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BICYCLIC ARYL-SULFONIC ACID [1,3,4]-THIADIAZOL-2-YL-AMIDES, PROCESSES FOR THEIR PREPARATION AND THEIR USE AS PHARMACEUTICALS

BICYCLISCHE ARYL-SULFONSÄURE[1,3,4]-THIADIAZOL-2-YL-AMIDE, VERFAHREN ZU IHRER HERSTELLUNG UND IHRE VERWENDUNG ALS PHARMAZEUTIKA

[1,3,4]-THIADIAZOL-2-YL-AMIDES BICYCLIQUES DE L’ACIDE ARYL-SULFONIQUE, LEURS PROCEDES DE PREPARATION, ET LEUR UTILISATION EN TANT QUE SUBSTANCES PHARMACEUTIQUES

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The invention relates to Bicyclic aryl-sulfonic acid [1,3,4]thiadiazol-2-yl-amides and to their physiologically acceptable salts and physiologically functional derivatives showing PPAR agonistic activity.

Monocyclic aryl-sulfonic acid [1,3,4]-thiadiazol-2-ylamides as modulators of PPARs are described in EP 1 277 729.

Benzenesulfonamino compounds which bind to PPARs are described in WO 2005/005421. Sulfonamide compounds showing hypoglycemic activity are disclosed in Khimiko-Farmatsevticheskii Zhurnal (1987), 21(8), 965-8. From WO 97/40017 compounds having a phenyl group linked to heterocycles are known as modulators of molecules with phosphotyrosine recognition units.

The invention is based on the object of providing compounds which permit therapeutically utilizable modulation of lipid and/or carbohydrate metabolism and are thus suitable for the prevention and/or treatment of diseases such as type 2 diabetes and atherosclerosis and the diverse sequelae thereof. Another purpose of the invention is to treat demyelinating and other neurodegenerative disorders of the central and peripheral nervous systems.

A series of hitherto unknown compounds which modulate the activity of PPA receptors has been found. The compounds are suitable in particular for activating PPARdelta or PPARdelta and PPARgamma, however it is possible that the relative activation varies depending on the specific compounds.

The compounds of the present invention are described by formula I:

![Formula 1]

wherein

R₁ is (C₁-C₄) alkyl, (C₀-C₂) alkylene (C₃-C₆) cycloalkyl, (C₀-C₂) alkylene-(C₆-C₁₀) aryl, wherein alkyl, aryl, and cycloalkyl can be unsubstituted or mono, di- or trisubstituted by F;

R₂ is H, halogen, (C₁-C₆) alkyl, O-(C₀-C₄) alkylene-H, wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstituted by F;

R₃ is H;

R₄ is H;

R₅ is H, (C₁-C₄) alkyl;

A is (C₆) aryl or (C₅-C₆) heteroaryl;

n is 1, 2;

z is 1;

R₆ is (C₁-C₄) alkyl, halogen, (C₀-C₂) alkylene-O-(C₀-C₆) alkylene-H, (C₀-C₂) alkylene-(C₆-C₁₀) aryl, wherein alkyl, aryl and alkylene are unsubstituted or mono, di- or trisubstituted by F and aryl can be unsubstituted or monosubstituted by CF₃;
R7 is H, (C1-C4) alkyl, halogen, wherein alkyl is unsubstituted or mono, di- or trisubstituted by F;

R8 is H, F;

in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

[0007] Another embodiment according to the invention are compounds of the formula 1, where

R1 is (C1-C4) alkyl, (C3-C6) cycloalkyl, phenyl, wherein alkyl can be unsubstituted or mono, di- or tri substituted by F;

R2 is H, F, Cl, O-(C1-C4) alkyne-H, wherein alkyne is unsubstituted or mono, di- or trisubstituted by F;

R3 is H;

R4 is H;

R5 is H, (C1-C4) alkyl;

A is phenyl, thiophen, thiazol, pyridine;

n is 1, 2;

z is 1;

R6 is (C1-C4) alkyl, F, Cl, O-(C0-C6) alkyne-H, phenyl, wherein phenyl can be unsubstituted or monosubstituted by CF3;

R7 is H, (C1-C4) alkyl, Cl, wherein alkyl is unsubstituted or mono, di- or trisubstituted by F;

R8 is H, F;

in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

[0008] Another embodiment according to the invention are compounds of the formula 1, where

R1 is ethyl, isopropyl, tert.butyl, cyclopropyl, cyclohexyl, phenyl or trifluoromethyl;

R2, R3, R4, R5 are H, F, Cl, OCH3, OCH2CF3;

A is phenyl;

n is 1;

z is 1;

R6 is in ortho position and Cl, Br, or O(C1-C2)-alkyl;

R7 is in para position and Cl, Br or CF3;

R8 is H;

in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

[0009] Another embodiment according to the invention are compounds of the formula 1, where

R1 is isopropyl;

R2, R3, R4, R5 are H;

A is phenyl;

n is 1;

z is 1;
R6 is O(C1-C2)-alkyl and in ortho position;
R7 is in para position and Cl or CF3;
R8 is H;
in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

Another embodiment according to the invention are compounds of the formula 1, where

R1 is trifluoromethyl;
R2, R3, R4, R5 are H;
A is phenyl;
n is 1;
z is 1;
R6 is O-ethyl and in ortho position;
R7 is in para position and Cl or CF3;
R8 is H;
in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

Another embodiment according to the invention are compounds of the formula 1, where

R1 is cyclohexyl;
R2, R3, R4, R5 are H;
A is phenyl;
n is 1;
z is 1;
R6 is O-ethyl and in ortho position;
R7 is in para position and Cl or CF3;
R8 is H;
in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

Another embodiment according to the invention are compounds of the formula 1, where

R1 is phenyl;
R2, R3, R4, R5 are H;
A is phenyl;
n is 1;
Another embodiment according to the invention are compounds of the formula 1, where

R1 is cyclopropyl;

R2, R3, R4, R5 are H;

A is phenyl;

n is 1;

z is 1;

R6 is O-ethyl and in ortho position;

R7 is in para position and Cl or CF3;

R8 is H;

in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

Another embodiment according to the invention are compounds of the formula 1, where

R1 is isopropyl;

R2, R3, R4, R5 are H;

A is thiophen;

n is 1;

z is 1;

R6 is O-ethyl and in ortho position;

R7 is in para position and Cl or CF3;

R8 is H;

in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

Another embodiment according to the invention are the compounds:

2-Ethoxy-N-[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-4-trifluoromethyl-benzamide

2-Ethoxy-N-[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-4-trifluoromethyl-benzamide (Enantiomer 1)

2-Ethoxy-N-[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-4-trifluoromethyl-benzamide (Enantiomer 2)

2-Ethoxy-4-trifluoromethyl-N-[5-(5-trifluoromethyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-benzamide
This invention also encompasses all combinations of preferred aspects of the invention described herein.

As used herein, the term alkyl is to be understood in the broadest sense to mean saturated hydrocarbon residues which can be linear, i.e. straight-chain, or branched. If not otherwise defined alkyl has 1 to 8 carbon atoms.
Examples of "-(C1-C8)-alkyl" are alkyl residues containing 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl or octyl, the n-isomers of all these residues, isopropyl, isobutyl, 1-methylbutyl, isopentyl, neopentyl, 2,2-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, isohexyl, sec-butyl, tert-butyl or tert-pentyl. The term "-(C0-C8)"alkyl" is a hydrocarbon residue containing 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms, in which the term -"CO-alkyl" is a covalent bond. All these statements also apply to the term alkylene.

[0018] If not otherwise defined, alkyl and alkylene are unsubstituted or mono, di- or trisubstituted independently of one another by suitable groups such as, for example: F:

[0019] The term cycloalkyl is to be understood to mean saturated hydrocarbon cycle containing from 3 to 6 carbon atoms in a monocyclic, ring. Examples of (C3-C6)-cycloalkyl cyclic alkyl residues are cycloalkyl residues containing 3, 4, 5, or 6, ring carbon atoms like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, Halogen is fluorine, chlorine, bromine or iodine.

[0020] Optically active carbon atoms present in the compounds of the formula I can independently of each other have R configuration or S configuration. The compounds of the formula I can be present in the form of pure enantiomers or pure diastereomers or in the form of mixtures of enantiomers and/or diastereomers, for example in the form of racemates. The present invention relates to pure enantiomers and mixtures of enantiomers as well as to pure diastereomers and mixtures of diastereomers. The invention comprises mixtures of two or of more than two stereoisomers of the formula I and it comprises all ratios of the stereoisomers in the mixtures. In case the compounds of the formula I can be present as E isomers or Z isomers (or cis isomers or trans isomers) the invention relates both to pure E isomers and pure Z isomers and to E/Z mixtures in all ratios. The invention also comprises all tautomeric forms of the compounds of the formula I.

[0021] Diastereomers, including E/Z isomers, can be separated into the individual isomers, for example, by chromatography. Racemates can be separated into the two enantiomers by customary methods, for example by chromatography on chiral phases or by resolution, for example by crystallization of diastereomeric salts obtained with optically active acids or bases. Stereochemically uniform compounds of the formula I can also be obtained by employing stereochemically uniform starting materials or by using stereoselective reactions.

[0022] The compounds of the formula I may exist in the form of their racemates, racemic mixtures, pure enantiomers, diastereomers and mixtures of diastereomers as well in their tautomeric forms. The present invention encompasses all these isomeric and tautomeric forms of the compounds of the formula I. These isomeric forms can be obtained by known methods even if not specifically described in some cases.

[0023] Pharmaceutically acceptable salts are, because their solubility in water is greater than that of the initial or basic compounds, particularly suitable for medical applications. These salts must have a pharmaceutically acceptable anion or cation. Suitable Pharmaceutical acceptable acid addition salts of the compounds of the invention are salts of inorganic acids such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acid, and of organic acids such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic and tartaric acid. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts), alkaline earth metal salts (such as magnesium and calcium salts), and salts of trometamol (2-amino-2-hydroxymethyl-1,3-propanediol), diethanolamine, lysine or ethylenediamine.

[0024] Salts with a pharmaceutically unacceptable anion such as, for example, trifluoroacetate likewise belong within the framework of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

[0025] All references to "compound(s) of formula I" hereinafter refer to compound(s) of the formula I as described above, and their salts, solvates and physiologically functional derivatives as described herein.

Use

[0026] This invention relates further to the compounds of the formula I and their pharmaceutical compositions for use as PPAR ligands. The PPAR ligands of the invention are suitable as modulators of PPAR activity.

[0027] Peroxisome proliferator-activated receptors (PPAR) are transcription factors which can be activated by ligands and belong to the class of nuclear hormone receptors. There are three PPAR isoforms, PPARalpha, PPARgamma and PPARdelta (identical to PPARbeta), which are encoded by different genes (Peroxisome proliferator-activated receptor (PPAR): structure, mechanisms of activation and diverse functions: Motojima K., Cell Struct Funct., 1993, 18(5), 267-77).

[0028] In humans, PPARgamma exists in three variants, PPARgamma1, gamma2, and gamma3, which are the result of alternative use of promoters and differential mRNA splicing. Different PPARs have different tissue distribution and modulate different physiological functions. The PPARs play a key role in various aspects of the regulation of a large number of genes, the products of which genes are directly or indirectly crucially involved in lipid and carbohydrate metabolism. Thus, for example, the PPARalpha receptor plays an important part in the regulation of fatty acid catabolism or lipoprotein metabolism in the liver, while PPARgamma is crucially involved in regulating adipose cell


PPARdelta appears to be significantly expressed in the CNS; however much of its function there still remains undiscovered. Of singular interest however, is the discovery that PPARdelta was expressed in rodent oligodendrocytes, the major lipid producing cells of the CNS (J. Granneman, et al., J. Neurosci., Res., 1998, 51, 563-573). Moreover, it was also found that a PPARdelta selective agonist was found to significantly increase oligodendroglial myelin gene expression and myelin sheath diameter in mouse cultures (I. Saluja et al., Glia, 2001, 33, 194-204). Thus, PPARdelta activators may be of use for the treatment of demyelinating and dysmyelinating diseases. The use of peroxisome proliferator activated receptor delta agonists for the treatment of MS and other demyelinating diseases can be shown as described in WO2005/097098.

Demyelinating conditions are manifested in loss of myelin - the multiple dense layers of lipids and protein which cover many nerve fibers. These layers are provided by oligodendroglia in the central nervous system (CNS), and Schwann cells in the peripheral nervous system (PNS). In patients with demyelinating conditions, demyelination may be irreversible; it is usually accompanied or followed by axonal degeneration, and often by cellular degeneration. Demyelination can occur as a result of neuronal damage or damage to the myelin itself - whether due to aberrant immune responses, local injury, ischemia, metabolic disorders, toxic agents, or viral infections (Prineas and McDonald, Demyelinating Diseases. In Greenfield’s Neuropathology, 6.sup.th ed. (Edward Arnold: New York, 1997) 813-811, Beers and Berkow, eds., The Merck Manual of Diagnosis and Therapy, 17.sup.th ed. (Whitehouse Station, N.J.: Merck Research Laboratories, 1999) 1299, 1437, 1473-76, 1483).

