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(54) **SUBSTITUTED PIPERIDINES WITH SELECTIVE BINDING TO HISTAMINE H3-RECEPTOR**

SUBSTITUIERTE PIPERIDINEN MIT SELEKTIVER BINDUNGSFÄHIGKEIT ZU HISTAMIN H3-REZEPTOREN

PIPERIDINES SUBSTITUEES AVEC LIAISON SELECTIVE AU RECEPTEUR H3 DE L'HISTAMINE

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- **WADE W S ET AL: "APPLICATION OF BASE CLEAVABLE SAFETY CATCH LINKERS TO SOLID PHASE LIBRARY PRODUCTION" JOURNAL OF COMBINATORIAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 2, no. 3, 2000, pages 266-275, XP002946305 ISSN: 1520-4766**

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The file contains technical information submitted after the application was filed and not included in this specification

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to novel substituted piperidines, to the use of these compounds as pharmaceutical compositions and to pharmaceutical compositions comprising the compounds. 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 and/or prevention of diseases and disorders related to the histamine H3 receptor.

BACKGROUND OF THE INVENTION

[0002] 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 show 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.

[0003] Piperidines similar to the compounds of the present invention have previously been prepared, and their biological properties have been investigated, cf US 3,577,440, WO 01/44191, J. Comb. Chemical (2000), 2(3), 266-275, WO 96/29307, WO 95/00512 and GB 2000136.

[0004] However, these references neither disclose nor suggest that these substituted piperidines may have a histamine H3 receptor antagonistic or agonistic activity.

[0005] 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.

[0006] 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.

[0007] Due to their interaction with the histamine H3 receptor, the present compounds are useful in the treatment and/or prevention 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

[0008] In the structural formulae given herein and throughout the present specification, the following terms have the indicated meaning:

[0009] The term "halogen" means F, Cl, Br or I.

[0010] The term "C_{1-6}-alkyl " as used herein represent 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.

[0011] 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.

[0012] 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.

[0013] 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.

[0014] 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.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] 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.

[0019] 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.

[0020] 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.

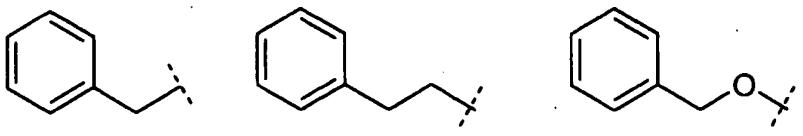
[0021] The term "heteroaryl" as used herein is intended to include heterocyclic aromatic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulfur such as furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 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.

[0022] 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.

[0023] 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.

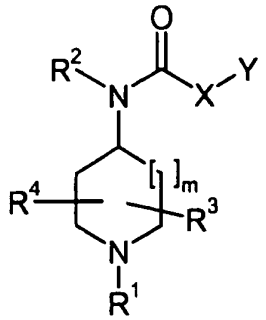
[0024] The term "optionally substituted" as used herein means that the group in question is either unsubstituted or substituted with one or more of the substituents specified. When the group in question is substituted with more than one substituent the substituents may be the same or different.

[0025] "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:



DESCRIPTION OF THE INVENTION

[0026] The invention relates to a compound of the general formula (I):



(I)

wherein
m is 1,
R^1 is
C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl,

- which may optionally be substituted with one or more substituents selected from halogen, C_{1-6}-alkoxy and hydroxy,

C_{3-8}-cycloalkyl, C_{5-8}cycloalkenyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, di(C_{3-8}-cycloalkyl)-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{5-8}-cycloalkenyl-C_{1-6}-alkyl, C_{5-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{5-8}-cycloalkenyl-C_{2-6}-alkynyl,

- wherein the cyclic moieties may optionally be substituted with one or more substituents selected from C_{1-6}-alkyl, halogen, trifluoromethyl and 2,2,2-trifluoroethyl,

R^2 is C_{2-6}-alkenyl, C_{2-6}alkynyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,
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^3 and R^4 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, oxo, 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, 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 $-O-(CH_2)_{1-3}-O-$,

- aryl, aryloxy, 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, $-NR^7R^8$ 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 $-O-(CH_2)_{1-3}-O-$

(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}-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,

(c) C_{1-6}-alkyl, C_{2-6}-alkenyl or 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, $-NR^{11}R^{12}$ 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,

- 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_{3-6}-cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^{13}R^{14}$ and $-O(C=O)NR^{13}R^{14}$,
  wherein R^{13} and R^{14} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^{13} and R^{14} 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.

[0027] In one embodiment of the invention Y is

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

- halogen, nitro, cyano, hydroxy, oxo, 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, 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 $-O-(CH_2)_{1-3}-O-$,
- 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, $-NR^7R^8$ 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 $-O-(CH_2)_{1-3}-O-$

(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}-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,

(c) C_{1-6}-alkyl, C_{2-6}-alkenyl or 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, $-NR^{11}R^{12}$ 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,

- 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, $-NR^{13}R^{14}$ and $-O(C=O)NR^{13}R^{14}$,
    wherein R^{13} and R^{14} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^{13} and R^{14} 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 $-O-(CH_2)_{1-3}-O-$

[0028] In another embodiment of the invention R^3 and R^4 are both hydrogen.

[0029] In yet another embodiment of the invention R^1 is C_{1-6}-alkyl which may optionally be substituted with one or more substituents selected from halogen, C_{1-6}-alkoxy and hydroxy.

[0030] In an embodiment thereof R^1 is C_{1-6}-alkyl such as isopropyl, tert-butyl or 2-methyl-2-butyl.

[0031] In still another embodiment of the invention R^1 is di(C_{3-8}-cycloalkyl)-C_{1-6}-alkyl, wherein the cyclic moieties may optionally be substituted with one or more substituents selected from C_{1-6}-alkyl, halogen, trifluoromethyl and 2,2,2-trifluoroethyl.

[0032] In an embodiment thereof R^1 is dicyclopropylmethyl.

[0033] In still a further embodiment of the invention X is $-CH_2-(CH_2)_n-$, $-(CH_2)_n-CH=CH=(CH_2)_p-$, $-CH_2-(CH_2)_n-O-(CH_2)_p-$, $-CH_2-(CH_2)_n-C(=O)-(CH_2)_p-$, $-CH_2-(CH_2)_n-S-(CH_2)_p-$, wherein n and p are as defined for formula (I).

[0034] In an embodiment thereof 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.

[0035] In yet an embodiment thereof 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 $-CH_2-S-$, such as $-CH_2-$.

[0036] In another embodiment of the invention Y is C_{1-6}-alkyl, C_{3-8}-cycloalkyl, aryl or heteroaryl, which may optionally be substituted as defined for formula (I).

[0037] In an embodiment thereof Y is C_{1-6}-alkyl, cyclohexyl, phenyl, naphthyl, pyridyl, benzoxazolyl or benzothiophenyl, which may optionally be substituted as defined for formula (I).

[0038] In yet an embodiment thereof Y is phenyl or naphthyl which may optionally be substituted with one or more substituents selected from

[0039] trifluoromethyl, trifluoromethoxy, halogen, C_{1-6}-alkyl, and $-O(C=O)NR^5R^6$, C_{1-7}-alkanoyl, 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,

[0040] aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryloxy and aryl, which may optionally be substituted with halogen or C_{1-6}-alkyl,

[0041] or wherein two substituents in adjacent positions form a radical $-O-(CH_2)_{1-3}-O-$.

[0042] In an embodiment thereof Y is phenyl or naphthyl which may optionally be substituted with one or more substituents selected from

[0043] trifluoromethyl, trifluoromethoxy, halogen, C_{1-6}-alkyl, and -O(C=O)NR^5R^6 and C_{1-7}-alkanoyl, wherein R^5 and R^6 independently are hydrogen or C_{1-6}-alkyl,

[0044] phenyl-C_{1-6}-alkoxy, phenyl-C_{1-6}-alkyl, phenyloxy and phenyl, which may optionally be substituted with halogen or C_{1-6}-alkyl,

[0045] or wherein two substituents in adjacent positions form a radical-O-$(CH_2)_{1-3}$-O-.

[0046] In yet an embodiment thereof Y is phenyl, which is substituted with phenyl.

[0047] 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.

[0048] 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.

[0049] 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.

[0050] 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. 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.

[0051] Also intended as pharmaceutically acceptable acid addition salts are the hydrates, which the present compounds are able to form.

[0052] 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.

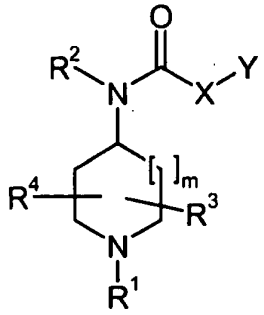
[0053] The compounds of the present invention may form solvates with standard low molecular weight solvents using methods well known to the person skilled in the art. Such solvates are also contemplated as being within the scope of the present invention.

[0054] The compounds of the present invention interact with the histamine H3 receptor and are accordingly useful for the treatment and/or prevention of a wide variety of conditions and disorders in which histamine H3 receptor interactions are beneficial.

[0055] 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.

[0056] 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.

[0057] Furthermore, the invention relates to the use of a compound of the general formula (I'):



(I')

wherein
m is 0 or 1,
R^1 is
C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}alkynyl,

- which may optionally be substituted with one or more substituents selected from halogen, C_{1-6}-alkoxy and hydroxy,

C_{3-8}-cycloalkyl, C_{5-8}-cycloalkenyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, di(C_{3-8}-cycloalkyl)-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{5-8}-cycloalkenyl-C_{1-6}-alkyl, C_{5-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{5-8}-cycloalkenyl-C_{2-6}-alkynyl,

- wherein the cyclic moieties may optionally be substituted with one or more substituents selected from C_{1-6}-alkyl, halogen, trifluoromethyl and 2,2,2-trifluoroethyl,

R^2 is C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,
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^3 and R^4 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, oxo, 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 $-O-(CH_2)_{1-3}-O-$,

- aryl, aryloxy, 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, $-NR^7R^8$ 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 $-O-(CH_2)_{1-3}-O-$

(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}-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,

(c) C_{1-6}-alkyl, C_{2-6}-alkenyl or 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, $-NR^{11}R^{12}$ 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,

- 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, $-NR^{13}R^{14}$ and $-O(C=O)NR^{13}R^{14}$,
  wherein R^{13} and R^{14} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl, or R^{13} and R^{14} 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 and/or prevention of disorders and diseases related to the histamine H3 receptor.

[0058] The treatment and/or prevention of diseases and disorders related to the histamine H3 receptor can be performed by 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.

[0059] 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.

[0060] 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.

[0061] In a preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the reduction of weight.

[0062] In a preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of overweight or obesity.

[0063] In another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the suppression of appetite or satiety induction.

[0064] In a further preferred embodiment of the invention 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)), dyslipidaemia, coronary heart disease, gallbladder disease, osteoarthritis and various types of cancer such as endometrial, breast, prostate and colon cancers.

[0065] In yet a further preferred embodiment of the invention 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.

[0066] In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of IGT.

[0067] In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 2 diabetes.

[0068] In another preferred embodiment of the invention 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.

[0069] In a further preferred embodiment of the invention 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.

[0070] 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.

[0071] 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.

[0072] Moreover, the compounds of the invention may be used as CNS stimulants or as sedatives.

[0073] 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.

[0074] Further, the compounds of the present invention may be used for the treatment of dementia and Alzheimer's disease.

[0075] The compounds of the present invention may also be useful for the treatment of allergic rhinitis, ulcer or anorexia.

[0076] 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.

[0077] In a further aspect of the invention the present compounds are combined with diet and/or exercise.

[0078] 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 and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity.

[0079] 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.

[0080] Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonist, 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.

[0081] In one embodiment of the invention the antiobesity agent is leptin.

[0082] In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

[0083] In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

[0084] In still another embodiment the antiobesity agent is sibutramine.

[0085] In a further embodiment the antiobesity agent is orlistat.

[0086] In another embodiment the antiobesity agent is mazindol or phentermine.

[0087] In still another embodiment the antiobesity agent is phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate or ecopipam.

[0088] Suitable antidiabetic agents comprise 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, GLP-1 derivatives such as those disclosed in WO 98/08871 (Novo Nordisk A/S), as well as orally active hypoglycaemic agents.

[0089] 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), 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.), GLP-1 agonists such as those disclosed in WO 00/42026 (Novo Nordisk A/S and Agouron Pharmaceuticals, Inc.), 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.

[0090] In one embodiment of the invention the present compounds are administered in combination with insulin.

[0091] 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.

[0092] In another embodiment of the invention the present compounds are administered in combination with a biguanide eg metformin.

[0093] In yet another embodiment of the invention the present compounds are administered in combination with a meglitinide eg repaglinide or nateglinide.

[0094] 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/Cl-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).

[0095] 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).

[0096] 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.

[0097] 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.

[0098] In yet another embodiment of the invention the present compounds may be administered in combination with nateglinide.

[0099] 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.

[0100] 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.

[0101] 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.

[0102] 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

[0103] 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.

[0104] 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.

[0105] 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.

[0106] Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

[0107] 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.

[0108] Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

[0109] 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.

[0110] 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.

[0111] 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.

[0112] 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.

[0113] 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.

[0114] 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.

[0115] 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.

[0116] 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.

[0117] 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.

[0118] 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

[0119] The preparation of the compounds of this invention can be realized in many different ways. The compounds of the present invention were prepared using standard synthetic procedures, well-known by those skilled in the art, as described, for instance, in Houben Weyl: Methoden der Organischen Chemie, Thieme Verlag, Stuttgart.

[0120] The amides were prepared either in solution or with the aid of an insoluble nitrophenol from the corresponding amines and carboxylic acids, using standard methodology (see eg J.J. Parlow, J.E. Normansell, Mol. Diversity 1996, 1, 266-269; R. Kalir, M. Fridkin, A. Patchornik, Eur. J. Biochem. 1974, 42, 151-156; B.J. Cohen, H. Karoly-Hafeli, A. Patchornik, J. Org. Chem. 1984, 49, 922-924). In solution the carboxylic acid was activated by treatment with carbonyl diimidazole or di-(*N*-succinimidyl)carbonate and then treated with the amine. The carbamates were prepared by activating an alcohol with phosgene or 4-nitrophenyl chloroformate, and treating the resulting chloroformate or 4-nitrophenyl carbonate with an amine. The ureas were prepared by treating an amine with a suitable isocyanate or carbamoyl chloride.

[0121] 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
PS: Polystyrene

[0122] NMR spectra were recorded on Bruker 300 MHz and 400 MHz instruments. HPLC-MS was performed on a Perkin Elmer instrument (API 100).

[0123] 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.

[0124] Furthermore, where stated the following HPLC method h8 was used:

[0125] 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.

General procedures for the preparation of compounds of the general formula (I):

[0126] An insoluble nitrophenol was prepared by acylating commercially available aminomethyl polystyrene (1% cross-linked with divinyl benzene, 0.8 mmol/g) with 4-hydroxy-3-nitrobenzoic acid. The resulting support was acylated with a carboxylic acid (DCM/DMF, DIC, 2 hours, room temperature), filtered and washed with three times with DCM and then

treated with less than one equivalent of an amine (DCM/acetonitrile, room temperature, overnight). Filtration and concentration yielded the pure products, which were either tested directly, or further purified by recrystallization or column chromatography. The products were analyzed by ^{1}H NMR and HPLC-MS.

[0127] Most of the 4-aminopiperidines required for the preparation of the compounds of the present invention were commercially available. The preparation of those amines which were not commercially available is described below.

1-Isopropyl-4-methylaminopiperidine

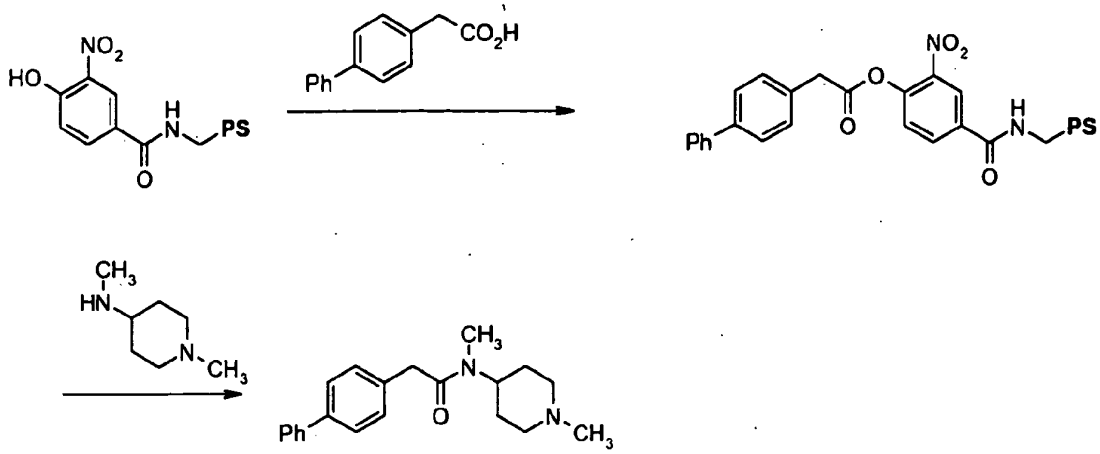
[0128] To a stirred mixture of methylamine hydrochloride (2.62 g, 38.8 mmol), THF (30 ml), ethanol (15 ml), *N*-isopropyl-4-piperidinone (3.0 ml, 20.2 mmol), and acetic acid (3.60 ml) was added sodium cyanoborohydride (30 ml, 1 molar solution in THF, 30 mmol), and the mixture was stirred at 60°C for 6 hours and then at room temperature overnight. The mixture was concentrated under reduced pressure, water (50 ml) and potassium carbonate (47.0 g) were added, and the mixture was extracted with ethyl acetate (6 x 50 ml). The combined extracts were dried over magnesium sulphate and concentrated, to yield 3.78 g (quant.) of the title compound as an oil, which was used without further purification.

