with a heterocycle.

[0021] In another embodiment, the present invention provides a novel compound of formula IIb, wherein X¹ is O.

[0022] In another embodiment, the present invention provides a novel compound of formula IIb, wherein X¹ is S.

[0023] In another embodiment, the present invention provides a novel compound of formula IIb, wherein R¹ is C₁₋₆ alkyl substituted with R¹b, and wherein R¹b is aryl substituted with 0-1 R¹d; and wherein R¹d is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl.

[0024] In another embodiment, the present invention provides a novel compound of formula IIb, wherein: R¹ is C₁₋₆ alkyl substituted with R¹a, wherein R¹a is heteroaryl substituted with 0-1 R¹b; and wherein R¹b is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl.

[0025] In another embodiment, the present invention provides a novel compound of formula IIb, wherein: R¹ is C₁₋₆ alkyl substituted with R¹a, wherein R¹a is heterocyclyl substituted with 0-1 R¹b; and wherein R¹b is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl.

[0026] In another embodiment, the present invention provides a novel compound of formula IIb, wherein: R¹ is C₁₋₆ alkyl substituted with R¹a, wherein R¹a is C₅₋₆ cycloalkyl substituted with 0-2 R¹b; and wherein R¹b is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl.

[0027] In another embodiment, the present invention provides a novel compound of formula IIb, wherein: R²a is aryl substituted with R²b; wherein R²b is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl.

[0028] In another embodiment, the present invention provides a novel compound of formula IIb, wherein: R²a is C₁₋₆ alkyl substituted with R²b; wherein R²b is selected from aryl substituted with R²c; and wherein R²c is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl.
In another embodiment, the present invention provides a novel compound of formula IIb, wherein: R²a is C₁₋₆ alkyl substituted with R²b; wherein R²b is selected from heteroaryl substituted with R²c; and wherein R²c is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl.

In another embodiment, the present invention provides a novel compound selected from:

- {4-[3-Cyclohexylmethoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy}-acetic acid;
- [0037]
- [0036]
- or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a novel compound of formula IIb, wherein: R²a is C₁₋₆ alkyl substituted with R²b; wherein R²b is selected from heteroaryl substituted with R²c; and wherein R²c is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl.

In another embodiment, the present invention provides a novel compound of formula IIb, wherein: R²a is C₁₋₆ alkyl substituted with R²b; wherein R²b is selected from heteroaryl substituted with R²c; and wherein R²c is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl.

In another embodiment, the present invention provides a novel compound of formula IIb, wherein: R²a is C₁₋₆ alkyl substituted with R²b; wherein R²b is selected from heteroaryl substituted with R²c; and wherein R²c is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl.

In another embodiment, the present invention provides a novel compound of formula IIb, wherein: R²a is C₁₋₆ alkyl substituted with R²b; wherein R²b is selected from heteroaryl substituted with R²c; and wherein R²c is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl.

In another embodiment, the present invention provides a novel compound pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a compound of the present invention or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a novel compound of formula IIb, wherein: R²a is C₁₋₆ alkyl substituted with R²b; wherein R²b is selected from heteroaryl substituted with R²c; and wherein R²c is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl.

In another embodiment, the present invention provides a novel compound of formula IIb, wherein: R²a is C₁₋₆ alkyl substituted with R²b; wherein R²b is selected from heteroaryl substituted with R²c; and wherein R²c is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl.

In another embodiment, the present invention provides a novel compound of formula IIb, wherein: R²a is C₁₋₆ alkyl substituted with R²b; wherein R²b is selected from heteroaryl substituted with R²c; and wherein R²c is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl.

Suitable antiobesity agents include leptin, dexamphetamine, amphetamine, fenfluramine, dexfenfluramine, sibutramine, orlistat, mazindol, and phentermine.

Suitable antidiabetics include insulin, orally active hypoglycaemic agents, and GLP-1 (glucagon like peptide-1) derivatives (see WO 98/08871).
It is preferred that the compounds of the present invention are zwitter-ionic with one ionized amine group and one ionized carboxylic acid group at pH 7.4. More preferably the compounds are zwitter-ionic with one ionized amine group and one ionized carboxylic acid group at a pH of from 6.5-7.5. Still more preferably, the compounds are zwitter-ionic with one ionized amine group and one ionized carboxylic acid group at a pH of from 5.5-9. More preferably the compounds are zwitter-ionic with one ionized amine group and one ionized carboxylic acid group at pH 7.4.

PHARMACEUTICAL COMPOSITIONS

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions of the present invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995. The compositions may appear in conventional forms, which include capsules, tablets, aerosols, solutions, suspensions, and topical applications.

Typical compositions include a compound of the present invention a pharmaceutically acceptable acid addition forms, which include capsules, tablets, aerosols, solutions, suspensions, and topical applications.
The present invention is related to the delivery of a therapeutically active compound to a patient by employing procedures well known in the art. The active compound can be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient. The carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

If desired, the pharmaceutical composition of the invention may comprise a compound of the present invention in combination with further pharmacologically active substances such as those described in the foregoing.

The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of diseases related to the regulation of blood sugar. Mammals also include animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

The compounds of the present invention are expected to be effective over a wide dosage range. A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain of from 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

DEFINITIONS

All references described herein are incorporated in there entirety by reference.

"Substituted" signifies that one or more hydrogen atoms are replaced by the designated substituent. Only pharmaceutically stable compounds are intended to be covered.

When examples of definitions are provided, the definition is not meant to be limited to the specific examples.

The present invention includes all isotopes of atoms occurring in the present compounds. Isotopes include...
those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

When O or S is listed as a substituent, o xo and su loufo, respectively, it is intended that a carbon atom be replaced by either the O or S. For example if alkyl were substituted by O, then an ether would be formed. Preferably heteroatom-heteroatom bonds such as O-O, O-S, O-N, S-S, and S-N are not formed.

"Alkyl" includes both straight chain and branched alkyl groups having the designated number of carbon atoms (e.g., 1, 2, 3, 4, 5, 6, 7, or 8). Examples of alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, 2-methyl-butyl, and 2-ethyl-butyl.

"Alkenyl" includes both straight chain and branched alkenyl groups having the designated number of carbon atoms (e.g., 2, 3, 4, 5, 6, 7, or 8). Examples of alkenyl groups include ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, and 2-methyl-butenyl.

"Alkynyl" includes both straight chain and branched alkynyl groups having the designated number of carbon atoms (e.g., 2, 3, 4, 5, 6, 7, or 8). Examples of alkynyl groups include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, and 2-methyl-butynyl.

"Aryl" includes phenyl, naphthyl, fluorene, anthracene, phenanthrenyl, azulenyl, and a partially saturated bicyclic carbocyclic ring. The partially saturated bicyclic carbocyclic ring consists of 8, 9, 10, 11, or 12 carbon atoms, preferably 8 or 9, or 10 carbon atoms. Examples of partially saturated bicyclic carbocyclic rings include 1,2,3,4-tetrahydronaphthyl, indanyl, indenyl, 1,2,4,5,6,8,9-hexahydrodiphenyl, and 1,3-dihydroptalene. A preferred aryl group is phenyl.

"Cycloalkyl" means a ring having the number of designated carbon atoms and having only single bonds between the carbon atoms. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. Preferred cycloalkyl groups are cyclopentyl and cyclohexyl.

"Heteroaryl" signifies a mono-, bi-, or tricyclic ring consisting of carbon atoms and from one heteroatom to 5, wherein the heteroatom is selected from oxygen, nitrogen, and sulphur. If sulphur is present, then it can be mono- or di-oxidized. If a nitrogen is present, then it can be N, N, or substituted N. The heterocycle can be attached via a carbon or nitrogen atom, unless linking the nitrogen atom would lead to a quaternary nitrogen. If the heteroaryl is bicyclic, then one or both of the rings may have a heteroatom(s) present. If the heteroaryl is tricyclic, then one, two, or all three of the rings may have a heteroatom(s) present. If the heterocycle is monocyclic, then this ring is aromatic (e.g., fully unsaturated). If the heteroaryl is bicyclic or tricyclic, then at least one ring is aromatic.

