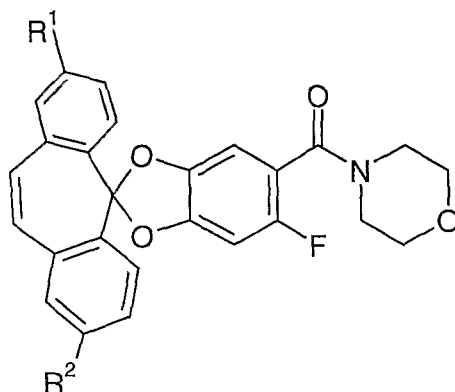


Dibenzosuberone derivatives

The present invention relates to 4-[(6-fluoro-spiro[1,3-benzodioxole-2,5'-[5H]dibenzo[a,d]cyclohepten]-5-yl)carbonyl]-morpholines of the formula



I

wherein

- 5 R^1 and R^2 are each independently hydrogen or halogen.

The invention further relates the manufacture of the compounds of formula I, pharmaceutical compositions containing the compounds of formula I and its use as medicament, especially for treating obesity and other disorders.

- 10 It has been found, that the compounds of formula I are modulators of the CB₁ receptor.

- Two different subtypes of cannabinoid receptors (CB₁ and CB₂) have been isolated and both belong to G protein coupled receptor superfamily. Alternative spliced forms of CB₁, CB_{1A} and CB_{1B} have also been described, but are expressed only at low levels in the tissues tested. (D.Shire, C. Carrillon, M. Kaghad, B. Calandra, M. Rinaldi-Carmona, G. Le Fur, D. Caput, P. Ferrara, J. Biol. Chem. 270 (8) (1995) 3726-31; E. Ryberg, H. K. Vu, N. Larsson, T. Groblewski, S. Hjorth, T. Elebring, S. Sjögren, P. J. Greasley, FEBS Lett. 579 (2005) 259-264). The CB₁ receptor is mainly located in the brain and to a lesser extent in several peripheral organs, whereas the CB₂ receptor is predominately distributed in the periphery primarily localized in spleen and cells of the immune system (S. Munro, K.L. Thomas, M. Abu-Shaar, Nature 365 (1993) 61-61). Therefore in order to avoid side effects a CB₁-selective compound is desirable.
- 20

DK/ 08.09.2005

Δ^9 -tetrahydrocannabinol (Δ^9 -THC) is the principal psychoactive compound in the Indian hemp (Y. Gaoni, R. Mechoulam, J. Am. Chem. Soc., 86 (1964) 1646), *cannabis sativa* (marijuanan), which is used in medicine since ages (R. Mechoulam (Ed.) in "Cannabinoids as therapeutic Agents", 1986, pp. 1-20, CRC Press). Δ^9 -THC is a non-selective CB_{1/2} receptor agonist and is available in the USA as dronabinol (marinol®) for the alleviation of cancer chemotherapy-induced emesis (CIE) and the reversal of body weight loss experienced by AIDS patients through appetite stimulation. In the UK Nabolinone (LY-109514, Cesamet®), a synthetic analogue of Δ^9 -THC, is used for CIE (R. G. Pertwee, Pharmaceut. Sci. 3 (11) (1997) 539-545, E. M. Williamson, F. J. Evans, Drugs 60 (6) (2000) 1303-1314).

Anandamide (arachidonylethanolamide) was identified as the endogenous ligand (agonist) for the CB₁ receptor (R.G. Pertwee, Curr. Med. Chem., 6 (8) (1999) 635-664; W.A. Devane, L. Hanus, A. Breuer, R.G. Pertwee, L.A. Stevenson, G. Griffin, D. Gibson, A. Mandelbaum, A. Etinger, R. Mechoulam, Science 258 (1992) 1946-9). Anandamide and 2-arachidonoylglycerol (2-AG) modulate at the presynaptic nerve terminal negatively adenylate cyclase and voltage-sensitive Ca²⁺ channels and activates the inwardly rectifying K⁺ channel (V. Di Marzo, D. Melck, T. Bisogno, L. De Petrocellis, Trends in Neuroscience 21 (12) (1998) 521-8), thereby affecting neurotransmitter release and/or action, which decreases the release of neurotransmitter (A. C. Porter, C.C. Felder, Pharmacol. Ther., 90 (1) (2001) 45-60).

Anandamide as Δ^9 -THC also increases feeding through CB₁ receptor-mediated mechanism. CB₁ receptor selective antagonists block the increase in feeding associated with administration of anandamide (C.M. Williams, T.C. Kirkham, Psychopharmacology 143 (3) (1999) 315-317; C. C. Felder, E. M. Briley, J. Axelrod, J. T. Simpson, K. Mackie, W. A. Devane, Proc. Natl. Acad. Sci. U. S. A. 90 (16) (1993) 7656-60) and caused appetite suppression and weight loss (G. Colombo, R. Agabio, G. Diaz, C. Lobina, R. Reali, G. L. Gessa, Life Sci. 63 (8) (1998) L113-PL117).

Leptin is the primary signal through which the hypothalamus senses nutritional state and modulates food intake and energy balance. Following temporary food restriction, CB₁ receptor knockout mice eat less than their wild-type littermates, and the CB₁ antagonist SR141716A reduces food intake in wild-type but not knockout mice. Furthermore, defective leptin signaling is associated with elevated hypothalamic, but not cerebellar, levels of endocannabinoids in obese db/db and ob/ob mice and Zucker rats. Acute leptin treatment of normal rats and ob/ob mice reduces anandamide and 2-arachidonoyl glycerol in the hypothalamus. These findings indicate that endocannabinoids in the hypothalamus may tonically activate CB₁ receptors to maintain

food intake and form part of the neural circuitry regulated by leptin (V. Di Marzo, S. K. Goparaju, L. Wang, J. Liu, S. Bitkai, Z. Jarai, F. Fezza, G. I. Miura, R. D. Palmiter, T. Sugiura, G. Kunos, Nature 410 (6830) 822-825).

