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(54) **Title:** USE OF COMPOUNDS BINDING TO THE SIGMA RECEPTOR FOR THE TREATMENT OF METABOLIC SYNDROME

(57) **Abstract:** The present invention refers to the use of compounds binding to the sigma receptor for the treatment of metabolic syndrome.

Use of compounds binding to the sigma receptor for the treatment of metabolic syndrome

Field of the invention

The present invention refers to the use of compounds binding to the sigma receptor for the treatment of metabolic syndrome, especially hyperlipidemias, in particular hypertriglyceridemias and the prevention or the prophylaxis of the symptoms of metabolic syndrome, especially hyperlipidemias, in particular hypertriglyceridemias.

Background of the invention

The treatment of metabolic syndrome is of great importance in medicine. The metabolic syndrome is a widespread disease, particularly in the United States and Europe. Based on survey data from 1988 to 1994 and 2000 census data, the American Center for Disease Control and Prevention estimates that 47 million people in the US have metabolic syndrom. There is currently a world-wide need for treatment of this syndrome as it is identified as heightening the risk of cardiovascular mortality.

Consequently, it was an object of the present invention to provide medicaments, which are suitable for the treatment of metabolic syndrome.

Therefore, it was the underlying problem solved by this invention to find new ways of treating metabolic syndrome.

So, the main object of this invention is the use of a compound binding to the sigma receptor in the production of a medicament for the treatment of metabolic syndrome.

Another preferred object of the invention is the use of at least one compound binding to the sigma receptor and having an IC_{50} value of ≤ 500 nM for the production of a medicament for the treatment of metabolic syndrome.

The metabolic syndrome and definitions thereof are described in detail by Eckel et al., The Lancet, Vol. 365 (2005), 1415-1428, included herewith by reference. One of the respective definitions was established by the WHO in 1998 (as described in Alberti et al., Diabet. Med. 1998, 15, pages 539-53, the respective description thereof is herewith incorporated by reference and forms part of the present disclosure). The other, more widely accepted, definition of the metabolic syndrome was established by the Adult Treatment Panel (ATP III) of the US National Cholesterol Education Program (NCEP) in 2001, as described in JAMA 2001; 285; 2486-97, the respective description thereof is herewith incorporated by reference and forms part of the present disclosure.

The metabolic syndrome is characterized by an interaction of several physiological parameters such as triglycerides, lipids, blood pressure, glucose levels and insulin levels. Thus it includes especially hyperlipidemias and hypertriglyceridemia.

Even though obesity may play a critical role in the development of metabolic syndrome, many of its aspects are weight independent, especially some lipid parameters. Especially the positive influence on the weight independent aspects of the metabolic syndrome (see e.g. Pagotto and Pasquali, The Lancet, Vol. 365 (2005), 1363, 1364, included herewith by reference) like some blood parameters, especially lipid parameters is one of the major and surprising advantages of the inventively used compounds binding to the sigma receptor.

Hypertriglyceridemia can be categorized by the Fredrickson classification of lipid disorders (Fredrickson, 1971; Beaumont et al., 1970). All hyperlipidemias (types I, IIb, III, IV and V) except type IIa are characterized by elevated triglyceride levels. Thus, the present invention claims the use of sigma-1 receptor antagonists for treating the following types of hypertriglyceridemias:

- **Type I:** It is characterized by severe elevations in chylomicrons and elevated triglycerides. Because chylomicrons also contain a small amount of cholesterol, serum cholesterol levels also are quite high.
- **Type IIb:** It is the classic mixed hyperlipidemia (high cholesterol and triglycerides) caused by elevations in both low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL).
- **Type III:** It is also known as dysbetalipoproteinemia, remnant removal disease, or broad-beta disease. Typically, these patients have elevated total cholesterol and triglyceride levels and are easily confused with patients with type IIb hyperlipidemia. Patients with type III hyperlipidemia have elevations in intermediate-density lipoprotein (IDL), a VLDL remnant.
- **Type IV:** It is characterized by abnormal elevations of VLDL and triglycerides. Serum cholesterol levels are normal.
- **Type V:** It is the combination of types I and IV (elevations of both chylomicrons and VLDL). Serum cholesterol levels always are elevated, but the LDL cholesterol levels are normal. Given the rarity of type I disease, when elevated triglycerides are noted, the most likely cause is type V hyperlipidemia.

This/these compound/s may be in neutral form, the form of a base or acid, in the form of a salt, preferably a physiologically acceptable salt, in the form of a solvate or of a polymorph and/or in the form of in the form of its racemate, pure stereoisomers, especially enantiomers or diastereomers or in the form of mixtures of stereoisomers, especially enantiomers or diastereomers, in any suitable mixing ratio.

While working on compounds binding to the sigma receptor and with models like knock-out mice it was surprisingly found out that metabolic syndrome is connected to the sigma receptor so that compounds binding to the sigma receptor were acting on metabolic syndrome with a high potency.

The term “treatment” as used in the present application encompasses prevention, amelioration and/or complete recovery from the disease. Said term also includes

the prevention, amelioration and/or complete recovery of one or more symptoms associated with the disease.

"The sigma receptor/s" as used in this application is/are well known and defined using the following citation: This binding site represents a typical protein different from opioid, NMDA, dopaminergic, and other known neurotransmitter or hormone receptor families (G. Ronsisvalle et al. Pure Appl. Chem. 73, 1499-1509 (2001)). Pharmacological data based on ligand binding studies, anatomical distribution and biochemical features distinguish at least two subtypes of σ receptors (R. Quiron et al., Trends Pharmacol. Sci. 13, 85-86 (1992); M.L.Leitner, Eur. J. Pharmacol. 259, 65-69 (1994); S.B. Hellewell and W.D. Bowen; Brain Res. 527, 244-253 (1990)) (G. Ronsisvalle et al. Pure Appl. Chem. 73, 1499-1509 (2001)). The protein sequence of sigma-1 (σ1) receptors is known (e.g. Prasad, P.D. et al., J. Neurochem. 70 (2), 443-451 (1998)) and they show a very high affinity for e.g. pentazocine.

"Compound/s binding to the sigma receptor" or "sigma ligand" as used in this application is/are defined as having an IC_{50} value of ≤ 5000 nM, more preferably ≤ 1000 nM, more preferably ≤ 500 nM. More preferably, the IC_{50} value is ≤ 250 nM. More preferably, the IC_{50} value is ≤ 100 nM. Most preferably, the IC_{50} value is ≤ 50 nM. Additionally, the wording "Compound/s binding to the sigma receptor", as used in the present application is defined as having at least ≥50% displacement using 10 mM radioligand specific for the sigma receptor (e.g. preferably ^3H-pentazocine) whereby the sigma receptor may be any sigma receptor subtype (sigma-1 or sigma-2). Preferably, said compounds bind to the sigma-1 receptor subtype.