Typical procedure:

Example 11:

2-Biphenyl-4-yl-*N*-methyl-*N*-(1-methylpipeddin-4-yl)acetamide hydrochloride

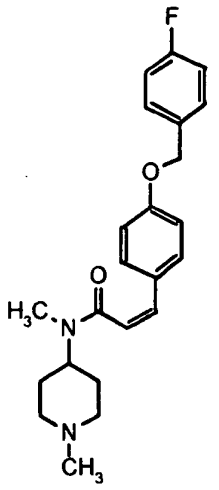
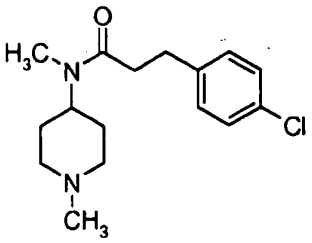
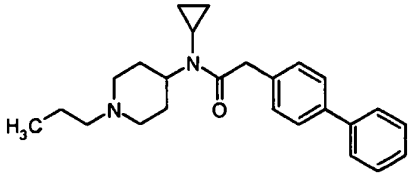
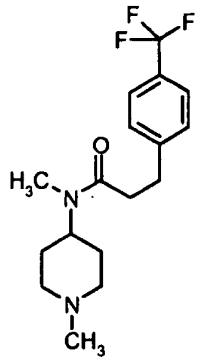
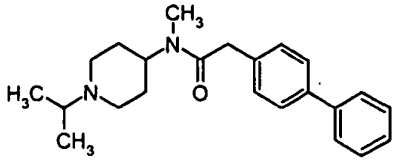
[0129]



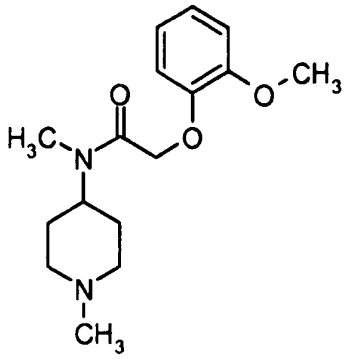
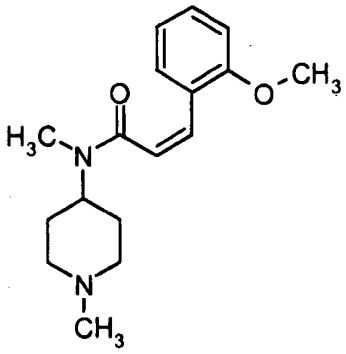
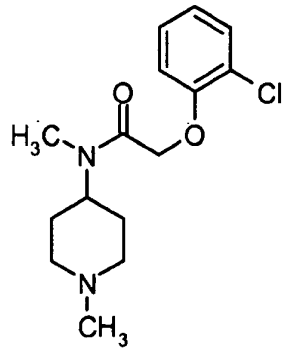
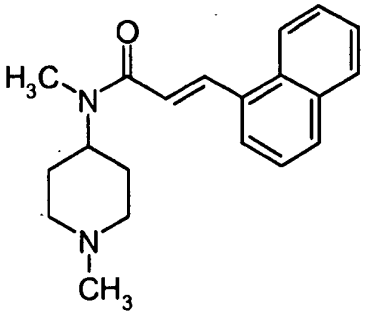
[0130] To the polymeric nitrophenol (1.5 g, approx. 1 mmol) was added a filtered solution of 4-biphenylylacetic acid (1.10 g, 5.18 mmol) in a mixture of 1,2-dichloropropane (18 ml) and DMF (2ml), followed by the addition of a solution of DIC (0.63 g, 4.99 mmol) in 1,2-dichloropropane (5 ml). The mixture 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 1-methyl-4-methylaminopiperidine (0.10 g, 0.78 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 purified by column chromatography (silicagel, gradient elution with DCM/methanol). The amine was mixed with ethanol and 1 molar aqueous hydrochloric acid, concentrated, and the residual hydrochloride was recrystallized from acetone. 120 mg (42%) of the title compound was obtained.

^{1}H NMR (400 MHz, DMSO, mixture of rotamers): δ1.64 (m, 2H), 2.05 (m, 2H), 2.71 (m, 4H), 2.87 (s, 2H), 3.06 (m, 2H), 3.41 (m, 2H), 3.75 and 3.83 (2 x s, 2H), 4.13 (m, 0.5H), 4.54 (m, 0.5H), 7.27-7.38 (m, 3H), 7.45 (t, J = 8 Hz, 2H), 7.58-7.66 (m, 4H), 10.25 (m, 1H); HPLC-MS: m/z 323 (MH^+); R_t: 4.1 min.

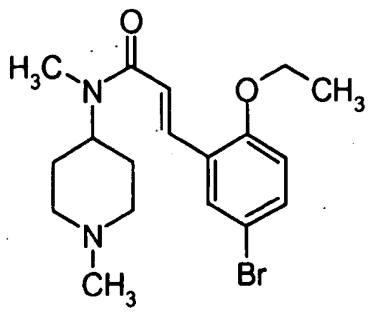
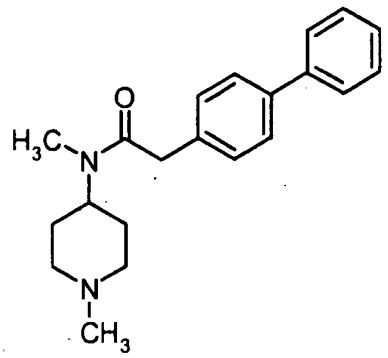
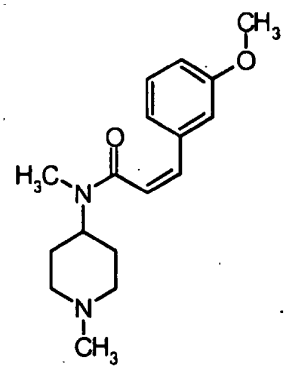
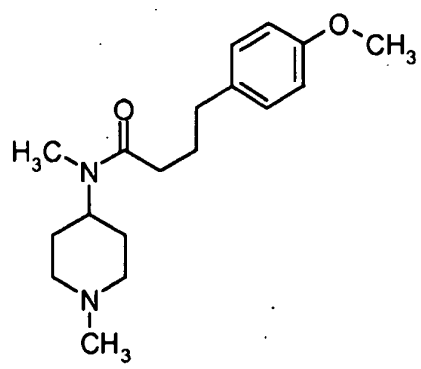
[0131] Using this methodology the following compounds were prepared:

No	Structure	Name	Found MH+
1		3-[4-(4-Fluorobenzyloxy)phenyl]-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-acrylamide	383
2		3-(4-Chlorophenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)propionamide	295
3		2-Biphenyl-4-yl-*N*-cyclopropyl-*N*-(1-propylpiperidin-4-yl)acetamide	377
4		*N*-Methyl-*N*-(1-methylpiperidin-4-yl)-3-(4-trifluoromethylphenyl)propionamide	329
5		2-Biphenyl-4-yl-*N*-(1-isopropyl-piperidin-4-yl)-*N*-methylacetamide	351

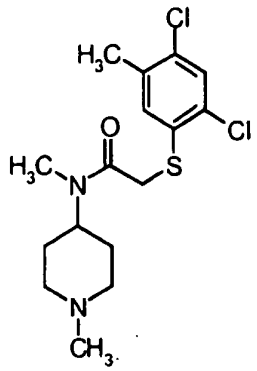
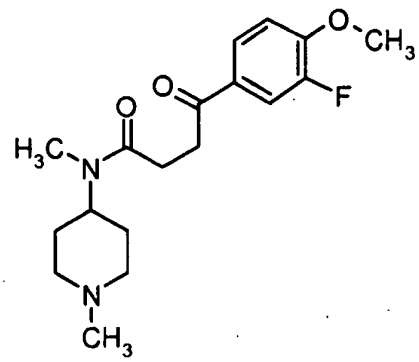
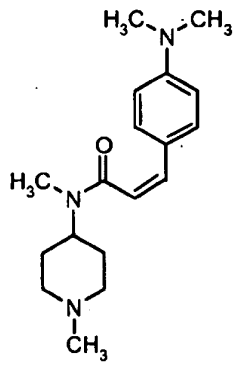
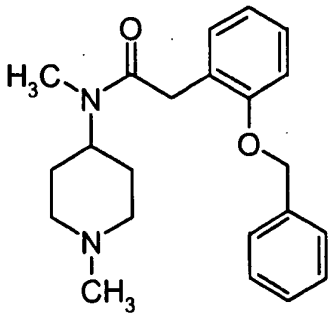
(continued)

No	Structure	Name	Found MH+
6		2-(2-Methoxyphenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide	293
7		3-(2-Methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide	289
8		2-(2-Chlorophenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide	297
9		*N*-Methyl-*N*-(1-methylpiperidin-4-yl)-3-naphthalen-1-ylacrylamide	309

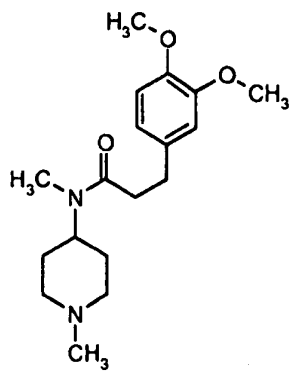
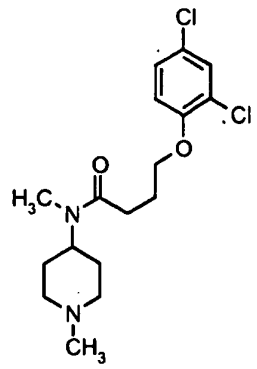
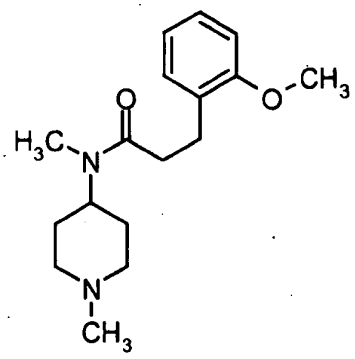
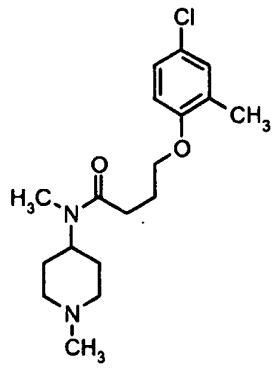
(continued)

No	Structure	Name	Found MH+
10		3-(5-Bromo-2-ethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-acrylamide	381
11		2-Biphenyl-4-yl-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide	323
12		3-(3-Methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide	289
13		4-(4-Methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)butyramide	305

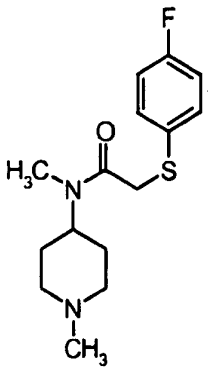
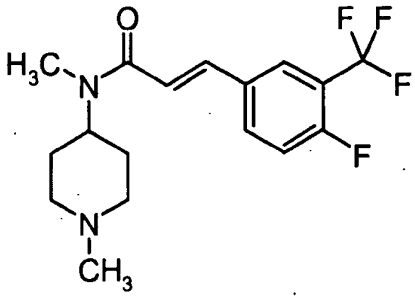
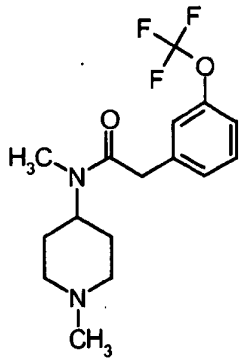
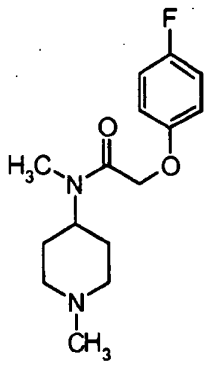
(continued)

No	Structure	Name	Found MH+
14		2-(2,4-Dichloro-5-methylphenyl-sulfanyl)-*N*-methyl-*N*-(1-methyl-piperidin-4-yl)acetamide	362
15		4-(3-Fluoro-4-methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-4-oxobutyramide	337
16		3-(4-Dimethylaminophenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide	302
17		2-(2-Benzyloxyphenyl)-*N*-methyl-*N* (1-methylpiperidin-4-yl)acetamide	353

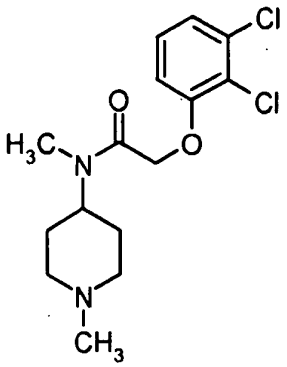
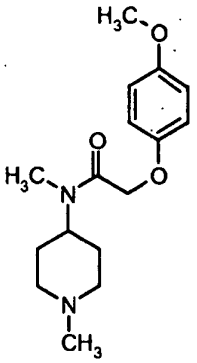
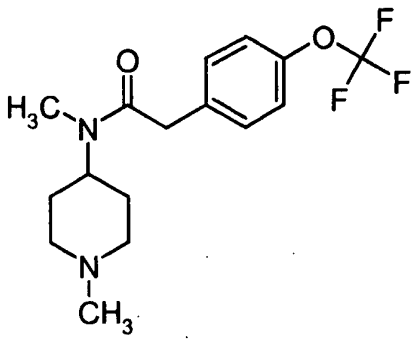
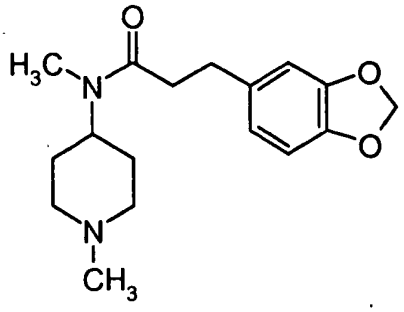
(continued)

No	Structure	Name	Found MH+
18		3-(3,4-Dimethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)propionamide	321
19		4-(2,4-Dichlorophenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)butyramide	360
20		3-(2-Methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)propionamide	391
21		4-(4-Chloro-2-methylphenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-butyramide	339

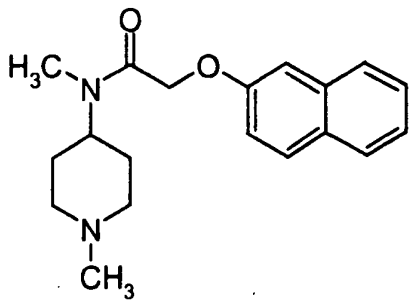
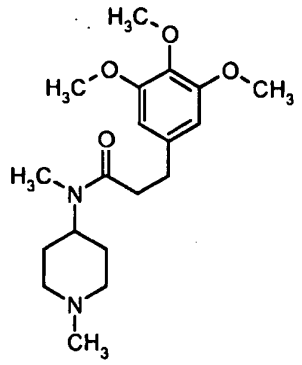
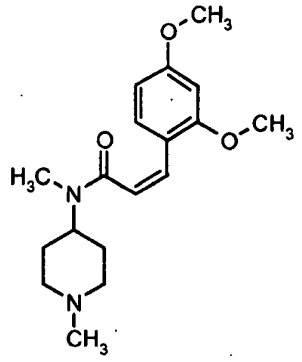
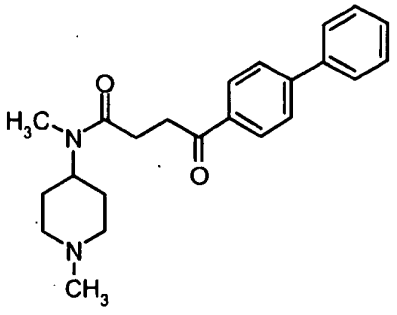
(continued)

No	Structure	Name	Found MH+
22		2-(4-Fluorophenylsulfanyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide	297
23		3-(4-Fluoro-3-trifluoromethylphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-acrylamide	345
24		*N*-Methyl-*N*-(1-methylpiperidin-4-yl)-2-(3-trifluoromethoxyphenyl)acetamide	331
25		2-(4-Fluorophenoxy)-*N*-methyl-*N*-(1methylpiperidin-4-yl)acetamide	281

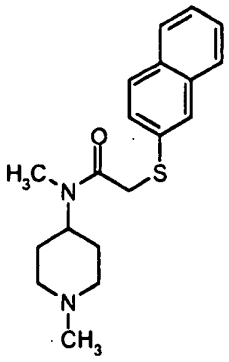
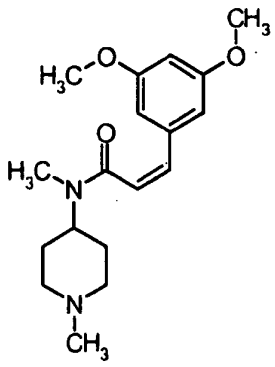
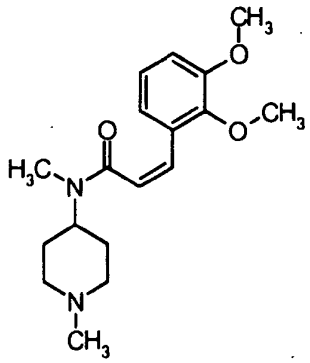
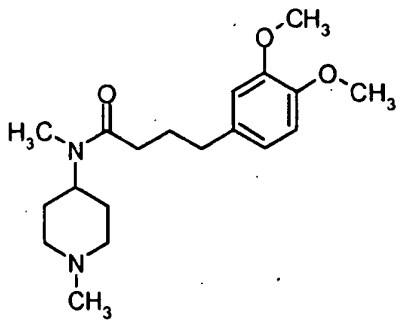
(continued)

No	Structure	Name	Found MH+
26		2-(2,3-Dichlorophenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide	332
27		2-(4-Methoxyphenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide	293
28		*N*-Methyl-*N*-(1-methylpiperidin-4-yl)-2-(4-trifluoromethoxyphenyl)acetamide	331
29		3-Benzo[1,3]dioxol-5-yl-*N*-methyl-*N*-(1-methylpiperidin-4-yl)propionamide	305

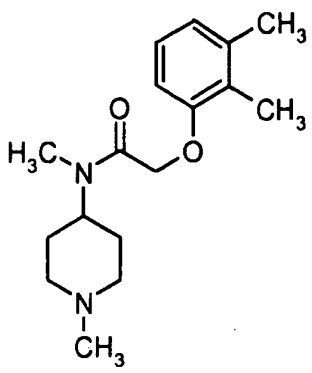
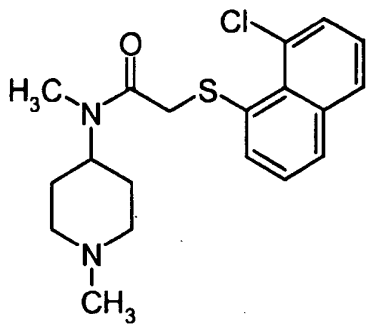
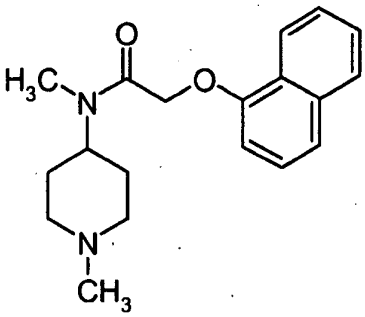
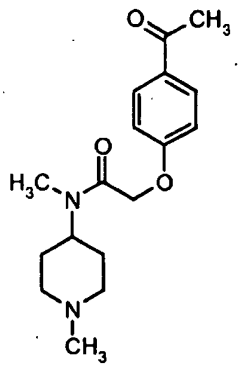
(continued)

No	Structure	Name	Found MH+
30		*N*-Methyl-*N*-(1-methylpiperidin-4-yl)-2-(naphthalen-2-yloxy)acetamide	313
31		*N*-Methyl-*N*-(1-methylpiperidin-4-yl)-3-(3,4,5-trimethoxyphenyl)propionamide	351
32		3-(2,4-Dimethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide	319
33		4-Biphenyl-4-yl-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-4-oxobutyramide	365