It has also been reported that the CB1 receptor plays a role in the regulation of bone mass and bone loss resulting from estrogen deficiency. Antagonists of CB1 and CB2 receptors prevented ovariectomy-induced bone loss *in vivo* and caused osteoclast inhibition *in vitro* by promoting osteoclast apoptosis and inhibiting production of several osteoclast survival factors (A.I. Idris, R.J. van't Hof, I.R. Greig, S.A. Ridge, D. Baker, R.A. Ross, S.H. Wilson, Nature Medicine 11 (7) (2005), 774-779). Cannabinoid receptor antagonists can therefore be useful for the treatment of osteoporosis and other bone diseases such as cancer associated bone disease and Paget's disease of bone.

At least two CB1 selective antagonist / inverse agonists (SR-141716 and SLV-319) are currently undergoing clinical trials for the treatment of obesity and/or smoking cessation. In a double blind placebo-controlled study, at the doses of 10 and 20 mg daily, SR 141716 significantly reduced body weight when compared to placebo (F. Barth, M. Rinaldi-Carmona, M. Arnone, H. Heshmati, G. Le Fur, "Cannabinoid antagonists: From research tools to potential new drugs." Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30, 2001). SR-141716 reduced body weight, waist circumference and improved metabolic parameters (plasma HDL, triglycerides and insulin sensitivity) in several phase III studies (RIO-lipids, RIO-Europe and RIO-North America). Additionally SR-141716 has shown efficacy in a phase III trial for smoking cessation (STRATUS-US). There still remains a need for potent low molecular weight CB1 modulators that have pharmacokinetic and pharmacodynamic properties suitable for use as human pharmaceuticals.

Other compounds which have been proposed as CB₁ receptor antagonists respectively inverse agonists are aminoalkylindoles (AAI; M. Pacheco, S. R. Childers, R. Arnold, F. Casiano, S. J. Ward, J. Pharmacol. Exp. Ther. 257 (1) (1991) 170-183), like 6-bromo- (WIN54661; F. M. Casiano, R. Arnold, D. Haycock, J. Kuster, S. J. Ward, NIDA Res. Monogr. 105 (1991) 295-6) or 6-iodopravadoline (AM630, K. Hosohata, R. M. Quock, R.M; Hosohata, T. H. Burkey, A. Makriyannis, P. Consroe, W. R. Roeske, H. I. Yamamura, Life Sci. 61 (1997) 115 – 118; R. Pertwee, G. Griffin, S. Fernando, X. Li, A. Hill, A. Makriyannis, Life Sci. 56 (23-24) (1995) 1949-55). Arylbenzo[b]thiophene and benzo[b]furan (LY320135, C. C. Felder, K. E. Joyce, E. M. Briley, M. Glass, K. P. Mackie, K. J. Fahey, G. J. Cullinan, D. C. Hunden, D. W. Johnson, M. O. Chaney, G. A. Koppel, M. Brownstein, J. Pharmacol. Exp. Ther. 284 (1) (1998) 291-7) disclosed in WO9602248, US5596106, 3-alkyl-(5,5-diphenyl)imidazolidinediones (M. Kanyonyo, S. J. Govaerts, E.

Hermans, J. H. Poupaert, D. M. Lambert, *Bioorg. Med. Chem. Lett.* 9 (15) (1999) 2233 – 2236.) as well as 3-alkyl-5-arylimidazolidinediones (F. Ooms, J. Wouters, O. Oscaro. T. Happaerts, G. Bouchard, P.-A. Carrupt, B. Testa, D. M. Lambert, *J. Med. Chem.* 45 (9) (2002) 1748-1756) are known to antagonize the CB₁ receptor respectively act as an
5 inverse agonist on the hCB₁ receptor. WO0015609 (FR2783246-A1), WO0164634 (FR2805817-A1), WO0228346, WO0164632 (FR2805818-A1), WO0164633 (FR2805810-A1) disclosed substituted 1-bis(aryl)methyl-azetidines derivatives as antagonists of CB₁. In WO0170700, WO02076949, and WO0276949A1 4,5-dihydro-1H-pyrazole derivatives are described as CB₁ antagonists. In several patents and publications bridged and non-
10 bridged 3-pyrazolecarboxamide derivatives are disclosed as CB₁ antagonists/inverse agonists (WO0132663, WO0046209, WO9719063, EP658546, EP656354, US5624941, EP576357, US3940418, WO03020217, WO0335005, J.M. Mussinu *et al.*, *Bioorg.Med.Chem.* 2003,11,251; S. Ruiu *et al.*, *J.Pharm.Expt.Ther.*, 2003,306,363). Pyrrole CB₁ cannabinoid receptor agonists have been described in G. Tarzia *et al.*,
15 *Bioorg.Med.Chem.* 2003,11,3965. Phenethyl amides have been claimed as CB₁ cannabinoid receptor antagonists/inverse agonists in WO03077847, WO03082190, WO03086288 and WO03087037. Various aza heterocycles (imidazoles, triazoles and thiazoles) are described in WO0337332, WO03040107, WO03063781, WO03082833 and WO03078413. Diphenylpyrazine carboxamides are described in WO03051850,
20 diphenylpyridine carboxamides in WO03084930 and diphenylbenzene carboxamides in WO03084943.

It is an object of this invention to provide selective, directly acting CB₁ receptor antagonists respectively inverse agonists. Such antagonists / inverse antagonists are useful in medical therapy, particularly in the treatment and/or prevention of diseases which are
25 associated with the modulation of CB₁ receptors.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

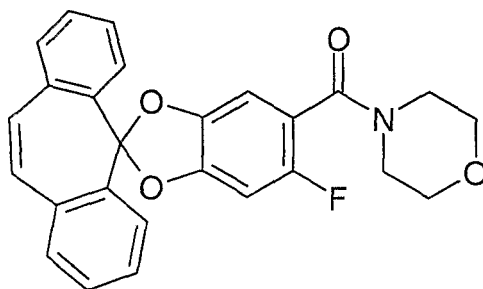
The term "halogen" refers to fluorine, chlorine, bromine and iodine, preferably to chlorine and fluorine.