Compounds binding to the sigma receptor generally also known as sigma ligands are well known in the art with many of them falling under the definition for "Compound/s binding to the sigma receptor" set up above. Still even though there are many uses known for sigma ligands such as antipsychotic drugs, anxiolytics, antidepressants, the treatment of stroke, antiepileptic drugs and many other indications there is nowhere any mentioning of these compounds being useful against metabolic syndrome.

Compounds binding to the sigma receptor known in the art and matching the criteria of sigma ligand (i.e. having an $IC_{50} \leq$ 5000 nM) as mentioned above, are listed below. Some of these compounds may bind to the sigma-1 and/or the sigma-2 receptor. Preferably, these compounds are in form of a salt, a base or an acid. Also preferably, the salts/bases/acids indicated in the list are to be understood as being exemplary and therefore may represent any salt, base or acid of the compound.

(-)-Cyanopindolol hemifumarate	(-)-SPARTEINE SULFATE PENTAHYDRATE
(+)-HIMBACINE	(2-Dibutylamino-Ethyl)-Carbamic Acid 2-(4-Benzofuran-2-Ylmethyl-Piperazin-1-Yl)-Ethyl Ester
(4-[1,2,3]Thiadiazol-4-Yl-Benzyl)-Carbamic Acid 1-(3-Methoxy-2-Nitro-Benzyl)-Piperidin-3-Ylmethyl Ester	(S)-Methamphetamine HCl
[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-Carbamic Acid 1-(3-Benzyloxy-4-Methoxy-Benzyl)-Piperidin-3-Ylmethyl Ester	[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-Carbamic Acid 2-(Tert-Butoxycarbonyl-Naphthalen-1-Ylmethyl-Amino)-Ethyl Ester
[4-(4-Ethyl-3,5-Dimethyl-Pyrazol-1-Yl)-Phenyl]-[4-(3-Phenyl-Allyl)-Piperazin-1-Yl]-Methanone	1-(1,2-Diphenylethyl)Piperidine Maleate, (+/-)
1-(1-Naphthyl)Piperazine HCl	1-(3-Chlorophenyl)Piperazine HCl
1-(4-Bromo-Benzenesulfonyl)-4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine	2-(2-{[1-(3-Chloro-Benzyl)-Pyrrolidin-3-Yl]-Methyl-Carbamoyl}-2-Methyl-Propyl)-4,6-Dimethyl-Benzoic Acid
2-Chloro-11-(4-Methylpiperazino)Dibenz[B,F]Oxepin Maleate	3,3'-Diethylthiacarbocyanine Iodide
3-Mercapto-2-Methylpropanoic Acid 1,2- Diphenylethylamine Salt	3-Quinuclidinyl Benzilate
3-Tropanyl-3,5-Dichlorobenzoate	3-Tropanyl-Indole-3-Carboxylate HCl
4-(1H-Indol-4-Yl)-Piperazine-1-Carboxylic Acid 2-(5-Bromo-2-Ethoxy-Phenylamino)-Cyclohexylmethyl Ester	4-(2-Tert-Butylsulfanyl-Benzyl)-Piperazine-1-Carboxylic Acid 2-Thiophen-2-Yl-Ethyl Ester
4-(3,5-Dimethoxy-Phenyl)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-Benzyl)-Piperidin-2-Ylmethyl Ester	4-(3-Nitro-5-Sulfamoyl-Thiophen-2-Yl)-Piperazine-1-Carboxylic Acid 1-(2-Fluoro-5-Methoxy-Benzyl)-Piperidin-3-Ylmethyl Ester
4-(4-Fluorobenzoyl)-1-(4-Phenylbutyl)Piperidine Oxalate	4-(5-Trifluoromethyl-Pyridin-2-Yl)-Piperazine-1-Carboxylic Acid Pent-2-Ynyl Ester
4,4'-Bis[4-(P-Chlorophenyl)-4-Hydroxypiperidino]Butyrophenone	4-[1-(4-Chlorobenzyl)-4-(benzylpiperidin-4-yl]-2-hydroxy-4-

	oxobut-2-enoic acid
4-Bromo-N-[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-2-Trifluoromethoxy-Benzenesulfonamide	4'-Chloro-3-Alpha-(Diphenylmethoxy)Tropane HCl
4-Furan-2-Ylmethyl-Piperazine-1-Carboxylic Acid 2-{4-[3-(2-Trifluoromethyl-Phenothiazin-10-Yl)-Propyl]-Piperazin-1-Yl}-Ethyl Ester	4-Methoxy-N-[1-(7-Methoxy-Benzo[1,3]Dioxol-5-Ylmethyl)-Pyrrolidin-3-Yl]-Benzenesulfonamide
5-(N-Ethyl-N-Isopropyl)-Amiloride	7-Hydroxy-DPAT HBr, (±)-
8-Hydroxy-DPAT HBr, (R)-(+)-	8-Hydroxy-DPAT HBr, S(-)-
9-[4-({[4'-(trifluoromethyl)-1,1'-biphenyl-2-yl]carbonyl}amino)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide	Acepromazine Maleate
Acetophenazine Maleate	Acrinol
Ajmaline	Alaproclate HCl
Aloe-Emodin	Alprenolol D-Tartrate Salt Hydrate
Alprenolol HCl	AMI-193
Aminobenztropine	Amiodarone HCl
Amodiaquine HCl	Amorolfine HCl
Amoxapine	Anileridine HCl
Anisotropine Methylbromide	Anpirtoline
ARC 239 DiHCl	Astemizole
Auramine O HCl	Azaperone
Azatadine Maleate	Azelastine HCl
Bamethan sulfate	BD 1008 DiHBr
BD-1047	BD-1063
Benextramine TetraHCl	Benfluorex HCl
Benidipine HCl	Benoxathian HCl
Benoxinate HCl	Benperidol
Benproperine Phosphate	Benzododecinium bromide
Benzphetamine HCl	Benztropine Mesylate
Benzydamine HCl	Bephenium Hydroxynaphthoate
Bepridil HCl	Berberine chloride
Betaxolol HCl	Bifemelane
BMY 7378 DiHCl	Bopindolol Malonate
BP 554 Maleate	Bromhexine HCl
Bromodiphenhydramine HCl	Bromperidol
Brompheniramine Maleate	BTCP HCl
Buclizine HCl	Buflomedil HCl
Bupropion HCl	Buspirone HCl
Butacaine Sulfate	Butaclamol HCl, (±)-
Butenafine HCl	Butoconazole Nitrate
BW 723C86 HCl	Carbetapentane Citrate
Carbinoxamine Maleate	Carpipramine DiHCl DiH2O
Carvedilol	Cephapirin Benzathine
CGS-12066A Maleate	Chloroprocaine HCl
Chloroquine Phosphate	Chlorpheniramine Maleate

