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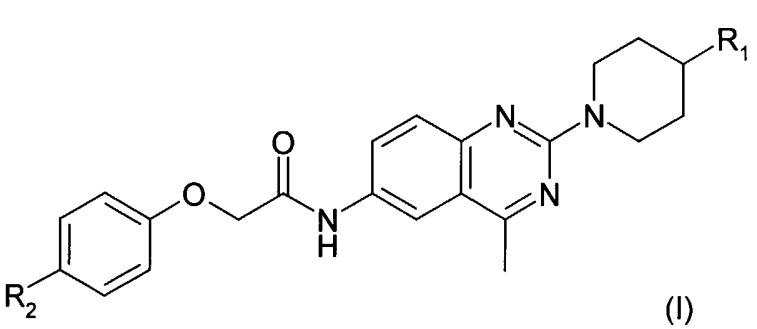
(54) Title: QUINAZOLINE COMPOUNDS AND THEIR USE IN MCH-RELATED DISEASE



(I)

(57) Abstract: Compounds of formula (I), are Melanin Concentrating Hormone (MCH) ligands, useful in the treatment of obesity and other MCH-related conditions (I) wherein R_1 is: (I) and R_2 is CI-, CH_3 CF_3, or F_3C-O-.

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QUINAZOLINE COMPOUNDS AND THEIR USE IN MCH-RELATED DISEASE

Field of the invention

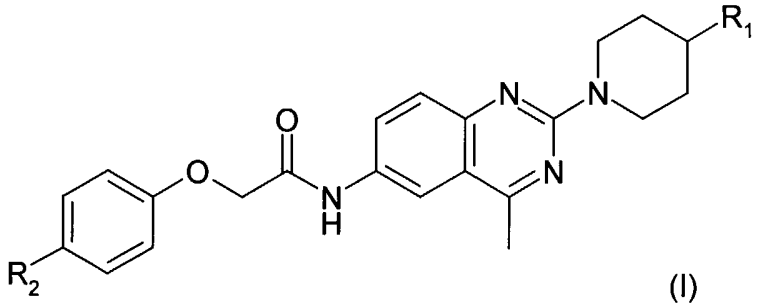
The present invention relates to novel quinazoline compounds and their use in the treatment, prophylaxis and/or diagnosis of conditions involving a melanin-concentrating hormone.

Background of the invention

Melanin-concentrating hormone (MCH) is a cyclic peptide that originally was isolated from salmoid pituitaries. In the fish, the 17 amino acid peptide causes aggregation of melanin and inhibits the release of ACTH. Mammalian MCH (19 amino acids) is highly conserved between rat, mouse and human exhibiting 100% amino acid identity. In the last decades there has been increasing activity in the research in the physiologic roles of MCH. It has been reported that MCH is involved in the feeding or body weight regulation, in energy balance, in response to stress, in water balance, in energy metabolism, in the general arousal/attention state, memory and cognitive functions and in psychiatric disorders. The biological effects of MCH are believed to be mediated by specific MCH receptors, and the MCH1 and MCH2 receptors have been described. Antagonists of MCH receptor (e.g. MCH1 receptor) are considered useful as obesity or weight reducing agents, and as antidepressant and/or anxiolytic agents.

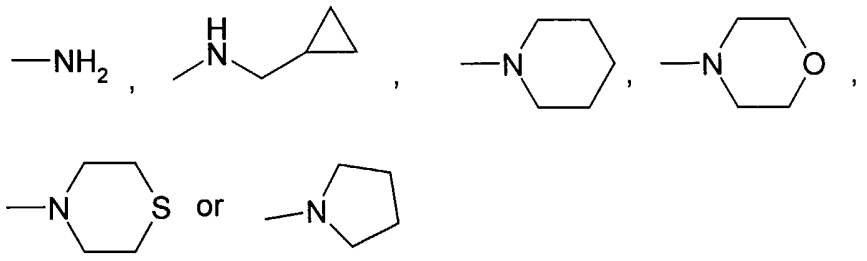
Description of the Invention

The present invention provides a compound of formula (I), or a salt, hydrate or solvate thereof:



(I)

wherein R_1 is:



and R_2 is Cl-, CH_3-, CF_3-, or F_3C-O-.