30 The term "pharmaceutically acceptable salts" embraces salts of the compounds of formula (I) with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, fumaric acid, succinic acid, tartaric acid, methanesulphonic acid, salicylic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms. Preferred

- 5 -

salts with acids are formates, maleates, citrates, hydrochlorides, hydrobromides and methanesulfonic acid salts, with hydrochlorides being especially preferred.

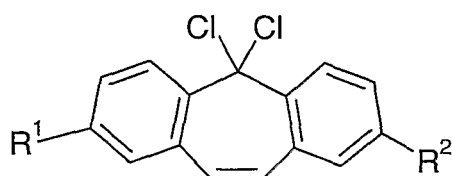
In one embodiment, the present invention relates to a compound of formula I as defined above, which compound is 4-[(6-fluoro-spiro[1,3-benzodioxole-2,5'-
5 [5H]dibenzo[a,d]cyclohepten]-5-yl)carbonyl]-morpholine, the compound of the formula



I a

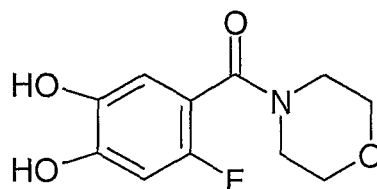
The compounds of formula I of the present invention can be prepared by methods known in the art, or they can be prepared by a process as described below, which process
10 comprises

reacting a 5,5-dichloro-5H-dibenzo[a,d]cycloheptene of the formula



II

wherein R¹ and R² are each independently hydrogen or halogen,
with the catechol derivative of the formula

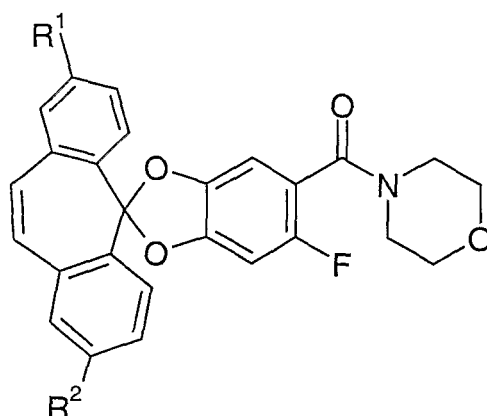


III

15

at elevated temperature to obtain a compound of the formula

- 6 -



I

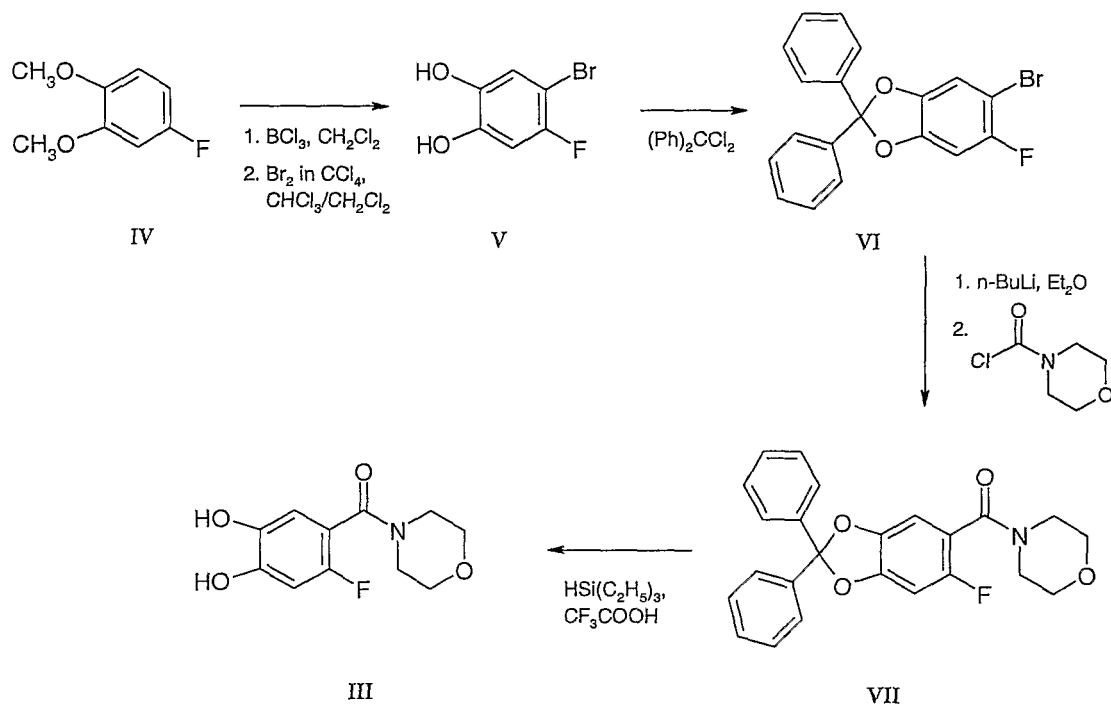
Elevated temperature means a temperature from 100 °C to 180 °C, preferably a temperature of 110 to 130 °C.

Thus, the catechol intermediate of formula III can be ketalized with a bis-
5 substituted dichloromethane derivative of formula II in an inert solvent (e.g. toluene or pyridine) or neat, with or without the presence of a base (e.g. pyridine) at elevated temperature (e.g. >100 °C) to yield a compound of formula I.