Chlorphenoxamine HCl	Chlorpromazine HCl
Chlorprothixene	Cinanserin HCl
Cinnarizine	Cirazoline HCl
Cis-(+/-)-N-Methyl-N-[2-(3,4-Dichlorophenyl)Ethyl]-2-(1-Pyrrolidinyl)Cyclohexamine DiHBr	Cis(Z)-Flupentixol DiHCl
Cisapride Hydrate	Citalopram HBr
Clebopride Maleate Salt	Clemastine Fumarate
Clemizole HCl	Clenbuterol HCl
Clidinium Bromide	Clobenpropit 2HBr
Clofazimine	Clofilium Tosylate
Clomiphene Citrate	Clomiphene Related Compound A
Clomipramine	Cloperastine HCl
Clorgyline HCl	Clozapine
CONESSINE	Cyclizine
Cyclobenzaprine HCl	Cycloheximide
Cyproheptadine HCl	Darrow Red HCl
Demecarium Bromide	Denatonium Benzoate
Deptropine Citrate	Desloratadine
Dexbrompheniramine Maleate	Dexchlorpheniramine Maleate
Dexfenfluramine HCl	Dibucaine HCl
Dicyclomine HCl	Diethylpropion HCl
Dimethisoquin HCl	Dimetindene Maleate
Diphemanil Methylsulfate	Diphenidol HCl
Diphenoxylate HCl	Diphenylpyraline HCl
Dipropyldopamine HBr	Dobutamine HCl
Donepezil HCl	Doxepin HCl
Droperidol	Duloxetine
Dyclonine HCl	Ebastine
Econazole Nitrate	Epinastine HCl
Ethaverine HCl	Ethopropazine HCl
Eticlopride HCl, S(-)-	Etofenamate
Etonitazenyl Isothiocyanate	Femoxetine HCl
Fenfluramine HCl	Fentanyl Citrate
Fenticonazole Nitrate	Fipexide HCl
Flavoxate HCl	Flunarizine diHCl
Fluoxetine Related Compound B	Fluperlapine
Fluphenazine Decanoate DiHCl	Fluphenazine Enanthate DiHCl
Fluphenazine HCl	Fluphenazine N-Mustard DiHCl
Flurazepam Related Compound C	Fluspirilene
Fluvoxamine Maleate	GBR 12783 DiHCl
GBR 12909 DiHCl	GBR 13069 DiHCl
GBR-12935 DiHCl	GR 89696 Fumarate
Guanabenz Acetate	Guanadrel Sulfate
Guanethidine Sulfate	Halofantrine HCl
Haloperidol	HEAT HCl
Hexylcaine HCl	Hycanthone
Hydroxychloroquine Sulfate	Hydroxyzine HCl

Hyoscyamine Sulfate	IBZM, S(-)-
ICI-199,441 HCl	Ifenprodil Tartrate
Imipramine HCl	Indatraline HCl
Iofetamine HCl	Irinotecan HCl
Isamoltane Hemifumarate	Isopromethazine HCl
Isoxsuprine HCl	Ketanserin L-Tartrate
Ketoconazole	Ketotifen Fumarate Salt
L-693,403 Maleate	L-741,626
L-741,742 HCl	L-745,870 TriHCl
Labetalol HCl	Levetimide HCl, R(-)
Levobunolol HCl	Lidoflazine
Lisuride Hydrogen Maleate, R(+)-	Lobeline HCl
lomerizine diHCl	Loperamide HCl
Loxapine Succinate	LY-53,857 Maleate
Maprotiline HCl	Mazindol
MDL 12,330A HCl	Mebhydroline 1,5-naphthalendisulfonate Salt
Meclizine HCl	Mefloquine HCl
Meprylcaine HCl	Mesoridazine Besylate
Metaphit Methanesulfonate	Metergoline
Methantheline Bromide	Methdilazine
Methiothepin Mesylate	Methixene HCl
Methoctramine	Methotrimeprazine Maleate
Methylene Violet 3Rax HCl	Metipranolol
Mexiletine HCl	Mianserin HCl
Miconazole	ML-9 HCl
Morantel Hydrogen L-Tartrate	MR 16728 HCl
N-(2-Chloroethyl)-N-Ethyl-2-Bromobenzylamine HCl	N'-[2-(Benzo[1,2,5]Thiadiazole-4-Sulfonylamino)-Acetyl]-Hydrazinecarboxylic Acid 2-(2-{4-[(4-Chloro-Phenyl)-Phenyl-Methyl]-Piperazin-1-Yl}-Ethoxy)-Ethyl Ester
Nafronyl Oxalate Salt	Naftifine
Naftopidil diHCl	Naltriben Mesylate
NAN-190 HBr	NE-100
Nefazodone	Nefopam HCl
Nicardipine HCl	Nicergoline
Niguldipine HCl, (+/-)-	Nisoxetine HCl
Nortriptyline HCl	Nylidrin HCl
Octoclothepin Maleate, (±)-	Orphenadrine Citrate
Oxamniquine	Oxamniquine Related Compound A
Oxamniquine Related Compound B	Oxatomide
Oxiconazole Nitrate	Oxybutynin HCl
Panaxatriol	PAPP
Paroxetine	Paxilline
p-Chlorobenzhydrylpiperazine	Penbutolol Sulfate
Pentamidine Isethionate	Pentazocine, (±)-
Pergolide Methanesulfonate	Perhexiline Maleate Salt

Perospirone	Perphenazine
Perphenazine Sulfoxide	Phenamil Methanesulfonate
Phencyclidine HCl	Phenosafranin HCl
Phenoxybenzamine HCl	Phenyltoloxamine Citrate Salt
Piboserod	Pimozide
Pinacyanol Chloride	Pindobind, (+/-)-
Piperacetazine	Piperazine-1,4-Dicarboxylic Acid Benzyl Ester 2-[4-(4-Dimethylamino-Benzyl)-Piperazin-1-Yl]-Ethyl Ester
Piperidolate HCl	Pirenperone
PPHT HCl, (±)-	Pramoxine HCl
Prenylamine Lactate Salt	Pridinol Methanesulfonate Salt
Prochlorperazine Maleate	Procyclidine HCl
Proflavine Hemisulfate Salt	Progesterone
Promazine HCl	Promethazine HCl
Propafenone HCl	Proparacaine HCl
Propericyazine	Propiomazine
Propranolol HCl	Protokylol
Protriptyline HCl	Pyrilamine Maleate
Pyrimethamine	Pyrrolidine-1,2-Dicarboxylic Acid 1-[1-(4-Allyloxy-Benzyl)-Piperidin-2-Ylmethyl] Ester 2-Benzyl Ester
Pyrvinium Pamoate	Quetiapine Fumarate
Quinacrine HCl	Quinaldine Red
Quipazine Dimaleate	Quipazine, 6-Nitro-, Maleate
Raloxifene	Rimantadine HCl
Risperidone	Ritanserin
Ritodrine HCl	RS 23597-190 HCl
RS 67333 HCl	RS 67506 HCl
Safranin O HCl	Salmeterol
SB203186	SCH-23390 HCl, R(+)-
Sertaconazole Nitrate	Sertindole
Sertraline	Sibutramine HCl
SKF-525A HCl	SKF-96365 HCl
SNC 121	Spiperone HCl
Sufentanil	T-226296
Tamoxifen Citrate	Tamsulosin HCl
Tegaserod Maleate	Terbinafine HCl
Terconazole	Terfenadine
Terfenadine Related Compound A	Tetracaine HCl
Tetrindole Mesylate	Thiethylperazine Malate
Thioperamide Maleate	Thioproperazine
Thioridazine	Thiothixene
Thiothixene, (E)-	Thonzonium Bromide
Tioconazole Related Compound A	TMB-8 HCl
Tolterodine L-Tartrate	Toremifene Citrate
Tramazoline HCl	Trans-U-50488 Methanesulfonate, (±)-