Specific preferred compounds of formula (I) are those of the Examples herein.

Compounds of the invention have a particularly useful combination of drug-like properties, including aqueous solubility and acceptable plasma protein binding.

Pharmaceutical and veterinary compositions comprising a compound of formula (I) or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof, together with a pharmaceutically or veterinarily acceptable carrier, are also included in the invention.

As used herein the term "salt" includes base addition, acid addition and quaternary salts. Compounds of the invention which are acidic can form salts, including pharmaceutically or veterinarily acceptable salts, with bases such as alkali metal hydroxides, e.g. sodium and potassium hydroxides; alkaline earth metal hydroxides e.g. calcium, barium and magnesium hydroxides; with organic bases e.g. *N*-ethyl piperidine, dibenzylamine and the like. Those compounds (I) which are basic can form salts, including pharmaceutically or veterinarily acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or phosphoric acid and the like, and with organic acids e.g. with acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic and p-toluene sulphonic acids and the like.

The compounds of the invention are highly potent antagonists of the MCH receptor, and are useful for the treatment of MHC -related disorders in mammals, including humans.

MHC-related disorders include overweight, adiposity, obesity and bulimia (e.g. malignant mastocytosis, exogeneous obesity, hyperinsulinar obesity, hyperplasmic

obesity, hypophyseal adposity, hypoplasmic obesity, hypophysal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity, systemic mastocytosis, simple obesity, central obesity etc.), hyperfagia, emotional disorders, dementia, hormonal disorders, lifestyle diseases such as, e.g., diabetes, diabetic complications (e.g. retinopathy, neuropathy, nephropathy etc.), arteriosclerosis and gonitis..

In the present context the term body mass index or BMI is defined as body weight (kg)/height^2 (m^2), and the term overweight is intended to indicate a BMI in a range from about 25 to about 29.9, whereas obesity is intended to indicate a BMI, which is at least about 30.

Hence the invention includes

(i) the use of a compound of formula (I) above, or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof, in the preparation of a composition for the treatment of an MHC-related disorder and

(ii) a method of treating a mammal, including a human, suffering from a MHC-related disorder, comprising administering to the mammal an effective amount of a compound of formula (I) above, or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof.

The MHC-related disorder referred to in these aspects (i) and (ii) of the invention may be, for example, overweight; bulimia; bulimia nervosa; obesity; Syndrome X (metabolic syndrome); a combination of obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension; Type II diabetes or Non Insulin Dependent Diabetes Mellitus (NIDDM), depression and/or anxiety.

Other MHC-related disorders to which aspects (i) and (ii) of the invention apply include a steroid or pituitary hormone disorder, an epinephrine release disorder, a gastrointestinal disorder, a cardiovascular disorder, an electrolyte balance disorder, hypertension, diabetes, a respiratory disorder, asthma, a reproductive function disorder, a muscoskeletal disorder, a neuroendocrine disorder, a cognitive disorder, a memory disorder such as, e.g., Alzheimer's disease, a sensory modulation and transmission disorder, a motor coordination disorder, a sensory integration disorder, a motor integration disorder, a dopaminergic function disorder such as, e.g. Parkinson's disease, a sensory transmission disorder, an olfaction disorder, a

sympathetic innervation disorder, an affective disorder such as, e.g. depression, a stress-related disorder, a fluid-balance disorder, a urinary disorder such as, e.g., urinary incontinence, a seizure disorder, pain, psychotic behaviour such as, e.g., schizophrenia, morphine or opioid tolerance, opiate addiction or migraine.

In other specific aspects the invention includes

(iii) the use of a compound of formula (I) above, or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof, in the preparation of a composition for (a) modifying the feeding behaviour and/or reducing the body mass of a mammal, including a human and

(iv) a method of modifying the feeding behaviour and/or reducing the body mass of a mammal, including a human, comprising administering to the mammal an effective amount of a compound of formula (I) above, or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof.