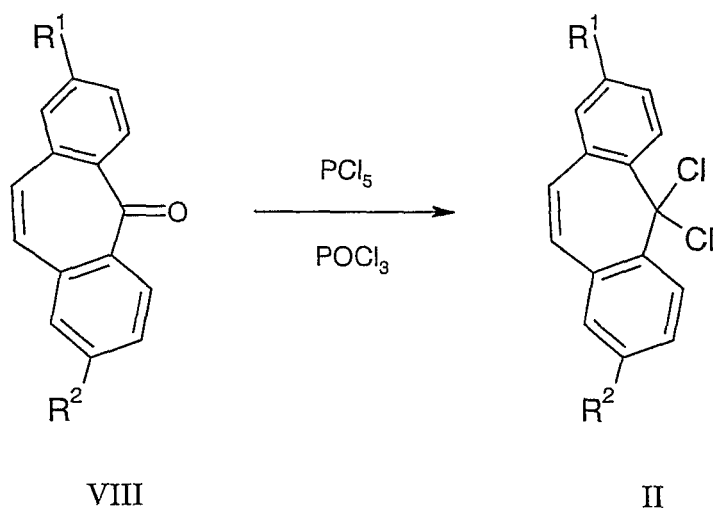
(2-Fluoro-4,5-dihydroxy-phenyl)-morpholin-4-yl-methanone (III) can be easily prepared from the corresponding diphenylmethylene protected ketal of formula VII by
10 treatment with an acid (e.g. trifluoroacetic acid) in a suitable inert solvent (e.g. methylene chloride) or by treatment with an acid (e.g. trifluoroacetic acid) in the presence of a suitable reducing agent (e.g. triethylsilane), neat or with a suitable inert solvent (e.g. methylene chloride).

The diphenylmethylene protected ketal of formula VII is prepared from 4-
15 fluoroveratrole following the route as described in Scheme 1. The reaction sequence is described in more detail in Example 1.

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Scheme 1

The bis-substituted dichloromethane derivatives of formula II may be prepared by methods known in the art from the corresponding ketone VIII by reaction with thionyl chloride in the presence of DMF or another N-formylated agent, or by reaction with phosphorus pentachloride with or without the presence of a suitable solvent, e.g. phosphorus oxide chloride (Scheme 2).

Scheme 2

The dibenzosuberones of formula VIII are commercially available or may be prepared by methods known in the art.

Some compounds of formula I may possess asymmetric centres and are therefore capable of existing in more than one stereoisomeric form. The invention thus also relates to compounds in substantially pure isomeric form at one or more asymmetric centres as well as mixtures, including racemic mixtures, thereof. Such isomers may be prepared by asymmetric synthesis, for example using chiral intermediate, or mixtures may be resolved by conventional methods, eg., chromatography (chromatography with a chiral adsorbent or eluant), or use of a resolving agent.

As described above, the compounds of formula I can be used as therapeutically active substances, especially as therapeutically active substances for the treatment and/or prophylaxis of diseases which are associated with the modulation of the CB₁ receptors. In one embodiment, the invention therefore relates to compounds as defined above for use as therapeutic active substances, particularly as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB₁ receptors.

The invention also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB₁ receptors, which method comprises administering a compound as defined above to a human being or animal.

The invention further relates to the use of compounds as defined above for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB₁ receptors.

In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB₁ receptors. Such medicaments comprise a compound as defined above.

In this context, the expression 'diseases associated with modulation of CB₁ receptors' means diseases which can be treated and/or prevented by modulation of CB₁ receptors. Such diseases encompass, but are not limited to, psychic disorders, especially anxiety, psychosis, schizophrenia, depression, abuse of psychotropes, for example for the abuse and/or dependence of a substances, including alcohol dependency and nicotine dependency, neuropathies, multiple sclerosis, migraine, stress, epilepsy, dyskinesias, Parkinson's disease, amnesia, cognitive disorders, memory deficits, senile dementia,

Alzheimer's disease, eating disorders, obesity, diabetes type II or non insulin dependent diabetes (NIDD), gastrointestinal diseases, vomiting, diarrhea, urinary disorders, cardiovascular disorders, infertility disorders, inflammations, infections, cancer, neuroinflammation, in particular in atherosclerosis, or the Guillain-Barré syndrome,
5 viral encephalitis, cerebral vascular incidents and cranial trauma as well as bone diseases such as osteoporosis, particularly osteoporosis associated with a genetic predisposition, hormone deficiency or ageing, cancer associated bone disease and Paget's disease of bone.

In a preferable aspect, the expression 'diseases associated with modulation of CB₁ receptors' relates to eating disorders, obesity, diabetes type II or non insulin dependent
10 diabetes (NIDD), neuroinflammation, diarrhea, abuse and/or dependence of a substances, including alcohol dependency and nicotine dependency. In a more preferable aspect, the said term related to eating disorders, obesity, diabetes type II or non insulin dependent diabetes (NIDD), abuse and/or dependence of a substances, including alcohol dependency and nicotine dependency, with obesity being especially preferred.

15 In another prefable aspect, the expression 'diseases associated with modulation of CB₁ receptors' relates to bone diseases such as osteoporosis, particularly osteoporosis associated with a genetic predisposition, hormone deficiency or ageing, cancer associated bone disease and Paget's disease of bone.

It is a further preferred object to provide a method for the treatment or prevention
20 of obesity and obesity related disorders which comprises administration of a therapeutically effective amount of a compound according to formula I in combination or association with a therapeutically effective amount of other drugs for the treatment of obesity or eating disorders so that together they give effective relief. Suitable other drugs include but are not limited to anorectic agents, lipase inhibitors and selective serotonin
25 reuptake inhibitors (SSRI). Combinations or associations of the above agents may be encompassing separate, sequential or simultaneous administration.

Preferable lipase inhibitor is tetrahydrolipstatin.

Suitable anorectic agents of use in combination with a compound of the present invention include, but are not limited to, aminorex, amphechloral, amphetamine,
30 benzphetamine, chlorphentermine, clobenzorex, cloforex, clominorex, clortermine, cyclexedrine, dexfenfluramine, dextroamphetamine, diethylpropion, diphemethoxidine, N-ethylamphetamine, fenbutrazate, fenfluramine, fenisorex, fenproporex, fludorex, fluminorex, furfurylmethylamphetamine, levamfetamine, levophacetoperane, mazindol, mefenorex, metamfepramone, methamphetamine, norpseudoephedrine, pentorex,

phendimetrazine, phenmetrazine, phentermine, phenylpropanolamine, picilorex and sibutramine, and pharmaceutically acceptable salts thereof.