Examples of "heteroaryl" are pyrrolyl (e.g. pyrrol-1-yl, pyrrol-2-yl, pyrrol-3-yl), furanyl (e.g. furan-2-yl, furan-3-yl), thiienyl (e.g. thien-2-yl, thien-3-yl), oxazolyl (e.g. oxazol-2-yl, oxazol-4-yl, oxazol-5-yl), thiazolyl (e.g. thiazol-2-yl, thiazol-4-yl, thiazol-5-yl), imidazolyl (e.g. imidazol-2-yl, imidazol-4-yl, imidazol-5-yl), pyrazolyl (e.g. pyrazol-1-yl, pyrazol-3-yl, pyrazol-5-yl), isoxazolyl (e.g. isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl), isothiazolyl (e.g. isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl), 1,3,4-oxadiazolyl (e.g. 1,3,4-oxadiazol-2-yl, 1,3,4-oxadiazol-5-yl), 1,2,4-oxadiazolyl (e.g. 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl), 1,3,4-oxadiazolyl (e.g. 1,3,4-oxadiazol-2-yl, 1,3,4-oxadiazol-5-yl), 1,2,4-thiadiazolyl (e.g. 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl), 1,3,4-thiadiazolyl (e.g. 1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol-5-yl), 1,2,4-triazolyl (e.g. 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl), 1,2,3-triazolyl (e.g. 1,2,3-triazol-1-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl), 1,2,4-triazolyl (e.g. 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl), 1,2,3-oxadiazolyl (e.g. 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl), 1,2,4-oxadiazolyl (e.g. 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl), 1,2,4-thiadiazolyl (e.g. 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl), 1,2,3-thiadiazolyl (e.g. 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl), 1,2,4-thiadiazolyl (e.g. 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl), 1,2,3-thiadiazolyl (e.g. 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl), 1,2,4-thiadiazolyl (e.g. 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl), 1,2,3-thiadiazolyl (e.g. 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl), 1,2,4-thiadiazolyl (e.g. 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl), 1,2,3-thiadiazolyl (e.g. 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl).

If the heteroaryl is bicyclic or tricyclic, then at least one ring is aromatic.
zolopyrimidinyl (e.g. 8-azapurinyl), carbazolyl (e.g. carbazol-2-yl, carbazol-3-yl, carbazol-9-yl), phenoxazinyl (e.g. phenoxazin-10-yl), phenazinyl (e.g. phenazin-5-yl), acridinyl (e.g. acridin-9-yl, acridin-10-yl), phenothiazinyl (e.g. phenothiazin-10-yl), carbolyl (e.g. pyrido[3,4-b]indol-1-yl, pyrido[3,4-b]indol-3-yl), phenanthroline (e.g. phenanthrolin-5-yl), pyrrolyl, pyrazolinyl, imidazolinyl (e.g. 4,5-dihydroimidazol-2-yl, 4,5-dihydroimidazol-1-yl), indolinyl (e.g. 2,3-dihydroindol-1-yl, 2,3-dihydroindol-5-yl), dihydrobenzo[5,6]pyran-2-yl, 2,3-dihydrobenzo[b]furan-4-yl, dihydrobenzothienyl (e.g. 2,3-dihydrobenzo[b]thien-2-yl, 2,3-dihydrobenzo[b]thien-5-yl), 4,6,7-tetrahydrobenzo[b]furan-5-yl), dihydrobenzopyran (e.g. 3,4-dihydrobenzo[b]pyran-3-yl, 3,4-dihydrobenzo[b]pyran-6-yl, 3,4-dihydrobenzo[c]pyran-1-yl, dihydrobenzo[c]pyran-7-yl), oxazolinyl (e.g. 4,5-dihydrooxazol-2-yl, 4,5-dihydrooxazol-4-yl, 4,5-dihydrooxazol-5-yl), isoxazolinyl, oxazepinyl, tetrahydroimidazolyl (e.g. 4,5,6,7-tetrahydroimidazol-1-yl, 4,5,6,7-tetrahydroimidazol-3-yl, 4,5,6,7-tetrahydroimidazol-4-yl, 4,5,6,7-tetrahydroimidazol-6-yl), tetrahydrobenzimidazolyl (e.g. 4,5,6,7-tetrahydrobenzimidazol-1-yl, 4,5,6,7-tetrahydrobenzimidazol-5-yl), tetrahydroimidazol[4,5-c]pyridyl (e.g. 4,5,6,7-tetrahydroimidazol[4,5-c]pyrid-1-yl, 4,5,6,7-tetrahydroimidazol[4,5-c]pyrid-5-yl, 4,5,6,7-tetrahydroimidazol[4,5-c]pyrid-6-yl), tetrahydroquinolinyl (e.g. 1,2,3,4-tetrahydroquinolinyl, 5,6,7-tetrahydroquinolinyl), tetrahydroisoquinolinyl (e.g. 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, spiro[isoquinoline-3,1'-cyclohexan]-1-yl, spiro[piperidine-4,1'-benzo[c]thiophen]-1-yl, spiro[piperidine-4,1'-coumarin]-1-yl. A preferred heteroaryl is pyridinyl.

Other examples of "heteroaryl" are furyl, thienyl, pyrrollyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyrimidinyl, pyridazinyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, quinolinyl, quinoxalinyl, isoquinolinyl, indolyl, benzimidazolyl, benzothienyl, pteridinyl and purinyl.

"Heterocyclc" or "heterocycle" (heterocycle) signifies a mono-, bi-, or tricyclic ring consisting of carbon atoms and from one heteroatom to 4, wherein the heteroatom is selected from oxygen, nitrogen, and sulphur. If sulphur is present, then it can be S, S(O), or S(O)2. If nitrogen is present, then it can be N, NH, substituted N, or N-oxide. The heterocycle is a saturated or partially saturated ring. From 0-2 CH2 groups of the heterocycle can be replaced by C(O).

The heterocycle can be attached via a carbon or nitrogen atom, unless linking the nitrogen atom would lead to a quaternary nitrogen. If the heterocycle is bicyclic, then one or both of the rings may have a heteroatom(s) present. If the heterocycle is tricyclic, then one, two, or all three of the rings may have a heteroatom(s) present.

Examples of "heteroaryl" are aziridinyl (e.g. aziridin-1-yl), azetidinyl (e.g. azetidin-1-yl, azetidin-3-yl), oxetanyl, pyrrolidinyl (e.g. pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl), imidazolidinyl (e.g. imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-4-yl), oxazolidinyl (e.g. oxazolidin-2-yl, oxazolidin-3-yl, oxazolidin-4-yl), thiazolidinyl (e.g. thiazolidin-2-yl, thiazolidin-3-yl, thiazolidin-4-yl), isothiazolidinyl, piperidinyl (e.g. piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl), homopiperidinyl (e.g. homopiperidin-1-yl, homopiperidin-2-yl, homopiperidin-3-yl, homopiperidin-4-yl), piperazinyl (e.g. piperazin-1-yl, piperazin-2-yl), morpholinyl (e.g. morpholin-2-yl, morpholin-3-yl, morpholin-4-yl), thiomorpholinyl (e.g. thiomorpholin-2-yl, thiomorpholin-3-yl, thiomorpholin-4-yl), 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, tetrahydrofuranyl (e.g. tetrahydrofurany1-2-yl, tetrahydrofuranyl-3-yl), tetrahydrothiophenyl, tetrahydro-1,1-dioxothiophenyl, tetrahydropranyl (e.g. 2-tetrahydropranyl), tetrahydrothiophanyl (e.g. 2-tetrahydrothiophanyl), 1,4-dioxany1, 1,3-dioxany1, octahydroindolyl (e.g. octahydroindol-1-yl, octahydroindol-2-yl, octahydroindol-3-yl, octahydroindol-5-yl), decachydroquinolinyl (e.g. decachydroquinolin-1-yl, decachydroquinolin-2-yl, decachydroquinolin-3-yl, decachydroquinolin-4-yl, decachydroquinolin-6-yl), decahydroquinoxalinyl (e.g. decahydroquinoxalin-1-yl, decahydroquinoxalin-2-yl, decahydroquinoxalin-6-yl), 3-azabicyclo[3.3.2]nonyl, 2-azabicyclo[2.2.1]heptyl, 3-azabicyclo[3.1.0]hexyl, 2,5-diazabicyclo[2.2.1]heptyl, tropanyl, tropinyl, quinolinidinyl, 1,4-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[4.5]decany1 (e.g. 1,4-diazabicyclo[4.5]decan-2-yl, 1,4-diazabicyclo[4.5]decan-7-yl), 1,4-dioxa-8-azaspiro[4.5]decany1 (e.g. 1,4-dioxa-8-azaspiro[4.5]decan-2-yl, 1,4-dioxa-8-azaspiro[4.5]decan-8-yl), 8-azaspiro[4.5]decany1 (e.g. 8-azaspiro[4.5]decan-1-yl, 8-azaspiro[4.5]decan-2-yl, 2-azaspiro[5.5]undecany1 (e.g. 2-azaspiro[5.5]undecan-2-yl), 2,8-diaza-spiro[4.5]decany1 (e.g. 2,8-diaza-spiro[4.5]decan-2-yl, 2,8-diaza-spiro[4.5]decan-8-yl), 1,3,8-triaza-spiro[4.5]decany1 (e.g. 1,3,8-triaza-spiro[4.5]decan-1-yl, 1,3,8-triaza-spiro[4.5]decan-3-yl, and 1,3,8-triaza-spiro[4.5]decan-8-yl).