Pharmaceutical compositions

The compounds with which the invention is concerned are normally presented in the form of a pharmaceutical or a cosmetic composition comprising the specific compound or a physiologically acceptable salt thereof together with one or more physiologically acceptable excipients.

The compounds may be administered to the subject by any convenient administration route such as, e.g., the oral, buccal, nasal, ocular, pulmonary, topical, transdermal, vaginal, rectal, ocular, parenteral (including *inter alia* subcutaneous, intramuscular, and intravenous), route in a dose that is effective for the individual purposes. A person skilled in the art will know how to chose a suitable administration route.

The pharmaceutical or cosmetic composition comprising a compound according to the invention may be in the form of a solid, semi-solid or fluid composition.

The solid composition may be in the form of tablets such as, e.g. conventional tablets, effervescent tablets, coated tablets, melt tablets or sublingual tablets, pellets, powders, granules, granulates, particulate material, solid dispersions or solid solutions.

A semi-solid form of the composition may be a chewing gum, an ointment, a cream, a liniment, a paste, a gel or a hydrogel.

The fluid form of the composition may be a solution, an emulsion including nano-emulsions, a suspension, a dispersion, a liposomal composition, a spray, a mixture, a syrup or a aerosol.

Fluid compositions, which are sterile solutions or dispersions can be utilized by for example intraveneous, intramuscular, intrathecal, epidural, intraperitoneal or subcutaneous injection of infusion. The compounds may also be prepared as a sterile solid composition, which may be dissolved or dispersed before or at the time of administration using e.g. sterile water, saline or other appropriate sterile injectable medium.

Other suitable dosages forms of the pharmaceutical compositions according to the invention may be vagitories, suppositories, plasters, patches, tablets, capsules, sachets, troches, devices etc.

The dosage form may be designed to release the compound freely or in a controlled manner e.g. with respect to tablets by suitable coatings.

The pharmaceutical composition may comprise a therapeutically effective amount of a compound according to the invention.

The content of a compound of the invention in a pharmaceutical composition of the invention is e.g. from about 0.1 to about 100% w/w of the pharmaceutical composition.

The pharmaceutical or cosmetic compositions may be prepared by any of the method well known to a person skilled in pharmaceutical or cosmetic formulation.

In pharmaceutical or cosmetic compositions, the compounds are normally combined with a pharmaceutical excipient, i.e. a therapeutically inert substance or carrier.

The carrier may take a wide variety of forms depending on the desired dosage form and administration route.

The pharmaceutically or cosmetically acceptable excipients may be e.g. fillers, binders, disintegrants, diluents, glidants, solvents, emulsifying agents, suspending agents, stabilizers, enhancers, flavours, colors, pH adjusting agents, retarding agents, wetting agents, surface active agents, preservatives, antioxidants etc. Details can be found in pharmaceutical handbooks such as, e.g., Remington's Pharmaceutical Science or Pharmaceutical Excipient Handbook.

Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the composition, the route of administration, the frequency of administration, the age, weight, gender, diet and condition of the subject to be treated and the condition being treated and the advancement of the disease condition etc.

Suitable dosages may be from about 0.001 mg to about 1 g such as, e.g. from about 0.005 to about 750 mg, from about 0.01 to about 500 mg, from about 0.05 to about 500 mg, from about 0.1 to about 250 mg, from about 0.1 to about 100 mg or from about 0.5 to about 50 mg.

The amounts can be divided into one or several doses for administration daily, every second day, weekly, every two weeks, monthly or with any other suitable frequency. Normally, the administration is daily.

A compound or a pharmaceutical composition according to the invention may be used in combination with other drug substances such as agents for treating disorders like e.g. diabetes, diabetes complications, obesity, hypertension, hyperlipidemia, arteriosclerosis, arthritis, anxiety, and/or depression etc.