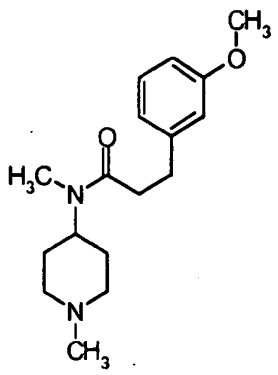
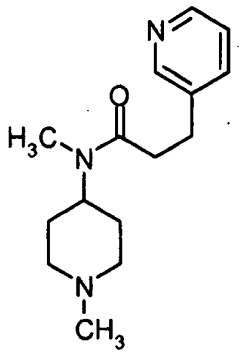
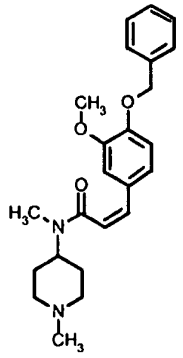
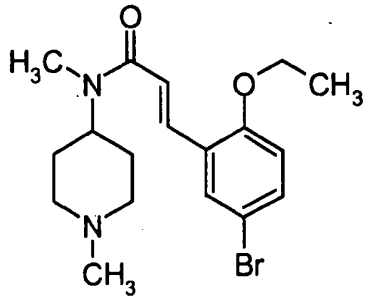
(continued)

No	Structure	Name	Found MH+
34		*N*-Methyl-*N*-(1-methylpiperidin-4-yl)-2-(naphthalen-2-ylsulfanyl)acetamide	329
35		3-(3,5-Dimethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide	319
36		3-(2,3-Dimethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide	319
37		4-(3,4-Dimethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)butyramide	335

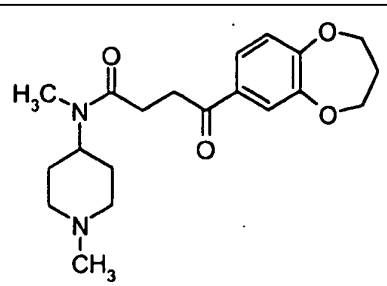
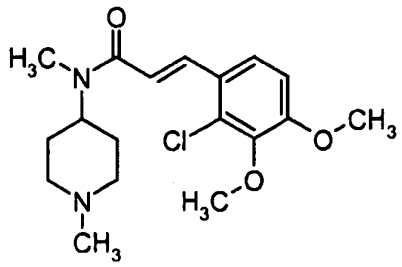
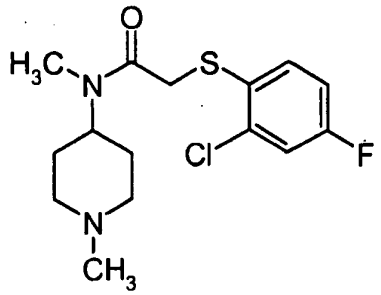
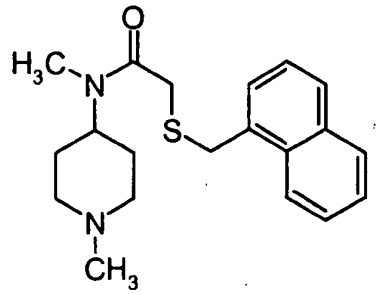
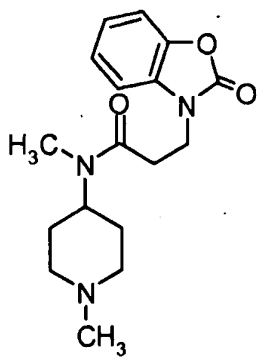
(continued)

No	Structure	Name	Found MH+
38		2-(2,3-Dimethylphenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide	291
39		2-(8-Chloronaphthalen-1-ylsulfanyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-acetamide	363
40		*N*-Methyl-*N*-(1-methylpiperidin-4-yl)-2-(naphthalen-1-yloxy)acetamide	313
41		2-(4-Acetylphenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide	305

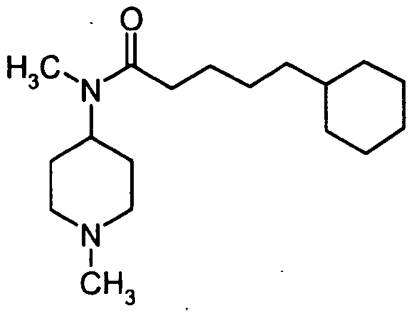
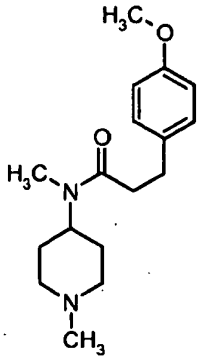
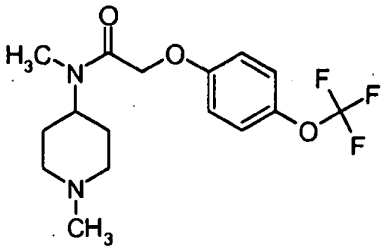
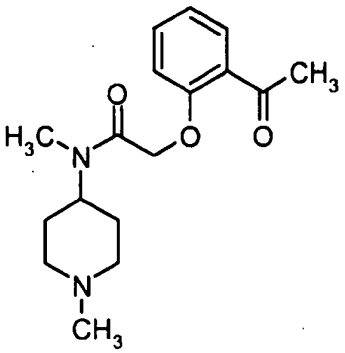
(continued)

No	Structure	Name	Found MH+
42		3-(3-Methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)propionamide	291
43		*N*-Methyl-*N*-(1-methylpiperidin-4-yl)-3-pyridin-3-ylpropionamide	262
44		3-(4-Benzyloxy-3-methoxyphenyly)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-acrylamide	395
45		3-(5-Bromo-2-ethoxyphenyl)-*N*- methyl-*N*-(1-methylpiperidin-4-yl)- acrylamide	382

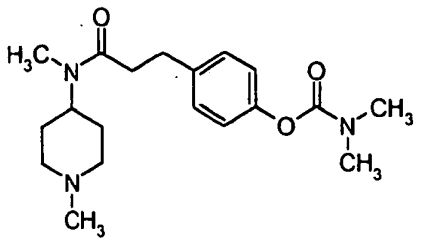
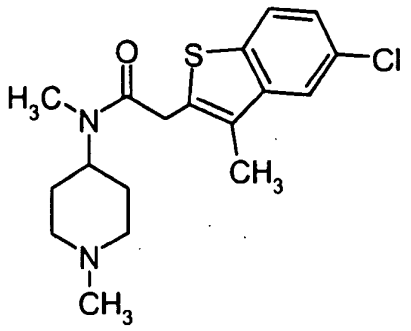
(continued)

No	Structure	Name	Found MH+
46		4-(3,4-Dihydro-2*H*-benzo[b][1,4]-dioxepin-7-yl)-*N*-methyl-*N*-(1-methyl-piperidin-4-yl)-4-oxobutyramide	361
47		3-(2-Chloro-3,4-dimethoxyphenyly)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-acrylamide	353
48		2-(2-Chloro-4-fluorophenylsulfanyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-acetamide	331
49		*N*-Methyl-*N*-(1-methylpiperidin-4-yl)-2-(naphthalen-1-ylmethylsulfanyl)-acetamide	343
50		*N*-Methyl-*N*-(1-methylpiperidin-4-yl)-3-(2-oxo-benzooxazol-3-yl)propionamide	318

(continued)

No	Structure	Name	Found MH+
51		5-Cyclohexylpentanoic acid methyl-(1-methylpiperidin-4-yl)amide	295
52		3-(4-Methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)propionamide	291
53		*N*-Methyl-*N*-(1-methylpipedin-4-yl)-2-4-trifluoromethoxyphenoxy)acetamide	247
54		2-(2-Acetylphenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide	305

(continued)

No	Structure	Name	Found MH+
55		Dimethylcarbamic acid 4-{2-[methyl-(1-methylpiperidin-4-yl)carbamoyl]-ethyl}-phenyl ester	348
56		2-(5-Chloro-3-methyl-benzo[b]thio-phen-2-yl)-*N*-methyl-*N*-(1-methyl-piperidin-4-yl) acetamide	351

Spectral data for selected examples

Example 2:

[0132] 3-(4-Chlorophenyl)-*N*-methey)-*N*-(1-methylpiperidin-4-yl)propionamide hydrochloride
^{1}H NMR(400 MHz, DMSO, mixture of rotamers): δ1.55-1.76 (m, 2H), 2.05 (m, 2H), 2.56-2.83 (m, 9H), 3.05 (m, 2H), 3.39 (m, 2H), 3.95 (m, 1H), 4.52 (m, 1H), 7.30 (m, 4H), 10.36 (br s, 1H); HPLC-MS: m/z 295 (MH^+); R_t: 4.1 min.

Example 3:

[0133] 2-Biphenyl-4-yl-*N*-cyclopropyl-*N*-(1-propylpiperidin-4-yl)acetamide hydrochloride
^{1}H NMR (400 MHz, DMSO, mixture of rotamers): δ0.89 (m, 7H), 1.68 (m, 2H), 1.82 (m, 2H), 2.38 (m, 2H), 2.63 (m, 1H), 2.93 (m, 4H), 3.46 (m, 2H), 3.91 (s, 2H), 4.03 (m, 1H), 7.29-7.38 (m, 3H), 7.46 (t, *J* = 8 Hz, 2H), 7.58-7.68 (m, 4H), 9.84 (br s, 1H); HPLC-MS: *m/z* 377 (MH^+); R_t: 5.0 min.

Example 5:

[0134] 2-Biphenyl-4-yl-*N*-(1-isopropylpiperidin-4-yl)-*N*-methylacetamide hydrochloride
^{1}H NMR (400 MHz, DMSO, mixture of rotamers): δ1.18-1.30 (m, 6H), 1.66 (m, 2H), 2.10-2.32 (m, 3H), 2.82 and 2.89 (2 x s, 3H), 3.08 (m, 3H), 3.76 and 3.82 (2 x s, 2H), 4.25 (m, 1H), 4.61 (m, 1H), 7.28-7.39 (m, 3H), 7.46 (t, J = 8 Hz, 2H), 7.58-7.68 (m, 4H), 10.1 (br s, 1H); HPLC-MS: m/z 351 (MH^+); R_t: 4.5 min.

PHARMACOLOGICAL METHODS

[0135] 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)

[0136] 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 ug/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)

[0137] 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.

[0138] 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.

[0139] 50 µl test-compound, 100 µl membrane (200 ug/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 1 hour 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.

[0140] 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)

[0141] 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 teflonhomogenizer, 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.

[0142] 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.

[0143] When tested, the present compounds of the formula (I) generally show a high binding affinity to the histamine H3 receptor.

[0144] 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)

[0145] 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.

[0146] 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.

[0147] 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 rightward 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

[0148] The ability of the present compounds to reduce weight is determined using the *in vivo* open cage Schedule-fed rat model.

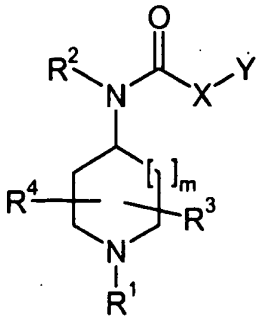
[0149] Sprague-Dawley (SD) male rats of an age of about $1\frac{1}{2}$ to 2 months and a weight of about 200-250 g are purchased from Møllegård Breeding and Research Centre A/S (Denmark). On arrival they are allowed some days of acclimatisation before being placed in individual open plastic cages. They 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 to 14.30 h all days a week. Water is present ad libitum. As the consumption of food has stabilise after 7 to 9 days, the animals are ready for use.

[0150] 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.

[0151] 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
mist,
R^1 is
C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl,

- which may optionally be substituted with one or more substituents selected from halogen, C_{1-6}-alkoxy and hydroxy,

C_{3-8}cycloalkyl, C_{5-8}-cycloalkenyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, di(C_{3-8}-cycloalkyly-C_{1-6}-alkyl, C_{3-8}-cydoalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}alkynyl, C_{5-8}-cycloalkenyl-C_{1-6}-alkyl, C_{5-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{5-8}-cycloalkenyl-C_{2-6}-alkynyl,

- wherein the cyclic moieties may optionally be substituted with one or more substituents selected from C_{1-6}-alkyl, halogen, trifluoromethyl and 2,2,2-trifluoroethyl,

R^2 is C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,
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^3 and R^4 are independently hydrogen, methyl or trifluoromethyl,
Y is

(a) aryl being carbocyclic aromatic ring systems and the partially hydrogenated derivatives of said carbocyclic systems or heteroaryl being heterocyclic aromatic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulfur and the partially hydrogenated derivatives of said heterocyclic systems, which may optionally be substituted with one or more substituents selected from

- halogen, nitro, cyano, hydroxy, -oxo, C_{1-7}alkanoyl, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-6}-cycloalkyl, trifluoromethyl, trifluoromethoxy and $-O(C=O)NR^5R^6$,
  wherein R^5 and R^6 independently are hydrogen, C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{1-7}-alkanoyl or aryl as defined above, 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 $-O-(CH_2)_{1-3}-O-$,
- aryl as defined above, aryloxy, 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_{3-6}-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_{3-6}-cycloalkyl, . C_{1-7}-alkanoyl or aryl as defined above, 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 $-O-(CH_2)_1$-$_3-O-$

(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 as defined above 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}-alkoxy, C_{3-8}cycloalkyl, trifluoromethyl, trifluoromethoxy, $-NR^9R^{10}$ and $-O(C=O)N\ R^9R^{10}$,
  wherein R^9 and R^{10} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl as defined above, 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,

(c) C_{1-6}-alkyl, C_{2-6}-alkenylor 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, $-NR^{11}R^{12}$ 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 as defined above, 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,
- aryl as defined above, 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, $-NR^{13}R^{14}$ and $-O(C=O)NR^{13}R^{14}$,
  wherein R^{13} and R^{14} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}alkanoyl or aryl as defined above, or R^{13} and R^{14} 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 $-Q-(CH_2)_{1-3}-O-$

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

2. A compound according to claim 1, wherein R^3 and R^4 are both hydrogen.

3. A compound according to any one of the preceding claims 1 or 2, wherein R^1 is C_{1-6}-alkyl which may optionally be substituted with one or more substituents selected from halogen, C_{1-6}-alkoxy and hydroxy.

4. A compound according to claim 3, wherein R^1 is C_{1-6}alkyl.

5. A compound according to any of the preceding claims 1 to 3, wherein R_1 is di(C_{3-8}-cyclo-alkyl)-C_{1-6}-alkyl, wherein the cyclic moieties may optionally be substituted with one or more substituents selected from C_{1-6}-alkyl, halogen, trifluoromethyl and 2,2,2-trifluoroethyl.

6. A compound according to claim 5, wherein R^1 is dicyclopropylmethyl.

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

8. A compound according to claim 7, 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.

9. A compound according to claim 8, 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 $-CH_2S-$.

10. A compound according to claim 9, wherein X is $-CH_2-$.

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

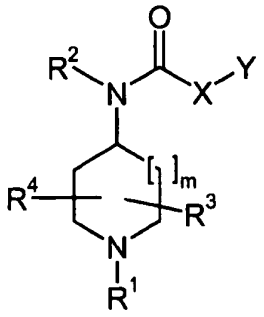
12. A compound according to claim 11, wherein Y is C_{1-6}-alkyl, cyclohexyl, phenyl, naphthyl, pyridyl, benzoxazolyl or benzothiophenyl, which may optionally be substituted as defined in claim 1.

13. A compound according to claim 12, wherein Y is phenyl or naphthyl which may optionally be substituted with one or more substituents selected from
trifluoromethyl, trifluoromethoxy, halogen, C_{1-6}-alkyl, -O(C=O)NR^5R^6 and C_{1-7}-alkanoyl, wherein R^5 and R^6 independently are hydrogen, C_{1-6}-alkyl, C_{3-4}-cydoalkyl, C_{1-7}-alkanoyl or aryl as defined above, 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,
aryl-C_{1-6}-alkoxy, aryloxy, aryl-C_{1-6}-alkyl and aryl as defined above, which may optionally be substituted with halogen or C_{1-4}-alkyl,
or wherein two substituents in adjacent positions form a radical -O-$(CH_2)_{1-3}$-O-:

14. A compound according to claim 13, wherein Y is phenyl or naphthyl which may optionally be substituted with one or more substituents selected from
trifluoromethyl, trifluoromethoxy, halogen, C_{1-6}-alkyl, -O(C=O)NR^5R^6 and C_{1-7}-alkanoyl, wherein R^5 and R^6 independently are hydrogen or C_{1-6}-alkyl,
phenyl-C_{1-6}-alkoxy, phenyl-C_{1-6}-alkyl, phenyloxy 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-.

15. A compound according to claim 14, wherein Y is phenyl, which is substituted with phenyl.

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



(I)

wherein
m ist 1,
R^1 is
C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl,

- which may optionally be substituted with one or more substituents selected from halogen, C_{1-6}-alkoxy and hydroxy,
  C_{3-4}-cycloalkyl, C_{5-8}-cycloalkenyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, di(C_{3-8}-cycloalkyl)-C_{1-6}-alkyl, C_{3-8}cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{5-8}-cycloalkenyl-C_{1-6}-alkyl, C_{5-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{5-8}-cycloal kenyl-C_{2-6}-alkynyl,
- wherein the cyclic moieties may optionally be substituted with one or more substituents selected from C_{1-6}-alkyl, halogen, trifluoromethyl and 2,2,2-trifluoroethyl,

R^2 is C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,
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^3 and R^4 are independently hydrogen, methyl or trifluoromethyl,
Y is

(a) aryl as defined above or heteroaryl as defined above, which may optionally be substituted with one or more

substituents selected from

• halogen, nitro, cyano, hydroxy, oxo, 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 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 as defined above, 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-,
• aryl as defined above, aryloxy, 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^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 as defined above, 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-

(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 as defined above 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}-alkoxy, C_{3-8}-cycloalkyl, trifluoromethyl, trifluoromethoxy, -NR^9R^{10} and -O(C=O)N R^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 as defined above, 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,

(c) C_{1-6}-alkyl, C_{2-6}-alkenyl or 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, -$NR^{11}R^{12}$ 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,
• aryl as defined above, 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, -$NR^{13}R^{14}$ and -O(C=O)$NR^{13}R^{14}$,
wherein R^{13} and R^{14} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}alkanoyl or aryl as defined above, or R^{13} and R^{14} 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 use as a medicament.

