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WO 03/031432 A1

(54) **Title:** SUBSTITUTED PIPERIDINES AND THEIR USE FOR THE TREATMENT OF DISEASES RELATED TO THE HISTAMINE H3 RECEPTOR

(57) **Abstract:** A novel class of substituted piperidines, pharmaceutical compositions comprising them and use thereof in the treatment of diseases and disorders related to the histamine H3 receptor. More particularly, the compounds are useful for the treatment of diseases and dis-orders in which an interaction with the histamine H3 receptor is beneficial.

SUBSTITUTED PIPERIDINES AND THEIR USE FOR THE TREATMENT OF DISEASES RELATED TO THE HISTAMINE H3 RECEPTOR

FIELD OF THE INVENTION

The present invention relates to novel substituted piperidines, to the use of these compounds as pharmaceutical compositions, to pharmaceutical compositions comprising the compounds, and to a method of treatment employing these compounds and compositions. The present compounds show a high and selective binding affinity to the histamine H3 receptor indicating histamine H3 receptor antagonistic, inverse agonistic or agonistic activity. As a result, the compounds are useful for the treatment of diseases and disorders related to the histamine H3 receptor.

BACKGROUND OF THE INVENTION

The existence of the histamine H3 receptor has been known for several years and the receptor is of current interest for the development of new medicaments (see eg Stark, H.; Schlicker, E.; Schunack, W., *Drugs Fut.* **1996**, *21*, 507-520; Leurs, R.; Timmerman, H.; Vollinga, R. C., *Progress in Drug Research* **1995**, *45*, 107-165). Recently, the human histamine H3 receptor has been cloned, cf Lovenberg, T.W. et al, *Molecular Pharmacology*, **June 1999**, *55*, 1101-1107. The histamine H3 receptor is a presynaptic autoreceptor located both in the central and the peripheral nervous system, the skin and in organs such as the lung, the intestine, probably the spleen and the gastrointestinal tract. Recent evidence suggests that the H3 receptor shows intrinsic, constitutive activity, in vitro as well as in vivo (ie it is active in the absence of an agonist; see eg Morisset et al., *Nature* **2000,** 408, 860-864). Compounds acting as inverse agonists can inhibit this activity. The histamine H3 receptor has been demonstrated to regulate the release of histamine and also of other neurotransmitters such as serotonin and acetylcholine. A histamine H3 receptor antagonist or inverse agonist would therefore be expected to increase the release of these neurotransmitters in the brain. A histamine H3 receptor agonist, on the contrary, leads to an inhibition of the biosynthesis of histamine and an inhibition of the release of histamine and also of other neurotransmitters such as serotonin and acetylcholine. These findings suggest that histamine H3 receptor agonists, inverse agonists and antagonists could be important mediators of neuronal activity. Accordingly, the histamine H3 receptor is an important target for new therapeutics.

Piperidines similar to the compounds of the present invention have previously been prepared, and their biological properties have been investigated, cf Chemical Abstracts **1966**, 46341; *Arch. Pharm.* **1979**, 312(8), 670-681; Meanwell, N. A. et al., *J. Med. Chem.* **1992**, 35; 14; 2688-2696; *Drugs Des. Discovery* **1995**, 12(3), 249-258; US 4,943,573; WO 01/21206;

WO 99/48491; WO 97/43282; WO 97/43292; WO 84/03089; WO 84/01576; WO 83/03410; Weinstock, L. T. et al., *J. Pharm. Sci.* **1981**, 70(8), 956-959; and US 3,337,551.

However, these references neither disclose nor suggest that these substituted piperidines may have a histamine H3 receptor antagonistic or agonistic activity.

Several publications disclose the preparation and use of histamine H3 agonists and antagonists. Most of these are imidazole derivatives (see eg Stark et al., *Drugs of the Future* **1996**, *21*, 507-520; Tozer, Kalinddjian, *Expert Opinion on Therapeutic Patents* **2000**, *10*, 1045-1055). However, recently some imidazole-free ligands of the rat histamine H3 receptor have been described. Thus, Walczynski et al. (*Arch. Pharm. Pharm. Med. Chem.* **1999**, *332*, 389-398), Linney et al. (*J. Med. Chem.* **2000**, *43*, 2362-2370), Ganellin et al. (*Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 395-404), Walczynski et al. (*Il Farmaco* **1999**, *54*, 684-694), Kalindjian et al. (WO 99/42458), Schwartz et al. (EP 0 978 512), and Ludwig et al. (WO 97/17345) disclose cyclic amines having rat histamine H3 receptor agonistic or antagonistic activity. However, the structures of these amines are quite different from that of the present compounds. Thus, none of the amines disclosed in these publications contain a piperidine structure, as is the case in the present compounds.

In view of the art's interest in histamine H3 receptor agonists, inverse agonists and antagonists, novel compounds which interact with the histamine H3 receptor would be a highly desirable contribution to the art. The present invention provides such a contribution to the art being based on the finding that a novel class of substituted piperidines has a high and specific affinity to the histamine H3 receptor.

Due to their interaction with the histamine H3 receptor, the present compounds are useful in the treatment of a wide range of conditions and disorders in which an interaction with the histamine H3 receptor is beneficial. Thus, the compounds may find use eg in the treatment of diseases of the central nervous system, the peripheral nervous system, the cardiovascular system, the pulmonary system, the gastrointestinal system and the endocrinological system.

DEFINITIONS

In the structural formulae given herein and throughout the present specification, the following terms have the indicated meaning:

The term "halogen" means F, Cl, Br or I.

The term "C_{1-6}-alkyl " as used herein represents a branched or straight hydrocarbon group having from 1 to 6 carbon atoms. Typical C_{1-6}-alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, hexyl, isohexyl and the like.

The term "C_{2-6}-alkenyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, allyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 1-hexenyl, 2-hexenyl and the like.

The term "C_{2-6}-alkynyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 1-hexynyl, 2-hexynyl and the like.

The term "C_{1-6}-alkoxy" as used herein, alone or in combination, refers to the radical -O-C_{1-6}-alkyl wherein C_{1-6}-alkyl is as defined above. Representative examples are methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term "C_{1-6}-alkylthio" as used herein, alone or in combination, refers to the radical -S-C_{1-6}-alkyl wherein C_{1-6}-alkyl is as defined above. Representative examples are methylthio, ethylthio, isopropylthio, n-propylthio, butylthio, pentylthio and the like.

The term "C_{1-6}-alkylsulfonyl" as used herein, alone or in combination, refers to the radical $-S(=O)_2$-C_{1-6}-alkyl wherein C_{1-6}-alkyl is as defined above. Representative examples are methylsulfonyl, ethylsulfonyl, isopropylsulfonyl, n-propylsulfonyl, butylsulfonyl, pentylsulfonyl and the like.

The term "C_{1-7}-alkanoyl" as used herein, alone or in combination, refers to the radical $-C(=O)H$ or $-C(=O)C_{1-6}$-alkyl wherein C_{1-6}-alkyl is as defined above. Representative examples are formyl, acetyl, propionyl, butanoyl, pentanoyl, hexanoyl, heptanoyl and the like.

The term "C_{3-8}-cycloalkyl" as used herein represents a monocyclic, carbocyclic group having from from 3 to 8 carbon atoms. Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

The term " C_{5-8}-cycloalkenyl " as used herein represents a monocyclic, carbocyclic, non-aromatic group having from 5 to 8 carbon atoms and at least one double bond. Representative examples are cyclopentenyl, cyclohexenyl, cyclohepentyl, cyclooctenyl, and the like.

The term "aryl" as used herein is intended to include carbocyclic aromatic ring systems such as phenyl, biphenylyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, pentalenyl, azulenyl and the like. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl and the like.

The term “aryloxy” as used herein refers to the radical -O-aryl where aryl is as defined above. Non-limiting examples are phenoxy, naphthoxy, anthracenyloxy, phenantrenyloxy, fluorenyloxy, indenyloxy and the like.

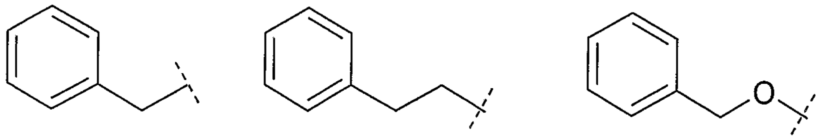
The term “heteroaryl” as used herein is intended to include heterocyclic aromatic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulfur such as furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl and the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the heterocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuranyl, pyrrolinyl, pyrazolinyl, indolinyl, oxazolidinyl, oxazolinyl, oxazepinyl and the like.

As used herein, the phrase “4 to 7 membered, saturated or unsaturated heterocyclic ring” is intended to include heterocyclic rings which are saturated or contain one or two double bonds.

Certain of the above defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

The term “optionally substituted” as used herein means that the group in question is either unsubstituted or substituted with one or more of the substituents specified. When the group in question is substituted with more than one substituent the substituents may be the same or different.

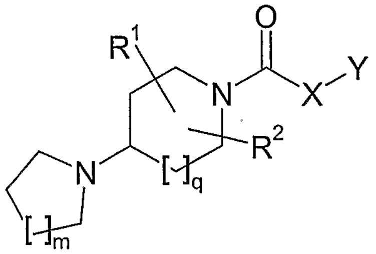
“Aryl-C_{1-6}-alkyl”, “aryl-C_{1-6}-alkoxy” etc. mean C_{1-6}-alkyl or C_{1-6}-alkoxy as defined above, substituted by aryl as defined above, for example:



The term “treatment” as used herein means the management and care of a patient for the purpose of combating a disease, disorder or condition. The term is intended to include the delaying of the progression of the disease, disorder or condition, the alleviation or relief of symptoms and complications, and/or the cure or elimination of the disease, disorder or condition. The patient to be treated is preferably a mammal, in particular a human being.