Central demyelination (demyelination of the CNS) occurs in several conditions, often of uncertain etiology, that have come to be known as the primary demyelinating diseases. Of these, multiple sclerosis (MS) is the most prevalent. Other primary demyelinating diseases include adrenoleukodystrophy (ALD), adrenomyeloneuropathy, AIDS-vacular myelopathy, HTLV-associated myelopathy, Leber’s hereditary optic atrophy, progressive multifocal leukoencephalopathy (PML), subacute sclerosing pancecephalitis, Guillian-Barre syndrome and tropical spastic paraparesis. In addition, there are acute conditions in which demyelination can occur in the CNS, e.g., acute disseminated encephalomyelitis (ADEM) and acute viral encephalitis. Furthermore, acute transverse myelitis, a syndrome in which an acute spinal cord transection of unknown cause affects both gray and white matter in one or more adjacent thoracic segments, can also result in demyelination. Also, disorders in which myelin forming glial cells are damaged including spinal cord injuries, neuropathies and nerve injury.

The present invention relates to compounds of the formula I suitable for modulating the activity of PPARs, including the activity of PPARdelta and PPARalpha. Depending on the modulation profile, the compounds of the formula I are suitable for the treatment, control and prophylaxis of the indications described hereinafter, and for a number of other pharmaceutical applications connected thereto (see, for example, Berger, J., et al., Annu. Rev. Med., 2002, 53,
Compounds of this type are particularly suitable for the treatment and/or prevention of:

1. Disorders of fatty acid metabolism and glucose utilization disorders.
   - Disorders in which insulin resistance is involved

2. Diabetes mellitus, especially type 2 diabetes, including the prevention of the sequelae associated therewith. Particular aspects in this connection are
   - hyperglycemia,
   - improvement in insulin resistance,
   - improvement in glucose tolerance,
   - protection of the pancreatic β cells
   - prevention of macro- and microvascular disorders

3. Dyslipidemias and their sequelae such as, for example, atherosclerosis, coronary heart disease, cerebrovascular disorders etc, especially those (but not restricted thereto) which are characterized by one or more of the following factors:
   - high plasma triglyceride concentrations, high postprandial plasma triglyceride concentrations,
   - low HDL cholesterol concentrations
   - low ApoA lipoprotein concentrations
   - high LDL cholesterol concentrations
   - small dense LDL cholesterol particles
   - high ApoB lipoprotein concentrations

4. Various other conditions which may be associated with the metabolic syndrome, such as:
   - obesity (excess weight), including central obesity
   - thromboses, hypercoagulable and prothrombotic states (arterial and venous)
   - high blood pressure
   - heart failure such as, for example (but not restricted thereto), following myocardial infarction, hypertensive heart disease or cardiomyopathy

5. Disorders or conditions in which inflammatory reactions are involved:
   - atherosclerosis such as, for example (but not restricted thereto), coronary sclerosis including angina pectoris or myocardial infarction, stroke
   - vascular restenosis or reocclusion
   - chronic inflammatory bowel diseases such as, for example, Crohn’s disease and ulcerative colitis
   - asthma
   - lupus erythematosus (LE) or inflammatory rheumatic disorders such as, for example, rheumatoid arthritis
   - other inflammatory states

6. Disorders of cell cycle or cell differentiation processes:
   - adipose cell tumors
   - lipomatous carcinomas such as, for example, liposarcomas
   - solid tumors and neoplasms such as, for example (but not restricted thereto), carcinomas of the gastrointestinal tract, of the liver, of the biliary tract and of the pancreas, endocrine tumors, carcinomas of the lungs, of the kidneys and the urinary tract, of the genital tract, prostate carcinomas etc
   - acute and chronic myeloproliferative disorders and lymphomas
   - angiogenesis

7. Demyelinating and other neurodegenerative disorders of the central and peripheral nervous systems including:
- Alzheimer’s disease
- multiple sclerosis
- Parkinson’s disease
- adrenoleukodystrophy (ALD)
- adrenomyeloneuropathy
- AIDS-vacuolar myelopathy
- HTLV-associated myelopathy
- Leber’s hereditary optic atrophy
- progressive multifocal leukoencephalopathy (PML)
- subacute sclerosing panencephalitis
- Guillain-Barre syndrome
- tropical spastic paraparesis
- acute disseminated encephalomyelitis (ADEM)
- acute viral encephalitis
- acute transverse myelitis
- spinal cord and brain trauma
- Charcot-Marie-Tooth disease

8. Skin disorders and/or disorders of wound healing processes:
- erythematous-squamous dermatoses such as, for example, psoriasis
- acne vulgaris
- other skin disorders and dermatological conditions which are modulated by PPAR
- eczemas and neurodermitis
- dermatitis such as, for example, seborrheic dermatitis or photodermatitis
- keratitis and keratoses such as, for example, seborrheic keratoses, senile keratoses, actinic keratosis, photo-induced keratoses or keratosis follicularis
- keloids and keloid prophylaxis
- warts, including condylomata or condylomata acuminata
- human papilloma viral (HPV) infections such as, for example, venereal papillomata, viral warts such as, for example, molluscum contagiosum, leukoplakia
- papular dermatoses such as, for example, Lichen planus
- skin cancer such as, for example, basal-cell carcinomas, melanomas or cutaneous T-cell lymphomas
- localized benign epidermal tumors such as, for example, keratoderma, epidermal naevi
- chilblains
- wound healing

9. Other disorders
- high blood pressure
- pancreatitis
- syndrome X
- polycystic ovary syndrome (PCOS)
- asthma
- osteoarthritis
- lupus erythematosus (LE) or inflammatory rheumatic disorders such as, for example, rheumatoid arthritis
- vasculitis
- wasting (cachexia)
- gout
- ischemia/reperfusion syndrome
- acute respiratory distress syndrome (ARDS)

Formulations

[0036] The amount of a compound of formula I necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.001 mg to 100 mg (typically from 0.01 mg to 50 mg) per day and per kilogram of bodyweight, for example 0.1-10 mg/kg/day. An intravenous dose may be, for example,
in the range from 0.001 mg to 1.0 mg/kg, which can suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1 ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active ingredient. Thus, ampoules for injections may contain, for example, from 1 mg to 100 mg, and single-dose formulations which can be administered orally, such as, for example, capsules or tablets, may contain, for example, from 0.05 to 1000 mg, typically from 0.5 to 600 mg. For the therapy of the abovementioned conditions, the compounds of formula I may be used as the compound itself, but they are preferably in the form of a pharmaceutical composition with an acceptable carrier. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient’s health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain from 0.05% to 95% by weight of the active ingredient. Other pharmaceutically active substances may likewise be present, including other compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmaceutically acceptable carriers and/or excipients.

[0037] Pharmaceutical compositions of the invention are those suitable for oral, rectal, topical, peroral (for example sublingual) and parenteral (for example subcutaneous, intramuscular, intradermal or intravenous) administration, although the most suitable mode of administration depends in each individual case on the nature and severity of the condition to be treated and on the nature of the compound of formula I used in each case. Coated formulations and coated slow-release formulations also belong within the framework of the invention. Preference is given to acid- and gastric juice-resistant formulations. Suitable coatings resistant to gastric juice comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

[0038] Suitable pharmaceutical preparations for oral administration may be in the form of separate units such as, for example, capsules, cachets, suckable tablets or tablets, each of which contain a defined amount of the compound of formula I; as powders or granules, as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact. The compositions are generally produced by uniform and homogeneous mixing of the active ingredient with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or molding a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets can be produced by tabletting the compound in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one (or more) surface-active/dispersing agent(s) in a suitable machine. Molded tablets can be produced by molding the compound, which is in powder form and is moistened with an inert liquid diluent, in a suitable machine.

[0039] Pharmaceutical compositions which are suitable for peroral (sublingual) administration comprise suckable tablets which contain a compound of formula I with a flavoring, normally sucrose and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

[0040] Pharmaceutical compositions suitable for parenteral administration comprise preferably sterile aqueous preparations of a compound of formula I, which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions of the invention generally contain from 0.1 to 5% by weight of the active compound.

[0041] Pharmaceutical compositions suitable for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing a compound of the formula I with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

[0042] Pharmaceutical compositions suitable for topical use on the skin are preferably in the form of ointment, cream, lotion, paste, spray, aerosol or oil. Carriers which can be used are petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active ingredient is generally present in a concentration of from 0.1 to 15% by weight of the composition, for example from 0.5 to 2%.

[0043] Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal uses can be in the form of single plasters which are suitable for long-term close contact with the patient’s epidermis. Such plasters suitably contain the active ingredient in an aqueous solution which is buffered where appropriate, dissolved and/or dispersed in an adhesive or dispersed in a polymer A suitable active ingredient concentration is about 1% to 35%, preferably about 3% to 15%. A particular possibility is for the active ingredient to be released by electrotransport or iontophoresis as described, for example, in Pharmaceutical Research, 2(6): 318 (1986).

[0044] The compounds of the formula I are distinguished by favorable effects on metabolic disorders. They beneficially influence lipid and sugar metabolism, in particular they lower the triglyceride level and are suitable for the prevention...
and treatment of type II diabetes and atheriosclerosis and the diverse sequelae thereof.

Combinations with other medicaments

[0045] The compounds of the invention can be administered alone or in combination with one or more further pharmaceutically active substances. In particular, the compounds of the invention can be administered in combination with active ingredients having a similar pharmacological action. For example, they can be administered in combination with active ingredients which have favorable effects on metabolic disturbances or disorders frequently associated therewith. Examples of such medicaments are

1. medicaments which lower blood glucose, antidiabetics,
2. active ingredients for the treatment of dyslipidemias,
3. antiatherosclerotic medicaments,
4. antiobesity agents,
5. antiinflammatory active ingredients
6. active ingredients for the treatment of malignant tumors
7. antithrombotic active ingredients
8. active ingredients for the treatment of high blood pressure
9. active ingredients for the treatment of heart failure and
10. active ingredients for the treatment and/or prevention of complications caused by diabetes or associated with diabetes.
11. active ingredients for the treatment of neurodegenerative diseases
12. active ingredients for the treatment of disorders of the central nervous system
13. active ingredients for the treatment of drug, nicotine and alcohol addiction
14. analgesics

[0046] They can be combined with the compounds of the invention of the formula I in particular for a synergistic enhancement of activity. Administration of the active ingredient combination can take place either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present in one pharmaceutical preparation.

[0047] Particularly suitable further active ingredients for the combination preparations are:

[0048] All antidiabetics mentioned in the Rote Liste 2006, Chapter 12; all slimming agents/appetite suppressants mentioned in the Rote Liste 2006, Chapter 1; all lipid-lowering agents mentioned in the Rote Liste 2006, Chapter 58. They can be combined with the compound of the formula I according to the invention in particular for a synergistic enhancement of activity. The active compound combination can be administered either by separate administration of the active compounds to the patient or in the form of combination preparations in which a plurality of active compounds are present in a pharmaceutical preparation. Most of the active compounds listed below are disclosed in USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2001.

[0049] Antidiabetics include insulin and insulin derivatives, such as, for example, Lantus® (see www.lantus.com) or HMR 1964 or those descibed in WO2005005477 (Novo Nordisk), fast-acting insulins (see US 6,221,633), inhalable insulins, such as, for example, Exubera® or oral insulins, such as, for example, IN-105 (Nobex) or Oral-lyn™ (Generex Biotechnology), GLP-1 derivatives, such as, for example, Exenatide, Liraglutide or those disclosed in WO 98/08871 or WO2005027978 by Novo Nordisk A/S, in WO 01/04156 by Zealand or in WO 00/34331 by Beaufour-Ipsen, pramlintide acetate (Symlin; Amylin Pharmaceuticals), and also orally effective hypoglycemic active ingredients.

[0050] The active compounds preferably include

sulfonylureas,
biguanidines,
meglitinides,
oxadiazolidinediones,
thiazolidinediones,
glucosidase inhibitors,
inhibitors of glycogen phosphorylase,
glucagon antagonists,
glucokinase activators,
inhibitors of fructose-1,6-bisphosphatase,
modulators of the glucose transporter 4 (GLUT4),
inhibitors of glutamine:fructose-6-phosphate amidotransferase (GFAT),
GLP-1 agonists,
potassium channel openers, such as, for example, those disclosed in WO 97/26265 and WO 99/03861 by Novo Nordisk A/S,
inhibitors of dipeptidylpeptidase IV (DPP-IV),
insulin sensitizers,
inhibitors of liver enzymes involved in the stimulation of gluconeogenesis and/or glycogenolysis,
modulators of glucose uptake, glucose transport and glucose backresorption, inhibitors of 11ß-HSD1,
inhibitors of protein tyrosine phosphatase 1 B (PTP1 B),
modulators of the sodium/glucose cotransporter 1 or 2 (SGLT1, SGLT2), compounds which alter lipid metabolism, such as
antihyperlipidemic active ingredients and antilipidemic active ingredients,
compounds which reduce food intake or food absorption,
compounds which increase thermogenesis,
PPAR and RXR modulators and
active ingredients which act on the ATP-dependent potassium channel of the beta cells.