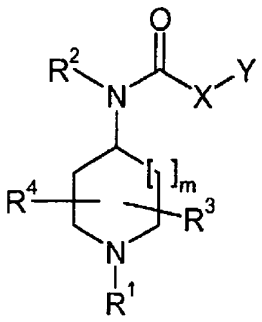
17. A compound according to claim 1 which is 3-[4-(4-fluorobenzyloxy)phenyl]-*N*-methyl-N (1-methylpiperidin-4-yl)acrylamide; 3-(4-chlorophenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)propionamide; 2-biphenyl-4-yl-*N*-cyclopropyl-*N*-(1-propylpiperidin-4-yl)-acetamide; *N*-methy)-*N*-(1-methylpiperidin-4-yl)-3-(4-trifluoromethylphenyl)propionamide; 2-biphenyl-4-yl-*N*-(1-isopropylpiperidin-4-yl)-*N*-methylacetamide; 2-(2-methoxyphenoxy)-*N*-methyt-*N*-(1-methylpiperidin-4-yl)acetamide; 3-(2-methoxyphenyl)-*N*-methyl-*N*-methylpiperidin-4-yl)acrylamide; 2-(2-chlorophenoxy)-*N*-

methyl-*N*-(1-methylpiperidin-4-yl)acetamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-3-naphthalen-1-ylacrylamide; 3-(5-bromo-2-ethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; 2-biphenyl-4-yl-*N*-methyl-*N*-(1methyl-piperidin-4-yl)acetamide; 3-(3-methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-acrylamide; 4-(4-methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)butyramide; 2-(2,4-di-chloro-5-methylphenylsulfanyl)-*N*-methyl-*N*-(1-methylpipeddin-4-yl)acetamide; 4-(3-fluoro-4-methoxyphenylr*N*-methyl-*N*-(1-methylpiperidin-4-yl)-4-oxobutyramide; 3-(4-dimethylaminophenyl)-*N*-methyl-*N*-(-methylpiperidin-4-yl)acrylamide; 2-(2-benzyloxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide; 3-(3,4-dimethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)propionamide; 4-(2, 4-dichlorophenoxy)-*N*-(1-methyl-*N*-(1-methylpiperidin-4-yl)butyramide; 3-(2-methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)propionamide; 4-(4-chloro-2-methylphenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)butyramide; 2-(4-fluorophenylsulfanyl)-*N*-methyl-*N*-(1-methylpiperldin-4-yl)acetamide; 3-(4-fluoro-3-trifluoromethylphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)2-(3-trifluoromethoxyphenyl) acetamide; 2-(4-fluorophenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide; 2-(2,3-dichlorophenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide 2-(4-methoxyphenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-2-(4-trifluoromethoxyphenyl)acetamide; 3-benzo[1,3]dioxol-5-yl-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-propionamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-2-(naphthalen-2-yloxy)acetamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl-3-(3,4,5-trimethoxyphenyl)propionamide; 3-(2,4-dimethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; 4-biphenyl-4-yl-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-4-oxobutyramide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-2-(naphthalen-2-ylsulfanyl)acetamide; 3-(3,5-dimethoxyphenyl)-*N*-methyl-*N*-(1-methyl-piperidin-4-yl)acrylamide; 3-(2,3-dimethoxyphenyl)-*N*-methyl-*N*-(1-methylplperidin-4-yl)acrylamide; 4-(3,4-dimethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)butyramide; 2-(2,3-dimethylphenoxy)-*N*-methyl-(1-methylpiperidin-4-yl)acetamide; 2-(8-chloronaphthalen-1-ylsulfanyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide;*N*-methyl-*N*-(1-methylpiperidin-4-yl)-2-(naphthalen-1-yl-oxy)acetamide; 2-(4-acetylphenoxy)-*N*-methylpiperidin4-yl)acetamide; 3-(3-methoxyphenyl}-*N*-methyl-*N*-(1-methylpiperidin-4-yl)propionamide; *N*-methyl-*N*-(1-methylpiperldin-4-yl)-3-pyridin-3-ylpropionamide; 3-(4-benzyloxy-3-methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; 3-(5-bromo-2-ethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; 4-(3,4-dihydro-2*H*-benzo[b][1,4]dioxepin-7-yl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-4-oxobutyramide; 3-(2-chloro-3,4-dimethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; 2-(2-chloro-4-fluorophenylsulfanyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-2-(naphthalen-1-ylmethylsulfanyl)acetamide; *N*-methyl-*N*-(1-methyl-piperidin-4-yl)-3-(2-oxo-benzooxazol-3-yl)propionamide; 5-cyclohexylpentanoic acid methyl-(1-methylpiperidin-4-yl)amide; 3-(4-methoxyphenyly)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)propionamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-2-(4-trifluoromethoxyphenoxy)acetamide; 2-(2-acetylphenoxy)-N-methyl-*N*-(1-methylpiperidin-4-yl)-acetamide; dimethylcarbamic acid 4-{2-[methyl-(1-methylpiperidin-4-yl)carbamoyl]-ethyl}-phenyl ester and 2-(5-chloro-3-methyl-benzo[b]thiophen-2-yl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide.

18. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 15, or 17 and one or more pharmaceutically acceptable carriers or excipients.

19. A pharmaceutical composition as defined in claim 18 in unit dosage form, comprising from 0.05 mg to 1000 mg, preferably from 0.1 mg to 500 mg, and especially preferred from 0.5 mg to 200 mg, of a compound of formula (I) as defined in claim 1.

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



(I')

wherein
m is 0 or 1,

R^1 is
C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl,

- which may optionally be substituted with one or more substituents selected from halogen, C_{1-6}-alkoxy and hydroxy,

C_{3-8}-cycloalkyl, C_{5-8}-cycloalkenyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, di(C_{3-8}-cycloalkyl)-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloal kyl-C_{2-6}-alkynyl, C_{5-8}-cycloalkenyl-C_{1-6}-alkyl, C_{5-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{5-8}-cydoalkenyl-C_{2-6}-alkynyl,

- wherein the cyclic moieties may optionally be substituted with one or more substituents selected from C_{1-6}-alkyl, halogen, trifluoromethyl and 2,2,2-trifluoroethyl,

R^2 is C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,
X is $-CH_2-(CH_2)_n-$, $-(CH_2)_n-CH=CH-(CH_2)_p-$, $-CH_2-(CH_2)_n-O-(CH_2)_p-$, $-CH_2(CH_2)_n-C(=O)-(CH_2)_p-$, $-CH_2(CH_2)_n-S-(CH_2)_p-$, $-CH_2(CH_2)_n(=O)-(CH_2)_p-$ or $-CH_2(CH_2)_nS(=O)_2(CH_2)_p-$,
n and p are independently 0,1, 2, 3 or 4,
R^3 and R^4 are independently hydrogen, methyl or trifluoromethyl,
Y is

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

- halogen, nitro, cyano, hydroxy, oxo, 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 as defined above, 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 $-O-(CH_2)_{1-3}-O-$,
- aryl as defined above, aryloxy, 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, $-NR^7R^8$ 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 as defined above, 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 $-Q-(CH_2)_{1-3}-O-$

(b) C_{3-8}cydoalkyl or C_{5-8}-cydoalkenyl, 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 as defined above 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}-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 as defined above, 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,

(c) C_{1-6}-alkyl, C_{2-6}-alkenyl or 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, $-NR^{11}R^{12}$ and $-O(C=O)NR^{11}R^2$,

wherein R^{11} and R^{12} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}cycloalkyl, C_{1-7}-alkanoyl or aryl as defined above, 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,

- aryl as defined above, 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^{13} R^{14} and -O(C=O)$NR^{13}R^{14}$, wherein R^{13} and R^{14} independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{1-7}-alkanoyl or aryl as defined above, or R^{13} and R^{14} 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 and/or prevention of disorders and diseases related-to the histamine H3 receptor.

21. Use of a compound as defined in claim 20 for the preparation of a pharmaceutical composition for the treatment and/or prevention of diseases and disorders in which an inhibition of the H3 histamine receptor has a beneficial effect.

22. Use of a compound as defined in claim 20 for the preparation of a pharmaceutical composition having histamine H3 antagonistic activity or histamine H3 inverse agonistic activity.

23. Use of a compound as defined in claim 20 for the preparation of a pharmaceutical composition for the reduction of weight.

24. Use of a compound as defined in claim 20 for the preparation of a pharmaceutical composition for the treatment and/or prevention of overweight or obesity.

25. Use of a compound as defined in claim 20 the preparation of a pharmaceutical composition for the suppression of appetite or for satiety induction.

26. Use of a compound as defined in claim 20 for the preparation of a pharmaceutical composition for the prevention and/or treatment of disorders and diseases related to overweight or obesity.

27. Use of a compound as defined in claim 20 for the preparation of a pharmaceutical composition for the prevention and/or treatment of eating disorders such as bulimia and binge eating.

28. Use of a compound as defined in claim 20 for the preparation of a pharmaceutical composition for the treatment and/or prevention of IGT.

29. Use of a compound as defined in claims 20 for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 2 diabetes.

30. Use of a compound as defined in claim 20 for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to Type 2 diabetes.

31. Use of a compound as defined in claim 20 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.

32. Use of a compound as defined in claim 20 for the preparation of a pharmaceutical composition for the treatment and/or prevention of diseases and disorders in which a stimulation of the H3 histamine receptor has a beneficial effect.

33. Use of a compound as defined in claim 20 for the preparation of a pharmaceutical composition having histamine H3 agonistic activity.

34. Use of a compound as defined in claim 20 for the preparation of a pharmaceutical composition for the treatment and/or prevention of allergic rhinitis, ulcer or anorexia.

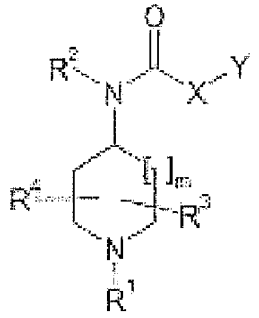
35. Use according to any one of the claims 22-34 wherein the compound is 3-[4-(4-fluorobenzyloxy)phenyl]-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; 3-(4-chlorophenyl)-N methyl-*N*-(1-methylpiperidin-4-yl)propionamide; 2-biphenyl-4-yl-*N*-cyclopropyl-*N*-(1-propylpiperidin-4-yl)acetamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-3-(4-trifluoromethylphenyl)-propionamide; 2-biphenyl-4-yl-*N*-(1-isopropylpiperidin-4-yl)-*N*-methylacetamide; 2-(2-methoxyphenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide; 3-(2-methoxyphenyl)-N methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; 2-(2-chlorophenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-3-naphthalen-1-ylacrylamide; 3-(5-bromo-2-ethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; 2-biphenyl-4-yl-N methyl-*N*-(1-methylpiperidin-4-yl)acetamide; 3-(3-methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; 4-(4-methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)butyramide; 2-(2,4-dichloro-5-methylphenylsulfanyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide; 4-(3-fluoro-4-methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-4-oxobutyramide; 3-(4-dimethylaminophenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; 2-(2-benzyloxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide; 3-(3,4-dimethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)propionamide; 4-(2,4-dichlorophenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)butyramide; 3-(2-methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)propionamide; 4-(4-chloro-2-methylphenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)butyramide; 2-(4-fluorophenylsulfanyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide; 3-(4-fluoro-3-trifluoromethylphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-2-(3-trifluoromethoxyphenyl)acetamide; 2-(4-fluorophenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide; 2-(2,3-dichlorophenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-acetamide; 2-(4-methoxyphenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-2-(4-trifluoromethoxyphenyl)acetamide; 3-benzo[1,3]dioxol-5-yl-*N*-methyl-*N*-(1-methylpiperidin-4-yl)propionamide; *N*-methyl-*N*-(1-methyl piperidin-4-yl)-2-(naphthalen-2-yloxy)acetamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-3-(3,4,5-trimethoxyphenyl)propionamide; 3-(2,4-dimethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acry)-amide; 4-biphenyl-4-yl-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-4-oxobutyramide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-2-(naphthalen-2-ylsulfanyl)acetamide; 3-(3,5-dimethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; 3-(2,3-dimethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; 4-(3,4-dimethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)butyramide; 2-(2,3-dimethylphenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide; 2-(8-chloronaphthalen-1-ylsulfanyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-2-(naphthalen-1-yloxy)acetamide; 2-(4-acetylphenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide; 3-(3-methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-propionamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-3-pyridin-3-ylpropionamide; 3-(4-benzyloxy-3-methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; 3-(5-bromo-2-ethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; 4-(3,4-dihydro-2*H*-benzo[b][1,4]dioxepin-7-yl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)-4-oxobutyramide; 3-(2-chloro-3,4-dimethoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acrylamide; 2-(2-chloro-4-fluorophenylsulfanyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-2-(naphthalen-1-ylmethylsulfanyl)acetamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-3-(2-oxo-benzooxazol-3-yl)propionamide; 5-cyclohexylpentanoic acid methyl-(1-methylpiperidin-4-yl)-amide; 3-(4-methoxyphenyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)propionamide; *N*-methyl-*N*-(1-methylpiperidin-4-yl)-2-(4-trifluoromethoxyphenoxy)acetamide; 2-(2-acetylphenoxy)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide; dimethylcarbamic acid 4-{2-[methyl-(1-methylpiperidin-4-yl)carbamoyl]-ethyl)-phenyl ester and 2-(5-chloro-3-methyl-benzo[b]thiophen-2-yl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)acetamide.

36. A combination of a compound as defined in any are of claims 1 to 15, or 17 and one or more further pharmaceutically active substances.

37. A compound as defined in any one of claims 1 to 15, or 17 for use in the treatment and/or prevention of a disorder or disease as defined in any one of claims 20, 21, 23 to 32, or 34.

Patentansprüche

1. Verbindung der allgemeinen Formel (I):



(I)

wobei
m gleich 1 ist,
R^1
C_{1-6}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl,

- das optional mit einem oder mehreren Substituenten substituiert sein kann, die aus Halogen, C_{1-6}-Alkoxy und Hydroxy ausgewählt sind,
  C_{3-8}-Cycloalkyl, C_{5-8}-Cycloalkenyl, C_{3-8}-Cycloalkyl-C_{1-6}-Alkyl, Di(C_{3-8}-Cycloalkyl)-C_{1-6}-Alkyl, C_{3-8}-Cycloal kyl-C_{2-6}-Alkenyl, C_{3-8}-Cycloalkyl-C_{2-6}-Alkinyl, C_{5-8}-Cycloalkenyl-C_{1-6}-Alkyl, C_{5-8}-Cycloalkenyl-C_{2-6}-Alkenyl, C_{5-8}-Cycloalkenyl-C_{2-6}-Alkinyl ist,
- wobei die cyclischen Gruppen optional mit einem oder mehreren Substituenten substituiert sein können, die aus C_{1-6}-Alkyl, Halogen, Trifluormethyl und 2,2,2- Trifluorethyl ausgewählt sind,

R^2 C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{3-8}-Cycloalkyl oder C_{3-8}-Cycloalkyl-C_{1-6}-Alkyl ist,
X $-CH_2-(CH_2)_n-$, $-(CH_2)_n-CH=CH-(CH_2)_p-$, $-CH_2-(CH_2)_n-O-(CH_2)_p-$, $-CH_2-(CH2)_n-C(=O)-(CH2)_p-$, $-CH_2-(CH_2)n-S-(CH_2)_p-$, $-CH_2-(CH_2)_n-S(=O)-(CH_2)_p-$ oder $-CH_2-(CH_2)_n-S(=O)_2-(CH_2)_p-$ ist,
n und p unabhängig 0, 1, 2, 3 oder 4 sind,
R^3 und R^4 unabhängig Wasserstoff, Methyl oder Trifluormethyl sind,
Y

(a) Aryl als carbocyclische aromatische Ringsysteme und die partiell hydrierten Derivate der carbocyclischen Systeme oder Heteroaryl als heterocyclische aromatische Ringsysteme, die ein oder mehrere Heteroatome enthalten, die ausgewählt sind aus Stickstoff, Sauerstoff und Schwefel, und die partiell hydrierten Derivate der heterocyclischen Systeme, die optional mit einem oder mehreren Substituenten substituiert sein können, die ausgewählt sind aus

- Halogen, Nitro, Cyano, Hydroxy, Oxo, C_{1-7}-Alkanoyl, C_{1-6}-Alkylthio, C_{1-6}-Alkylsulfonyl, C_{1-6}-Alkyl, C_{1-6}-Alkoxy, C_{3-8}-Cycloalkyl, Trifluormethyl, Trifluormethoxy und $-O(C=O)NR^5R^6$,
  wobei R^5 und R^6 unabhängig Wasserstoff, C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl, C_{1-7}-Alkanoyl oder Aryl sind, wie oben definiert, oder R^5 und R^6 zusammen mit dem Stickstoffatom, mit dem sie verknüpft sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring bilden,
- oder wobei zwei Substituenten in benachbarten Positionen ein Radikal $-O-(CH_2)_{1-3}-O-$ bilden,
- Aryl wie oben definiert, Aryloxy, Aryl-C_{1-6}-Alkyl und Aryl-C_{1-6}-Alkoxy, wobei die Ringgruppen optional mit einem oder mehreren Substituenten substituiert sein können, die ausgewählt sind aus

  - 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, Trifluormethyl, Trifluormethoxy, $-NR^7R^8$ und $-O(O=O)NR^7R^8$,
    wobei R^7 und R^3 unabhängig Wasserstoff, C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl, C_{1-7}-Alkanoyl oder Aryl sind, wie oben definiert, oder R^7 und R^8 zusammen mit dem Stickstoffatom, mit dem sie verknüpft sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring bilden,
  - oder wobei zwei Substituenten in benachbarten Positionen ein Radikal $-O-(CH_2)_{1-3}-O-$ bilden,

(b) C_{3-8}-Cycloalkyl oder C_{5-8}-Cycloalkenyl, die optional mit einem oder mehreren Substituenten substituiert

sein können, die ausgewählt sind aus

- C_{1-6}-Alkyl, C_{1-6}-Alkoxy, C_{1-6}-Alkylthio, Cyano, Trifluormethyl, Trifluormethoxy und Halogen,
- Aryl wie oben definiert und Aryloxy, wobei die Ringgruppen optional mit einem oder mehreren Substituenten substituiert sein können, die ausgewählt sind aus
  - Halogen, Nitro, Cyano, Hydroxy, C_{1-7}-Alkanoyl, C_{1-6}-Alkylthio, C_{1-6}-Alkylsulfonyl, C_{1-6}-Alkoxy, C_{3-8}-Cycloalkyl, Trifluormethyl, Trifluormethoxy, $-NR^9R^{10}$ und $-O(C=O)NR^9R^{10}$,
    wobei R^9 und R^{10} unabhängig Wasserstoff, C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl, C_{1-7}-Alkanoyl oder Aryl sind, wie oben definiert, oder R^9 und R^{10} zusammen mit dem Stickstoffatom, mit dem sie verknüpft sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring bilden,

(c) C_{1-6}-Alkyl, C_{2-6}-Alkenyl oder C_{2-6}-Alkinyl ist, das optional mit einem oder mehreren Substituenten substituiert sein kann, die ausgewählt sind aus

- Halogen, Nitro, Cyano, Hydroxy, C_{1-7}-Alkanoyl, C_{1-6}-Alkylthio, C_{1-6}-Alkylsulfonyl, C_{1-6}-Alkoxy, C_{3-8}-Cycloalkyl, Trifluormethyl, Trifluormethoxy, $-NR^{11}R^{12}$ und $-O(C=O)NR^{11}R^{12}$,
  wobei R^{11} und R^{12} unabhängig Wasserstoff, C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl, C_{1-7}-Alkanoyl oder Aryl sind, wie oben definiert, oder R^{11} und R^{12} zusammen mit dem Stickstoffatom, mit dem sie verknüpft sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring bilden,
- Aryl wie oben definiert, Aryl-C_{1-6}-Alkyl und Aryl-C_{1-6}-Alkoxy, wobei die Ringgruppen optional mit einem oder mehreren Substituenten substituiert sein können, die ausgewählt sind aus
  - 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, Trifluormethyl, Trifluormethoxy, $-NR^{13}R^{14}$ und $-O(C=O)NR^{13}R^{14}$,
    wobei R^{13} und R^{14} unabhängig Wasserstoff, C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl, C_{1-7}-Alkanoyl oder Aryl sind, wie oben definiert, oder R^{13} und R^{14} zusammen mit dem Stickstoffatom, mit dem sie verknüpft sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring bilden,
  - oder wobei zwei Substituenten in benachbarten Positionen ein Radikal $-O-(CH_2)_{1-3}-O-$ bilden,

sowie eine beliebige diastereomere oder enantiomere oder tautomere Form davon, darunter Mischungen davon oder ein pharmazeutisch akzeptables Salz davon.