DESCRIPTION OF THE INVENTION

The invention relates to a compound of the general formula (I):



(I)

wherein

m is 1, 2 or 3,

q is 0, 1 or 2,

X is $-CH_2-(CH_2)_n-$, $-(CH_2)_n-CH=CH-(CH_2)_p-$, $-CH_2-(CH_2)_n-O-(CH_2)_p-$, $-CH_2-(CH_2)_n-C(=O)-(CH_2)_p-$, $-CH_2-(CH_2)_n-S-(CH_2)_p-$, $-CH_2-(CH_2)_n-S(=O)-(CH_2)_p-$ or $-CH_2-(CH_2)_n-S(=O)_2-(CH_2)_p-$,

n and p are independently 0, 1, 2, 3 or 4,

R^1 and R^2 are independently hydrogen, methyl or trifluoromethyl,

Y is

(a) aryl or heteroaryl, which may optionally be substituted with one or more substituents selected from

- halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^3R^4$ and $-O(C=O)NR^3R^4$, wherein R^3 and R^4 independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^3 and R^4 together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

- or wherein two substituents in adjacent positions form a radical –O-$(CH_2)_{1-3}$-O-,

- aryl, aryl-C_{1-6}-alkyl and aryl-C_{1-6}-alkoxy, wherein the ring moieties optionally may be substituted with one or more substituents selected from
    - halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, -NR^5R^6 and -O(C=O)NR^5R^6,

      wherein R^5 and R^6 independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

    - or wherein two substituents in adjacent positions form a radical –O-$(CH_2)_{1-3}$-O

(b) C_{3-8}-cycloalkyl or C_{5-8}-cycloalkenyl, which may optionally be substituted with one or more substituents selected from

- C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, cyano, trifluoromethyl, trifluoromethoxy and halogen,

- aryl and aryloxy, wherein the ring moieties optionally may be substituted with one or more substituents selected from
    - halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, -NR^7R^8 and -O(C=O)NR^7R^8,

      wherein R^7 and R^8 independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^7 and R^8 together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

    - or wherein two substituents in adjacent positions form a radical –O-$(CH_2)_{1-3}$-O-

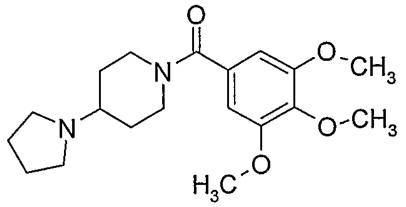
(c) C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl, which may optionally be substituted with one or more substituents selected from

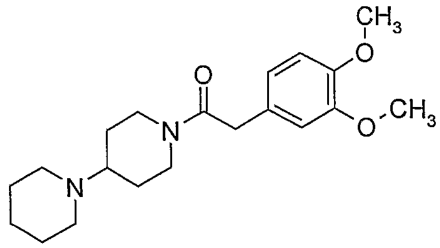
- halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^9R^{10}$ and $-O(C=O)NR^9R^{10}$,
  wherein R^9 and R^{10} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

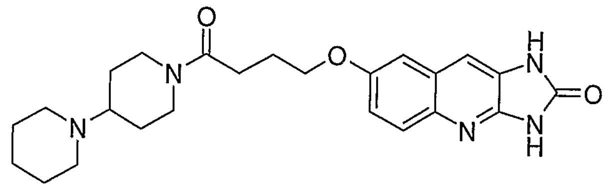
- aryl, aryl-C_{1-6}-alkyl and aryl-C_{1-6}-alkoxy, wherein the ring moieties optionally may be substituted with one or more substituents selected from
  - halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^{11}R^{12}$ and $-O(C=O)NR^{11}R^{12}$,
    wherein R^{11} and R^{12} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

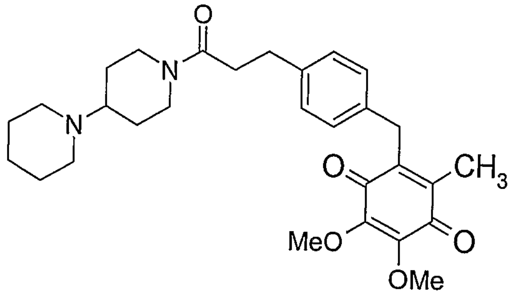
  - or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O-$

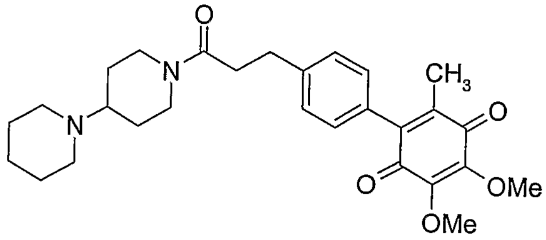
with the proviso that the compound must not be

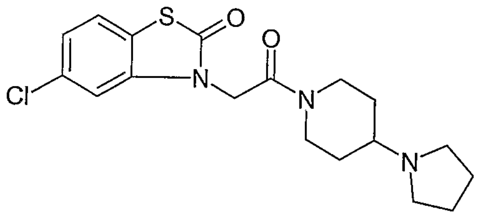


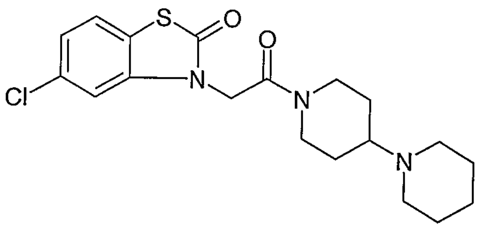


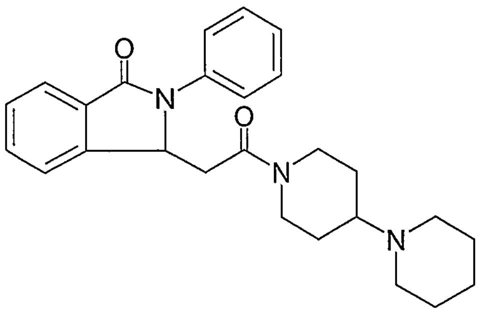


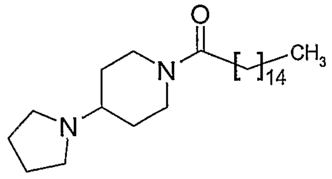


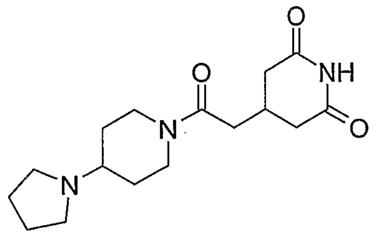












as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

In one embodiment, m is 1.

In another embodiment, m is 2.

In still another embodiment, q is 1.

In yet another embodiment, R^1 and R^2 are both hydrogen.

In a further embodiment, X is $-CH_2-(CH_2)_n-$, $-(CH_2)_n-CH=CH-(CH_2)_p-$, $-CH_2-(CH_2)_n-O-(CH_2)_p-$, $-CH_2-(CH_2)_n-C(=O)-(CH_2)_p-$, or $-CH_2-(CH_2)_n-S-(CH_2)_p-$, wherein n and p are as defined for formula (I).

In still a further embodiment, X is $-CH_2-(CH_2)_n-$, $-CH=CH-$, $-CH_2-(CH_2)_n-O-$, $-CH_2-(CH_2)_n-C(=O)-$, $-CH_2-S-(CH_2)_p-$, wherein n is 0, 1, 2 or 3, and p is 0 or 1, such as $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH=CH-$, $-CH_2-O-$, $-(CH_2)_3-O-$, $-(CH_2)_2-C(=O)-$, $-CH_2-S-CH_2-$ or $-CH_2-S-$.

In another embodiment, Y is C_{1-6}-alkyl, C_{3-8}-cycloalkyl, aryl or heteroaryl, which may optionally be substituted as defined for formula (I).

In yet another embodiment, Y is C_{1-6}-alkyl, cyclohexyl, phenyl, naphthyl, pyridyl, benzoxazolyl, imidazolyl or benzothiophenyl, which may optionally be substituted as defined for formula (I).

In a further embodiment, Y is phenyl or naphthyl, which may optionally be substituted with one or more substituents selected from

- trifluoromethyl, trifluoromethoxy, halogen, nitro, C_{1-6}-alkyl, $-NR^3R^4$, $-O(C=O)NR^3R^4$ and C_{1-7}-alkanoyl, wherein R^3 and R^4 independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^3 and R^4 together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

- aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl and aryl, which may optionally be substituted with halogen or C_{1-6}-alkyl,

- or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O-$.

In still another embodiment, Y is phenyl or naphthyl, which may optionally be substituted with one or more substituents selected from

- trifluoromethyl, trifluoromethoxy, halogen, nitro, C_{1-6}-alkyl, $-NR^3R^4$, $-O(C=O)NR^3R^4$ and C_{1-7}-alkanoyl, wherein R^3 and R^4 independently are hydrogen or C_{1-6}-alkyl, or R^3 and R^4 together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

- phenyl-C_{1-6}-alkoxy, phenyl-C_{1-6}-alkyl and phenyl, which may optionally be substituted with halogen or C_{1-6}-alkyl,

- or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O-$.

The compounds of the present invention may be chiral, and it is intended that any enantiomers, as separated, pure or partially purified enantiomers or racemic mixtures thereof are included within the scope of the invention.

Furthermore, when a double bond or a fully or partially saturated ring system or more than one center of asymmetry or a bond with restricted rotatability is present in the molecule, diastereomers may be formed. It is intended that any diastereomers, as separated, pure or partially purified diastereomers or mixtures thereof are included within the scope of the invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms, which the compounds are able to form, are included within the scope of the present invention.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like.

Also intended as pharmaceutically acceptable acid addition salts are the hydrates, which the present compounds are able to form.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The compounds of the present invention may form solvates with standard low molecular weight solvents using methods well known to the person skilled in the art. Such solvates are also contemplated as being within the scope of the present invention.

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

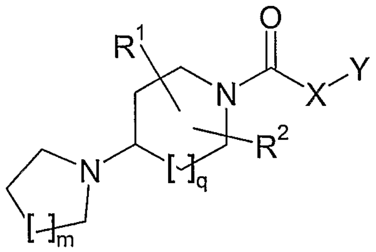
The invention also encompasses active metabolites of the present compounds.

The compounds of the present invention interact with the histamine H3 receptor and are accordingly useful for the treatment of a wide variety of conditions and disorders in which histamine H3 receptor interactions are beneficial.

Accordingly, in another aspect the present invention relates to a compound of the general formula (I) as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for use as a pharmaceutical composition.

The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound of the formula (I) or any diastereomer or enantiomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers or diluents.

Furthermore, the invention relates to the use of a compound of the general formula (I'):



(I')

wherein

m is 1, 2 or 3,

q is 0, 1 or 2,

X is $-CH_2-(CH_2)_n-$, $-(CH_2)_n-CH=CH-(CH_2)_p-$, $-CH_2-(CH_2)_n-O-(CH_2)_p-$, $-CH_2-(CH_2)_n-C(=O)-(CH_2)_p-$, $-CH_2-(CH_2)_n-S-(CH_2)_p-$, $-CH_2-(CH_2)_n-S(=O)-(CH_2)_p-$ or $-CH_2-(CH_2)_n-S(=O)_2-(CH_2)_p-$,

n and p are independently 0, 1, 2, 3 or 4,

R^1 and R^2 are independently hydrogen, methyl or trifluoromethyl,

Y is

(a) aryl or heteroaryl, which may optionally be substituted with one or more substituents selected from

- halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^3R^4$ and $-O(C=O)NR^3R^4$,
  wherein R^3 and R^4 independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^3 and R^4 together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

- or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O-$,

- aryl, aryl-C_{1-6}-alkyl and aryl-C_{1-6}-alkoxy, wherein the ring moieties optionally may be substituted with one or more substituents selected from
  - halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^5R^6$ and $-O(C=O)NR^5R^6$,
    wherein R^5 and R^6 independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

  - or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O$

(b) C_{3-8}-cycloalkyl or C_{5-8}-cycloalkenyl, which may optionally be substituted with one or more substituents selected from

- C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, cyano, trifluoromethyl, trifluoromethoxy and halogen,

- aryl and aryloxy, wherein the ring moieties optionally may be substituted with one or more substituents selected from
  - halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^7R^8$ and $-O(C=O)NR^7R^8$,
    wherein R^7 and R^8 independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^7 and R^8 together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

  - or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O-$

(c) C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl, which may optionally be substituted with one or more substituents selected from

- halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^9R^{10}$ and $-O(C=O)NR^9R^{10}$,
  wherein R^9 and R^{10} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

- aryl, aryl-C_{1-6}-alkyl and aryl-C_{1-6}-alkoxy, wherein the ring moieties optionally may be substituted with one or more substituents selected from
  - halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^{11}R^{12}$ and $-O(C=O)NR^{11}R^{12}$,
    wherein R^{11} and R^{12} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

- or wherein two substituents in adjacent positions form a radical $–O-(CH_2)_{1-3}-O-$

as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment of disorders and diseases related to the histamine H3 receptor.