Most preferable anorectic agents are sibutramine and phentermine.

Suitable selective serotonin reuptake inhibitors of use in combination with a
5 compound of the present invention include: fluoxetine, fluvoxamine, paroxetine and sertraline, and pharmaceutically acceptable salts thereof.

It is a further preferred object to provide a method of treatment or prevention of Type II diabetes (non-insulin dependent diabetes mellitus (NIDDM) in a human which comprises administration of a therapeutically effective amount of a compound according
10 to formula I in combination or association with a therapeutically effective amount of a lipase inhibitor, particularly, wherein the lipase inhibitor is orlistat. Also an object of the invention is the method as described above for the simultaneous, separate or sequential administration of a compound according to formula I and a lipase inhibitor, particularly tetrahydrolipstatin.

15 It is a further preferred object to provide a method of treatment or prevention of Type II diabetes (non-insulin dependent diabetes mellitus (NIDDM) in a human which comprises administration of a therapeutically effective amount of a compound according to formula I in combination or association with a therapeutically effective amount of an anti-diabetic agent selected from the group consisting of 1) PPAR γ agonists such as
20 pioglitazone or rosiglitazone, and the like; 2) biguanides such as metformin, and the like; 3) sulfonylureas such as glibenclamide, and the like; 4) PPAR α/γ agonists such as GW-2331, and the like 5) DPP-IV- inhibitors such as LAF-237 (Vildagliptin) or MK-0431, and the like; 6) Glucokinase activators such as the compounds disclosed in e.g. WO 00/58293 A1, and the like. Also an object of the invention is the method as described
25 above for the simultaneous, separate or sequential administration of a compound according to formula I and a therapeutically effective amount of an anti-diabetic agent as 1) PPAR γ agonists such as pioglitazone or rosiglitazone, and the like; 2) biguanides such as metformin, and the like; 3) sulfonylureas such as glibenclamide, and the like; 4) PPAR α/γ agonists such as GW-2331 GW-2331 and the like; 5) DPP-IV- inhibitors such
30 as LAF-237 (Vildagliptin) or MK-0431, and the like; 6) Glucokinase activators such as the compounds disclosed in e.g. WO 00/58293 A1, and the like.

It is a further preferred object to provide a method of treatment or prevention of dyslipidemias in a human which comprises administration of a therapeutically effective amount of a compound according to formula I in combination or association with a
35 therapeutically effective amount of a lipid lowering agent as 1) bile acid sequestrants such

as cholestyramine, and the like; 2) HMG-CoA reductase inhibitors such as atorvastatin, and the like; 3) cholesterol absorption inhibitors such as ezetimibe, and the like; 4) CETP inhibitors such as torcetrapib, JTT 705, and the like; 5) PPAR α -agonists such as beclofibrate, fenofibrate, and the like; 6) lipoprotein synthesis inhibitors such as niacin, and the like; and 7) niacin receptor agonists. Also an object of the invention is the method as described above for the simultaneous, separate or sequential administration of a compound according to formula I and a therapeutically effective amount of a lipid lowering agent as 1) bile acid sequestrants such as cholestyramine, and the like; 2) HMG-CoA reductase inhibitors such as atorvastatin, and the like; 3) cholesterol absorption inhibitors such as ezetimibe, and the like; 4) CETP inhibitors such as torcetrapib, JTT 705, and the like; 5) PPAR α -agonists such as beclofibrate, fenofibrate, and the like; 6) lipoprotein synthesis inhibitors such as niacin, and the like; and 7) niacin receptor agonists.

Demonstration of additional biological activities of the compounds of the present invention may be accomplished through in vitro, ex vivo, and in vivo assays that are well known in the art. For example, to demonstrate the efficacy of a pharmaceutical agent for the treatment of obesity-related disorders such as diabetes, Syndrome X, or atherosclerotic disease and related disorders such as hypertriglyceridemia and hypercholesteremia, the following assays may be used.

Method for Measuring Blood Glucose Levels

db/db mice (obtained from Jackson Laboratories, Bar Harbor, ME) are bled (by either eye or tail vein) and grouped according to equivalent mean blood glucose levels. They are dosed orally (by gavage in a pharmaceutically acceptable vehicle) with the test compound once daily for 7 to 14 days. At this point, the animals are bled again by eye or tail vein and blood glucose levels are determined.

Method for Measuring Triglyceride Levels

hApoA1 mice (obtained from Jackson Laboratories, Bar Harbor, ME) are bled (by either eye or tail vein) and grouped according to equivalent mean serum triglyceride levels. They are dosed orally (by gavage in a pharmaceutically acceptable vehicle) with the test compound once daily for 7 to 14 days. The animals are then bled again by eye or tail vein, and serum triglyceride levels are determined.

Method for Measuring HDL-Cholesterol Levels

To determine plasma HDL-cholesterol levels, hApoA1 mice are bled and grouped with equivalent mean plasma HDL-cholesterol levels. The mice are orally dosed once

daily with vehicle or test compound for 7 to 14 days, and then bled on the following day. Plasma is analyzed for HDL-cholesterol.

In addition, to demonstrate CNS activities of the compounds of the present invention, the following in vivo assays may be used.

5 Method for Testing Task Learning and Spatial Memory

The Morris Water Maze is routinely used to assess task learning and spatial memory (Jaspers et al., *Neurosci. Lett.* 117:149-153, 1990; Morris, J. *Neurosci. Methods* 11:47-60, 1984). In this assay, animals are placed in a water pool which is divided into quadrants. One platform is hidden in one of the quadrants. The animal is placed in the water pool and is expected to locate the hidden platform within a predetermined time. During a number of training trials, the animal learns the location of the platform and escapes from the pool. The animal receives multiple trials in this task. Total distance traveled, number of trials to locate platform, latency to find platform, and the swimming path is recorded for each animal. The animal's learning ability is measured by the length of time or number of trials required to find the hidden platform. Memory deficit or improvement is determined by the number of trials or the latency to find the platform at predetermined delay time after acquisition. Learning and memory may be measured by the number of times that the animal crosses the quadrant where the platform was located during the acquisition phase.

