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(54) Title: PIPERIDIN-4-YLPIPERAZINE COMPOUNDS FOR THE TREATMENT OF HCV INFECTION

(57) Abstract: The invention relates to new piperazine-pieridine compounds having anti-viral activity and particularly anti-HCV activity. The invention further relates to pharmaceutical compositions comprising compounds according to the invention.

COMPOUNDS FOR THE TREATMENT OF HCV INFECTION

Hepatitis C virus (HCV) is the major cause of liver disease worldwide and a potential source of high morbidity in the future. The WHO estimates that approximately 170 million people (3% of the world's population) are chronically infected with HCV, with a mortality rate of 500 000 people; 3-4 million new infections occur each year. C hepatitis is a real problem of public health, with a current prevalence for some of the world's poorest areas. In Europe for example, prevalence of HCV infection is different depending on countries and the estimated HCV genotype distribution is also different among HCV-infected individuals.

The current standard of care for HCV is a combination of PEGylated-interferon (PEG-INF) and ribavirin and it is estimated that the overall clinical success rate, referred to as sustained virological response, of this combination therapy is only around 50%.

The treatment is lengthy (48 weeks for genotype 1 HCV), associated with frequent and sometimes serious side effects (neuropsychiatric events, flu-like symptoms and haematological toxicities) and contraindicated for many patients. It is also estimated that only 10% of patients with chronic HCV are successfully treated with the current standard of care.

Nowadays, the main targets are focused on Protease inhibitors (NS3-4A) and Polymerase inhibitors (NS5B); numerous molecules are being studied for their potential to supplement or replace either or both elements of the standard PEG-INF/ribavirin combination.

Considering the high heterogeneity and high mutation rate of HCV, drug resistance is likely to emerge during treatment with specific inhibitors of Protease and Polymerase inhibitors, even in a combination setting. Although the short term goal would be to add such drugs to IFN (IFN seems to be fundamental in future HCV therapies), it is likely to involve novel drugs that have different modes of action. Consequently, exploring additional targets (cyclophilin inhibitors, inhibition of viral entry into the cell, IRES inhibitors...) that are vital for various stages of the viral life cycle remains important. A search for new therapeutic strategies, characterized by higher efficacy, shorter duration of treatment, convenient route of administration and favourable side-effect profile are needed.

WO9940108, WO2003032962 and WO2005330266 disclose piperazine-piperidine compounds having antimicrobial activity for use as antibacterial agents or for treatment of tuberculosis. EP0503411 and WO2006135839 also disclose such compounds for use as antiarrythmics, psychotropics and agonists of the 5-HT1A as well as their use in the treatment of CNS disorders.

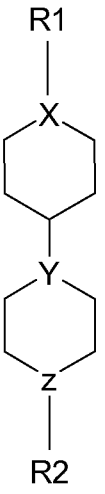
WO2005042542 discloses piperazine-piperidine for treatment of tuberculosis. WO9316057, WO2006135839 US2007/0027160 and WO20080667399 also disclose such compounds which are antagonists and agonists of 5-HT1A receptors for use as psychotropics, antihistaminics and/or spasmolytics and for treatment of CNS disorders, particularly Alzheimer disease. WO2007084319 discloses piperazine-piperidine compounds which are CB1 modulators and their use for the treatment of metabolic syndrome, neuroinflammatory and psychiatric disorders.

WO2006135839, WO2007146073 and Bioorganic and Medicinal Chemistry Letters (2006 p2654-2657) describe piperazine-piperidine compounds for treatment of CNS disorders and more particularly Alzheimer disease. EP542363 and WO9314077 also describe such compounds as inhibitors of fibrinogen-dependent blood platelet aggregation. WO2003031441, WO2003031443 and WO2003032962 disclose compounds effective against multi-drug resistant bacteria. WO2006060461, WO2002062784, WO2004110451 and WO 9716440 disclose compounds for treatment of metabolic disorders (CB1 antagonists), as neurokinin 1 antagonists, opioid analgesics and substance-P antagonists inducing relaxation of the pig coronary arteries. WO2006088840 discloses CXCR3 antagonist for the treatment of chemokine-mediated diseases; among numerous applications, these compounds are mentioned to be antiviral agents without any experimental data or details on the activity. WO2006135839 describes piperazine-piperidine antagonists and agonists of the 5-HT1A receptor and their preparation, pharmaceutical compositions, and use in the treatment of central nervous system disorders; antiviral activities are not described.

Numerous publications (Bioorganic & Medicinal Chemistry Letters (2002), 12(5), 791-794 and 795-798; Bioorganic & Medicinal Chemistry (2004), 12(2), 319-326, WO9800412, WO9805292, WO2002088087) disclose piperazine-piperidine for treatment of Alzheimer's disease. ChemMedChem (2007), 2(7), 1000-1005 discloses novel dopamine D3 receptor ligands; WO9620173 discloses cell aggregation inhibitors; WO9716440 discloses substance-P antagonists inducing relaxation of the pig coronary arteries; JP2008179621 discloses acetyl-CoA carboxylate inhibitors; WO 2006088919 discloses CXCR3 antagonists and their use in the treatment of chemokine mediated diseases. Bioorganic & Medicinal Chemistry Letters (2001), 11(16), 2143-2146 and (2003), 13(3), 567-571; Journal of Medicinal Chemistry (2001), 44(21), 3343-3346 and (2003), 46(21), 4501-4515; US2006105964, WO2008030853 disclose compounds that are active against HIV. However, these compounds have been found in the present invention to be not or poorly active on HCV. Finally, WO2004080966 and US2005261310 also disclose piperazine-piperidine compounds as chemokine receptor CCR5 antagonists and drugs; hepatitis and antiviral activities are cited among numerous potential applications but no experimental data is provided demonstrating this activity.

The present invention relates to novel piperazine-piperidine compounds useful as antiviral agents; particularly, they show an important effect for the treatment of HCV infection.

The present invention is related to compounds for use as an antiviral agent having the general formula (I):



(I)

wherein

X, Y and Z represent independantly N or N^{+}-H,

R1 is phenyl, pyrimidine, pyridine, thiophen, pyrrole, quinoline or a heterocyclic group, each of which is unsubstituted or substituted with one or more substituent groups, or

R1 is -R'-R3, in which R' is a methylene group, unsubstituted or substituted with one or more substituent groups, wherein the substituent groups are selected from C1-C6 alkyl and CF_3,

R3 is phenyl, quinoline or a heterocyclic group, each of which is unsubstituted or substituted with one or more substituent groups,

R2 is phenyl, pyrimidine, pyridine, thiophen, pyrrole, quinoline or a heterocyclic group, each of which is unsubstituted or substituted with one or more substituent groups, or

R2 is -R''-R4, in which R" is a methylene group, unsubstituted or substituted with one or more substituent groups, wherein the substituent groups are selected from C1-C6 alkyl,

R4 is phenyl, quinoline or a heterocyclic group, each of which is unsubstituted or substituted with one or more substituent groups,

and the pharmaceutically acceptable salts thereof.

In a first embodiment, the invention relates to compound for use as an antiviral agent of formula (I) wherein R1 is phenyl, pyridine or quinoline each of which is unsubstituted or substituted with one or more substituent groups, and R2 is phenyl or quinoline each of which is unsubstituted or substituted with one or more substituent groups.

In a second embodiment, the invention relates to compound for use as an antiviral agent of formula (I) wherein R1 is phenyl, pyridine or quinoline each of which is unsubstituted or substituted with one or more substituent groups, and R2 is benzyl which is unsubstituted or substituted with one or more substituent groups or R2 is $-CH_2$-R4 or -$CH(CH_3)$-R4, and R4 is a phenyl or quinoline each of which is unsubstituted or substituted with one or more substituted groups.

In a third embodiment, the invention relates to compound for use as an antiviral agent of formula (I) wherein R1 is benzyl each of which is unsubstituted or substituted with one or more substituent groups or R1 is selected from $-CH_2$-R3, $-CH(CH_3)$-R3, -$C(CH_3)_2$-R3 or $-CH(CF_3)$-R3, R2 is phenyl, pyridine or quinoline, each of which is unsubstituted or substituted with one or more substituent groups, and R3 is phenyl or quinoline each of which is unsubstituted or substituted with one or more substituent groups.

In a fourth embodiment, the invention relates to compounds for use as an antiviral agent of formula (I) wherein R1 is benzyl which is unsubstituted or substituted with one or more substituent groups or R1 is $-CH_2$-R3 or $-CH(CH_3)$-R3, and R2 is benzyl which is unsubstituted or substituted with one or more substituent groups or R2 is $-CH_2$-R4 or -$CH(CH_3)$-R4, R3 and R4 are independently selected from phenyl or quinoline which are unsubstituted or substituted with one or more substituent groups.

Preferably, the invention is directed to compounds for use as an antiviral agent of formula (I) wherein R1 and R2 are independently selected in the group consisting of phenyl, benzyl, pyridine and quinoline, each of which is unsubstituted or substituted with one or more substituent groups.

Preferably, X, Y and Z represent N.

Advantageously, R' and R" are independently $-CH_2$-, $-CH(CH_3)$-, $-CH(CF_3)$- or -$C(CH_3)_2$ -.

In a preferred embodiment, the substituent groups are independently selected from Cl, F, I, Br, C1-C6 alkyl, C1-C6 alkyl substituted with one or more halogens, C1-C6 alkoxy, C3-C6 cycloalkyl, phenyl, pyridinyl, hydroxy, -CCH or $-NH-CS-NH_2$, nitro and NR5R6 with R5 and R6 representing independently hydrogen, C1-C6 alkyl,

More preferably, the substituent groups are independently selected in the group consisting of Cl, F, methoxy, methyl and $-CF_3$.

Another object of the invention is a compound for use as an antiviral agent according to formula (I) selected in the group consisting of 1-(2-methoxy-phenyl)-4-(1-phenyl-piperidin-4-yl) piperazine (IP-153), 1-(2-methoxy-phenyl)-4-(1-phenyl-piperidin-4-yl) piperazine hydrochloride (IP-179), 4-(4-phenyl-piperazin-1-yl)-3,4,5,6-tetrahydro-2H-[1,4']-bipyridinyl (IP-189), 4-(4-phenyl-piperazin-1-yl)-3,4,5,6-tetrahydro-2H-[1,4']-bipyridinyl hydrochloride (IP-193), 7-chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-

yl]-quinoline (IP-224), 7-chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl]-quinoline hydrochloride (IP-233), 7-Chloro-4-[4-(4-phenyl-piperazin-1-yl)-piperidin-1-yl]-quinoline trifluoroacetic (IP-292), 1-benzyl-4-(phenyl-piperido-4-yl)-piperazine (IP-119), 4-[4-(4-benzyl-piperazin-1-yl)-piperidin-1-yl]-7-chloro-quinoline (IP-122), 4-[4-(4-benzyl-piperazin-1-yl)-piperidin-1-yl]-7-chloro-quinoline hydrochloride (IP-140), 1-benzyl-4-(phenyl-piperido-4-yl)-piperazine hydrochloride (IP-154), 1-(4-Fluoro-benzyl)-4-[1-(4-fluoro-phenyl)-piperidin-4-yl]-piperazine hydrochloride (IP-275), 1-[1-(4-Fluoro-phenyl)-ethyl]-4-[1-(4-fluoro-phenyl)-piperidin-4-yl]-piperazine hydrochloride (IP-308), 7-Chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl-methyl]-quinoline hydrochloride (IP-385), 1-(1-Phenyl-ethyl)-4-(1-*o*-tolyl-piperidin-4-yl)-piperazine hydrochloride (IP-453), 1-(2-methoxy-phenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl] piperazine (IP-038), 1-(1-benzyl-piperidin-4-yl)-4-(2-methoxy-phenyl)-piperazine (IP-074), 1-[1-(2-Methoxy-benzyl)-piperidin-4-yl]-4-(2-methoxy-phenyl)-piperazine (IP-075), 1-[1-(2-Chloro-benzyl)-piperidin-4-yl]-4-(2-methoxy-phenyl)-piperazine (IP-076), 1-(2-Fluoro-phenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl]-piperazine (IP-077), 1-(1-Benzyl-piperidin-4-yl)-4-(4-methoxy-phenyl)-piperazine (IP-078), 1-[1-(4-Ethyl-benzyl)-piperidin-4-yl]-4-phenyl-piperazine (IP-079), 4-[4-(1-benzyl-piperidin-4-yl)-piperazin-1-yl]-7-chloro-quinoline (IP-139), 1-(2-methoxy-phenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl] piperazine hydrochloride (IP-145), 1-[1-(4-fluoro-benzyl)-piperidin-4-yl]-4(4-fluorophenyl)-piperazine hydrochloride (IP-156),1-(1-benzylpiperidin-4-yl)-4-(2-chlorophenyl)-piperazine (IP-158), 1-[1-(4-fluoro-benzyl)-piperidin-4-yl]-4(4-fluorophenyl)-piperazine (IP-159), 4-[4-(1-benzyl-piperidin-4-yl)-piperazin-1-yl]-7-chloro-quinoline hydrochloride (IP-162), 1-(1-benzylpiperidin-4-yl)-4-(2-chlorophenyl)-piperazine hydrochloride (IP-163), 1-(1-benzylpiperidin-4-yl)-4-o-tolyl-piperazine hydrochloride (IP-164), 1-(1-benzyl-piperidin-4-yl)-4-(2-methoxy-phenyl)-piperazine hydrochloride (IP165), 1-o-tolyl-4-[1-(2-trifluoromethylbenzyl)-piperidin-4-yl] piperazine hydrochloride (IP-169), 1-phenyl-4-[1-(2-trifluoromehtylbenzyl)-piperidin-4-yl] piperazine hydrochloride (IP-175), 1-(2-chlorophenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl]-piperazine hydrochloride (IP-176), 1-[1-(1-phenyl-ethyl-) piperidin-4-yl]-4-o-tolyl-piperazine (IP-213), 1-[1-(1-phenyl-ethyl-) piperidin-4-yl]-4-o-tolyl-piperazine hydrochloride (IP-223), 1-(4-Fluoro-phenyl)-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-278), 1-(1-Benzyl-piperidin-4-yl)-4-pyridin-4-yl-piperazine hydrochloride (IP-283), 1-(4-Fluoro-phenyl)-4-{1-[1-(4-fluoro-phenyl)-1-methyl-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-334), 7-Chloro-4-[4-(4-phenyl-piperazin-1-yl)-piperidin-1-ylmethyl]-quinoline hydrochloride (IP-408), 1-[1-(1-Methyl-1-phenyl-ethyl)-piperidin-4-yl]-4-*o*-tolyl-piperazine hydrochloride (IP-440), 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-pyridin-4-yl-piperazine hydrochloride (IP-454), 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-*m*-tolyl-piperazine hydrochloride (IP-464), 1-[1-(1-Phenyl-ethyl)-

piperidin-4-yl]-4-*p*-tolyl-piperazine hydrochloride (IP-465), 1-(1-Benzyl-piperidin-4-yl)-4-phenyl-piperazine hydrochloride (IP-468), 1-(4-Nitro-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-469), 1-(3-Methyl-pyridin-4-yl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-473), 4-{4-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-phenylamine hydrochloride (IP-474), (4-{4-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-phenyl)-thiourea hydrochloride (IP-476), 1-Phenyl-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-477), 1-*o*-Tolyl-4-[1-(1-*p*-tolyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-483), 1-{1-[1-(4-Methoxy-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-484), 1-(4-Methoxy-2-methyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-485), 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-(4-propyl-phenyl)-piperazine (IP-490), 1-(4-Ethyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-503), 1-(4-Butyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-506), 1-(4-Fluoro-2-methyl-phenyl)-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-508), 1-{1-[1-(4-Fluoro-phenyl)-ethyl]-piperidin-4-yl}-4-(4-fluoro-2-trifluoromethyl-phenyl)-piperazine hydrochloride (IP-516), 1-*o*-Tolyl-4-[1-(2,2,2-trifluoro-1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-531), 1-{1-[1-(4-Chloro-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-536), 1-[1-(4-Fluoro-benzyl)-piperidin-4-yl]-4-(4-fluoro-2-methyl-phenyl)-piperazine hydrochloride (IP-543), 1-{1-[1-(4-Ethynyl-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-544), 1-{1-[1-(3,4-Dichloro-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine (IP-545), 1-benzyl-4-(1-benzyl-piperidin-4-yl)-piperazine (IP-121) and 1-benzyl-4-(1-benzyl-piperidin-4-yl)-piperazine hydrochloride (IP-138), 4-[4-(1-Benzyl-piperidin-4-yl)-piperazin-1-ylmethyl]-quinoline hydrochloride (IP-366), 4-[4-(1-Benzyl-piperidin-4-yl)-piperazin-1-ylmethyl]-7-chloro-quinoline hydrochloride (IP-384), 4-[4-(4-Benzyl-piperazin-1-yl)-piperidin-1-ylmethyl]-7-chloro-quinoline hydrochloride (IP-409), 4-[4-(1-quinoline-4-ylmethyl-piperidin-4-yl)-piperazin-1-ylmethyl]-quinoline hydrochloride (IP-439), 1-(4-Fluoro-benzyl)-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-529), 1-[1-(4-Fluoro-phenyl)-ethyl]-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-532).

Preferably, the compound is for treatment of infection by HCV.

The invention also encompasses compound selected in the group consisting of 1-(2-methoxy-phenyl)-4-(1-phenyl-piperidin-4-yl) piperazine (IP-153), 1-(2-methoxy-phenyl)-4-(1-phenyl-piperidin-4-yl) piperazine hydrochloride (IP-179), 4-(4-phenyl-piperazin-1-yl)-3,4,5,6-tetrahydro-2H-[1,4']-bipyridinyl (IP-189), 4-(4-phenyl-piperazin-1-yl)-3,4,5,6-tetrahydro-2H-[1,4']-bipyridinyl hydrochloride (IP-193), 7-chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl]-quinoline (IP-224), 7-chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl]-quinoline hydrochloride (IP-233), 7-Chloro-4-[4-(4-phenyl-

piperazin-1-yl)-piperidin-1-yl]-quinoline trifluoroacetic (IP-292), 1-benzyl-4-(phenyl-piperido-4-yl)-piperazine (IP-119), 4-[4-(4-benzyl-piperazin-1-yl)-piperidin-1-yl]-7-chloro-quinoline (IP-122), 4-[4-(4-benzyl-piperazin-1-yl)-piperidin-1-yl]-7-chloro-quinoline hydrochloride (IP-140), 1-benzyl-4-(phenyl-piperido-4-yl)-piperazine hydrochloride (IP-154), 1-(4-Fluoro-benzyl)-4-[1-(4-fluoro-phenyl)-piperidin-4-yl]-piperazine hydrochloride (IP-275), 1-[1-(4-Fluoro-phenyl)-ethyl]-4-[1-(4-fluoro-phenyl)-piperidin-4-yl]-piperazine hydrochloride (IP-308), 7-Chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl-methyl]-quinoline hydrochloride (IP-385), 1-(1-Phenyl-ethyl)-4-(1-*o*-tolyl-piperidin-4-yl)-piperazine hydrochloride (IP-453), 4-[4-(1-benzyl-piperidin-4-yl)-piperazin-1-yl]-7-chloro-quinoline (IP-139), 1-[1-(4-fluoro-benzyl)-piperidin-4-yl]-4(4-fluorophenyl)-piperazine hydrochloride (IP-156), 1-[1-(4-fluoro-benzyl)-piperidin-4-yl]-4(4-fluorophenyl)-piperazine (IP-159), 4-[4-(1-benzyl-piperidin-4-yl)-piperazin-1-yl]-7-chloro-quinoline hydrochloride (IP-162), 1-(1-benzylpiperidin-4-yl)-4-o-tolyl-piperazine hydrochloride (IP-164), 1-o-tolyl-4-[1-(2-trifluoromethylbenzyl)-piperidin-4-yl] piperazine hydrochloride (IP-169), 1-(2-chlorophenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl]-piperazine hydrochloride (IP-176), 1-[1-(1-phenyl-ethyl-) piperidin-4-yl]-4-o-tolyl-piperazine (IP-213) and 1-[1-(1-phenyl-ethyl-) piperidin-4-yl]-4-o-tolyl-piperazine hydrochloride (IP-223), 1-(4-Fluoro-phenyl)-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-278), 1-(1-Benzyl-piperidin-4-yl)-4-pyridin-4-yl-piperazine hydrochloride (IP-283), 1-(4-Fluoro-phenyl)-4-{1-[1-(4-fluoro-phenyl)-1-methyl-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-334), 7-Chloro-4-[4-(4-phenyl-piperazin-1-yl)-piperidin-1-ylmethyl]-quinoline hydrochloride (IP-408), 1-[1-(1-Methyl-1-phenyl-ethyl)-piperidin-4-yl]-4-*o*-tolyl-piperazine hydrochloride (IP-440), 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-pyridin-4-yl-piperazine hydrochloride (IP-454), 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-*m*-tolyl-piperazine hydrochloride (IP-464), 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-*p*-tolyl-piperazine hydrochloride (IP-465), 1-(4-Nitro-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-469), 1-(3-Methyl-pyridin-4-yl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-473), 4-{4-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-phenylamine hydrochloride (IP-474), (4-{4-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-phenyl)-thiourea hydrochloride (IP-476), 1-Phenyl-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-477), 1-*o*-Tolyl-4-[1-(1-*p*-tolyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-483), 1-{1-[1-(4-Methoxy-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-484), 1-(4-Methoxy-2-methyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-485), 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-(4-propyl-phenyl)-piperazine (IP-490), 1-(4-Ethyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-503), 1-(4-Butyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-506), 1-(4-Fluoro-2-methyl-phenyl)-4-{1-[1-(4-fluoro-

phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-508), 1-{1-[1-(4-Fluoro-phenyl)-ethyl]-piperidin-4-yl}-4-(4-fluoro-2-trifluoromethyl-phenyl)-piperazine hydrochloride (IP-516), 1-*o*-Tolyl-4-[1-(2,2,2-trifluoro-1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-531), 1-{1-[1-(4-Chloro-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-536), 1-[1-(4-Fluoro-benzyl)-piperidin-4-yl]-4-(4-fluoro-2-methyl-phenyl)-piperazine hydrochloride (IP-543), 1-{1-[1-(4-Ethynyl-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-544), 1-{1-[1-(3,4-Dichloro-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine (IP-545).

Preferably, these compounds are for use as a medicament.

The invention further encompasses compounds for use as a medicament selected in the group consisting of 1-(2-methoxy-phenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl] piperazine (IP-038), 1-[1-(2-Methoxy-benzyl)-piperidin-4-yl]-4-(2-methoxy-phenyl)-piperazine (IP-075), 1-[1-(2-Chloro-benzyl)-piperidin-4-yl]-4-(2-methoxy-phenyl)-piperazine (IP-076), 1-(2-Fluoro-phenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl]-piperazine (IP-077), 1-(1-Benzyl-piperidin-4-yl)-4-(4-methoxy-phenyl)-piperazine (IP-078), 1-[1-(4-Ethyl-benzyl)-piperidin-4-yl]-4-phenyl-piperazine (IP-079), 1-(2-methoxy-phenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl] piperazine hydrochloride (IP-145), 1-(1-benzylpiperidin-4-yl)-4-(2-chlorophenyl)-piperazine (IP-158), 1-(1-benzylpiperidin-4-yl)-4-(2-chlorophenyl)-piperazine hydrochloride (IP-163), 1-phenyl-4-[1-(2-trifluoromethylbenzyl)-piperidin-4-yl] piperazine hydrochloride (IP-175), 1-benzyl-4-(1-benzyl-piperidin-4-yl)-piperazine (IP-121) and 1-benzyl-4-(1-benzyl-piperidin-4-yl)-piperazine hydrochloride (IP-138), 1-(1-Benzyl-piperidin-4-yl)-4-phenyl-piperazine hydrochloride (IP-468).

Preferably, these compounds are for use as an antiviral agent.

Even more preferably, these compounds are for treatment of HCV infection.

The invention also relates to pharmaceutical compositions comprising:

- an effective amount of a compound according to the invention,
- a pharmaceutically acceptable carrier.

The term "C1-C6 alkyl " refers to straight or branched hydrocarbon groups having 1 to 6 carbon atoms such as methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl or *t*-butyl.

The term "C1-C6 alkoxy" refers to a C1-C6 alkyl linked to an oxygen atom. Preferred alkoxy groups are methoxy and ethoxy groups.

The term "C3-C6 cycloalkyl" refers to cyclic hydrocarbon groups of 3 to 6 carbon atoms. Preferred, cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "heterocyclic group" refers to fully saturated or unsaturated, including aromatic or nonaromatic cyclic groups, for example 5 to 6 membered monocyclic groups or 7 to 11 membered bicyclic ring systems which have at least one heteroatom. Each ring

of the heterocyclic group may have at least one heteroatom selected from nitrogen atoms, oxygen atoms and/or sulphur atoms. Preferred heterocyclic groups are pyrimidine, pyridine, thiophene and pyrrole.

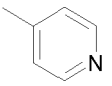
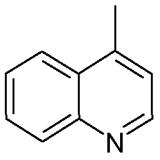
The term 'halogen" refers to F, Cl, Br and I.

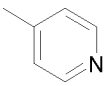
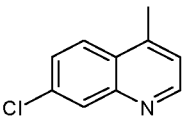
The compounds of formula I form salts which are also within the scope of this invention. Reference to a compound of the present invention is understood to include reference to salts thereof. The term "salts" refers to acidic or basic salts formed with organic and/or inorganic acids and bases.