Preferred examples of "heterocycle" are pyrrolidinyl, pyrrolinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, imidazolidinyl, imidazolinyl, pyrazolinyl, pyrazolinyl, oxazolinyl, oxazolinyl, isoxazolidinyl, isoxazolinyl, thioxazolinyl, thioxazolinyl, isothiazolidinyl, isothiazolidinyl, triazolinyl, triazolinyl, tetrazolinyl, tetrazolinyl, dihydropyranyl, dihydropyranyl, pyran, pyridinyl, piperazinyl, homopiperazinyl, morpholinyl. Preferred heterocycle groups are piperidinyl and morpholinyl.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination to activate glucokinase.

"Treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, e.g., arresting or slowing its development; and/or (c) relieving the disease-state, e.g., causing regression of the disease state itself or some
symptom of the disease state.

[0094] Pharmaceutically acceptable include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable base addition salts, pharmaceutically acceptable metal salts, ammonium salts, and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, and nitric acids. Representative examples of suitable organic acids include formic, acetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, bromoacetic, bisulfonic, salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluene sulfonic acids, sulphates, nitrates, phosphates, perchlorates, borates, acetates, benzoates, hydroxynaphthoates, glycerophosphates, and ketoglutarates. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium, zinc, and calcium salts. Examples of amines and organic amines include ammonium, methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, propylamine, butylamine, tetramethylamine, ethanoldamine, diethanolamine, triethanolamine, meglumine, ethylenediamine, choline, N,N-dibenzylethylenediamine, N-benzylpipediethylamine, N-methyl-D-glucamine, and guanidine. Examples of cationic amino acids include lysine, arginine, and histidine.

[0095] The pharmaceutically acceptable salts are prepared by reacting the compound of formula I with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, and magnesium hydroxide, in solvents such as ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases such as llysine, arginine, diethanolamine, choline, guanidine and their derivatives etc. may also be used. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluene sulfonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, and tartaric acid in solvents such as ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.

[0096] The stereoisomers of the compounds forming part of this invention may be prepared by using reagents in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, enzymatic resolution, resolving the diastereomic salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, and lactic acid wherever applicable or chiral bases such as brucine, (R)- or (S)-phenylethylamine, cinchona alkaloids and their derivatives. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically a compound of the present invention may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, amino acid, amino acid derived from amino acid; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula I may be prepared by hydrolysing the pure diastereomeric amide.

[0097] The invention also encompasses produgs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of the present compounds, which are readily convertible in vivo into a compound of the present invention. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

[0098] This invention will be better understood from the following examples, which are for purposes of illustration and are not intended to limit the invention defined in the claims which follow thereafter.

EXAMPLES

[0099] All reactions involving air-sensitive reagents were performed under nitrogen using syringe-septum cap techniques. The glassware was dried by heating with a heat-gun. MgSO₄ was used to dry solutions. Solvents were removed in vacuo by rotary evaporation. Melting points were recorded on a Büchi 535. Bruker AMX 400 and Bruker DRX 300 instruments were used to record ¹H NMR spectra at 400 and 300 MHz, respectively, with tetramethylsilane (TMS) as internal standard. Coupling constants (J) are given in Hz.

Materials

[0100] Test compounds were synthesized or when commercially available they were purchased from Aldrich, Specs, Maybridge, or Bionet. For the synthesized compounds, the procedure for synthesis and measured characteristics of the compound are stated in the example. All compounds for which no synthesis procedure is stated in the examples are
commercially available and have been purchased or were prepared by standard methods described in the literature.

A general procedure may be as follows (wherein R₅a-c and R₄a-c represent H):

Scheme 1:
The synthetic intermediate of formula I with R1 = H, R2 = Br and a carboxylic ester group e.g. [4-(3-Bromo-5-hydroxy-phenylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl acetate can be converted via a classical Mitsunobu reaction or a reaction can be performed between the phenol and an alkyl halides (or an alkyl mesylate, triflate, tosylate or alike)
to a new intermediate of formula I where X1-R1 forms a ether or thioether group and R = Br. The new intermediate can be converted via a classical Sonogashira, Heck or Suzuki coupling protocol to a new intermediate where R2 is \(-C=CR^2\). It is also possible to perform the reaction in the opposite way by first performing the Sonogashira, Heck or Suzuki coupling followed by the ether forming reaction as described above. The claimed compounds can also be performed by condensing e.g. 1,3-dibromo-5-cyclopropylmethoxy-benzene or another substituted dibromophenyle ether with (4-Mercapto-2-methyl-phenoxy)-acetic acid ethyl ester or another substituted mercaptobenzene. The intermediates formed can be converted to the claimed compounds by a classical ester hydrolyses reaction from the respective esters of I (scheme 1-3).

General procedure (A)

HPLC systems

HPLC method A

[0103] The RP-purification was performed on a Gilson system (4 Gilson 306 pumps, Gilson 155 detector, Gilson reodyne manual injection, Gilson 811C mixer and a Gilson 202 fraction collector) using a Phenomenex RP synergi-MAX column (3 \(\mu\)m, 30 mm x 250 mm) with gradient elution, 5 % to 100 % solvent B (acetonitrile) in solvent A (water) within 40 min, 60 mL/min, detection at 210 nm, room temperature. The pooled fractions were either evaporated to dryness in vacuo, or evaporated in vacuo until the MeCN is removed, and then frozen and freeze dried.

HPLC method B

[0104] The RP-purification was performed on a Gilson system (3 Gilson 306 pumps, Gilson 170 DAD detector and a Gilson 215 liquid-handler) using a Waters X-terra RP (10 \(\mu\)m, 30 mm x 150 mm) with gradient elution, 5% to 95% solvent B (0.05% TFA in acetonitrile) in solvent A (0.05% TFA in water) within 15 min, 40 mL/min, detection at 210 nm, room temperature. The pooled fractions were either evaporated to dryness in vacuo or evaporated in vacuo until the MeCN is removed and then frozen and freeze dried.

HPLC-MS (System 1)

[0105] The RP-analysis was performed on an Agilent HPLC system (1100 degasser, 1100 pump, 1100 injector and a 1100 DAD) fitted with an Agilent MS detector system Model VL (MW 0-1000) and a S.E.D.E.RE Model Sedex 55 ELS detector system using a Waters X-terra MS C18 column (5 \(\mu\)m, 3.0 mm x 50 mm) with gradient elution, 5% to 95% solvent B (0.05% TFA in acetonitrile) in solvent A (0.05% TFA in water) within 3 min, 2.7 mL/min.

[0106] Thin layer chromatography was performed on Merck DC-Alufolien, silica gel 60 F_{254} and components were visualized by UV_{254}. Flash chromatography was performed using silica gel Merck 60 size 0.04-0.063 mm and a Quad 12/25 flash system.

[0107] 3,5-dibromophenol was prepared as described by Yang, et al., Synth Commun; 2003, 33, 19, 3317-3326.