Trazodone HCl	Tridihexethyl Chloride
Trifluoperazine HCl	Trifluperidol HCl
Triflupromazine HCl	Trihexyphenidyl HCl
Trimebutine	Trimeprazine Hemi-L-Tartrate
Trimipramine Maleate	Tripelennamine HCl
Triprolidine HCl	Triprolidine HCl Z Isomer
Tropanyl 3,5-Dimethylbenzoate	Tropine 2-(4-Chlorophenoxy)Butanoate, Maleate
U-50488 HCl, (-)-	U-62066
UH 232 Maleate, (+)-	Vecuronium Bromide
Verapamil HCl	Verapamil Related Compound B
Vesamicol HCl	Vinpocetine
W-7 HCl	WB-4101 HCl
Xylazine	Xylometazoline HCl

The following list is based on the list immediately above and – being especially preferred - lists compounds binding to the sigma receptor known in the art and having an $IC_{50} \leq 500$ nM. Preferably, these compounds are in form of a salt, a base or an acid. Also preferably, the salts/bases/acids indicated in the list are to be understood as being exemplary and therefore may represent any salt, base or acid of the compound.

(2-Dibutylamino-Ethyl)-Carbamic Acid 2-(4-Benzofuran-2-Ylmethyl-Piperazin-1-Yl)-Ethyl Ester	(4-[1,2,3]Thiadiazol-4-Yl-Benzyl)-Carbamic Acid 1-(3-Methoxy-2-Nitro-Benzyl)-Piperidin-3-Ylmethyl Ester
4-(4-Fluorobenzoyl)-1-(4-Phenylbutyl)Piperidine Oxalate	4-[1-(4-Chlorobenzyl)-4-(benzylpiperidin-4-yl]-2-hydroxy-4-oxobut-2-enoic acid
4-Bromo-N-[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-2-Trifluoromethoxy-Benzenesulfonamide	4'-Chloro-3-Alpha-(Diphenylmethoxy)Tropane HCl
4-Furan-2-Ylmethyl-Piperazine-1-Carboxylic Acid 2-{4-[3-(2-Trifluoromethyl-Phenothiazin-10-Yl)-Propyl]-Piperazin-1-Yl}-Ethyl Ester	Acetophenazine Maleate
Aminobenztropine	Amiodarone HCl
Amodiaquine HCl	Amorolfine HCl
Anileridine HCl	Astemizole
Azaperone	Azelastine HCl
BD 1008 DiHBr	BD-1047
BD-1063	Benextramine TetraHCl
Benfluorex HCl	Benoxathian HCl
Benperidol	Benproperine Phosphate
Benzododecinium bromide	Benztropine Mesylate
Bepridil HCl	Berberine chloride
Bifemelane	BP 554 Maleate

Bromhexine HCl	Bromodiphenhydramine HCl
Bromperidol	Buflomedil HCl
Butacaine Sulfate	Butaclamol HCl, (±)-
Butenafine HCl	Carbetapentane Citrate
Carpipramine DiHCl DiH2O	Cinnarizine
Cis-(+/-)-N-Methyl-N-[2-(3,4-Dichlorophenyl)Ethyl]-2-(1-Pyrrolidinyl)Cyclohexamine DiHBr	Cis(Z)-Flupentixol DiHCl
Cisapride Hydrate	Clofilium Tosylate
Clomiphene Citrate	Clomiphene Related Compound A
Clomipramine	Cloperastine HCl
Clorgyline HCl	Cyclobenzaprine HCl
Cyproheptadine HCl	Demecarium Bromide
Deptropine Citrate	Dibucaine HCl
Dicyclomine HCl	Diphenylpyraline HCl
Donepezil HCl	Doxepin HCl
Dyclonine HCl	Femoxetine HCl
Flunarizine diHCl	Fluphenazine Decanoate DiHCl
Fluphenazine Enanthate DiHCl	Fluphenazine HCl
Fluphenazine N-Mustard DiHCl	GBR 12783 DiHCl
GBR 12909 DiHCl	GBR 13069 DiHCl
GBR-12935 DiHCl	Haloperidol
HEAT HCl	Hexylcaine HCl
Hydroxyzine HCl	Ifenprodil Tartrate
Isopromethazine HCl	Isoxsuprine HCl
L-693,403 Maleate	L-741,626
L-741,742 HCl	L-745,870 TriHCl
Lidoflazine	Lobeline HCl
lomerizine diHCl	Loperamide HCl
LY-53,857 Maleate	Metergoline
Methdilazine	Methixene HCl
Metipranolol	ML-9 HCl
MR 16728 HCl	Naftifine
Naftopidil diHCl	NAN-190 HBr
Nicardipine HCl	Nylidrin HCl
Octoclothepin Maleate, (±)-	Oxamniquine Related Compound A
Oxybutynin HCl	PAPP
Penbutolol Sulfate	Pentazocine, (±)-
Perphenazine	Phenoxybenzamine HCl
Pimozide	Piperidolate HCl
PPHT HCl, (±)-	Prenylamine Lactate Salt
Prochlorperazine Maleate	Promazine HCl
Proparacaine HCl	Protriptyline HCl
Pyrrolidine-1,2-Dicarboxylic Acid 1-[1-(4-Allyloxy-Benzyl)-Piperidin-2-Ylmethyl] Ester 2-Benzyl Ester	Pyrvinium Pamoate
Raloxifene	Ritanserin
RS 67333 HCl	RS 67506 HCl

Salmeterol	Sertindole
Sertraline	SKF-525A HCl
Tamoxifen Citrate	Tegaserod Maleate
Terbinafine HCl	Terconazole
Thioridazine	Toremifene Citrate
TMB-8 HCl	Trifluperidol HCl
Trifluoperazine HCl	Trimeprazine Hemi-L-Tartrate
Triflupromazine HCl	Tripelennamine HCl
Trimipramine Maleate	Verapamil HCl
U-50488 HCl, (-)-	Xylazine
WB-4101 HCl	

Unless otherwise stated, the compounds of the invention are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon or ^{15}N-enriched nitrogen are within the scope of this invention.