20 Method for Testing Drug Dependence

Self-administration in animals is a predictor of a compound's abuse potential in humans. Modifications to this procedure may also be used to identify compounds that prevent or block the reinforcing properties of drugs that have abuse potential. A compound that extinguishes the self-administration of a drug may prevent that drug's abuse or its dependence. (Ranaldi et al., *Psychopharmacol.* 161:442-448, 2002; Campbell et al., *Exp. Clin. Psychopharmacol.* 8:312-25, 2000). In a self-administration test, animals are placed in the operant chambers containing both an active and inactive lever. Each response on the active lever produces an infusion of either the test compound or a drug known to be self-administered. Presses on the inactive lever have no effect, but are also recorded. Animals are then trained to self-administer compound/drug over a set period of time by having drug access during each daily session. Illumination of the chamber house light signals the beginning of the session and the availability of the compound/drug. When the session ends, the house light is turned off. Initially, a drug infusion occurs with every press of the active lever. Once lever-pressing behavior has been established, the number of presses to produce a drug infusion is increased. After stable compound/drug self-

administration is obtained, the effect of a second compound on the drug-reinforced behavior may be evaluated. Administration of this second compound prior to the session can either potentiate, extinguish, or produce no change to the self-administrating behavior.

- 5 The following tests were carried out in order to determine the activity of a compound of formula I.

 The affinity of the compounds of the invention for cannabinoid CB₁ receptors was determined using membrane preparations of human embryonic kidney (HEK) cells in which the human cannabis CB₁ receptor is transiently transfected using the Semliki
10 Forest Virus system in conjunction with [3H]-CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

15 The affinity of the compounds of the invention for cannabinoid CB₂ receptors was determined using membrane preparations of human embryonic kidney (HEK) cells in which the human cannabis CB₂ receptor is transiently transfected using the Semliki Forest virus system in conjunction with [3H]-CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [3H]-ligand, with or without
20 addition of compounds of the invention, separation of bound of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

 The cannabinoid CB₁ antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB₁
25 receptors are stably expressed (see M. Rinaldi-Carmona et. al., J. Pharmacol. Exp. Ther. 278 (1996) 871). The stable expression of the human cannabinoid receptor in cell systems was first described in Nature 1990, 346, 561-564 (CB₁) and Nature 1993, 365, 61-65 (CB₂) respectively. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB₁
30 receptors by CB₁ receptor agonists (e.g. CP-55,940 or (R)-WIN-55212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration dependent manner. This CB₁ receptor mediated response can be antagonised by CB₁ receptor antagonists such as the compounds of the invention.

 The compounds of formula I show an excellent affinity for the CB₁ receptor,
35 determined with the experimental conditions described in Devane et.al. Mol. Pharmacol.

34 (1988) 605-613. The compounds of the present invention or the pharmaceutically acceptable salts or solvates are antagonists and selective for the CB₁ receptor with affinities below IC₅₀ = 1 µM, preferably below 0.100 µM. They exhibit at least a 10 fold selectivity against the CB₂ receptor.

Compound of Example	IC ₅₀ [µM]
3	0.006

5

Effect of CB₁ receptor antagonist/inverse agonist on CP 55,940-induced Hypothermia in NMRI mice

Animals

Male NMRI mice were used in this study and were obtained from Research
10 Consulting Company Ltd (RCC) of Füllinsdorf (Switzerland). Mice, weighing 30-31g were used in this study. Ambient temperature is approximately 20-21°C and relative humidity 55-65%. A 12 hours light-dark cycle is maintained in the rooms with all tests being performed during the light phase. Access to tap water and food are ad libitum.

Method

15 All measurements were made between 12:00 am and 5:00 pm. Mice were brought in this environment and habituated for at least two hours before the start of the experiment. They had always free access to food and water. For each dose, 8 mice were used. Rectal body temperature measurements were recorded by mean of a rectal probe (RET2 of Physitemp) and digital thermometer (Digi-sense n°8528-20 of Cole Parmer,
20 Chicago USA). The probe was inserted about 3.5 cm in each mouse.

The body temperature was taken 15 min before administration of either Vehicle or CB₁ receptor antagonist/inverse agonist. 30 or 90 min after i.p. or p.o. administration of this compound, respectively, rectal body temperature was recorded in order to evaluate any influence of the compound itself. The CB receptor agonist CP 55,940 (0.3 mg/kg)
25 was immediately administered intravenously, then 20 min after i.v. administration of CP 55940, body temperature was again measured.

The in vivo activity of compounds of formula (1) was assessed for their ability to regulate feeding behaviour by recording food consumption in food deprived animals.

Rats were trained to have access to food for 2h per day and were food deprived for 22h. When they were trained under this schedule, the amount of food taken every day during these 2h food intake session was consistent day after day.

To test the ability of compounds of formula (1) to decrease food intake, 8 animals
5 were used in a cross-over study. Rats were individually housed in Plexiglas boxes with a grid on the floor and a paper was placed below the cage floor to collect any spillage. A food dispenser (beaker) filled with a pre-weighed amount of food was presented to them for 2h. At the end of the food intake session, rats returned to their home cage. Each rat was weighed before the start of the experiment and the amount of food consumed during
10 this 2h food intake session was recorded. Either various doses of test compound or vehicle was administered orally 60 min before the 2h food intake session. A positive control Rimonabant (SR141716) was included in the experiment. An Anova analysis with repeated measures was used followed by a posthoc test Student Neumann-Keuls. * $P < 0.05$ compared to Saline-treated rats.