The following examples describe the preparation of specific compounds of the invention. Other compounds within the scope of formula (I) above may be synthesised by methods directly analogous to those of the examples

Examples

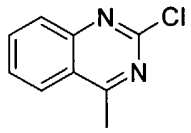
General comments;

^{1}H-NMR data are given either in full detail or with selected characteristic peaks. LC/MS was performed on an Agilent 1100-series instrument with the column, Waters

XTerra MS C18 (2.1x5 mm, 5 μ). The method in use; Flow: 1.0 mL/min; Gradient: 0-5 min: 10-100% MeCN, 5-7.5 min: 100% MeCN; MS-ionization mode API-ES (pos.).

Example 1

Step 1

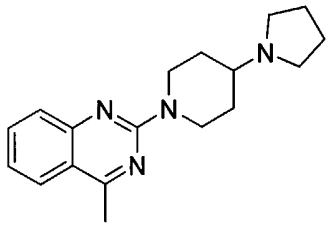


2-Chloro-4-methyl-quinazoline. The title compound was synthesized by adding dimethyl aniline (1.5 mL) to a suspension of 4-Methyl-1H-quinazolin-2-one (3.3 g, 20 mmol) in Phosphorus oxychloride (30 mL) (*ref. Shigeho Inaba et al, 1975, US3859237, Quinazoline Derivatives*). The reaction mixture was heated to 120 ° C until the reactants came into solution. The reaction mixture was cooled and poured onto ice water followed by extraction with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered, and evaporated. The crude product was chromatographed (Silica, EtOAc/Heptane, 1:1) yielding 2.2 g of the product.

LC/MS : Rt = 2.85 min, m/z 178.8 [M^+].

^{1}H-NMR(300MHz,$CDCl_3$): δ = 3.0 (s, 3H), 7.65 (t, 1H), 7.95 (m, 2H), 8.15 (d, 1H)

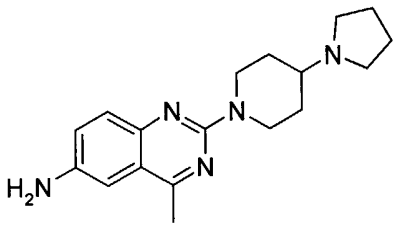
Step 2



4-Methyl-2-(4-pyrrolidin-1-yl-piperidin-1-yl)-quinazoline. 2-Chloro-4-methyl-quinazoline (0.8 g, 4.5 mmol) and 4-(1-pyrrolidinyl)-piperidine (1.0 g, 6.5 mmol) were mixed and subjected to microwave heating (150 ° C, 8 min, fixed hold time, 10 sec prestirring). The mixture was dissolved in EtOAc/water, neutralized with NaOH, and extracted with EtOAc. The combined organic phases were washed twice with 4 M HCl. The water phase was neutralized (pH = 8-9) followed by extraction with EtOAc. The organic phases were dried over Na_2SO_4, filtered, and evaporated, yielding 1.3 g of the title product.

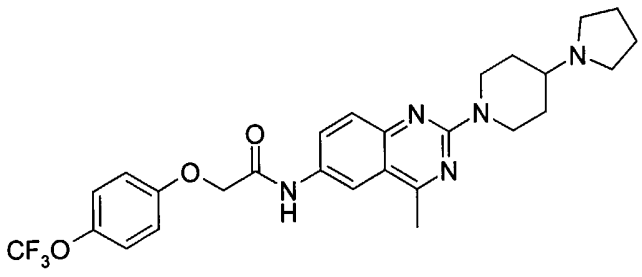
^{1}H-NMR(300MHz,$CDCl_3$): δ = 1.6 – 2.9 (m + s, 13H + 3H), 3.0 (t, 2H), 5.05 (d, 2H), 7.2 (t, 1H), 7.6 (m, 2H), 7.85 (d, 1H)