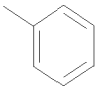
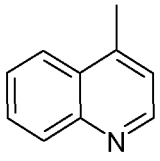
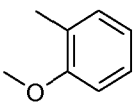
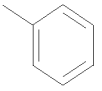
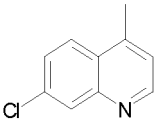
For convenience, the compounds of the invention have been classified into 4 clusters:

Cluster 1

Includes all the compounds disclosed in the present invention having the formula I, wherein R1 and R2 are, each independently, an optionally substituted phenyl, heterocyclic group or quinoline (in this cluster, R1 is never -R'-R3 and R2 is never -R''-R4) such as previously defined. Preferably, R1 is phenyl, pyridine or quinoline, each of which is unsubstituted or substituted with one or more substituent groups and R2 is phenyl or quinoline, each of which is unsubstituted or substituted with one or more substituent groups.

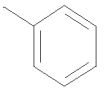
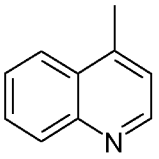
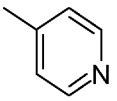
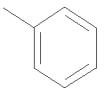
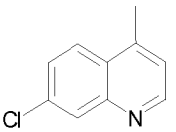
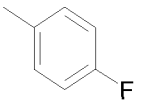
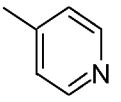
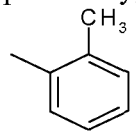
In this cluster of compounds, R1 is preferably selected from  ,  and  , which are unsubstituted or substituted with one or more substituent group.

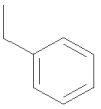
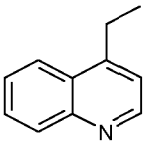
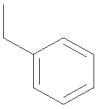
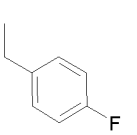
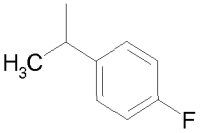
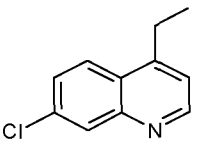
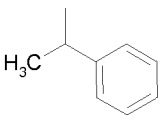
More preferably, R1 is selected from  ,  and  , which are unsubstituted or substituted with one or more substituent group.

In this cluster of compounds, R2 is preferably selected from  and  , which are substituted or not with one or more substituent group. More preferably, R2 is selected from  ,  and  , which are unsubstituted or substituted with one or more substituent group.

Cluster 2

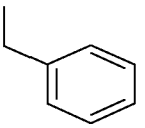
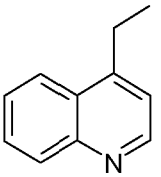
Includes all the compounds disclosed in the present invention having the formula I, wherein R1 is an optionally substituted phenyl, heterocyclic group or quinoline (in this cluster, R1 is never –R'-R3) such as previously defined. R2 is -R''-R4 such as previously defined: R'' is a methylene group, optionally substituted by one or two lower alkyl groups, R4 is phenyl, a heterocyclic group or quinoline optionally substituted by one or more substituent groups. Preferably, R1 is phenyl or quinoline each of which is unsubstituted or substituted with one or more substituent groups and R2 is benzyl which is unsubstituted or substituted with one or more substituent groups, or R2 is CH_2-R4 or -$CH(CH_3)$-R4, and R4 is a phenyl or quinoline each of which is unsubstituted or substituted with one or more substituted groups.

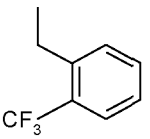
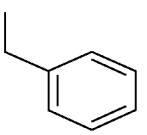
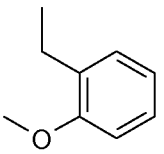
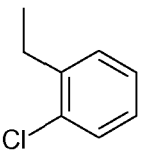
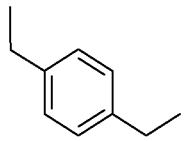
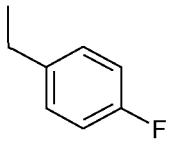
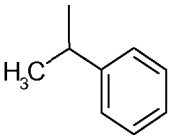
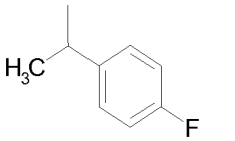
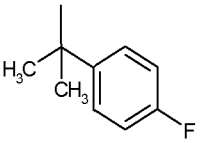
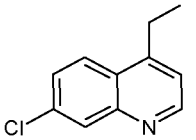
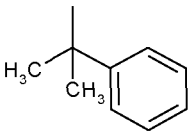
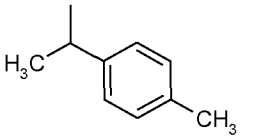
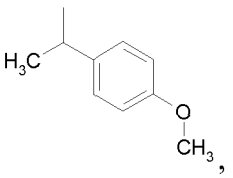
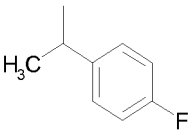
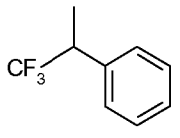
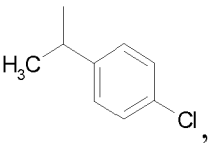
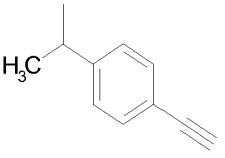
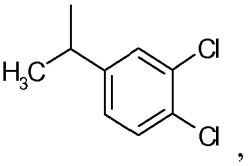
In this cluster of compounds, R1 is preferably selected from  ,  and  which are unsubstituted or substituted with one or more substituent groups. More preferably, R1 is selected from  ,  ,  ,  and  , which are unsubstituted or substituted with one or more substituent groups.

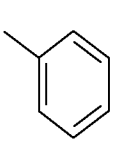
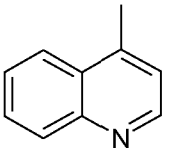
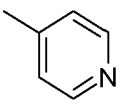
R2 is preferably selected from  and  which are substituted or not with one or more substituent group. More preferably, R2 is selected from  ,  ,  ,  and  , which are unsubstituted or substituted with one or more substituent groups.

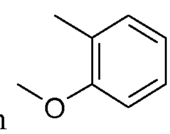
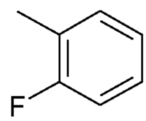
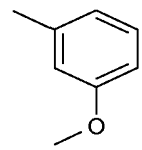
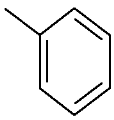
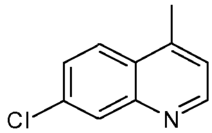
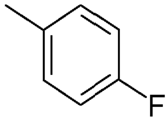
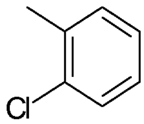
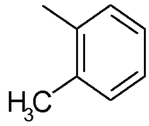
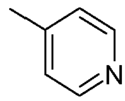
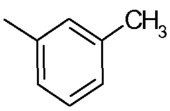
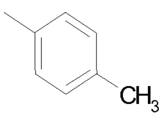
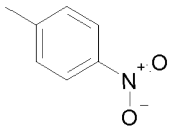
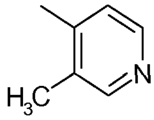
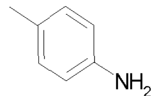
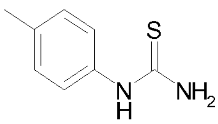
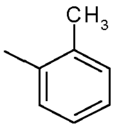
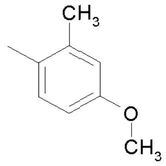
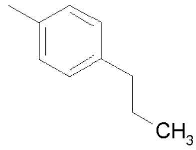
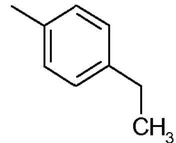
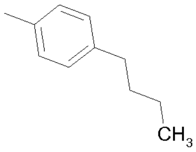
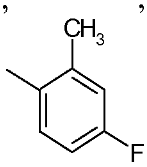
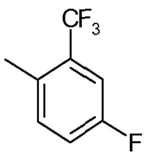
Cluster 3

Includes all the compounds disclosed in the present invention having the formula I, wherein R1 is -R'-R3 such as previously defined: R' is a methylene group, unsubstituted or substituted with one or more substituent groups wherein the substituent groups are selected from C1-C6 alkyl and CF_3, R3 is phenyl, a heterocyclic group or quinoline optionally substituted by one or more substituent groups. R2 is an optionally substituted phenyl, heterocyclic group or quinoline (R2 is never -R"-R4) such as previously defined. Preferably, R1 is benzyl which is unsubstituted or substituted with one or more substituent groups or R1 is $-CH_2$-R3, $CH(CH_3)$-R3, $-C(CH_3)_2$-R3 or $-CH(CF_3)$-R3; R2 is phenyl, pyridine or quinoline, each of which is unsubstituted or substituted with one or more substituent groups, and R3 is phenyl which is unsubstituted or substituted with one or more substituent groups, or quinoline which is unsubstituted or substituted with one or more substituent groups.

In preferred embodiments, R1 is selected from  and  , which are unsubstituted or substituted with one or more substituent groups.

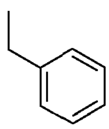
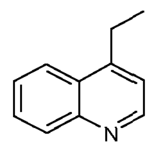
More preferably, R1 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  , which are unsubstituted or substituted with one or more substituent groups.

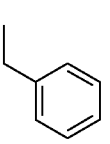
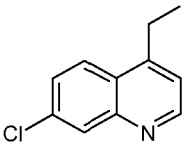
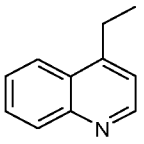
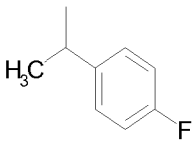
Preferably, R2 is selected from,  ,  and  , which are unsubstituted or substituted with one or more substituent groups.

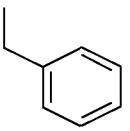
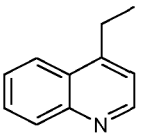
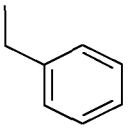
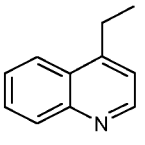
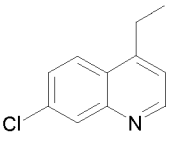
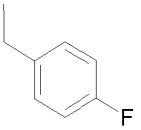
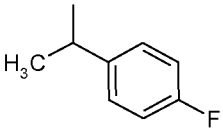
More preferably, R2 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  , which are unsubstituted or substituted with one or more substituent groups.

Cluster 4

Includes all the compounds disclosed in the present invention having the formula I, wherein R1 is –R'-R3 and R2 is –R"-R4 such as previously defined: R' and R" are independently a methylene group, optionally and independently substituted by one or two C1-C6 alkyl groups, R3 and R4 are, each independently, phenyl, a heterocyclic group or quinoline optionally substituted by one or more substituents. Preferably, R1 is benzyl which is unsubstituted or substituted with one or more substituent groups or R1 is -CH_2-R3 or -CH(CH_3)-R3 and R2 is benzyl which is unsubstituted or substituted with one or more substituent groups or R2 is -CH_2-R4 or -CH(CH_3)-R4, R3 and R4 are independently selected from phenyl or quinoline unsubstituted or substituted with one or more substituent groups.

In preferred embodiments, R1 is selected from  and  which are unsubstituted or substituted with one or more substituent groups.

In more preferred embodiments, R1 is selected from  ,  ,  and  , which are unsubstituted or substituted with one or more substituent groups.

In preferred embodiments, R2 is selected from  and  , which are unsubstituted or substituted with one or more substituent groups. In more preferred embodiments, R2 is selected from  ,  ,  ,  and  , which are unsubstituted or substituted with one or more substituent groups.

The compounds of formula I and their salts are characterized by valuable therapeutic antiviral properties. Further, it has been surprisingly found that the compounds of the present invention are active on HCV.

The present invention relates to compounds as described herein for use as a medicament.

Preferably the compounds of the present invention are for treatment of viral infections including HCV infection.

The present invention also encompasses pharmaceutical compositions comprising compounds as described herein. The present invention provides pharmaceutical compositions comprising:

a) an effective amount of a compound as described herein,

b) a pharmaceutically acceptable carrier.

As used herein, "pharmaceutically-acceptable carriers" includes any and all solvents, dispersion media, coatings, and the like that are physiologically compatible.

The compositions of the invention may be in a variety of forms. These include for example liquid, semi-solid, and solid dosage forms, but the preferred form depends on the intended mode of administration and therapeutic application.

These pharmaceutical compositions are preferably for systemic administration such as oral, percutaneous and parenteral administration. For example, in preparing the compositions for parenteral administration, the carrier will usually comprises sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprise saline solution, glucose solution or a mixture of saline and glucose solution. Injectable solutions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the composition suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin.

The compound as described herein may be orally administered. As solid compositions for oral administration, tablets, pills, powders (gelatine capsules, sachets) or granules may be used. In these compositions, the active ingredient according to the invention is mixed with one or more inert diluents, such as starch, cellulose, sucrose, lactose or silica, under an argon stream. These compositions may also comprise substances other than diluents, for example one or more lubricants such as magnesium stearate or talc, a coloring, a coating (sugar-coated tablet) or a glaze.

As liquid compositions for oral administration, there may be used pharmaceutically acceptable solutions, suspensions, emulsions, syrups and elixirs containing inert diluents such as water, ethanol, glycerol, vegetable oils or paraffin oil. These compositions may comprise substances other than diluents, for example wetting, sweetening, thickening, flavouring or stabilizing products.

The doses depend on the desired effect, the duration of the treatment and the route of administration used.

The invention is also related to the use of a compound as described herein for the manufacture of a medicament for the treatment of viral infections including treatment of HCV infections.

The present invention also provides methods for treating viral infections and particularly HCV infections including administering an effective amount of a compound as described herein to a human or to a patient in need thereof.

Exemplary compounds of the present invention can be readily prepared according to the methods described herein using readily available starting materials, reagents and conventional synthetic procedures. It is also possible to make use of variants of these process steps, which in themselves are known to and well within the preparatory skill of the medicinal chemist.

FIGURES

Figure 1 : Structure of the HCV RNA replicon of cell line Huh7. The structure of HCV RNA replicon is composed of the 5' UTR contains HCV-IRES, the NPTII gene, the EMCV-IRES, and HCV sequences from NS3 up to the autenthic 3' UTR : NPTII gene drives the production of neomycin phosphotransferase II (NPTII) protein. NPTII expression is under the control of the HCV IRES, whereas expression of proteins NS3 to NS5B is controlled by the EMCV IRES. The NS3 protein cleaves the HCV polyprotein to release the mature NS3, NS4A, NS4B, NS5A and NS5B proteins that are required for HCV replication.

Figure 2 : Detection of HCV Replicon by Real-Time RT-PCR versus NPTII ELISA.

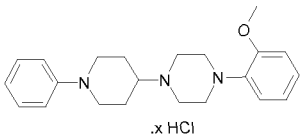
Figure 3 : Correlation of molecule inhibitor activity in Real-Time RT-PCR and NPTII ELISA assays

Figures 4, 5, 6 : Dose-dependent inhibition of HCV replicon by compounds according to the invention

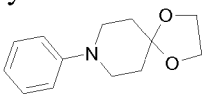
EXAMPLES

Example 1 : Synthesis of molecules of Cluster 1

I/ 1-(2-methoxy-phenyl)-4-(1-phenyl-piperidin-4-yl) piperazine hydrochloride :



I-1/ 1-phenyl-4-piperidone ethylene ketal

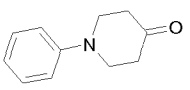


1.6 ml (15.36 mmol) of bromobenzene, 1.8 ml (13.97 mmol) of 4-piperidone ethylene ketal, 157 mg (0.7 mmol) of Palladium acetate 5% mol, 1.3g (13.97 mmol) of sodium tert-butoxyde, 297 mg (0.7 mmol) of 2-Di-tert-butylphosphino-2,4,6-triisopropylbiphenyl were added in 8 ml of anhydrous toluene and 1.6 ml of butanol under nitrogen atmosphere. The reaction mixture was heated for 12h at 130°C.

The reaction mixture was filtered through a plug of Celite, washed with ethyl acetate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum ether ethyl acetate 5/5) to give 1.68g of brown oil (yield 55%).

LCMS: M+1=220; ^{1}H NMR ($CDCl_3$)

I-2/ 1-phenyl-4-piperidone:



1.68g (7.66 mmol) of 1-phenyl-4-piperidone ethylene ketal obtained in the previous step were added in 13 ml of HCl (4N), 13 ml of tetrahydrofuran and stirred at room temperature for two days. The reaction mixture was heated at 60°C for 7h (TLC petroleum ether-ethyl acetate 9/1) and was allowed to stand at room temperature for a night before heating for 4h at 60°C. After being cooled, the reaction mixture was basified with NaOH (1N) then extracted with ethyl acetate. Organic layer was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (CH_3CN-H_2O 4/6) to yield 895 mg of yellow oil (67%). ^1H NMR ($CDCl_3$) as described in the literature (Org.Lett.5 (23), 2003, p4397)

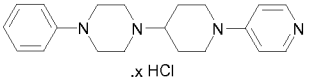
I-3/ 1-(2-methoxy-phenyl)-4-(1-phenyl-piperidin-4-yl) piperazine (IP-153):

808 mg (4.12 mmol) of 1-(2-Methoxyphenyl) piperazine and 491 mg (2.8 mmol) of 1-phenyl-4-piperidone were added in 2 ml of dichloromethane and stirred. After evaporation of the dichloromethane, 1.17 ml (3.92 mmol) of Titanium (IV) isopropoxyde was added under nitrogen atmosphere and heated for 15 minutes at 45°C. 4 ml of pure and dry ethanol were then added and the reaction mixture was heated for 3h30 at 45°C. 390 mg (6.17 mmol) of sodium cyanoborohydride were added slowly and the reaction was further stirred at 45°C for 3h45. After one night at room temperature, the reaction mixture was poured onto 117 ml of water and stirred for 1h. The mixture was filtered through a plug of Celite, washed with dichloromethane and the aqueous layer was extracted with dichloromethane. Organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane-ethanol 99/1) and triturated with diethyl ether to give 37 mg of white solid (yield 4%). LCMS: M+1=352; ^1H NMR ($CDCl_3$)

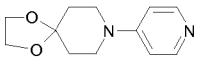
I-4/ 1-(2-methoxy-phenyl)-4-(1-phenyl-piperidin-4-yl) piperazine hydrochloride (IP-179):

397 mg (1.13 mmol) of the previous product were added onto 1 ml of dichloromethane. 3.4 ml of 1N HCl aqueous solution were added to the reaction mixture and then stirred at room temperature for 3h. Both layers were separated and the aqueous one was concentred *in vacuo*. The solid residue was recrystallized in 6 ml of ethanol to yield 309 mg of a white solid (72%). LCMS: M+1=352; ^1H NMR (DMSO).

II/ 4-(4-phenyl-piperazin-1-yl)-3,4,5,6-tetrahydro-2H-[1,4']-bipyridinyl hydrochloride :



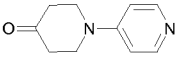
II-1/ 8-pyridin-4-yl-1,4-dioxa-8-aza-spiro [4.5] decane :



8.4g (43.2 mmol) of 4-Bromopyridine hydrochloride, 5.5 ml (43.2 mmol) of 4-piperidone ethylene ketal, 485 mg (2.16 mmol) of Palladium acetate 5% mol, 8.3g (86.4 mmol) of sodium tert-butoxyde, 917 mg (2.16 mmol) of 2-Di-tert-butylphosphino-2,4,6-triisopropylbiphenyl were added in 25 ml of anhydrous toluene and 5 ml of butanol under argon atmosphere. The reaction mixture was refluxed for 16h. One more equivalent of sodium tert-butoxyde was added and the reflux was maintained for 8h.

The reaction mixture was filtered through a plug of Celite, washed with ethyl acetate and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (dichloromethane 100% to dichloromethane-methanol 95/5) to give 3.6g of brown solid (yield 38%). ^{1}H NMR ($CDCl_3$).

II-2/ 2,3,5,6-tetrahydro-[1,4']bipyridinyl-4-one:



3.29g (14.94 mmol) of 8-pyridin-4-yl-1,4-dioxa-8-aza-spiro [4.5] decane obtained in the previous step were added in 30 ml of HCl (4N), 30 ml of tetrahydrofuran and refluxed for two days (TLC dichloromethane 100%). After being cooled, the reaction mixture was basified with NaOH (2N) then extracted with ethyl acetate. Organic layer was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (CH_3CN-H_2O 15/85) to yield 2.3g of light brown solid (87%). ^{1}H NMR ($CDCl_3$).

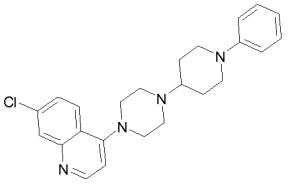
II-3/ 4-(4-phenyl-piperazin-1-yl)-3,4,5,6-tetrahydro-2H-[1,4']-bipyridinyl (IP-189):

1.58g (7.94 mmol) of 1-Phenylpiperazine hydrochloride was washed with NaOH 1N just before addition to a solution of 700 mg (3.97 mmol) of 2,3,5,6-tetrahydro-[1,4']bipyridinyl-4-one (obtained in the previous step) in 4 ml of dichloromethane. After evaporation of the dichloromethane, 1.66 ml (5.56 mmol) of Titanium (IV) isopropoxyde were added under nitrogen and heated for 4h at 45°C. 8 ml of freshly distilled ethanol and 550 mg (8.74 mmol) of sodium cyanoborohydride were successively added slowly and the reaction was further stirred at 45°C for 3h. After one night at room temperature, the reaction mixture was poured onto 166 ml of water and stirred for 1h. The mixture was filtered through a plug of Celite and washed with dichloromethane. Aqueous layer was then extracted with dichloromethane and organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane-ethanol 99/1 to 9/1) and triturated with diethyl ether to give 409 mg of a white solid (yield 32%). LCMS: M+1=323; ^{1}H NMR ($CDCl_3$).

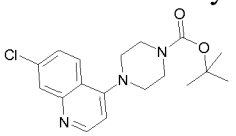
II-4/ 4-(4-phenyl-piperazin-1-yl)-3,4,5,6-tetrahydro-2H-[1,4']-bipyridinyl hydrochloride (IP-193):

217 mg (0.67 mmol) of the previous product was added onto 500µl of dichloromethane; 1.4 ml of HCl (1N in Et_2O) was added to the reaction mixture and stirred for 2h at room temperature. The precipitate was filtered, washed with chloroform and diethyl ether. The solid was finally washed with hot ethanol to yield 188 mg of a white solid (71%). LCMS: M+1=323; ^1H NMR (DMSO).

III/ 7-chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl]-quinoline:

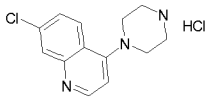


III-1/ 4-(7-chloro-quinolin-4-yl)-piperazine-1-carboxylic acid tert-butyl ester:



In a microwave sealed tube, 5 ml of dimethylformamide, 600 mg (3.03 mmol) of 4,7-Dichloroquinoline and 1.69g (9.09 mmol) of 1-Boc-piperazine were successively added. After heating the reaction mixture at 160°C for 40 minutes in a microwaves oven (TLC dichloromethane-methanol 95/5), it was treated with NaOH (1N), extracted with ethyl acetate and dichloromethane. Organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (acetonitrile-water 1/9 up to 95/5) to yield 919 mg of orange oil (87%). ^1H NMR ($CDCl_3$).

III-2/ 7-chloro-4-piperazin-1-yl-quinoline hydrochloride :

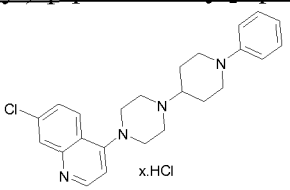


919 mg (2.64 mmol) of 4-(7-chloro-quinolin-4-yl)-piperazine-1-carboxylic acid tert-butyl ester previously obtained were solubilised into 16 ml of anhydrous methanol under argon atmosphere. 9.45 ml (13.2 mmol) of acetyl chloride were added and the reaction mixture was stirred at room temperature for two days (TLC dichloromethane-methanol 95/5). The mixture was evaporated to dryness and triturated with dichloromethane to yield 735 mg of pale yellow solid (98%). ^1H NMR (DMSO).

III-3/ 7-chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl]-quinoline (IP-224):

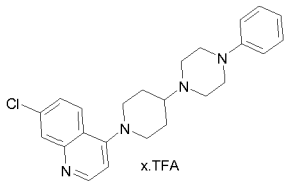
620 mg (2.5 mmol) of 1-chloro-4-piperazin-1-yl-quinoline hydrochloride previously obtained and 293 mg (1.67 mmol) of 1-phenyl-4-piperidone (obtained as described in protocol I/2) were solubilised into 6ml of freshly distilled ethanol and 696 µl (2.34 mmol) of Titanium (IV) isopropoxyde were added under nitrogen atmosphere. After heating the mixture during 3h at 45°C, 230 mg (3.67 mmol) of sodium cyanoborohydride were slowly added. The mixture was further stirred at 45°C for 3h, poured onto 70 ml of water and stirred for 1h. After filtration through a plug of Celite, the mixture was washed with dichloromethane and the aqueous layer was extracted with dichloromethane. Organic layer was dried over $MgSO_4$, filtered and concentrated under reduce pressure. The residue was then purified by silica gel column chromatography (acetonitrile-water 4/6 up to 95/5) to yield 230 mg of the expected compound (33%). LCMS: M+1=408; ^1H NMR (DMSO).

7-chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl]-quinoline hydrochloride (IP-233):

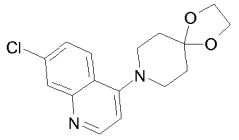


165 mg (0.41 mmol) of the previous product were solubilised in 1 ml of anhydrous dichloromethane and 860µl (0.86 mmol) of HCl 1N in diethyl ether were added. After stirring at room temperature for 4h, the precipitate was filtered and washed with dichloromethane to yield 120 mg of pale pink solid (65%). LCMS: M+1=407/409. ^1H NMR (DMSO).