In still another aspect, the invention relates to a method for the treatment of diseases and disorders related to the histamine H3 receptor, the method comprising administering to a subject in need thereof an effective amount of a compound of the formula (I') or any diastereomer or enantiomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the same.

In one aspect the invention relates to compounds with histamine H3 receptor antagonistic activity or inverse agonistic activity which may accordingly be useful in the treatment of a wide range of conditions and disorders in which histamine H3 receptor blockade is beneficial.

In another aspect the invention relates to compounds with histamine H3 receptor agonistic activity and which may accordingly be useful in the treatment of a wide range of conditions and disorders in which histamine H3 receptor activation is beneficial.

In one embodiment, the present compounds are used for the preparation of a pharmaceutical composition for the reduction of weight.

In another embodiment, the present compounds are used for the preparation of a pharmaceutical composition for the treatment of overweight or obesity.

In yet another embodiment, the present compounds are used for the preparation of a pharmaceutical composition for the suppression of appetite or satiety induction.

In still a further embodiment, the present compounds are used for the preparation of a pharmaceutical composition for the prevention and/or treatment of disorders and diseases related to overweight or obesity such as atherosclerosis, hypertension, IGT (impaired glucose tolerance), diabetes, especially Type 2 diabetes (NIDDM (non-insulin dependent diabetes mellitus)), dyslipidemia, coronary heart disease, gallbladder disease, osteoarthritis and various types of cancer such as endometrial, breast, prostate and colon cancers.

In yet a further embodiment, the present compounds are used for the preparation of a pharmaceutical composition for the prevention and/or treatment of eating disorders such as bulimia and binge eating.

In another embodiment, the present compounds are used for the preparation of a pharmaceutical composition for the treatment of IGT.

In still another further embodiment, the present compounds are used for the preparation of a pharmaceutical composition for the treatment of Type 2 diabetes.

In yet another embodiment, the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to Type 2 diabetes.

In a further embodiment, the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

The compounds of the present invention may also be used for the treatment of airway disorders such as asthma, as anti-diarrhoeals and for the modulation of gastric acid secretion.

Furthermore, the compounds of the present invention may be used for the treatment of diseases associated with the regulation of sleep and wakefulness and for the treatment of narcolepsy and attention deficit disorders.

Moreover, the compounds of the invention may be used as CNS stimulants or as sedatives.

The present compounds may also be used for the treatment of conditions associated with epilepsy. Additionally, the present compounds may be used for the treatment of motion sickness and vertigo. Furthermore, they may be useful as regulators of hypothalamo-hypophyseal secretion, antidepressants, modulators of cerebral circulation, and in the treatment of irritable bowel syndrome.

Further, the compounds of the present invention may be used for the treatment of dementia and Alzheimer's disease.

The compounds of the present invention may also be useful for the treatment of allergic rhinitis, ulcer or anorexia.

The compounds of the present invention may furthermore be useful for the treatment of migraine, see R.L. McLeod et al., *The Journal of Pharmacology and Experimental Therapeutics* **287** (1998), 43-50, and for the treatment of myocardial infarction, see C.J. Mackins and R. Levi, *Expert Opinion on Investigational Drugs* **9** (2000), 2537-2542.

In a further aspect of the invention, treatment of a patient with the present compounds is combined with diet and/or exercise.

In a further aspect of the invention the present compounds may be administered in combination with one or more further pharmacologically active substances in any suitable ratios. Such further active agents may be selected from antiobesity agents, antidiabetics, antihypertensive agents, agents for the treatment of complications resulting from or associated with diabetes and agents for the treatment of complications and disorders resulting from or associated with obesity.

Thus, in a further aspect of the invention the present compounds may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonists, MC3 (melanocortin 3) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, β3 adrenergic agonists such as CL-316243, AJ-9677, GW-0604, LY362884, LY377267 or AZ-40140, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors such as fluoxetine, seroxat or citalopram, serotonin and noradrenaline re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth factors such as prolactin or placental lactogen, growth hormone releasing compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR (peroxisome proliferator-activated receptor) modulators, RXR (retinoid X receptor) modulators, TR β agonists, AGRP (Agouti related protein) inhibitors, opioid antagonists (such as naltrexone), exendin-4, GLP-1 and ciliary neurotrophic factor.

In one embodiment of the invention the antiobesity agent is leptin.

In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

In still another embodiment the antiobesity agent is sibutramine.

In a further embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is mazindol or phentermine.

In still another embodiment the antiobesity agent is phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate or ecopipam.

Suitable antidiabetic agents include insulin, insulin analogues and derivatives such as those disclosed in EP 792 290 (Novo Nordisk A/S), eg $N^{\varepsilon B29}$-tetradecanoyl des (B30) human insulin, EP 214 826 and EP 705 275 (Novo Nordisk A/S), eg Asp^{B28} human insulin, US 5,504,188 (Eli Lilly), eg Lys^{B28} Pro^{B29} human insulin, EP 368 187 (Aventis), eg Lantus, which are all incorporated herein by reference, GLP-1 derivatives such as those disclosed in WO 98/08871 (Novo Nordisk A/S), which is incorporated herein by reference, as well as orally active hypoglycaemic agents.

The orally active hypoglycaemic agents preferably comprise imidazolines, sulphonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, insulin sensitizers, α-glucosidase inhibitors, agents acting on the ATP-dependent potassium channel of the β-cells eg potassium channel openers such as those disclosed in WO 97/26265, WO 99/03861 and WO 00/37474 (Novo Nordisk A/S) which are incorporated herein by reference, or mitiglinide, or a potassium channel blocker, such as BTS-67582, nateglinide, glucagon antagonists such as those disclosed in WO 99/01423 and WO 00/39088 (Novo Nordisk A/S and Agouron Pharmaceuticals, Inc.), which are incorporated herein by reference, GLP-1 agonists such as those disclosed in WO 00/42026 (Novo Nordisk A/S and Agouron Pharmaceuticals, Inc.), which are incorporated herein by reference, DPP-IV (dipeptidyl peptidase-IV) inhibitors, PTPase (protein tyrosine phosphatase) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, GSK-3 (glycogen synthase kinase-3) inhibitors, compounds modifying the lipid metabolism such as antilipidemic agents, compounds lowering food intake, PPAR (peroxisome proliferator-activated receptor) and RXR (retinoid X receptor) agonists, such as ALRT-268, LG-1268 or LG-1069.

In one embodiment of the invention the present compounds are administered in combination with insulin.

In a further embodiment of the invention the present compounds are administered in combination with a sulphonylurea eg tolbutamide, chlorpropamide, tolazamide, glibenclamide, glipizide, glimepiride, glicazide or glyburide.

In another embodiment of the invention the present compounds are administered in combination with a biguanide eg metformin.

In yet another embodiment of the invention the present compounds are administered in combination with a meglitinide eg repaglinide or nateglinide.

In still another embodiment of the invention the present compounds are administered in combination with a thiazolidinedione insulin sensitizer eg troglitazone, ciglitazone, pioglitazone, rosiglitazone, isaglitazone, darglitazone, englitazone, CS-011/CI-1037 or T 174 or the compounds disclosed in WO 97/41097, WO 97/41119, WO 97/41120, WO 00/41121 and WO 98/45292 (Dr. Reddy's Research Foundation), which are incorporated herein by reference.

In still another embodiment of the invention the present compounds may be administered in combination with an insulin sensitizer eg such as GI 262570, YM-440, MCC-555, JTT-501, AR-H039242, KRP-297, GW-409544, CRE-16336, AR-H049020, LY510929, MBX-102, CLX-0940, GW-501516 or the compounds disclosed in WO 99/19313, WO 00/50414, WO 00/63191, WO 00/63192, WO 00/63193 (Dr. Reddy's Research Foundation) and WO 00/23425, WO 00/23415, WO 00/23451, WO 00/23445, WO 00/23417, WO 00/23416, WO 00/63153, WO 00/63196, WO 00/63209, WO 00/63190 and WO 00/63189 (Novo Nordisk A/S), which are incorporated herein by reference.

In a further embodiment of the invention the present compounds are administered in combination with an α-glucosidase inhibitor eg voglibose, emiglitate, miglitol or acarbose.

In another embodiment of the invention the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β-cells eg tolbutamide, glibenclamide, glipizide, glicazide, BTS-67582 or repaglinide.

In yet another embodiment of the invention the present compounds may be administered in combination with nateglinide.

In still another embodiment of the invention the present compounds are administered in combination with an antilipidemic agent eg cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

In another aspect of the invention, the present compounds are administered in combination with more than one of the above-mentioned compounds eg in combination with metformin and a sulphonylurea such as glyburide; a sulphonylurea and acarbose; nateglinide and metformin; acarbose and metformin; a sulfonylurea, metformin and troglitazone; insulin and a sulfonylurea; insulin and metformin; insulin, metformin and a sulfonylurea; insulin and troglitazone; insulin and lovastatin; etc.

Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β-blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α-blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

It should be understood that any suitable combination of the compounds according to the invention with diet and/or exercise, one or more of the above-mentioned compounds and optionally one or more other active substances are considered to be within the scope of the present invention.

PHARMACEUTICAL COMPOSITIONS

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

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

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

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

For parenteral routes, such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound of the formula (I) contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of the formula (I) with a chemical equivalent of a pharmaceutically acceptable acid, for example, inorganic and organic acids. Representative examples are mentioned above. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as sodium or ammonium ion.

For parenteral administration, solutions of the novel compounds of the formula (I) in sterile aqueous solution, aqueous propylene glycol or sesame or peanut oil may be employed. Such aqueous solutions should be suitable buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid or lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene or water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the novel compounds of the formula (I) and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. These formulations may be in the form of powder or granules, as a solution or suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

A typical tablet, which may be prepared by conventional tabletting techniques, may contain:

Core:		
Active compound (as free compound or salt thereof)		5.0 mg
Lactosum Ph. Eur.		67.8 mg
Cellulose, microcryst. (Avicel)		31.4 mg
Amberlite® IRP88*		1.0 mg
Magnesii stearas Ph. Eur.		q.s.
Coating:		
Hydroxypropyl methylcellulose	approx.	9 mg
Mywacett 9-40 T**	approx.	0.9 mg

* Polacrillin potassium NF, tablet disintegrant, Rohm and Haas.

** Acylated monoglyceride used as plasticizer for film coating.

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

EXAMPLES

In the examples the following terms are intended to have the following, general meanings:

DCM: dichloromethane, methylenechloride
DIC: diisopropylcarbodiimide
DMF: *N,N*-dimethyl formamide
DMSO: dimethyl sulphoxide
THF: tetrahydrofuran

NMR spectra were recorded on Bruker 300 MHz and 400 MHz instruments. HPLC-MS was performed on a Perkin Elmer instrument (API 100).

HPLC-systems from Merck-Hitachi (Hibar™ RT 250-4, Lichrosorb™ RP 18, 5.0 µm, 4.0 x 250 mm, gradient elution, 20% to 80% acetonitrile in water within 30 min, 1.0 ml/min, detection at 254 nm) and Waters (Symmetry™, C18, 3.5 µm, 3.0 x 150 mm, gradient elution, 5% to 90% acetonitrile in water within 15 min, 1.0 ml/min, detection at 214 nm) were used.