[0051] In one embodiment of the invention, the compound of the formula I is administered in combination with a
HMGCoA reductase inhibitor, such as, for example, simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin, rosvastatin or L-659699.

[0052] In one embodiment of the invention, the compound of the formula I is administered in combination with a
cholesterol resorption inhibitor, such as, for example, ezetimibe, tiqueside, pamaqueside, FM-VP4 (sitostanol/campes-
terol ascorbyl phosphate; Forbes Medi-Tech, WO2005042692), MD-0727 (Microbia Inc., W02005021497) or with com-
pounds as described in WO2002066464 (Kotobuki Pharmaceutical Co. Ltd.), WO2005062824 (Merck & Co.) or
WO2005061451 and WO2005061452 (AstraZeneca AB).

[0053] In one embodiment of the invention, the compound of the formula I is administered in combination with a PPAR
gamma agonist, such as, for example, rosiglitazone, pioglitazone, JTT-501, LY-674, KRP-101 or DRF-10945.

[0054] In one embodiment of the invention, the compound of the formula I is administered in combination with a PPAR
alpha agonist, such as, for example, GW9578, GW-590735, K-111, LY-674, KRP-101 or DRF-10945.

[0055] In one embodiment of the invention, the compound of the formula I is administered in combination with a mixed
PPAR alpha/gamma agonist, such as, for example, muraglitazar, tesaglitazar, navelitazar, LY-510929, ONO-5129, E-
3030 or as described in WO00/64888, WO00/64876, WO03/02069, WO2004075891, WO2004076402,
WO2004075815, WO2004076447, WO2004076428, WO2004076401, WO2004076426, WO2004076427,
WO2006018118, WO2006018115, and W02006018116 or in J.P. Berger et al., TRENDS in Pharmacological Sciences
28(5), 244-251, 2005.

[0056] In one embodiment of the invention, the compound of the formula I is administered in combination with a PPAR
delta agonist, such as, for example, GW-501516 or as described in WO2005097762, WO2005097786, WO2005097763,
and W02006029699.

[0057] In one embodiment of the invention, the compound of the formula I is administered in combination with me-
taglidasen or with MBX-2044 or other partial PPAR gamma agonists/antagonists.

[0058] In one embodiment of the invention, the compound of the formula I is administered in combination with a fibrate,
such as, for example, fenofibrate, clofibrate or bezafibrate.

[0059] In one embodiment of the invention, the compound of the formula I is administered in combination with an MTP
inhibitor, such as, for example, implitapide, BMS-201038, R-103757 or those described in WO2005085226.

[0060] In one embodiment of the invention, the compound of the formula I is administered in combination with a CETP
inhibitor, such as, for example, torcetrapib or JTT-705.

[0061] In one embodiment of the invention, the compound of the formula I is administered in combination with a bile
acid resorption inhibitor (see, for example, US 6,245,744, US 6,221,897 or WO00/61568), such as, for example, HMR
1741 or those described in DE 10 2005 033099.1 and DE 10 2005 033100.9.

[0062] In one embodiment of the invention, the compound of the formula I is administered in combination with a polymeric bile acid adsorber, such as, for example, cholestyramine or colesevelam.

[0063] In one embodiment of the invention, the compound of the formula I is administered in combination with an LDL
receptor inducer (see US 6,342,512), such as, for example, HMR1171, HMR1586 or those described in WO2005097738.

[0064] In one embodiment of the invention, the compound of the formula I is administered in combination with Omacor® (omega-3 fatty acids; highly concentrated ethyl esters of eicosapentaenoic acid and docosahexaenoic acid).

[0065] In one embodiment of the invention, the compound of the formula I is administered in combination with an ACAT inhibitor, such as, for example, avasimibe.

[0066] In one embodiment of the invention, the compound of the formula I is administered in combination with an antioxidant, such as, for example, OPC-14117, probucol, tocopherol, ascorbic acid, β-carotene or selenium.

[0067] In one embodiment of the invention, the compound of the formula I is administered in combination with a
vitamin, such as, for example, vitamin B6 or vitamin B12.

[0068] In one embodiment of the invention, the compound of the formula I is administered in combination with a
lipoprotein lipase modulator, such as, for example, ibrolipin (NO-1886).

In one embodiment of the invention, the compound of the formula I is administered in combination with an
ATP-citrate lyase inhibitor, such as, for example, SB-204990.

In one embodiment of the invention, the compound of the formula I is administered in combination with a
squalene synthetase inhibitor, such as, for example, BMS-188494 or as described in WO2005077907.

In one embodiment of the invention, the compound of the formula I is administered in combination with a
lipoprotein(a) antagonist, such as, for example, gemcabene (Cl-1027).

In one embodiment of the invention, the compound of the formula I is administered in combination with an
HM74A receptor agonists, such as, for example, nicotinic acid.

In one embodiment of the invention, the compound of the formula I is administered in combination with
a thiazolidinedione, such as, for example, troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds
disclosed in WO 97/41097 by Dr. Reddy's Research Foundation, in particular 5-[[4-[[3,4-dihydro-3-methyl-4-oxo-2-quinazolinyl-
methoxy]phenyl]methyl]-2,4-thiazolidinedione.

In one embodiment of the invention, the compound of the formula I is administered in combination with an α-
glucosidase inhibitor, such as, for example, migliitol or acarbose.

In one embodiment of the invention, the compound of the formula I is administered in combination with a
active ingredient which acts on the ATP-dependent potassium channel of the beta cells, such as, for example, tolbutamide,
glibenclamide, glipizide, glimepiride or repaglinide.

In one embodiment of the invention, the compound of the formula I is administered in combination with more
than one of the compounds mentioned above, for example in combination with a sulfonylurea and metformin, a sulfo-
ylurea and acarbose, repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin, insulin and trogli-
tazone, insulin and lovastatin, etc.

In one embodiment of the invention, the compound of the formula I is administered in combination with an
inhibitor of glucogen phosphorylase, such as, for example, PSN-357 or FR-258900 or those described in W02003084922,
WO2004007455, WO2005073229-31 or WO2005067932.

In one embodiment of the invention, the compound of the formula I is administered in combination with glucagon
receptor antagonists, such as, for example, A-770077, NNC-25-2504 or such as in W02004100875 or W02005065680.

In one embodiment of the invention, the compound of the formula I is administered in combination with activators
of glucokinase, such as, for example, RO-4389620, LY-2121260 (WO2004063179), PSN-105, PSN-110, GKA-50 or those
described, for example, by Prosidion in WO2004072031, WO2004072066, WO 05103021 or WO 06016178, by
Roche in WO 00058293, WO 00183465, WO 00183476, WO 00185706, WO 00185707, WO 01044216, GB 2385328,
WO 0208209, WO 0214312, WO 0246173, WO 0248106, DE 10293786, WO 03095438, US 04067939 or WO 04052869,
Merck/Banyu in WO 03080585, WO3097824, WO 04081001, WO 05063738 or WO 05090332, by Eli Lilly in WO 04063194,
or by Astra Zeneca in WO 01020327, WO 03000262, WO 03000267, WO 03015774, WO 04045614, WO 04046139, WO 05044801,

In one embodiment of the invention, the compound of the formula I is administered in combination with an
inhibitor of gluconeogenesis, such as, for example, FR-225654.

In one embodiment of the invention, the compound of the formula I is administered in combination with inhibitors
of fructose-1,6-bisphosphatase (FBPase), such as, for example, CS-917.

In one embodiment of the invention, the compound of the formula I is administered in combination with mod-
ulators of the glucose transporter 4 (GLUT4), such as, for example, KST-48 (D-O. Lee et al.: Arzneim.-Forsch. Drug
Res. 54 (12), 835 (2004)).

In one embodiment of the invention, the compound of the formula I is administered in combination with inhibitors
depeptidase IV (DPP-IV), such as, for example, vildagliptin (LAF-237), sitagliptin (MK-0431), saxagliptin (BMS-
477118), GSK-823093, PSN-9301, SYR-322, SYR-619, TA-6666, TS-021, GRC-8200, GW-825964X or as described


In one embodiment of the invention, the compound of the formula I is administered in combination with inhibitors of hormone-sensitive lipase (HSL), such as those described, for example, in WO01/17981, WO01/66531, WO2004035550, W02005073199 or WO/03/051842.

In one embodiment of the invention, the compound of the formula I is administered in combination with inhibitors of acetyl-CoA carboxylase (ACC) such as those described, for example, in WO199946262, WO200372197, WO2003072197 or W02005044814.

In one embodiment of the invention, the compound of the formula I is administered in combination with an inhibitor of phosphoenolpyruvate carboxykinase (PEPCK), such as those described, for example, in WO2004074288.

In one embodiment of the invention, the compound of the formula I is administered in combination with an inhibitor of glycogen synthase kinase-3 beta (GSK-3 beta), such as those described, for example, in US2005222220, WO2004022544, WO2003106410, WO2005058908, US2005038023, WO2005009997, US2005026984, WO200500836, WO2004106343, EP1460075, WO2004041910, WO2003076442, WO2005087727 or W02004046117.

In one embodiment of the invention, the compound of the formula I is administered in combination with an inhibitor of protein kinase C beta (PKC beta), such as, for example, ruboxistaurin.

In one embodiment of the invention, the compound of the formula I is administered in combination with an endothelin-A receptor antagonist, such as, for example, avosentan (SPP-301).

In one embodiment of the invention, the compound of the formula I is administered in combination with inhibitors of "I-kappaB kinase" (IKK inhibitors), such as those described, for example, in WO2001000610, WO2001030774, W02004022553 or W02005097129.

agonists (for example [2-(3a-benzyl-2-methyl-3-oxo-2,3a,4,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl]-1-(4-chlorophenyl)-2-oxoethyl]-1-amino-1,2,3,4,5,6,7-tetrahydrophthalalene-2-carboxamide; (WO 01/91752)) or LB53260, LB53279, LB53278 or THIQ, MB243, RY764, CHIR-785, PT-141 or those described in WO2005060985, WO2005009950, WO20040487159, WO20040478717, WO20040478716, WO2004024720, US20050124652, WO2005051391, WO2004112793, WO200505022014, US20050176628, US20050164914, US20050124636, US20050130988, US200404167201, WO2004005324, WO20040437797, WO2005042516, WO2005040109, WO2005030797, US20040224901, WO200501921, WO200509184, WO2005000339, EP1460069, WO2005047253, WO2005047251, EP1538159, WO2004072076, WO2004072077 or WO2006024390; orexin receptor antagonists (for example 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea hydrochloride (SB-334867-A) or those described, for example, in WO200196302, WO200185693, WO2004085403 or W02005075458); histamine H3 receptor agonists (for example 3-cyclohexyl-1-(4,4-dimethyl-1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)-propan-1-one oxalic acid salt (WO 00/63208) or those described in WO200064884, WO2005082893); CRF antagonists (for example [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 01/83451)); MCH (melanin-concentrating hormone) receptor antagonists (such as, for example, NBI-845, A-761, A-665798, A-798, ATC-0175, T-226296, T-71, GW-803430 or those compounds described in WO2003/15769, WO2005085200, WO2005019240, WO2004011438, WO2004012648, WO2003015769, WO2004072025, WO2005070898, WO2005070925, WO2006018280, WO2006018279, WO2004039780, WO2003033476, WO2002006245, WO2002002744, WO200304027 or FR2868780); CCK-A agonists (such as, for example, 2[(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexylethyl)-thiazol-2-ylcarbamoyl]-5,7-dimethylindol-1-yl]acetamide trifluoroacetic acid salt (WO 99/15552), SR-146131 (WO 0244150) or SSR-125180); serotonin reuptake inhibitors (for example dexfenfluramine); mixed serotonin- and noradrenergic compounds (for example WO 00/71549); 5-HT receptor agonists, for example 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111); 5-HT2C receptor agonists (such as, for example, APD-356, BVT-933 or those described in WO200077010, WO20077001-02, WO2005019180, WO2003064423, WO200242304 or WO2005082859); 5-HT6 receptor antagonists, such as, for example, WO2005058858; bombesin receptor agonists (BRS-3 agonists); galanin receptor antagonists; growth hormone releasing compounds (for example human growth hormone or AOD-9604); growth hormone releasing compounds (tert-butyl 6-benzyloxy-1-(2-diisopropylamino-ethylcarbamoyl)-3,4-dihydro-1H-isouquinoline-2-carboxylate (WO 01/85695)); growth hormone secretagog receptor antagonists (ghrelin antagonists) such as, for example, A-778193 or those described in WO2005030734; TRH agonists (see, for example, EP 0462 884); uncoupling protein 2 or 3 modulators; leptin agonists (see for example Lee, Daniel W.; Leinung, Matthew C.; Rozhavskaya-Arena, Marina; Grasso, Patricia. Leptin agonists as a potential approach to the treatment of obesity. Drugs of the Future (2001), 26(9), 873-881); DA agonists (bromocriptine or Doprexin); lipase/amylase inhibitors (as described, for example, in WO 00/40569); inhibitors of diacylglycerol O-acyltransferases (DGATs) such as described, for example, in US2004/0229497, WO2004094618, WO200508491, WO2005044250, WO2005072740, JP2005206492 or WO2005013907; inhibitors of fatty acid synthase (FAS) such as, for example, C75 or those described in WO2004005277; oxyntomodulin; oleoyl-estrone or thyroid hormone receptor agonists, such as, for example, KB-2115 or those described in WO200582979, WO200172692, WO200194293, WO2003084915, WO2004018421 or WO2005092316. [0102] In one embodiment of the invention, the further active ingredient is lepitin; see for example "Perspectives in the therapeutic use of leptin", Salvador, Javier; Gomez-Ambrosi, Javier; Fruhbeck, Gema, Expert Opinion on Pharmacotherapy (2001), 2(10), 1615-1622. [0103] In one embodiment of the invention, the further active ingredient is desamphetamine or amphetamine. [0104] In one embodiment of the invention, the further active ingredient is fenfluramine or dexfenfluramine. [0105] In another embodiment of the invention, the further active ingredient is sibutramine. [0106] In one embodiment of the invention, the further active ingredient is mazindol or phentermine.
In one embodiment, the compounds of the formula I are administered in combination with bulking agents, preferably insoluble bulking agents (see, for example, carob/Caromax® (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 18(5), 230-6). Caromax is a carob-containing product from Nutrinova, Nutrition Specialties & Food Ingredients GmbH, Industriepark Höchst, 65926 Frankfurt/Main). Combination with Caromax® is possible in one preparation or by separate administration of compounds of the formula I and Caromax®. Caromax® can in this connection also be administered in the form of food products such as, for example, in bakery products or muesli bars.