A preferred embodiment of the invention includes the use of at least one compound binding to the sigma receptor for the production of a medicament for the treatment of elevated triglyceride levels. Also preferred is the use of at least one compound binding to the sigma receptor for the production of a medicament for treatment of chylomicronemia, hyperlipoproteinemia, hyperlipidemia (especially mixed hyperlipidemia), hypercholesterolemia, lipoprotein disorders and dysbetalipoproteinemia. An especially preferred embodiment is drawn to the use of at least one compound binding to the sigma receptor for the production of a medicament for the treatment hypertriglyceridemia including both the sporadic and familial disorder (inherited hypertriglyceridemia).

Generally the use of compounds binding to the sigma-1 receptor to produce a medicament for the treatment of metabolic syndrome does not have to cover the treatment of all its aspects. Thus a treatment reducing plasma levels of triglycerides for treating excess triglycerides in plasma (hypertriglyceridemia), does not necessarily include treatment of plasma cholesterol and glucose levels, that may be

also concomitantly elevated (hypercholesterolemia and hyperglycemia, respectively) in metabolic syndrome.

In addition the use of sigma-1 receptor ligands to produce a medicament for the treatment of hypertriglyceridemia includes also treatment of elevated levels of triglycerides, which exist as a consequence of an abnormal diet or diseases such as diabetes, obesity or any disease or disturbance causing elevations in triglyceride levels.

Finally the use of sigma-1 receptor ligands to produce a medicament for the treatment of hypertriglyceridemia includes also the treatment of different pathological conditions involving elevated triglyceride levels, such as chylomicronemia, hyperlipoproteinemia, mixed hyperlipidemia and dysbetalipoproteinemia.

The term "salt" is to be understood as meaning any form of the active compound according to the invention in which this assumes an ionic form or is charged and is coupled with a counter-ion (a cation or anion) or is in solution. By this are also to be understood complexes of the active compound with other molecules and ions, in particular complexes which are complexed via ionic interactions.

The term "physiologically acceptable salt" is understood in particular, in the context of this invention, as salt (as defined above) formed either with a physiologically tolerated acid, that is to say salts of the particular active compound with inorganic or organic acids which are physiologically tolerated - especially if used on humans and/or mammals - or with at least one, preferably inorganic, cation which are physiologically tolerated - especially if used on humans and/or mammals. Examples of physiologically tolerated salts of particular acids are salts of: hydrochloric acid, hydrobromic acid, sulfuric acid, hydrobromide, monohydrobromide, monohydrochloride or hydrochloride, methiodide, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, hippuric acid picric acid and/or aspartic acid. Examples of physiologically tolerated salts of particular bases are salts of alkali metals and alkaline earth metals and with NH_4.

The term "solvate" according to this invention is to be understood as meaning any form of the active compound according to the invention in which this compound has attached to it via non-covalent binding another molecule (most likely a polar solvent) especially including hydrates and alcoholates, e.g. methanolate.

In one embodiment of the invention the following proviso applies:

with the proviso that the compounds orlistat, sibutramine, phentermine, diethylpropion, benzphetamine, phendimetrazine are excluded from the compounds to be used.

In a very preferred embodiment of the invention the compound binding to the sigma receptor used is acting on the sigma receptor as an antagonist.

In a very preferred embodiment of the invention the compound binding to the sigma receptor used is acting on the sigma receptor as an inverse agonist.

In a very preferred embodiment of the invention the compound binding to the sigma receptor used is acting on the sigma receptor as a partial antagonist.

In another possible embodiment of the invention the compound binding to the sigma receptor used is acting on the sigma receptor as an agonist.

In another embodiment of the invention the compound binding to the sigma receptor used is acting on the sigma receptor as a mixed agonist/antagonist, a partial agonist or a partial antagonist.

In another embodiment of the invention the sigma receptor to which the "compound binding to the sigma receptor" is binding to is the sigma-1 receptor. Under this embodiment "Compound/s binding to the sigma receptor" as used in this application is/are defined as having an IC50 value ≤ 5000 nM, more preferably ≤ 1000 nM, more preferably ≤ 500 nM. More preferably, the IC_{50} value is ≤ 250 nM. More preferably, the IC_{50} value is ≤ 100 nM. Most preferably, the IC_{50} value is ≤ 50 nM.

Additionally, the wording "Compound/s binding to the sigma receptor", as used in the present application is defined as having at least ≥ 50% displacement using 10 mM radioligand specific for the sigma receptor (e.g. preferably ^{3}H-pentazocine) whereby the sigma receptor may be any sigma receptor subtype.

In another preferred embodiment of the invention, the compound binding to the sigma receptor, as defined above, has an IC_{50} value of ≤ 1000 nM.

In another preferred embodiment of the invention, the compound binding to the sigma receptor, as defined above, has an IC_{50} value of ≤ 500 nM.

In another preferred embodiment of the invention, the compound binding to the sigma receptor, as defined above, has an IC_{50} value of ≤ 250 nM.

In another preferred embodiment of the invention, the compound binding to the sigma receptor, as defined above, has an IC_{50} value of ≤ 100 nM.

In another preferred embodiment of the invention, the compound binding to the sigma receptor, as defined above, has an IC_{50} value of ≤ 50 nM.

Most preferably, "compounds highly specific for the sigma receptor" are defined as being "Compound/s binding to the sigma receptor", as defined above, having an IC_{50} value of ≤ 100 nM.

In a highly preferred embodiment of the present invention, the compound binding to the sigma receptor as defined above, is binding to the sigma-1 receptor subtype.

In another possible aspect of the invention, the compound binding to the sigma receptor as defined above, may bind to the sigma-2 receptor subtype.

In human therapeutics, the dose administered can be quite low depending on the route of administration and is well known in the art because sigma compounds are known therapeutics.

The daily dosage for humans and animals may vary depending on factors that have their basis in the respective species or other factors, such as age, sex, weight or degree of illness and so forth. The daily dosage for humans may preferably be in the range from 1 to 2000, preferably 1 to 1500, more preferably 1 to 1000 milligrams of active substance to be administered during one or several intakes per day.

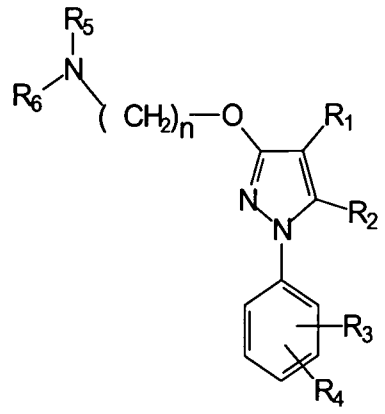
Any medicament according to the invention contains the active ingredient as well as optionally at least one auxiliary material and/or additive and/or optionally another active ingredient.