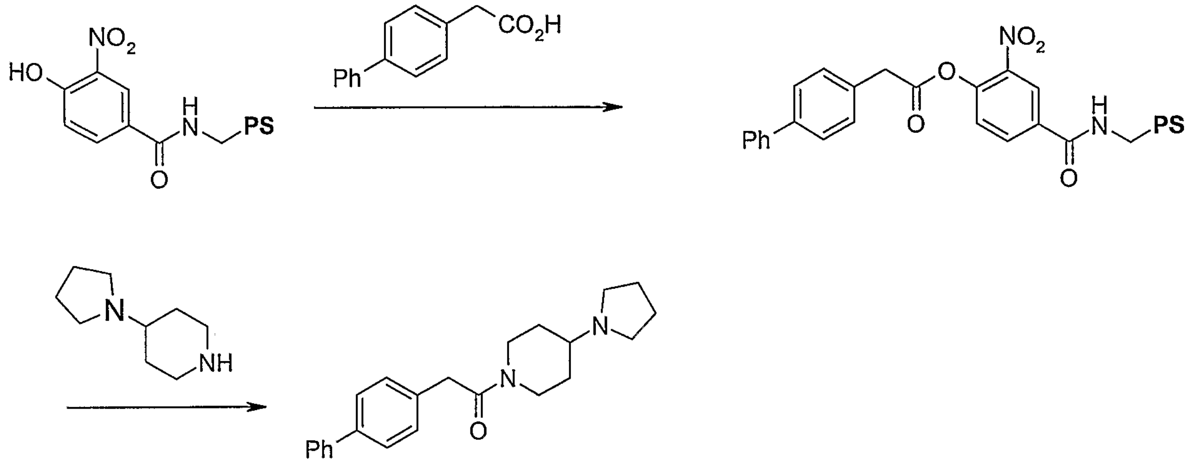
Furthermore, where stated the following HPLC method h8 was used:

The reverse phase analysis was performed using UV detections at 214, 254, 276 and 301 nm on a 218TP54 4.6 mm x 150 mm C-18 silica column, which was eluted at 1 ml/min at 42 °C. The column was equilibrated with 5% acetonitrile, 85% water and 10% of a solution of 0.5% trifluoroacetic acid in water and eluted by a linear gradient from 5% acetonitrile, 85% water and 10% of a solution of 0.5% trifluoroacetic acid to 90% acetonitrile and 10% of a solution of 0.5% trifluoroacetic acid over 15 min.

Typical procedure

Example 10

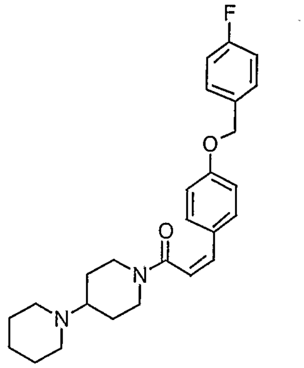
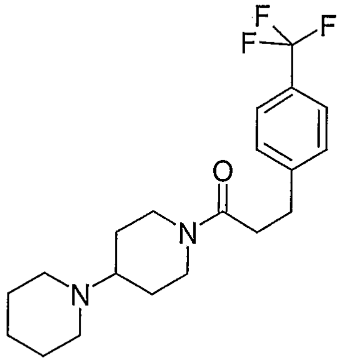
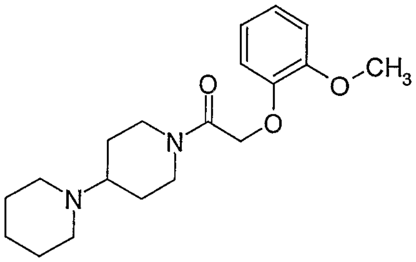
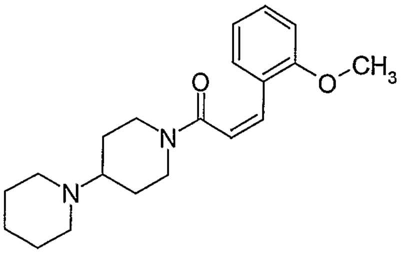
2-Biphenyl-4-yl-1-(4-pyrrolidin-1-ylpiperidin-1-yl)ethanone hydrochloride

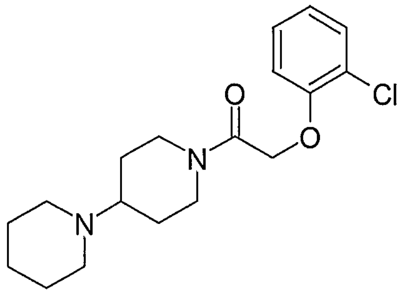
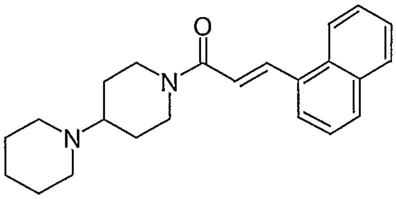
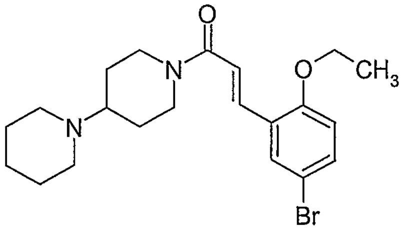
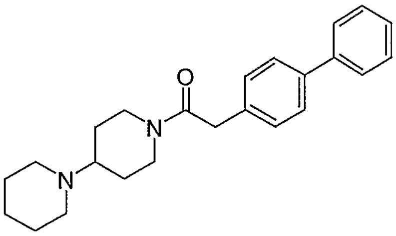
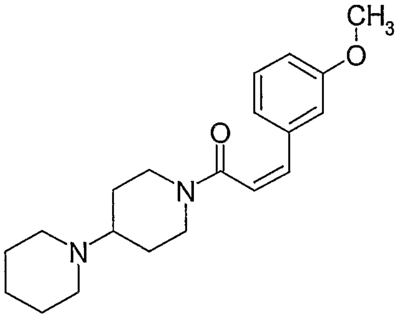
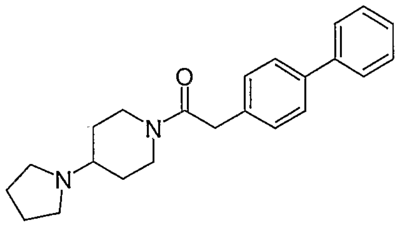


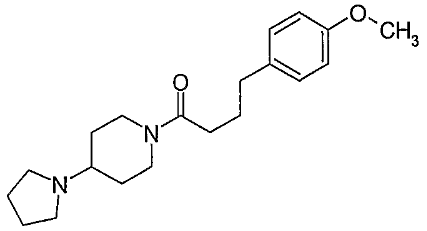
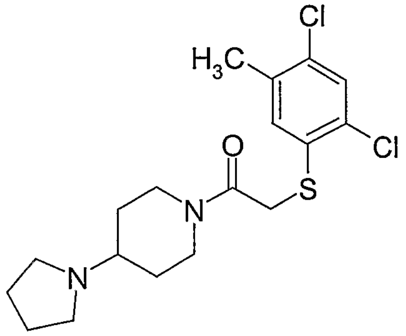
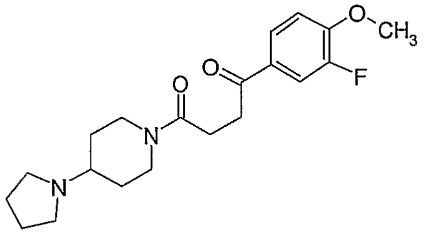
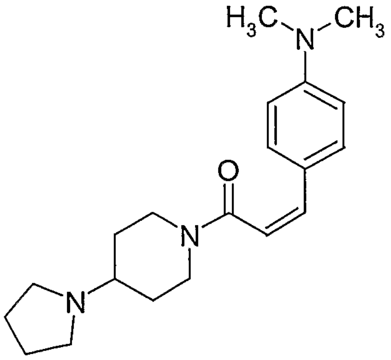
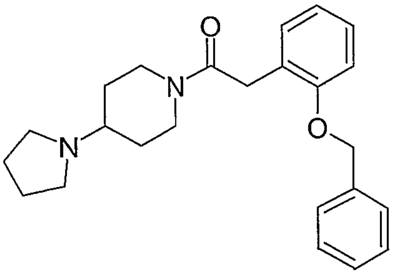
To the polymeric nitrophenol (1.5 g, approx. 1 mmol) was added a filtered solution of 4-biphenylylacetic acid (1.10 g, 5.18 mmol) in a mixture of 1,2-dichloropropane (18 ml) and DMF (2 ml), followed by the addition of a solution of DIC (0.63 g, 4.99 mmol) in 1,2-dichloropropane (5 ml). The mixture was shaken at room temperature for 15 hours, filtered, and the polymer was extensively washed with DCM, DMF, and 1,2-dichloropropane. To the polymer was added 1,2-dichloropropane (5 ml) and a solution of 4-(1-pyrrolidinyl)piperidine (0.123 g, 0.80 mmol) in 1,2-dichloropropane (10 ml). The resulting mixture was shaken at room temperature for 21 hours and then at 60 °C for one hour, filtered, and the polymer was carefully washed with DCM and methanol. The combined filtrates were concentrated to yield the crude product, which was mixed with ethanol and 1 molar aqueous hydrochloric acid, concentrated, and the residual hydrochloride was recrystallized from ethanol. 90 mg (29%) of the title compound was obtained.

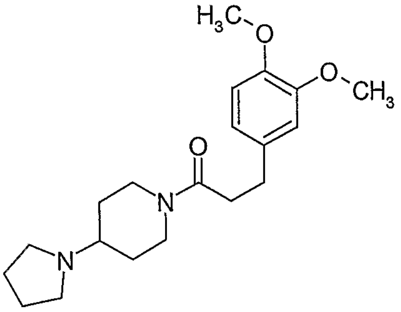
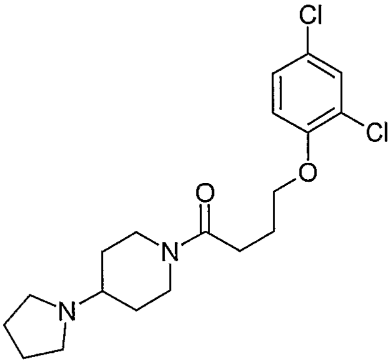
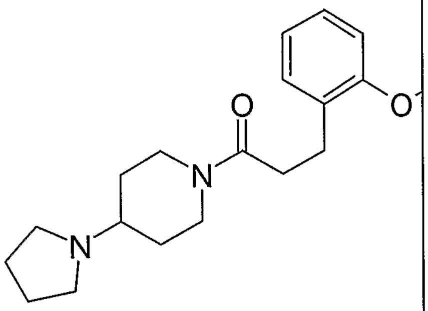
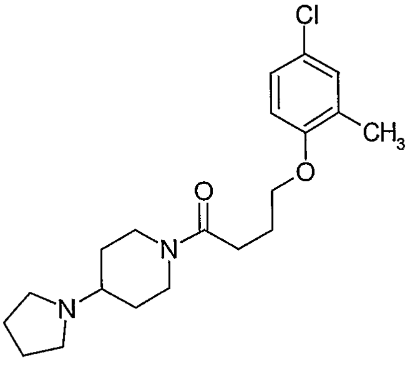
1H NMR (400 MHz, DMSO): δ 1.54 (m, 2H), 1.80-2.12 (m, 6H), 2.20 (m, 1H), 2.59 (m, 1H), 2.88 (m, 1H), 3.01 (m, 2H), 3.42 (m, 2H), 3.78 (m, 2H), 4.11 (m, 1H), 4.51 (m, 1H), 7.28-7.38 (m, 3H), 7.46 (t, J = 8 Hz, 2H), 7.60-7.68 (m, 4H), 10.9 (br s, 1H); HPLC-MS: *m/z* 349 (MH+); R_t: 4.3 min.