In one embodiment of the invention, the compound of the formula I is administered in combination with PDE (phosphodiesterase) inhibitors, as described, for example, in WO2003/077949 or WO2005012485.

In one embodiment of the invention, the compound of the formula I is administered in combination with NAR-1 (nicotinic acid receptor) agonists as described, for example, in WO2004094429.

In one embodiment of the invention, the compound of the formula I is administered in combination with CB2 (cannabinoid receptor) agonists as described, for example, in US2005/143448.

In one embodiment of the invention, the compound of the formula I is administered in combination with histamine 1 agonists as described, for example, in WO2005101979.

In one embodiment of the invention, the compound of the formula I is administered in combination with bupropion, as described in WO2006017504.

In one embodiment of the invention, the compound of the formula I is administered in combination with opioid antagonists as described, for example, in WO2005107806 or WO2004094429.

In one embodiment of the invention, the compound of the formula I is administered in combination with neutral endopeptidase inhibitors as described, for example, in WO200202513, WO2002/06492, WO 2002040008, WO2002040022 or WO2002047670.

In one embodiment of the invention, the compound of the formula I is administered in combination with NPY inhibitors (neuropeptide Y) as described, for example, in WO2002047670.

In one embodiment of the invention, the compound of the formula I is administered in combination with sodium/hydrogen exchange inhibitors as described, for example, in WO2003092694.

In one embodiment of the invention, the compound of the formula I is administered in combination with modulators of the glucocorticoid receptor as described, for example, in WO2005090336.

In one embodiment of the invention, the compound of the formula I is administered in combination with nicotine receptor agonists as described, for example, in WO2004094429.

In one embodiment of the invention, the compound of the formula I is administered in combination with NRIs (norepinephrine reuptake inhibitors) as described, for example, in WO2002053140.

In one embodiment of the invention, the compound of the formula I is administered in combination with MOA (E-beta-methoxyacrylate), such as, for example, segeline, or as described, for example, in WO2002053140.

In one embodiment of the invention, the compound of the formula I is administered in combination with anti-thrombotic active ingredients, such as, for example, clopidrogel.

It is to be understood that each suitable combination of the compounds according to the invention with one or more of the compounds mentioned above and optionally one or more further pharmacologically active substances is meant to be included in the scope of the present invention.

The formulae for some of the development codes mentioned above are given below:
The activity of the compounds was tested as follows:

Determination of EC50 values of PPAR agonists in the cellular PPARalpha assay

Principle

The potency of substances which bind to human PPARalpha and activate it in an agonistic manner is analyzed using a stably transfected HEK cell line (HEK= human embryo kidney) which is referred to here as PPARalpha reporter cell line. It contains two genetic elements, a luciferase reporter element (pdeltaM-GAL4-Luc-Zeo) and a PPARalpha fusion protein (GR-GAL4-humanPPARalpha-LBD) which mediates expression of the luciferase reporter element depending on a PPARalpha ligand. The stably and constitutively expressed fusion protein GR-GAL4-humanPPARalpha-LBD binds in the cell nucleus of the PPARalpha reporter cell line via the GAL4 protein portion to the GAL4 DNA binding motifs 5'-upstream of the luciferase reporter element which is stably integrated in the genome of the cell line. There is only weak expression of the luciferase reporter gene in the absence of a PPARalpha ligand if fatty acid-depleted fetal calf serum (cs-FCS) is used in the assay. PPARalpha ligands bind and activate the PPARalpha fusion protein and thereby stimulate the expression of the luciferase reporter gene. The luciferase which is formed can be detected by means of chemiluminescence via an appropriate substrate.

Construction of the PPARalpha reporter cell line

The PPARalpha reporter cell line was prepared in two stages. Firstly, the luciferase reporter element was constructed and stably transfected into HEK cells. For this purpose, five binding sites of the yeast transcription factor GAL4 (Accession # AF264724) were cloned in 5'-upstream of a 68 bp-long minimal MMTV promoter (Accession # V01175). The minimal MMTV promoter section contains a CCAAT box and a TATA element in order to enable efficient transcription by RNA polymerase II. The cloning and sequencing of the GAL4-MMTV construct took place in analogy to the description of Sambrook J. et. al. (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989). Then the complete Photinus pyralis gene (Accession # M15077) was cloned in 3'-downstream of the GAL4-MMTV element. After sequencing, the luciferase reporter element consisting of five GAL4 binding sites, MMTV promoter and luciferase gene
was recloned into a plasmid which confers zeocin resistance in order to obtain the plasmid pdeltaM-GAL4-Luc-Zeo. This vector was transfected into HEK cells in accordance with the statements in Ausubel, F.M. et al. (Current protocols in molecular biology, Vol. 1-3, John Wiley & Sons, Inc., 1995). Then zeocin-containing medium (0.5 mg/ml) was used to select a suitable stable cell clone which showed very low basal expression of the luciferase gene.

[0128] In a second step, the PPARalpha fusion protein (GR-GAL4-humanPPARalpha-LBD) was introduced into the stable cell clone described. For this purpose, initially the cDNA coding for the N-terminal 76 amino acids of the glucocorticoid receptor (Accession # P04150) was linked to the cDNA section coding for amino acids 1-147 of the yeast transcription factor GAL4 (Accession # P04386). The cDNA of the ligand-binding domain of the human PPARalpha receptor (amino acids S167-Y468; Accession # S74349) was cloned in at the 3'-end of this GR-GAL4 construct. The fusion construct prepared in this way (GR-GAL4-humanPPARalpha-LBD) was recloned into the plasmid pcDNA3 (Invitrogen) in order to enable constitutive expression therein by the cytomegalovirus promoter. This plasmid was linearized with a restriction endonuclease and stably transfected into the previously described cell clone containing the luciferase reporter element. The finished PPARalpha reporter cell line which contains a luciferase reporter element and constitutively expresses the PPARalpha fusion protein (GR-GAL4-human PPARalpha-LBD) was isolated by selection with zeocin (0.5 mg/ml) and G418 (0.5 mg/ml).

Assay procedure

[0129] The activity of PPARalpha agonists is determined in a 3-day assay which is described below:

Day 1

[0130] The PPARalpha reporter cell line is cultivated to 80% confluence in DMEM (# 41965-039, Invitrogen) which is mixed with the following additions: 10% cs-FCS (fetal calf serum; #SH-30068.03, Hyclone), 0.5 mg/ml zeocin (#R250-01, Invitrogen), 0.5 mg/ml G418 (#10131-027, Invitrogen), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen). The cultivation takes place in standard cell culture bottles (# 353112, Becton Dickinson) in a cell culture incubator at 37˚C in the presence of 5% CO2. The 80%-confluent cells are washed once with 15 ml of PBS (#14190-094, Invitrogen), treated with 3 ml of trypsin solution (#25300-054, Invitrogen) at 37˚C for 2 min, taken up in 5 ml of the DMEM described and counted in a cell counter. After dilution to 500,000 cells/ml, 35,000 cells are seeded in each well of a 96 well microtiter plate with a clear plastic base (#3610, Corning Costar). The plates are incubated in the cell culture incubator at 37˚C and 5% CO2 for 24 h.

Day 2

[0131] PPARalpha agonists to be tested are dissolved in DMSO in a concentration of 10 mM. This stock solution is diluted in DMEM (#41965-039, Invitrogen) which is mixed with 5% cs-FCS (#SH-30068.03, Hyclone), 2 mM L-glutamine (#25030-024, Invitrogen) and the previously described antibiotics (zeocin, G418, penicillin and streptomycin).

[0132] Test substances are tested in 11 different concentrations in the range from 10 µM to 100 pM. More potent compounds are tested in concentration ranges from 1 µM to 10 pM or between 100 nM and 1 pM.

[0133] The medium of the PPARalpha reporter cell line seeded on day 1 is completely removed by aspiration, and the test substances diluted in medium are immediately added to the cells. The dilution and addition of the substances is carried out by a robot (Beckman FX). The final volume of the test substances diluted in medium is 100 µl per well of a 96 well microtiter plate. The DMSO concentration in the assay is less than 0.1 % v/v in order to avoid cytotoxic effects of the solvent.

[0134] Each plate was charged with a standard PPARalpha agonist, which was likewise diluted in 11 different concentrations, in order to demonstrate the functioning of the assay in each individual plate. The assay plates are incubated in an incubator at 37˚C and 5% CO2 for 24 h.

Day 3

[0135] The PPARalpha reporter cells treated with the test substances are removed from the incubator, and the medium is aspirated off. The cells are lysed by pipetting 50 µl of Bright Glo reagent (from Promega) into each well of a 96 well microtiter plate. After incubation at room temperature in the dark for 10 minutes, the microtiter plates are measured in the luminometer (Trilux from Wallac). The measuring time for each well of a microtiter plate is 1 sec.

Evaluation

[0136] The raw data from the luminometer are transferred into a Microsoft Excel file. Dose-effect plots and EC50
values of PPAR agonists are calculated using the XL.Fit program as specified by the manufacturer (IDBS).

Determination of EC50 values of PPAR agonists in the cellular PPARdelta assay

Principle

The potency of substances which bind to human PPARdelta and activate it in an agonistic manner is analyzed using a stably transfected HEK cell line (HEK= human embryo kidney) which is referred to here as PPARdelta reporter cell line. In analogy to the assay described for PPARalpha, the PPARdelta reporter cell line also contains two genetic elements, a luciferase reporter element (pdeltaM-GAL4-Luc-Zeo) and a PPARdelta fusion protein (GR-GAL4-humanPPARdelta-LBD) which mediates expression of the luciferase reporter element depending on a PPARdelta ligand. The stably and constitutively expressed fusion protein GR-GAL4-humanPPARdelta-LBD binds in the cell nucleus of the PPARdelta reporter cell line via the GAL4 protein portion to the GAL4 DNA binding motifs 5'-upstream of the luciferase reporter element which is stably integrated in the genome of the cell line. There is only little expression of the luciferase reporter gene in the absence of a PPARdelta ligand if fatty acid-depleted fetal calf serum (cs-FCS) is used in the assay. PPARdelta ligands bind and activate the PPARdelta fusion protein and thereby stimulate expression of the luciferase reporter gene. The luciferase which is formed can be detected by means of chemiluminescence via an appropriate substrate.

Construction of the PPARdelta reporter cell line

The production of the stable PPARdelta reporter cell line is based on a stable HEK-cell clone which was stably transfected with a luciferase reporter element. This step was already described above in the section "construction of the PPARalpha reporter cell line". In a second step, the PPARdelta fusion protein (GR-GAL4-humanPPARdelta-LBD was stably introduced into this cell clone. For this purpose, the cDNA coding for the N-terminal 76 amino acids of the glucocorticoid receptor (Accession # P04150) was linked to the cDNA section coding for amino acids 1-147 of the yeast transcription factor GAL4 (Accession # P04386). The cDNA of the ligand-binding domain of the human PPARdelta receptor (amino acids S139-Y441; Accession # L07592) was cloned in at the 3'-end of this GR-GAL4 construct. The fusion construct prepared in this way (GR-GAL4-humanPPARdelta-LBD) was recloned into the plasmid pcDNA3 (invitrogen) in order to enable constitutive expression by the cytomegalovirus promoter. This plasmid was linearized with a restriction endonuclease and stably transfected into the previously described cell clone containing the luciferase reporter element. The resulting PPARdelta reporter cell line which contains a luciferase reporter element and constitutively expresses the PPARdelta fusion protein (GR-GAL4-human PPARdelta-LBD) was isolated by selection with zeocin (0.5 mg/ml) and G418 (0.5 mg/ml).