15 Furthermore the utility of compounds of formula I in diseases or disorders may be demonstrated in animal disease models that have been reported in the literature. The following are examples of such animal disease models: a) reduction of sweet food intake in marmosets (Behavioural Pharm, 1998, 9,179-181); b) reduction of sucrose and ethanol intake in mice (Psychopharm. 1997, 132, 104-106); c) increased motor activity and place
20 conditioning in rats (Psychopharm. 1998, 135, 324-332; Psychopharmacol 2000, 151: 25-30); d) spontaneous locomotor activity in mice (J. Pharm. Exp. Ther. 1996, 277, 586-594); e) reduction in opiate self-administration in mice (Sci. 1999, 283, 401-404);

The compounds of formula I and/or their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral,
25 parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils. Oral administration is preferred.

30 The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula (I) and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible
35 solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for
5 example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and
10 vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

15 Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula I can vary within wide limits depending
20 on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 to 1000 mg, especially about 1 to 100 mg, comes into consideration. Depending on severity of the disease and the precise pharmacokinetic profile the compound could be administered with one or
25 several daily dosage units, e.g. in 1 to 3 dosage units.

The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 1-100 mg, of a compound of formula I.

The following examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples

MS = mass spectrometry, EI = electron impact, ISP = ion spray (positive ion). All experiments were conducted under an inert atmosphere (nitrogen or argon).

Example 1

5 Preparation of (2-fluoro-4,5-dihydroxy-phenyl)-morpholin-4-yl-methanone

a) Preparation of 4-bromo-5-fluoro-benzene-1,2-diol

To a cooled (-78°C) solution of 4-fluoroveratrole (5.0 g, 32 mmol) in dichloromethane (106 ml) was slowly added a solution of boron trichloride in dichloromethane (1M, 96 ml, 96 mmol, 3.0 eq.). The reaction mixture was warmed to 20°C and stirred overnight.
10 The reaction mixture was poured into ice water, extracted with ethyl acetate (3 times). The combined organic layer was washed with an aqueous solution of sodium bicarbonate, dried over sodium sulfate and filtered. The volatiles were removed *in vacuo*. The brown solid was diluted with chloroform (50 ml) and dichloromethane (10 ml). A solution of bromine in carbon tetrachloride (5 ml) was slowly added. After stirring 3h at
15 room temperature, the volatiles were removed *in vacuo*. Purification by flash chromatography afforded the title compound (6.51 g, 98%) as a brown solid.

ISP MS: $m/e = 207.9 ([M+H]^+)$.

b) Preparation of 5-bromo-6-fluoro-2,2-diphenyl-benzo[1,3]dioxole

A mixture of 4-bromo-5-fluoro-benzene-1,2-diol (12 g, 58.0 mmol) and
20 diphenyldichloromethane (1.2eq., 16.50 g) was stirred at room temperature until gaseous evolution ceased. The mixture was heated with stirring at 180°C for 20 min. The reaction mixture was allowed to cool to room temperature, diluted with methanol (50ml) and vigorously stirred. The precipitated product was collected by filtration and dissolved in toluene (50ml). Methanol (100ml) was added and the mixture stirred 30min at room
25 temperature. The precipitated product was collected by filtration (yield 10.3g, 48%), a further batch (6.4g, 30%) was recovered from the mother liquors.

ISP MS: $m/e = 370.0 ([M+H]^+)$.

c) Preparation of (6-fluoro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-morpholin-4-yl-methanone

30 To a cooled (-78°C) solution of 5-bromo-6-fluoro-2,2-diphenyl-benzo[1,3]dioxole (17.59 g, 47.4 mmol) in diethyl ether (300 ml) was slowly added a solution of n-butyl

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lithium in hexanes (1.6M, 30 ml, 48 mmol, 1.0 eq.). The reaction mixture was stirred 1h at -78°C before the addition of 4-morpholinecarbonylchloride (8.5 g, 56.9 mmol, 1.2 eq.). The reaction mixture was allowed to warm to 20°C and poured into an aqueous solution of sodium bicarbonate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine. Volatiles were removed *in vacuo*. Purification by flash chromatography afforded (6-fluoro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-morpholin-4-yl-methanone compound (13.0 g, 68%) as a light yellow solid.

ISP MS: $m/e = 406.2$ ($[M+H]^+$).

d) Preparation of (2-fluoro-4,5-dihydroxy-phenyl)-morpholin-4-yl-methanone

To a cooled (ice-bath) solution of (6-fluoro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-morpholin-4-yl-methanone (5.70g, 14.06mMol) in trifluoroacetic acid (60ml) was added triethylsilane (2.1eq, 4.7ml) over 10min. The mixture was stirred 20min at 0°C and 4h at room temperature. The volatiles were removed under reduced pressure and the residue purified by column chromatography on silica gel (2:1 ethyl acetate/heptane-ethyl acetate-10:1 ethyl acetate/methanol) to afford (2-fluoro-4,5-dihydroxy-phenyl)-morpholin-4-yl-methanone as light brown solid (3.19g, 94%).

ISP MS: $m/e = 242.2$ ($[M+H]^+$).

Example 2

Preparation of 5,5-dichloro-5H-dibenzo[a,d]cycloheptene

5,5-Dichloro-5H-dibenzo[a,d]cycloheptene was prepared according to J.J. Looker, *J. Org. Chem.* 1966, 31, 3599: 5-dibenzosuberone (2 g, 9.7 mmol) was dissolved in phosphorus oxychloride (4.5 ml) and phosphorus pentachloride (3.13 g, 15.03 mmol) added. The mixture was heated 4 h at 120 °C. The mixture was allowed to cool to room temperature and the solvent removed under reduced pressure. The crude product was used without further purification.