IV/ 7-Chloro-4-[4-(4-phenyl-piperazin-1-yl)-piperidin-1-yl]-quinoline trifluoroacetic salt : (IP-292)



IV-1/ 7-chloro-4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-quinoline :

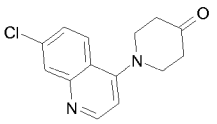


In a microwave sealed tube, 300 mg (1.51 mmol) of 4,7-Dichloroquinoline and 2.9 ml (22.7 mmol) of 4-Piperidone ethylene ketal were successively added with a few drops of NMP. The reaction mixture was heated at 200°C for 30 minutes in a microwaves oven (TLC petroleum ether-ethyl acetate 8/2). NaOH 1N was added to the mixture to reach

pH=12 and the aqueous layer was extracted with ethyl acetate. Organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane-ethanol 99/1) to yield 354 mg of yellow oil (85%).

LCMS: M+1=305; ^1H NMR ($CDCl_3$).

IV-2/ 1-(7-chloro-quinolin-4-yl)-piperidin-4-one:



348 mg (1.14 mmol) of 7-chloro-4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-quinoline previously obtained were added in a mixture of 2 ml of HCl (2N) and 2 ml of tetrahydrofuran. After heating the reaction mixture for 6h at 60°C (TLC acetonitrile-water 9/1), it was cooled and basified with NaOH (1N) then extracted with ethyl acetate. Organic layer was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (CH_3CN-H_2O 6/4) to yield 200 mg of yellow oil (67%).

LCMS: M+1=261; ^1H NMR ($CDCl_3$).

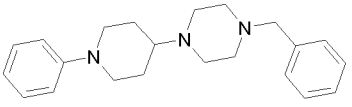
IV-3/ 7-Chloro-4-[4-(4-phenyl-piperazin-1-yl)-piperidin-1-yl]-quinoline trifluoroacetic salt: (IP-292):

In 0.5 ml of freshly distilled ethanol were added under argon 85 mg (0.33 mmol) of 1-(7-chloro-quinolin-4-yl)-piperidin-4-one previously obtained, 99 mg (0.5 mmol) of 1-Phenylpiperazine hydrochloride, 137 µl (0.46 mmol) of Titanium (IV) isopropoxyde. After refluxing the mixture during 4h, 46 mg (0.73 mmol) of sodium cyanoborohydride were added slowly. The mixture was further refluxed for 3h, then poured onto 10 ml of water and stirred for 1h at room temperature. After filtration through a plug of Celite, the mixture was washed with dichloromethane and the aqueous layer was extracted with dichloromethane. Organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by LCMS semi preparative (acetonitrile-water-trifluoroacetic acid) to yield 21 mg (10%) of the expected product.

LCMS: M+1=407, ^1H NMR (CD_3CN and CD_3CN+D_2O)

Exemple 2 : Synthesis of molecules of Cluster 2

I/ 1-benzyl-4-(phenyl-piperido-4-yl)-piperazine:



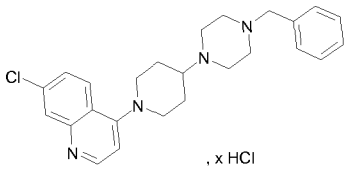
I-1/ 1-benzyl-4-(phenyl-piperido-4-yl)-piperazine (IP-119):

643 µl (3.71 mmol) of 1-Benzylpiperazine and 433 mg (2.48 mmol) of 1-phenyl-4-piperidone (obtained as described in protocol I/2 – molecules of cluster 1) were solubilised into 2 ml of dichloromethane. After evaporation of the dichloromethane, 1.03 ml (3.47 mmol) of Titanium (IV) isopropoxyde was added under nitrogen. After heating for 30 minutes at 45°C, 4 ml of freshly distilled ethanol were added and the mixture was further stirred at 45°C for 4h. 342 mg (5.45 mmol) of sodium cyanoborohydride were slowly added and the reaction was further stirred at 45°C for 3h. After one night at room temperature, the reaction mixture was poured onto 103 ml of water and stirred for 1h. After filtration through a plug of Celite, it was washed with dichloromethane and the aqueous layer was extracted with dichloromethane. Organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane-ethanol) to yield 358 mg of white solid (43%). LCMS: M+1=336; ^1H NMR ($CDCl_3$).

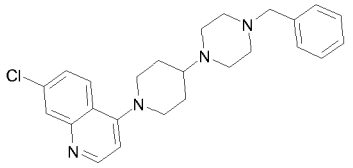
I-2/ 1-benzyl-4-(phenyl-piperido-4-yl)-piperazine hydrochloride (IP-154):

300 mg (0.89 mmol) of the product previously obtained were added onto 1 ml of dichloromethane; 3 ml of HCl 1N were then added and the reaction mixture was stirred at room temperature for 2h. Organic layer was separated and washed with HCl 1N; aqueous layer was then concentred *in vacuo* and the residue washed in hot ethanol to yield 321 mg of white solid (88%). LCMS: M+1=336. ^1H NMR (DMSO and DMSO+D_2O).

II/ 4-[4-(4-benzyl-piperazin-1-yl)-piperidin-1-yl]-7-chloro-quinoline hydrochloride.



II-1/ 4-[4-(4-benzyl-piperazin-1-yl)-piperidin-1-yl]-7-chloro-quinoline: (IP-122)

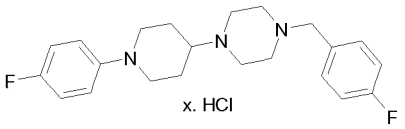


199µl (1.15 mmol) of 1-Benzylpiperazine and 200 mg (0.77 mmol) of 1-(7-chloro-quinolin-4-yl)-piperidin-4-one (obtained as described in Example 1, IV-2) were solubilised into 1 ml of dichloromethane. After evaporation of the solvent, 320 µl (1.07 mmol) of Titanium (IV) isopropoxyde were added under nitrogen. After heating for 1 h at 45°C, 2 ml of distilled ethanol and 106 mg (1.69 mmol) of sodium cyanoborohydride were successively added and the reaction mixture was further stirred at 45°C for 1h. After one night at room temperature, it was poured onto 32 ml of water and stirred for 1h then

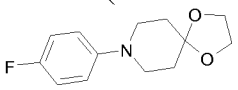
filtered through a plug of Celite and washed with dichloromethane. Aqueous layer was then extracted with dichloromethane and organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol-water 7/3) to yield 90 mg of a yellow gummy solid (28%).
LCMS: M+1=421; ^1H NMR ($CDCl_3$).

II-2/ 4-[4-(4-benzyl-piperazin-1-yl)-piperidin-1-yl]-7-chloro-quinoline hydrochloride (IP-140):
84.4 mg (0.2 mmol) of the product previously obtained were added onto 500µl of dichloromethane; 600 µl of HCl 1N were then added and the reaction mixture was then stirred at room temperature for 4h. Aqueous layer was concentred *in vacuo* and the residue was washed in hot ethanol (2 ml) to yield 40 mg of beige solid (38%).
LCMS : M+1=421 ; ^1H NMR (DMSO).

III/ 1-(4-Fluoro-benzyl)-4-[1-(4-fluoro-phenyl)-piperidin-4-yl]-piperazine hydrochloride (IP-275):

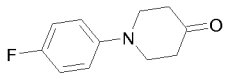


III-1/ 8-(4-Fluoro-phenyl)-1,4-dioxa-8-aza-spiro[4.5]decane:



Following the procedure previously described (Example 1, I-1) 1.02 ml (9.27 mmol) of 1-bromo-4-fluorobenzene, 1.08 ml (8.43 mmol) of 4-piperidone ethylene ketal, 95 mg (0.42 mmol) Palladium acetate 5% mol, 810 mg (8.43 mmol) of sodium tert-butoxyde, 178 mg (0.42 mmol) of 2-Di-tert-butylphosphino-2,4,6-triisopropylbiphenyl were allowed to react for one night at 130°C.
After workup and purification by silica gel column chromatography (cyclohexane-ethyl acetate 90/10) a yellow solid is obtained with 24% yield.
^1H NMR $CDCl_3$

III-2/ 1-(4-Fluoro-phenyl)-piperidin-4-one:

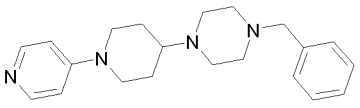


485 mg (2.04 mmol) of 8-(4-Fluoro-phenyl)-1,4-dioxa-8-aza-spiro[4.5]decane obtained in the previous step were added in 3.8 ml of aqueous HCl (4N), 3.8 ml of tetrahydrofuran and were refluxed for two days. The reaction mixture was basified with NaOH (6N) then extracted with ethyl acetate. Organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by reverse phase silica gel column chromatography (CH_3CN-H_2O 2/8) to yield 669 mg of yellow oil (69%).
LCMS M+1=194, ^1H NMR ($CDCl_3$)

III-3/ 1-(4-Fluoro-benzyl)-4-[1-(4-fluoro-phenyl)-piperidin-4-yl]-piperazine:
498 mg (2.56 mmol) of 1-(4-Fluorobenzyl)-piperazine and 330 mg (1.71 mmol) of 1-(4-Fluoro-phenyl)-piperidin-4-one (obtained in the previous step) were solubilised into 5 ml of dichloromethane. After evaporation of the dichloromethane, 712 µl (2.39 mmol) of Titanium (IV) isopropoxyde were added under nitrogen atmosphere. After heating for 4h at 45°C, 2 ml of freshly distilled ethanol and 236 mg (3.76 mmol) of sodium cyanoborohydride were added and the mixture was further stirred at 45°C for 4h. After one night at room temperature, the reaction mixture was poured onto water and stirred for 1h. After filtration through a plug of Celite, it was washed with dichloromethane and the aqueous layer was extracted with dichloromethane. Organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by reverse phase silica gel column chromatography (acetonitrile-water 50/50) to yield 89 mg of solid (14%).
^1H NMR (DMSO).

III-4/ 1-(4-Fluoro-benzyl)-4-[1-(4-fluoro-phenyl)-piperidin-4-yl]-piperazine hydrochloride (275):
The product obtained in the previous step (69 mg, 0.185 mmol) was dissolved in 0.5 ml of anhydrous dichloromethane, under nitrogen. 370µl (0.37 mmol) of HCl 1N in diethyl ether were added. The mixture was stirred for 2h at room temperature. The precipitate was filtered and washed with diethyl ether and chloroform, then dried under vacuum at 45°C to yield 44 mg of white solid (54%).
LCMS M+1=372, ^1H NMR (DMSO and DMSO+D_2O).

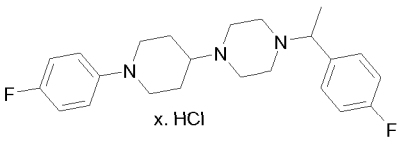
<u>IV/ 4-(4-Benzyl-piperazin-1-yl)-3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl (IP-282) and its hydrochloride salt:</u>



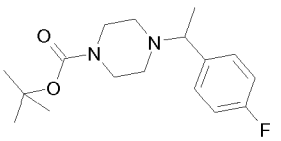
IV-1/ 4-(4-Benzyl-piperazin-1-yl)-3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl: (IP-282):
1.62 ml (9.36 mmol) of 1-Benzylpiperazine and 1.1g (6.24 mmol) of 2,3,5,6-tetrahydro-[1,4']bipyridinyl-4-one (obtained as described in Example 1, II-2) were solubilised into 5 ml of dichloromethane. After evaporation of the dichloromethane, 2 ml (8.74 mmol) of Titanium (IV) isopropoxyde were added under nitrogen atmosphere. After heating for 4h at 45°C, 8 ml of freshly distilled ethanol and 863 mg (13.76 mmol) of sodium cyanoborohydride were added and the mixture was further stirred at 45°C for 3h30. After one night at room temperature, the reaction mixture was poured onto 200 ml of water and stirred for 1h. After filtration through a plug of Celite, it was washed with dichloromethane and the aqueous layer was extracted with dichloromethane. Organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane-ethyl acetate 8/2) then triturated in diethyl ether to yield 447 mg of an off-white solid (21%).
LCMS M+1=337, ^{1}H NMR ($CDCl_3$).

IV-2/ 4-(4-Benzyl-piperazin-1-yl)-3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl hydrochloride:
The product obtained in the previous step (200 mg, 0.6 mmol) was dissolved in 1 ml of anhydrous dichloromethane, under nitrogen atmosphere. 2ml (1.8 mmol) of HCl 1N in diethyl ether were added. The mixture was stirred for 1h at room temperature. The precipitate was filtered and washed with cold ethanol, then freeze-dried to yield 99 mg of an off-white solid (37%).
LCMS M+1=337, ^{1}H NMR (DMSO and DMSO+D_2O).

V/ 1-[1-(4-Fluoro-phenyl)-ethyl]-4-[1-(4-fluoro-phenyl)-piperidin-4-yl]-piperazine hydrochloride (IP-308):



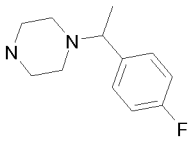
V-1/ 4-[1-(4-Fluoro-phenyl)-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester:



1g (5.36 mmol) of 1-Boc-piperazine and 975 µl (8.05 mmol) of 4'-fluoroacetophenone were solubilised into 15 ml of dichloromethane. After evaporation of the solvent, 2.2 ml (7.5 mmol) of Titanium (IV) isopropoxyde were added under nitrogen atmosphere and the mixture was heated for 4h at 45°C. 6 ml of distilled ethanol and 741 mg (11.8 mmol) of sodium cyanoborohydride were added and the mixture was further stirred at 45°C for 4h.

After one night at room temperature, the reaction mixture was poured onto water and stirred for 1h then; it was filtered through a plug of Celite and washed with dichloromethane. Aqueous layer was then extracted with dichloromethane and Organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by reverse phase silica gel column chromatography (methanol-water 50/50 to 100-0) to yield 657 mg of yellow oil (39%).
LCMS M+1=309, ^1H NMR ($CDCl_3$).

V-2/ 1-[1-(4-Fluoro-phenyl)-ethyl]-piperazine:



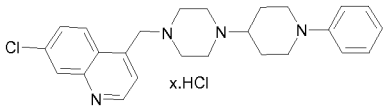
607 mg (1.968 mmol) of 4-[1-(4-Fluoro-phenyl)-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester obtained in the previous step were solubilised in 3 ml of dichloromethane. 253 µl (3.29 mmol) of trifluoroacetic acid were added dropwise to the solution and the reaction mixture was stirred for 1.5 day at room temperature. After evaporation to dryness, the residue was taken up in dichloromethane and washed with NaOH (1N). Organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to yield 403 mg of yellow oil (99%) which was used in the next step without further purification.
LCMS M+1=209, ^1H NMR ($CDCl_3$).

V-3/ 1-[1-(4-Fluoro-phenyl)-ethyl]-4-[1-(4-fluoro-phenyl)-piperidin-4-yl]-piperazine hydrochloride (IP-308):
400mg (1.92 mmol) of 1-[1-(4-Fluoro-phenyl)-ethyl]-piperazine and 300 mg (1.55 mmol) of 1-(4-Fluoro-phenyl)-piperidin-4-one (prepared as described in Example 2, III-2) were solubilised into dichloromethane. After evaporation of the solvent, 628 µl (2.17 mmol) of Titanium (IV) isopropoxyde were added under nitrogen atmosphere and the mixture was heated for 4h at 45°C. 2 ml of distilled ethanol and 214 mg (11.62 mmol) of sodium cyanoborohydride were added and the mixture was further stirred at 45°C for 4h. After one night at room temperature, the reaction mixture was poured onto water and stirred for 1h then; it was filtered through a plug of Celite and washed with dichloromethane. Aqueous layer was then extracted with dichloromethane and Organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by LCMS semi preparative (acetonitrile-water-trifluoroacetic acid) to yield 47 mg of white solid as a trifluoroacetic acid salt.
LCMS M+1=386, ^1H NMR (DMSO and DMSO+D_2O).

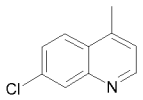
A sample of this compound was taken up in water and basified with NaOH (1N). Aqueous layer was extracted with dichloromethane, dried over $MgSO_4$ and evaporated to dryness. The residue was solubilised in anhydrous dichloromethane and two equivalents of HCl 1N in diethyl ether were added. The mixture was stirred for 2h at room temperature. The precipitate was filtered and washed with diethyl ether. The solid was freeze-dried to yield a white solid as hydrochloride salt (IP-308).

LCMS M+1=386, ^{1}H NMR (DMSO and DMSO+D_2O).

VI/ 7-Chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl-methyl]-quinoline hydrochloride: (IP-385)



VI-1/ 7-Chloro-4-methyl-quinoline:

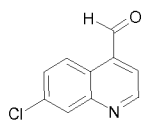


Prepared as described in J.Med.Chem.2008.p1278: 10g (50 mmol) of 4,7-dichloroquinoline were added in 70 ml of anhydrous tetrahydrofuran under nitrogen atmosphere. Thereafter, 213 mg (0.4 mmol) of [1,2-Bis(diphenylphosphino)ethane]dichloronickel(II) were added. The reaction mixture was then cooled to 0°C and 72 ml (101 mmol) of methyl magnesium bromide 1.4M solution in toluene/THF (75/25) was slowly added. The mixture was allowed to warm at room temperature and was stirred for 2h, and then it was refluxed for 8h.

The reaction mixture was poured onto saturated NH_4Cl and it was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by silica gel column chromatography (petroleum ether-ethyl acetate 85/15) to yield 5.91g (66%) of solid.

LCMS M+1=178, ^{1}H NMR ($CDCl_3$).

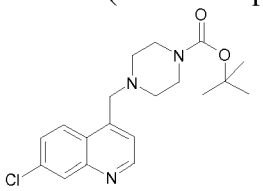
VI-2/ 7-Chloro-quinoline-4-carbaldehyde:



Prepared as described in J.Med.Chem.2008.p1278: 5.91g (33.27 mmol) of 7-Chloro-4-methyl-quinoline (obtained in the previous step) and 5.9g (53 mmol) of Selenium (IV) oxide were added in 70 ml of bromobenzene and heated at 170°C for 18h. The reaction mixture was filtered through a plug of Celite and the filtrate was concentrated to dryness.

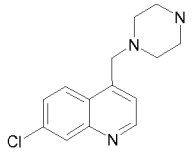
The residue was purified by silica gel column chromatography (petroleum ether-ethyl acetate 8/2) to yield 2.7g (42%) of solid.
^{1}H NMR ($CDCl_3$).

VI-3/ 4-(7-Chloro-quinolin-4-ylmethyl)-piperazine-1-carboxylic acid tert-butyl ester:



500 mg (2.61 mmol) of 7-Chloro-quinoline-4-carbaldehyde (obtained in the previous step) and 535 mg (2.87 mmol) of Boc-piperazine were added in dry methanol, under nitrogen atmosphere. A few drops of glacial acetic acid were added and the mixture was stirred at room temperature for 5h30. Thereafter, 197 mg (3.13 mmol) of sodium cyanoborohydride were slowly added and the mixture was stirred for one night further at the same temperature. The reaction mixture was basified with saturated $NaHCO_3$ and extracted with dichloromethane, dried over $MgSO_4$ and evaporated to dryness. The residue was purified by silica gel column chromatography (dichloromethane-ethyl acetate 9/1) to yield 730 mg (77%) of white solid.
LCMS M+1=362/364, ^{1}H NMR ($CDCl_3$).

VI-4/ 7-Chloro-4-piperazin-1-yl-methyl-quinoline :



730 mg (2.02 mmol) of 4-(7-Chloro-quinolin-4-ylmethyl)-piperazine-1-carboxylic acid tert-butyl ester (obtained in the previous step) were solubilised in 14 ml of dry methanol under nitrogen atmosphere. 720 µl (10.09 mmol) of acetyl chloride were added and the reaction mixture was stirred for 8h at room temperature. The precipitate was then filtered, washed with chloroform and taken up in NaOH 1N. Aqueous layer was extracted with chloroform, dried over $MgSO_4$, filtered and evaporated to dryness to afford 294 mg (56%) of a white solid which was used without further purification.
LCMS M+1=262/264, ^{1}H NMR ($CDCl_3$).

VI-5/ 7-Chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl-methyl]-quinoline: (IP-377):
260 mg (0.99 mmol) of 7-Chloro-4-piperazin-1-yl-methyl-quinoline (obtained in the previous step) and 116 mg (0.66 mmol) of 1-phenyl-4-piperidone (obtained as described in

Example 1, I-2) were treated as described in Example 2, I-1. The residue was purified by silica gel column chromatography (dichloromethane-methanol 95/5) to yield 48 mg (17%) of solid.

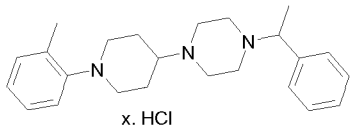
LCMS M+1=421/423, ^{1}H NMR ($CDCl_3$).

VI-6/ 7-Chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl-methyl]-quinoline hydrochloride: (IP-385):

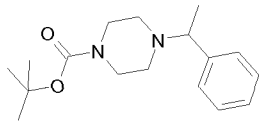
38 mg (0.09 mmol) of the product obtained in the previous step were solubilised in 300µl of anhydrous dichloromethane and 270 µl (0.27 mmol) of HCl 1N in diethyl ether were added. The mixture was stirred for 1h at room temperature. The mixture was concentrated and the solid was taken up in EtOH (solubilisation) then five volumes of petroleum ether were added in order to precipitate a pure product. The pale yellow solid was then freeze-dried to afford 39 mg (89%) of pure product.

LCMS M+1=421/423, ^{1}H NMR (DMSO).

VII/ 1-(1-Phenyl-ethyl)-4-(1-*o*-tolyl-piperidin-4-yl)-piperazine hydrochloride:(IP-453):



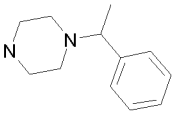
VII-1/ 4-(1-Phenyl-ethyl)-piperazine-1-carboxylic acid *tert*-butyl ester:



500 mg (2.68 mmol) of 1-Boc-piperazine and 366 µl (2.68 mmol) of (1-Bromoethyl)-benzene were added in 5.5 ml of acetone. Thereafter, 500 mg (3.62 mmol) of potassium carbonate were added and the reaction mixture was refluxed until the material product disappeared on TLC (petroleum ether-ethyl acetate 9/1). The salts were filtered off, and the filtrate was concentrated to dryness. The residue was taken up in water and ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by silica gel column chromatography (petroleum ether-ethyl acetate 98/2) to yield 407 mg of oil (53%).

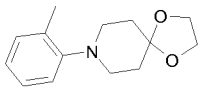
LCMS M+1=291, ^{1}H NMR ($CDCl_3$).

VII-2/ 1-(1-Phenyl-ethyl)-piperazine:



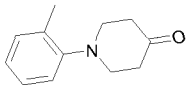
400 mg (1.38 mmol) of 4-(1-Phenyl-ethyl)-piperazine-1-carboxylic acid *tert*-butyl ester obtained in the previous step was treated in a similar manner as in Example 2/VI-4 to yield 174 mg of yellow solid (67%) which was used without further purification.
LCMS M+1=191, ^{1}H NMR ($CDCl_3$).

VII-3/ 8-*o*-Tolyl-1, 4-dioxa-8-aza-spiro[4.5]decane:



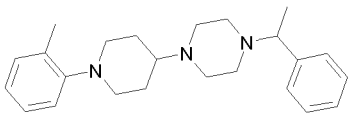
Following the procedure previously described (Example 1, I-1) 1.7 ml (14 mmol) of 2-Bromotoluene, 1.8 ml (14 mmol) of 4-Piperidone ethylene ketal, 157 mg (0.7 mmol) Palladium acetate 5% mol, 2.7g (28 mmol) of sodium tert-butoxyde, 297 mg (0.7 mmol) of 2-Di-tert-butylphosphino-2,4,6-triisopropylbiphenyl were allowed to reflux for one night. After workup and purification by silica gel column chromatography (petroleum ether-ethyl acetate 99/1) colourless oil is obtained with 29% yield.
LCMS M+1=234, ^{1}H NMR ($CDCl_3$).

VII-4/ 1-*o*-Tolyl-piperidin-4-one:



940 mg (4.03 mmol) of the product obtained in the previous step was treated as described in Example 2/ III-2 to afford 274 mg (36%) of yellow oil after purification by reverse phase silica gel column chromatography (methanol-water 6/4).
^{1}H NMR ($CDCl_3$).

VII-5/ 1-(1-Phenyl-ethyl)-4-(1-*o*-tolyl-piperidin-4-yl)-piperazine:

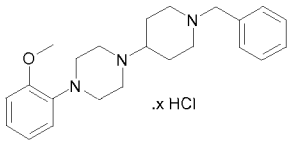


115 mg (0.61 mmol) of 1-*o*-Tolyl-piperidin-4-one (obtained in the previous step) and 174 mg (0.92 mmol) of 1-(1-Phenyl-ethyl)-piperazine (obtained in VII-2) were added in 500µl of dichloroethane under argon atmosphere. Thereafter, 220 mg (1.04 mmol) of Sodium triacetoxyborohydride were added and the reaction mixture was stirred for one night at room temperature. The mixture was concentrated and the residue was taken up in NaOH (1N) and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by silica gel column chromatography (petroleum ether-ethyl acetate 95/5) to yield 84 mg (38%) of brown solid.
LCMS M+1=364, ^{1}H NMR ($CDCl_3$).