Intermediates

[4-(3-Bromo-5-hydroxy-benzylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester

[0108]
Step A: tert-Butyl-(3,5-dibromo-phenoxy)-dimethyl-silane

[0109]

3,5-Dibromophenol (59.6 mmol; 15 g) and imidazole (65.5 mmol; 4.5 g) were dissolved in dichloromethane (150 mL) and tert-butyl-dimethylsilylchloride (65.5 mmol; 9.9 g) was added. The reaction mixture was stirred at room temperature for 16 hours, diluted with diethyl ether, and filtered. The organic solution was washed with saturated ammonium chloride, saturated sodium hydrogen carbonate, and water and dried and evaporated to dryness. Yield: 22 g. HPLC-MS: m/z: 366.9 (M+); Rt: 3.09 min.

Step B: 3-Bromo-5-(tert-butyl-dimethyl-silyloxy)-benzaldehyde

[0111]

tert-Butyl-(3,5-dibromo-phenoxy)-dimethyl-silane (22 g; 60.08 mmol) was dissolved in THF (200 mL) in a dried reaction flask under an atmosphere of nitrogen. The mixture was cooled to -78°C and n-BuLi (1.6 N in hexane; 41.25 mL; 66.09 mmol) was added while the temperature was kept between -60 and -78°C. The mixture was stirred for 15 min. and DMF (4.83 g; 66.08 mmol) was added. The reaction mixture was stirred for 1 h and methanol (5 mL) followed by saturated ammonium chloride was added. Etyl acetate (200 mL) was added and the organic phase was separated from the aqueous phase. The organic phase was washed with water, dried, and evaporated to dryness. The crude product was purified by flash chromatography (heptane: dichloromethane (1:1). Yield 7 g. HPLC-MS: m/z: 317.0 (M+1); Rt: 2.7 min.

Step C: [3-Bromo-5-(tert-butyl-dimethyl-silyloxy)-phenyl]-methanol

[0113]

3-Bromo-5-(tert-butyl-dimethyl-silyloxy)-benzaldehyde (7 g, 22.2 mmol) was dissolved in THF and sodium borohydride (0.92 g; 24.4 mmol) waas added. The reaction mixture was stirred at room temperature for 2 h and water...
was added, and the reaction mixture was partly evaporated to strip off THF. Ethyl acetate was added and the phases separated. The organic phase was washed with water, dried, and evaporated to dryness. Yield: 6.4 g; HPLC-MS: m/z: 317.0 (M+); Rt: 2.37 min.

Step D: {4-[3-Bromo-5-((tert-butyl-dimethyl-silyloxy)-benzylsulfanyl]-2-methyl-phenoxy} -acetic acid ethyl ester

[0115]

[0116] [3-Bromo-5-((tert-butyl-dimethyl-silyloxy)-phenyl]-methanol (6.4 g; 20.17 mmol) and (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (5.02 g; 22.19 mmol) were dissolved in THF (200 mL). Tributylyphosphine (8.15 g; 40.34 mmol) and 1,1’-(azodicarbonyl)-dipiperidine (10.17 g; 40.34 mmol) were added, and the reaction mixture was stirred for 14 h at room temperature. Water and ethyl acetate were added to the reaction mixture. The phases were separated. The organic phase was washed with water, dried, and evaporated. The crude product was purified by flash chromatography (heptane: dichloromethane (1:1)). Yield: 8 g; 80%. HPLC-MS: m/z: 527.0 (M+1); Rt: 3.10 min.

Step E: [4-(3-Bromo-5-hydroxy-benzylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester

[0117]

[0118] [4-[3-Bromo-5-((tert-butyl-dimethyl-silyloxy)-benzylsulfanyl]-2-methyl-phenoxy]-acetic acid ethyl ester 7 g, 13.3 mmol] was dissolved in THF under an atmosphere of nitrogen. Tetrabutylammonium fluoride 1 N in THF (15 mL) was added, and the reaction mixture was stirred at 60°C for 2h. Saturated sodium carbonate and water were added together with ethyl acetate, and the organic phase was separated. The organic phase was washed with water, dried, and evaporated to dryness. Yield: 3.2 g. HPLC-MS: m/z: 435.4 (M+Na); Rt: 2.22 min.

{4-[3-Hydroxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy} -acetic acid ethyl ester

[0119]
[0120] [4-(3-Bromo-5-hydroxy-benzylsulfanyl)-2-methyl-phenoxyl]-acetic acid ethyl ester (2.3 g; 5.6 mmol), 4-prop-2-ynyl-morpholine (2.1 g; 16.8 mmol), bis(triphenylphosphine)-palladium (II) chloride (0.31 g; 0.45 mmol) and copper iodide (0.06 g; 0.34 mmol) were dissolved in a mixture of triethylamine (5 mL) and DMF (10 mL) under an atmosphere of nitrogen. The reaction mixture was reacted in a microwave oven at 100 °C for 1h. The reaction mixture was purified by preparative HPLC (method A). Yield: 0.9 g. HPLC- MS: m/z: 456.1 (M+); Rt: 1.53 min.

{4-[3-Hydroxy-5-(3-phenyl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxyl]-acetic acid ethyl ester

[0121]

[0122] [4-(3-Bromo-5-hydroxy-benzylsulfanyl)-2-methyl-phenoxyl]-acetic acid ethyl ester (2 g; 4.9 mmol), 3-phenyl-1-propyn (1.7 g; 14.6 mmol), bis(triphenylphosphine)palladium (II) chloride (0.27 g; 0.39 mmol) and copper iodide (0.056 g; 0.29 mmol) were dissolved in a mixture of triethylamine (5 mL) and DMF (10 mL) under an atmosphere of nitrogen. The reaction mixture was reacted in a microwave oven at 100 °C for 1h. Further 3-phenyl-1-propyn (1.7 g; 14.6 mmol) was added and the reaction mixture was reacted in a microwave oven at 100 °C for further 1h. The reaction mixture was purified by preparative HPLC (method A). Yield: 0.8 g. HPLC-MS: m/z: 434.6 (M+1); Rt: 2.43 min.

[4-(3-Bromo-5-cyclopropylmethoxy-benzylsulfanyl)-2-methyl-phenoxyl]-acetic acid ethyl ester

[0123]

[0124] [4-(3-Bromo-5-hydroxy-benzylsulfanyl)-2-methyl-phenoxyl]-acetic acid ethyl ester (1.0 g; 2.43 mmol), cyclopropylcarbinol (175 mg; 2.43 mmol) and tributylphosphine (1.07 mL; 4.38 mmol) was dissolved in THF (100 mL) in a dried reaction flask under an atmosphere of nitrogen. 1,1’-(Azodicarbonyl)dipiperidine (1.1 g; 4.38 mmol) dissolved in THF
(20 mL) was added to the reaction mixture, which was stirred at room temperature for 16 hours. The reaction mixture was filtered, evaporated to dryness and purified by flash chromatography (ethyl acetate: heptane 1:9 → 2:3). Yield: 980 mg; 86%; HPLC-MS: m/z: 465.0 (M+); Rt: 2.74 min.

Example 1

{2-Methyl-4-[3-(3-morpholin-4-yl-propoxy)-5-(3-phenyl-prop-1-ynyl)-benzyl-sulfanyl]-phenoxy}-acetic acid

Step A: {2-Methyl-4-[3-(3-morpholin-4-yl-propoxy)-5-(3-phenyl-prop-1-ynyl)-benzylsulfanyl]-phenoxy}-acetic acid ethyl ester

Step B: {2-Methyl-4-[3-(3-morpholin-4-yl-propoxy)-5-(3-phenyl-prop-1-ynyl)-benzylsulfanyl]-phenoxy}-acetic acid

Example 2

{4-[3-(4-Fluoro-benzyloxy)-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy} -acetic acid

Step A: {4-[3-Hydroxy-5-(3-phenyl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester

Step B: {2-Methyl-4-[3-(3-morpholin-4-yl-propoxy)-5-(3-phenyl-prop-1-ynyl)-benzylsulfanyl]-phenoxy}-acetic acid

Example 2
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Step A: {4-[3-(4-Fluoro-benzyloxy)-5-(3-morpholin-4-yl-prop-1-ynyl)-benzyl-sulfanyl]-2-methyl-phenoxy} -acetic acid ethyl ester

[0129] 4-[3-Hydroxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester (250 mg; 0.55 mmol), 1-fluoro-4-methoxymethyl-benzene (103.8 mg; 0.82 mmol), tributylphosphine (0.33 mg; 1.65 mmol) and 1,1’-(azodicarbonyl)-dipiperidine (0.414 g; 1.65 mmol) were dissolved in THF (15 mL) in a dried reaction flask under an atmosphere of nitrogen. The reaction mixture was stirred for 16h and purified by prep. HPLC (method A). Yield: 160 mg. HPLC-MS: m/z: 564.1 (M+H); Rt: 1.99 min.