The auxiliary material and/or additive can be specifically selected from conserving agents, emulsifiers and/or carriers for parenteral application. The selection of these auxiliary materials and/or additives and of the amounts to be used depends upon how the pharmaceutical composition is to be applied. Examples include here especially parenteral like intravenous subcutaneous or intramuscular application formulations but which could also be used for other administration routes.

Routes of administration preferably include intramuscular injection, intraveneous injection, subcutaneous injection, sublingual, bucal, patch through skin, oral ingestion, implantable osmotic pump, collagen implants, aerosols or suppository.

Included in this invention are especially also methods of treatments of a patient or a mammal, including men, suffering from metabolic syndrome using compounds binding to the sigma receptor.

In another embodiment the use according to the invention; especially for the production of a medicament for the treatment of lipoprotein disorders; of a compound according to formula II



(II)

wherein

R_1 is selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$ $-C=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

R_2 is selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$ $-C=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

R_3 and R_4 are independently selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$ $-C=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO2$, $-N=CR_8R_9$, or halogen, or together they form a fused ring system,

R_5 and R_6 are independently selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$ $-C=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

together form, with the nitrogen atom to which they are attached, a substituted or unsubstituted heterocyclyl group;

n is selected from 1, 2, 3, 4, 5, 6, 7 or 8;

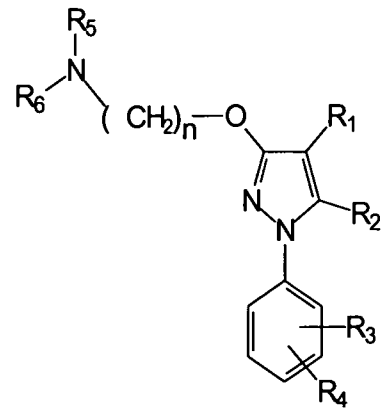
t is 1,2 or 3;

R_8 and R_9 are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, or halogen;

or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof.

or

of a compound of the formula IIB:



(IIB)

wherein

R_1 is selected from the group formed by substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$ $-C=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO2$, $-N=CR_8R_9$ or halogen,

R_2 is selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$ $-C=NR_8$, $-CN$, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

R_3 and R_4 are independently selected from the group formed by substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$ $-C=NR_8$, $-CN$,

$-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, -NO2, $-N=CR_8R_9$, or halogen, or together they form a fused ring system,

R_5 and R_6 are independently selected from the group formed by hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, $-COR_8$, $-C(O)OR_8$, $-C(O)NR_8R_9$ $-C=NR_8$, -CN, $-OR_8$, $-OC(O)R_8$, $-S(O)_t-R_8$, $-NR_8R_9$, $-NR_8C(O)R_9$, $-NO_2$, $-N=CR_8R_9$, or halogen;

together form, with the nitrogen atom to which they are attached, a substituted or unsubstituted heterocyclyl group;

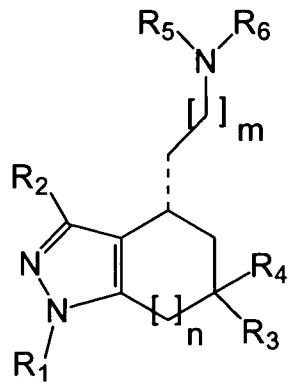
n is selected from 1, 2, 3, 4, 5, 6, 7 or 8;

t is 1,2 or 3;

R_8 and R_9 are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, or halogen;
or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof;

is excluded/disclaimed.

In another embodiment the use according to the invention; especially for the production of a medicament for the treatment of lipoprotein disorders, hyperlipidemia, hypertriglyceridemia or hypercholesterolemia, of compounds according to general formula I



(I)

wherein

R_1 is selected from the group formed by hydrogen, susbtituted or unsubstituted alkyl, susbtituted or unsubstituted cycloalkyl, susbtituted or unsubstituted heterocyclyl, susbtituted or unsubstituted aryl, susbtituted or unsubstituted arylalkyl, and susbtituted or unsubstituted heterocyclylalkyl;

R_2 is selected from the group formed by hydrogen, susbtituted or unsubstituted alkyl, susbtituted or unsubstituted cycloalkyl, susbtituted or unsubstituted alkoxy, susbtituted or unsubstituted aryl, susbtituted or unsubstituted heterocyclyl, susbtituted or unsubstituted arylalkyl, and susbtituted or unsubstituted heterocyclylalkyl;

R_3 and R_4 are independently selected from the group formed by hydrogen, susbtituted or unsubstituted alkyl, susbtituted or unsubstituted cycloalkyl, susbtituted or unsubstituted heterocyclyl, susbtituted or unsubstituted aryl, susbtituted or unsubstituted arylalkyl and susbtituted or unsubstituted heterocyclylalkyl or, together, R_3 and R_4 form a 3 to 6 substituted or unsubstituted member ring;

R_5 and R_6 are independently selected from the group formed by hydrogen, susbtituted or unsubstituted alkyl, susbtituted or unsubstituted cycloalkyl, susbtituted or unsubstituted heterocyclyl, susbtituted or unsubstituted aryl, susbtituted or unsubstituted arylalkyl and susbtituted or unsubstituted heterocyclylalkyl or, R_5 and R_6 together, form a substituted or unsubstituted heterocyclyl having 3 to 7 atoms in the ring;

n is selected from 0, 1 and 2;

m is selected from 0, 1, 2, 3, 4;

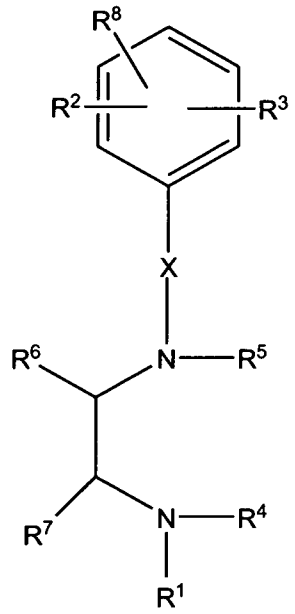
the dotted line ------ is either a single or a double bond;

with the proviso that when R_1 is phenyl, R_2 is H, the dotted line ------ is a double bond, m is 1, and R_5 and R_6 form a 2,5-dioxopyrrolidine or a 5-ethoxy,2-oxo-pyrrolidine; then R_3 and R_4 are not both at the same time H or methyl;

or a pharmaceutically acceptable salt, isomer, prodrug or solvate thereof

is excluded/disclaimed.