Assay procedure and evaluation

The activity of PPARdelta agonists is determined in a 3-day assay in exact analogy to the procedure already described for the PPARalpha reporter cell line except that the PPARdelta reporter cell line and a specific PPARdelta agonist was used as a standard to control efficacy.

PPARdelta EC50 values in the range from 1nM to >10μM were measured for the PPAR agonists of Examples 1 to 25 described in this application. Compounds of the invention of the formula I activate the PPARdelta receptor partially.

Determination of EC50 values of PPAR agonists in the cellular PPARgamma assay

Principle

A transient transfection system is employed to determine the cellular PPARgamma activity of PPAR agonists. It is based on the use of a luciferase reporter plasmid (pGL3basic-5xGAL4-TK) and of a PPARgamma expression plasmid (pcDNA3-GAL4-humanPPARgammaLBD). Both plasmids are transiently transfected into human embryonic kidney cells (HEK cells). There is then expression in these cells of the fusion protein GAL4-humanPPARgammaLBD which binds to the GAL4 binding sites of the reporter plasmid. In the presence of a PPARgamma-active ligand, the activated fusion protein GAL4-humanPPARgammaLBD induces expression of the luciferase reporter gene, which can be detected in the form of a chemiluminescence signal after addition of a luciferase substrate. As a difference from the stably transfected PPARalpha reporter cell line, in the cellular PPARgamma assay the two components (luciferase reporter plasmid and PPARgamma expression plasmid) are transiently transfected into HEK cells because stable and permanent expression of the PPARgamma fusion protein is cytotoxic.
Construction of the plasmids

[0144] The luciferase reporter plasmid pGL3basic-5xGAL4-TK is based on the vector pGL3basic from Promega. The reporter plasmid is prepared by cloning five binding sites of the yeast transcription factor GAL4 (each binding site with the sequence 5’-CTCGGAGGACAGTACTCCG-3’), together with a 160 bp-long thymidine kinase promoter section (Genbank Accession # AF027128) 5’-upstream into pGL3basic. 3’-downstream of the thymidine kinase promoter is the complete luciferase gene from Photinus pyralis (Genbank Accession # M15077) which is already a constituent of the plasmid pGL3basic used. The cloning and sequencing of the reporter plasmid pGL3basic-5xGAL4-TK took place in analogy to the description in Sambrook J. et. al. (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989). The PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD was prepared by first cloning the cDNA coding for amino acids 1-147 of the yeast transcription factor GAL4 (Genbank Accession # P04386) into the plasmid pcDNA3 (from Invitrogen) 3’-downstream of the cytomegalovirus promoter. Subsequently, the cDNA of the ligand-binding domain (LBD) of the human PPARgamma receptor (amino acids I152-Y475; Accession # g1480099) 3’-downstream of the GAL4 DNA binding domain. Cloning and sequencing of the PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD again took place in analogy to the description in Sambrook J. et. al. (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989). Besides the luciferase reporter plasmid pGL3basic-5xGAL4-TK and the PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD, also used for the cellular PPARgamma assay are the reference plasmid pRL-CMV (from Promega) and the plasmid pBluescript SK(+) from Stratagene. All four plasmids were prepared using a plasmid preparation kit from Qiagen, which ensured a plasmid quality with a minimal endotoxin content, before transfection into HEK cells.

Assay procedure

[0145] The activity of PPARgamma agonists is determined in a 4-day assay which is described below. Before the transfection, HEK cells are cultivated in DMEM (# 41965-039, Invitrogen) which is mixed with the following additions: 10% FCS (#16000-044, Invitrogen), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen).

Day 1

[0146] Firstly, solution A, a transfection mixture which contains all four plasmids previously described in addition to DMEM, is prepared. The following amounts are used to make up 3 ml of solution A for each 96 well microtiter plate for an assay: 2622 μl of antibiotic- and serum-free DMEM (# 41965-039, Invitrogen), 100 μl of reference plasmid pRL-CMV (1 ng/μl), 100 μl of luciferase reporter plasmid pGL3basic-5xGAL4-TK (10 ng/μl), 100 μl of PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD (100 ng/μl) and 78 μl of plasmid pBluescript SK(+) (500 ng/μl). Then 2 ml of solution B are prepared by mixing 1.9 ml of DMEM (# 41965-039, Invitrogen) with 100 μl of PolyFect transfection reagent (from Qiagen) for each 96 well microtiter plate. Subsequently, 3 ml of solution A are mixed with 2 ml of solution B to give 5 ml of solution C, which is thoroughly mixed by multiple pipetting and incubated at room temperature for 10 min.

[0147] 80%-confluent HEK cells from a cell culture bottle with a capacity of 175 cm² are washed once with 15 ml of PBS (#14190-094, Invitrogen) and treated with 3 ml of trypsin solution (#25300-054, Invitrogen) at 37°C for 2 min. The cells are then taken up in 15 ml of DMEM (# 41965-039, Invitrogen) which is mixed with 10% FCS (# 16000-044, Invitrogen), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen). After the cell suspension has been counted in a cell counter, the suspension is diluted to 250,000 cells/ml. 15 ml of this cell suspension are mixed with 5 ml of solution C for each well microtiter plate. Subsequently, 3 ml of solution A are mixed with 2 ml of solution B to give 5 ml of solution C, which is thoroughly mixed by multiple pipetting and incubated at room temperature for 10 min.

Day 2

[0148] PPAR agonists to be tested are dissolved in DMSO in a concentration of 10 mM. This stock solution is diluted in DMEM (# 41965-039, Invitrogen) which is mixed with 2% Ultroser (#12039-012, Biosaera), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen). Test substances are tested in a total of 11 different concentrations in the range from 10 μM to 100 pM. More potent compounds are tested in concentration ranges from 1 μM to 10 pM.

[0149] The medium of the HEK cells transfected and seeded on day 1 is completely removed by aspiration, and the test substances diluted in medium are immediately added to the cells. The dilution and addition of the substances is carried out by a robot (Beckman FX). The final volume of the test substances diluted in medium is 100 μl per well of a 96 well microtiter plate. Each plate is charged with a standard PPARgamma agonist, which is likewise diluted in 11
different concentrations, in order to demonstrate the functioning of the assay in each individual plate. The assay plates are incubated in an incubator at 37°C and 5% CO2.

Day 4

[0150] After removal of the medium by aspiration, 50 μl of Dual-GloTM reagent (Dual-GloTM Luciferase Assay System; Promega) are added to each well in accordance with the manufacturer’s instructions in order to lyze the cells and provide the substrate for the firefly luciferase (Photinus pyralis) formed in the cells. After incubation at room temperature in the dark for 10 minutes, the firefly luciferase-mediated chemiluminescence is measured in a measuring instrument (measuring time/well 1 sec; Trilux from Wallac). Then 50 μl of the Dual-GloTM Stop & Glo reagent (Dual-GloTM Luciferase Assay System; Promega) is added to each well in order to stop the activity of the firefly luciferase and provide the substrate for the Renilla luciferase expressed by the reference plasmid pRL-CMV. After incubation at room temperature in the dark for a further 10 minutes, a chemiluminescence mediated by the Renilla luciferase is again measured for 1 sec/well in the measuring instrument.

Evaluation

[0151] The crude data from the luminometer are transferred into a Microsoft Excel file. The firefly/Renilla luciferase activity ratio is determined for each measurement derived from one well of the microtiter plate. The dose-effect plots and EC50 values of PPAR agonists are calculated from the ratios by the XL.Fit program as specified by the manufacturer (IDBS).

[0152] PPARgamma EC50 values in the range from 1 nM to >10 μM were measured for the PPAR agonists of Examples 1 to 25 described in this application. Compounds of the invention of the formula I activate the PPARgamma receptor partially.

[0153] The examples given in Table I, where a dotted line means the point of attachment to the amide, serve to illustrate the invention, but without limiting it.
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<th>R3</th>
<th>R4</th>
<th>R5</th>
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<th>R7</th>
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(continued)

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(continued)
The potency of some of the described examples are indicated in the following table:

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<th>Example</th>
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<th>PPARgamma EC50 (µM)</th>
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Processes

The compounds of the general formula I according to the invention where A, n, z, R1, R2, R3, R4, R5, R6, R7, R8 are as defined can be obtained as outlined in the reaction schemes below:

An amino bicyclic compound of general formula 2 is treated with an acylating agent like acetic anhydride or acetyl chloride to yield the intermediate 3, which on action with chlorosulfonic acid leads the benzenesulfonyl chloride of general formula 4. The benzenesulfonyl chloride of general formula 4 is coupled with the [1,3,4]thiadiazol-2-ylamine of the general formula 5 in the presence of a base or in a basic solvent like pyridine to obtain the sulfonamide that after refluxing in 2N hydrochloric acid to remove the N-acetyl group gives the amine of general formula 6 as its hydrochloric acid salt.

The amine of general formula 6 is coupled with a carboxylic acid of general formula 7, where X = OH, with a coupling reagent as O-((Ethoxycarbonyl)cyano)ethylenediamine)-N,N,N',N'-tetramethyluronium tetrafluoroborat in the presence of a base such as triethylamine in an appropriate solvent like dimethylformamide or tetrahydrofuran to obtain the compound of general formula 1. Alternatively the amine of general formula 6 is coupled with a carbonyl chloride of
general formula 7, where X = Cl - or with other known derivatives of acids that are able to react with amines - in a solvent as dichloromethane and in the presence of a base like triethylamine to obtain the compound of general formula 1.

A further method to prepare the compounds of the general formula 1 consists in the acylation of the amino indanes 2 with the carboxylic acid derivatives 7 and the subsequent reaction with chloro sulfonic acid followed by reaction with the amino heterocycle 5.

List of abbreviation:

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<td>AlBN</td>
<td>2,2’-azobis(2-methylpropionitrile)</td>
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<tr>
<td>Bn</td>
<td>benzyl</td>
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Experimental part

1) 2-Ethoxy-N-[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-4-trifluoromethyl-benzamide

[0160]

1a) 2-Methoxy-4-trifluoromethoxy-benzoic acid methyl ester

[0161]

1.0 g 2-hydroxy-(trifluoromethoxy)benzoic acid were dissolved in 30 ml dimethylformamide. 640 mg iodomethane and 4.70 g cesium carbonate were added and the reaction mixture was stirred at room temperature for three hours. The reaction mixture was diluted by addition of 100 ml ethyl acetate, washed with 30 ml water and brine and then dried over MgSO4. The solvent was removed in vacuo to obtain 590 mg 2-methoxy-4-trifluoromethoxy-benzoic acid methyl ester.

MS(ESI): (M+1) = 251

1 b) 2-Methoxy-4-trifluoromethoxy-benzoic acid

[0163]
590 mg 2-Methoxy-4-trifluoromethoxy-benzoic acid methyl ester was dissolved in a mixture of 30 ml tetrahydrofuran and 10 ml water. 367 mg lithium hydroxide were added and the reaction mixture stirred at 60°C for two hours. The cooled reaction mixture was acidified by dropwise addition of concentrated hydrochloric acid, then the mixture was extracted three times with portions of 80 ml ethyl acetate. The combined organic layers were dried over MgSO4. The solvent was removed in vacuo to obtain 518 mg 2-methoxy-4-trifluoromethoxy-benzoic acid.

MS(ESI): (M+1) = 237

1c) N-Indan-2-yl-acetamide

Acetic anhydride (3,55 ml) was dropped to the mixture of 6,37 g 2-amino indane hydrochloride, 60 ml of ethyl acetate and 10,4 ml triethylamine and the reaction mixture was stirred at room temperature for 15 hours. The solvents were evaporated in vacuo and the solid residue was digerated with water, filtered and dried at 40 °C in vacuo.

Yield: 5,5 g Mp.: 126,5 °C

1d) 2-Acetylamino-indan-5-sulfonyl chloride

1,6 ml of chloro sulfonic acid was dropped to the stirred solution of 1,06 g N-Indan-2-yl-acetamide and 50 ml of dichloromethane and the mixture was stirred for 15 hours at room temperature. The reaction was than quenched with cold water and die organic phase separated, dried over sodium sulfate evaporated. The resulting residue was used for further reaction without further purification.

Yield: 1,4 g

1e) N-[5-(5-Isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-acetamide

2-Acetylamino-indan-5-sulfonyl chloride (500 mg) was dissolved in 5 ml of pyridine and a catalytic amount of 4-dimethylamino pyridine was added. After addition of 262 mg of 5-isopropyl-[1,3,4]thiadiazol-2-ylamine the mixture was stirred at 60 °C for 1 hour followed by evaporation. The resulting crude material was purified by column chromatography (silica gel, eluent: dichloromethane:methanol = 95:5).