Step B: {4-[3-(4-Fluoro-benzyloxy)-5-(3-morpholin-4-yl-prop-1-ynyl)-benzyl-sulfanyl]-2-methyl-phenoxy} -acetic acid

[0130] 4-[3-(4-Fluoro-benzyloxy)-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester (150 mg; 0.30 mmol) was dissolved in ethanol (20 mL), and aqueous 1 N sodium hydroxide (3 mL) was added. The reaction mixture was stirred for 1 h, acidified with 1 N aqueous hydrochloric acid, and extracted with ethyl acetate. The organic phase was dried and evaporated to dryness. Yield: 190 mg. HPLC-MS: m/z: 536.1 (M+); Rt: 1.76 min.

Example 3

(2-Methyl-4-[3-(3-morpholin-4-yl-ethoxy)-5-(3-phenyl-prop-1-ynyl)-benzyl-sulfanyl]-phenoxy} -acetic acid

[0131] Step A: {2-Methyl-4-[3-(3-morpholin-4-yl-ethoxy)-5-(3-phenyl-prop-1-ynyl)-benzylsulfanyl]-phenoxy}-acetic acid ethyl ester

[0132] 4-[3-Hydroxy-5-(3-phenyl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester (150 mg; 0.30 mmol) was dissolved in ethanol (20 mL), and aqueous 1 N sodium hydroxide (3 mL) was added. The reaction mixture was stirred for 2 h the reaction mixture was purified by prep. HPLC (method A). Yield: 50 mg. HPLC-MS: m/z: 560.2 (M+H); Rt: 2.03 min.

Step B: {2-Methyl-4-[3-(3-morpholin-4-yl-ethoxy)-5-(3-phenyl-prop-1-ynyl)-benzyl-sulfanyl]-phenoxy}-acetic acid

[0133] 2-Methyl-4-[3-(3-morpholin-4-yl-ethoxy)-5-(3-phenyl-prop-1-ynyl)-benzyl-sulfanyl]-phenoxy}-acetic acid ethyl ester (50 mg; 0.09 mmol) was dissolved in ethanol (10 mL), and aqueous 1 N sodium hydroxide (2 mL) was added. The reaction mixture was stirred for 16 h, acidified with 1 N aqueous hydrochloric acid and extracted with dichloromethane. The organic phase was dried and evaporated to dryness. Yield: 45 mg. HPLC-MS: m/z: 532.1 (M+); Rt: 1.79 min.

Example 5

(4-[3-Isobutoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy} -acetic acid

[0134]
The title product was prepared from [4-(3-Bromo-5-isobutoxy-benzylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (300 mg; 0.64 mmol) and 4-prop-2-ynyl-morpholine (221 mg; 2.6 mmol) applying the procedure described for [4-[3-[2-(4-Chloro-phenyl)-ethoxy]-5-(4-hydroxymethyl-phenylethynyl)-phenylsulfanyl]-2-methyl-phenoxy]-acetic acid ethyl ester. The crude product was purified by preparative HPLC (method B). Yield: 140 mg (44%). HPLC-MS: m/z: 511.9 (M)+; Rt: 2.00 min.

Step B: [4-[3-Isobutoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy]-acetic acid

The title product was prepared from [4-(3-Isobutoxy-5-phenylethynyl-benzylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (140 mg; 0.27 mmol) was dissolved in ethanol (15 mL), and aqueous 1 N sodium hydroxide (3 mL) was added. The reaction mixture was stirred for 16 h. acidified with 1 N aqueous hydrochloric acid and extracted with ethyl acetate. The organic phase was dried and evaporated to dryness, redissolved in dichloromethane and evaporated to dryness. Yield: 113 mg (86%). HPLC-MS: m/z: 484.9 (M+H)+; Rt: 1.70 min. \( \delta \) (400 MHz; CDCl₃) 1.03 (d, 6H), 2.04-2.12 (m, 1H), 2.24 (s, 3H), 2.90-3.30 (m, 2H), 3.40-3.70 (m, 2H), 3.71 (d, 2H), 3.74 (s, 2H), 3.95-4.05 (m, 4H), 4.17 (s, 2H), 4.69 (s, 2H), 6.14 (m, 1H), 6.53 (d, 1H), 6.77(dd, 1H), 6.81 (m, 1H), 6.89 (m, 1H), 7.23 (d, 1H).

Example 6

[4-(3-Isobutoxy-5-phenylethynyl-benzylsulfanyl)-2-methyl-phenoxy]-acetic acid
Step B: [4-(3-Isobutoxy-5-phenylethynyl-benzylsulfanyl)-2-methyl-phenoxy]-acetic acid

[0139] [4-(3-Isobutoxy-5-phenylethynyl-benzylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (130 mg; 0.27 mmol) was dissolved in ethanol (15 mL), and aqueous 1 N sodium hydroxide (3 mL) was added. The reaction mixture was stirred for 16 h. acidified with 1 N aqueous hydrochloric acid and extracted with ethyl acetate. The organic phase was dried and evaporated to dryness, redissolved in dichloromethane and evaporated to dryness. Yield: 120 mg (97%). HPLC-MS: m/z: 461.7 (M+H)+; Rt: 2.82 min.

Example 7

{4-[3-Isobutoxy-5-(4-methanesulfonyl-phenylethynyl)-benzylsulfanyl]-2-methyl-phenoxy}-acetic acid

[0140]

{4-[3-Isobutoxy-5-(4-methanesulfonyl-phenylethynyl)-benzylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester

Step A: {[4-[3-Isobutoxy-5-(4-methanesulfonyl-phenylethynyl)-benzylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester

[0141] The title product was prepared from [4-(3-Bromo-5-isobutoxy-benzylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (300 mg; 0.64 mmol) and 1-Ethynyl-4-methane-sulfonyl-benzene (347.0 mg; 1.93 mmol) applying the procedure described for {4-[3-[2-(4-Chloro-phenyl)-ethoxy]-5-(4-hydroxymethyl-phenylethynyl)-phenylsulfanyl]-2-methyl-phenoxy} -acetic acid ethyl ester. The crude product was purified by preparative HPLC (method A). Yield: 260 mg (72%). HPLC-MS: m/z: 567.6 (M+H)+; Rt: 2.77 min.

Step B: {4-[3-Isobutoxy-5-(4-methanesulfonyl-phenylethynyl)-benzylsulfanyl]-2-methyl-phenoxy}-acetic acid.

[0142] [4-(3-Isobutoxy-5-(4-methanesulfonyl-phenylethynyl)-benzylsulfanyl)-2-methyl-phenoxy]-acetic acid ethyl ester (130 mg; 0.27 mmol) was dissolved in ethanol (15 mL), and aqueous 1 N sodium hydroxide (3 mL) was added. The reaction mixture was stirred for 16 h. acidified with 1 N aqueous hydrochloric acid and extracted with ethyl acetate. The organic phase was dried and evaporated to dryness, redissolved in dichloromethane and evaporated to dryness. Yield: 230 mg (%). HPLC-MS: m/z: 539.5 (M+H)+; Rt: 2.49 min.

Example 8

{4-[3-Cyclopropylmethoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy}-acetic acid

[0143]
Step A: \(\text{4-\{3-Cyclopropylmethoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl\}-2-methyl-phenoxy\}-acetic acid ethyl ester}\)

[0144] The title product was prepared from \(\text{4-(3-Bromo-5-cyclopropylmethoxy-benzylsulfanyl)-2-methyl-phenoxy\}-acetic acid ethyl ester (200 mg; 0.43 mmol) and 4-prop-2-ynyl-morpholine (161 mg; 1.3 mmol) applying the procedure described for \(\text{4-\{3-\{2-(4-Chloro-phenyl)-ethoxy\}-5-(4-hydroxymethyl-phenylethynyl)-phenylsulfanyl\}-2-methyl-phenoxy\}-acetic acid ethyl ester. The crude product was purified by preparative HPLC (method B). Yield: 173 mg; 79%. HPLC-MS: m/z: 510.1 (M)+; Rt: 1.9 min.