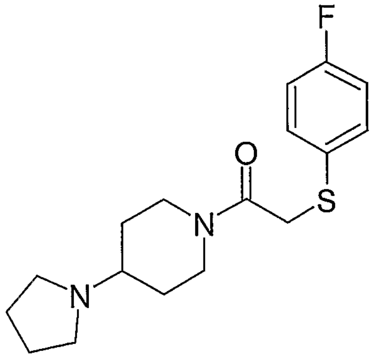
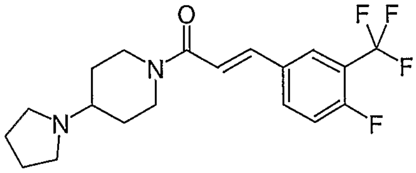
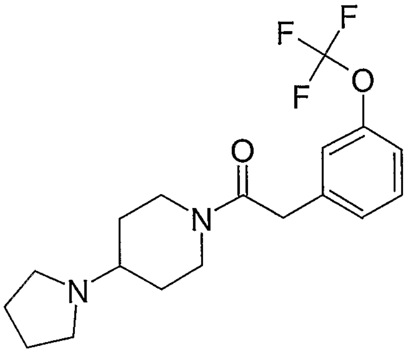
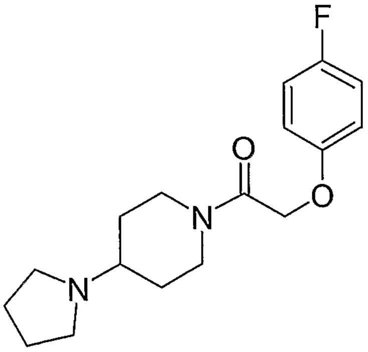
Using this methodology the following compounds were prepared:

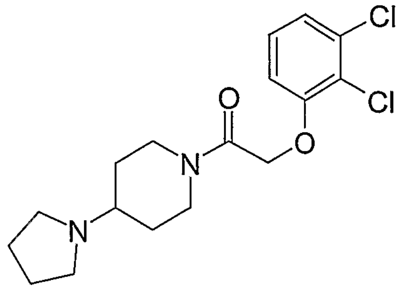
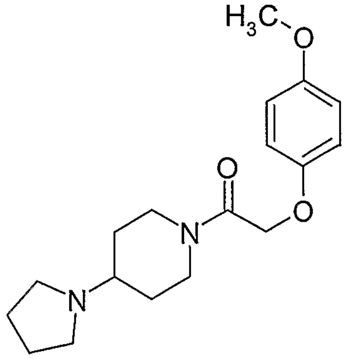
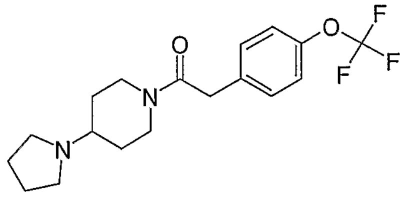
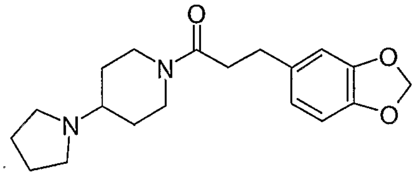
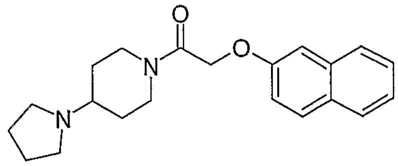
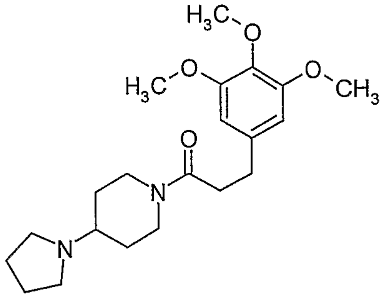
No	Structure	Name	Found MH+
1		1-[1,4']Bipiperidinyl-1'-yl-3-[4-(4-fluorobenzyloxy)phenyl]propenone	423
2		1-[1,4']Bipiperidinyl-1'-yl-3-(4-trifluoromethylphenyl)propan-1-one	369
3		1-[1,4']Bipiperidinyl-1'-yl-2-(2-methoxyphenoxy)ethanone	333
4		1-[1,4']Bipiperidinyl-1'-yl-3-(2-methoxyphenyl)propenone	329

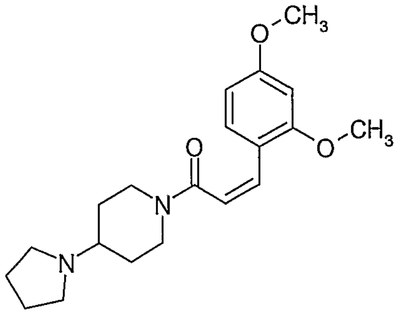
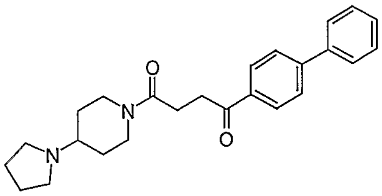
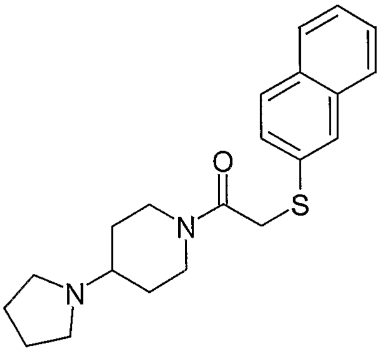
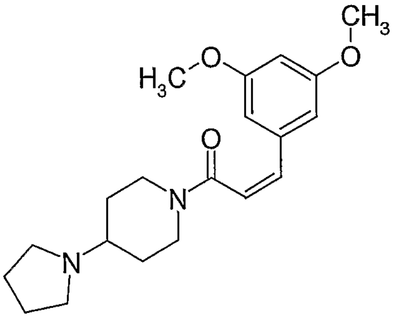
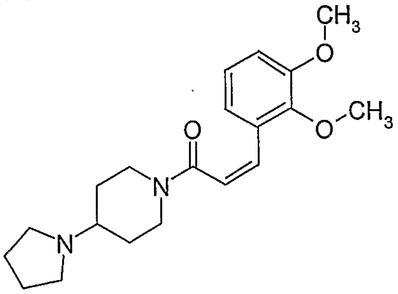
5		1-[1,4']Bipiperidinyl-1'-yl-2-(2-chloro-phenoxy)ethanone	337
6		1-[1,4']Bipiperidinyl-1'-yl-3-naphthalen-1-ylpropenone	349
7		1-[1,4']Bipiperidinyl-1'-yl-3-(5-bromo-2-ethoxyphenyl)propenone	421
8		2-Biphenyl-4-yl-1-[1,4']bipiperidinyl-1'-ylethanone	363
9		1-[1,4']Bipiperidinyl-1'-yl-3-(3-methoxyphenyl)propenone	329
10		2-Biphenyl-4-yl-1-(4-pyrrolidin-1-yl-piperidin-1-yl)ethanone	349

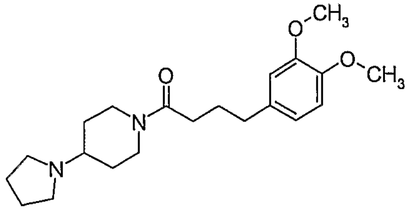
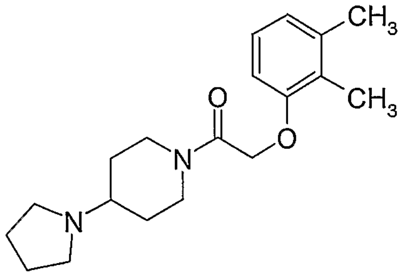
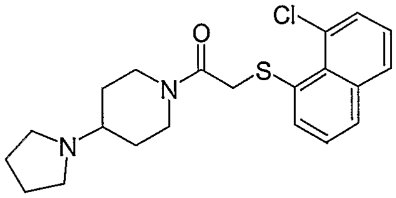
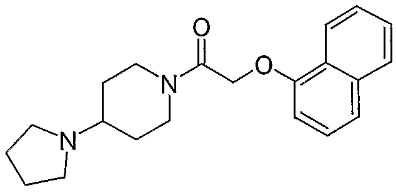
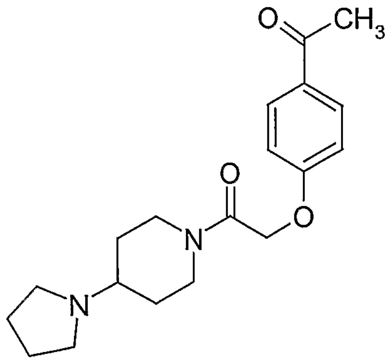
11		4-(4-Methoxyphenyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)butan-1-one	331
12		2-(2,4-Dichloro-5-methylphenylsulfanyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)ethanone	388
13		1-(3-Fluoro-4-methoxyphenyl)-4-(4-pyrrolidin-1-ylpiperidin-1-yl)butane-1,4-dione	363
14		3-(4-Dimethylamino-phenyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)propenone	328
15		2-(2-Benzyloxyphenyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)ethanone	379

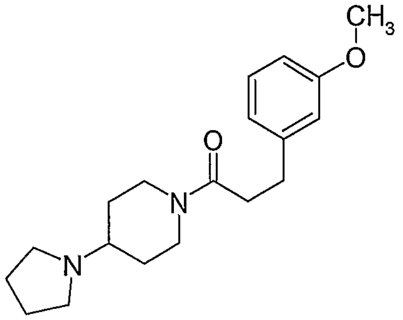
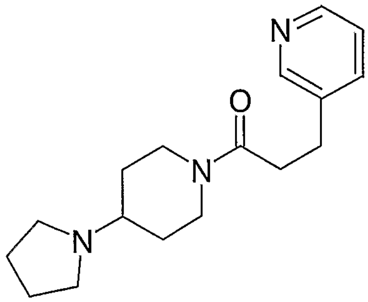
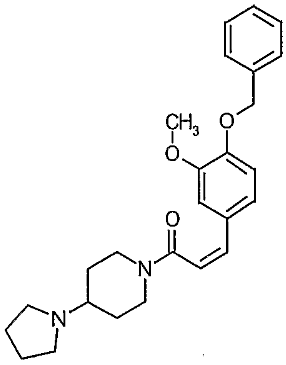
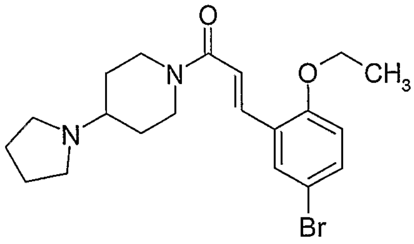
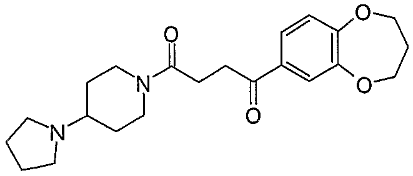
16		3-(3,4-Dimethoxyphenyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)propan-1-one	347
17		4-(2,4-Dichlorophenoxy)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)butan-1-one	386
18		3-(2-Methoxyphenyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)propan-1-one	317
19		4-(4-Chloro-2-methylphenoxy)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)butan-1-one	365