VII-6/ 1-(1-Phenyl-ethyl)-4-(1-*o*-tolyl-piperidin-4-yl)-piperazine hydrochloride (IP-453):
84 mg (0.23 mmol) of the product obtained in the previous step was solubilised in 500µl of anhydrous dichloromethane and 460 µl (0.46 mmol) of HCl 1N in diethyl ether were added. The mixture was stirred for 1h30 at room temperature. The precipitate was filtered off and washed with diethyl ether. Thereafter, the solid was freeze-dried to provide 47 mg (47%) of white solid.
LCMS M+1=364, ^{1}H NMR (DMSO and DMSO+D_2O).

Exemple 3 : Synthesis of molecules of Cluster 3

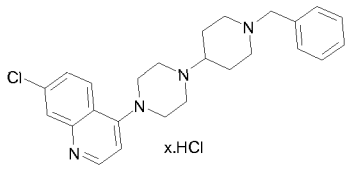
I/ 1-(1-benzyl-piperidin-4-yl)-4-(2-methoxy-phenyl)-piperazine hydrochloride (IP-165):



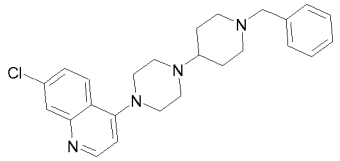
1.52g (7.93 mmol) of 1-(2-Methoxyphenyl) piperazine and 940 µl (5.28 mmol) of N-Benzyl-4-piperidone were solubilised into 4 ml of dichloromethane. After evaporation of the solvent, 2.2 ml (7.4 mmol) of Titanium (IV) isopropoxyde were added under nitrogen atmosphere and the mixture was heated for 3h30 at 45°C. 8 ml of distilled ethanol and 730 mg (11.62 mmol) of sodium cyanoborohydride were added and the mixture was further stirred at 45°C for 3h30. After one night at room temperature, the reaction mixture was poured onto 220 ml of water and stirred for 1h then; it was filtered through a plug of Celite and washed with dichloromethane. Aqueous layer was then extracted with dichloromethane and Organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane-ethanol 95/5) to yield 909 mg of white solid 1-(1-benzyl-piperidin-4-yl)-4-(2-methoxy-phenyl)-piperazine (IP-074) (47%).
LCMS: M+1=366; ^{1}H NMR $CDCl_3$.

470 mg (1.29 mmol) of the previous product were added onto 2 ml of dichloromethane and 4 ml of aqueous HCl 1N were added to the mixture. After stirring at room temperature for 3h, organic layer was washed with HCl 1N. Aqueous layer was concentrated *in vacuo* and the residue was washed with hot ethanol to yield 411 mg of 1-(1-benzyl-piperidin-4-yl)-4-(2-methoxy-phenyl)-piperazine hydrochloride (IP165) (78%) as a white solid.
LCMS: M+1=366; ^{1}H NMR DMSO+D_2O.

II/ 4-[4-(1-benzyl-piperidin-4-yl)-piperazin-1-yl]-7-chloro-quinoline hydrochloride (IP-162):



II-1/ 4-[4-(1-benzyl-piperidin-4-yl)-piperazin-1-yl]-7-chloro-quinoline: (IP-139):



0.38 mmol of 7-chloro-4-piperazin-1-yl-quinoline hydrochloride (prepared as described in Example 1, III-2) and 45 µl (0.25 mmol) of N-Benzyl-4-piperidone were solubilised into 1 ml of dichloromethane. After evaporation of the solvent, 105µl (0.35 mmol) of Titanium (IV) isopropoxyde were added under nitrogen atmosphere and the mixture was heated for 2h30 at 45°C. 1 ml of distilled ethanol and 35 mg (0.55 mmol) of sodium cyanoborohydride were added and the mixture was further stirred at 45°C for 2h. After one night at room temperature, the reaction mixture was poured onto 10 ml of water and stirred for 1h30, then filtered through a plug of Celite and washed with dichloromethane. Aqueous layer was then extracted with dichloromethane and organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane-ethanol 99/1 up to 95/5) to yield 15 mg of solid (15%).

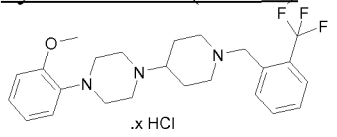
LCMS: M+1=421; ^1H NMR ($CDCl_3$).

II-2/ 4-[4-(1-benzyl-piperidin-4-yl)-piperazin-1-yl]-7-chloro-quinoline hydrochloride (IP-162):

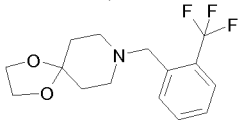
200 mg (0.48 mmol) of the previous product were added onto 1 ml of dichloromethane; 2 ml of aqueous HCl 1N were added and the mixture was stirred at room temperature for 2h30. Organic layer was washed with HCl 1N and the aqueous layer was concentrated *in vacuo*. The residue was washed with hot ethanol to yield 169 mg of a white solid (72%).

LCMS: M+1=421/423; ^1H NMR DMSO+D_2O.

III/1-(2-methoxy-phenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl] piperazine hydrochloride (IP-145):

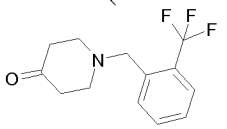


III-1/ 8-(2-trifluoromethyl)-1,4-dioxa-8-aza-spiro [4.5] decane:



2.7 ml (20.92 mmol) of 1,4-dioxa-8-aza-spiro-[4.5] decane were solubilised into 50 ml of anhydrous acetonitrile under argon atmosphere and 4.3g (31.38 mmol) of potassium carbonate were added. The mixture was refluxed and 5g (20.92 mmol) of 2-(trifluoromethyl) benzyl bromide were added in solution into 20 ml of acetonitrile, then the mixture was further refluxed for 3h30. After one night at room temperature, the mixture was concentrated to dryness; water and ethyl acetate were added and organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield 6.06g of crude product (yellow oil, 96%). ^1H NMR ($CDCl_3$).

III-2/ 1-(2-trifluoromethyl-benzyl)-piperidin-4-one:



6.02g (19.98 mmol) of 8-(2-trifluoromethyl)-1,4-dioxa-8-aza-spiro [4.5] decane previously obtained were added into a mixture of 50 ml of aqueous HCl (4N) and 50 ml of tetrahydrofuran and heated for 7h at 60°C (TLC petroleum ether-ethyl acetate 9/1). After being cooled, the reaction mixture was basified with NaOH (2N) then extracted with ethyl acetate. Organic layer was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (CH_3CN-H_2O 3/7) to yield 4.05g of colourless oil (79%).
LCMS: M+1=258; ^1H NMR ($CDCl_3$).

III-3/ 1-(2-methoxy-phenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl] piperazine: (IP-038).

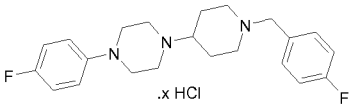
2.15g (11.18 mmol) of 1-(2-Methoxyphenyl) piperazine and 1.92g (7.46 mmol) of 1-(2-trifluoromethyl-benzyl)-piperidin-4-one previously obtained were solubilised into 4 ml of dichloromethane. After evaporation of the solvent, 3.1 ml (10.44 mmol) of Titanium (IV) isopropoxyde were added under nitrogen atmosphere and the mixture was heated for 3h30 at 45°C. 6 ml of distilled ethanol and 1g (16.4 mmol) of sodium cyanoborohydride were added and the mixture was further stirred at 45°C for 3h. After one night at room temperature, the mixture was poured onto 300 ml of water and stirred for 1h; it was filtered through a plug of Celite and washed with dichloromethane. Aqueous layer was then extracted with dichloromethane and organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane-ethanol 99/1) to yield 1.55g of a white solid (48%).

LCMS: M+1=434; ^{1}H NMR ($CDCl_3$).

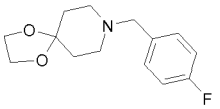
III-4/ 1-(2-methoxy-phenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl] piperazine hydrochloride (IP-145):

200 mg (0.46 mmol) of product previously obtained were added onto 1 ml of dichloromethane and 2 ml of aqueous HCl 1N were added and the mixture was stirred at room temperature for 2h. Organic layer was washed with HCl 1N and aqueous layer was concentrated *in vacuo*. The residue was washed in hot ethanol to yield 164 mg of a white solid (33%) containing 2.92 mol HCl per mol of product. LCMS: M+1=434; ^{1}H NMR DMSO+D_2O.

IV/ 1-[1-(4-fluoro-benzyl)-piperidin-4-yl]-4(4-fluorophenyl)-piperazine hydrochloride: (IP-156)

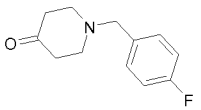


IV-1/ 8-(4-fluoro-benzyl)-1,4-dioxa-8-aza-spiro[4.5] decane :



As described in the previous protocol III-1, 460 µl (3.61 mmol) of 1,4-dioxa-8-aza-spiro-[4.5] decane and 682 mg (3.61 mmol) of 4-fluoro benzyl bromide were allowed to react. After workup, 825 mg of oil were obtained (91% yield). This product was used without further purification. ^{1}H NMR ($CDCl_3$).

IV-2/ 1-(4-fluorobenzyl)-piperidin-4-one:



825 mg (3.29 mmol) of 8-(4-fluorobenzyl)-1,4-dioxa-8-aza-spiro[4.5] decane were treated as described in the previous protocol III-2, to obtain 389 mg of yellow oil (57% yield). ^{1}H NMR ($CDCl_3$).

IV-3/ 1-[1-(4-fluoro-benzyl)-piperidin-4-yl]-4(4-fluorophenyl)-piperazine (IP-159):

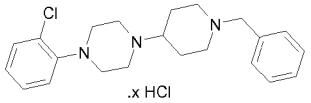
502 mg (2.79 mmol) of N-(4-fluorophenyl) piperazine and 385 mg (1.86 mmol) of 1-(4-fluorobenzyl)-piperidin-4-one previously prepared were treated as described in protocol III-3, to yield 316 mg of a white solid (46%). LCMS: M+1=372; ^{1}H NMR ($CDCl_3$).

IV-4/1-[1-(4-fluoro-benzyl)-piperidin-4-yl]-4(4-fluorophenyl)-piperazine hydrochloride (IP-156):

268 mg (0.72 mmol) of the product previously prepared were added onto 1 ml of dichloromethane; 2.5 ml of aqueous HCl 1N were added and the mixture was stirred at room temperature for 2h30. Organic layer was washed with HCl 1N and the aqueous layer was concentrated *in vacuo*. The residue was washed with hot ethanol to yield 109 mg of a white solid (34%).

LCMS : M+1=372 ; ^{1}H NMR (DMSO).

V/ 1-(1-benzylpiperidin-4-yl)-4-(2-chlorophenyl)-piperazine hydrochloride (IP-163):

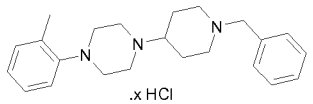


1.56g (7.93 mmol) of 1-(2-chlorophenyl) piperazine and 940 µl (5.28 mmol) of N-Benzyl-4-piperidone were treated as described in the previous protocol III-3 to yield 1.06g of solid 1-(1-benzylpiperidin-4-yl)-4-(2-chlorophenyl)-piperazine (54%). (IP-158).

LCMS: M+1=370; ^{1}H NMR ($CDCl_3$).

500 mg (1.35 mmol) of the product previously obtained were added onto a mixture of 2 ml of dichloromethane and 4 ml of aqueous HCl 1N and the mixture was then stirred at room temperature for 2h. Organic layer was washed with HCl 1N and the aqueous layer was concentrated *in vacuo*. The residue was washed with hot ethanol to yield 551 mg of a white solid (92%). LCMS: M+1=370; ^{1}H NMR (DMSO). (IP-163).

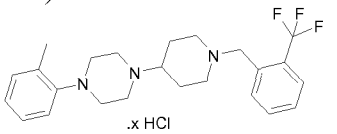
VI/ 1-(1-benzylpiperidin-4-yl)-4-o-tolyl-piperazine hydrochloride (IP-164):



2.3g (13 mmol) of 1-(o-tolyl) piperazine and 1.55 ml (8.7 mmol) of N-Benzyl-4-piperidone were treated as described in protocol III-3 to yield 1.9g of solid 1-(1-benzylpiperidin-4-yl)-4-o-tolyl-piperazine (63%). LCMS: M+1=350; ^{1}H NMR ($CDCl_3$).

500 mg (1.43 mmol) of the product previously obtained were added onto a mixture of 2 ml of dichloromethane and 4.5 ml of aqueous HCl 1N and the mixture was then stirred at room temperature for 2h. Organic layer was washed with HCl 1N and the aqueous layer was concentrated *in vacuo*. The residue was washed with hot ethanol to yield 475 mg of a white solid (79%). LCMS: M+1=350 ; ^{1}H NMR (DMSO).

VII/ 1-o-tolyl-4-[1-(2-trifluoromethylbenzyl)-piperidin-4-yl] piperazine hydrochloride (IP-169):



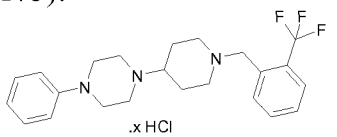
As described in protocol III-3, 1-(o-tolyl) piperazine and 1-(2-trifluoromethyl-benzyl)-piperidin-4-one (described in III-2) were allowed to react to yield 930 mg of orange oil (57%).

LCMS: M+1=418 ; ^{1}H NMR ($CDCl_3$).

300 mg (0.72 mmol) of the product previously obtained were added onto a mixture of 1 ml of dichloromethane and 2.16 ml (3eq) of aqueous HCl 1N and the mixture was then stirred at room temperature for 2h. Organic layer was washed with HCl 1N and the aqueous layer was concentrated *in vacuo*. The residue was washed with hot ethanol to yield 244 mg of a white solid (78%).

LCMS: M+1=418 ; ^{1}H NMR (DMSO).

VIII/1-phenyl-4-[1-(2-trifluoromehtylbenzyl)-piperidin-4-yl] piperazine hydrochloride (IP-175):



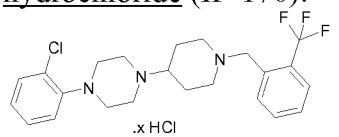
As described in protocol III-3, 1-Phenylpiperazine (5.83 mmol) and 1-(2-trifluoromethyl-benzyl)-piperidin-4-one (3.89 mmol) (described in III-2) were allowed to react to yield 906 mg of solid 1-phenyl-4-[1-(2-trifluoromehtylbenzyl)-piperidin-4-yl] piperazine (58%).

LCMS: M+1=404; ^{1}H NMR ($CDCl_3$).

400 mg (0.99 mmol) of the product previously obtained were added onto a mixture of 1 ml of dichloromethane and 3 ml (3eq) of aqueous HCl 1N and the mixture was then stirred at room temperature for 1h. Organic layer was washed with HCl 1N and the aqueous layer was concentrated *in vacuo*. The residue was washed with hot ethanol to yield 341 mg of a white solid (72%).

LCMS: M+1=404 ; ^{1}H NMR (DMSO).

IX/ 1-(2-chlorophenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl]-piperazine hydrochloride (IP-176):



As described in protocol III-3, 1-(2-Chlorophenyl)piperazine (5.83 mmol) and 1-(2-trifluoromethyl-benzyl)-piperidin-4-one (3.89 mmol) (described in III-2) were allowed to

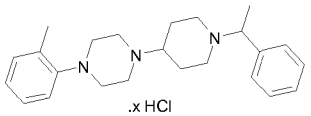
react to yield 1.06g of solid 1-(2-chlorophenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl]-piperazine (62%).

LCMS: M+1=438; ^{1}H NMR ($CDCl_3$).

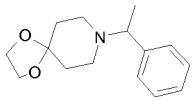
528 mg (1.21 mmol) of the product previously obtained were added onto a mixture of 1 ml of dichloromethane and 3.6 ml (3.6 eq) of aqueous HCl 1N and the mixture was then stirred at room temperature for 1h. Organic layer was washed with HCl 1N and the aqueous layer was concentrated *in vacuo*. The residue was washed with hot ethanol to yield 384 mg of a white solid (62%).

LCMS: M+1=438 ; ^{1}H NMR (DMSO).

X/ 1-[1-(1-phenyl-ethyl-)piperidin-4-yl]-4-o-tolyl-piperazine hydrochloride : (IP-223)



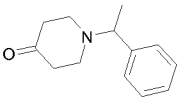
X-1/ 8-(1-phenyl-ethyl)-1,4-dioxa-8-aza-spiro-[4.5] decane :



As described in protocol III-1, 4 ml (29.3 mmol) of (1-Bromoethyl) benzene and 3.8 ml (1 eq) of 1,4-dioxa-8-aza-spiro-[4.5] decane were allowed to react using acetone instead of acetonitrile. The crude product was purified by silica gel column chromatography (CH_2Cl_2-AcOEt 50/50) to yield 6.7g of the expected product (93%).

LCMS: M+1=248; ^{1}H NMR (DMSO).

X-2/ 1-(1-phenyl-ethyl)-piperidin-4-one:



6.70g (27 mmol) of the product previously obtained were added into a mixture of 70 ml of aqueous HCl (4N) and 70 ml of tetrahydrofuran. The solution was refluxed for one night (TLC CH_2Cl_2-MeOH 95/5). The solvent was evaporated; the residue was then taken up in water and was basified with NaOH 50%. Aqueous layer was extracted three times with ethyl acetate. Organic layer was concentrated *in vacuo* and the residue was purified on reverse phase silica gel column chromatography (MeOH-H_2O 5/5) to yield 4g of colourless oil (73%)

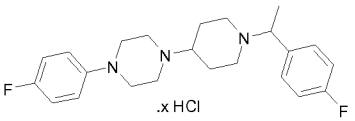
LCMS: M+1=204; ^{1}H NMR ($CDCl_3$).

X-3/ 1-[1-(1-phenyl-ethyl-) piperidin-4-yl]-4-o-tolyl-piperazine: (IP-213):
As described in protocol III-3, 4.65 mmol of 1-(o-tolyl) piperazine and 3.1 mmol of 1-(1-phenyl-ethyl)-piperidin-4-one were allowed to react to yield 764 mg of solid (67%).
LCMS: M+1=364; ^{1}H NMR ($CDCl_3$).

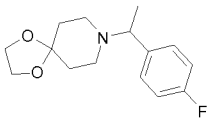
An other method to obtain the expected product is as follow: 14 mmol (1.05 eq) of 1-(o-tolyl) piperazine and 2.7g (13.3 mmol) of 1-(1-phenyl-ethyl)-piperidin-4-one were added in 60 ml of dichloroethane. 4.79g (22.6 mmol) of Sodium triacetoxyborohydride were added to the mixture under argon atmosphere and stirred for 20 h at room temperature.
The mixture was evaporated to dryness and treated with CH_2Cl_2 and $NaHCO_3$ sat. Organic layer was dried over $MgSO_4$, and evaporated to dryness. The residue was purified by silica gel column chromatography (CH_2Cl_2-EtOH 95/5) to yield 4.49 g of solid (84%).
LCMS: M+1=364; ^{1}H NMR ($CDCl_3$).

X-4/ 1-[1-(1-phenyl-ethyl-) piperidin-4-yl]-4-o-tolyl-piperazine hydrochloride (IP-223):
4.49 g (12.35 mmol) of the product previously obtained were added (under argon atmosphere) onto anhydrous dichloromethane (100 ml). 24.7 ml (2eq) of HCl 1N in diethyl ether were added and the mixture was stirred at room temperature for 2h. The precipitate was filtered and washed successively with diethyl ether and hot ethanol, and then dried under vacuum at 45°C. The white solid was freeze-dried to yield 3.37g of product (63%).
LCMS: M+1=364; ^{1}H NMR (DMSO and DMSO+D2O).

<u>XI/ 1-(4-Fluoro-phenyl)-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride :(IP-278)</u>

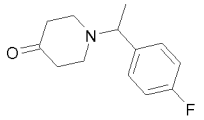


XI-1/ 8-[1-(4-Fluoro-phenyl)-ethyl]-1,4-dioxa-8-aza-spiro[4.5]decane:



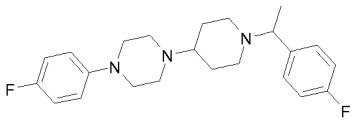
As described in protocol Example 3, III-3, 1.59 ml (12.4 mmol) of 4-Piperidone ethylene ketal and 1 ml (8.26 mmol) of 4-fluoroacetophenone were allowed to react. The crude product was purified by reverse phase silica gel column chromatography (acetonitrile-water 1/9 to 7/3) to yield 988mg of pure product (45%).
^{1}H NMR ($CDCl_3$).

XI-2/ 1-[1-(4-Fluoro-phenyl)-ethyl]-piperidin-4-one:



988 mg (3.74 mmol) of the product obtained in the previous step was treated as described in protocol X-2. After purification by reverse phase silica gel column chromatography (acetonitrile-water 4/6 to 7/3) 571mg of pure product were obtained in 69% yield.
LCMS M+1=222, ^{1}H NMR ($CDCl_3$).

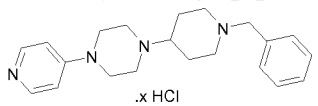
XI-3/ 1-(4-Fluoro-phenyl)-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine:



571mg (2.59 mmol) of 1-[1-(4-Fluoro-phenyl)-ethyl]-piperidin-4-one (obtained in the previous step) and 701mg (3.89 mmol) of N-(4-Fluorophenyl)piperazine were allowed to react as described in protocol III-3. After purification by reverse phase silica gel column chromatography (acetonitrile-water 3/7 to 7/3) 588 mg of solid were obtained in 59% yield.
LCMS M+1=386, ^{1}H NMR ($CDCl_3$).

XI-4/1-(4-Fluoro-phenyl)-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-278):
550mg (1.43 mmol) of the product previously obtained were added (under argon atmosphere) onto anhydrous dichloromethane (10 ml). 3 ml (3 mmol) of HCl 1N in diethyl ether were added and the mixture was stirred at room temperature for 36h. The precipitate was filtered and washed with dichloromethane and then dried under vacuum to afford 670 mg of white solid in quantitative yield.
LCMS M+1=386, ^{1}H NMR (DMSO and D_2O).

XII/ 1-(1-Benzyl-piperidin-4-yl)-4-pyridin-4-yl-piperazine hydrochloride (IP-283):



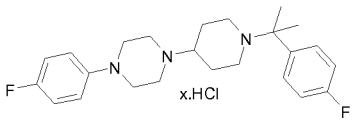
399 mg (1.69 mmol) of 1-(4-pyridyl)-piperazine and 202 µl (1.13 mmol) of N-Benzyl-4-piperidone were allowed to react as described in protocol III-3. After purification by silica gel column chromatography (ethyl acetate-triethylamine 99/1) 65 mg of pure product was obtained as an off-white solid with 11% yield (IP-264) (another fraction was obtained with impurities).

LCMS M+1=336, ^{1}H NMR ($CDCl_3$).

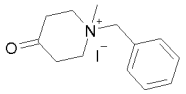
43 mg (0.13 mmol) of the product obtained in the previous step was solubilised in 400µl of anhydrous dichloromethane under nitrogen atmosphere. 400µl (0.38 mmol) of HCl 1N in diethyl ether were added and the mixture was stirred at room temperature for 1h. The precipitate was filtered and washed with diethyl ether to afford 42 mg of an off-white solid with 74% yield.

LCMS M+1=337, ^{1}H NMR (DMSO and DMSO+D_2O).

XIII/ 1-(4-Fluoro-phenyl)-4-{1-[1-(4-fluoro-phenyl)-1-methyl-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-334):



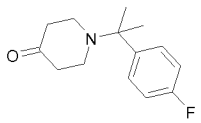
XIII-1/ 1-Benzyl-1-methyl-4-oxo-piperidinium iodide:



283µl (1.59 mmol) of N-benzyl-4-piperidone were solubilised in 2ml of acetone. 118µl (1.90 mmol) of iodomethane were added dropwise and the mixture was stirred for one night at room temperature. The precipitate was filtered and washed with acetone. The product was dried under vacuum at 45°C to provide 407mg (78%) of white solid.

^{1}H NMR (DMSO).

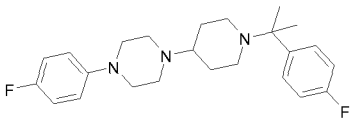
XIII-2/ 1-[1-(4-Fluoro-phenyl)-1-methyl-ethyl]-piperidin-4-one:



285mg (1.86 mmol) of 1-(4-Fluorophenyl)-1-methylethylamine were solubilised in 1.5ml of ethanol. To this solution were added 26 mg (0.186 mmol) of potassium carbonate and 400mg (1.21 mmol) of 1-Benzyl-1-methyl-4-oxo-piperidinium iodide (in solution in 1ml of water). The reaction mixture was refluxed for 6h. The mixture was diluted with 20ml of water and then extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, dried and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2-EtOH 9/1) to yield 168 mg (59%) of yellow oil.

LCMS M+1=236, ^{1}H NMR ($CDCl_3$).

XIII-3/ 1-(4-Fluoro-phenyl)-4-{1-[1-(4-fluoro-phenyl)-1-methyl-ethyl]-piperidin-4-yl}-piperazine:



As described in protocol III-3, 160mg (0.68 mmol) of 1-[1-(4-Fluoro-phenyl)-1-methyl-ethyl]-piperidin-4-one (obtained in the previous step) and 184 mg (1.02 mmol) of N-(4-Fluorophenyl)-piperazine were allowed to react. The crude product was purified by reverse phase silica gel column chromatography (water-methanol 50/50 to 100% methanol) to afford 72mg of white solid with 26% yield.

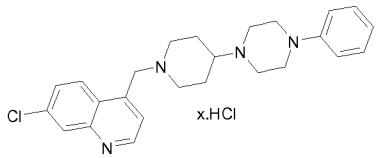
LCMS M+1=400, ^{1}H NMR (DMSO).