Step B: \(\text{4-\{3-Cyclopropylmethoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl\}-2-methyl-phenoxy\}-acetic acid acid ethyl ester (173 mg; 0.34 mmol) was dissolved in ethanol (15 mL), and aqueous 1 N sodium hydroxide (3 mL) was added. The reaction mixture was stirred for 16 h. acidified with 1 N aqueous hydrochloric acid and extracted with ethyl acetate. The organic phase was dried and evaporated to dryness. Yield: 107 mg; 66%. HPLC-MS: m/z: 482.0 (M+H)+; Rt: 1.62 min.

PHARMACOLOGICAL METHODS

IN VITRO PPAR-\(\delta\) ACTIVATION ACTIVITY

[0146] The PPAR transient transactivation assay is based on transient transfection into human HEK293 cells of two plasmids encoding a chimeric test protein and a reporter protein respectively. The chimeric test protein is a fusion of the DNA binding domain (DBD) from the yeast GAL4 transcription factor to the ligand binding domain (LBD) of the human PPAR proteins. The PPAR-LBD moiety harbored in addition to the ligand binding pocket also the native activation domain (activating function 2 = AF2) allowing the fusion protein to function as a PPAR ligand dependent transcription factor. The GAL4 DBD will direct the chimeric protein to bind only to Gal4 enhancers (of which none existed in HEK293 cells). The reporter plasmid contained a Gal4 enhancer driving the expression of the firefly luciferase protein. After transfection, HEK293 cells expressed the GAL4-DBD-PPAR-LBD fusion protein. The fusion protein will in turn bind to the Gal4 enhancer controlling the luciferase expression, and do nothing in the absence of ligand. Upon addition to the cells of a PPAR ligand luciferase protein will be produced in amounts corresponding to the activation of the PPAR protein. The amount of luciferase protein is measured by light emission after addition of the appropriate substrate.

CELL CULTURE AND TRANSFECTION

[0147] HEK293 cells were grown in DMEM + 10% FCS. Cells were seeded in 96-well plates the day before transfection to give a confluency of 50-80% at transfection. A total of 0.8 \(\mu\)g DNA containing 0.64 \(\mu\)g pM1\(\alpha\)/LBD, 0.1 \(\mu\)g pCMV\(\beta\)Gal, 0.08 \(\mu\)g pGL2(Gal4)\(\delta\) and 0.02 \(\mu\)g pADVANTAGE was transfected per well using FuGene transfection reagent according to the manufacturers instructions (Roche). Cells were allowed to express protein for 48 h followed by addition of compound.

[0148] Plasmids: Human PPAR-\(\delta\) was obtained by PCR amplification using cDNA synthesized by reverse transcription of mRNA from human liver, adipose tissue and placenta respectively. Amplified cDNAs were cloned into pCR2.1 and sequenced. The ligand binding domain (LBD) of each PPAR isoform was generated by PCR (PPAR\(\delta\): aa 128 - C-terminus) and fused to the DNA binding domain (DBD) of the yeast transcription factor GAL4 by subcloning fragments in frame into the vector pM1 (Sadowski et al. (1992), Gene 118, 137) generating the plasmids pM1\(\alpha\)LBD, pM1\(\beta\)LBD and pM1\(\delta\). Ensuing fusions were verified by sequencing. The reporter was constructed by inserting an oligonucleotide encoding five repeats of the GAL4 recognition sequence (5 x CGAGACTGTCTCTCCG(A)G) (Webster et al. (1988), Nucleic Acids Res. 16, 8192) into the vector pGL2 promoter (Promega) generating the plasmid pGL2(GAL4)\(\delta\), pCMV\(\beta\)Gal
was purchased from Clontech and pADVANTAGE was purchased from Promega.

IN VITRO TRANSACTIVATION ASSAY

[0149] Compounds: All compounds were dissolved in DMSO and diluted 1:1000 upon addition to the cells. Compounds were tested in quadruple in concentrations ranging from 0.001 to 300 μM. Cells were treated with compound for 24 h followed by luciferase assay. Each compound was tested in at least two separate experiments.

[0150] Luciferase assay: Medium including test compound was aspirated and 100 μl PBS incl. 1mM Mg++ and Ca++ were added to each well. The luciferase assay was performed using the LucLite kit according to the manufacturer’s instructions (Packard Instruments). Light emission was quantified by counting on a Packard LumiCounter. To measure β-galactosidase activity 25 μl supernatant from each transfection lysate was transferred to a new microplate. β-Galactosidase assays were performed in the microwell plates using a kit from Promega and read in a Labsystems Ascent Multiscan reader. The β-galactosidase data were used to normalize (transfection efficiency, cell growth etc.) the luciferase data.

STATISTICAL METHODS

[0151] The activity of a compound is calculated as fold induction compared to an untreated sample. For each compound the efficacy (maximal activity) is given as a relative activity compared to Wy14,643 for PPARα, Rosiglitazone for PPARγ and Carbacyclin for PPARδ. The EC50 is the concentration giving 50% of maximal observed activity. EC50 values were calculated via non-linear regression using GraphPad PRISM 3.02 (GraphPad Software, San Diego, Ca).

[0152] While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications, and substitutions can be made therein. For example, effective dosages other than the preferred dosages as set forth herein may be applicable as a consequence of variations in the responsiveness of the mammal being treated for PPAR-δ mediated disease(s). Likewise, the specific pharmacological responses observed may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention.

Claims

1. A compound of formula IIb:

or a pharmaceutically acceptable salt thereof, wherein:

| X is SCH₂; |
| X₁ is O or S; |
| R₁ is H, C₁₋₈ alkyl, heteroaryl, or C₃₋₁₀ cycloalkyl, wherein each R₁ group is substituted with 0-4 R₁a; |
| R₁a, at each occurrence, is selected from C₁₋₆ alkyl substituted with 0-3 R₁b; C₂₋₆ alkenyl substituted with 0-2 R₁b; aryl substituted with 0-2 R₁b, heteroaryl substituted with 0-2 R₁b, C₃₋₁₀ cycloalkyl substituted with 0-2 R₁b, and a heterocycle substituted with 0-2 R₁b; |
| R₁b, at each occurrence, is selected from OH substituted with 0-1 R₁c, SH substituted with 0-1 R₁c, Cl, F, NH₂ substituted with 0-2 R₁c, -CN, NO₂, methanesulfonfyl, C₁₋₄ alkyl substituted with 0-3 R₁c, C₂₋₄ alkenyl substituted with 0-2 R₁c, aryl substituted with 0-2 R₁c, heteroaryl substituted with 0-2 R₁c, C₃₋₆ cycloalkyl substituted with 0-2 R₁₆, and a heterocycle substituted with 0-2 R₁c; |
R₁c, at each occurrence, is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl, and C₂₋₄ alkenyl, aryl substituted with 0-2 R₁d, heteroaryl substituted with 0-2 R₁d, C₃₋₆ cycloalkyl substituted with 0-2 R₁d, and a heterocycle substituted with 0-2 R₁d;

R₁d, at each occurrence, is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl, and C₂₋₄ alkenyl;

R₂a is selected from Chalkyl substituted with 0-2 R₂b, aryl substituted with 0-2 R₂b, and heteroaryl substituted with 0-2 R₂b;

R₂b, at each occurrence, is selected from OH substituted with 0-1 R₂c, SH substituted with 0-1 R₂c, Cl, F, NH₂ substituted with 0-2 R₂c, -CN, NO₂, methanesulfonyl, C₁₋₄ alkyl substituted with 0-2 R₂c, C₂₋₄ alkenyl substituted with 0-2 R₂c, aryl substituted with 0-2 R₂c, and a heterocycle substituted with 0-2 R₂c;

R₂c, at each occurrence, is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl, C₂₋₄ alkenyl, aryl substituted with 0-2 R₂d, and heteroaryl substituted with 0-2 R₂d;

R₂d, at each occurrence, is selected from OH, SH, Cl, F, NH₂, -CN, NO₂, C₁₋₄ alkyl, and C₂₋₄ alkenyl; and

R₃ is selected from Cl, F, CH₃, and CH₂CH₃.