2. Verbindung nach Anspruch 1, wobei R^3 und R^4 beide Wasserstoff sind.

3. Verbindung nach einem der vorhergehenden Ansprüche 1 oder 2, wobei R^1 C_{1-6}-Alkyl ist, das optional mit einem oder mehreren Substituenten substituiert sein kann, die aus Halogen, C_{1-6}-Alkoxy und Hydroxy ausgewählt sind.

4. Verbindung nach Anspruch 3, wobei R^1 C_{1-6}-Alkyl ist.

5. Verbindung nach einem der vorhergehenden Ansprüche 1 bis 3, wobei R^1 Di(C_{3-8}-Cycloalkyl)-C_{1-6}-Alkyl ist, wobei die cyclischen Gruppen optional mit einem oder mehreren Substituenten substituiert sein können, die ausgewählt sind aus C_{1-6}-Alkyl, Halogen, Trifluormethyl und 2,2,2-Trifluorethyl.

6. Verbindung nach Anspruch 5, wobei R^1 Dicyclopropylmethyl ist.

7. Verbindung nach einem der vorhergehenden Ansprüche, wobei X $-CH_2-(CH_2)_n-$, $-(CH_2)_n-CH=CH-(CH_2)p-$, $-CH_2-(CH_2)_n-O-(CH_2)_p-$, $-CH_2-(CH_2)_n-C(=O)-(CH_2)_p-$, $-CH_2-(CH_2)_n-S-(CH_2)_p-$ ist, wobei n und p wie in Anspruch 1 definiert sind.

8. Verbindung nach Anspruch 7, wobei X $-CH_2-(CH_2)_n-$, -CH=CH-, $-CH_2-(CH_2)_n-O-$, $-CH_2-(CH_2)_n-C(=O)-$, $CH_2-S-(CH_2)_p-$ ist, wobei n gleich 0, 1, 2 oder 3 ist und p gleich 0 oder 1 ist.

9. Verbindung nach Anspruch 8, wobei X $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, -CH=CH-, $-CH_2-O-$, $-(CH_2)_3-O-$, $-(CH_2)_2-C(=O)-$, $-CH_2-S-CH_2-$ oder $-CH_2-S-$ ist.

10. Verbindung nach Anspruch 9, wobei X $-CH_2-$ ist.

11. Verbindung nach einem der vorhergehenden Ansprüche, wobei Y C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl, Aryl ist, wie oben definiert, oder Heteroaryl ist, wie oben definiert, das optional substituiert sind kann, wie oben in Anspruch 1 definiert.

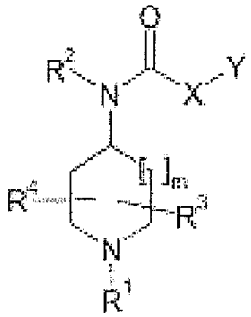
12. Verbindung nach Anspruch 11, wobei Y C_{1-6}-Alkyl, Cyclohexyl, Phenyl, Naphthyl, Pyridyl, Benzoxazolyl oder Benzothiophenyl ist, das optional substituiert sind kann, wie oben in Anspruch 1 definiert.

13. Verbindung nach Anspruch 12, wobei Y Phenyl oder Naphthyl ist, das optional mit einem oder mehreren Substituenten substituiert sein kann, die ausgewählt sind aus Trifluormethyl, Trifluormethoxy, Halogen, C_{1-6}-Alkyl, -O(C=O)NR^5R^6 und C_{1-7}Alkanoyl, wobei R^5 und R^6 unabhängig Wasserstoff, C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl, C_{1-7}-Alkanoyl oder Aryl sind, wie oben definiert, oder R^5 und R^6 zusammen mit dem Stickstoffatom, mit dem sie verknüpft sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring bilden,
Aryl-C_{1-6}-Alkoxy, Aryloxy, Aryl-C_{1-6}-Alkyl und Aryl, wie oben definiert, das optional mit Halogen oder C_{1-6}-Alkyl substituiert sein kann,
oder wobei zwei Substituenten in benachbarten Positionen ein Radikal - O-$(CH_2)_{1-3}$-O- bilden.

14. Verbindung nach Anspruch 13, wobei Y Phenyl oder Naphthyl ist, das optional mit einem oder mehreren Substituenten substituiert sein kann, die ausgewählt sind aus
Trifluormethyl, Trifluormethoxy, Halogen, C_{1-6}-Alkyl, -O(C=O)NR^5R^6 und C_{1-7}-Alkanoyl, wobei R^5 und R^6 unabhängig Wasserstoff oder C_{1-6}-Alkyl sind,
Phenyl-C_{1-6}-Alkoxy, Phenyl-C_{1-6}-Alkyl, Phenyloxy und Phenyl, die optional mit Halogen oder C_{1-6}-Alkyl substituiert sein können,
oder wobei zwei Substituenten in benachbarten Positionen ein Radikal - O-$(CH_2)_{1-3}$-O- bilden.

15. Verbindung nach Anspruch 14, wobei Y Phenyl ist, das mit Phenyl substituiert ist.

16. Verbindung der allgemeinen Formel (I):



(I)

wobei
m gleich 1 ist,
R^1
C_{1-6}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl,

- das optional mit einem oder mehreren Substituenten substituiert sein kann, die aus Halogen, C_{1-6}-Alkoxy und Hydroxy ausgewählt sind,
  C_{3-8}-Cycloalkyl, C_{5-8}-Cycloalkenyl, C_{3-8}-Cycloalkyl-C_{1-6}-Alkyl, Di(C_{3-8}-Cycloalkyl)-C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl-C_{2-6}-Alkenyl, C_{3-8}-Cycloalkyl-C_{2-6}-Alkinyl, C_{5-8}-Cycloalkenyl-C_{1-6}-Alkyl, C_{5-8}-Cycloalkenyl-C_{2-6}-Alkenyl, C_{5-8}-Cycloalkenyl-C_{2-6}-Alkinyl ist,
- wobei die cyclischen Gruppen optional mit einem oder mehreren Substituenten substituiert sein können, die aus C_{1-6}-Alkyl, Halogen, Trifluormethyl und 2,2,2-Trifluorethyl ausgewählt sind,

R^2 C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{3-8}-Cycloalkyl oder C_{3-8}-Cycloalkyl-C_{1-6}-Alkyl ist,
X -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)-$(CH_2)_p$- oder -CH_2-$(CH_2)_n$-$S(=C)_2$-$(CH_2)_p$- ist,
n und p unabhängig 0, 1, 2, 3 oder 4 sind,

R^3 und R^4 unabhängig Wasserstoff, Methyl oder Trifluormethyl sind,
Y

(a) Aryl, wie oben definiert, oder Heteroaryl, wie oben definiert, das optional mit einem oder mehreren Substituenten substituiert sein kann, die ausgewählt sind aus

- Halogen, Nitro, Cyano, Hydroxy, Oxo, C_{1-7}-Alkanoyl, C_{1-6}-Alkylthio, C_{1-6}-Alkylsulfonyl, C_{1-6}-Alkyl, C_{1-6}-Alkoxy, C_{3-8}-Cycloalkyl, Trifluormethyl, Trifluormethoxy, und -O(C=O)NR^5R^6,
  wobei R^5 und R^6 unabhängig Wasserstoff, C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl, C_{1-7}-Alkanoyl oder Aryl sind, wie oben definiert, oder R^5 und R^6 zusammen mit dem Stickstoffatom, mit dem sie verknüpft sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring bilden,
- oder wobei zwei Substituenten in benachbarten Positionen ein Radikal -O-$(CH_2)_{1-3}$-O- bilden,
- Aryl, wie oben definiert, Aryloxy, Aryl-C_{1-6}-Alkyl und Aryl-C_{1-6}-Alkoxy, wobei die Ringgruppen optional mit einem oder mehreren Substituenten substituiert sein können, die ausgewählt sind aus

  - 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, Trifluormethyl, Trifluormethoxy, -NR^7R^8 und -O(C=O)NR^7R^8,
    wobei R^7 und R^8 unabhängig Wasserstoff, C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl, C_{1-7}-Alkanoyl oder Aryl sind, wie oben definiert, oder R^7 und R^8 zusammen mit dem Stickstoffatom, mit dem sie verknüpft sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring bilden,
  - oder wobei zwei Substituenten in benachbarten Positionen ein Radikal -O-$(CH_2)_{1-3}$-O- bilden,

(b) C_{3-8}-Cycloatkyl oder C_{5-8}-Cycloalkenyl, das optional mit einem oder mehreren Substituenten substituiert sein kann, die ausgewählt sind aus

- C_{1-6}-Alkyl, C_{1-6}-Alkoxy, C_{1-6}-Alkylthio, Cyano, Trifluormethyl, Trifluormethoxy und Halogen,
- Aryl, wie oben definiert, und Aryloxy, wobei die Ringgruppen optional mit einem oder mehreren Substituenten substituiert sein können, die ausgewählt sind aus

  - Halogen, Nitro, Cyano, Hydroxy, C_{1-7}-Alkanoyl, C_{1-6}-Alkylthio, C_{1-6}-Alkylsulfonyl, C_{1-6}-Alkoxy, C_{3-8}-Cycloalkyl, Trifluormethyl, Trifluormethoxy, -NR^9R^{10} und -O(C=O)NR^9R^{10},
    wobei R^9 und R^{10} unabhängig Wasserstoff, C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl, C_{1-7}-Alkanoyl oder Aryl sind, wie oben definiert, oder R^9 und R^{10} zusammen mit dem Stickstoffatom, mit dem sie verknüpft sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring bilden,

(c) C_{1-6}-Alkyl, C_{2-6}-Alkenyl oder C_{2-6}-Alkinyl ist, das optional mit einem oder mehreren Substituenten substituiert sein kann, die ausgewählt sind aus

- Halogen, Nitro, Cyano, Hydroxy, C_{1-7}-Alkanoyl, C_{1-6}-Alkylthio, C_{1-6}-Alkylsulfonyl, C_{1-6}-Alkoxy, C_{3-8}-Cycloalkyl, Trifluormethyl, Trifluormethoxy, -$NR^{11}R^{12}$ und -O(C=O)$NR^{11}R^{12}$,
  wobei R^{11} und R^{12} unabhängig Wasserstoff, C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl, C_{1-7}-Alkanoyl oder Aryl sind oder R^{11} und R^{12} zusammen mit dem Stickstoffatom, mit dem sie verknüpft sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring bilden,
- Aryl, wie oben definiert, Aryl-C_{1-6}-Alkyl und Aryl-C_{1-6}-Alkoxy, wobei die Ringgruppen optional mit einem oder mehreren Substituenten substituiert sein können, die ausgewählt sind aus

  - 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, Trifluormethyl, Trifluormethoxy, -$NR^{13}R^{14}$ und -O(C=O)$NR^{13}R^{14}$,
    wobei R^{13} und R^{14} unabhängig Wasserstoff, C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl, C_{1-7}-Alkanoyl oder Aryl sind, wie oben definiert, oder R^{13} und R^{14} zusammen mit dem Stickstoffatom, mit dem sie verknüpft sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring bilden,
  - oder wobei zwei Substituenten in benachbarten Positionen ein Radikal -O-$(CH_2)_{1-3}$-O- bilden,

sowie eine beliebige diastereomere oder enantiomere oder tautomere Form davon, darunter Mischungen davon oder ein pharmazeutisch akzeptables Salz davon.

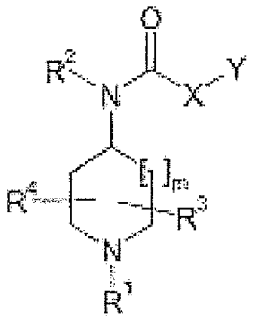
17. Verbindung nach Anspruch 1, die 3-[4-(4-Fluorbenzyloxy)phenyl]-N-methyl-N-(1-methylpiperidin-4-yl)acrylamid, 3-(4-Chlorphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)propionamid, 2-Biphenyl-4-yl-N-cyclopropyl-N-(1-propylpi-

peridin-4-yl)acetamid, N-Methyl-N-(1-methylpiperidin-4-yl)-3-(4-trifluormethylphenyl)propionamid, 2-Biphenyl-4-yl-N-(1-isopropylpiperidin-4-yl)-N-methylacetamid, 2-(2-Methoxyphenoxy)-N-methyl-N-(1 -methylpiperidin-4-yl)acetamid, 3-(2-Methoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl)acrylamid, 2-(2-Chlorphenoxy)-N-methyl-N-(1 -methylpiperidin-4-yl)acetamid, N-Methyl-N-(1-methylpiperidin-4-yl)-3-naphthalen-1ylacrylamid, 3-(5-Brom-2-ethoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl)acrylamid, 2-Biphenyl-4-yl-N-methyl-N-(1-methylpiperidin-4-yl)acetamid, 3-(3-Methoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl)acrylamid, 4-(4-Methoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl)butyramid, 2-(2,4-Dichlor-5-methylphenylsulfanyl)-N-methyl-N-(1 -methylpiperidin-4-yl)acetamid, 4-(3-Fluor-4-methoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl)-4-oxobutyramid, 3-(4-Dimethylaminophenyl)-N-methyl-N-(1-methylpiperidin-4-yl)acrylamid, 2-(2-Benzyloxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl) acetamid, 3-(3,4-Dimethoxyphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)propionamid, 4-(2,4-Dichlorphenoxy)-N-methyl-N-(1-methylpiperidin-4-yl)butyramid, 3-(2-Methoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl)propionamid, 4-(4-Chlor-2-methylphenoxy)-N-methyl-N-(1-methylpiperidin-4-yl)butyramid, 2-(4-Fluorphenylsulfanyl)-N-methyl-N-(1 -methylpiperidin-4-yl)acetamid, 3-(4-Fluor-3-trifluormethylphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl) acrylamid, N-Methyl-N-(1-methylpiperidin-4-yl)-2-(3-trifluormethoxyphenyl)acetamid, 2-(4-Fluorphenoxy)-N-methyl-N-(1-methylpiperidin-4-yl)acetamid, 2-(2,3-Dichlorphenoxy)-N-methyl-N-(1 -methylpiperidin-4-yl)acetamid, 2-(4-Methoxyphenoxy)-N-methyl-N-(1 -methylpiperidin-4-yl)acetamid, N-Methyl-N-(1-methylpiperidin-4-yl)-2-(4-trifluormethoxyphenyl)acetamid, 3-Benzo[1,3]dioxol-5-yl-N-methyl-N-(1 -methylpiperidin-4-yl)propionamid, N-Methyl-N-(1-methylpiperidin-4-yl)-2-(naphthalen-2-yloxy)acetamid, N-Methyl-N-(1-methylpiperidin-4-yl)-3-(3,4,5-trimethoxyphenyl)propionamid, 3-(2,4-Dimethoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl)acrylamid, 4-Biphenyl-4-yl-N-methyl-N-(1-methylpiperidin-4-yl)-4-oxobutyramid, N-Methyl-N-(1 -methylpiperidin-4-yl)-2-(naphthalen-2-yl-sulfanyl)acetamid, 3-(3,5-Dimethoxyphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)acrylamid, 3-(2,3-Dimethoxyphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)acrylamid, 4-(3,4-Dimethoxyphenyl)-N-methyl-N-(1-methylpiperidin-4-yl) butyramid, 2-(2,3-Dimethylphenoxy)-N-methyl-N-(1 -methylpiperidin-4-yl)acetamid, 2-(8-Chlomaphthalen-1-ylsulfanyl)-N-methyl-N-(1-methylpiperidin-4-yl)acetamid, N-Methyl-N-(1-methylpiperidin-4-yl)-2-(naphthalen-1-yloxy) acetamid, 2-(4-Acetylphenoxy)-N-methyl-N-(1-methylpiperidin-4-yl)acetamid, 3-(3-Methoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl)propionamid, N-Methyl-N-(1 -methylpiperidin-4-yl)-3-pyridin-3-ylpropionamid, 3-(4-Benzyloxy-3-methoxyphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)acrylamid, 3-(5-Brom-2-ethoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl)acrylamid, 4-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-N-methyl-N-(1 - methylpiperidin-4-yl)-4-oxobutyramid, 3-(2-Chlor-3,4-dimethoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl)acrylamid, 2-(2-Chlor-4-fluorphenylsulfanyl)-N-methyl-N-(1-methylpiperidin-4-yl)acetamid,N-Methyl-N-(1-methylpiperidin-4-yl)-2-(naphthalen-1-ylmethylsulfanyl)acetamid, N-Methyl-N-(1-methylpiperidin-4-yl)-3-(2-oxo-benzooxazol-3-yl)propionamid, 5-Cyclohexylpentansäuremethyl-(1 -methylpiperidin-4-yl)amid, 3-(4-Methoxyphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)propionamid, N-Methyl-N-(1-methylpiperidin-4-yl)-2-(4-trifluormethoxyphenoxy)acetamid, 2-(2-Acetylphenoxy)-N-methyl-N-(1-methylpiperidin-4-yl)acetamid, Dimethylcarbaminsäure-4-{2-[methyl-(1-methylpiperidin-4-yl) carbamoyl]-ethyl}-phenylester und 2-(5-Chlor-3-methyl-benzo[b]thiophen-2-yl)-N-methyl-N-(1-methylpiperidin-4-yl) acetamid ist.

18. Pharmazeutische Zusammensetzung, umfassend eine Verbindung mit der Formel (I) wie in einem der Ansprüche 1 bis 15 oder 17 definiert und einen oder mehrere pharmazeutisch akzeptable Träger oder Exzipienten.

19. Pharmazeutische Zusammensetzung wie in Anspruch 18 definiert, in Dosiseinheitenform, umfassend von 0,05 mg bis 1000 mg, bevorzugt von 0,1 mg bis 500 mg und besonders bevorzugt von 0,5 mg bis 200 mg einer Verbindung mit der Formel (I) wie in Anspruch 1 definiert.