Example 3

Preparation of 4-[(6-fluoro-spiro[1,3-benzodioxole-2,5'-[5H]dibenzo[a,d]cyclohepten]-5-yl)carbonyl]-morpholine

5,5-Dichloro-5H-dibenzo[a,d]cycloheptene (0.783 g, 3.0 mmol) was dissolved in toluene (8 ml) and heated to 120 °C. A solution of 4-(2-fluoro-4,5-dihydroxybenzoyl)-morpholine (0.36 g, 1.5 mmol) in toluene (4 ml) was added dropwise over 20 min. When the addition was complete, the mixture was heated a further 1 h at 120 °C. The mixture

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was cooled to room temperature and evaporated. The residue was purified by column chromatography on silica gel (1:0 to 10:1 dichloromethane/ethyl acetate eluant) to afford the title compound as an off-white foam.

MS: m/e 430.4 [(M+H)⁺]

- 5 NMR: δ (CDCl₃) 3.33 (br s, 2H), 3.60 (br s, 2H), 3.74 (br s, 4H), 6.54, (d, 1H, J=8.8Hz), 6.87 (d, 1H, J=5.2Hz), 7.17, (s, 2H), 7.44 (m, 4H), 7.50 (m, 2H), 7.93 (m, 2H) ppm.

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Galenical Examples**Example A**

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

<u>Ingredients</u>	<u>Per tablet</u>	
Kernel:		
Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg
Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxide (yellow)	0.8 mg	1.6 mg
Titanium dioxide	0.8 mg	1.6 mg

5

The active ingredient is sieved and mixed with microcrystalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidone in water. The granulate is mixed with sodium starch glycolate and magnesium stearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aq. solution / suspension of the above mentioned film coat.

10

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

<u>Ingredients</u>	<u>Per capsule</u>
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

- 5 The components are sieved and mixed and filled into capsules of size 2.

Example C

Injection solutions can have the following composition:

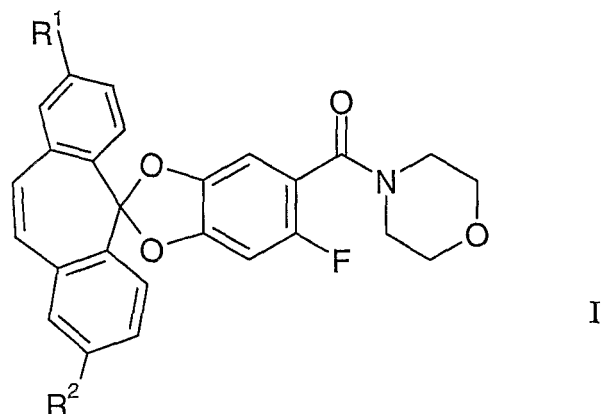
Compound of formula (I)	3.0 mg
Polyethylene glycol 400	150.0 mg
Acetic acid	q.s. ad pH 5.0
Water for injection solutions	ad 1.0 ml

- 10 The active ingredient is dissolved in a mixture of Polyethylene glycol 400 and water for injection (part). The pH is adjusted to 5.0 by addition of acetic acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

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Claims

1. Compounds of the general formula



wherein

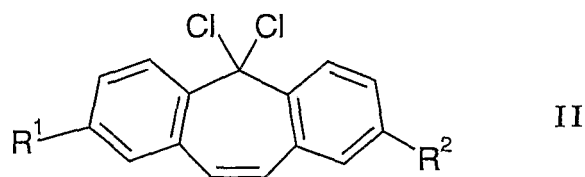
5 R^1 and R^2 are each independently hydrogen or halogen.

2. The compound according to claim 1, wherein R^1 and R^2 are hydrogen.

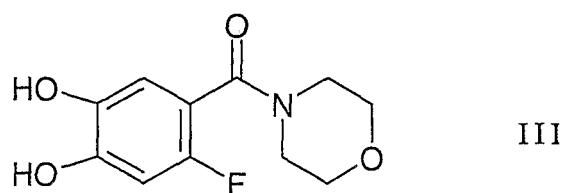
3. The compound according to claims 1 or 2, which is 4-[(6-fluoro-spiro[1,3-benzodioxole-2,5'-[5H]dibenzo[a,d]cyclohepten]-5-yl)carbonyl]-morpholine.

4. A process for the manufacture of compounds of formula I as defined in any of
10 claims 1 to 3, which process comprises

reacting a 5,5-dichloro-5H-dibenzo[a,d]cycloheptene of the formula

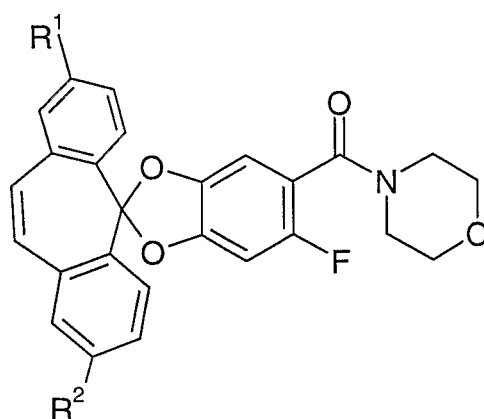


wherein R^1 and R^2 are each independently hydrogen or halogen,
with the catechol derivative of the formula



15

at elevated temperature to obtain a compound of the formula



5. Compounds according to any of claims 1 to 3 when manufactured by a process according to claim 4.

6. Pharmaceutical compositions comprising a compound according to any of
5 claims 1 to 3 and a pharmaceutically acceptable carrier and/or adjuvant.

7. Pharmaceutical compositions according to claim 6 for the treatment and/or prophylaxis of diseases which are associated with modulation of the CB₁ receptor.

8. Compounds according to any of claims 1 to 3 for use as therapeutic active substances.

10 9. Compounds according to any of claims 1 to 3 for use as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with modulation of the CB₁ receptor.

10. A method for the treatment and/or prophylaxis of diseases which are associated with the modulation of the CB₁ receptors which method comprises administering a
15 compound according to any of claims 1 to 3 to a human being or animal.

11. The use of compounds according to any of claims 1 to 3 for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB₁ receptors.

12. The use of compounds according to any of claims 1 to 3 for the preparation of
20 medicaments for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB₁ receptors.

13. The novel compounds, processes and methods as well as the use of such compounds substantially as described hereinbefore.