Step 3



4-Methyl-2-(4-pyrrolidin-1-yl-piperidin-1-yl)-quinazolin-6-ylamine. 4-Methyl-2-(4-pyrrolidin-1-yl-piperidin-1-yl)-quinazoline (0.50 g /1.5 mmol) was added portionwise to HNO_3 (90%, 25 mL) at -35 ° C and the reaction mixture was stirred for 2h at -30 ° C. The reaction was poured onto ice before NaOH (8M) was added (pH = 8) and a precipitate were formed. The solid was collected, washed with water, and dried in vacuo, yielding 0.38 g of 4-Methyl-6-nitro-2-(4-pyrrolidin-1-yl-piperidin-1-yl)-quinazoline. LC/MS; Rt = 4.88 min, m/z 342.2 [MH^+].
4-Methyl-6-nitro-2-(4-pyrrolidin-1-yl-piperidin-1-yl)-quinazoline (0.3 g, 0.88 mmol) was dissolved in MeOH (20 mL) and 10 % Pd/C (60 mg) was added. The reaction mixture was heated to 60 ° C under hydrogen atmosphere and stirred for 3h, thereafter was the mixture filtered and the solvent removed *in vacuo*. The crude product was chromatographed (Silica, CH_2Cl_2/MeOH/NH_3, 100:10:1) yielding 0.31 g of the product. LC/MS: Rt = 1.77 min, m/z 311.8 [MH^+].

Step 4



***N*-[4-Methyl-2-(4-pyrrolidin-1-yl-piperidin-1-yl)-quinazolin-6-yl]-2-(4-trifluoromethoxy-phenoxy)-acetamide.** *p*-Trifluoromethoxy-phenol (0.78 mL, 6.0 mmol) and bromoethylacetat (0.7 mL, 6.0 mmol) were dissolved in acetone (10 mL), followed by addition of potassium carbonate (0.91 g, 6.6 mmol). The reaction mixture

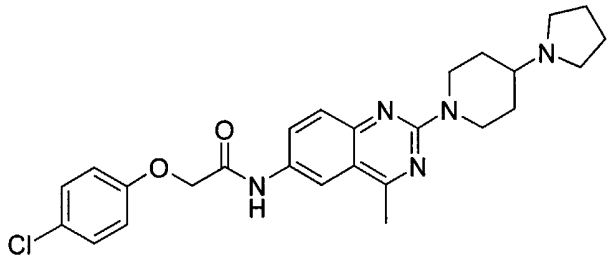
was heated to 150 ° C for 10 min and then cooled to room temperature whereupon water was added. The reaction mixture was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, and evaporated. The crude product was chromatographed (Silica, CH_2Cl_2/MeOH/NH_3, 100:10:1) yielding 1.0 g of (4-trifluoromethoxy-phenoxy)-acetic acid ethyl ester.

To this ester were methanol and lithium hydroxid monohydrate added and the suspension was stirred in room temperature for 2 h followed by stirring at 60 ° C for 2h. The reaction mixture was cooled to room temperature before the solvent was removed *in vacuo*, yielding 1.21 g of the lithium salt of the hydrolyzed ester.

To lithium (4-trifluoromethoxy-phenoxy)-acetic carboxylate (0.09 g, 0.35 mmol) dissolved in CH_2Cl_2 (6 mL) was hydroxybenzotriazole (0.07 g, 0.48 mmol) added. The solution was cooled to 0 ° C, whereupon 1-ethyl-3(-3-dimethylaminopropyl)carbodiimid hydrochlorid (0.08 g, 0.42 mmol) and diisopropyl ethyl amine (0.02g, 0.16 mmol) were added. The reaction mixture was stirred at room temperature for 12 h before some $NaHCO_3$-solution was added, followed by extraction with EtOAc. The combined organic phases was dried over $MgSO_4$, filtered and evaporated. The crude product was chromatographed (silica, CH_2Cl_2/MeOH/NH_3, 100:10:1) yielding the title product. LC/MS: Rt = 5.22 min, m/z 530.2 [MH^+].

^{1}H-NMR(300MHz,$CDCl_3$): δ = 8.29 (s, 1H), 7.53-7.64 (m, 2H), 7.23 (d, 2H), 7.03 (d, 2H), 4.92 (d, 2H), 4.64 (s, 2H), 2.95-3.04 (m, 2H), 2.77 (s, 3H), 2.50-2.67 (m, 6H), 2.25-2.33 (m, 2H), 2.00-2.04 (m, 3H), 1.51-1.63 (m, 3H).