XIII-4/ 1-(4-Fluoro-phenyl)-4-{1-[1-(4-fluoro-phenyl)-1-methyl-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-334):

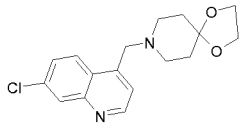
To a solution of 48mg (0.12 mmol) of the product obtained in the previous step, in 4ml of anhydrous dichloromethane were added 240µl (0.24 mmol) of HCl 1N in diethyl ether under nitrogen atmosphere. The mixture was stirred at room temperature for 2h. The product was collected by filtration and washed with diethyl ether. The solid was freeze-dried and 50mg of white solid were obtained in 88% yield.

LCMS M+1=400, ^{1}H NMR (DMSO and DMSO+D_2O).

XIV/ 7-Chloro-4-[4-(4-phenyl-piperazin-1-yl)-piperidin-1-ylmethyl]-quinoline hydrochloride (IP-408):



XIV-1/ 7-Chloro-4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-ylmethyl)-quinoline:

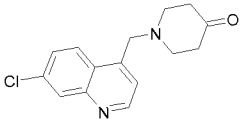


1g (5.22 mmol) of 7-Chloro-quinoline-4-carbaldehyde (obtained as described in protocol Example 2, VI-2) and 736µl (5.74 mmol) of 4-Piperidone ethylene ketal were added in 15 ml of anhydrous methanol under nitrogen atmosphere. Thereafter, a few drops of glacial acetic acid were added and the reaction mixture was stirred for 5h at room temperature. 394 mg (6.26 mmol) of sodium cyanoborohydride were then added to the mixture which was stirred one night further. After the reaction mixture was made basic with addition of saturated $NaHCO_3$ solution, the aqueous layer was extracted with dichloromethane. The

organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by silica gel column chromatography (dichloromethane-ethyl acetate 9/1) to yield 1.02g (61%) of yellow oil.

LCMS M+1=319/321, ^1H NMR ($CDCl_3$).

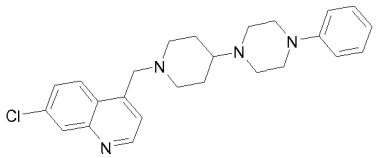
XIV-2/ 1-(7-Chloro-quinolin-4-ylmethyl)-piperidin-4-one:



1.02g (3.2 mmol) of the product obtained in the previously step was treated as described in protocol Example 3, X-2. The crude product was purified by reverse phase silica gel column chromatography (water-methanol 35/65) to afford 612 mg (70%) of yellow oil.

LCMS M+1=275, ^1H NMR ($CDCl_3$).

XIV-3/ 7-Chloro-4-[4-(4-phenyl-piperazin-1-yl)-piperidin-1-ylmethyl]-quinoline:



200 mg (0.73 mmol) of 1-(7-Chloro-quinolin-4-ylmethyl)-piperidin-4-one and 176 mg (1.09 mmol) of 1-phenylpiperazine were added in 4 ml of dichloroethane under nitrogen atmosphere. 262 mg (1.24 mmol) of Sodium triacetoxyborohydride were added to the solution and the reaction mixture was stirred for 24 h at room temperature.

The mixture was evaporated to dryness and treated with CH_2Cl_2 and $NaHCO_3$ sat. Organic layer was dried over $MgSO_4$, and evaporated to dryness. The residue was purified by silica gel column chromatography (ethyl acetate-ethanol 95/5) to provide a white solid with 62% yield.

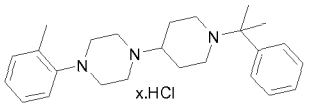
LCMS M+1=421/423, ^1H NMR ($CDCl_3$).

XIV-4/ 7-Chloro-4-[4-(4-phenyl-piperazin-1-yl)-piperidin-1-ylmethyl]-quinoline hydrochloride (IP-408):

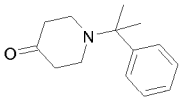
156 mg (0.37 mmol) of the product obtained in the previous step was suspended in 1 ml of anhydrous dichloromethane and 500µl of anhydrous methanol under nitrogen atmosphere.1.11ml (1.11 mmol) of HCl 1N in diethyl ether were added and the mixture was stirred for 1h at room temperature. The reaction mixture was concentrated and the solid was then solubilised in a minimum of ethanol. Diethyl ether was added until precipitation of the product. The solid was freeze-dried to provide 58 mg of the expected product with 32% yield.

LCMS M+1=421/423, ^1H NMR (DMSO and DMSO+D_2O).

XV/ 1-[1-(1-Methyl-1-phenyl-ethyl)-piperidin-4-yl]-4-*o*-tolyl-piperazine hydrochloride (IP-440):

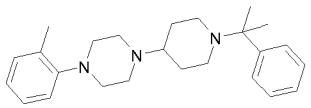


XV-1/ 1-(1-Methyl-1-phenyl-ethyl)-piperidin-4-one:



As described in the protocol Example 3, XIII-2, 414 mg (3.07 mmol) of cumylamine was allowed to react with 660 mg (1.99 mmol) of 1-Benzyl-1-methyl-4-oxo-piperidinium iodide. The crude product was purified by silica gel column chromatography (dichloromethane-ethyl acetate) to yield 179 mg (41%) of orange oil.
^{1}H NMR ($CDCl_3$).

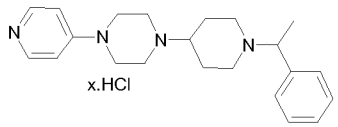
XV-2/ 1-[1-(1-Methyl-1-phenyl-ethyl)-piperidin-4-yl]-4-*o*-tolyl-piperazine:



179 mg (0.82 mmol) of 1-(1-Methyl-1-phenyl-ethyl)-piperidin-4-one (obtained in the previous step) and 174 mg (0.99 mmol) of 1-(*o*-tolyl)-piperazine were allowed to react as described in protocol XIV-3. The crude product was purified by silica gel column chromatography (dichloromethane-methanol 9/1) to yield 181 mg (58%) of yellow oil.
LCMS M+1=378, ^{1}H NMR ($CDCl_3$).

XV-3/ 1-[1-(1-Methyl-1-phenyl-ethyl)-piperidin-4-yl]-4-*o*-tolyl-piperazine hydrochloride (IP-440):
170mg (0.45 mmol) of the product obtained in the previous step was treated following the protocol XIII-4. The product was solubilised in dichloromethane and petroleum ether was added until precipitation. The solid was freeze-dried to provide 137 mg of yellow solid with 67% yield.
LCMS M+1=378, ^{1}H NMR (DMSO and DMSO+D_2O).

XVI/ 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-pyridin-4-yl-piperazine hydrochloride (IP-454):



193 mg (1.18 mmol) of 1-(4-Pyridyl)-Piperazine and 200 mg (0.98 mmol) of 1-(1-phenyl-ethyl)-piperidin-4-one (prepared as described in protocol X-2) were dissolved in 5 ml of dichloroethane. 353 mg (1.67 mmol) of Sodium triacetoxyborohydride were added to the mixture under argon atmosphere and stirred for 1.5 day at room temperature.

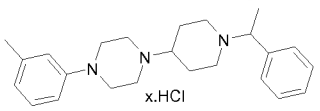
The mixture was evaporated to dryness and treated with CH_2Cl_2 and $NaHCO_3$ sat. Organic layer was dried over $MgSO_4$, and evaporated to dryness. The residue was purified by silica gel column chromatography (CH_2Cl_2-EtOH 9/1) to yield 115 mg (34%) of 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-pyridin-4-yl-piperazine as a beige solid.

LCMS M+1=351, ^{1}H NMR ($CDCl_3$).

110 mg (0.31 mmol) of this product were solubilised in 5 ml of anhydrous dichloromethane and 940µl (0.94 mmol) of HCl 1N in diethyl ether were added. The mixture was stirred for 2h at room temperature. The reaction mixture was concentrated and the solid was triturated in hot diethyl ether. After filtration, the product was freeze-dried to provide 105 mg (73%) of the expected hydrochloride salt as a white solid.

LCMS M+1=351, ^{1}H NMR (DMSO and DMSO+D_2O).

XVII/ 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-*m*-tolyl-piperazine hydrochloride (IP-464):



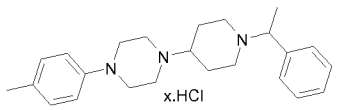
137 mg (0.78 mmol) of 1-(3-Methylphenyl)-piperazine and 150 mg (0.74 mmol) of 1-(1-phenyl-ethyl)-piperidin-4-one (prepared as described in protocol X-2) were treated as described in the first part of protocol XVI. The crude product was purified by silica gel column chromatography (dichloromethane-ethanol 9/1) to yield 174 mg (65%) of 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-*m*-tolyl-piperazine as a yellow solid.

LCMS M+1=364, ^{1}H NMR ($CDCl_3$).

170 mg (0.47 mmol) of this product were solubilised in 10 ml of anhydrous dichloromethane and 940µl (0.94 mmol) of HCl 1N in diethyl ether were added. The mixture was stirred for 2h at room temperature. The reaction mixture was concentrated and the solid was triturated in hot diethyl ether. After filtration, the product was freeze-dried to provide 178 mg (87%) of the expected hydrochloride salt as a white solid.

LCMS M+1=364, ^{1}H NMR (DMSO and DMSO+D_2O).

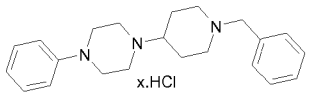
XVIII/ 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-*p*-tolyl-piperazine hydrochloride (IP-465):



137 mg (0.78 mmol) of 1-(4-Methylphenyl) piperazine and 150 mg (0.74 mmol) of 1-(1-phenyl-ethyl)-piperidin-4-one (prepared as described in protocol X-2) were treated as described in the first part of protocol XVI. The crude product was purified by silica gel column chromatography (dichloromethane-ethanol 9/1) to yield 132 mg (49%) of 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-*p*-tolyl-piperazine as a pale pink solid.
LCMS M+1=364, ^{1}H NMR ($CDCl_3$).

130 mg (0.36 mmol) of this product were solubilised in 7 ml of anhydrous dichloromethane and 720µl (0.72 mmol) of HCl 1N in diethyl ether were added. The mixture was stirred for 2h at room temperature. The reaction mixture was concentrated and the solid was triturated in hot diethyl ether. After filtration, the product was freeze-dried to provide 90 mg (57%) of the expected hydrochloride salt as a white solid.
LCMS M+1=364, ^{1}H NMR (DMSO and DMSO+D_2O).

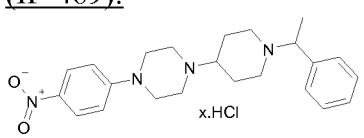
IXX/ 1-(1-Benzyl-piperidin-4-yl)-4-phenyl-piperazine hydrochloride (IP-468):



200 mg (1.05 mmol) of N-Benzyl-4-piperidone and 205 mg (1.268 mmol) of 1-Phenylpiperazine were allowed to react as described in the first part of protocol XVI. The crude product was purified by silica gel column chromatography (dichloromethane-methanol 96/4) to yield 213 mg (60%) of 1-(1-Benzyl-piperidin-4-yl)-4-phenyl-piperazine as a white solid (cas 416870-81-0, no bibliographic references)
LCMS M+1=336, ^{1}H NMR ($CDCl_3$).

200 mg (0.5961 mmol) of this product were solubilised in anhydrous dichloromethane and 1.2 ml (1.2 mmol) of HCl 1N in diethyl ether was added. The mixture was stirred for 1h at room temperature. The reaction mixture was concentrated and the solid was triturated in dichloromethane. After filtration, the product was freeze-dried to provide 257 mg (quantitative yield) of the expected hydrochloride salt as a white solid.
LCMS M+1=336, ^{1}H NMR (DMSO and DMSO+D_2O).

XX/ 1-(4-Nitro-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-469):



790 mg (3.8 mmol) of 1-(4-Nitrophenyl) piperazine and 515 mg (2.5 mmol) of 1-(1-phenyl-ethyl)-piperidin-4-one (prepared as described in protocol X-2) were treated as

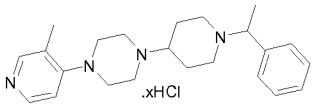
described in the first part of protocol XVI. The crude product was purified by silica gel column chromatography (ethyl acetate 100%) to yield 580 mg (58%) of 1-(4-Nitro-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine as an orange solid.

LCMS M+1=395, ^{1}H NMR (MeOD).

108 mg (0.27 mmol) of this product were solubilised in 500µl of anhydrous dichloromethane and 550 µl (0.55 mmol) of HCl 1N in diethyl ether was added. The mixture was stirred for 1h at room temperature. The precipitate was filtered off and the product was freeze-dried to provide 110 mg (86%) of 1-(4-Nitro-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride as a yellow solid.

LCMS M+1=395, ^{1}H NMR (DMSO and DMSO+D_2O).

XXI/ 1-(3-Methyl-pyridin-4-yl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-473):



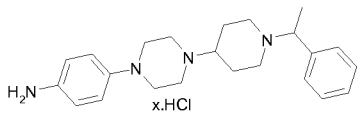
80 mg (0.45 mmol) of 1-(3-methylpyrid-4-yl) piperazine (obtained as described in Journal of Medicinal Chemistry, 1997, vol. 40, No. 17, p 2674) and 61 mg (0.3 mmol) of 1-(1-phenyl-ethyl)-piperidin-4-one (prepared as described in protocol X-2) were treated as described in the first part of protocol XVI. The crude product was purified by reverse phase silica gel column chromatography (water-methanol (+ 10% triethylamine) 5/5) to yield 49 mg (30%) of 1-(3-Methyl-pyridin-4-yl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine as yellow oil.

LCMS M+1=365, ^{1}H NMR (MeOD).

49 mg (0.13 mmol) of this product were solubilised in 300µl of anhydrous dichloromethane and 400 µl (0.4 mmol) of HCl 1N in diethyl ether was added. The mixture was stirred for 1h at room temperature. The precipitate was filtered off and washed with diethyl ether. The product was then freeze-dried to provide 46 mg (78%) of 1-(3-Methyl-pyridin-4-yl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride as an off-white solid.

LCMS M+1=365, ^{1}H NMR (DMSO and DMSO+D_2O).

XXII/ 4-{4-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-phenylamine hydrochloride (IP-474):



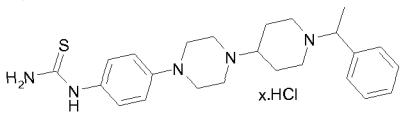
456 mg (1.15 mmol) of 1-(4-Nitro-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine (obtained as described in protocol XX) were suspended in 3 ml of ethanol. 1.3g (5.78 mmol) of Tin (II) chloride dihydrate was added and the reaction mixture was refluxed for 5h and thereafter, it was allowed to stand at room temperature for the night. The mixture was concentrated under vacuum and the residue was taken up in saturated aqueous $NaHCO_3$ and ethyl acetate. The slurry was then filtered through a plug of Celite and the aqueous layer was extracted twice with ethyl acetate. Organics were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by reverse phase silica gel column chromatography (water-methanol 5/5 +10% NEt_3) to provide 193 mg (46%) of 4-{4-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-phenylamine as a pink solid.

LCMS M+1=365, ^{1}H NMR (MeOD).

90 mg (0.25 mmol) of this product were solubilised in 500µl of anhydrous dichloromethane and 500 µl (0.5 mmol) of HCl 1N in diethyl ether was added. The mixture was stirred for 1h at room temperature. The precipitate was filtered off, washed with diethyl ether and the product was freeze-dried to provide 100 mg (93%) of 4-{4-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-phenylamine hydrochloride as a grey solid.

LCMS M+1=365, ^{1}H NMR (DMSO and DMSO+D_2O).

XXIII/ (4-{4-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-phenyl)-thiourea hydrochloride (IP-476):



100 mg (0.27 mmol) of 4-{4-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-phenylamine (obtained as described in protocol XXII) were solubilised in 2 ml of anhydrous dichloromethane under argon atmosphere. 59 mg (0.33 mmol) of 1,1'-thiocarbonyldiimidazole were added and the reaction mixture was stirred for 4h at room temperature. Thereafter, 160µl (1.1 mmol) of ammoniac 7N in methanol were added and the mixture was stirred for 48h further at room temperature. The reaction mixture was concentrated to dryness. The residue was taken up in ethanol and filtered to provide 48 mg (45%) of (4-{4-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-phenyl)-thiourea as an off-white solid.

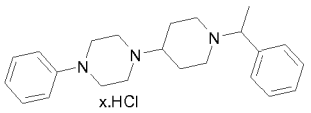
LCMS M+1=424, ^{1}H NMR (MeOD+DMSO).

48 mg (0.11 mmol) of this product were solubilised in 200µl of anhydrous methanol and 230 µl (0.23 mmol) of HCl 1N in diethyl ether were added. The mixture was stirred for 1h30 at room temperature and then concentrated to dryness. The residue was

triturated with diethyl ether and filtered. The solid was freeze-dried to provide 49 mg (87%) of (4-{4-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-phenyl)-thiourea hydrochloride as a grey solid.

LCMS M+1=424, ^{1}H NMR (DMSO and DMSO+D_2O).

XXIV/ 1-Phenyl-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-477):



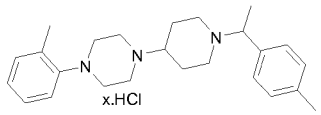
205 mg (1.268 mmol) of 1-Phenylpiperazine and 214 mg (1.057 mmol) of 1-(1-phenyl-ethyl)-piperidin-4-one (prepared as described in protocol X-2) were treated as described in the first part of protocol XVI. The crude product was purified by silica gel column chromatography (dichloromethane-ethanol 98/2) to yield 267 mg (72%) of 1-Phenyl-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine as an off-white solid.

LCMS M+1=350, ^{1}H NMR (DMSO).

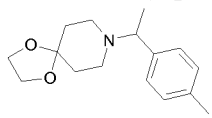
260 mg (0.744 mmol) of this product were solubilised in 2 ml of anhydrous dichloromethane and 1.48 ml (1.48 mmol) of HCl 1N in diethyl ether was added. The mixture was stirred for 2h at room temperature, and then it was evaporated to dryness. The residue was taken up in a minimum of dichloromethane and petroleum ether was added until precipitation. The solid was then freeze-dried to yield 221 mg (70%) of the desired product as a white solid.

LCMS M+1=350, ^{1}H NMR (DMSO and DMSO+D_2O).

XXV/ 1-*o*-Tolyl-4-[1-(1-*p*-tolyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-483):



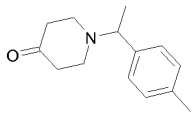
XXV-1/ 8-(1-*p*-Tolyl-ethyl)-1,4-dioxa-8-aza-spiro[4.5]decane:



As described in protocol Example 3, III-3, 500 mg (3.73 mmol) of 4-methylacetophenone and 526 µl (4.1 mmol) of 4-piperidone ethylene ketal were allowed to react. The crude product was purified by silica gel column chromatography (dichloromethane-ethyl acetate 100% to 50/50) to yield 724 mg (74%) of yellow oil.

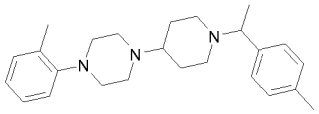
LCMS M+1=262, ^{1}H NMR ($CDCl_3$).

XXV-2/ 1-(1-*p*-Tolyl-ethyl)-piperidin-4-one:



720 mg (2.75 mmol) of the product obtained in the previous step was treated as described in protocol X-2. The crude product was purified by reverse phase silica gel column chromatography (water-methanol 5/5 to 0/100) to yield 592 mg (99%) of yellow oil.
LCMS M+1=218, ^{1}H NMR ($CDCl_3$).

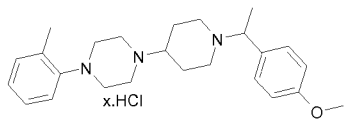
XXV-3/ 1-*o*-Tolyl-4-[1-(1-*p*-tolyl-ethyl)-piperidin-4-yl]-piperazine:



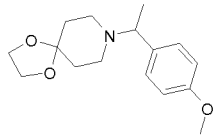
590 mg (2.71 mmol) of 1-(1-*p*-Tolyl-ethyl)-piperidin-4-one obtained in the previous step and 525 mg (2.98 mmol) of 1-(o-tolyl)-piperazine were treated as described in the first part of protocol XVI. The crude product was purified by silica gel column chromatography (dichloromethane-ethanol 9/1) to yield 372 mg (36%) of yellow oil.
LCMS M+1=378, ^{1}H NMR ($CDCl_3$).

XXV-4/ 1-*o*-Tolyl-4-[1-(1-*p*-tolyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-483):
365 mg (0.97 mmol) of the product obtained in the previous step were solubilised in 10 ml of anhydrous dichloromethane and 1.93 ml (1.93 mmol) of HCl 1N in diethyl ether was added. The mixture was stirred for 2h at room temperature and evaporated to dryness. The solid was triturated with ethanol and then freeze-dried to provide 185 mg (42%) of white solid.
LCMS M+1=378, ^{1}H NMR (DMSO and DMSO+D_2O).

XXVI/ 1-{1-[1-(4-Methoxy-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-484):



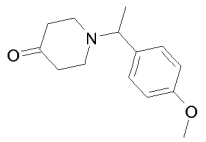
XXVI-1/ 8-[1-(4-Methoxy-phenyl)-ethyl]-1,4-dioxa-8-aza-spiro[4.5]decane:



As described in protocol Example 3, III-3, 939 µl (7.33 mmol) of 4-piperidone ethylene ketal and 1g (6.66 mmol) of 4-metoxyacetophenone were allowed to react. The crude product was purified by silica gel column chromatography (dichloromethane-ethyl acetate 100% to 50/50) to provide 1.57g (85%) of yellow oil.

LCMS M+1=278, ^{1}H NMR ($CDCl_3$).

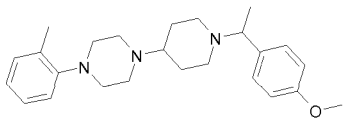
XXVI-2/ 1-[1-(4-Methoxy-phenyl)-ethyl]-piperidin-4-one:



1.57g (5.66 mmol) of product obtained in the previous step was treated as described in protocol X-2. The crude product was purified by reverse phase silica gel column chromatography (water-methanol 50/50) to afford 1.04g (79%) of yellow oil.

LCMS M+1=234, ^{1}H NMR ($CDCl_3$).

XXVI-3/ 1-{1-[1-(4-Methoxy-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine:



1.04g (4.45 mmol) of 1-[1-(4-Methoxy-phenyl)-ethyl]-piperidin-4-one and 863 mg (4.9 mmol) of 1-(o-tolyl)-piperazine were treated as described in the first part of protocol XVI. The crude product was purified by silica gel column chromatography (dichloromethane-ethanol 9/1) to yield 645 mg (37%) yellow oil.

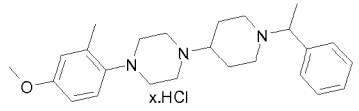
LCMS M+1=394, ^{1}H NMR ($CDCl_3$).

XXVI-4/1-{1-[1-(4-Methoxy-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-484):

100 mg (0.25 mmol) of the product obtained in the previous step were solubilised in 5 ml of anhydrous dichloromethane and 500µl (0.5 mmol) of HCl 1N in diethyl ether was added. The mixture was stirred for 2h at room temperature and evaporated to dryness. The solid was triturated with diethyl ether and then freeze-dried to provide 65 mg (56%) of white solid.

LCMS M+1=394, ^{1}H NMR (DMSO and DMSO+D_2O).

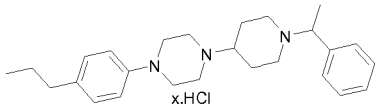
XXVII/ 1-(4-Methoxy-2-methyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-485):



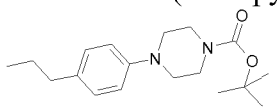
1.28g 6.2 mmol) of 1-(4-methoxy-2-methyl-phenyl)-piperazine (obtained as described in Journal of Medicinal Chemistry, 1996, Vol. 39, No.20, p4017) and 841 mg (4.14 mmol) of 1-(1-phenyl-ethyl)-piperidin-4-one (prepared as described in protocol X-2) were treated as described in the first part of protocol XVI. The crude product was purified by silica gel column chromatography (ethyl acetate 100%) to yield 651 mg (58%) of 1-(4-Methoxy-2-methyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine as a white solid.
LCMS M+1=394, ^{1}H NMR (MeOD).

100 mg (0.25 mmol) of the product obtained in the previous step were solubilised in 500 µl of anhydrous dichloromethane and 500µl (0.5 mmol) of HCl 1N in diethyl ether were added. The mixture was stirred for 1h at room temperature. The precipitate was filtered off; the solid was washed with diethyl ether and then freeze-dried to provide 107 mg (90%) of the expected hydrochloride salt as a white solid.
LCMS M+1=394, ^{1}H NMR (DMSO and DMSO+D_2O).

XXVIII/ 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-(4-propyl-phenyl)-piperazine (IP-490):

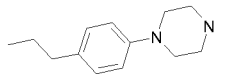


XXVIII-1/ 4-(4-Propyl-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester:



468 mg (2.511 mmol) of 1-Boc-piperazine and 500 mg (2.511 mmol) of 1-Bromo-4-propylbenzene were treated as described in protocol Example 1, I-1. The crude product was purified by silica gel column chromatography (dichloromethane-ethyl acetate 98/2) to provide 312 mg (40%) of orange oil.
LCMS M+1=305, ^{1}H NMR ($CDCl_3$).