Yield: 250 mg MS(ESI): (M+1) = 381

1f) N-(5-Sulfamoyl-indan-2-yl)-acetamide
was prepared from 2-Acetylamino-indan-5-sulfonyl chloride and an excess of ammonia. 
MS(ESI): (M+1) = 255

1g) 2-Amino-indan-5-sulfonic acid (5-isopropyl-[1,3,4]thiadiazol-2-yl)-amide hydrochloride

[N-\[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-acetamide (96 mg) was heated and stirred for 27 hours in 10 ml 2N hydrochloric acid at 100°C. After completion a clear solution occurred. This was evaporated to dryness and the solid residue was used without further purification. 
MS(ESI): (M+1) = 339

1) 2-Ethoxy-N-[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-4-trifluoromethyl-benzamide (A003541307)

The mixture of 2-amino-indan-5-sulfonic acid (5-isopropyl-[1,3,4]thiadiazol-2-yl)-amide hydrochloride (40 mg), 1.5 ml of dimethyl formamide, 0.037 ml of triethylamine, 41 mg of HATU and 25 mg of 2-ethoxy-4-trifluoromethyl-benzoic acid was stirred at room temperature over night. The solvents were evaporated in vacuo and the resulting crude material was purified by column chromatography (silica gel, eluent: dichloromethane:methanol = 95:5). 
MS(ESI): (M+1) = 555

1.1) 2-Ethoxy-N-[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-4-trifluoromethyl-benzamide (Enantiomer 1) and

1.2) 2-Ethoxy-N-[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-4-trifluoromethyl-benzamide (Enantiomer 2)

were prepared by separation of the racemic compound of example 1 on a chiral column (chiralcel OJ-H/73, eluent: MeOH+0.1 % TFA, 30°C)

2) 2-Ethoxy-4-trifluoromethyl-N-[5-(5-trifluoromethyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-benzamide
was prepared by a method similar to example 1) starting with the intermediate of example 2a).

MS(ESI): (M+1) = 581

2a) N-[5-(5-Trifluoromethyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-acetamide

[0177]

[0178] The mixture of 300 mg of 2-chloro-5-trifluoromethyl-[1,3,4]thiadiazol, 300 mg of N-(5-sulfamoyl-indan-2-yl)-acetamide, 1.8 g cesium carbonate und 10 ml of NMP was stirred at 70 °C for 3 hours. After cooling to room temperature 50 ml of water were added and with 2N hydrochloric acid a pH = 3 was adjusted. The product was extracted twice with 30 ml of ethyl acetate, the organic layer was washed with 20 ml of water, dried over sodium sulfate and evaporated in vacuo. The resulting crude material was purified by column chromatography (silica gel, eluent: dichloromethane:methanol = 90:10).

MS(ESI): (M+1) = 407

[0179] The following compounds were prepared by similar methods:

3) 4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-carbonsaure-[5-(5 -isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-amid

[0180] MS(ESI): (M+1) = 608

4) 4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-carbonsaure-[5-(5 -cyclopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-amid

[0181] MS(ESI): (M+1) = 606

5) 2-Ethoxy-N-[(S)-7-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-trifluoromethyl-benzamide

[0182]
was prepared by a method similar to example 1) starting with the intermediate of example 5d).
MS(ESI): (M+1) = 569

5a) (S)-N-(1,2,3,4-Tetrahydro-naphthalen-2-yl)-acetamide

[0183]

was prepared by reaction of the commercially available (S)-7-amino-5,6,7,8-tetrahydronaphthalene with acetic anhydride according to known methods.
MS(ESI): (M+1) = 190

5b) (S)-7-Acetylamino-5,6,7,8-tetrahydro-naphthalene-2-sulfonyl chloride

[0184]

was prepared by sulfochlorination of the compound of the example 5a) with chloro sulfonic acid.
MS(ESI): (M+1) = 288

5c) (S)-N-[(S)-7-(5-Isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-1,2,3,4-tetrahydronaphthalene-2-yl]-acetamide

[0185]

was prepared by reaction of the compound of the example 5b) with 5-isopropyl-[1,3,4]thiadiazol-ylamine in pyridine.
MS(ESI): (M+1) = 395

5d) (S)-7-Amino-5,6,7,8-tetrahydro-naphthalene-2-sulfonic acid-(5-isopropyl-[1,3,4]thiadiazol-2-yl)-amide-hydrochloride

[0186]
was prepared by reaction of the compound of the example 5c) with 5N hydrochloric acid at 100 °C for 25 hours.
MS(ESI): (M+1) = 353

6) 2-Ethoxy-N-[(R)-7-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-1,2,3,4-tetrahydro-naphthalene-2-yl]-4-trifluoromethyl-benzamide

was prepared by a reaction sequence similar to the preparation of the compound of example 5) starting with the commercially available (R)-7-amino-5,6,7,8-tetrahydro-naphthalene.
MS(ESI): (M+1) = 569

7) N-[5-Chloro-6-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-inden-2-yl]-2-ethoxy-4-trifluoromethyl-benzamide

was prepared by a reaction sequence similar to the preparation of the compound of example 1) starting with 5-chloro-indan-2-ylamine.
MS(ESI): (M+1) = 589

8) 2-Ethoxy-N-[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl]-6-methoxy-indan-2-yl]-4-trifluoromethyl-benzamide

was prepared by a reaction sequence similar to the preparation of the compound of example 1) starting with 5-methoxy-indan-2-ylamine.
9) 3-Ethoxy-5-trifluoromethyl-thiophene-2-carboxylic acid [5-chloro-6-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-amide

[0190]

[0191] This compound was prepared by reaction of 2-Amino-6-chloro-indan-5-sulfonic acid (5-isopropyl-[1,3,4]thiadiazol-2-yl)-hydrochloride with 3-ethoxy-5-trifluoromethyl-thiophene-2-carboxylic acid (mp.: 143.7°C) obtained from 3-ethoxy-5-trifluoromethyl-thiophene-2-carboxylic acid methyl ester by hydrolysis with lithium hydroxide in water/methanol.

[0192] The 3-ethoxy-5-trifluoromethyl-thiophene-2-carboxylic acid methyl ester (mp.: 93.6°C) was prepared from the known 3-hydroxy-5-trifluoromethyl-thiophene-2-carboxylic acid methyl ester (Synthesis 2000, No.8, 1078-1080) by alkylation with ethyliodide in the presence of cesium carbonate in DMF as solvent.

MS(ESI): (M+1) = 595

10) 3-Ethoxy-5-trifluoromethyl-thiophene-2-carboxylic acid [5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-6-methoxy-indan-2-yl]-amide

[0193]

[0194] This compound was prepared similarly by reaction of 2-Amino-6-methoxi-indan-5-sulfonic acid (5-isopropyl-[1,3,4]thiadiazol-2-yl)-hydrochloride with 3-ethoxy-5-trifluoromethyl-thiophene-2-carboxylic acid.

MS(ESI): (M+1) = 591

11) 3-Ethoxy-5-trifluoromethyl-thiophene-2-carboxylic acid [5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-amide

[0195]

[0196] This compound was prepared similarly by reaction of 2-Amino-indan-5-sulfonic acid (5-isopropyl-[1,3,4]thiadiazol-2-yl)-hydrochloride with 3-ethoxy-5-trifluoromethyl-thiophene-2-carboxylic acid.

MS(ESI): (M+1) = 561
12) 2-Ethoxy-N-[2-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-6,7,8,9-tetrahydro-5H-benzocyclohepten-7-yl]-4-trifluoromethyl-benzamide

was prepared by a reaction sequence similar to the preparation of the compound of example 1) starting with 6,7,8,9-tetrahydro-5H-benzocyclohepten-7-ylamine.
MS(ESI): (M+1) = 583

13) 2-Chloro-N-[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-5-trifluoromethyl-benzamide

This compound was prepared similarly by reaction of 2-amino-indan-5-sulfonic acid (5-isopropyl-[1,3,4]thiadiazol-2-yl)-hydrochloride with 2-chloro-5-trifluoromethyl-benzoic acid.
MS(ESI): (M+1) = 545

14) 4-Chloro-N-[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-2-methylbenzamide

This compound was prepared similarly by reaction of 2-amino-indan-5-sulfonic acid (5-isopropyl-[1,3,4]thiadiazol-2-yl)-hydrochloride with 4-chloro-2-methyl-benzoic acid.
MS(ESI): (M+1) = 491

15) 2,3-Difluoro-N-[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-4-trifluoromethyl-benzamide

[0202]
[0203] This compound was prepared similarly by reaction of 2-amino-indan-5-sulfonic acid (5-isopropyl-[1,3,4]thiadiazol-2-yl)-hydrochloride with 2,3-difluoro 4-trifluoromethyl-benzoic acid.

MS(ESI): (M+1) = 547

16) 2-Fluoro-N-[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-inden-2-yl]-4-trifluoromethyl-benzamide

[0204]

[0205] This compound was prepared similarly by reaction of 2-amino-indan-5-sulfonic acid (5-isopropyl-[1,3,4]thiadiazol-2-yl)-hydrochloride with 2-fluoro 4-trifluoromethyl-benzoic acid.

MS(ESI): (M+1) = 529

17) 4-Chloro-N-[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-inden-2-yl]-2-methoxybenzamide

[0206]

[0207] This compound was prepared similarly by reaction of 2-amino-indan-5-sulfonic acid (5-isopropyl-[1,3,4]thiadiazol-2-yl)-hydrochloride with 4-chloro-2-methoxy-benzoic acid.

MS(ESI): (M+1) = 507

18) 2,4-Dichloro-N-[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-inden-2-yl]-benzamide

[0208]
0209] This compound was prepared similarly by reaction of 2-amino-indan-5-sulfonic acid (5-isopropyl-[1,3,4]thiadiazol-2-yl)-hydrochloride with 2,4-dichloro-benzoic acid.
MS(ESI): (M+1) = 511

19) 2-Ethoxy-N-[5-fluoro-6-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-indan-2-yl]-4-trifluoromethyl-benzamide

0210]

0211] This compound was prepared similarly to the procedure described in example 1 starting from 5-fluoro-indan-2-yl-amine.
MS(ESI): (M+1) = 573

20) 2-Ethoxy-N-[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-1-methyl-indan-2-yl]-4-trifluoromethyl-benzamide

0212]

0213] This compound was prepared similarly to the procedure described in example 1 starting from 1-methyl-indan-2-yl-amine.
MS(ESI): (M+1) = 569

21) 2-Ethoxy-N-[5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-6-(2,2,2-trifluoroethoxy)-indan-2-yl]-4-trifluoromethyl-benzamide

0214]

0215] This compound was prepared similarly to the procedure described in example 1 starting from 5-(2,2,2-trifluoro-
ethoxy)-inden-2-yl-amine:
MS(ESI): \((M+1) = 653\)

22) \(N\)-[5-(5-Cyclopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-inden-2-yl]-2-ethoxy-4-trifluoromethyl-benzamide

[0216]

[0217] This compound was prepared similarly to the procedure described in example 1 starting from 5-cyclopropyl-[1,3,4]thiadiazol-2-ylamine.
MS(ESI): \((M+1) = 553\)

23) -Ethoxy-N-[5-(5-phenyl-[1,3,4]thiadiazol-2-ylsulfamoyl]-inden-2-yl]-4-trifluoromethyl-benzamide

[0218]

[0219] This compound was prepared similarly to the procedure described in example 1 starting from 5-phenyl-[1,3,4]thiadiazol-2-ylamine.
MS(ESI): \((M+1) = 589\)

24) 2-Ethoxy-N-[5-(5-cyclohexyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-inden-2-yl]-4-trifluoromethyl-benzamide

[0220]

[0221] This compound was prepared similarly to the procedure described in example 1 starting from 5-cyclohexyl-[1,3,4]thiadiazol-2-ylamine.
MS(ESI): \((M+1) = 595\)

25) 3-Methoxy-pyridine-2-carboxylic acid [5-(5-isopropyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-inden-2-yl]-amide

[0222]
This compound was prepared similarly to the procedure described in example 1 starting from 3-methoxy-pyridine-2-carboxylic acid.