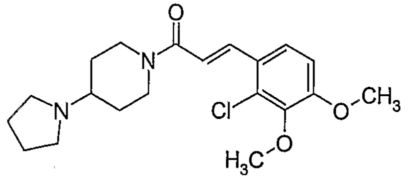
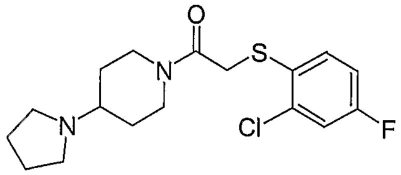
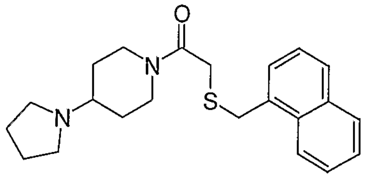
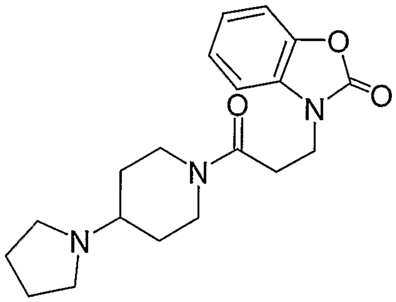
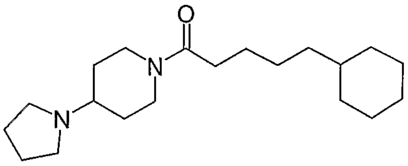
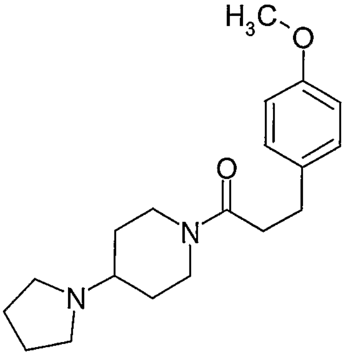
20		2-(4-Fluorophenylsulfanyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)ethanone	323
21		3-(4-Fluoro-3-trifluoromethylphenyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)-propenone	371
22		1-(4-Pyrrolidin-1-ylpiperidin-1-yl)-2-(3-trifluoromethoxyphenyl)ethanone	357
23		2-(4-Fluorophenoxy)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)ethanone	307

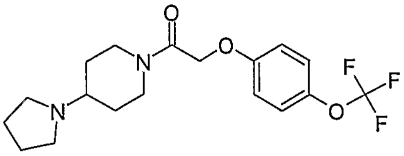
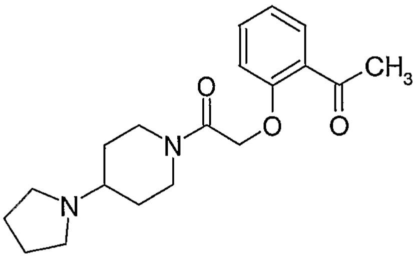
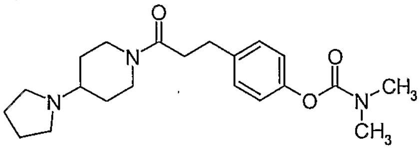
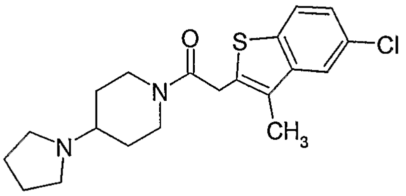
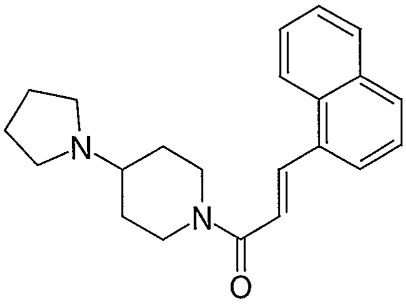
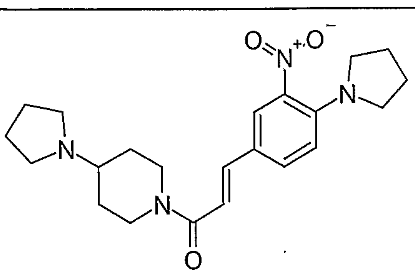
24		2-(2,3-Dichlorophenoxy)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)ethanone	358
25		2-(4-Methoxyphenoxy)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)ethanone	319
26		1-(4-Pyrrolidin-1-ylpiperidin-1-yl)-2-(4-trifluoromethoxyphenyl)ethanone	357
27		3-Benzo[1,3]dioxol-5-yl-1-(4-pyrrolidin-1-ylpiperidin-1-yl)propan-1-one	331
28		2-(Naphthalen-2-yloxy)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)ethanone	339
29		1-(4-Pyrrolidin-1-ylpiperidin-1-yl)-3-(3,4,5-trimethoxyphenyl)propan-1-one	377

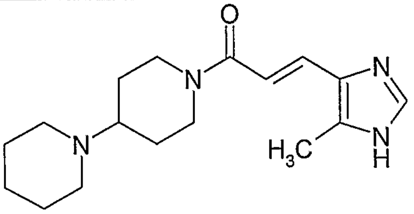
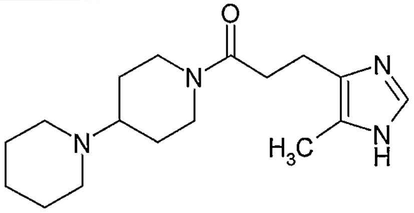
30		3-(2,4-Dimethoxyphenyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)propenone	345
31		1-Biphenyl-4-yl-4-(4-pyrrolidin-1-ylpiperidin-1-yl)butane-1,4-dione	391
32		2-(Naphthalen-2-ylsulfanyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)ethanone	355
33		3-(3,5-Dimethoxyphenyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)propenone	345
34		3-(2,3-Dimethoxyphenyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)propenone	345

35		4-(3,4-Dimethoxyphenyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)butan-1-one	361
36		2-(2,3-Dimethylphenoxy)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)ethanone	317
37		2-(8-Chloronaphthalen-1-ylsulfanyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)-ethanone	390
38		2-(Naphthalen-1-yloxy)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)ethanone	339
39		2-(4-Acetylphenoxy)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)ethanone	331

40		3-(3-Methoxyphenyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)propan-1-one	317
41		3-Pyridin-3-yl-1-(4-pyrrolidin-1-ylpiperidin-1-yl)propan-1-one	288
42		3-(4-Benzyloxy-3-methoxyphenyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)-propenone	421
43		3-(5-Bromo-2-ethoxyphenyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)propenone	408
44		1-(3,4-Dihydro-2*H*-benzo[b][1,4]-dioxepin-7-yl)-4-(4-pyrrolidin-1-ylpiperidin-1-yl)butane-1,4-dione	387

45		3-(2-Chloro-3,4-dimethoxyphenyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)-propenone	379
46		2-(2-Chloro-4-fluorophenylsulfanyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)-ethanone	357
47		2-(Naphthalen-1-ylmethylsulfanyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)-ethanone	369
48		3-[3-Oxo-3-(4-pyrrolidin-1-ylpiperidin-1-yl)propyl]-3*H*-benzoxazol-2-one	344
49		5-Cyclohexyl-1-(4-pyrrolidin-1-ylpiperidin-1-yl)pentan-1-one	321
50		3-(4-Methoxyphenyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)propan-1-one	317

51		1-(4-Pyrrolidin-1-ylpiperidin-1-yl)-2-(4-trifluoromethoxyphenoxy)-ethanone	373
52		2-(2-Acetylphenoxy)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)ethanone	331
53		Dimethylcarbamic acid 4-[3-oxo-3-(4-pyrrolidin-1-ylpiperidin-1-yl)propyl]-phenyl ester	374
54		2-(5-Chloro-3-methyl-benzo[b]thiophen-2-yl)-1-(4-pyrrolidin-1-yl-piperidin-1-yl)ethanone	378
55		3-Naphthalen-1-yl-1-(4-pyrrolidin-1-yl-piperidin-1-yl)propenone	335
56		3-(3-Nitro-4-pyrrolidin-1-ylphenyl)-1-(4-pyrrolidin-1-ylpiperidin-1-yl)-propenone	399

57		1-[1,4']Bipiperidinyl-1'-yl-3-(5-methyl-1*H*-imidazol-4-yl)propenone	303.6
58		1-[1,4']Bipiperidinyl-1'-yl-3-(5-methyl-1*H*-imidazol-4-yl)propan-1-one	305.4

The ability of the compounds to interact with the histamine H3 receptor can be determined by the following *in vitro* binding assays.

Binding assay (I)

Rat cerebral cortex is homogenized in ice cold K-Hepes, 5 mM $MgCl_2$ pH 7.1 buffer. After two differential centrifugations the last pellet is resuspended in fresh Hepes buffer containing 1 mg/ml bacitracin. Aliquots of the membrane suspension (400 µg/ml) are incubated for 60 min at 25 °C with 30 pM [^{125}I]-iodoproxifan, a known histamine H3 receptor antagonist, and the test compound at various concentrations. The incubation is stopped by dilution with ice-cold medium, followed by rapid filtration through Whatman GF/B filters pretreated for 1 hour with 0.5% polyethyleneimine. The radioactivity retained on the filters is counted using a Cobra II auto gamma counter. The radioactivity of the filters is indirectly proportional to the binding affinity of the tested compound. The results are analyzed by nonlinear regression analysis.

Binding assay (II)

The H3-receptor agonist ligand R-α-methyl[^{3}H]histamine (RAMHA) is incubated with isolated rat cortex cell-membranes at 25 °C for 1 hour, followed by a filtration of the incubate through Whatman GF/B filters. Radioactivity retained on the filters is measured using a beta counter.

Male Wistar rats (150-200 g) are decapitated and cerebral cortex is quickly dissected out and frozen immediately on dry ice. Tissue is kept at –80 °C until membrane preparation. During the membrane preparation the tissue is kept on ice all the time. Rat cerebral cortex is homogenized in 10 volumes (w/w) ice-cold Hepes buffer (20 mM Hepes, 5 mM

$MgCl_2$ pH 7.1 (KOH) + 1 mg/ml bacitracin) using an Ultra-Turrax homogenizer for 30 seconds. The homogenate is centrifuged at 140 g in 10 min. The supernatant is transferred to a new test tube and centrifuged for 30 min at 23 000 g. Pellet is resuspended in 5-10 ml Hepes buffer, homogenized and centrifuged for 10 min at 23 000 g. This short centrifugation step is repeated twice. After the last centrifugation the pellet is resuspended in 2-4 ml Hepes buffer and the protein concentration is determined. The membranes are diluted to a protein concentration of 5 mg/ml using Hepes buffer, aliquoted and stored at –80 °C until use.

50 μl test-compound, 100 μl membrane (200 μg/ml), 300 μl Hepes buffer and 50 μl R-α-methyl[^{3}H]histamine (1 nM) are mixed in a test tube. The compounds to be tested are dissolved in DMSO and further diluted in H_2O to the desired concentrations. Radioligand and membranes are diluted in Hepes buffer + 1 mg/ml bacitracin. The mixture is incubated for 60 min at 25 °C. Incubation is terminated by adding 5 ml ice-cold 0.9% NaCl, followed by rapid filtration through Whatman GF/B filters pre-treated for 1hour with 0.5% polyethyleneimine. The filters are washed with 2 x 5 ml ice-cold NaCl. To each filter a 3 ml scintillation cocktail is added and the radioactivity retained is measured with a Packard Tri-Carb beta counter.

IC_{50} values are calculated by non-linear regression analysis of binding curves (6 points minimum) using the windows program GraphPad Prism, GraphPad software, USA.