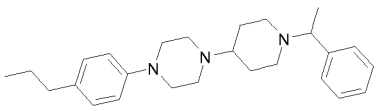
XVIII-2/ 1-(4-Propyl-phenyl)-piperazine:



310 mg (1.018 mmol) of the product obtained in the previous step was solubilised in 6.2 ml (20 vol) of methanol. 364µl (5.09 mmol) of acetyl chloride were slowly added and the reaction mixture was stirred for one night at room temperature. The mixture was concentrated to dryness. The residue was taken up in NaOH 1N and was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness to give 204 mg (98%) of orange oil which was used without further purification.

LCMS M+1=205, ^{1}H NMR ($CDCl_3$).

XVIII-3/ 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-(4-propyl-phenyl)-piperazine:



200 mg (0.97 mmol) of 1-(4-Propyl-phenyl)-piperazine and 199 mg (0.97 mmol) of 1-(1-phenyl-ethyl)-piperidin-4-one (prepared as described in protocol X-2) were treated as described in the first part of protocol XVI. The crude product was purified by silica gel column chromatography (dichloromethane-methanol 98/2) to provide 92 mg (24%) of white solid.

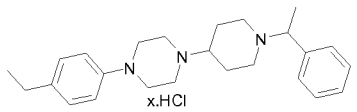
LCMS M+1=392, ^{1}H NMR (MeOD).

XVIII-4/1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-(4-propyl-phenyl)-piperazine hydrochloride (IP-490):

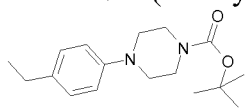
90 mg (0.229 mmol) of the product obtained in the previous step were solubilised in anhydrous dichloromethane and 460µl (0.46 mmol) of HCl 1N in diethyl ether were added. The mixture was stirred for 1h at room temperature. The precipitate was filtered off; the solid was washed with diethyl ether and then freeze-dried to provide 98 mg (92%) of the expected hydrochloride salt as a white solid.

LCMS M+1=392, ^{1}H NMR (DMSO and DMSO+D_2O).

XXIX/ 1-(4-Ethyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-503):



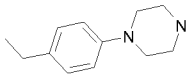
XXIX-1/ 4-(4-Ethyl-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester:



500 mg (2.684 mmol) of 1-Boc-piperazine and 371 µl (2.684 mmol) of 1-Bromo-4-ethylbenzene were treated as described in protocol Example 1, I-1. The crude product was purified by silica gel column chromatography (dichloromethane 100%) to provide 192 mg (24%) of orange oil.

LCMS M+1=291, ^{1}H NMR ($CDCl_3$).

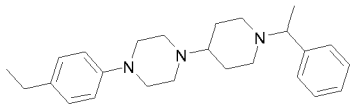
XXIX-2/ 1-(4-Ethyl-phenyl)-piperazine:



185 mg (0.637 mmol) of the product obtained in the previous step was treated as described in protocol XVIII-2 to yield 127 mg (quantitative) of orange oil.

LCMS M+1=191, ^{1}H NMR ($CDCl_3$).

XXIX-3/ 1-(4-Ethyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine:



125 mg (0.656 mmol) of 1-(4-Ethyl-phenyl)-piperazine and 111 mg (0.547 mmol) of 1-(1-phenyl-ethyl)-piperidin-4-one (prepared as described in protocol X-2) were treated as described in the first part of protocol XVI. The crude product was purified by silica gel column chromatography (dichloromethane-ethyl acetate 95/5) to provide 133 mg (64%) of colourless oil.

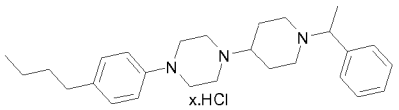
LCMS M+1=378, ^{1}H NMR ($CDCl_3$).

XXIX-4/ 1-(4-Ethyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-503):

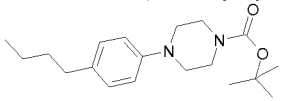
125 mg (0.331 mmol) of the product obtained in the previous step were solubilised in anhydrous dichloromethane and 662µl (0.662 mmol) of HCl 1N in diethyl ether were added. The mixture was stirred for 1h at room temperature. The reaction mixture was concentrated and the residue was triturated with successively: dichloromethane, diethyl ether and petroleum ether. The product was then freeze-dried to provide 143 mg (95%) of the expected hydrochloride salt as an off-white solid.

LCMS M+1=378, ^{1}H NMR (DMSO and DMSO+D_2O).

XXX/ 1-(4-Butyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-506):



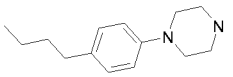
XXX-1/ 4-(4-Butyl-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester:



750 mg (4.027 mmol) of 1-Boc-piperazine and 858 mg (4.027 mmol) of 1-Bromo-4-butylbenzene were treated as described in protocol Example 1, I-1. The crude product was

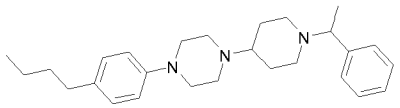
purified by silica gel column chromatography (dichloromethane-ethyl acetate 98/2) to provide 100 mg (7%) of maroon oil.
LCMS M+1=319, ^{1}H NMR ($CDCl_3$).

XXX-2/ 4-(4-Butyl-phenyl)-piperazine:



100 mg (0.314 mmol) of the product obtained in the previous step was treated as described in protocol XVIII-2 to yield 110 mg of maroon solid which was used in the next step without further purification.
LCMS M+1=219, ^{1}H NMR ($CDCl_3$).

XXX-3/ 1-(4-Butyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine:

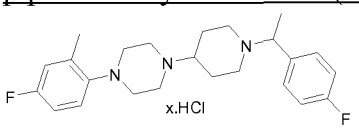


110 mg (0.504 mmol) of 4-(4-Butyl-phenyl)-piperazine and 102 mg (0.504 mmol) of 1-(1-phenyl-ethyl)-piperidin-4-one (prepared as described in protocol X-2) were treated as described in the first part of protocol XVI. The crude product was purified by silica gel column chromatography (dichloromethane-methanol 95/5) to yield 55 mg (26%) of beige solid.
LCMS M+1=406, ^{1}H NMR (MeOD).

<u>XXX-4/ 1-(4-Butyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-506):</u>

55 mg (0.136 mmol) of the product obtained in the previous step were solubilised in 2ml of anhydrous dichloromethane and 272µl (0.272 mmol) of HCl 1N in diethyl ether were added. The mixture was stirred for 2h at room temperature. The precipitate was filtered and washed with petroleum ether. The product was then freeze-dried to provide 55 mg (84%) of the expected hydrochloride salt as beige solid.
LCMS M+1=406, ^{1}H NMR (DMSO and DMSO+D_2O).

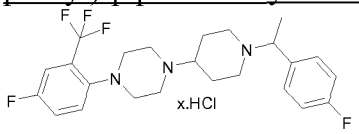
<u>XXXI/ 1-(4-Fluoro-2-methyl-phenyl)-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-508):</u>



356 mg (1.608 mmol) of 1-[1-(4-Fluoro-phenyl)-ethyl]-piperidin-4-one (obtained as described in protocol XI-2) and 375 mg (1.93 mmol) of 1-(4-Fluoro-2-methyl-phenyl)-piperazine (prepared as described in WO2001029015) were treated as described in the first part of protocol XVI. The crude product was purified by silica gel column chromatography (dichloromethane-methanol 9/1) to yield 404 mg (62%) of 1-(4-Fluoro-2-methyl-phenyl)-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine as a colourless oil.
LCMS M+1=400, ^{1}H NMR ($CDCl_3$).

395 mg (0.99 mmol) of the product obtained in the previous step were solubilised in anhydrous dichloromethane and 1.98 ml (1.98 mmol) of HCl 1N in diethyl ether was added. The mixture was stirred for 1h at room temperature. The reaction mixture was concentrated and the solid was triturated successively with dichloromethane and petroleum ether. The product was then freeze-dried to provide 394 mg (84%) of white solid.
LCMS M+1=400, ^{1}H NMR (DMSO and DMSO+D_2O).

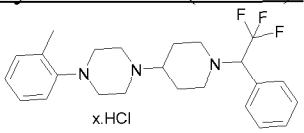
XXXII/ 1-{1-[1-(4-Fluoro-phenyl)-ethyl]-piperidin-4-yl}-4-(4-fluoro-2-trifluoromethyl-phenyl)-piperazine hydrochloride (IP-516):



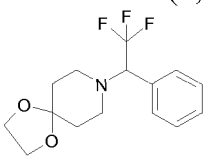
100 mg (0.403 mmol) of 1-(4-Fluoro-2-trifluoromethyl-phenyl)-piperazine (prepared as described in the literature: Journal of Medicinal Chemistry 2008, 51, 4068-4071) and 90 mg (0.403 mmol) of 1-[1-(4-Fluoro-phenyl)-ethyl]-piperidin-4-one (obtained as described in protocol XI-2) were treated as described in the first part of protocol XVI. The crude product was purified by silica gel column chromatography (dichloromethane-methanol 95/5) to yield 94 mg (51%) of 1-{1-[1-(4-Fluoro-phenyl)-ethyl]-piperidin-4-yl}-4-(4-fluoro-2-trifluoromethyl-phenyl)-piperazine as an oil.
LCMS M+1=454, ^{1}H NMR ($CDCl_3$).

90 mg (0.198 mmol) of the product obtained in the previous step were solubilised in anhydrous dichloromethane and 397µl (0.397 mmol) of HCl 1N in diethyl ether was added. The mixture was stirred for 1h at room temperature. The reaction mixture was concentrated and the solid was triturated successively with dichloromethane and petroleum ether. The product was then freeze-dried to provide 68 mg (65%) of the expected hydrochloride salt as a white solid.
LCMS M+1=454, ^{1}H NMR (DMSO and DMSO+D_2O).

XXXIII/ 1-*o*-Tolyl-4-[1-(2,2,2-trifluoro-1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-531):

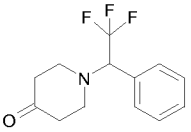


XXXIII-1/ 8-(2,2,2-Trifluoro-1-phenyl-ethyl)-1,4-dioxa-8-aza-spiro[4.5]decane:



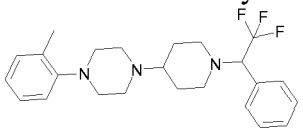
403µl (2.87 mmol) of 2,2,2-trifluoroacetophenone and 368 µl (2.87 mmol) of 4-piperidone-ethylene ketal were solubilised in 25 ml of dichloromethane under argon atmosphere. 157 µl (1.44 mmol) of Titanium (IV) chloride and 1.2 ml (8.61 mmol) of triethylamine were successively added and the mixture was stirred for one night at room temperature. Thereafter, a solution of 541 mg (8.61 mmol) of Sodium cyanoborohydride in 7 ml of anhydrous methanol was added and the reaction mixture was stirred for 15 minutes further. The mixture was basified with NaOH 1N and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography (petroleum ether-ethyl acetate) to yield 547 mg (63%) of yellow oil.
LCMS M+1=302, ^1H NMR ($CDCl_3$).

XXXIII-2/ 1-(2,2,2-Trifluoro-1-phenyl-ethyl)-piperidin-4-one:



547 mg (1.81 mmol) of 8-(2,2,2-Trifluoro-1-phenyl-ethyl)-1,4-dioxa-8-aza-spiro [4.5] decane (obtained in the previous step) was treated as described in protocol X-2. After work-up, the residue was purified by silica gel column chromatography (petroleum ether-ethyl acetate 9/1) to yield 273 mg (58%) of yellow oil.
LCMS M+1=258, ^1H NMR ($CDCl_3$).

XXXIII-3/ 1-*o*-Tolyl-4-[1-(2,2,2-trifluoro-1-phenyl-ethyl)-piperidin-4-yl]-piperazine:



270 mg (1.05 mmol) of 1-(2,2,2-Trifluoro-1-phenyl-ethyl)-piperidin-4-one and 185 mg (1.05 mmol) of 1-(*o*-Tolyl) piperazine were treated as described in protocol II-1. The residue was purified by silica gel column chromatography (dichloromethane-ethyl acetate 7/3) to give 187 mg (43%) of orange oil.

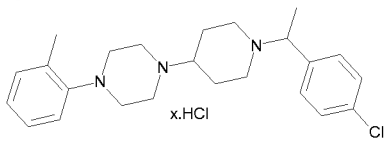
LCMS M+1=418, ^{1}H NMR ($CDCl_3$).

XXXIII-4/ 1-*o*-Tolyl-4-[1-(2,2,2-trifluoro-1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-531):

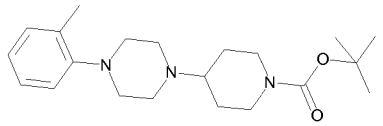
180 mg (0.43 mmol) of the product obtained in the previous step were solubilised in 5 ml of anhydrous dichloromethane and 860 µl (0.86 mmol) of HCl 1N in diethyl ether was added. The mixture was stirred for 2h at room temperature. The mixture was evaporated to dryness. The residue was solubilised in a minimum of ethanol and diethyl ether was added until precipitation. The solid was filtered and then freeze-dried to give 126 mg (65%) of the expected hydrochloride salt as an off-white solid.

LCMS M+1=418, ^{1}H NMR (DMSO and DMSO+D_2O).

XXXIV/ 1-{1-[1-(4-Chloro-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-536):



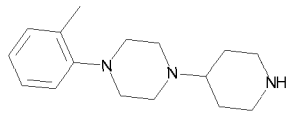
XXXIV-1/ 4-(4-o-Tolyl-piperazin-1-yl)-piperidine-1-carboxylic acid tert-butyl ester:



705 mg (4 mmol) of 1-(*o*-tolyl)-piperazine and 799 mg (4 mmol) of 1-Boc-piperidone were treated as described in protocol Example 3/III-3 to yield 1.04g (71%) of yellow oil.

LCMS M+1=360, ^{1}H NMR ($CDCl_3$).

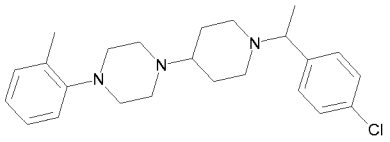
XXXIV-2/ 1-Piperidin-4-yl-4-o-tolyl-piperazine:



1.04g (2.89 mmol) of the product obtained in the previous step was treated as described in protocol Example 1/V-2, to yield 650 mg (87%) of orange wax.

LCMS M+1=260, ^{1}H NMR ($CDCl_3$).

XXXIV-3/ 1-{1-[1-(4-Chloro-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine:



100 mg (0.385 mmol) of 1-Piperidin-4-yl-4-o-tolyl-piperazine (obtained in the previous step) and 50 µl (0.385 mmol) of 4-chloroacetophenone were treated as described in protocol Example 3/III-3 to yield 67 mg (43%) of yellow oil.

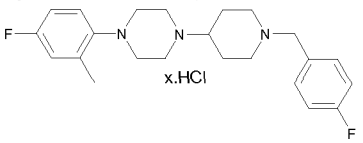
LCMS M+1=398, ^{1}H NMR ($CDCl_3$).

XXXIV-4/ 1-{1-[1-(4-Chloro-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-536):

63 mg (0.158 mmol) of the product obtained in the previous step were solubilised in 1 ml of anhydrous dichloromethane and 317 µl (0.317 mmol) of HCl 1N in diethyl ether was added. The mixture was stirred for 1h at room temperature. The mixture was evaporated to dryness. The residue was triturated successively with dichloromethane and petroleum ether. The solid was filtered and then freeze-dried to give 49 mg (66%) of the expected hydrochloride salt as a white solid.

LCMS M+1=398, ^{1}H NMR (DMSO and DMSO+D_2O).

<u>XXXV/ 1-[1-(4-Fluoro-benzyl)-piperidin-4-yl]-4-(4-fluoro-2-methyl-phenyl)-piperazine hydrochloride (IP-543)</u>



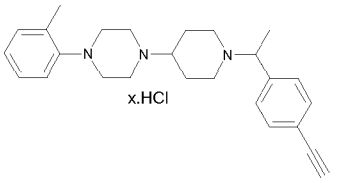
200 mg (0.96 mmol) of 1-(4-fluorobenzyl)-piperidin-4-one (prepared as described in protocol IV-2) and 225 mg (1.158 mmol) of 1-(4-Fluoro-2-methyl-phenyl)-piperazine (prepared as described in WO2001029015) were treated as described in protocol II-1 to yield 269 mg (72%) of a yellow oil.

LCMS M+1=386, ^{1}H NMR ($CDCl_3$).

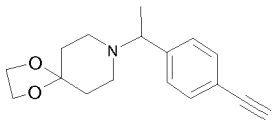
260 mg (0.674 mmol) of the product obtained in the previous step were solubilised in 2.6 ml of anhydrous dichloromethane and 1.4 ml (1.4 mmol) of HCl 1N in diethyl ether was added. The mixture was stirred for 1h at room temperature. The mixture was evaporated to dryness. The residue was triturated successively with dichloromethane and petroleum ether. The solid was filtered and then freeze-dried to give 228 mg (80%) of the expected hydrochloride salt as a white solid.

LCMS M+1=386, ^{1}H NMR (DMSO and DMSO+D_2O).

XXXVI/ 1-{1-[1-(4-Ethynyl-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-544):



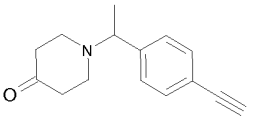
XXXVI-1/ 8-[1-(4-Ethynyl-phenyl)-ethyl]-1,4-dioxa-8-aza-spiro[4.5]decane:



550 mg (3.81 mmol) of 4'-Ethynylacetophenone and 587 µl (4.57 mmol) of 4-Piperidone ethylene ketal were allowed to react as described in protocol XXXIII-1 to yield 650 mg (60%) of orange oil.

LCMS M+1=272, ^{1}H NMR (CDCl3).

XXXVI-2/ 1-[1-(4-Ethynyl-phenyl)-ethyl]-piperidin-4-one:



645 mg (2.37 mmol) of the product obtained in the previous step was treated as described in protocol X-2. After work-up, the residue was purified by silica gel column chromatography (dichloromethane-methanol 98/2) to yield 200 mg (37%) of yellow oil.
LCMS M+1=246, ^{1}H NMR (CDCl3).

XXXVI-3/ 1-{1-[1-(4-Ethynyl-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-544):

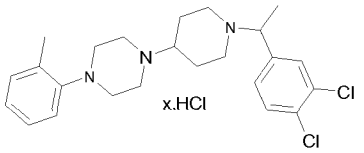
100 mg (0.439 mmol) of 1-[1-(4-Ethynyl-phenyl)-ethyl]-piperidin-4-one and 0.527 mmol of 1-(O-tolyl) piperazine were allowed to react as described in protocol XIV-3. The crude product was purified by silica gel column chromatography (dichloromethane-methanol 96/4)) to provide 150 mg of colourless oil.
LCMS M+1=388, ^{1}H NMR ($CDCl_3$).

140 mg (0.36 mmol) of the product obtained in the previous step were solubilised in 2 ml of anhydrous dichloromethane and 723µl (0.72 mmol) of HCl 1N in diethyl ether was added. The mixture was stirred for 1h at room temperature. The mixture was evaporated to dryness. The residue was triturated successively with dichloromethane and

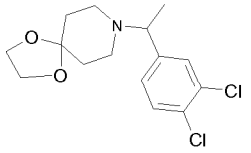
petroleum ether. The solid was filtered and then freeze-dried to give 138 mg (83%) of the expected hydrochloride salt as a white solid.

LCMS M+1=388, ^{1}H NMR (DMSO and DMSO+D_2O).

XXXVII/ 1-{1-[1-(3,4-Dichloro-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine (IP-545)



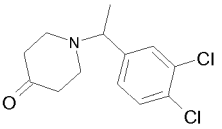
XXXVII-1/ 8-[1-(3,4-Dichloro-phenyl)-ethyl]-1,4-dioxa-8-aza-spiro[4.5]decane:



500 mg (2.64 mmol) of 3',4'-dichloroacetophenone and 407 µl (3.17 mmol) of 4-Piperidone ethylene ketal were allowed to react as described in protocol XXXIII-1 to yield 360 mg (43%) of colourless oil.

LCMS M+1=316-318, ^{1}H NMR ($CDCl_3$).

XXXVII-2/ 1-[1-(3,4-Dichloro-phenyl)-ethyl]-piperidin-4-one:



360 mg (1.13 mmol) of the product obtained in the previous step was treated as described in protocol X-2. After work-up, the residue was purified by silica gel column chromatography (dichloromethane-methanol 99/1) to yield 223 mg (72%) of colourless oil. ^{1}H NMR ($CDCl_3$).

XXXVII-3/ 1-{1-[1-(3,4-Dichloro-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine (IP-545):

220 mg (0.8 mmol) of 1-[1-(3,4-Dichloro-phenyl)-ethyl]-piperidin-4-one and 0.97 mmol of 1-(O-tolyl) piperazine were allowed to react as described in protocol XIV-3. The crude product was purified by silica gel column chromatography (dichloromethane-methanol 98/2) to provide 270 mg of colourless oil with 77% yield.

LCMS M+1=432-434, ^{1}H NMR ($CDCl_3$).

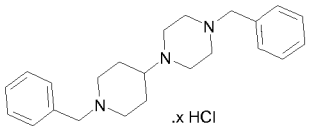
265 mg (0.61 mmol) of the product obtained in the previous step were solubilised in 3 ml of anhydrous dichloromethane and 1.3ml (1.3 mmol) of HCl 1N in diethyl ether

was added. The mixture was stirred for 1h at room temperature. The mixture was evaporated to dryness. The residue was triturated with dichloromethane. The solid was filtered and then freeze-dried to give 208 mg (67%) of the expected hydrochloride salt as a white solid.

LCMS M+1=432-434, ^{1}H NMR (DMSO and DMSO+D_2O).

Exemple 4 : Synthesis of molecules of Cluster 4

I/ 1-benzyl-4-(1-benzyl-piperidin-4-yl)-piperazine hydrochloride (IP-138):



I-1/ 1-benzyl-4-(1-benzyl-piperidin-4-yl)-piperazine: (IP-121):

687 µl (3.96 mmol) of 1-Benzylpiperazine and 472 µl (2.64 mmol) of N-Benzyl-4-piperidone were solubilised into 4 ml of dichloromethane. After evaporation of the dichloromethane, 1.1 ml (3.7 mmol) of Titanium (IV) isopropoxyde were added under nitrogen atmosphere and the mixture was heated for 1h at 45°C. 4 ml of distilled ethanol and 365 mg (5.8 mmol) of sodium cyanoborohydride were then added and the mixture was further stirred at 45°C for 1h. After one night at room temperature, the mixture was poured onto 100 ml of water, stirred for 1h, filtered through a plug of Celite and washed with dichloromethane. Aqueous layer was then extracted with dichloromethane and the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane-ethanol 99/1 up to 95/5 with triethylamine (10%)) to yield 489 mg of beige solid (53%).

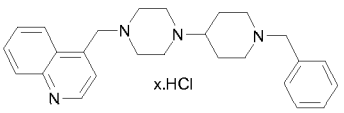
LCMS: M+1=350; ^{1}H NMR ($CDCl_3$).

I-2/ 1-benzyl-4-(1-benzyl-piperidin-4-yl)-piperazine hydrochloride (IP-138):

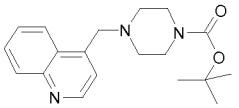
468 mg (1.34 mmol) of the product previously obtained were added onto a mixture of 2 ml of dichloromethane and 4 ml of aqueous HCl 1N and the mixture was then stirred at room temperature for 4h. Aqueous layer was concentred *in vacuo*. The residue was washed with hot ethanol to yield 414 mg of a white solid (67%).

LCMS: M+1=350, ^{1}H NMR (DMSO+D_2O).

II/ 4-[4-(1-Benzyl-piperidin-4-yl)-piperazin-1-ylmethyl]-quinoline hydrochloride (IP-366):



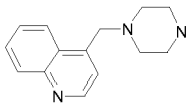
II-1/ 4-Quinolin-4-ylmethyl-piperazine-1-carboxylic acid *tert*-butyl ester:



500 mg (3.181 mmol) of 4-Quinoline-carboxaldehyde and 889 mg (4.772 mmol) of 1-Boc-piperazine were treated as described in protocol Example 4, I-1. The crude product was purified by silica gel column chromatography (dichloromethane-methanol 99/1) to yield 602 mg of yellow oil.

LCMS: M+1=328, ^{1}H NMR ($CDCl_3$).

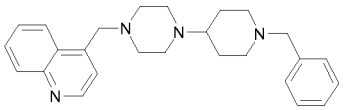
II-2/ 4-Piperazin-1-ylmethyl-quinoline:



600 mg (1.832 mmol) of the product obtained in the previous step was treated as described in protocol XVIII-2 of Example 3. The residue was purified by silica gel column chromatography (dichloromethane-methanol 9/1) to yield 280 mg (67%) of yellow oil.

LCMS: M+1=228, ^{1}H NMR ($CDCl_3$).

II-3/ 4-[4-(1-Benzyl-piperidin-4-yl)-piperazin-1-ylmethyl]-quinoline:



275 mg (1.209 mmol) of 4-Piperazin-1-ylmethyl-quinoline and 324 µl (1.814 mmol) of N-Benzyl-4-piperidone were treated as described in protocol Example 4, I-1. The crude product was purified by silica gel column chromatography (dichloromethane-methanol 95/5) to yield 165 mg of orange oil.

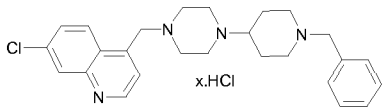
LCMS: M+1=401, ^{1}H NMR ($CDCl_3$).

II-4/ 4-[4-(1-Benzyl-piperidin-4-yl)-piperazin-1-ylmethyl]-quinoline hydrochloride: (IP-366)

150 mg (0.374 mmol) of the product obtained in the previous step were solubilised in anhydrous dichloromethane and 1.5 ml (1.5 mmol) of HCl 1N in diethyl ether was added. The mixture was stirred for 1h at room temperature. The mixture was evaporated to dryness. The residue was solubilised in a minimum of ethanol and petroleum ether was added until precipitation. After filtration, the solid was freeze-dried to afford 171 mg (83%) of the expected hydrochloride salt as beige solid.