2. The compound of claim 1, wherein R₃ is selected from Cl and CH₃.

3. The compound of claim 1 or 2, wherein X₁ is O.

4. The compound of claim 1 wherein the compound is selected from:

{2-Methyl-4-[3-(3-morpholin-4-yl-propoxy)-5-(3-phenyl-prop-1-ynyl)-benzylsulfanyl]-phenoxy}-acetic acid;
{4-[3-(4-Fluoro-benzyloxy)-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy} -acetic acid;
{2-Methyl-4-[3-(3-morpholin-4-yl-ethoxy)-5-(3-phenyl-prop-1-ynyl)-benzylsulfanyl]-phenoxy}-acetic acid;
{4-[3-Isobutoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy} -acetic acid;
{4-[3-Isobutoxy-5-(phenylethynyl)-benzylsulfanyl]-2-methyl-phenoxy} -acetic acid;
{4-[3-Cyclopropylmethoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy} -acetic acid;
or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1, where the compound is {4-[3-isobutoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy}-acetic acid or a pharmaceutically acceptable salt thereof.

6. A combination of a compound as defined in any one of claims 1 to 5 and one or more further pharmacologically active substances selected from antiobesity agents, appetite regulating agents, antidiabetics, antihypertensive agents, agents for the treatment of complications resulting from or associated with diabetes, and agents for the treatment of complications and disorders resulting from or associated with obesity.

7. A pharmaceutical composition comprising:

a compound of one of the claims 1 to 5 or a pharmaceutically acceptable salt thereof, or a combination according to claim 6; and

one or more pharmaceutically acceptable carriers or excipients.

8. A compound as defined in any one of claims 1 to 5, a combination as defined in claim 6 or a composition as defined in claim 7, for use in therapy.

9. A compound, combination or composition according to claim 8 for use in treating type 2 diabetes.

10. A compound, combination or composition according to claim 8 for use in treating dyslipidemia, syndrome X (including the metabolic syndrome, e.g., hypertension, impaired glucose tolerance (IGT), insulin resistance, hypertriglyceridaemia, and obesity), cardiovascular diseases (e.g., atherosclerosis and related diseases, including mortality reduction, coronary artery diseases, coronary heart diseases, heart attack, myocardial ischemia, myocardial infarct, coronary infarct, transient ischemic attack (TIA), and stroke), hyperglycemia, hyperlipidemia, hypercholesterolemia or hyperinsulinemia.
Patentansprüche

1. Verbindung der Formel IIb:

X SCH₂ ist;
X₁ 0 oder S ist;
R₁ H, ein C₁-8-Alkyl, Heteroaryl oder ein C₃-10-Cycloalkyl ist, wobei jede R₁-Gruppe substituiert ist mit 0-4 R₁a;
R₁b bei jedem Auftreten aus einem C₁-8-Alkyl, das mit 0-3 R₁b substituiert ist; C₂-₆-Alkynyl, das mit 0-2 R₁b substituiert ist; Aryl, das mit 0-2 R₁b substituiert ist, Heteroaryl, das mit 0-2 R₁b substituiert ist, C₃-10-Cycloalkyl, das mit 0-2 R₁b substituiert ist und aus einem Heterocyclus, der mit 0-2 R₁b substituiert ist, ausgewählt ist;
R₁b bei jedem Auftreten aus OH, das mit 0-1 R₁c substituiert ist, SH, das mit 0-1 R₁c substituiert ist, Cl, F, NH₂, das mit 0-2 R₁c substituiert ist, -CN, NO₂, Methansulfonyl, C₁-₄-Alkyl, das mit 0-3 R₁c substituiert ist, C₂-₄-Alkenyl, das mit 0-2 R₁c substituiert ist, Aryl, das mit 0-2 R₁c substituiert ist, Heteroaryl, das mit 0-2 R₁c substituiert ist, C₃-₆-Cycloalkyl, das mit 0-2 R₁c substituiert ist, und aus einem Heterocyclus, der mit 0-2 R₁c substituiert ist, ausgewählt ist;
R₁c bei jedem Auftreten aus OH, SH, Cl, F, NH₂, -CN, NO₂, einem C₁-₄-Alkyl und C₂-₄-Alkenyl, Aryl, das mit 0-2 R₁d substituiert ist, substituiert ist, und aus einem Heterocyclus, der mit 0-2 R₁d substituiert ist, ausgewählt ist;
R₁d bei jedem Auftreten aus OH, SH, Cl, F, NH₂, -CN, NO₂, einem C₁-₄-Alkyl und C₂-₄-Alkenyl ausgewählt ist;
R₂a aus einem C₁-₆-Alkyl, das mit 0-2 R₂b substituiert ist, Aryl, das mit 0-2 R₂b substituiert ist, und Heteroaryl, das mit 0-2 R₂b substituiert ist, ausgewählt ist;
R₂b bei jedem Auftreten aus OH, das mit 0-1 R₂c substituiert ist, SH, das mit 0-1 R₂c substituiert ist, Cl, F, NH₂, das mit 0-2 R₂c substituiert ist, -CN, NO₂, Methansulfonyl, einem C₁-₄-Alkyl, das mit 0-2 R₂c substituiert ist, C₂-₄-Alkenyl, das mit 0-2 R₂c substituiert ist, Aryl, das mit 0-2 R₂c substituiert ist, Heteroaryl, das mit 0-2 R₂c substituiert ist, C₃-₆-Cycloalkyl, das mit 0-2 R₂c substituiert ist, und aus einem Heterocyclus, der mit 0-2 R₂c substituiert ist, ausgewählt ist;
R₂c bei jedem Auftreten aus OH, SH, Cl, F, NH₂, -CN, NO₂, einem C₁-₄-Alkyl, C₂-₄-Alkenyl, Aryl, das mit 0-2 R₂d substituiert ist, und einem Heterocyclus, das mit 0-2 R₂d substituiert ist, ausgewählt ist;
R₂d bei jedem Auftreten aus OH, SH, Cl, F, NH₂, -CN, NO₂, einem C₁-₄-Alkyl und einem C₂-₄-Alkenyl ausgewählt ist; und
R₃ aus Cl, F, CH₃ und CH₂CH₃ ausgewählt ist.

2. Verbindung nach Anspruch 1, wobei R³ aus Cl und CH₃ ausgewählt ist.

3. Verbindung nach Anspruch 1 oder 2, wobei X₁ 0 ist.

4. Verbindung nach Anspruch 1, wobei die Verbindung ausgewählt ist aus:

- {2-Methyl-4-[3-(3-morpholin-4-yl-propoxy)-5-(3-phenyl-prop-1-ynyl)-benzylsulfanyl]-phenoxy}-Essigsäure;
- {4-[3-(4-Fluorbenzoxoxy)-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy}-Essigsäure;
- {2-Methyl-4-[3-(4-Fluorbenzyloxy)-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy}-Essigsäure;
- {4-[3-Isobutoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy}-Essigsäure;
- {4-[3-Isobutoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy}-Essigsäure;
- {4-[3-Isobutoxy-5-(4-methansulfonyl-phenylethynyl)-benzylsulfanyl]-2-methyl-phenoxy}-Essigsäure;
- {4-[3-Cyclopropylmethoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-methyl-phenoxy}-Essigsäure;

oder ein pharmazeutisch annehmbares Salz derselben.
nyl]-2-methyl-phenoxy}-Essigsäure oder ein pharmazeutisch annehmbares Salz derselben ist.

6. Kombination einer Verbindung nach einem der Ansprüche 1 bis 5 und von einer oder mehreren weiteren pharmakologisch aktiven Substanzen, die aus Mitteln gegen Fettleibigkeit (Antiadiposita), appetitregulierenden Mitteln, Antidiabetika, blutdrucksenkenden Mitteln, aus Mitteln für die Behandlung von Komplikationen, die aus Diabetes resultieren oder damit verbunden sind, und aus Mitteln für die Behandlung von Komplikationen und Störungen, die aus Fettleibigkeit (Adipositas) resultieren oder damit verbunden sind, ausgewählt sind.

7. Pharmazeutische Zusammensetzung, die umfasst:

   eine Verbindung nach einem der Ansprüche 1 bis 5 oder ein pharmazeutisch annehmbares Salz derselben oder eine Kombination nach Anspruch 6; und

   ein oder mehrere pharmazeutisch annehmbare Trägerstoffe oder Exzipienten.