Binding assay (III)

The human H3 receptor is cloned by PCR and subcloned into the pcDNA3 expression vector. Cells stably expressing the H3 receptor are generated by transfecting the H3-expression vectors into HEK 293 cells and using G418 to select for H3 clones. The human H3-HEK 293 clones are cultured in DMEM (GIBCO-BRL) with glutamax, 10% foetal calf serum, 1% penicillin/streptavidin and 1 mg/ml G 418 at 37 °C and 5% CO_2. Before harvesting, the confluent cells are rinsed with PBS and incubated with Versene (proteinase, GIBCO-BRL) for approximately 5 min. The cells are flushed with PBS and DMEM and the cellsuspension collected in a tube and centrifuged for 5-10 min at 1500 rpm in a Heraeus Sepatech Megafuge 1.0. The pellet is resuspended in 10-20 vol. Hepes buffer (20 mM Hepes, 5 mM $MgCl_2$, pH 7.1 (KOH)) and homogenized for 10-20 seconds using an Ultra-Turrax homogenizer. The homogenate is centrifuged for 30 min at 23 000 g. The pellet is resuspended in 5-10 ml Hepes buffer, homogenized 5-10 seconds with the Ultra-Turrax and centrifuged for 10 min at 23 000 g. Following this centrifugation step, the membrane pellet is resuspended in 2-4 ml Hepes buffer, homogenized with a syringe or teflon homogenizer, and the protein concentration determined. The membranes are diluted to a protein concentration of 1-5 mg/ml in Hepes buffer, aliquoted and kept at –80 °C until use.

Aliquots of the membrane suspension are incubated for 60 min at 25 °C with 30 pM [^{125}I]-iodoproxifan, a known compound with high affinity for the H3 receptor, and the test compound at various concentrations. The incubation is stopped by dilution with ice-cold medium, followed by rapid filtration through Whatman GF/B filters pretreated for 1 hour with 0.5% polyethyleneimine. The radioactivity retained on the filters is counted using a Cobra II auto gamma counter. The radioactivity of the filters is indirectly proportional to the binding affinity of the tested compound. The results are analysed by nonlinear regression analysis.

When tested, some of the compounds show potent inverse agonism at the human histamine H3 receptor.

Preferably, the compounds according to the invention have an IC_{50} value as determined by one or more of the assays of less than 10 µM, more preferred of less than 1 µM, and even more preferred of less than 500 nM, such as of less than 100 nM.

Functional assay (I)

The ability of the compounds to interact with the histamine H3 receptor as agonists, inverse agonists and/or antagonists, is determined by an *in vitro* functional assay utilizing membranes from HEK 293 cell expressing the human H3 receptors.

The H3 receptor is cloned by PCR and subcloned into the pcDNA3 expression vector. Cells stably expressing the H3 receptor are generated by transfecting the H3-expression vectors into HEK 293 cells and using G418 to select for H3 clones. The human H3-HEK 293 clones are cultured in DMEM with glutamax, 10% foetal calf serum, 1% penicillin/streptavidin and 1 mg/ml G 418 at 37 °C and 5% CO_2.

The H3 receptor expressing cells are washed once with phosphate buffered saline (PBS) and harvested using versene (GIBCO-BRL). PBS is added and the cells are centrifuged for 5 min at 188 g. The cell pellet is resuspended in stimulation buffer to a concentration of 1 x 10^6 cells/ml. cAMP accumulation is measured using the Flash Plate® cAMP assay (NEN™ Life Science Products). The assay is generally performed as described by the manufacturer. Briefly, 50 µl cell suspension is added to each well of the Flashplate which also contained 25 µl 40 µM isoprenaline, to stimulate cAMP generation, and 25 µl of test compound (either agonists or inverse agonists alone, or agonist and antagonist in combination). The assay can be run in "agonist-mode" which means that the test compound is added, in increasing concentration, on its own, to the cells, and cAMP is measured. If cAMP goes up, it is an inverse agonist; if cAMP does not change, it is a neutral antagonist, and if cAMP goes down, it is an agonist. The assay can also be run in the "antagonist-mode" which means that a test compound is added, in increasing concentrations, together with increasing concentrations of a known H3 agonist (eg RAMHA). If the compound is an antagonist, increasing concentrations of it cause a right-ward shift in the H3-agonist's dose-response curves. The final volume in each well is 100 µl. Test compounds are dissolved in DMSO and diluted in H_2O. The mixture is shaken for 5 min, and allowed to stand for 25 min at room temperature. The reaction is stopped with 100 µl "Detection Mix" per well. The plates are then sealed with plastic, shaken for 30 min, allowed to stand overnight, and finally the radioactivity is counted in the Cobra II auto gamma topcounter. EC_{50} values are calculated by non-linear regression analysis of dose response curves (6 points minimum) using GraphPad Prism. Kb values are calculated by Schild plot analysis.

The open cage Schedule-fed rat model

The ability of the present compounds to reduce weight is determined using the *in vivo* open cage Schedule-fed rat model.

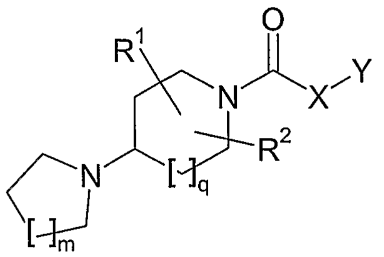
Sprague-Dawley (SD) male rats of an age of about 1½ to 2 months and a weight of about 200-250 g are purchased from Møllegård Breeding and Research Centre A/S (Denmark). On arrival they are allowed some days of acclimatisation before being placed in individual open plastic cages. They are habituated to the presence of food (Altromin pelleted rat chow) in their home cage only during 7 hours in the morning from 07.30 to14.30 h all days a week. Water is present ad libitum. As the consumption of food has stabilised after 7 to 9 days, the animals are ready for use.

Each animal is used only once to avoid carry-over effects between treatments. During the test sessions, the test compound is administered intraperitoneally or orally 30 min before the start of the sessions. One group of animals is administered the test compound at different doses and a control group of animals is given a vehicle. Food and water intake are monitored at 1, 2 and 3 hours post administration.

Any side effects may rapidly be discovered (barrel-rolling, bushy fur etc.) since the animals are kept in transparent plastic cages to enable continuous monitoring.

CLAIMS

1. A compound of the general formula (I):



(I)

wherein

m is 1, 2 or 3,

q is 0, 1 or 2,

X is $-CH_2-(CH_2)_n-$, $-(CH_2)_n-CH=CH-(CH_2)_p-$, $-CH_2-(CH_2)_n-O-(CH_2)_p-$, $-CH_2-(CH_2)_n-C(=O)-(CH_2)_p-$, $-CH_2-(CH_2)_n-S-(CH_2)_p-$, $-CH_2-(CH_2)_n-S(=O)-(CH_2)_p-$ or $-CH_2-(CH_2)_n-S(=O)_2-(CH_2)_p-$,

n and p are independently 0, 1, 2, 3 or 4,

R^1 and R^2 are independently hydrogen, methyl or trifluoromethyl,

Y is

(a) aryl or heteroaryl, which may optionally be substituted with one or more substituents selected from

- halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^3R^4$ and $-O(C=O)NR^3R^4$,
  wherein R^3 and R^4 independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^3 and R^4 together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

- or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O-$,

- aryl, aryl-C_{1-6}-alkyl and aryl-C_{1-6}-alkoxy, wherein the ring moieties optionally may be substituted with one or more substituents selected from
    - o halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^5R^6$ and $-O(C=O)NR^5R^6$,
      wherein R^5 and R^6 independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,
    - o or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O$

(b) C_{3-8}-cycloalkyl or C_{5-8}-cycloalkenyl, which may optionally be substituted with one or more substituents selected from

- C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, cyano, trifluoromethyl, trifluoromethoxy and halogen,

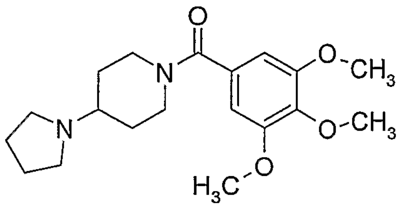
- aryl and aryloxy, wherein the ring moieties optionally may be substituted with one or more substituents selected from
    - o halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^7R^8$ and $-O(C=O)NR^7R^8$,
      wherein R^7 and R^8 independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^7 and R^8 together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,
    - o or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O-$

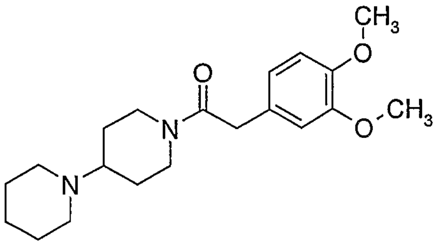
(c) C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl, which may optionally be substituted with one or more substituents selected from

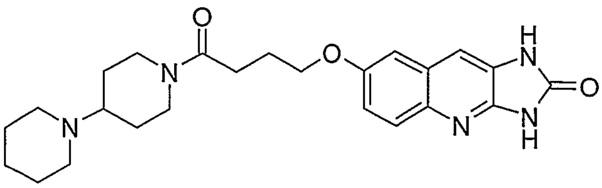
- halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^9R^{10}$ and $-O(C=O)NR^9R^{10}$, wherein R^9 and R^{10} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

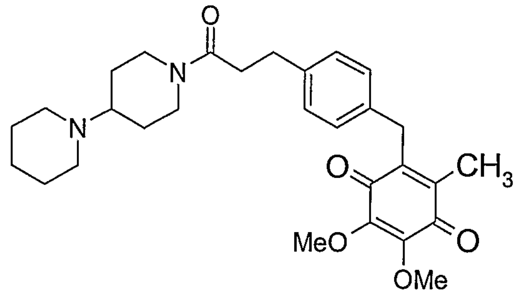
- aryl, aryl-C_{1-6}-alkyl and aryl-C_{1-6}-alkoxy, wherein the ring moieties optionally may be substituted with one or more substituents selected from
    - halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^{11}R^{12}$ and $-O(C=O)NR^{11}R^{12}$,
      wherein R^{11} and R^{12} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,
    - or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O-$

with the proviso that the compound must not be





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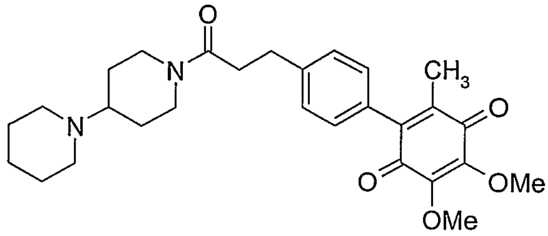
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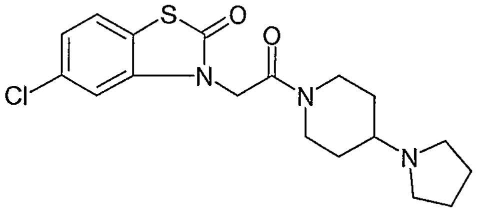
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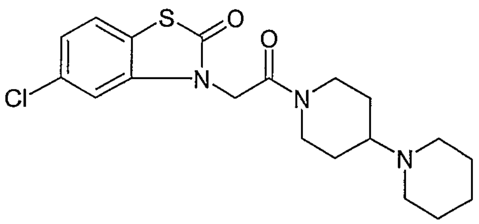
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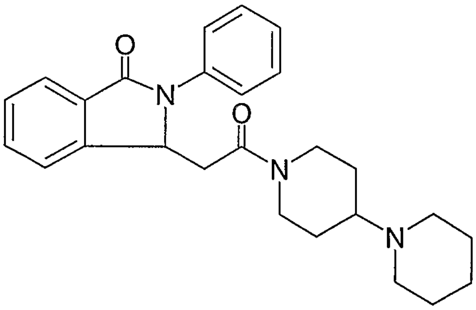
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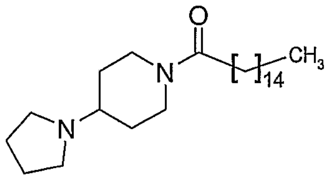
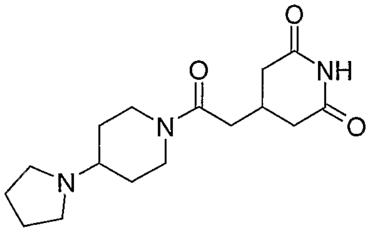




as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein m is 1.