LCMS: M+1=401, ^{1}H NMR (DMSO+D_2O).

III/ 4-[4-(1-Benzyl-piperidin-4-yl)-piperazin-1-ylmethyl]-7-chloro-quinoline hydrochloride (IP-384)



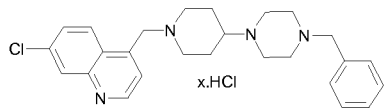
200 mg (0.76 mmol) of 7-Chloro-4-piperazin-1-yl-methyl-quinoline (obtained as described in protocol VI-4 of Example 2) and 91 µl (0.51 mmol) of N-Benzyl-4-piperidone were treated as described in protocol Example 4, I-1. The crude product was purified by silica gel column chromatography (ethyl acetate-triethylamine 95/5) to yield 142 mg (43%) of 4-[4-(1-Benzyl-piperidin-4-yl)-piperazin-1-ylmethyl]-7-chloro-quinoline as an off-white solid.

LCMS: M+1=435/437, ^{1}H NMR ($CDCl_3$).

94 mg (0.22 mmol) of this product were solubilised in 500 µl of anhydrous dichloromethane and 650 µl (0.65 mmol) of HCl 1N in diethyl ether was added. The mixture was stirred for 1h30 at room temperature. The precipitate was filtered and washed with hot ethanol. The product was freeze-dried to provide 89 mg (81%) of white solid.

LCMS: M+1=435/437, ^{1}H NMR (DMSO+D_2O).

IV/ 4-[4-(4-Benzyl-piperazin-1-yl)-piperidin-1-ylmethyl]-7-chloro-quinoline hydrochloride (IP-409):



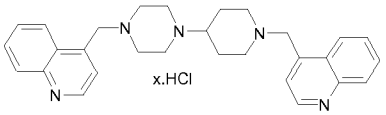
290 mg (1.06 mmol) of 1-(7-Chloro-quinolin-4-ylmethyl)-piperidin-4-one (obtained as described in protocol XIV-2 of Example 3) and 279 mg (1.56 mmol) of 1-Benzylpiperazine were treated as described in the first part of protocol XVI in Example 3. The crude product was purified by silica gel column chromatography (dichloromethane-ethanol 98/2) to yield 293 mg (64%) of 4-[4-(4-Benzyl-piperazin-1-yl)-piperidin-1-ylmethyl]-7-chloro-quinoline as an off-white solid.

LCMS: M+1=435/437, ^{1}H NMR ($CDCl_3$).

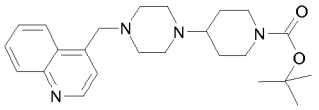
155 mg (0.36 mmol) of this product were solubilised in 1 ml of anhydrous dichloromethane and 1 ml (1 mmol) of HCl 1N in diethyl ether was added. The mixture was stirred for 1h at room temperature. The precipitate was filtered and washed with diethyl ether. The product was then freeze-dried to provide 134 mg of white solid.

LCMS: M+1=435/437, ^{1}H NMR (DMSO+D_2O).

V/ 4-[4-(1-quinoline-4-ylmethyl-piperidin-4-yl)-piperazin-1-ylmethyl]-quinoline hydrochloride (IP-439):

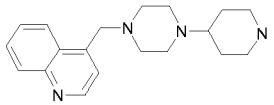


V-1/ 4-(4-Quinolin-4-ylmethyl-piperazin-1-yl)-piperidine-1-carboxylic acid *tert*-butyl ester



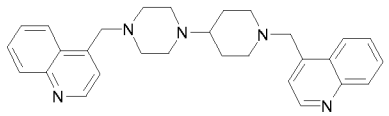
324 mg (1.43 mmol) of 4-Piperazin-1-ylmethyl-quinoline (obtained as described in protocol II-2) and 190 mg (0.95 mmol) of 1-Boc-4-piperidone were treated as described in the first part of protocol XVI in Example 3. The crude product was purified by silica gel column chromatography (dichloromethane-ethyl acetate) to yield 240 mg of yellow oil.
LCMS: M+1=411, ^{1}H NMR ($CDCl_3$).

V-2/ 4-(4-Piperidin-4-yl-piperazin-1-ylmethyl)-quinoline:



240 mg (0.58 mmol) of the product obtained in the previous step was treated as described in protocol XVIII-2 of Example 3 to give 181 mg of product which was used without further purification in the next step.
LCMS: M+1=311, ^{1}H NMR ($CDCl_3$).

V-3/ 4-[4-(1-quinoline-4-ylmethyl-piperidin-4-yl)-piperazin-1-ylmethyl]-quinoline



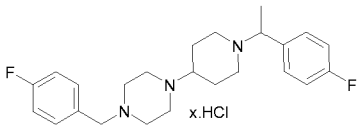
181 mg (0.58 mmol) of 4-(4-Piperidin-4-yl-piperazin-1-ylmethyl)-quinoline and 61 mg (0.39 mmol) of 4-Quinolinecarboxaldehyde were treated as described in the first part of protocol XVI in Example 3. The crude product was purified by silica gel column chromatography (dichloromethane-methanol 98/2), to yield 105 mg (60%) of an off-white solid.
LCMS: M+1=452, ^{1}H NMR ($CDCl_3$).

V-4/ 4-[4-(1-quinoline-4-ylmethyl-piperidin-4-yl)-piperazin-1-ylmethyl]-quinoline hydrochloride (IP-439):
74 mg (0.17 mmol) of the product obtained in the previous step were solubilised in 1 ml of anhydrous dichloromethane and 830µl (0.83 mmol) of HCl 1N in diethyl ether was added.

The mixture was stirred for 1h at room temperature. The precipitate was filtered and washed with diethyl ether. The product was then freeze-dried to provide 80 mg (74%) of white solid.

LCMS: M+1=452, ^{1}H NMR (DMSO+D_2O).

VI/ 1-(4-Fluoro-benzyl)-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-529):



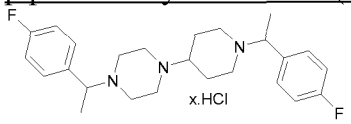
230 mg (1.039 mmol) of 1-[1-(4-Fluoro-phenyl)-ethyl]-piperidin-4-one (obtained as described in protocol XI-2) and 242 mg (1.247 mmol) of 1-(4-Fluorobenzyl)-piperazine were treated as described in the first part of protocol XVI in Example 3. The crude product was purified by silica gel column chromatography (dichloromethane-methanol 95/5+NH_4OH), to yield 324 mg (78%) of 1-(4-Fluoro-benzyl)-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine as a colourless oil.

LCMS M+1=400, ^{1}H NMR ($CDCl_3$).

320 mg (0.8 mmol) of this product were solubilised in 3.2 ml of anhydrous dichloromethane and 2.4 ml (2.4 mmol) of HCl 1N in diethyl ether were added. The mixture was stirred for 1h at room temperature. The reaction mixture was concentrated to dryness. The residue was then triturated successively with dichloromethane and petroleum ether. The product was then freeze-dried to provide 215 mg (56%) of the expected hydrochloride salt as a white solid.

LCMS M+1=400, ^{1}H NMR (DMSO+D_2O).

VII/ 1-[1-(4-Fluoro-phenyl)-ethyl]-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-532):



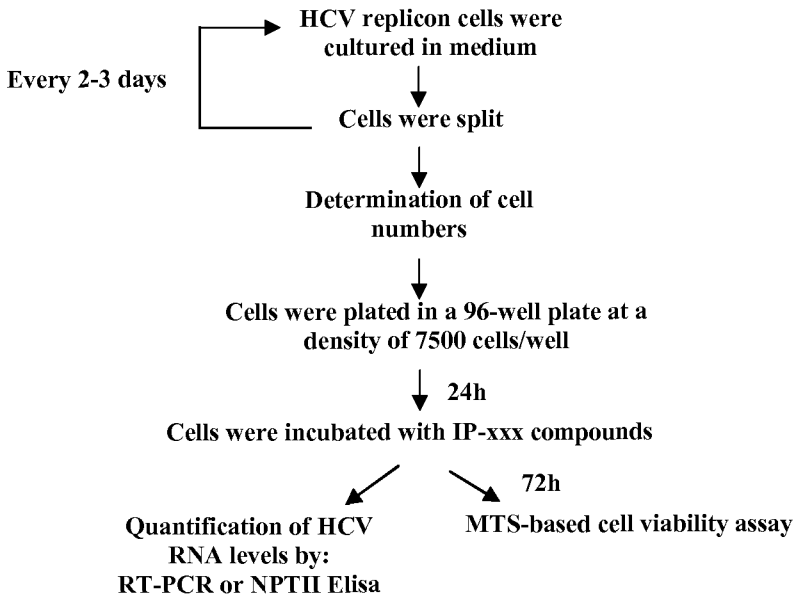
234 mg (1.057 mmol) of 1-[1-(4-Fluoro-phenyl)-ethyl]-piperidin-4-one (obtained as described in protocol Example 3, XI-2) and 264 mg (1.269 mmol) of 1-[1-(4-Fluoro-phenyl)-ethyl]-piperazine (prepared as described in protocol Example 2, V-2) were treated as described in the first part of protocol XVI in Example 3. The crude product was purified by silica gel column chromatography (dichloromethane-methanol 95/5+NH_4OH) to give 363 mg (83%) of 1-[1-(4-Fluoro-phenyl)-ethyl]-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine as colourless oil.

LCMS M+1=414, ^{1}H NMR ($CDCl_3$).

360 mg (0.87 mmol) of this product were solubilised in 4 ml of anhydrous dichloromethane and 2.7 ml (2.7 mmol) of HCl 1N in diethyl ether were added. The mixture was stirred for 1h at room temperature. The reaction mixture was concentrated to dryness. The residue was then triturated successively with dichloromethane and petroleum ether. The product was then freeze-dried to provide 367 mg (86%) of the expected hydrochloride salt as a white solid.

LCMS M+1=414, ^{1}H NMR (DMSO+D_2O).

Example 5 : HCV RNA Replicon assay (genotype 1b)



Exemple 6 : Description of the HCV RNA Replicon assay

Studies on hepatitis C virus (HCV) replication have been greatly advanced by the development of cell culture models known as replicon systems.

Our test use the hepatoma cell line Huh7, which is a subclone derived from cell line 9-13 expressing HCV genotype 1b replicon I_{377}/NS3-3' (accession No. AJ242652). This HCV subgenomic replicon, stably maintained in Huh7 hepatoma cells, was created by Lohmann and *al.* (Ref. 1). The replicon-containing cell culture, designated GS4.3, was obtained from Dr. Christoph Seeger of the Institute for Cancer Research, Fox Chase Cancer Center, Philadelphia, Pennsylvania (Ref. 2).

This replicon consists of a subgenomic HCV sequence in which the gene unit encoding the HCV structural proteins is replaced by the gene encoding the neomycin phosphotransferase II (NPTII). The translation of the region that produces HCV proteins NS3 to NS5 is controlled by the encephalomyocarditis virus (EMCV) internal ribosome entry site (IRES)

(structure of HCV subgenomic replicon is shown in figure 1). This construct is similar to the replicon present in the cell line 9-13 and provides stable NPTII expression for antiviral screening.

Expression of the NPTII reporter gene allows to perform an indirect measure of HCV replication. Indeed, the rate of its transcription and therefore the encoded activity are directly proportional to HCV RNA levels (Figures 2 and 3, Ref. 3). The use of the NPTII endpoint is more economical than HCV RNA and can be used for high-throughput screening applications (Figure 3).

Experimental procedure

HCV replicon cell culture, treatment and controls

This experimental procedure consists in 3 main steps:

- Culture of Huh7 cells

Huh7 cells are maintained at 37°C, 5% CO_2, in DMEM supplemented with L-glutamine 2mM, non-essential amino acids, 10% Fetal Bovine Serum (FBS) and 500µg/ml geneticin. Cells are sub-divided 1:3 or 1:4 every 2-3 days.

1. 24hr prior to the assay, Huh7 cells are collected, counted, plated in 96-well plates at 7500 cells/well in 100µl standard maintenance medium and incubated in the conditions above.
2. To initiate the assay, culture medium is removed, cells are washed once with PBS. For control compounds only, 90µl assay medium (DMEM, L-glutamine, NEAA, 10% FBS) are added.

Application of the compounds

Compounds and controls compounds are made as a 10X stock in assay medium, 10µl are added to duplicate wells, plates are rocked to mix, and incubated as above for 72 hr.

Quality controls

Human interferon alpha-2b (Peginterferon alpha-2b from Schering Plough) and ribavirin (R-9644, Sigma-Aldrich), two hepatitis C virus inhibitors that reduce RNA replication, are included in each run as positive control compounds.

Positive controls are added in duplicate at two different concentrations which will provide the low and high control values: 1 pM and 1 nM for interferon, and 100 µM and 200 µM for ribavirin.

Quantification of HCV levels

Neomycin phosphotransferase II Elisa kit, purchased from AGDIA (PSP 73000), is used to detect and measure NPTII after cell lysis (as described in the manufacturer's instructions).

HCV RNA levels are measured by using TaqMan RT-PCR. Total cellular RNA is isolated and amplified by using ABBOTT RealTime HCV assay (Abbott m1000™ Automated Sample Preparation System and Abbott m2000rt™ instrument for reverse transcription,

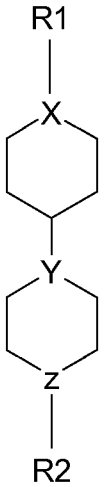
PCR amplification, and detection/quantitation, Abbott Molecular Inc., Des Plaines, IL). The molecular genotyping method target the 5'untranslated (UTR) region of the virus genome (Figure 1) and is based on an amplification of the viral genome. An internal control, simultaneously amplified by RT-PCR, serves to demonstrate that the process has proceeded correctly for each sample. Negative control, low positive control and high positive control are also introduced. Results are reported in International Units/mL (IU/mL), and 1 IU/ml = 4.3 copies/ml. The lower limit of detection is 12 IU/mL with ≥ 95% probability. The dynamic range of the assay extends from 12 to 100,000,000 IU/ml. The Abbott RealTime HCV assay detects and quantitates genotypes 1 – 6.

The EC_{50} is defined as the concentration of compound at which the HCV RNA level in the replicon cells is reduced by 50%.

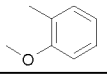
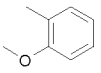
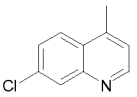
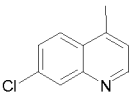
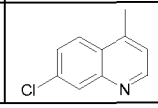
Quantification of cytotoxicity

To monitor any cytotoxic effect, the viabilities of the replicon cells following 72 h of treatment with compound are determined by using a tetrazolium compound (3-[4,5-dimethylthiazol-2-yl]-5-[3-carboxymethoxyphenyl]-2-[4-sulfophenyl]-2Htetrazolium, inner salt [MTS])-based assay (CellTiter 96 AQueous One Solution Cell Proliferation Assay; Promega, G3580). The CC_{50} is defined as the concentration of the compound at which cell viability was reduced by 50%.

Hereafter are the results obtained on the HCV RNA Replicon assay for the compounds of formula (I):

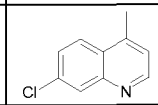
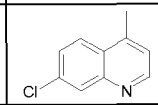
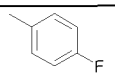
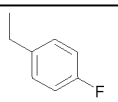
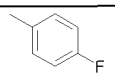
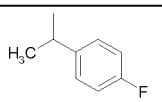


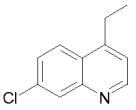
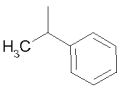
Compounds of cluster 1

Reference	R1	R2	% viral charge (1)	IC_{50} µM (2)
IP-153			65	
IP-179 .HCl			56	
IP-189			74	
IP-193 .HCl			63	>10
IP-224			82	
IP-233 .HCl			73	
IP-292. TFA			53	11

(1): % of viral charge remaining after a dose of 10µM

Compounds of cluster 2

Reference	R1	R2	% viral charge (1)	IC_{50} µM (2)
IP-119			40	10
IP-122			40	10
IP-140 .HCl			68	4.6
IP-154 .HCl			46	1.7 0.89 (3)
IP-275. HCl			65	
IP-282			33	4.4
IP-308. HCl			37.8	0.556

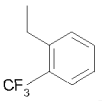
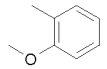
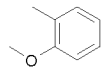
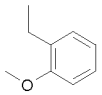
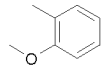
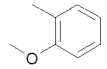
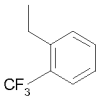
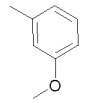
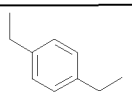
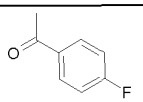
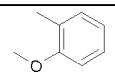
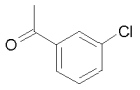
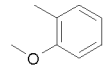
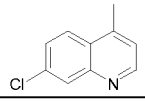
IP-385. HCl			60.2	
IP-453. HCl			21	1

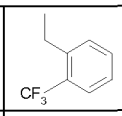
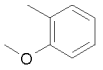
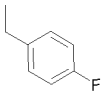
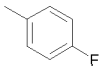
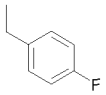
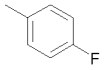
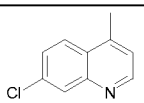
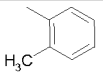
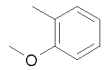
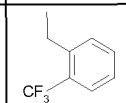
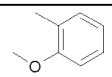
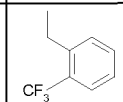
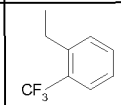
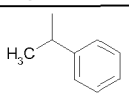
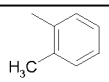
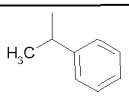
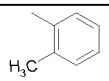
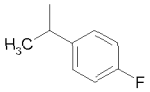
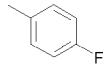
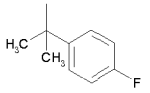
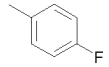
(1): % of viral charge remaining after a dose of 10µM

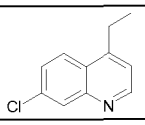
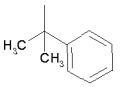
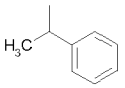
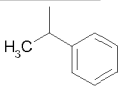
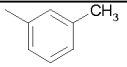
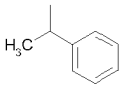
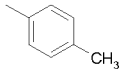
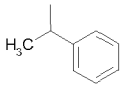
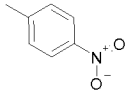
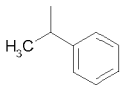
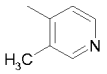
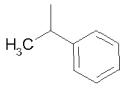
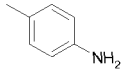
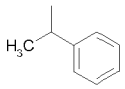
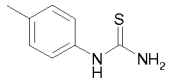
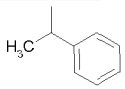
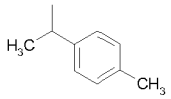
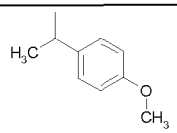
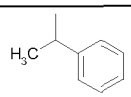
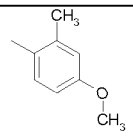
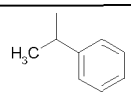
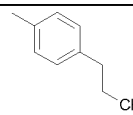
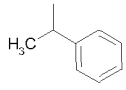
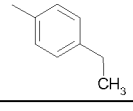
(2): IC50 obtained with NPT2

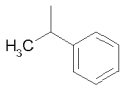
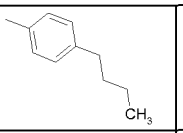
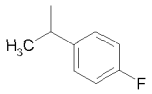
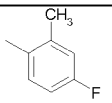
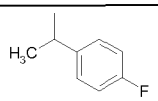
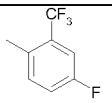
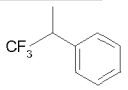
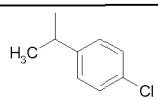
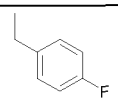
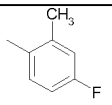
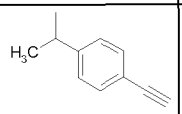
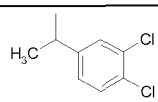
(3): IC50 obtained by RT-PCR

5 Compounds of cluster 3

Reference	**R1**	**R2**	**% viral charge (1)**	**IC_{50} µM (2)**
IP-038			22	4
IP-074			28	3
IP-075			51	
IP-076			44	10
IP-077			33	10
IP-078			70	
IP-079			74	
IP-081(not according to the invention)			*100*	
IP-092(not according to the invention)			*100*	
IP-139			40	

IP-145 .HCl			42	3.3
IP-156 .HCl			45	1.6 (2) 0.95 (3)
IP-158			26	1.6 (2) 1.15 (3)
IP-159			57	
IP-162 .HCl			32	2.1
IP-163 .HCl			28	1.7 (2) 1.05 (3)
IP-164 .HCl			26	1.5 (2) 1.02 (3)
IP-165 .HCl			40	3.4
IP-169 .HCl			37	2.1 (2) 4.35 (3)
IP-175 .HCl			36	10.7
IP-176 .HCl			30	8.4
IP-213			52	4.3
IP-223 .HCl			41	0.166
IP-264			41	2.5
IP-278. HCl			45	0.25
IP-283. HCl			36	5
IP-334. HCl			29.7	3.7

IP-408.HCl			67	
IP-440. HCl			28	2.6
IP-454. HCl			42	10
IP-464. HCl			15.8	0.722
IP-465. HCl			15.8	0.64
IP-468. HCl			36.8	0.944
IP-469. HCl			22.3	0.778
IP-473. HCl			52.6	
IP-474. HCl			15.8	2.4
IP-476. HCl			36.8	4.8
IP-477. HCl			29	0.639
IP-483. HCl				0.17
IP-484. HCl				0.611
IP-485. HCl				0.556
IP-490. HCl				0.417
IP-503. HCl				0.555

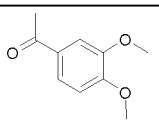
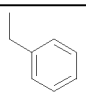
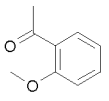
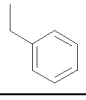
IP-506. HCl			14	
IP-508. HCl				0.090
IP-516. HCl			11.3	
IP-531. HCl			66.6	
IP-536. HCl				
IP-543. HCl				
IP-544. HCl				
IP-545. HCl				

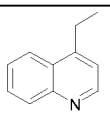
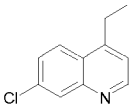
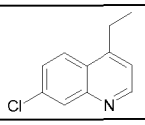
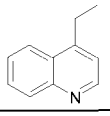
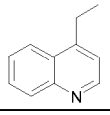
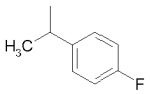
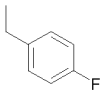
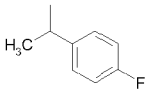
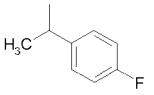
(1): % of viral charge remaining after a dose of 10µM

(2): IC50 obtained with NPT2

(3): IC50 obtained by RT-PCR

Compounds of cluster 4

Reference	**R1**	**R2**	**% viral charge (1)**	**IC_{50} µM (2)**
IP-082(not according to the invention)			*100*	
IP-083(not according to the invention)			*80*	
IP-121			40	10
IP-138 HCl			43	10.3

IP-366. HCl			72.6	
IP-384. HCl			26	
IP-409. HCl			35.6	>10
IP-439. HCl			71.8	
IP-529. HCl			30.5	0.583
IP-532. HCl			38.8	0.611

(1): % of viral charge remaining after a dose of 10µM

(2): IC50 obtained with NPT2

Dose-dependent inhibition of HCV replicon by compounds of the present invention is shown in figures 4-6 in the tables below.

Compound	Replicon EC50 (µM)	Cytotoxicity CC50 (µM)	Selectivity Index
IP-154	0,89	> 10	> 11,2
IP-156	0,95	> 10	> 10,5
IP-158	1,15	> 10	> 8,7
IP-162	3,33	> 10	> 3
IP-163	1,05	> 10	> 9,5
IP-164	1,02	> 10	> 9,8

- **EC_{50} values were determined in a genotype-1b replicon system using qRT-PCR.**
- **Cytotoxicity (CC_{50}) assays were performed on exponentially growing Huh7 cells using MTS (Promega) as a colorimetric method for determining the number of viable cells.**
- **Selectivity index was calculed as CC_{50} divided by EC_{50}.**

PK Parameters : Plama Kinetic

Compounds	Analytical score r^2	Route	Dose (mg/kg)		Cmax levels (ng/mL)		Tmax levels (h)		AUC (ng.h/mL)		AUC/Dose		AUC PO/AUC IV levels %
			rat 1	rat 2	rat 1	rat 2	rat 1	rat 2	rat 1	rat 2	rat 1	rat 2	
IP-154	0,9785	PO	10,0	10,0	5,39	6,78	0,50	0,50	9	7	1	1	1,0
		IV	2,0	2,0	418,00	309,00	0,05	0,05	186	140	93	70	
IP-156	0,9666	PO	10,0	10,0	73,20	62,70	10,02	0,50	243	272	24	27	73,5
		IV	2,0	2,0	241,00	57,20	0,05	0,05	100	54	50	27	
IP-162	0,9852	PO	10,0	10,0	138,00	143,00	10,47	4,00	498	494	50	49	60,0
		IV	2,0	2,0	140,00	255,00	0,05	0,05	137	209	68	104	
IP-155	0,9891	PO	10,0	10,0	2,80	2,89	0,50	0,50	5	6	0	1	4,0
		IV	2,0	2,0	46,90	66,10	0,05	0,05	19	41	9	21	
IP-223	0,9637	PO	10,0	10,0	*48,53*	*47,90*	0,50	0,50	117	234	12	23	11,0
		IV	2,0	2,0	240,66	268,41	0,05	0,05	240	470	120	235	
IP-251	0,9853	PO	10,0	10,0	72,03	54,77	1,93	1,93	370	265	37	27	20,1
		IV	2,0	2,0	178,25	281,78	0,07	0,05	292	344	146	172	
IP-278		PO	10,0		49.8		0.5		387.8				18.5*
		IV	2,0		256.0		0,05		419.7				
IP-508		PO	10,0		35.0		0.5		163.1				10.3
		IV	2,0		248.8		0,05		317.8				

* Study has been stopped after 10 hours; concentration after PO administration forms a plate that does not reach 0, so this value is truncated. The estimated percentage ranks between 25 and 30%.