MS(ESI): (M+1) = 474

Claims

1. Compounds of the formula I:

   wherein

   R1 is (C1-C4) alkyl, (C0-C2) alkylene (C3-C6) cycloalkyl, (C0-C2) alkylene-(C6-C10) aryl, wherein alkyl, aryl, and cycloalkyl can be unsubstituted or mono, di- or trisubstituted by F;
   R2 is H, halogen, (C1-C6) alkyl, O-(C0-C4) alkylene-H, wherein alkyl and alkylene are unsubstituted or mono, di- or trisubstituted by F;
   R3 is H;
   R4 is H;
   R5 is H, (C1-C4) alkyl;
   A is (C6) aryl or (C5-C6) heteroaryl;
   n is 1, 2;
   z is 1;
   R6 is (C1-C4) alkyl, halogen, (C0-C2) alkylene-O-(C0-C6) alkylene-H, (C0-C2) alkylene-(C6-C10) aryl, wherein alkyl, aryl and alkylene are unsubstituted or mono, di- or trisubstituted by F and aryl can be unsubstituted or monosubstituted by CF3;
   R7 is H, (C1-C4) alkyl, halogen, wherein alkyl is unsubstituted or mono, di- or trisubstituted by F;
   R8 is H, F;

   in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

2. Compounds of the formula I as claimed in claim 1, wherein

   R1 is (C1-C4) alkyl, (C3-C6) cycloalkyl, phenyl, wherein alkyl can be unsubstituted or mono, di- or tri substituted by F;
   R2 is H, F, Cl, O-(C1-C4) alkylene-H, wherein alkylene is unsubstituted or mono, di- or trisubstituted by F;
   R3 is H;
   R4 is H;
   R5 is H, (C1-C4) alkyl;
   A is phenyl, thiophen, thiazol, pyridine;
   n is 1, 2;
   z is 1;
   R6 is (C1-C4) alkyl, F, Cl, O-(C0-C6) alkylene-H, phenyl, wherein phenyl can be unsubstituted or monosubstituted by CF3;
R7 is H, (C1-C4) alkyl, Cl, wherein alkyl is unsubstituted or mono, di- or trisubstituted by F;
R8 is H, F,

in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

3. Compounds of the formula 1 as claimed in claims 1 to 2, wherein

R1 is ethyl, isopropyl, tert.butyl, cyclopropyl, cyclohexyl, phenyl or trifluoromethyl;
R2, R3, R4, R5 are H, F, Cl, CH3, OCH3;
A is phenyl;
n is 1;
z is 1;
R6 is in ortho position and Cl, Br, or O(C1-C2)-alkyl;
R7 is in para position and Cl, Br or CF3;
R8 is H;

in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

4. Compounds of the formula 1 as claimed in claims 1 to 3, wherein

R1 is isopropyl;
R2, R3, R4, R5 are H;
A is phenyl;
n is 1;
z is 1;
R6 is O(C1-C2)-alkyl and in ortho position ;
R7 is in para position and Cl or CF3;
R8 is H;

in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

5. Compounds of the formula 1 as claimed in claims 1 to 4, wherein

R1 is trifluoromethyl;
R2, R3, R4, R5 are H;
A is phenyl;
n is 1;
z is 1;
R6 is O-ethyl and in ortho position ;
R7 is in para position and Cl or CF3;
R8 is H;

in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

6. Compounds of the formula 1 as claimed in claims 1 to 5, wherein

R1 is cyclohexyl;
R2, R3, R4, R5 are H;
A is phenyl;
n is 1;
z is 1;
R6 is O-ethyl and in ortho position ;
R7 is in para position and Cl or CF3;
R8 is H;
7. Compounds of the formula 1 as claimed in claims 1 to 6, wherein

   R1 is phenyl;
   R2, R3, R4, R5 are H;
   A is phenyl;
   n is 1;
   z is 1;
   R6 is O-ethyl and in ortho position;
   R7 is in para position and Cl or CF3;
   R8 is H;

in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

8. Compounds of the formula 1 as claimed in claims 1 to 7, wherein

   R1 is cyclopropyl;
   R2, R3, R4, R5 are H;
   A is phenyl;
   n is 1;
   z is 1;
   R6 is O-ethyl and in ortho position;
   R7 is in para position and Cl or CF3;
   R8 is H;

in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

9. Compounds of the formula 1 as claimed in claims 1 to 8, wherein

   R1 is isopropyl;
   R2, R3, R4, R5 are H;
   A is thiophen;
   n is 1;
   z is 1;
   R6 is O-ethyl and in ortho position;
   R7 is in para position and Cl or CF3;
   R8 is H;

in all its stereoisomeric forms, enantiomeric forms and mixtures in any ratio, and its physiologically acceptable salts and tautomeric forms.

10. A pharmaceutical comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 8.

11. A pharmaceutical comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 8 and one or more active substances which have favorable effects on metabolic disturbances or disorders frequently associated therewith.

12. A pharmaceutical comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 8 and one or more antidiabetics.

13. A pharmaceutical comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 8 and one or more lipid modulators.

14. Compounds of the formula I as claimed in one or more of claims 1 to 8 for use in the treatment and/or prevention
of disorders of fatty acid metabolism and glucose utilization disorders.

15. Compounds of the formula I as claimed in one or more of claims 1 to 8 for use in the treatment and/or prevention of disorders in which insulin resistance is involved.

16. Compounds of the formula I as claimed in one or more of claims 1 to 8 for use in the treatment and/or prevention of diabetes mellitus including the prevention of the sequelae associated therewith.

17. Compounds of the formula I as claimed in one or more of claims 1 to 8 for use in the treatment and/or prevention of dyslipidemias and their sequelae.

18. Compounds of the formula I as claimed in one or more of claims 1 to 8 for use in the treatment and/or prevention of conditions which may be associated with the metabolic syndrome.

19. Compounds of the formula I as claimed in one or more of claims 1 to 8 for use in the treatment and/or prevention of demyelinating and other neurodegenerative disorders of the central and peripheral nervous system.

20. Compounds as claimed in one or more of claims 1 to 8 in combination with at least one further active compound for use in the treatment of disorders of fatty acid metabolism and glucose utilization disorders.

21. Compounds as claimed in one or more of claims 1 to 8 in combination with at least one further active compound for use in the treatment of disorders in which insulin resistance is involved.

22. A process for preparing a pharmaceutical comprising one or more of the compounds as claimed in one or more of claims 1 to 8, which comprises mixing the active compound with a pharmaceutically suitable carrier and bringing this mixture into a form suitable for administration.

Patentansprüche

1. Verbindungen der Formel I:

\[
\begin{align*}
\text{wobei} & \\
R1 & \text{für (C1-C4)-Alkyl, (C0-C2)-Alkylen, (C3-C6)- Cycloalkyl, (C0-C2)-Alkylen-(C6-C10)-aryl steht, wobei Alkyl, } \\
& \text{Aryl und Cycloalkyl unsubstituiert oder mono-, di- oder trisubstituiert durch F sein können; } \\
R2 & \text{für H, Halogen, (C1-C6)-Alkyl, O-(C0-C4)-Alkylen-H steht, wobei Alkyl und Alkylen unsubstituiert oder mono-, } \\
& \text{di- oder trisubstituiert durch F sind; } \\
R3 & \text{für H steht; } \\
R4 & \text{für H steht; } \\
R5 & \text{für H, (C1-C4)-Alkyl steht; } \\
A & \text{für (C6)-Aryl oder (C5-C6)-Heteroaryl steht; } \\
n & \text{für 1, 2 steht; }
\end{align*}
\]
z für 1 steht;  
R7 für H, (C1-C4)-Alkyl, Halogen steht, wobei Alkyl unsubstituiert oder mono-, di- oder trisubstituiert durch F ist;  
R8 für H, F steht;  
in all ihren stereoisomeren Formen, enantiomeren Formen und Mischungen in einem beliebigen Verhältnis, und ihre physiologisch unbedenklichen Salze und tautomeren Formen.

2. Verbindungen der Formel I nach Anspruch 1, wobei

R1 für (C1-C4)-Alkyl, (C3-C6)-Cycloalkyl, Phenyl steht, wobei Alkyl unsubstituiert oder mono-, di- oder trisubstituiert durch F sein kann;  
R2 für H, F, C1, O-(C1-C4)-Alkylen-H steht, wobei Alkylen unsubstituiert oder mono-, di- oder trisubstituiert durch F ist;  
R3 für H steht;  
R4 für H steht;  
R5 für H, (C1-C4)-Alkyl steht;  
A für Phenyl, Thiopen, Thiazol, Pyridin steht;  
n für 1, 2 steht;  
z für 1 steht;  
R6 (C1-C4)-Alkyl, F, C1, O-(C0-C6)-Alkylen-H, Phenyl steht, wobei Phenyl unsubstituiert oder monosubstituiert durch CF3 sein kann;  
R7 für H, (C1-C4)-Alkyl, Cl steht, wobei Alkyl unsubstituiert oder mono-, di- oder trisubstituiert durch F ist;  
R8 für H, F steht;  
in all ihren stereoisomeren Formen, enantiomeren Formen und Mischungen in einem beliebigen Verhältnis, und ihre physiologisch unbedenklichen Salze und tautomeren Formen.

3. Verbindungen der Formel I nach Anspruch 1 oder 2, wobei

R1 für Ethyl, Isopropyl, tert.-Butyl, Cyclopropyl, Cyclohexyl, Phenyl oder Trifluormethyl steht;  
R2, R3, R4, R5 für H, F, Cl, CH3, OCH3 stehen;  
A für Phenyl steht;  
n für 1 steht;  
z für 1 steht;  
R6 in der ortho-Stellung steht und für Cl, Br oder O- (C1-C2)-Alkyl steht;  
R7 in der para-Stellung steht und für Cl, Br oder CF3 steht;  
R8 für H steht;  
in all ihren stereoisomeren Formen, enantiomeren Formen und Mischungen in einem beliebigen Verhältnis, und ihre physiologisch unbedenklichen Salze und tautomeren Formen.

4. Verbindungen der Formel I nach einem der Ansprüche 1 bis 3, wobei

R1 für Isopropyl steht;  
R2, R3, R4, R5 für H stehen;  
A für Phenyl steht;  
n für 1 steht;  
z für 1 steht;  
R6 für O-(C1-C2)-Alkyl steht und in der ortho-Stellung steht;  
R7 in der para-Stellung steht und für Cl oder CF3 steht;  
R8 für H steht;  
in all ihren stereoisomeren Formen, enantiomeren Formen und Mischungen in einem beliebigen Verhältnis, und ihre physiologisch unbedenklichen Salze und tautomeren Formen.
5. Verbindungen der Formel 1 nach einem der Ansprüche 1 bis 4, wobei

   R1 für Trifluormethyl steht;
   R2, R3, R4, R5 für H stehen;
   A für Phenyl steht;
   n für 1 steht;
   z für 1 steht;
   R6 für 0-Ethyl steht und in der ortho-Stellung steht;
   R7 in der para-Stellung steht und für Cl oder CF3 steht;
   R8 für H steht;

   in all ihren stereoisomeren Formen, enantiomeren Formen und Mischungen in einem beliebigen Verhältnis, und
   ihre physiologisch unbedenklichen Salze und tautomeren Formen.

6. Verbindungen der Formel 1 nach einem der Ansprüche 1 bis 5, wobei

   R1 für Cyclohexyl steht;
   R2, R3, R4, R5 für H stehen;
   A für Phenyl steht;
   n für 1 steht;
   z für 1 steht;
   R6 für O-Ethyl steht und in der ortho-Stellung steht;
   R7 in der para-Stellung steht und für Cl oder CF3 steht;
   R8 für H steht;

   in all ihren stereoisomeren Formen, enantiomeren Formen und Mischungen in einem beliebigen Verhältnis, und
   ihre physiologisch unbedenklichen Salze und tautomeren Formen.

7. Verbindungen der Formel 1 nach einem der Ansprüche 1 bis 6, wobei

   R1 für Phenyl steht;
   R2, R3, R4, R5 für H stehen;
   A für Phenyl steht;
   n für 1 steht;
   z für 1 steht;
   R6 für O-Ethyl steht und in der ortho-Stellung steht;
   R7 in der para-Stellung steht und für Cl oder CF3 steht;
   R8 für H steht;

   in all ihren stereoisomeren Formen, enantiomeren Formen und Mischungen in einem beliebigen Verhältnis, und
   ihre physiologisch unbedenklichen Salze und tautomeren Formen.

8. Verbindungen der Formel 1 nach einem der Ansprüche 1 bis 7, wobei

   R1 für Cyclopropyl steht;
   R2, R3, R4, R5 für H stehen;
   A für Phenyl steht;
   n für 1 steht;
   z für 1 steht;
   R6 für 0-Ethyl steht und in der ortho-Stellung steht;
   R7 in der para-Stellung steht und für Cl oder CF3 steht;
   R8 für H steht;

   in all ihren stereoisomeren Formen, enantiomeren Formen und Mischungen in einem beliebigen Verhältnis, und
   ihre physiologisch unbedenklichen Salze und tautomeren Formen.

9. Verbindungen der Formel 1 nach einem der Ansprüche 1 bis 8, wobei
R1 für Isopropyl steht;
R2, R3, R4, R5 für H stehen;
A für Thiophen steht;
n für 1 steht;
z für 1 steht;
R6 für O-Ethyl steht und in der ortho-Stellung steht;
R7 in der para-Stellung steht und für Cl oder CF3 steht;
R8 für H steht;
in all ihren stereoisomeren Formen, enantiomeren Formen und Mischungen in einem beliebigen Verhältnis, und
ihre physiologisch unbedenklichen Salze und tautomeren Formen.

10. Arzneimittel, welche eine oder mehrere Verbindungen der Formel I nach einem oder mehreren der Ansprüche 1
bis 8 enthalten.