20. Verwendung einer Verbindung der allgemeinen Formel (I'):



(I')

wobei
m gleich 0 oder 1 ist,
R^1
C_{1-6}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl,

- das optional mit einem oder mehreren Substituenten substituiert sein kann, die aus Halogen, C_{1-6}-Alkoxy und Hydroxy ausgewählt sind,
  C_{3-8}-Cycloalkyl, C_{5-8}-Cycloalkenyl, C_{3-8}-Cycloalkyl-C_{1-6}-Alkyl, Di(C_{3-8}-Cycloalkyl)-C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl-C_{2-6}-Alkenyl, C_{3-8}-Cycloalkyl-C_{2-6}-Alkinyl, C_{5-8}-Cycloalkenyl-C_{1-6}-Alkyl, C_{5-8}-Cycloalkenyl-C_{2-6}-Alkenyl, C_{5-8}-Cycloalkenyl-C_{2-6}-Alkinyl ist,
- wobei die cyclischen Gruppen optional mit einem oder mehreren Substituenten substituiert sein können, die aus C_{1-6}-Alkyl, Halogen, Trifluormethyl und 2,2,2-Trifluorethyl ausgewählt sind,

R^2 C_{1-6}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, C_{3-8}-Cycloalkyl oder C_{3-8}-Cycloalkyl-C_{1-6}-Alkyl ist,
X $-CH_2-(CH_2)_n-$, $-(CH_2)_n-CH=CH-(CH_2)_p-$, $-CH_2-(CH_2)_n-O-(CH_2)_p-$, $-CH_2-(CH_2)_n-C(=O)-(CH_2)_p-$, $-CH_2-(CH_2)_n-S-(CH_2)_p-$, $-CH_2-(CH_2)_n-S(=O)-(CH_2)_p-$ oder $-CH_2-(CH_2)_n-S(=O)_2-(CH_2)_p-$ ist,
n und p unabhängig 0, 1, 2, 3 oder 4 sind,
R^3 und R^4 unabhängig Wasserstoff, Methyl oder Trifluormethyl sind,
Y

(a) Aryl, wie oben definiert, oder Heteroaryl, wie oben definiert, das optional mit einem oder mehreren Substituenten substituiert sein kann, die ausgewählt sind aus

- Halogen, Nitro, Cyano, Hydroxy, Oxo, C_{1-7}-Alkanoyl, C_{1-6}-Alkylthio, C_{1-6}-Alkylsulfonyl, C_{1-6}-Alkyl, C_{1-6}-Alkoxy, C_{3-8}-Cycloalkyl, Trifluormethyl, Trifluormethoxy, $-NR^5R^6$ und $-O(C=O)NR^5R^6$;
  wobei R^5 und R^6 unabhängig Wasserstoff, C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl, C_{1-7}-Alkanoyl oder Aryl sind, wie oben definiert, oder R^5 und R^6 zusammen mit dem Stickstoffatom, mit dem sie verknüpft sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring bilden,
- oder wobei zwei Substituenten in benachbarten Positionen ein Radikal $-O-(CH_2)_{1-3}-O-$ bilden,
- Aryl, wie oben definiert, Aryloxy, Aryl-C_{1-6}-Alkyl und Aryl-C_{1-6}-Alkoxy, wobei die Ringgruppen optional mit einem oder mehreren Substituenten substituiert sein können, die ausgewählt sind aus

  ○ 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, Trifluormethyl, Trifluormethoxy, $-NR^7R^8$ und $-O(C=O)NR^7R^8$,
  wobei R^7 und R^8 unabhängig Wasserstoff, C_{16}-Alkyl, C_{3-8}-Cycloalkyl, C_{1-7}-Alkanoyl oder Aryl sind, wie oben definiert, oder R^7 und R^8 zusammen mit dem Stickstoffatom, mit dem sie verknüpft sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring bilden,
  ○ oder wobei zwei Substituenten in benachbarten Positionen ein Radikal $-O-(CH_2)_{1-3}-O-$ bilden,

(b) C_{3-8}-Cycloalkyl oder C_{5-8}-Cycloalkenyl, das optional mit einem oder mehreren Substituenten substituiert sein kann, die ausgewählt sind aus

- C_{1-6}-Alkyl, C_{1-6}-Alkoxy, C_{1-6}-Alkylthio, Cyano, Trifluormethyl, Trifluormethoxy und Halogen,

• Aryl, wie oben definiert, und Aryloxy, wobei die Ringgruppen optional mit einem oder mehreren Substituenten substituiert sein können, die ausgewählt sind aus

○ Halogen, Nitro, Cyano, Hydroxy, C_{1-7}-Alkanoyl, C_{1-6}-Alkylthio, C_{1-6}-Alkylsulfonyl, C_{1-6}-Alkoxy, C_{3-8}-Cycloalkyl, Trifluormethyl, Trifluormethoxy, $-NR^9R^{10}$ und $-O(C=O)NR^9R^{10}$,
wobei R^9 und R^{10} unabhängig Wasserstoff, C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl, C_{1-7}-Alkanoyl oder Aryl sind, wie oben definiert, oder R^9 und R^{10} zusammen mit dem Stickstoffatom, mit dem sie verknüpft sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring bilden,

(c) C_{1-6}-Alkyl, C_{2-6}-Alkenyl oder C_{2-6}-Alkinyl ist, das optional mit einem oder mehreren Substituenten substituiert sein kann, die ausgewählt sind aus

• Halogen, Nitro, Cyano, Hydroxy, C_{1-7}-Alkanoyl, C_{1-6}-Alkylthio, C_{1-6}-Alkylsulfonyl, C_{1-6}-Alkoxy, C_{3-8}-Cycloalkyl, Trifluormethyl, Trifluormethoxy, $-NR^{11}R^{12}$ und $-O(C=O)NR^{11}R^{12}$,
wobei R^{11} und R^{12} unabhängig Wasserstoff, C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl, C_{1-7}-Alkanoyl oder Aryl sind, wie oben definiert, oder R^{11} und R^{12} zusammen mit dem Stickstoffatom, mit dem sie verknüpft sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring bilden,
• Aryl, wie oben definiert, Aryl-C_{1-6}-Alkyl und Aryl-C_{1-6}-Alkoxy, wobei die Ringgruppen optional mit einem oder mehreren Substituenten substituiert sein können, die ausgewählt sind aus

○ 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, Trifluormethyl, Trifluormethoxy, $-NR^{13}R^{14}$ und $-O(C=O)NR^{13}R^{14}$,
wobei R^{13} und R^{14} unabhängig Wasserstoff, C_{1-6}-Alkyl, C_{3-8}-Cycloalkyl, C_{1-7}-Alkanoyl oder Aryl sind, wie oben definiert, oder R^{13} und R^{14} zusammen mit dem Stickstoffatom, mit dem sie verknüpft sind, einen 4- bis 7-gliedrigen, gesättigten oder ungesättigten Ring bilden,
○ oder wobei zwei Substituenten in benachbarten Positionen ein Radikal $-O-(CH_2)_{1-3}-O-$ bilden,

sowie eine beliebige diastereomere oder enantiomere oder tautomere Form davon, darunter Mischungen davon oder ein pharmazeutisch akzeptables Salz davon zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung und/oder Vorbeugung von Störungen und Erkrankungen, die mit dem Histamin-H3-Rezeptor in Zusammenhang stehen.

21. Verwendung einer Verbindung wie in Anspruch 20 definiert, zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung und/oder Vorbeugung von Erkrankungen und Störungen, bei denen eine Inhibierung des H3-Histamin-Rezeptors eine vorteilhafte Wirkung zeigt.

22. Verwendung einer Verbindung wie in Anspruch 20 definiert, zur Herstellung einer pharmazeutischen Zusammensetzung mit einer antagonistischen Aktivität auf Histamin H3 oder einer invers-agonistischen Aktivität auf Histamin H3.

23. Verwendung einer Verbindung wie in Anspruch 20 definiert, zur Herstellung einer pharmazeutischen Zusammensetzung zur Gewichtsreduzierung.

24. Verwendung einer Verbindung wie in Anspruch 20 definiert, zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung und/oder Vorbeugung von Übergewicht oder Adipositas.

25. Verwendung einer Verbindung wie in Anspruch 20 definiert, zur Herstellung einer pharmazeutischen Zusammensetzung zur Unterdrückung des Appetits oder zur Induktion des Sättigungsgefühls.

26. Verwendung einer Verbindung wie in Anspruch 20 definiert, zur Herstellung einer pharmazeutischen Zusammensetzung zur Vorbeugung und/oder Behandlung von Störungen und Erkrankungen, die mit Übergewicht oder Adipositas in Zusammenhang stehen.

27. Verwendung einer Verbindung wie in Anspruch 20 definiert, zur Herstellung einer pharmazeutischen Zusammensetzung zur Vorbeugung und/oder Behandlung von Essstörungen wie Bulimie und Fressanfällen (Binge Eating).

28. Verwendung einer Verbindung wie in Anspruch 20 definiert, zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung und/oder Vorbeugung von IGT (verminderter Glucosetoleranz).

29. Verwendung einer Verbindung wie in Anspruch 20 definiert, zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung und/oder Vorbeugung von Typ-2-Diabetes.

30. Verwendung einer Verbindung wie in Anspruch 20 definiert, zur Herstellung einer pharmazeutischen Zusammensetzung zur Verzögerung oder Vorbeugung des Fortschreitens von IGT zu Typ-2-Diabetes.

31. Verwendung einer Verbindung wie in Anspruch 20 definiert, zur Herstellung einer pharmazeutischen Zusammensetzung zur Verzögerung oder Vorbeugung des Fortschreitens von nicht insulinpflichtigem Typ-2-Diabetes zu insulinpflichtigem Typ-2-Diabetes.

32. Verwendung einer Verbindung wie in Anspruch 20 definiert, zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung und/oder Vorbeugung von Erkrankungen und Störungen, bei denen eine Stimulation des H3-Histamin-Rezeptors eine vorteilhafte Wirkung zeigt.

33. Verwendung einer Verbindung wie in Anspruch 20 definiert, zur Herstellung einer pharmazeutischen Zusammensetzung mit einer agonistischen Aktivität auf Histamin H3.

34. Verwendung einer Verbindung wie in Anspruch 20 definiert, zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung und/oder Vorbeugung von allergischer Rhinitis, Ulcus oder Anorexie.

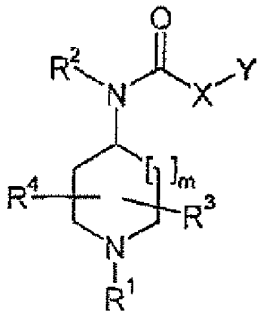
35. Verwendung nach einem der Ansprüche 22 bis 34, wobei die Verbindung 3-[4-(4-Fluorbenzyloxy)phenyl]-N-methyl-N-(1-methylpiperidin-4-yl)acrylamid, 3-(4-Chlorphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)propionamid, 2-Biphenyl-4-yl-N-cyclopropyl-N-(1-propylpiperidin-4-yl)-acetamid, N-Methyl-N-(1 -methylpiperidin-4-yl)-3-(4-trifluormethylphenyl)propionamid, 2-Biphenyl-4-yl-N-(1-isopropylpiperidin-4-yl)-N-methylacetamid, 2-(2-Methoxyphenoxy)-N-methyl-N-(1 -methylpiperidin-4-yl)acetamid, 3-(2-Methoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl) acrylamid, 2-(2-Chlorphenoxy)-N-methyl-N-(1 -methylpiperidin-4-yl)acetamid, N-Methyl-N-(1 -methylpiperidin-4-yl)-3-naphthalen-1 ylacrylamid, 3-(5-Brom-2-ethoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl)acrylamid, 2-Biphenyl-4-yl-N-methyl-N-(1 -methylpiperidin-4-yl)acetamid, 3-(3-Methoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl) acrylamid, 4-(4-Methoxyphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)butyramid, 2-(2,4-Dichlor-5-methylphenylsulfanyl)-N-methyl-N-(1-methylpiperidin-4-yl)acetamid, 4-(3-Fluor-4-methoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl)-4-oxobutyramid, 3-(4-Dimethylaminophenyl)-N-methyl-N-(1 -methylpiperidin-4-yl)acrylamid, 2-(2-Benzyloxyphenyl)-N-methyl-N-(1-methyl piperidin-4-yl)acetamid, 3-(3,4-Dimethoxyphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)propionamid, 4-(2,4-Dichlorphenoxy)-N-methyl-N-(1 -methylpiperidin-4-yl)butyramid, 3-(2-Methoxyphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)propionamid, 4-(4-Chlor-2-methylphenoxy)-N-methyl-N-(1 -methylpiperidin-4-yl) butyramid, 2-(4-Fluorphenylsulfanyl)-N-methyl-N-(1 -methylpiperidin-4-yl)acetamid, 3-(4-Fluor-3-trifluormethylphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)acrylamid, N-Methyl-N-(1-methylpiperidin-4-yl)-2-(3-trifluormethoxyphenyl)acetamid, 2-(4-Fluorphenoxy)-N-methyl-N-(1 -methylpiperidin-4-yl)acetamid, 2-(2,3-Dichlorphenoxy)-N-methyl-N-(1-methylpiperidin-4-yl)acetamid, 2-(4-Methoxyphenoxy)-N-methyl-N-(1-methylpiperidin-4-yl)acetamid, N-Methyl-N-(1-methylpiperidin-4-yl)-2-(4-trifluormethoxyphenyl)acetamid, 3-Benzo[1,3]dioxol-5-yl-N-methyl-N-(1 -methylpiperidin-4-yl)propionamid, N-Methyl-N-(1 -methylpiperidin-4-yl)-2-(naphthalen-2-yloxy)acetamid, N-Methyl-N-(1 -methylpiperidin-4-yl)-3-(3,4,5-trimethoxyphenyl)propionamid, 3-(2,4-Dimethoxyphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)acrylamid, 4-Biphenyl-4-yl-N-methyl-N-(1-methylpiperidin-4-yl)-4-oxobutyramid, N-Methyl-N-(1 -methylpiperidin-4-yl)-2-(naphthalen-2-ylsulfanyl)acetamid, 3-(3,5-Dimethoxyphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)acrylamid, 3-(2,3-Dimethoxyphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)acrylamid, 4-(3,4-Dimethoxyphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)butyramid, 2-(2,3-Dimethyfphenoxy)-N-methyl-N-(1-methylpiperidin-4-yl) acetamid, 2-(8-Chlornaphthalen-1-ylsulfanyl)-N-methyl-N-(1-methylpiperidin-4-yl)acetamid, N-Methyl-N-(1 -methylpiperidin-4-yl)-2-(naphthalen-1 -yloxy)acetamid, 2-(4-Acetylphenoxy)-N-methyl-N-(1 -methylpiperidin-4-yl)acetamid, 3-(3-Methoxyphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)propionamid, N-Methyl-N-(1 -methylpiperidin-4-yl)-3-pyridin-3-ylpropionamid, 3-(4-Benzyloxy-3-methoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl)acrylamid, 3-(5-Brom-2-ethoxyphenyl)-N-methyl-N-(1-methylpiperidin-4-yl)acrylamid, 4-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-N-methyl-N-(1-methylpiperidin-4-yl)-4-oxobutyramid, 3-(2-Chlor-3,4-dimethoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl)acrylamid, 2-(2-Chlor-4-fluorphenylsulfanyl)-N-methyl-N-(1-methylpiperidin-4-yl)acetamid, N-Methyl-N-(1-methylpiperidin-4-yl)-2-(naphthalen-1-ylmethylsulfanyl)acetamid, N-Methyl-N-(1-methylpiperidin-4-yl)-3-(2-oxo-benzooxazol-3-yl)propionamid, 5-Cyclohexylpentansäuremethyl-(1-methylpiperidin-4-yl)amid, 3-(4-Methoxyphenyl)-N-methyl-N-(1 -methylpiperidin-4-yl)propionamid, N-Methyl-N-(1-methylpiperidin-4-yl)-2-(4-trifluormethoxyphenoxy)acetamid, 2-(2-Acetylphenoxy)-N-methyl-N-(1 -methylpiperidin-4-yl)acetamid, Dimethylcarbaminsäure-4-{2-[methyl-(1-methylpiperidin-4-yl)carbamoyl]-ethyl}-phenylester und 2-(5-Chlor-3-methyl-benzo[b] thiophen-2-yl)-N-methyl-N-(1-methylpiperidin-4-yl)acetamid ist.

36. Kombination einer Verbindung wie in einem der Ansprüche 1 bis 15 oder 17 definiert und einer oder mehrerer weiterer pharmazeutisch wirksamer Substanzen.

37. Verbindung wie in einem der Ansprüche 1 bis 15 oder 17 definiert, zur Behandlung und/oder Vorbeugung einer Störung oder Erkrankung wie in einem der Ansprüche 20, 21, 23 bis 32 oder 34 definiert.

Revendications

1. Composé de formule générale (I) :



(I)

dans laquelle
m vaut 1,
R^1 est
un groupe alkyle en $C_{1 à 6}$, alcényle en $C_{2 à 6}$, alcynyle en $C_{2 à 6}$,

- qui peut être facultativement substitué par un ou plusieurs substituants choisis parmi un atome d'halogène, un groupe alcoxy en C_1 à $_6$ et un groupe hydroxy,
  un groupe cycloalkyle en $C_{3 à 8}$, cycloalcényle en $C_{5 à 8}$, cycloalkyl en $C_{3 à 8}$-alkyle en $C_{1 à 6}$, di(cycloalkyl en $C_{3 à 8}$)-alkyle en $C_{1 à 6}$, cycloalkyl en $C_{3 à 8}$-alcényle en $C_{2 à 6}$, cycloalkyl en $C_{3 à 8}$-alcynyle en $C_{2 à 6}$, cycloalcényl en $C_{5 à 8}$-alkyle en $C_{1 à 6}$, cycloalcényl en $C_{5 à 8}$-alcényle en $C_{2 à 6}$, cycloalcényl en $C_{5 à 8}$-alcynyle en $C_{2 à 6}$,
- où les fragments cycliques peuvent facultativement être substitués par un ou plusieurs substituants choisis parmi un groupe alkyle en $C_{1 à 6}$, un atome d'halogène, un groupe trifluorométhyle et un groupe 2,2,2-trifluoroéthyle,

R^2 est un groupe alcényle en $C_{2 à 6}$, alcynyle en $C_{2 à 6}$, cycloalkyle en $C_{3 à 8}$ ou cycloalkyl en $C_{3 à 8}$-alkyle en $C_{1 à 6}$,
X est $-CH_2-(CH_2)_n-$, $-(CH_2)_n-CH=CH-(CH_2)_p-$, $-CH_2-(CH_2)n-O-(CH_2)_p-$, $-CH_2-(CH_2)_n-C(=O)-(CH_2)_p-$, $-CH_2-(CH_2)_n-S-(CH_2)_p-$, $-CH_2-(CH_2)_n-S(=O)-(CH_2)_p-$ ou $-CH_2-(CH_2)_n-S(=O)_2-(CH_2)_p-$,
n et p valent indépendamment 0, 1, 2, 3 ou 4,
R^3 et R^4 sont indépendamment un atome d'hydrogène, un groupe méthyle ou trifluorométhyle,
Y est

(a) un groupe aryle étant des systèmes de cycle aromatique carbocycliques et des dérivés partiellement hydrogénés desdits systèmes carbocycliques ou un groupe hétéroaryle étant des systèmes de cycle aromatique hétérocycliques contenant un ou plusieurs hétéroatomes choisis parmi l'azote, l'oxygène et le soufre et des dérivés partiellement hydrogénés desdits systèmes hétérocycliques, qui peuvent facultativement être substitués par un ou plusieurs substituants choisi parmi