3. A compound according to claim 1, wherein m is 2.

4. A compound according to any one of the preceding claims, wherein q is 1.

5. A compound according to any one of the preceding claims, wherein R^1 and R^2 are both hydrogen.

6. A compound according to any one of the preceding claims, wherein X is $-CH_2-(CH_2)_n-$, $-(CH_2)_n-CH=CH-(CH_2)_p-$, $-CH_2-(CH_2)_n-O-(CH_2)_p-$, $-CH_2-(CH_2)_n-C(=O)-(CH_2)_p-$, or $-CH_2-(CH_2)_n-S-(CH_2)_p-$, wherein n and p are as defined in claim 1.

7. A compound according to claim 6, wherein X is $-CH_2-(CH_2)_n-$, $-CH=CH-$, $-CH_2-(CH_2)_n-O-$, $-CH_2-(CH_2)_n-C(=O)-$, $-CH_2-S-(CH_2)_p-$, wherein n is 0, 1, 2 or 3, and p is 0 or 1.

8. A compound according to claim 7, wherein X is $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH=CH-$, $-CH_2-O-$, $-(CH_2)_3-O-$, $-(CH_2)_2-C(=O)-$, $-CH_2-S-CH_2-$ or $-CH_2-S-$.

9. A compound according to any one of the preceding claims, wherein Y is C_{1-6}-alkyl, C_{3-8}-cycloalkyl, aryl or heteroaryl, which may optionally be substituted as defined in claim 1.

10. A compound according to claim 9, wherein Y is C_{1-6}-alkyl, cyclohexyl, phenyl, naphthyl, pyridyl, benzoxazolyl, imidazolyl or benzothiophenyl, which may optionally be substituted as defined in claim 1.

11. A compound according to claim 10, wherein Y is phenyl or naphthyl, which may optionally be substituted with one or more substituents selected from

- trifluoromethyl, trifluoromethoxy, halogen, nitro, C_{1-6}-alkyl, $-NR^3R^4$, $-O(C=O)NR^3R^4$ and C_{1-7}-alkanoyl, wherein R^3 and R^4 independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^3 and R^4 together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

- aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl and aryl, which may optionally be substituted with halogen or C_{1-6}-alkyl,

- or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O-$.

12. A compound according to claim 11, wherein Y is phenyl or naphthyl, which may optionally be substituted with one or more substituents selected from

- trifluoromethyl, trifluoromethoxy, halogen, nitro, C_{1-6}-alkyl, $-NR^3R^4$, $-O(C=O)NR^3R^4$ and C_{1-7}-alkanoyl, wherein R^3 and R^4 independently are hydrogen or C_{1-6}-alkyl, or R^3 and R^4 together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

- phenyl-C_{1-6}-alkoxy, phenyl-C_{1-6}-alkyl and phenyl, which may optionally be substituted with halogen or C_{1-6}-alkyl,

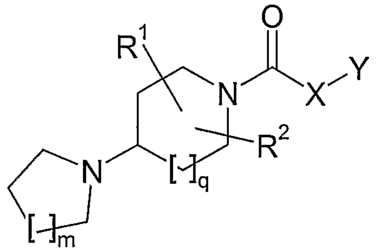
- or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O-$.

13. Use of a compound according to any one of the preceding claims 1 to 12 as a pharmaceutical composition.

14. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 1 to 12 together with one or more pharmaceutically acceptable carriers or excipients.

15. A pharmaceutical composition according to claim 14 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound according to any one of the claims 1 to 12.

16. Use of a compound of the general formula (I'):



(I')

wherein

m is 1, 2 or 3,

q is 0, 1 or 2,

X is $-CH_2-(CH_2)_n-$, $-(CH_2)_n-CH=CH-(CH_2)_p-$, $-CH_2-(CH_2)_n-O-(CH_2)_p-$, $-CH_2-(CH_2)_n-C(=O)-(CH_2)_p-$, $-CH_2-(CH_2)_n-S-(CH_2)_p-$, $-CH_2-(CH_2)_n-S(=O)-(CH_2)_p-$ or $-CH_2-(CH_2)_n-S(=O)_2-(CH_2)_p-$,

n and p are independently 0, 1, 2, 3 or 4,

R^1 and R^2 are independently hydrogen, methyl or trifluoromethyl, Y is

(a) aryl or heteroaryl, which may optionally be substituted with one or more substituents selected from

- halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^3R^4$ and $-O(C=O)NR^3R^4$,
  wherein R^3 and R^4 independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^3 and R^4 together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

- or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O-$,

- aryl, aryl-C_{1-6}-alkyl and aryl-C_{1-6}-alkoxy, wherein the ring moieties optionally may be substituted with one or more substituents selected from
  - halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^5R^6$ and $-O(C=O)NR^5R^6$,
    wherein R^5 and R^6 independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

  - or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O$

(b) C_{3-8}-cycloalkyl or C_{5-8}-cycloalkenyl, which may optionally be substituted with one or more substituents selected from

- C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, cyano, trifluoromethyl, trifluoromethoxy and halogen,

- aryl and aryloxy, wherein the ring moieties optionally may be substituted with one or more substituents selected from
  - halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^7R^8$ and $-O(C=O)NR^7R^8$,

wherein R^7 and R^8 independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^7 and R^8 together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

- o or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O-$

(c) C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl, which may optionally be substituted with one or more substituents selected from

- halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^9R^{10}$ and $-O(C=O)NR^9R^{10}$,
  wherein R^9 and R^{10} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

- aryl, aryl-C_{1-6}-alkyl and aryl-C_{1-6}-alkoxy, wherein the ring moieties optionally may be substituted with one or more substituents selected from
  - o halogen, nitro, cyano, hydroxy, C_{1-7}-alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^{11}R^{12}$ and $-O(C=O)NR^{11}R^{12}$,
    wherein R^{11} and R^{12} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4 to 7 membered, saturated or unsaturated ring,

  - o or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O-$

as well as any diastereomer or enantiomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment of disorders and diseases related to the histamine H3 receptor.

17. Use of a compound as defined in claim 16 for the preparation of a pharmaceutical composition for the treatment of diseases and disorders in which an inhibition of the H3 histamine receptor has a beneficial effect.

18. Use of a compound as defined in claim 16 for the preparation of a pharmaceutical composition having histamine H3 antagonistic activity or histamine H3 inverse agonistic activity.

19. Use of a compound as defined in claim 16 for the preparation of a pharmaceutical composition for the reduction of weight.

20. Use of a compound as defined in claim 16 for the preparation of a pharmaceutical composition for the treatment of overweight or obesity.

21. Use of a compound as defined in claim 16 for the preparation of a pharmaceutical composition for the suppression of appetite or for satiety induction.

22. Use of a compound as defined in claim 16 for the preparation of a pharmaceutical composition for the prevention and/or treatment of disorders and diseases related to overweight or obesity.

23. Use of a compound as defined in claim 16 for the preparation of a pharmaceutical composition for the prevention and/or treatment of eating disorders such as bulimia and binge eating.

24. Use of a compound as defined in claim 16 for the preparation of a pharmaceutical composition for the treatment of IGT.

25. Use of a compound as defined in claim 16 for the preparation of a pharmaceutical composition for the treatment of Type 2 diabetes.

26. Use of a compound as defined in claim 16 for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to Type 2 diabetes.

27. Use of a compound as defined in claim 16 for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

28. Use of a compound as defined in claim 16 for the preparation of a pharmaceutical composition for the treatment of diseases and disorders in which a stimulation of the H3 histamine receptor has a beneficial effect.

29. Use of a compound as defined in claim 16 for the preparation of a pharmaceutical composition having histamine H3 agonistic activity.

30. Use of a compound as defined in claim 16 for the preparation of a pharmaceutical composition for the treatment of allergic rhinitis, ulcer or anorexia.

31. A method for the treatment of treatment of disorders or diseases related to the H3 histamine receptor the method comprising administering to a subject in need thereof an effective amount of a compound as defined in claim 16 or a pharmaceutical composition comprising the same.

32. The method according to claim 31 wherein the effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, preferably from about 0.1 mg to about 1000 mg and especially preferred from about 0.5 mg to about 500 mg per day.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 02/00664

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/02 C07D405/14 C07D409/14 C07D413/14 A61K31/4523
A61P3/00 A61P11/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 06254 A (SCHUNACK WALTER G ;SIGURD ELZ (DE); STARK HOLGER (DE); BIOPROJET S) 10 February 2000 (2000-02-10) see particularly compound 124, page 97; compound 176, page 107 and claims ---	1-32
X	DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS accession no. 1995:240010, document no. 122:31580; YAMANOCHI PHARMACEUTICAL CO., LTD.: "Preparation of dihydrobenzazepines, tetrahydrobenzodiazepines, and tetrahydrobenzazepiner as arginine vasopressin antagonists" XP002225365 see CAS RN 159588-75-7 & WO,A1,9420473, 19940915 --- -/--	1,3-9, 13-15

☒ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in 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 17 December 2002	Date of mailing of the international search report 10. 03. 2003
Name and mailing address of the ISA 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	Authorized officer NEBIL GECER /ELY

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 02/00664

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 43292 A (KLINGE CO CHEM PHARM FAB ;EISENBURGER ROLF (DE); REITER FRIEDEMANN) 20 November 1997 (1997-11-20) see page 5 - page 6; table 1, example 37; table 2, examples 36 and 282	1-18,28, 29,31,32
X	WO 97 43282 A (REITER FRIEDEMANN ;SCHEMAINDA ISABEL (DE); SEIBEL KLAUS (DE); EISE) 20 November 1997 (1997-11-20) see page 5 - page 6; table 1, examples 38,49 and 218; table 2, example 49	1-18,28, 29,31,32
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X	DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS accession no. 1981:603242, document no. 95:203242; WEINSTOCK, LOUIS T ET AL: "Synthesis of new polyamine derivatives for cancer chemotherapeutic studies" XP002225366 see CAS RN 79692-15-2- & Journal of Pharmaceutical Sciences (1981), 70(8), 956-9	1-18,28, 29,31,32
P,X	US 2001/039286 A1 (ELLIOTT JASON MATTHEW ET AL) 8 November 2001 (2001-11-08) see page 5 and example 8, page 22	1-18, 28-32
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A	DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS accession no. 1979:568231, document no. 91:168231; REHSE, KLAUS ET AL: "Neuropsychotropic activity of dopamine-analogous piperdine and piperazine derivatives" XP002225367 & Archiv der Pharmazie (Weinheim, Gemany)(1979), 312(8), 670-81	1-32

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 02/00664

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 31-32
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 31-32

Claims 31-32 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK 02/00664

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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