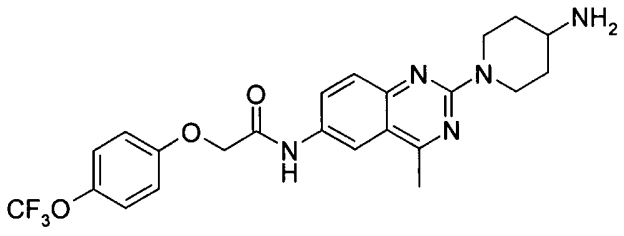
Example 2



2-(4-Chloro-phenoxy)-*N*-[4-methyl-2-(4-pyrrolidin-1-yl-piperidin-1-yl)-quinazolin-6-yl]-acetamide. To a solution of 4-Methyl-2-(4-pyrrolidin-1-yl-piperidin-1-yl)-quinazolin-6-ylamine (1.5 g, 4.8 mmol) in CH_2Cl_2 was added (4-Chloro-phenoxy)-acetyl chloride dropwise at 0 ° C. The reaction mixture was stirred under N_2 atmosphere until complete. The product was precipitated by the addition of HCl in

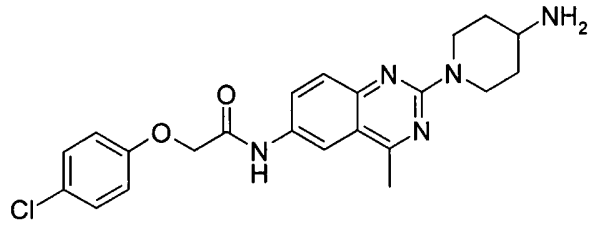
ether (2 M, 2 mL). The crude product was recrystallised and triturated from hot methanol giving 1.2 g of the title product. LC/MS; Rt = 5.85, m/z 479.6 [MH^+]. ^{1}H-NMR (300MHz, D_2O): δ = 8.18 (s, 1H), 7.84 (d, 1H), 7.56 (d, 1H), 7.12 (d, 2H), 6.71 (d, 2H), 4.70 (2H, obscured by solvent signal), 4.38 (s, 2H), 3.52-3.63 (m 3H), 3.11-3.28 (m, 5H), 2.75 (s, 3H), 2.35 (d, 2H), 2.05-2.19 (m, 2H), 1.91-1.96 (m, 2H), 1.73-1.79 (m, 2H).

Example 3



***N*-[2-(4-Amino-piperidin-1-yl)-4-methyl-quinazolin-6-yl]-2-(4-trifluoromethoxy-phenoxy)-acetamide.** The title compound was synthesized according to the method of Example 1 utilizing 4-BOC-amino piperidine in the coupling with2-Chloro-4-methyl-quinazoline. LC/MS; Rt = 3.47 min, m/z 475.6 [MH^+].^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.29-8.32 (m, 2H), 7.54-7.64 (m, 2H), 7.24 (d, 2H), 7.05 (d, 2H), 4.92 (d, 2H), 4.66 (s, 2H), 2.94-3.10 (m, 3H), 2.80 (s, 3H), 1.93-1.98 (m, 2H) and 1.36-1.56 (m, 4H).

Example 4



***N*-[2-(4-Amino-piperidin-1-yl)-4-methyl-quinazolin-6-yl]-2-(4-chloro-phenoxy)-acetamide.** The title compound was synthesized according to the method of Example 2 utilizing 4-BOC-amino piperidine in the coupling with 2-Chloro-4-methyl-quinazoline.

LC/MS Rt = 3.26 min, m/z 425.6 [MH^+].