- un atome d'halogène, un groupe nitro, cyano, hydroxy, oxo, alcanoyle en $C_{1 à 7}$, alkylthio en $C_{1 à 6}$, alkylsulfonyle en $C_{1 à 6}$, alkyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, trifluorométhyle, trifluorométhoxy et $-O(C=O)NR^5R^6$,
  où R^5 et R^6 sont indépendamment un atome d'hydrogène, un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, alcanoyle en $C_{1 à 7}$ ou aryle tel que défini ci-dessus, ou R^5 et R^6 conjointement avec l'atome d'azote auquel ils sont attachés forment un cycle saturé ou insaturé à 4 à 7 chaînons,
- ou bien où deux substituants dans des positions adjacentes forment un radical $-O-(CH_2)_{1 à 3}-O-$,

• un groupe aryle tel que défini ci-dessus, aryloxy, aryl-alkyle en $C_{1 à 6}$ et aryl-alcoxy en $C_{1 à 6}$, où les fragments de cycle peuvent facultativement être substitués par un ou plusieurs substituants choisis parmi

○ un atome d'halogène, un groupe nitro, cyano, hydroxy, alcanoyle en $C_{1 à 7}$, alkylthio en $C_{1 à 6}$, alkylsulfonyle en $C_{1 à 6}$, alkyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, trifluorométhyle, trifluorométhoxy, $-NR^7R^8$ et $-O(C=O)NR^7R^8$,
où R^7 et R^8 sont indépendamment un atome d'hydrogène, un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, alcanoyle en $C_{1 à 7}$ ou aryle tel que défini ci-dessus, ou R^7 et R^8 conjointement avec l'atome d'azote auquel ils sont attachés forment un cycle saturé ou insaturé à 4 à 7 chaînons,
○ ou bien où deux substituants dans des positions adjacentes forment un radical $-O-(CH_2)_{1 à 3}-O-$,

(b) un groupe cycloalkyle en $C_{3 à 8}$ ou cycloalcényle en $C_{5 à 8}$, qui peut facultativement être substitué par un ou plusieurs substituants choisis parmi

• un groupe alkyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, alkylthio en $C_{1 à 6}$, cyano, trifluorométhyle, trifluorométhoxy et un atome d'halogène,
• un groupe aryle tel que défini ci-dessus et un groupe aryloxy, où les fragments de cycle peuvent facultativement être substitués par un ou plusieurs substituants choisis parmi

○ un atome d'halogène, un groupe nitro, cyano, hydroxy, alcanoyle en $C_{1 à 7}$, alkylthio en $C_{1 à 6}$, alkylsulfonyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, trifluorométhyle, trifluorométhoxy, $-NR^9R^{10}$ et $-O(C=O)NR^9R^{10}$,
où R9 et R10 sont indépendamment un atome d'hydrogène, un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, alcanoyle en $C_{1 à 7}$ ou aryle tel que défini ci-dessus, ou R^9 et R^{10} conjointement avec l'atome d'azote auquel ils sont attachés forment un cycle saturé ou insaturé à 4 à 7 chaînons,

(c) un groupe alkyle en $C_{1 à 6}$, alcényle en $C_{2 à 6}$ ou alcynyle en $C_{2 à 6}$, qui peut facultativement être substitué par un ou plusieurs substituants choisis parmi

• un atome d'halogène, un groupe nitro, cyano, hydroxy, alcanoyle en $C_{1 à 7}$, alkylthio en $C_{1 à 6}$, alkylsulfonyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, trifluorométhyle, trifluorométhoxy, $-NR^{11}R^{12}$ et $-O(C=O)NR^{11}R^{12}$,
où R^{11} et R^{12} sont indépendamment un atome d'hydrogène, un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, alcanoyle en $C_{1 à 7}$ ou aryle tel que défini ci-dessus, ou R^{11} et R^{12} conjointement avec l'atome d'azote auquel ils sont attachés forment un cycle saturé ou insaturé à 4 à 7 chaînons,
• un groupe aryle tel que défini ci-dessus, aryl-alkyle en $C_{1 à 6}$ et aryl-alcoxy en $C_{1 à 6}$, où les fragments de cycle peuvent facultativement être substitués par un ou plusieurs substituants choisis parmi

○ un atome d'halogène, un groupe nitro, cyano, hydroxy, alcanoyle en $C_{1 à 7}$, alkylthio en $C_{1 à 6}$, alkylsulfonyle en $C_{1 à 6}$, alkyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, trifluorométhyle, trifluorométhoxy, $-NR^{13}R^{14}$ et $-O(C=O)NR^{13}R^{14}$,
où R^{13} et R^{14} sont indépendamment un atome d'hydrogène, un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, alcanoyle en $C_{1 à 7}$ ou aryle tel que défini ci-dessus, ou R^{13} et R^{14} conjointement avec l'atome d'azote auquel ils sont attachés forment un cycle saturé ou insaturé à 4 à 7 chaînons,
O ou bien où deux substituants dans des positions adjacentes forment un radical $-O-(CH_2)_{1 à 3}-O-$,

ainsi que tout diastéréoisomère ou énantiomère ou forme tautomère de celui-ci comprenant des mélanges de ceux-ci ou un de leurs sels pharmaceutiquement acceptables.

2. Composé selon la revendication 1, dans lequel R^3 et R^4 sont tous deux un atome d'hydrogène.

3. Composé selon l'une quelconque des revendications précédentes 1 et 2, dans lequel R^1 est un groupe alkyle en $C_{1 à 6}$ qui peut être facultativement substitué par un ou plusieurs substituants choisis parmi un atome d'halogène, un groupe alcoxy en $C_{1 à 6}$ et un groupe hydroxy.

4. Composé selon la revendication 3, dans lequel R^1 est un groupe alkyle en $C_{1 à 6}$.

5. Composé selon l'une quelconque des revendications précédentes 1 à 3, dans lequel R^1 est un groupe di(cycloalkyl

en $C_{3 à 8}$)-alkyle en $C_{1 à 6}$, dans lequel les fragments cycliques peuvent facultativement être substitués par un ou plusieurs substituants choisis parmi un groupe alkyle en $C_{1 à 6}$, un atome d'halogène, un groupe trifluorométhyle et un groupe 2,2,2-trifluoroéthyle.

6. Composé selon la revendication 5, dans lequel R^1 est un groupe dicyclopropylméthyle.

7. Composé selon l'une quelconque des revendications précédentes, dans lequel X est $-CH_2-(CH_2)_n-$, $-(CH_2)_n-CH=CH-(CH_2)_p-$, $-CH_2-(CH_2)_n-O-(CH_2)_p-$, $-CH_2-(CH_2)_n,-C(=O)-(CH_2)_p-$, $-CH_2-(CH_2)_n-S-(CH_2)_p-$, où n et p sont tels que définis dans la revendication 1.

8. Composé selon la revendication 7, dans lequel X est $-CH_2-(CH_2)_n-$, $-CH=CH-$, $-CH_2-(CH_2)_n-O-$, $-CH_2-(CH_2)_n-C(=O)-$, $-CH_2-S-(CH_2)_p-$, où n vaut 0, 1, 2 ou 3, et p vaut 0 ou 1.

9. Composé selon la revendication 8, dans lequel X est $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH=CH-$, $-CH_2O-$, $-(CH_2)_3-O-$, $-(CH_2)_2-C(=O)-$, $-CH_2-S-CH_2-$ ou $-CH_2-S-$.

10. Composé selon la revendication 9, dans lequel X est $-CH_2-$.

11. Composé selon l'une quelconque des revendications précédentes, dans lequel Y est un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, aryle tel que défini ci-dessus ou hétéroaryle tel que défini ci-dessus, qui peut facultativement être substitué comme défini dans la revendication 1.

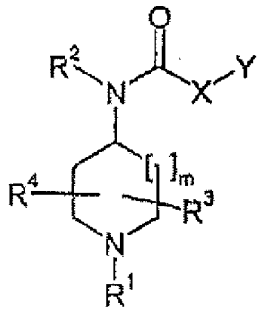
12. Composé selon la revendication 11, dans lequel Y est un groupe alkyle en $C_{1 à 6}$, cyclohexyle, phényle, naphtyle, pyridyle, benzoxazolyle ou benzothiophényle, qui peut facultativement être substitué comme défini dans la revendication 1.

13. Composé selon la revendication 12, dans lequel Y est un groupe phényle ou naphtyle qui peut facultativement être substitué par un ou plusieurs substituants choisis parmi
un groupe trifluorométhyle, trifluorométhoxy, un atome d'halogène, un groupe alkyle en $C_{1 à 6}$, $-O(C=O)NR^5R^6$ et alcanoyle en $C_{1 à 7}$, où R^5 et R^6 sont indépendamment un atome d'hydrogène, un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, alcanoyle en $C_{1 à 7}$ ou aryle tel que défini ci-dessus, ou R^5 et R^6 conjointement avec l'atome d'azote auquel ils sont attachés forment un cycle saturé ou insaturé à 4 à 7 chaînons,
un groupe aryl-alcoxy en $C_{1 à 6}$, aryloxy, aryl-alkyle en $C_{1 à 6}$ et aryle tel que défini ci-dessus, qui peuvent facultativement être substitués par un atome d'halogène ou un groupe alkyle en $C_{1 à 6}$,
ou bien où deux substituants dans des positions adjacentes forment un radical $-O-(CH_2)_{1 à 3}-O-$.

14. Composé selon la revendication 13, dans lequel Y est un groupe phényle ou naphtyle qui peut facultativement être substitué par un ou plusieurs substituants choisis parmi
un groupe trifluorométhyle, trifluorométhoxy, un atome d'halogène, un groupe alkyle en $C_{1 à 6}$, $-O(C=O)NR^5R^6$ et alcanoyle en $C_{1 à 7}$, où R^5 et R^6 sont indépendamment un atome d'hydrogène ou un groupe alkyle en $C_{1 à 6}$,
un groupe phényl-alcoxy en $C_{1 à 6}$, phényl-alkyle en $C_{1 à 6}$, phényloxy et phényle, qui peuvent être facultativement substitués par un atome d'halogène ou un groupe alkyle en $C_{1 à 6}$,
ou bien où deux substituants dans des positions adjacentes forment un radical $-O-(CH_2)_{1 à 3}-O-$.

15. Composé selon la revendication 14, dans lequel Y est un groupe phényle, qui est substitué par un groupe phényle.

16. Composé de formule générale (I) :



(I)

dans laquelle
m vaut 1,
R^1 est
un groupe alkyle en $C_{1 à 6}$, alcényle en $C_{2 à 6}$, alcynyle en $C_{2 à 6}$,

- qui peut être facultativement substitué par un ou plusieurs substituants choisis parmi un atome d'halogène un groupe alcoxy en $C_{1 à 6}$ et un groupe hydroxy,
  un groupe cycloalkyle en $C_{3 à 8}$, cycloalcényle en $C_{5 à 8}$, cycloalkyl en $C_{3 à 8}$-alkyle en $C_{1 à 6}$, di(cycloalkyl en $C_{3 à 8}$)-alkyle en $C_{1 à 6}$, cycloalkyl en $C_{3 à 8}$-alcényle en $C_{2 à 6}$, cycloalkyl en $C_{3 à 8}$-alcynyle en $C_{2 à 6}$, cycloalcényl en $C_{5 à 8}$-alkyle en $C_{1 à 6}$, cycloalcényl en $C_{5 à 8}$-alcényle en $C_{2 à 6}$, cycloalcényl en $C_{5 à 8}$-alcynyle en $C_{2 à 6}$,
- où les fragments cycliques peuvent facultativement être substitués par un ou plusieurs substituants choisis parmi un groupe alkyle en $C_{1 à 6}$, un atome d'halogène, un groupe trifluorométhyle et un groupe 2,2,2-trifluoroéthyle,

R^2 est un groupe alcényle en $C_{2 à 6}$, alcynyle en $C_{2 à 6}$, cycloalkyle en $C_{3 à 8}$ ou cycloalkyl en $C_{3 à 8}$-alkyle en $C_{1 à 6}$,
X est $-CH_2-(CH_2)_n-$, $-(CH_2)_n-CH=CH-(CH_2)_p-$, $-CH_2-(CH_2)_n-O-(CH_2)_p-$, $-CH_2-(CH_2)n-C(=O)-(CH_2)_p-$, $-CH_2-(CH_2)_n-S-(CH_2)_p-$, $-CH_2-(CH_2)_n-S(=O)-(CH_2)p-$ ou $-CH_2-(CH_2)_n-S(=O)_2-(CH_2)_p-$,
n et p valent indépendamment 0, 1, 2, 3 ou 4,
R^3 et R^4 sont indépendamment un atome d'hydrogène, un groupe méthyle ou trifluorométhyle,
Y est

(a) un groupe aryle tel que défini ci-dessus ou hétéroaryle tel que défini ci-dessus, qui peut facultativement être substitué par un ou plusieurs substituants choisis parmi

- un atome d'halogène, un groupe nitro, cyano, hydroxy, oxo, alcanoyle en $C_{1 à 7}$, alkylthio en $C_{1 à 6}$, alkylsulfonyle en $C_{1 à 6}$, alkyle en $C_{1 à 6}$, alcoxy en $C_{1 à 8}$, cycloalkyle en $C_{3 à 8}$, trifluorométhyle, trifluorométhoxy et $-O(C=O)NR^5R^6$,
  où R^5 et R^6 sont indépendamment un atome d'hydrogène, un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, alcanoyle en $C_{1 à 7}$ ou aryle tel que défini ci-dessus, ou R^5 et R^6 conjointement avec l'atome d'azote auquel ils sont attachés forment un cycle saturé ou insaturé à 4 à 7 chaînons,
- ou bien où deux substituants dans des positions adjacentes forment un radical $-O-(CH_2)_{1 à 3}-O-$,
- un groupe aryle tel que défini ci-dessus, aryloxy, aryl-alkyle en $C_{1 à 6}$ et aryl-alcoxy en $C_{1 à 6}$, où les fragments de cycle peuvent facultativement être substitués par un ou plusieurs substituants choisis parmi

  ○ un atome d'halogène, un groupe nitro, cyano, hydroxy, alcanoyle en $C_{1 à 7}$, alkylthio en $C_{1 à 6}$, alkylsulfonyle en $C_{1 à 6}$, alkyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, trifluorométhyle, trifluorométhoxy, $-NR^7R^8$ et $-O(C=O)NR^7R^8$,
  où R^7 et R^8 sont indépendamment un atome d'hydrogène, un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, alcanoyle en $C_{1 à 7}$ ou aryle tel que défini ci-dessus, ou R^7 et R^8 conjointement avec l'atome d'azote auquel ils sont attachés forment un cycle saturé ou insaturé à 4 à 7 chaînons,
  ○ ou bien où deux substituants dans des positions adjacentes forment un radical $-O-(CH_2)_{1 à 3}-O-$,

(b) un groupe cycloalkyle en $C_{3 à 8}$ ou cycloalcényle en $C_{5 à 8}$, qui peut facultativement être substitué par un ou plusieurs substituants choisis parmi

• un groupe alkyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, alkylthio en $C_{1 à 6}$, cyano, trifluorométhyle, trifluorométhoxy et un atome d'halogène,
• un groupe aryle tel que défini ci-dessus et aryloxy, où les fragments de cycle peuvent facultativement être substitués par un ou plusieurs substituants choisis parmi

○ un atome d'halogène, un groupe nitro, cyano, hydroxy, alcanoyle en $C_{1 à 7}$, alkylthio en $C_{1 à 6}$, alkylsulfonyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, trifluorométhyle, trifluorométhoxy,, $-NR^9R^{10}$ et $-O(C=O)NR^9R^{10}$,
où R^9 et R^{10} sont indépendamment un atome d'hydrogène, un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, alcanoyle en $C_{1 à 7}$ ou aryle tel que défini ci-dessus, ou R^9 et R^{10} conjointement avec l'atome d'azote auquel ils sont attachés forment un cycle saturé ou insaturé à 4 à 7 chaînons,

(c) un groupe alkyle en $C_{1 à 6}$, alcényle en $C_{2 à 6}$ ou alcynyle en $C_{2 à 6}$, qui peut facultativement être substitué par un ou plusieurs substituants choisis parmi

• un atome d'halogène, un groupe nitro, cyano, hydroxy, alcanoyle en $C_{1 à 7}$, alkylthio en $C_{1 à 6}$, alkylsulfonyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, trifluorométhyle, trifluorométhoxy, $-NR^{11}R^{12}$ et $-O(C=O)NR^{11}R^{12}$,
où R^{11} et R^{12} sont indépendamment un atome d'hydrogène, un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, alcanoyle en $C_{1 à 7}$ ou aryle, ou R^{11} et R^{12} conjointement avec l'atome d'azote auquel ils sont attachés forment un cycle saturé ou insaturé à 4 à 7 chaînons,
• un groupe aryle tel que défini ci-dessus, aryl-alkyle en $C_{1 à 6}$ et aryl-alcoxy en $C_{1 à 6}$, où les fragments de cycle peuvent facultativement être substitués par un ou plusieurs substituants choisis parmi

○ un atome d'halogène, un groupe nitro, cyano, hydroxy, alcanoyle en $C_{1 à 7}$, alkylthio en $C_{1 à 6}$, alkylsulfonyle en $C_{1 à 6}$, alkyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, trifluorométhyle, trifluorométhoxy, $-NR^{13}R^{14}$ et $-O(C=O)NR^{13}R^{14}$,
où R^{13} et R^{14} sont indépendamment un atome d'hydrogène, un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, alcanoyle en $C_{1 à 7}$ ou aryle tel que défini ci-dessus, ou R^{13} et R^{14} conjointement avec l'atome d'azote auquel ils sont attachés forment un cycle saturé ou insaturé à 4 à 7 chaînons,
○ ou bien où deux substituants dans des positions adjacentes forment un radical $-O-(CH_2)_{1 à 3}-O-$,

ainsi que tout diastéréoisomère ou énantiomère ou forme tautomère de ceux-ci comprenant des mélanges de ceux-ci ou un de leurs sels pharmaceutiquement acceptables pour une utilisation comme médicament.