In another embodiment the use according to the invention of compounds according to general formula IA



IA

wherein

R^1 is selected from C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;

R^2, R^3 and R^8 are independently of each other selected from H; OH, SH, NH_2, C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; Halogen; O-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; O—C(O)-C_{1-6}-Alkyl, saturated or

unsaturated, substituted or not substituted, branched or not branched; C(O)-O-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; or NH-C(O)-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;

R^4 and R^5 are independently of each other selected from H; OH, SH, NH_2, C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; Halogen; O-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;

or

R^4 and R^5 taken together are -$(CHR^9)_n$- forming a ring

with n is selected from 1, 2 or 3 and

each R^9 independently selected from H; OH, SH, NH_2, C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; Halogen; O-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;

R^6 and R^7 are independently of each other selected from H; OH, SH, NH_2, C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; Halogen; or O-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;

X is -$(CHR^{10})_m$-

with m selected from 0, 1, 2, 3 or 4 and

(if applicable) each R^{10} independently selected from H; OH, SH, NH_2, C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched; Halogen; O-C_{1-6}-Alkyl, saturated or unsaturated, substituted or not substituted, branched or not branched;

optionally in the form of its racemate, pure stereoisomers, especially enantiomers or diastereomers or in the form of mixtures of stereoisomers, especially enantiomers

or diastereomers, in any suitable ratio;
in the form shown or in form of the acid or base or in form of a salt, especially a physiologically acceptable salt, or in form of a solvate, especially a hydrate,

is excluded/disclaimed.

The examples and figures in the following section describing pharmacological trials are merely illustrative and the invention cannot be considered in any way as being restricted to these applications.

Examples

Rationale: The present invention provides evidence supporting the use of sigma-1 receptor antagonists to reduce plasma levels of triglycerides. From the experimental point of view, both genetic and pharmacological approaches support the use of sigma-1 receptor antagonists to reduce plasma levels of triglycerides.

Example 1:

Genetic approach: Knockout mice deficient for the sigma-1 receptor ($\sigma1^{-/-}$) show reduced plasma levels of triglycerides respect to wild type mice.

Male and female mice from the C57BL/6J strain, including wild type and knockout for the sigma-1 receptor, were used in these experiments. The number of animals per group ranged from 16 to 23. Age ranged from 9-15 weeks. All mice had free access to water ad food (standard diet for rodents SAFE A04C; Scientific Animal Food and Engineering, 91360-Villemoisson sur Orge, France; Batch 40123). After a fasting period of 3-5 hours, mice were slightly anesthetized with isofluorane, blood samples were obtained from the retroorbital sinus and plasma was obtained by centrifugation. Triglyceride levels in plasma were determined using the GPO/peroxidase method. Student t test was applied to determine statistical significance.

The results are presented below. Values are means ± standard deviation. Units are expressed as mg/100 mL.

-Triglyceride levels in male mice:

-Wild type (C57BL/6J $\sigma1^{+/+}$; n=20): 105.9 ± 39.39

-Knockout sigma-1 receptor (C57BL/6J $\sigma1^{-/-}$; n=16): 71.5 ± 18.58 **

** $p<0.01$ compared to the control wild type group

-Triglyceride levels in female mice

-Wild type (C57BL/6J $\sigma1^{+/+}$; n=20): 76.7 ± 29.08

-Knockout sigma-1 receptor (C57BL/6J $\sigma1^{-/-}$; n=23): 58.2 ± 12.41 *

* p<0.05 compared to the control wild type group

Example 2:

Pharmacologic approach: Treatment of obese (diet-induced obesity) wild type mice with a sigma-1 receptor antagonist results in a significant reduction in the concentration of triglycerides in blood.

Wild type male mice from the C57BL/6J strain were used in these experiments. Mice of 8-10 weeks of age were fed for two months with high fat diet (49 % fat content; Harlan Ibérica, TD97366). Treatment was administered subcutaneously, once a day, for 9 days. Treated animals received daily (for 9 days) a single dose of 50 mg/kg of BD-1063 (a sigma-1 receptor antagonist). Control animals received daily vehicle (saline). During the period of treatment, mice had free access to water and food (high fat diet). At the end of the treatment, on day 10, blood samples were obtained through intracardiac puncture and triglyceride levels were measured using the Cholestech LDX blood analyzer. Student t test was applied to determine statistical significance.

The results are presented below. Values are means ± standard deviation. Units are expressed as mg/100 mL.

-Triglyceride levels:

-Control untreated (vehicle treated) mice: 91.75 ± 32.88

-Treated (50 mg/Kg BD-1063, s.c., once a day, 9 days): 56.8 ± 9.41 *

* p<0.05 compared to the control wild type group

References

Fredrickson DS. An international classification of hyperlipidemias and hyperlipoproteinemias. Ann Intern Med. 1971 Sep;75(3):471-2.

Beaumont JL, Carlson LA, Cooper GR, Fejfar Z, Fredrickson DS, Strasser T. Classification of hyperlipidaemias and hyperlipoproteinaemias. Bull World Health Organ. 1970;43(6):891-915.

5

CLAIMS

1. Use of at least one compound binding to the sigma receptor and having an IC_{50} value of ≤ 500 nM for the production of a medicament for the treatment of metabolic syndrome.

2. Use, according to claim 1, characterized in that said compound may be in neutral form, the form of a base or acid, in the form of a salt, preferably a physiologically acceptable salt, in the form of a solvate or of a polymorph and/or in the form of its racemate, pure stereoisomers, especially enantiomers or diastereomers or in the form of mixtures of stereoisomers, especially enantiomers or diastereomers, in any suitable mixing ratio.

3. Use, according to claim 1, characterized in that said compound binding to the sigma receptor has an IC50 value of ≤ 250 nM.

4. Use, according to claim 1, characterized in that said compound binding to the sigma receptor has an IC50 value of ≤ 100 nM.

5. Use, according to claim 1, characterized in that said compound binding to the sigma receptor has an IC50 value of ≤ 50 nM.

6. Use, according to any of claims 1 to 5, characterized in that said compound binding to the sigma receptor used is acting on the sigma receptor as an antagonist.

7. Use, according to any of claims 1 to 5, characterized in that said compound binding to the sigma receptor used is acting on the sigma receptor as a partial antagonist.

8. Use, according to any of claims 1 to 5, characterized in that said compound binding to the sigma receptor used is acting on the sigma receptor as an inverse agonist.

9. Use, according to any of claims 1 to 8, characterized in that said compound binding to the sigma receptor is binding to the sigma-1 receptor subtype.