Biological assays

Materials and methods

Transfections and Tissue Culture - The cDNA encoding the human MCH-1 receptor was cloned from a human brain cDNA library and cloned into the eukaryotic expression vector pcDNA3.1 (Invitrogen). Assays were performed on transiently transfected COS-7 cells or stably transfected CHO (Chinese Hamster Ovary) cells, expressing the human MCH-1 receptor in pcDNA3.1. Stable MCH-1 receptor transfectants of CHO cells were obtained using 5 µg plasmid cDNA and a standard calcium phosphate transfection method (Johansen *et al.*, 1990; Gether *et al.*, 1992) with subsequent selection in 1 mg/ml G418 (Life Technology). Clones were screened by a MCH receptor radioligand binding assay (as described below). Stably transfected CHO cells were maintained in RPMI 1640 culture medium (Invitrogen), supplemented with 10 % fetal calf serum (Invitrogen), 100 U/ml penicillin, 100 µg/ml streptomycin (Life Technology), and 500 µg/ml G418 (Life Technology). COS-7 cells were grown in Dulbecco's modified Eagle's medium (DMEM) 1885 (Invitrogen) supplemented with 10 % fetal calf serum, 100 U/ml penicillin, 100 µg/ml streptomycin, and were transiently transfected by a standard calcium phosphate transfection method (Johansen *et al.*, 1990; Gether *et al.*, 1992) two days before assay.

Radioligand Binding Assay -Transiently transfected COS-7 cells or stably transfected CHO cells, expressing human MCH-1 receptor were seeded in multi-well culture plates one day before the assay. The number of cells per well was determined by the apparent expression efficiency of the cell line aiming at 5 - 10 % binding of the added radioligand. Cells were assayed by competition binding for 3 hours at room temperature using 15 pM [^{125}I]-MCH (Amersham Pharmacia Biotech) plus variable amounts of unlabeled ligand in 0.5 ml of a 25 mM Hepes buffer, pH 7.4, supplemented with 10 mM $MgCl_2$, 5 mM $MnCl_2$, 10 mM NaCl, 0.1 % (w/v) bovine serum albumin (BSA), 100 µg/ml bacitracin. The assay was performed in duplicate. Nonspecific binding was determined as the binding in the presence of 1 µM MCH (Bachem). Binding data were analyzed and IC_{50} values determined by non-linear regression using the Prism software (GraphPad software, San Diego).

The compounds of the examples had IC_{50}s in the above assay of 25nM or less.

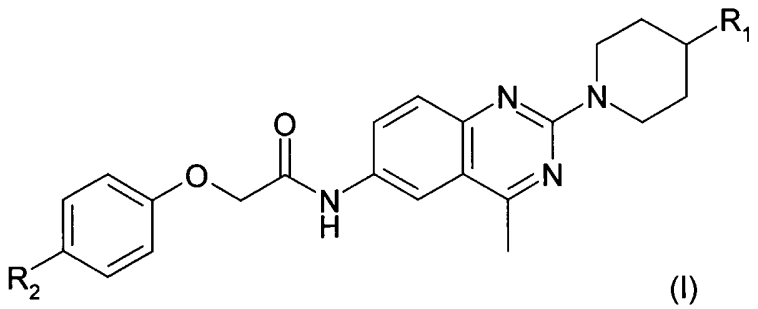
References:

Gether, U., Marray, T., Schwartz, T.W., and Johansen, T.E. (1992). Stable expression of high affinity NK_1 (substance P) and NK_2 (neurokinin A) receptors but low affinity NK_3 (neurokinin B) receptors in transfected CHO cells. FEBS Lett., 296, 241-244.

Johansen, T.E., Schøller, M.S., Tolstoy, S. and Schwartz, T.W. (1990). Biosynthesis of peptide precursors and protease inhibitors using new constitutive and inducible eukaryotic expressions vectors. FEBS Lett., 267, 289-294.