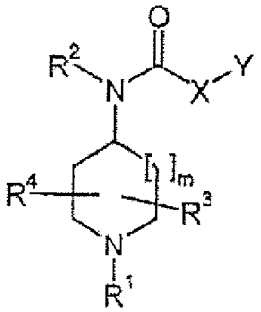
17. Composé selon la revendication 1, qui est le 3-[4-(4-fluorobenzyloxy)phényl]-*N*- méthyl-*N*-(1-méthylpipéridin-4-yl) acrylamide ; le 3-(4-chlorophényl)-*N*- méthyl-*N*-(1-méthylpipéridin-4-yl)propionamide ; le 2-biphényl-4-yl-*N*- cyclopropyl-*N*-(1-propylpipéfidin-4-yl)-acétamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-3-(4-trifluorométhylphényl) propionamide ; le 2-biphényl-4-yl-*N*-(1-zsopropylpipéridin-4-yl)-*N*-méthylacétamide ; le 2-(2-méthoxyphénoxy)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le 3-(2-méthoxyphényl)-*N*- méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le 2-(2-chlorophénoxy)-*N*- méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-3-naphtalén-1-ylacrylamide ; le 3-(5-bromo-2-éthoxyphényl)-*N*- méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le 2-biphényl-4-yl-*N*- méthyl-*N*-(1-méthylpipéridîn-4-yl)acétamide ; le 3-(3-méthoxyphényl)-*N*- méthyl-*N*-(1-méthylpipéridin-4-yl)-acrylamide ; le 4-(4-méthoxyphényl)-*N*- méthyl-*N*-(1-méthylpipéridin-4-yl)butyramide ; le 2-(2,4-dichloro-5-méthylphénylsulfanyl)-*N*- méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le 4-(3-fluoro-4-méthoxyphényl)-*N*- méthyl-*N*-(1-méthylpipéridin-4-yl)-4-oxobutyramide ; le 3-(4-diméthylaminophényl)-*N*- méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le 2-(2-benzyloxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le 3-(3,4-diméthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)propionamide ; le 4-(2,4-dichlorophénoxy)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)butyramide ; le 3-(2-méthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)propionamide ; le 4-(4-chloro-2-méthylphénoxy)-*N*- méthyl-*N*-(1-méthylpipéridin-4-yl)butyramide ; le 2-(4-fluorophénylsulfanyl)-*N*- méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le 3-(4-fluoro-3-trifluorométhylphényl)-*N*- méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-2-(3-trifluorométhoxyphényl)acétamide ; le 2-(4-fluorophénoxy)-*N*- méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le 2-(2,3-dichlorophénoxy)-*N*- méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le 2-(4-méthoxyphénoxy)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-2-(4-trifluorométhoxyphényl)acétamide ; le 3-benzo[1,3]dioxol-5-yl-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-propionamide; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-2-(naphtalén-2-yloxy)acétamide; le *N*-méthyl-*N*-(1-méthylpipéridin-4-y1)-3-(3,4,5-triméthoxyphényl)propionamide ; le 3-(2,4-diméthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le 4-biphényl-4-yl-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-4-oxobutyramide ; le *N*-méthyl-*N*-

(1-méthylpipéridin-4-yl)-2-(naphtalén-2-ylsulfanyl)acétamide ; le 3-(3,5-diméthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le 3-(2,3-diméthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le 4-(3,4-diméthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)butyramide ; le 2-(2,3-diméthylphénoxy)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le 2-(8-chloronaphtalén-1-ylsulfanyl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-2-(naphtalén-1-yloxy)acétamide ; le 2-(4-acétylphénoxy)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le 3-(3-méthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)propionamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-3-pyridin-3-ylpropionamide; le 3-(4-benzyloxy-3-méthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le 3-(5-bromo-2-éthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)aciylamide ; le 4-(3,4-dihydro-2*H*-benzo[b][1,4]dioxépin-7-yl)-*N*-méthyl-*N*-(1-méthyl-pipéridin-4-yl)-4-oxobutyramide; le 3-(2-chloro-3,4-climéthoxyphényl)-*N*-méthyl-*N*-(1-méthyl-pipéridin-4-yl)acrylamide ; le 2-(2-chloro-4-fluorophénylsulfanyl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-2-(naphtalén-1-ylméthylsulfanyl)acétamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-3-(2-oxo-benzooxazol-3-yl)propionamide ; le méthyl-(1-méthylpipéridin-4-yl)amide d'acide 5-cyclohexylpentanoïque ; le 3-(4-méthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)propionamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-2-(4-trifluorométhoxyphénoxy)acétamide ; le 2-(2-acétylphénoxy)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-acétamide; l'ester de 4-{2-[méthyl-(1-méthylpipéridin-4-yl)carbamoyl]-éthyl}-phényle d'acide diméthylcarbamique et le 2-(5-chloro-3-méthyl-benzo[b]thiophén-2-yl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide.

18. Composition pharmaceutique comprenant un composé de formule (I) comme défini dans l'une quelconque des revendications 1 à 15, ou 17 et un ou plusieurs supports ou excipients pharmaceutiquement acceptables.

19. Composition pharmaceutique comme défini dans la revendication 18 sous forme posologique unitaire, comprenant de 0,05 mg à 1 000 mg, de préférence de 0,1 mg à 500 mg, et de manière spécialement préférée de 0,5 mg à 200 mg, d'un composé de formule (I) comme défini dans la revendication 1.

20. Utilisation d'un composé de formule générale (I'):



(I')

dans laquelle
m vaut 0 ou 1,
R^1 est
un groupe alkyle en $C_{1 à 6}$, alcényle en $C_{2 à 6}$, alcynyle en $C_{2 à 6}$,

- qui peut facultativement être substitué par un ou plusieurs substituants choisis parmi un atome d'halogène un groupe alcoxy en $C_{1 à 6}$ et un groupe hydroxy,
  un groupe cycloalkyle en $C_{3 à 6}$, cycloalcényle en $C_{5 à 8}$, cycloalkyl en $C_{3 à 8}$-alkyle en $C_{1 à 6}$, di(cycloalkyl en $C_{3 à 8}$)-alkyle en $C_{1 à 6}$, cycloalkyl en $C_{3 à 8}$-alcényle en $C_{2 à 6}$, cycloalkyl en C_3 à s-alcynyle en $C_{2 à 6}$, cycloalcényl en $C_{5 à 8}$-alkyle en $C_{1 à 6}$, cycloalcényl en $C_{5 à 8}$-alcényle en $C_{2 à 6}$, cycloalcényl en $C_{5 à 8}$-alcynyle en $C_{2 à 6}$,
- où les fragments cycliques peuvent facultativement être substitués par un ou plusieurs substituants choisis parmi un groupe alkyle en $C_{1 à 6}$, un atome d'halogène, un groupe trifluorométhyle et un groupe 2,2,2-trifluoroéthyle,

R^2 est un groupe alkyle en $C_{1 à 6}$, alcényle en $C_{2 à 6}$, alcynyle en $C_{2 à 6}$, cycloalkyle en $C_{3 à 8}$ ou cycloalkyl en $C_{3 à 8}$-alkyle en $C_{1 à 6}$,
X est $-CH_2-(CH_2)_n-$, $-(CH_2)_n-CH=CH-(CH_2)_p-$, $-CH_2-(CH_2)_n-O-(CH_2)_p-$, $-CH_2-(CH_2)_n-C(=O)-(CH_2)_p-$, $-CH_2-(CH_2)_n-S-(CH_2)_p-$, $-CH_2-(CH_2)_n-S(=O)-(CH_2)_p-$ ou $-CH_2-(CH_2)_n-S(=O)_2-(CH_2)_p-$,

n et p valent indépendamment 0, 1, 2, 3 ou 4,
R^3 et R^4 sont indépendamment un atome d'hydrogène, un groupe méthyle ou trifluorométhyle,
Y est

(a) un groupe aryle tel que défini ci-dessus ou hétéroaryle tel que défini ci-dessus, qui peut facultativement être substitué par un ou plusieurs substituants choisis parmi

- un atome d'halogène, un groupe nitro, cyano, hydroxy, oxo, alcanoyle en $C_{1 à 7}$, alkylthio en $C_{1 à 6}$, alkylsulfonyle en $C_{1 à 6}$, alkyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, trifluorométhyle, trifluorométhoxy, $-NR^5R^6$ et $-O(C=O)NR^5R^6$,
  où R^5 et R^6 sont indépendamment un atome d'hydrogène, un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, alcanoyle en $C_{1 à 7}$ ou aryle tel que défini ci-dessus, ou R^5 et R^6 conjointement avec l'atome d'azote auquel ils sont attachés forment un cycle saturé ou insaturé à 4 à 7 chaînons,
- ou bien où deux substituants dans des positions adjacentes forment un radical $-O-(CH_2)_{1 à 3}-O-$,
- un groupe aryle tel que défini ci-dessus, aryloxy, aryl-alkyle en $C_{1 à 6}$ et aryl-alcoxy en $C_{1 à 6}$, où les fragments de cycle peuvent facultativement être substitués par un ou plusieurs substituants choisis parmi

  ○ un atome d'halogène, un groupe nitro, cyano, hydroxy, alcanoyle en $C_{1 à 7}$, alkylthio en $C_{1 à 6}$, alkylsulfonyle en $C_{1 à 6}$, alkyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, trifluorométhyle, trifluorométhoxy, $-NR^7R^8$ et $-O(C=O)NR^7R^8$,
  où R^7 et R^8 sont indépendamment un atome d'hydrogène, un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, alcanoyle en $C_{1 à 7}$ ou aryle tel que défini ci-dessus, ou R^7 et R^8 conjointement avec l'atome d'azote auquel ils sont attachés forment un cycle saturé ou insaturé à 4 à 7 chaînons,
  ○ ou bien où deux substituants dans des positions adjacentes forment un radical $-O-(CH_2)_{1 à 3}-O-$,

(b) un groupe cycloalkyle en $C_{3 à 8}$ ou cycloalcényle en $C_{5 à 8}$, qui peut facultativement être substitué par un ou plusieurs substituants choisis parmi

- un groupe alkyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, alkylthio en $C_{1 à 6}$, cyano, trifluorométhyle, trifluorométhoxy et un atome d'halogène,
- un groupe aryle tel que défini ci-dessus et aryloxy, où les fragments de cycle peuvent facultativement être substitués par un ou plusieurs substituants choisis parmi

  ○ un atome d'halogène, un groupe nitro, cyano, hydroxy, alcanoyle en $C_{1 à 7}$, alkylthio en $C_{1 à 6}$, alkylsulfonyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, trifluorométhyle, trifluorométhoxy, $-NR^9R^{10}$ et $-O(C=O)NR^9R^{10}$,
  où R^9 et R^{10}) sont indépendamment un atome d'hydrogène, un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, alcanoyle en $C_{1 à 7}$ ou aryle tel que défini ci-dessus, ou R^9 et R^{10} conjointement avec l'atome d'azote auquel ils sont attachés forment un cycle saturé ou insaturé à 4 à 7 chaînons,

(c) un groupe alkyle en $C_{1 à 6}$, alcényle en $C_{2 à 6}$ ou alcynyle en $C_{2 à 6}$, qui peut facultativement être substitué par un ou plusieurs substituants choisis parmi

- un atome d'halogène, un groupe nitro, cyano, hydroxy, alcanoyle en $C_{1 à 7}$, alkylthio en $C_{1 à 6}$, alkylsulfonyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, trifluorométhyle, trifluorométhoxy, $-NR^{11}R^{12}$ et $-O(C=O)NR^{11}R^{12}$,
  où R^{11} et R^{12} sont indépendamment un atome d'hydrogène, un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, alcanoyle en $C_{1 à 7}$ ou aryle tel que défini ci-dessus, ou R^{11} et R^{12} conjointement avec l'atome d'azote auquel ils sont attachés forment un cycle saturé ou insaturé à 4 à 7 chaînons,
- un groupe aryle tel que défini ci-dessus, aryl-alkyle en $C_{1 à 6}$ et aryl-alcoxy en $C_{1 à 6}$, où les fragments de cycle peuvent facultativement être substitués par un ou plusieurs substituants choisis parmi

  ○ un atome d'halogène, un groupe nitro, cyano, hydroxy, alcanoyle en $C_{1 à 7}$, alkylthio en $C_{1 à 6}$, alkylsulfonyle en $C_{1 à 6}$, alkyle en $C_{1 à 6}$, alcoxy en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, trifluorométhyle, trifluorométhoxy, $-NR^{13}R^{14}$ et $-O(C=O)NR^{13}R^{14}$,
  où R^{13} et R^{14} sont indépendamment un atome d'hydrogène, un groupe alkyle en $C_{1 à 6}$, cycloalkyle en $C_{3 à 8}$, alcanoyle en $C_{1 à 7}$ ou aryle tel que défini ci-dessus, ou R^{13} et R^{14} conjointement avec l'atome d'azote auquel ils sont attachés forment un cycle saturé ou insaturé à 4 à 7 chaînons,

○ ou bien où deux substituants dans des positions adjacentes forment un radical -O-$(CH_2)_{1 à 3}$-O-,

ainsi que de tout diastéréoisomère ou énantiomère ou forme tautomère de ceux-ci comprenant des mélanges de ceux-ci ou un de leurs sels pharmaceutiquement acceptables pour la préparation d'une composition pharmaceutique pour le traitement et/ou la prévention de troubles et de maladies liés au récepteur H3 de l'histamine.

21. Utilisation d'un composé selon la revendication 20, pour la préparation d'une composition pharmaceutique pour le traitement et/ou la prévention de maladies et de troubles dans lesquels une inhibition du récepteur H3 de l'histamine a un effet bénéfique.

22. Utilisation d'un composé selon la revendication 20, pour la préparation d'une composition pharmaceutique ayant une activité antagoniste sur le récepteur H3 de l'histamine, ou une activité agoniste inverse sur le récepteur H3 de l'histamine.

23. Utilisation d'un composé selon la revendication 20, pour la préparation d'une composition pharmaceutique pour la réduction de poids.

24. Utilisation d'un composé selon la revendication 20, pour la préparation d'une composition pharmaceutique pour le traitement et/ ou la prévention du surpoids ou de l'obésité.

25. Utilisation d'un composé selon la revendication 20, pour la préparation d'une composition pharmaceutique pour la suppression de l'appétit ou pour une induction de la satiété.

26. Utilisation d'un composé selon la revendication 20, pour la préparation d'une composition pharmaceutique pour la prévention et/ou le traitement de troubles et de maladies liés au surpoids ou à l'obésité.

27. Utilisation d'un composé selon la revendication 20, pour la préparation d'une composition pharmaceutique pour la prévention et/ou le traitement de troubles de l'alimentation tels que la boulimie et l'hyperphagie boulimique.

28. Utilisation d'un composé selon la revendication 20, pour la préparation d'une composition pharmaceutique pour le traitement et/ou la prévention de l'IGT (intolérance au glucose).

29. Utilisation d'un composé selon la revendication 20, pour la préparation d'une composition pharmaceutique pour le traitement et/ou la prévention du diabète de type II.

30. Utilisation d'un composé selon la revendication 20, pour la préparation d'une composition pharmaceutique pour le retardement ou la prévention de la progression de l'IGT en diabète de type II.

31. Utilisation d'un composé selon la revendication 20, pour la préparation d'une composition pharmaceutique pour le retardement ou la prévention de la progression de diabète de type II ne nécessitant pas d'insuline en diabète de type II nécessitant de l'insuline.

32. Utilisation d'un composé selon la revendication 20, pour la préparation d'une composition pharmaceutique pour le traitement et/ou la prévention de maladies et de troubles dans lesquels une stimulation du récepteur H3 de l'histamine a un effet bénéfique.

33. Utilisation d'un composé selon la revendication 20, pour la préparation d'une composition pharmaceutique ayant une activité agoniste sur le récepteur H3 de l'histamine.

34. Utilisation d'un composé selon la revendication 20, pour la préparation d'une composition pharmaceutique pour le traitement et/ ou la prévention de la rhinite allergique, de l'ulcère ou de l'anorexie.

35. Utilisation selon l'une quelconque des revendications 22 à 34, dans laquelle le composé est le 3-[4-(4-fluorobenzyloxy)phényl]-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le 3-(4-chlorophényl)-*N* méthyl-*N*-(1-méthylpipéridin-4-yl)propionamide; le 2-biphényl-4-yl-*N*-cyclopropyl-*N*-(1-propylpipëridin-4-yl)-acétamide ; le *N*-méthyl-N(1-méthylpipéridin-4-yl)-3-(4-trifluorométhylphényl)propionamide; le 2-biphényl-4-yl-*N*-(1-isopropylpipéridin-4-yl)-*N*-méthylacétamide ; le 2-(2-méthoxyphénoxy)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide; le 3-(2-méthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le 2-(2-chlorophénoxy)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)

acétamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-3-naphtalén-1-ylacrylamide ; le 3-(5-bromo-2-éthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le 2-biphényl-4-yl-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le 3-(3-méthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-acrylamide; le 4-(4-méthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)butyramide ; le 2-(2,4-dichloro-5-méthylphénylsulfanyl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide; le 4-(3-fluoro-4-méthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-4-oxobutyramide ; le 3-(4-diméthylaminophényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le 2-(2-benzyloxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le 3-(3,4-diméthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)propionamide; le 4-(2,4-dichlorophénoxy)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)butyramide ; le 3-(2-méthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)propionamide; le 4-(4-chloro-2-méthylphénoxy)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)butyramide ; le 2-(4-fluorophénylsulfanyl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le 3-(4-fluoro-3-trifluorométhylphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-2-(3-trifluorométhoxyphényl)acétamide ; le 2-(4-fluorophénoxy)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide; le 2-(2,3-dichlorophénoxy)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide; le 2-(4-méthoxyphénoxy)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-2-(4-trifluorométhoxyphényl)acétamide ; le 3-benzo[1,3]dioxol-5-yl-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-propionamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-2-(naphtalén-2-yloxy)acétamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-3-(3,4,5-triméthoxyphényl)propionamide; le 3-(2,4-diméthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le 4-biphényl-4-yl-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-4-oxobutyramide ; le *N*-méthyl-*N*-(1-méthylpipéridm-4-yl)-2-(naphtalén-2-ylsulfanyl)acétamide ; le 3-(3,5-diméthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le 3-(2,3-diméthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le 4-(3,4-diméthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)butyramide ; le 2-(2,3-diméthylphénoxy)-*N*-méthyl-*N*-(1-méthylpipéridin -4-yl)acétamide ; le 2-(8-chloronaphtalén-1-ylsulfanyl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-2-(naphtalén-1-yloxy) acétamide ; le 2-(4-acétylphénoxy)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide ; le 3-(3-méthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)propionamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-3-pyridin-3-ylpropionamide ; le 3-(4-benzyloxy-3-méthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamide ; le 3-(5-bromo-2-éthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acrylamidc ; le 4-(3,4-dihydro-2*H*-benzo[b][1,4]dioxépin-7-yl)-*N*-méthyl-*N*-(1-méthyl-pipéridin-4-yl)-4-oxobutyramide ; le 3-(2-chloro-3,4-diméthoxyphényl)-*N*-méthyl-*N*-(1-méthyl-pipéridin-4-yl)acrylamide ; le 2-(2-chloro-4-fluorophénylsulfanyl)-*N*-méthyl-*N*-(1-méthylpipëridin-4-yl)acétamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-2-(riaphtalén-1-ylméthylsulfanyl)acétamide; le *N*-méthyl-*N*-(1-méthylpipéridm-4-yl)-3-(2-oxo-benzooxazol-3-yl)propionamide ; le méthyl-(1-méthylpipéridin-4-yl)amide d'acide 5-cyclohexylpentanoïque ; le 3-(4-méthoxyphényl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)propionamide ; le *N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-2-(4-trifluorométhoxyphénoxy)acétamide; le 2-(2-acétylphénoxy)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)-acétamide ; l'ester de 4-{2-[méthyl-(1-niéthylpipéridin-4-yl)carbamoyl]-éthyl}-phényle d'acide diméthylcarbamique et le 2-(5-chloro-3-méthyl-benzo[b]thiophén-2-yl)-*N*-méthyl-*N*-(1-méthylpipéridin-4-yl)acétamide.

36. Combinaison d'un composé selon l'une quelconque des revendications 1 à 15, ou 17, et d'une ou plusieurs substances pharmaceutiquement actives supplémentaires.

37. Composé selon l'une quelconque des revendications 1 à 15, ou 17 pour une utilisation dans le traitement et/ou la prévention d'un trouble ou d'une maladie tel que défini dans l'une quelconque des revendications 20, 21, 23 à 32, ou 34.

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