10. Use, according to claim 1, characterized in that said compound binding to the sigma receptor is selected from the group consisting of:

(2-Dibutylamino-Ethyl)-Carbamic Acid 2-(4-Benzofuran-2-Ylmethyl-Piperazin-1-Yl)-Ethyl Ester	(4-[1,2,3]Thiadiazol-4-Yl-Benzyl)-Carbamic Acid 1-(3-Methoxy-2-Nitro-Benzyl)-Piperidin-3-Ylmethyl Ester
4-(4-Fluorobenzoyl)-1-(4-Phenylbutyl)Piperidine Oxalate	4-[1-(4-Chlorobenzyl)-4-(benzylpiperidin-4-yl]-2-hydroxy-4-oxobut-2-enoic acid
4-Bromo-N-[1-(9-Ethyl-9H-Carbazol-3-Ylmethyl)-Pyrrolidin-3-Yl]-2-Trifluoromethoxy-Benzenesulfonamide	4'-Chloro-3-Alpha-(Diphenylmethoxy)Tropane HCl
4-Furan-2-Ylmethyl-Piperazine-1-Carboxylic Acid 2-{4-[3-(2-Trifluoromethyl-Phenothiazin-10-Yl)-Propyl]-Piperazin-1-Yl}-Ethyl Ester	Acetophenazine Maleate
Aminobenztropine	Amiodarone HCl
Amodiaquine HCl	Amorolfine HCl
Anileridine HCl	Astemizole
Azaperone	Azelastine HCl
BD 1008 DiHBr	BD-1047
BD-1063	Benextramine TetraHCl
Benfluorex HCl	Benoxathian HCl
Benperidol	Benproperine Phosphate
Benzododecinium bromide	Benztropine Mesylate
Bepridil HCl	Berberine chloride
Bifemelane	BP 554 Maleate
Bromhexine HCl	Bromodiphenhydramine HCl
Bromperidol	Buflomedil HCl
Butacaine Sulfate	Butaclamol HCl, (±)-
Butenafine HCl	Carbetapentane Citrate
Carpipramine DiHCl DiH2O	Cinnarizine
Cis-(+/-)-N-Methyl-N-[2-(3,4-Dichlorophenyl)Ethyl]-2-(1-Pyrrolidinyl)Cyclohexamine DiHBr	Cis(Z)-Flupentixol DiHCl
Cisapride Hydrate	Clofilium Tosylate
Clomiphene Citrate	Clomiphene Related Compound A
Clomipramine	Cloperastine HCl
Clorgyline HCl	Cyclobenzaprine HCl
Cyproheptadine HCl	Demecarium Bromide
Deptropine Citrate	Dibucaine HCl
Dicyclomine HCl	Diphenylpyraline HCl
Donepezil HCl	Doxepin HCl
Dyclonine HCl	Femoxetine HCl
Flunarizine diHCl	Fluphenazine Decanoate DiHCl
Fluphenazine Enanthate DiHCl	Fluphenazine HCl
Fluphenazine N-Mustard DiHCl	GBR 12783 DiHCl
GBR 12909 DiHCl	GBR 13069 DiHCl

GBR-12935 DiHCl	Haloperidol
HEAT HCl	Hexylcaine HCl
Hydroxyzine HCl	Ifenprodil Tartrate
Isopromethazine HCl	Isoxsuprine HCl
L-693,403 Maleate	L-741,626
L-741,742 HCl	L-745,870 TriHCl
Lidoflazine	Lobeline HCl
lomerizine diHCl	Loperamide HCl
LY-53,857 Maleate	Metergoline
Methdilazine	Methixene HCl
Metipranolol	ML-9 HCl
MR 16728 HCl	Naftifine
Naftopidil diHCl	NAN-190 HBr
Nicardipine HCl	Nylidrin HCl
Octoclothepin Maleate, (±)-	Oxamniquine Related Compound A
Oxybutynin HCl	PAPP
Penbutolol Sulfate	Pentazocine, (±)-
Perphenazine	Phenoxybenzamine HCl
Pimozide	Piperidolate HCl
PPHT HCl, (±)-	Prenylamine Lactate Salt
Prochlorperazine Maleate	Promazine HCl
Proparacaine HCl	Protriptyline HCl
Pyrrolidine-1,2-Dicarboxylic Acid 1-[1-(4-Allyloxy-Benzyl)-Piperidin-2-Ylmethyl] Ester 2-Benzyl Ester	Pyrvinium Pamoate
Raloxifene	Ritanserin
RS 67333 HCl	RS 67506 HCl
Salmeterol	Sertindole
Sertraline	SKF-525A HCl
Tamoxifen Citrate	Tegaserod Maleate
Terbinafine HCl	Terconazole
Thioridazine	Toremifene Citrate
TMB-8 HCl	Trifluperidol HCl
Trifluoperazine HCl	Trimeprazine Hemi-L-Tartrate
Triflupromazine HCl	Tripelennamine HCl
Trimipramine Maleate	Verapamil HCl
U-50488 HCl, (-)-	Xylazine
WB-4101 HCl	

11. Use, according to claim 1, characterized in that the medicament produced is for the treatment of elevated triglyceride levels, chylomicronemia, hyperlipoproteinemia; hyperlipidemia, especially mixed hyperlipidemia; hypercholesterolemia, lipoprotein disorders and dysbetalipoproteinemia.

12. Use, according to claim 1, characterized in that the medicament produced is for the treatment hypertriglyceridemia including both the sporadic and familial disorder, inherited hypertriglyceridemia.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/001735

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/00 A61P3/00 A61P3/06 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ECKEL R H ET AL: "The metabolic syndrome" LANCET THE, LANCET LIMITED. LONDON, GB, vol. 365, no. 9468, 16 April 2005 (2005-04-16), pages 1415-1428, XP004849990 ISSN: 0140-6736 the whole document	1-12
P,X	WO 2006/021462 A (LABORATORIOS DEL DR. ESTEVE, S.A; LAGGNER, CHRISTIAN; CUBERES-ALTISENT) 2 March 2006 (2006-03-02) the whole document page 20, line 22 claims 14,15	1-9,11, 12

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 June 2007	19/06/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Economou, Dimitrios

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/001735

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2006/021463 A (LABORATORIOS DEL DR. ESTEVE, S.A; CORBERA ARJONA, JORDI; CUBERES-ALTIS) 2 March 2006 (2006-03-02) the whole document page 5, lines 13,14 claims 12,13	1-9,11, 12
P,X	EP 1 634 872 A (LABORATORIOS DEL DR. ESTEVE, S.A) 15 March 2006 (2006-03-15) the whole document claims 13,14	1-9,11, 12
P,X	EP 1 634 873 A (LABORATORIOS DEL DR. ESTEVE, S.A) 15 March 2006 (2006-03-15) the whole document claims 10,11	1-9,11, 12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/001735

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		CA 2576144 A1	02-03-2006
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		CA 2577089 A1	02-03-2006
EP 1634872 A	15-03-2006	US 2006106068 A1	18-05-2006
EP 1634873 A	15-03-2006	US 2006047127 A1	02-03-2006