11. Arzneimittel, welche eine oder mehrere Verbindungen der Formel I nach einem oder mehreren der Ansprüche 1
bis 8 und einen oder mehrere Wirkstoffe mit einer günstigen Wirkung auf Stoffwechselstörungen oder häufig damit
assozierten Erkrankungen enthalten.

12. Arzneimittel, welche eine oder mehrere Verbindungen der Formel I nach einem oder mehreren der Ansprüche 1
bis 8 und ein oder mehrere Antidiabetika enthalten.

13. Arzneimittel, welche eine oder mehrere Verbindungen der Formel I nach einem oder mehreren der Ansprüche 1
bis 8 und einen oder mehrere Lipidmodulatoren enthalten.

14. Verbindungen der Formel I nach einem oder mehreren der Ansprüche 1 bis 8 zur Verwendung bei der Behandlung
und/oder Prävention von Störungen des Fettsäuremetabolismus und Glukoseverwertungsstörungen.

15. Verbindungen der Formel I nach einem oder mehreren der Ansprüche 1 bis 8 zur Verwendung bei der Behandlung
und/oder Prävention von Erkrankungen, an denen eine Insulinresistenz beteiligt ist.

16. Verbindungen der Formel I nach einem oder mehreren der Ansprüche 1 bis 8 zur Verwendung bei der Behandlung
und/oder Prävention von Diabetes mellitus einschließlich der Prävention der damit assoziierten Folgeerscheinungen.

17. Verbindungen der Formel I nach einem oder mehreren der Ansprüche 1 bis 8 zur Verwendung bei der Behandlung
und/oder Prävention von Dyslipidemien und ihren Folgeerscheinungen.

18. Verbindungen der Formel I nach einem oder mehreren der Ansprüche 1 bis 8 zur Verwendung bei der Behandlung
und/oder Prävention von Leiden, die mit dem metabolischen Syndrom assoziiert sein können.

19. Verbindungen der Formel I nach einem oder mehreren der Ansprüche 1 bis 8 zur Verwendung bei der Behandlung
und/oder Prävention von demyelinisierenden und anderen neurodegenerativen Erkrankungen des zentralen und
peripheren Nervensystems.

20. Verbindungen nach einem oder mehreren der Ansprüche 1 bis 8 in Kombination mit wenigstens einem weiteren
Wirkstoff zur Verwendung bei der Behandlung von Störungen des Fettsäuremetabolismus und Glukoseverwer-
tungsstörungen.

21. Verbindungen nach einem der Ansprüche 1 bis 8 in Kombination mit wenigstens einem weiteren Wirkstoff zur
Verwendung bei der Behandlung von Erkrankungen, an denen eine Insulinresistenz beteiligt ist.

22. Verfahren zur Herstellung eines eine oder mehrere der Verbindungen nach einem oder mehreren der Ansprüche
1 bis 8 enthaltenden Arzneimittels, bei dem man den Wirkstoff mit einem pharmazeutisch unbedenklichen Träger
mischt und diese Mischung in eine für die Verabreichung geeignete Form bringt.
Revendications

1. Composés de formule I :

\[
\begin{align*}
\text{R1} & \text{ est un alkyle en C1-C4, un (alkylène en C0-C2)- (cycloalkyle en C3-C6), un (alkylène en C0-C2)- (aryleen C6-C10), où l’alkyle, l’aryle et le cycloalkyle peuvent être non substitués ou mono, di- ou trisubstitués par F ;} \\
\text{R2} & \text{ est H, un halogène, un alkyle en C1-C6, O-(alkylène en C0-C4)-H, où l’alkyle et l’alkylène sont non substitués ou mono, di- ou trisubstitués par F ;} \\
\text{R3} & \text{ est H ;} \\
\text{R4} & \text{ est H ;} \\
\text{R5} & \text{ est H, un alkyle en C1-C4 ;} \\
\text{A} & \text{ est un aryle en C6 ou un hétéroarylle en C5-C6 ;} \\
\text{n} & \text{ est 1, 2 ;} \\
\text{z} & \text{ est 1 ;} \\
\text{R6} & \text{ est un alkyle en C1-C4, un halogène, un (alkylène en C0-C2)-O-(alkylène en C0-C6)-H, un (alkylène en C0-C2)-(aryleen C6-C10), où l’alkyle, l’aryle et l’alkylène sont non substitués ou mono, di- ou trisubstitués par F et l’aryle peut être non substitué ou monosubstitué par CF3 ;} \\
\text{R7} & \text{ est H, un alkyle en C1-C4, un halogène, où l’alkyle est non substitué ou mono, di- ou trisubstitué par F ;} \\
\text{R8} & \text{ est H, F ;} \\
\end{align*}
\]

sous toutes leurs formes stéréoisomères, formes énantiomères et en mélange dans un rapport quelconque, et leurs sels physiologiquement acceptables et formes tautomères.

2. Composés de formule I selon la revendication 1, dans laquelle

\[
\begin{align*}
\text{R1} & \text{ est un alkyle en C1-C4, un cycloalkylle en C3-C6, un phényle, où l’alkyle peut être non substitué ou mono, di- ou trisubstitué par F ;} \\
\text{R2} & \text{ est H, F, Cl, O-(alkylène en C1-C4)-H, où l’alkylène est non substitué ou mono, di- ou trisubstitué par F ;} \\
\text{R3} & \text{ est H ;} \\
\text{R4} & \text{ est H ;} \\
\text{R5} & \text{ est H, un alkyle en C1-C4 ;} \\
\text{A} & \text{ est un phényle, un thiophène, un thiazole, une pyridine ;} \\
\text{n} & \text{ est 1, 2 ;} \\
\text{z} & \text{ est 1 ;} \\
\text{R6} & \text{ est un alkyle en C1-C4, F, Cl, O-(alkylène en C0-C6)-H, un phényle, où le phényle peut être non substitué ou monosubstitué par CF3 ;} \\
\text{R7} & \text{ est H, un alkyle en C1-C4, Cl, où l’alkyle est non substitué ou mono, di- ou trisubstitué par F ;} \\
\text{R8} & \text{ est H, F ;} \\
\end{align*}
\]

sous toutes leurs formes stéréoisomères, formes énantiomères et en mélange dans un rapport quelconque, et leurs
3. Composés de formule I selon les revendications 1 et 2, dans laquelle

- \( R_1 \) est un éthyle, un isopropyle, un tert-butyle, un cyclopropyle, un cyclohexyle, un phényle ou un trifluorométhyle ;
- \( R_2, R_3, R_4, R_5 \) sont H, F, Cl, CH₃, OCH₃ ;
- \( A \) est un phényle ;
- \( n \) est 1 ;
- \( z \) est 1 ;
- \( R_6 \) est en position ortho et Cl, Br, ou O-(alkyle en C1-C2) ;
- \( R_7 \) est en position para et Cl, Br ou CF₃ ;
- \( R_8 \) est H ;

sous toutes leurs formes stéréoisomères, formes énantiomères et en mélange dans un rapport quelconque, et leurs sels physiologiquement acceptables et formes tautomères.

4. Composés de formule I selon les revendications 1 à 3, dans laquelle

- \( R_1 \) est un isopropyle ;
- \( R_2, R_3, R_4, R_5 \) sont H ;
- \( A \) est un phényle ;
- \( n \) est 1 ;
- \( z \) est 1 ;
- \( R_6 \) est O-(alkyle en C1-C2) et en position ortho ;
- \( R_7 \) est en position para et Cl ou CF₃ ;
- \( R_8 \) est H ;

sous toutes leurs formes stéréoisomères, formes énantiomères et en mélange dans un rapport quelconque, et leurs sels physiologiquement acceptables et formes tautomères.

5. Composés de formule I selon les revendications 1 à 4, dans laquelle

- \( R_1 \) est un trifluorométhyle ;
- \( R_2, R_3, R_4, R_5 \) sont H ;
- \( A \) est un phényle ;
- \( n \) est 1 ;
- \( z \) est 1 ;
- \( R_6 \) est O-éthyle et en position ortho ;
- \( R_7 \) est en position para et Cl ou CF₃ ;
- \( R_8 \) est H ;

sous toutes leurs formes stéréoisomères, formes énantiomères et en mélange dans un rapport quelconque, et leurs sels physiologiquement acceptables et formes tautomères.

6. Composés de formule I selon les revendications 1 à 5, dans laquelle

- \( R_1 \) est un cyclohexyle ;
- \( R_2, R_3, R_4, R_5 \) sont H ;
- \( A \) est un phényle ;
- \( n \) est 1 ;
- \( z \) est 1 ;
- \( R_6 \) est O-éthyle et en position ortho ;
- \( R_7 \) est en position para et Cl ou CF₃ ;
- \( R_8 \) est H ;

sous toutes leurs formes stéréoisomères, formes énantiomères et en mélange dans un rapport quelconque, et leurs sels physiologiquement acceptables et formes tautomères.
7. Composés de formule I selon les revendications 1 à 6, dans laquelle

R1 est un phényle ;
R2, R3, R4, R5 sont H ;
A est un phényle ;
n est 1 ;
z est 1 ;
R6 est O-éthyle et en position ortho ;
R7 est en position para et Cl ou CF3 ;
R8 est H ;
sous toutes leurs formes stéréoisomères, formes énantiomères et en mélange dans un rapport quelconque, et leurs sels physiologiquement acceptables et formes tautomères.

8. Composés de formule I selon les revendications 1 à 7, dans laquelle

R1 est un cyclopropyle ;
R2, R3, R4, R5 sont H ;
A est un phényle ;
n est 1 ;
z est 1 ;
R6 est O-éthyle et en position ortho ;
R7 est en position para et Cl ou CF3 ;
R8 est H ;
sous toutes leurs formes stéréoisomères, formes énantiomères et en mélange dans un rapport quelconque, et leurs sels physiologiquement acceptables et formes tautomères.

9. Composés de formule I selon les revendications 1 à 8, dans laquelle

R1 est un isopropyle ;
R2, R3, R4, R5 sont H ;
A est un thiophène ;
n est 1 ;
z est 1 ;
R6 est O-éthyle et en position ortho ;
R7 est en position para et Cl ou CF3 ;
R8 est H ;
sous toutes leurs formes stéréoisomères, formes énantiomères et en mélange dans un rapport quelconque, et leurs sels physiologiquement acceptables et formes tautomères.

10. Produit pharmaceutique comprenant un ou plusieurs composés de formule I selon une ou plusieurs des revendications 1 à 8.

11. Produit pharmaceutique comprenant un ou plusieurs composés de formule I selon une ou plusieurs des revendications 1 à 8 et une ou plusieurs substances actives qui ont des effets favorables sur les dysfonctionnements métaboliques ou les troubles fréquemment associés à ceux-ci.

12. Produit pharmaceutique comprenant un ou plusieurs composés de formule I selon une ou plusieurs des revendications 1 à 8 et un ou plusieurs antidiabétiques.

13. Produit pharmaceutique comprenant un ou plusieurs composés de formule I selon une ou plusieurs des revendications 1 à 8 et un ou plusieurs modulateurs des lipides.

14. Composés de formule I selon une ou plusieurs des revendications 1 à 8 pour une utilisation dans le traitement et/ou la prévention de troubles du métabolisme des acides gras et de troubles d'utilisation du glucose.
15. Composés de formule I selon une ou plusieurs des revendications 1 à 8 pour une utilisation dans le traitement et/ou la prévention de troubles dans lesquels l’insulinorésistance est impliquée.

16. Composés de formule I selon une ou plusieurs des revendications 1 à 8 pour une utilisation dans le traitement et/ou la prévention du diabète sucré comprenant la prévention des séquelles associées à celui-ci.

17. Composés de formule I selon une ou plusieurs des revendications 1 à 8 pour une utilisation dans le traitement et/ou la prévention de dyslipidémies et leurs séquelles.

18. Composés de formule I selon une ou plusieurs des revendications 1 à 8 pour une utilisation dans le traitement et/ou la prévention de pathologies qui peuvent être associées au syndrome métabolique.

19. Composés de formule I selon une ou plusieurs des revendications 1 à 8 pour une utilisation dans le traitement et/ou la prévention de troubles neurodégénératifs démyélinisants et autres du système nerveux central et périphérique.

20. Composés selon une ou plusieurs des revendications 1 à 8 en combinaison avec au moins un composé actif supplémentaire pour une utilisation dans le traitement de troubles du métabolisme des acides gras et de troubles d’utilisation du glucose.

21. Composés selon une ou plusieurs des revendications 1 à 8 en combinaison avec au moins un composé actif supplémentaire pour une utilisation dans le traitement de troubles dans lesquels l’insulinorésistance est impliquée.

22. Procédé de préparation d’un produit pharmaceutique comprenant un ou plusieurs des composés selon une ou plusieurs des revendications 1 à 8, qui comprend les étapes consistant à mélanger le composé actif avec un véhicule pharmaceutiquement adapté et former ce mélange sous une forme adaptée pour administration.
REFERENCES CITED IN THE DESCRIPTION

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