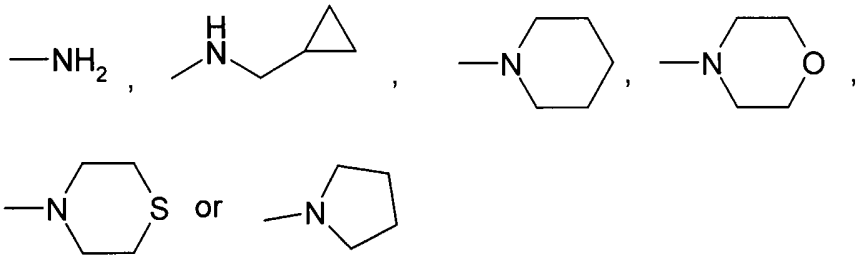
Claims:

1. A compound of formula (I), or a salt, hydrate or solvate thereof:



(I)

wherein R_1 is:



and R_2 is and R_2 is Cl-, CH_3-, CF_3-, or F_3C-O-.

2. A compound as claimed in claim 1 selected from the group consisting of :

N-[4-Methyl-2-(4-pyrrolidin-1-yl-piperidin-1-yl)-quinazolin-6-yl]-2-(4-trifluoromethoxy-phenoxy)-acetamide,

2-(4-Chloro-phenoxy)-*N*-[4-methyl-2-(4-pyrrolidin-1-yl-piperidin-1-yl)-quinazolin-6-yl]-acetamide,

N-[2-(4-Amino-piperidin-1-yl)-4-methyl-quinazolin-6-yl]-2-(4-trifluoromethoxy-phenoxy)-acetamide,

N-[2-(4-Amino-piperidin-1-yl)-4-methyl-quinazolin-6-yl]-2-(4-chloro-phenoxy)-acetamide, and

salts, hydrates and solvates thereof.

3. The use of a compound as claimed in claim 1 or claim 2, or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof, in the preparation of a composition for the treatment of an MHC-related disorder.

4. A method of treating a mammal, including a human, suffering from a MHC-related disorder, comprising administering to the mammal an effective amount of a compound as claimed in claim 1 or claim 2, or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof.

5. The use of a compound as claimed in claim 1 or claim 2, or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof, in the preparation of a composition for (a) modifying the feeding behaviour and/or reducing the body mass of a mammal, including a human.

6. A method of modifying the feeding behaviour and/or reducing the body mass of a mammal, including a human, comprising administering to the mammal an effective amount of a compound as claimed in claim 1 or claim 2, or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof.

7. A pharmaceutical or veterinary composition comprising a compound as claimed in claim 1 or claim 2, or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof, together with a pharmaceutically or veterinarily acceptable carrier.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP2004/006539

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/04 A61K31/517

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2004/052370 A (FRIMURER THOMAS MICHAEL ; LITTLE PAUL BRIAN (DK); RECEVEUR JEAN-MARIE) 24 June 2004 (2004-06-24) the whole document	1-7
E	WO 2004/052371 A (FRIMURER THOMAS MICHAEL ; LITTLE PAUL BRIAN (DK); RECEVEUR JEAN-MARIE) 24 June 2004 (2004-06-24) the whole document	1-7
A	WO 2004/011440 A (BANYU PHARMA CO LTD ; KANATANI AKIO (JP); MORIYA MINORU (JP); FUKAMI T) 5 February 2004 (2004-02-05) abstract; examples 70,84,85	1-7

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 January 2005	04/02/2005

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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/006539

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/045313 A (CHANG LEHUA ; JIANG JINLONG (US); LIN PETER (US); CHAUNG DANNY (US); D) 5 June 2003 (2003-06-05) Claims; Examples	1-7
A	WO 03/015769 A (AVENTIS PHARMA GMBH) 27 February 2003 (2003-02-27) page 14, line 31 - line 32; claim 1	1-7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/006539

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 4 and 6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

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

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

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

Remark on Protest

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

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/006539

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004052370 A	24-06-2004	WO 2004052370 A2	24-06-2004
		WO 2004052371 A2	24-06-2004
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		EE 200400055 A	15-04-2004
		WO 03015769 A1	27-02-2003
		EP 1418906 A1	19-05-2004
		HR 20040149 A2	31-08-2004
		HU 0401329 A2	28-12-2004
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		US 2004198731 A1	07-10-2004
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		US 2004198732 A1	07-10-2004
		US 2004198733 A1	07-10-2004