8. Verbindung nach einem der Ansprüche 1 bis 5, eine Kombination nach Anspruch 6 oder eine Zusammensetzung nach Anspruch 7 für eine Verwendung in der Therapie.


10. Verbindung, Kombination oder Zusammensetzung nach Anspruch 8 für eine Verwendung in der Behandlung von Dyslipidämie, Syndrom X (einschließlich des metabolischen Syndroms, z.B. Bluthochdruck, beeinträchtigte Glukosetoleranz (IGT), Insulinresistenz, Hypertriglyceridämie und Fettleibigkeit), Herz-Kreislaufkrankungen (z.B. Atherosklerose und verwandte Krankheiten einschließlich Verminderung der Sterblichkeit, koronare Herzkrankungen, Herzinfarkt, Myokardischämie, Herzinfarkt (Myocardinfarkt), koronarer Infarkt, transitorische ischämische Attacken (TIA) und Schlaganfall), Hyperglykämie, Hyperlipidämie, Hypercholesterinämie oder Hyperinsulinämie.

Revendications

1. Composé de formule IIb :

   ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel :

   X est SCH₂ ;
   X₁ est 0 ou S ;
   R₁ est H, un groupe alkyle en C₁ à C₈, un groupe hétéroaryle ou un groupe cycloalkyle en C₃ à C₁₀, chaque groupe R₁ étant substitué par 0 à 4 R₁ₐ ;
   R₁ₐ, dans chaque cas, est sélectionné parmi un groupe alkyle en C₁ à C₈ substitué par 0 à 3 R₁₉, un groupe alcynyle en C₂ à C₆ substitué par 0 à 2 R₁₉, un groupe aryle substitué par 0 à 2 R₁₉, un groupe hétéroaryle substitué par 0 à 2 R₁₉, un groupe cycloalkyle en C₃ à C₁₀ substitué par 0 à 2 R₁₉ et un groupe hétérocycle substitué par 0 à 2 R₁₉ ;
   R₁₉, dans chaque cas, est sélectionné parmi un groupe OH substitué par 0 à 1 R₁₉, un groupe SH substitué par 0 à 1 R₁₉, Cl, F, un groupe NH₂ substitué par 0 à 2 R₁₉, CN, NO₂, un groupe méthanesulfonyle, un groupe alkyle en C₁ à C₄ substitué par 0 à 3 R₁₉, un groupe alcényle en C₂ à C₄ substitué par 0 à 2 R₁₉, un groupe aryle substitué par 0 à 2 R₁₉, un groupe hétéroaryle substitué par 0 à 2 R₁₉, un groupe cycloalkyle en C₃ à C₆ substitué par 0 à 2 R₁₉.
substitué par 0 à 2 R1c et un groupe hétérocyclique substitué par 0 à 2 R1c;
R1c, dans chaque cas, est sélectionné parmi OH, SH, Cl, F, NH2, CN, NO2, un groupe alkyle en C1-C4 et un
groupe alcényle en C2 à C4, un groupe aryle substitué par 0 à 2 R1d, un groupe hétéroaryle substitué par 0 à
2 R1d, un groupe cycloalkyle en C3 à C6 substitué par 0 à 2 R1d et un groupe hétérocyclique substitué par 0 à 2 R1d;
R1d, dans chaque cas, est sélectionné parmi OH, SH, Cl, F, NH2, CN, NO2, un groupe alkyle en C1-C4 et un
groupe alcényle en C2 à C4 ;
R2a est sélectionné parmi un groupe alkyle en C1 à C6 substitué par 0 à 2 R2b, un groupe aryle substitué par
0 à 2 R2b et un groupe hétéroaryl substitué par 0 à 2 R2b;
R2b, dans chaque cas, est sélectionné parmi un groupe OH substitué par 0 à 1 R2c, un groupe SH substitué
par 0 à 1 R2c, Cl, F, un groupe NH2 substitué par 0 à 2 R2c, CN, NO2, un groupe méthanesulfonyle, un groupe
alkyle en C1-C4 substitué par 0 à 2 R2c, un groupe alcényle en C2 à C4 substitué par 0 à 2 R2c, un groupe aryle
substitué par 0 à 2 R2c, un groupe hétéroaryle substitué par 0 à 2 R2c, un groupe cycloalkyle en C3 à C6 substitué
par 0 à 2 R2c et un groupe hétérocyclique substitué par 0 à 2 R2c;
R2c, dans chaque cas, est sélectionné parmi un groupe OH substitué par 0 à 2 R2d, un groupe SH substitué
par 0 à 2 R2d, Cl, F, un groupe NH2 substitué par 0 à 2 R2d, CN, NO2, un groupe méthanesulfonyle, un groupe
alcényle en C2 à C4 substitué par 0 à 2 R2d, un groupe aryle substitué par 0 à 2 R2d, un groupe hétéroaryle substitué
par 0 à 2 R2d, un groupe cycloalkyle en C3 à C6 substitué par 0 à 2 R2d et un groupe hétérocyclique substitué par
0 à 2 R2d;
R2d, dans chaque cas, est sélectionné parmi un groupe OH substitué par 0 à 2 R2e, un groupe SH substitué
par 0 à 2 R2e, Cl, F, un groupe NH2 substitué par 0 à 2 R2e, CN, NO2, un groupe méthanesulfonyle, un groupe
alcényle en C2 à C4 substitué par 0 à 2 R2e, un groupe aryle substitué par 0 à 2 R2e, un groupe hétéroaryle substitué
par 0 à 2 R2e, un groupe cycloalkyle en C3 à C6 substitué par 0 à 2 R2e et un groupe hétérocyclique substitué par
0 à 2 R2e;
R3 est sélectionné parmi Cl, F, CH3 et CH2CH3.

2. Composé selon la revendication 1, dans lequel R3 est sélectionné parmi Cl et CH3.

3. Composé selon la revendication 1 ou 2, dans lequel X1 est O.

4. Composé selon la revendication 1, dans lequel le composé est sélectionné parmi :
   l’acide {2-méthyl-4-[3-(3-morpholin-4-yl-proproxy)-5-(3-phényl-prop-1-ylnyl)-benzylsulfanyl]-phénol}-acétique ;
   l’acide {4-[3-(4-fluoro-benzyloxy)-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-méthyl-phénol}-acétique ;
   l’acide (2-méthyl-4-[3-(3-morpholin-4-yl-théoxy)-5-(3-phényl-prop-1-ynyl)-benzylsulfanyl]-phénol)-acétique ;
   l’acide {4-[3-(isobutoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzylsulfanyl]-2-méthyl-phénol)-acétique ;
   l’acide {4-[3-(isobutoxy-5-(4-méthanesulfonyl-phényléthynyl)-benzyl-sulfanyl]-2-méthyl-phénol)-acétique ;
   l’acide {4-[3-cyclopropylméthoxy-5-(3-morpholin-4-yl-prop-1-ynyl)-benzyl-sulfanyl]-2-méthylphénol)-acétique ;
   ou un sel pharmaceutiquement acceptable de ceux-ci.

5. Composé selon la revendication 1, dans lequel le composé est l’acide {4-[3-isobutoxy-5-(3-morpholin-4-yl-prop-1-
ylnyl)-benzylsulfanyl]-2-méthyl-phénol)-acétique ou un sel pharmaceutiquement acceptable de celui-ci.

6. Association d’un composé selon l’une quelconque des revendications 1 à 5 et d’une ou plusieurs autres substances pharmacologiquement actives sélectionnées parmi les agents anti-obésité, les agents de régulation de l’appétit, les
antidiabétiques, les agents antihypertenseurs, les agents pour le traitement de complications résultant du ou asso-
ciées au diabète et les agents pour le traitement de complications et de troubles résultant de ou associés à l’obésité.

7. Composition pharmaceutique comprenant :
   un composé selon l’une quelconque des revendications 1 à 5 ou un sel pharmaceutiquement acceptable de
   celui-ci, ou une association selon la revendication 6 ; et
   un ou plusieurs véhicules ou excipients pharmaceutiquement acceptables.

8. Composé selon l’une quelconque des revendications 1 à 5, une association selon la revendication 6 ou une com-
position selon la revendication 7, pour une utilisation en thérapie.

9. Composé, association ou composition selon la revendication 8, pour une utilisation dans le traitement du diabète
de type 2.
REFERENCES CITED IN THE DESCRIPTION

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