Determination of Liver Level

Compounds	Analytical score r^2 Liver	Route	Sample Time h	Liver Level (ng/g)		Plasma Level (ng/mL)		Liver/Plasma	
				rat 1	rat 2	rat 1	rat 2	rat 1	rat 2
IP-154	0,9969	PO	10	668	605	BLQ	BLQ	NA	NA
		IV	6	407	409	BLQ	1,3	NA	309,8
IP-156	0,9965	PO	10	3830	3790	73,2	29,5	52,3	128,5
		IV	6	955	998	1,5	1,8	632,5	563,8

NA : Not Applicable

BLQ: Below The Limit of Quantification (1 ng/mL)

REFERENCES

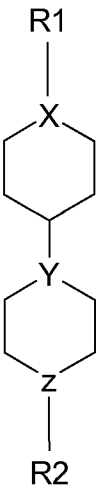
Lohmann V, Korner F, Koch JO, Herian U, Theilmann L and Bartenschlager R. 1999. Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. Science. 285: 110-113.

Zhu Q, Guo JT and Seeger C. 2003. Replication of hepatitis C virus subgenomic in nonhepatic epithelial and mouse hepatoma cells. J. Virol. 77(17): 9204-10.

Tan H, Hong J, Seiwert S and Blatt LM. 2004. High-Throughput Screening of Anti-HCV Drug Candidates Using an Elisa-Based HCV Replicon Assay. Hepatology. 40(4) 407A.

CLAIMS

1. Compound for use as an antiviral agent having the general formula (I):



(I)

wherein

X, Y and Z represent independantly N or N^{+}-H,

R1 is phenyl, pyrimidine, pyridine, thiophen, pyrrole, quinoline or a heterocyclic group, each of which is unsubstituted or substituted with one or more substituent groups, or

R1 is -R'-R3, in which R' is a methylene group, unsubstituted or substituted with one or more substituent groups, wherein the substituent groups are selected from C1-C6 alkyl and CF_3,

R3 is phenyl, quinoline or a heterocyclic group, each of which is unsubstituted or substituted with one or more substituent groups,

R2 is phenyl, pyrimidine, pyridine, thiophen, pyrrole, quinoline or a heterocyclic group, each of which is unsubstituted or substituted with one or more substituent groups, or

R2 is -R''-R4, in which R" is a methylene group, unsubstituted or substituted with one or more substituent groups, wherein the substituent groups are selected from C1-C6 alkyl,

R4 is phenyl, quinoline or a heterocyclic group, each of which is unsubstituted or substituted with one or more substituent groups,

and the pharmaceutically acceptable salts thereof.

2. Compound for use as an antiviral agent according to claim 1 wherein
R1 is phenyl, pyridine or quinoline each of which is unsubstituted or substituted with one or more substituent groups, and
R2 is phenyl or quinoline each of which is unsubstituted or substituted with one or more substituent groups.

3. Compound for use as an antiviral agent according to claim 1 wherein
R1 is phenyl, pyridine or quinoline each of which is unsubstituted or substituted with one or more substituent groups, and
R2 is benzyl which is unsubstituted or substituted with one or more substituent groups or R2 is $-CH_2$-R4 or $-CH(CH_3)$-R4, and R4 is a phenyl or quinoline each of which is unsubstituted or substituted with one or more substituted groups.

4. Compound for use as an antiviral agent according to claim 1 wherein
R1 is benzyl which is unsubstituted or substituted with one or more substituent groups or R1 is selected from $-CH_2$-R3, $-CH(CH_3)$-R3, $-C(CH_3)_2$-R3 or $-CH(CF_3)$-R3,
R2 is phenyl, pyridine or quinoline, each of which is unsubstituted or substituted with one or more substituent groups, and
R3 is phenyl or quinoline, each of which is unsubstituted or substituted with one or more substituent groups.

5. Compound for use as an antiviral agent according to claim 1 wherein
R1 is benzyl which is unsubstituted or substituted with one or more substituent groups or R1 is $-CH_2$-R3 or $-CH(CH_3)$-R3, and R2 is benzyl which is unsubstituted or substituted with one or more substituent groups, or R2 is $-CH_2$-R4 or $-CH(CH_3)$-R4, wherein R3 and R4 are independently selected from phenyl or quinoline which are unsubstituted or substituted with one or more substituent groups.

6. Compound for use as an antiviral agent according to claim 1 wherein R1 and R2 are independently selected in the group consisting of phenyl, benzyl, pyridine and quinoline, each of which is unsubstituted or substituted with one or more substituent groups.

7. Compound for use as an antiviral agent according to anyone of claims 1-6 wherein X, Y and Z represent N.

8. Compound for use as an antiviral agent according to anyone of claims 1-7 wherein R' and R" are independently $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$ or $-CH(CF_3)-$.

9. Compound for use as antiviral agent according to anyone of claims 1-8 wherein the substituent groups are independantly selected from Cl, F, I, Br, C1-C6 alkyl, C1-C6 alkyl substituted with one or more halogens, C1-C6 alkoxy, C3-C6 cycloalkyl, phenyl, pyridinyl, hydroxy, nitro, -CCH or -NH-CS-NH_2 and NR5R6 with R5 and R6 representing independently hydrogen or C1-C6 alkyl.

10. Compound for use as an antiviral agent according to anyone of claims 1-9 wherein the substituent groups are independently selected in the group consisting of Cl, F, methoxy, methyl and -CF_3.

11. Compound for use as an antiviral agent according to claim 1 selected in the group consisting of 1-(2-methoxy-phenyl)-4-(1-phenyl-piperidin-4-yl) piperazine (IP-153), 1-(2-methoxy-phenyl)-4-(1-phenyl-piperidin-4-yl) piperazine hydrochloride (IP-179), 4-(4-phenyl-piperazin-1-yl)-3,4,5,6-tetrahydro-2H-[1,4']-bipyridinyl (IP-189), 4-(4-phenyl-piperazin-1-yl)-3,4,5,6-tetrahydro-2H-[1,4']-bipyridinyl hydrochloride (IP-193), 7-chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl]-quinoline (IP-224), 7-chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl]-quinoline hydrochloride (IP-233), 7-Chloro-4-[4-(4-phenyl-piperazin-1-yl)-piperidin-1-yl]-quinoline trifluoroacetic (IP-292), 1-benzyl-4-(phenyl-piperido-4-yl)-piperazine (IP-119), 4-[4-(4-benzyl-piperazin-1-yl)-piperidin-1-yl]-7-chloro-quinoline (IP-122), 4-[4-(4-benzyl-piperazin-1-yl)-piperidin-1-yl]-7-chloro-quinoline hydrochloride (IP-140), 1-benzyl-4-(phenyl-piperido-4-yl)-piperazine hydrochloride (IP-154), 1-(4-Fluoro-benzyl)-4-[1-(4-fluoro-phenyl)-piperidin-4-yl]-piperazine hydrochloride (IP-275), 1-[1-(4-Fluoro-phenyl)-ethyl]-4-[1-(4-fluoro-phenyl)-piperidin-4-yl]-piperazine hydrochloride (IP-308), 7-Chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl-methyl]-quinoline hydrochloride (IP-385), 1-(1-Phenyl-ethyl)-4-(1-*o*-tolyl-piperidin-4-yl)-piperazine hydrochloride (IP-453), 1-(2-methoxy-phenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl] piperazine (IP-038), 1-(1-benzyl-piperidin-4-yl)-4-(2-methoxy-phenyl)-piperazine (IP-074), 1-[1-(2-Methoxy-benzyl)-piperidin-4-yl]-4-(2-methoxy-phenyl)-piperazine (IP-075), 1-[1-(2-Chloro-benzyl)-piperidin-4-yl]-4-(2-methoxy-phenyl)-piperazine (IP-076), 1-(2-Fluoro-phenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl]-piperazine (IP-077), 1-(1-Benzyl-piperidin-4-yl)-4-(4-methoxy-phenyl)-piperazine (IP-078), 1-[1-(4-Ethyl-benzyl)-piperidin-4-yl]-4-phenyl-piperazine (IP-079), 4-[4-(1-benzyl-piperidin-4-yl)-piperazin-1-yl]-7-chloro-quinoline (IP-139), 1-(2-methoxy-phenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl] piperazine hydrochloride (IP-145), 1-[1-(4-fluoro-benzyl)-piperidin-4-yl]-4(4-fluorophenyl)-piperazine hydrochloride (IP-156),1-(1-benzylpiperidin-4-yl)-4-(2-chlorophenyl)-piperazine (IP-158), 1-[1-(4-fluoro-benzyl)-piperidin-4-yl]-4(4-fluorophenyl)-piperazine (IP-159), 4-[4-(1-benzyl-

piperidin-4-yl)-piperazin-1-yl]-7-chloro-quinoline hydrochloride (IP-162), 1-(1-benzylpiperidin-4-yl)-4-(2-chlorophenyl)-piperazine hydrochloride (IP-163), 1-(1-benzylpiperidin-4-yl)-4-o-tolyl-piperazine hydrochloride (IP-164), 1-(1-benzyl-piperidin-4-yl)-4-(2-methoxy-phenyl)-piperazine hydrochloride (IP165), 1-o-tolyl-4-[1-(2-trifluoromethylbenzyl)-piperidin-4-yl] piperazine hydrochloride (IP-169), 1-phenyl-4-[1-(2-trifluoromehtylbenzyl)-piperidin-4-yl] piperazine hydrochloride (IP-175), 1-(2-chlorophenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl]-piperazine hydrochloride (IP-176), 1-[1-(1-phenyl-ethyl-) piperidin-4-yl]-4-o-tolyl-piperazine (IP-213), 1-[1-(1-phenyl-ethyl-) piperidin-4-yl]-4-o-tolyl-piperazine hydrochloride (IP-223), 1-(4-Fluoro-phenyl)-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-278), 1-(1-Benzyl-piperidin-4-yl)-4-pyridin-4-yl-piperazine hydrochloride (IP-283), 1-(4-Fluoro-phenyl)-4-{1-[1-(4-fluoro-phenyl)-1-methyl-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-334), 7-Chloro-4-[4-(4-phenyl-piperazin-1-yl)-piperidin-1-ylmethyl]-quinoline hydrochloride (IP-408), 1-[1-(1-Methyl-1-phenyl-ethyl)-piperidin-4-yl]-4-*o*-tolyl-piperazine hydrochloride (IP-440), 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-pyridin-4-yl-piperazine hydrochloride (IP-454), 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-*m*-tolyl-piperazine hydrochloride (IP-464), 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-*p*-tolyl-piperazine hydrochloride (IP-465), 1-(1-Benzyl-piperidin-4-yl)-4-phenyl-piperazine hydrochloride (IP-468), 1-(4-Nitro-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-469), 1-(3-Methyl-pyridin-4-yl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-473), 4-{4-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-phenylamine hydrochloride (IP-474), (4-{4-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-phenyl)-thiourea hydrochloride (IP-476), 1-Phenyl-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-477), 1-*o*-Tolyl-4-[1-(1-*p*-tolyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-483), 1-{1-[1-(4-Methoxy-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-484), 1-(4-Methoxy-2-methyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-485), 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-(4-propyl-phenyl)-piperazine (IP-490), 1-(4-Ethyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-503), 1-(4-Butyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-506), 1-(4-Fluoro-2-methyl-phenyl)-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-508), 1-{1-[1-(4-Fluoro-phenyl)-ethyl]-piperidin-4-yl}-4-(4-fluoro-2-trifluoromethyl-phenyl)-piperazine hydrochloride (IP-516), 1-*o*-Tolyl-4-[1-(2,2,2-trifluoro-1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-531), 1-{1-[1-(4-Chloro-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-536), 1-[1-(4-Fluoro-benzyl)-piperidin-4-yl]-4-(4-fluoro-2-methyl-phenyl)-piperazine hydrochloride (IP-543), 1-{1-[1-(4-Ethynyl-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-

piperazine hydrochloride (IP-544), 1-{1-[1-(3,4-Dichloro-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine (IP-545), 1-benzyl-4-(1-benzyl-piperidin-4-yl)-piperazine (IP-121) and 1-benzyl-4-(1-benzyl-piperidin-4-yl)-piperazine hydrochloride (IP-138), 4-[4-(1-Benzyl-piperidin-4-yl)-piperazin-1-ylmethyl]-quinoline hydrochloride (IP-366), 4-[4-(1-Benzyl-piperidin-4-yl)-piperazin-1-ylmethyl]-7-chloro-quinoline hydrochloride (IP-384), 4-[4-(4-Benzyl-piperazin-1-yl)-piperidin-1-ylmethyl]-7-chloro-quinoline hydrochloride (IP-409), 4-[4-(1-quinoline-4-ylmethyl-piperidin-4-yl)-piperazin-1-ylmethyl]-quinoline hydrochloride (IP-439), 1-(4-Fluoro-benzyl)-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-529), 1-[1-(4-Fluoro-phenyl)-ethyl]-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-532).

12. Compound according to anyone of claims 1-11 for treatment of infection by HCV.

13. Compound selected in the group consisting of 1-(2-methoxy-phenyl)-4-(1-phenyl-piperidin-4-yl) piperazine (IP-153), 1-(2-methoxy-phenyl)-4-(1-phenyl-piperidin-4-yl) piperazine hydrochloride (IP-179), 4-(4-phenyl-piperazin-1-yl)-3,4,5,6-tetrahydro-2H-[1,4']-bipyridinyl (IP-189), 4-(4-phenyl-piperazin-1-yl)-3,4,5,6-tetrahydro-2H-[1,4']-bipyridinyl hydrochloride (IP-193), 7-chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl]-quinoline (IP-224), 7-chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl]-quinoline hydrochloride (IP-233), 7-Chloro-4-[4-(4-phenyl-piperazin-1-yl)-piperidin-1-yl]-quinoline trifluoroacetic (IP-292), 1-benzyl-4-(phenyl-piperido-4-yl)-piperazine (IP-119), 4-[4-(4-benzyl-piperazin-1-yl)-piperidin-1-yl]-7-chloro-quinoline (IP-122), 4-[4-(4-benzyl-piperazin-1-yl)-piperidin-1-yl]-7-chloro-quinoline hydrochloride (IP-140), 1-benzyl-4-(phenyl-piperido-4-yl)-piperazine hydrochloride (IP-154), 1-(4-Fluoro-benzyl)-4-[1-(4-fluoro-phenyl)-piperidin-4-yl]-piperazine hydrochloride (IP-275), 1-[1-(4-Fluoro-phenyl)-ethyl]-4-[1-(4-fluoro-phenyl)-piperidin-4-yl]-piperazine hydrochloride (IP-308), 7-Chloro-4-[4-(1-phenyl-piperidin-4-yl)-piperazin-1-yl-methyl]-quinoline hydrochloride (IP-385), 1-(1-Phenyl-ethyl)-4-(1-*o*-tolyl-piperidin-4-yl)-piperazine hydrochloride (IP-453), 4-[4-(1-benzyl-piperidin-4-yl)-piperazin-1-yl]-7-chloro-quinoline (IP-139), 1-[1-(4-fluoro-benzyl)-piperidin-4-yl]-4(4-fluorophenyl)-piperazine hydrochloride (IP-156), 1-[1-(4-fluoro-benzyl)-piperidin-4-yl]-4(4-fluorophenyl)-piperazine (IP-159), 4-[4-(1-benzyl-piperidin-4-yl)-piperazin-1-yl]-7-chloro-quinoline hydrochloride (IP-162), 1-(1-benzylpiperidin-4-yl)-4-o-tolyl-piperazine hydrochloride (IP-164), 1-o-tolyl-4-[1-(2-trifluoromethylbenzyl)-piperidin-4-yl] piperazine hydrochloride (IP-169), 1-(2-chlorophenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl]-piperazine hydrochloride (IP-176), 1-[1-(1-phenyl-ethyl-) piperidin-4-yl]-4-o-tolyl-piperazine (IP-213) and 1-[1-(1-phenyl-ethyl-)

piperidin-4-yl]-4-o-tolyl-piperazine hydrochloride (IP-223), 1-(4-Fluoro-phenyl)-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-278), 1-(1-Benzyl-piperidin-4-yl)-4-pyridin-4-yl-piperazine hydrochloride (IP-283), 1-(4-Fluoro-phenyl)-4-{1-[1-(4-fluoro-phenyl)-1-methyl-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-334), 7-Chloro-4-[4-(4-phenyl-piperazin-1-yl)-piperidin-1-ylmethyl]-quinoline hydrochloride (IP-408), 1-[1-(1-Methyl-1-phenyl-ethyl)-piperidin-4-yl]-4-*o*-tolyl-piperazine hydrochloride (IP-440), 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-pyridin-4-yl-piperazine hydrochloride (IP-454), 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-*m*-tolyl-piperazine hydrochloride (IP-464), 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-*p*-tolyl-piperazine hydrochloride (IP-465), 1-(4-Nitro-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-469), 1-(3-Methyl-pyridin-4-yl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-473), 4-{4-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-phenylamine hydrochloride (IP-474), (4-{4-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-phenyl)-thiourea hydrochloride (IP-476), 1-Phenyl-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-477), 1-*o*-Tolyl-4-[1-(1-*p*-tolyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-483), 1-{1-[1-(4-Methoxy-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-484), 1-(4-Methoxy-2-methyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-485), 1-[1-(1-Phenyl-ethyl)-piperidin-4-yl]-4-(4-propyl-phenyl)-piperazine (IP-490), 1-(4-Ethyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-503), 1-(4-Butyl-phenyl)-4-[1-(1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-506), 1-(4-Fluoro-2-methyl-phenyl)-4-{1-[1-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-piperazine hydrochloride (IP-508), 1-{1-[1-(4-Fluoro-phenyl)-ethyl]-piperidin-4-yl}-4-(4-fluoro-2-trifluoromethyl-phenyl)-piperazine hydrochloride (IP-516), 1-*o*-Tolyl-4-[1-(2,2,2-trifluoro-1-phenyl-ethyl)-piperidin-4-yl]-piperazine hydrochloride (IP-531), 1-{1-[1-(4-Chloro-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-536), 1-[1-(4-Fluoro-benzyl)-piperidin-4-yl]-4-(4-fluoro-2-methyl-phenyl)-piperazine hydrochloride (IP-543), 1-{1-[1-(4-Ethynyl-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine hydrochloride (IP-544), 1-{1-[1-(3,4-Dichloro-phenyl)-ethyl]-piperidin-4-yl}-4-*o*-tolyl-piperazine (IP-545).

14. Compound according to claim 13 for use as a medicament.

15. Compound for use as a medicament selected in the group consisting 1-(2-methoxy-phenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl] piperazine (IP-038), 1-[1-(2-Methoxy-benzyl)-piperidin-4-yl]-4-(2-methoxy-phenyl)-piperazine (IP-075), 1-[1-(2-Chloro-benzyl)-piperidin-4-yl]-4-(2-methoxy-phenyl)-piperazine (IP-076), 1-(2-Fluoro-phenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl]-piperazine (IP-077), 1-(1-Benzyl-piperidin-4-yl)-4-(4-methoxy-phenyl)-piperazine (IP-078), 1-[1-(4-Ethyl-benzyl)-piperidin-4-yl]-4-phenyl-piperazine (IP-079), 1-(2-methoxy-phenyl)-4-[1-(2-trifluoromethyl-benzyl)-piperidin-4-yl] piperazine hydrochloride (IP-145), 1-(1-benzylpiperidin-4-yl)-4-(2-chlorophenyl)-piperazine (IP-158), 1-(1-benzylpiperidin-4-yl)-4-(2-chlorophenyl)-piperazine hydrochloride (IP-163), 1-phenyl-4-[1-(2-trifluoromethylbenzyl)-piperidin-4-yl] piperazine hydrochloride (IP-175), 1-benzyl-4-(1-benzyl-piperidin-4-yl)-piperazine (IP-121), 1-benzyl-4-(1-benzyl-piperidin-4-yl)-piperazine hydrochloride (IP-138), 1-(1-Benzyl-piperidin-4-yl)-4-phenyl-piperazine hydrochloride (IP-468).

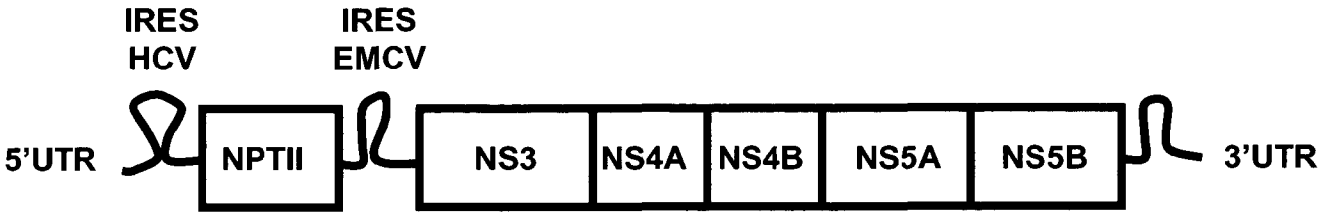


FIG. 1

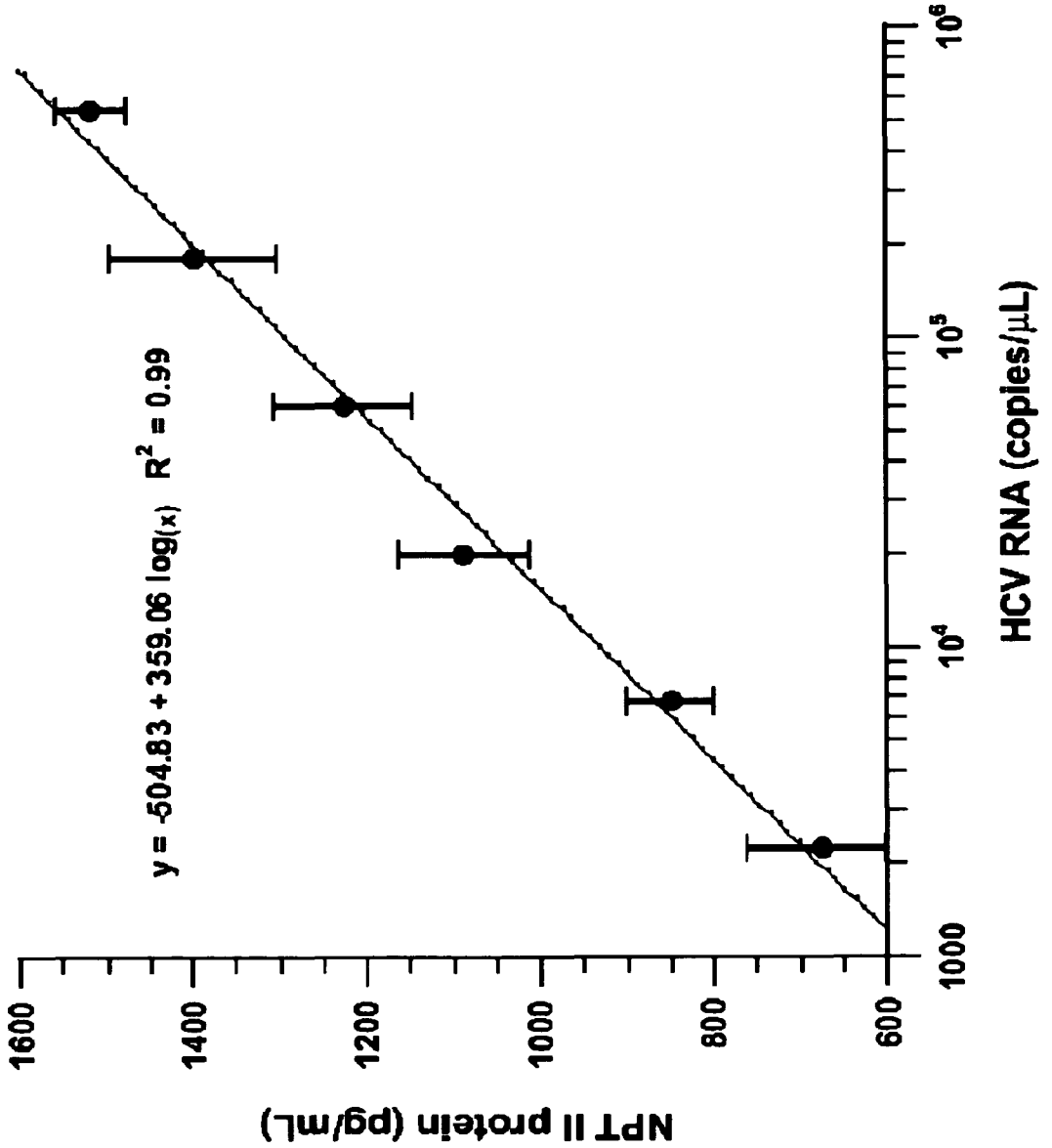

NPT II protein (pg/mL)
1600
1400
1200
1000
800
600
y = -504.83 + 359.06 log(x) R² = 0.99
1000
10⁴
10⁵
10⁶
HCV RNA (copies/µL)

FIG. 2

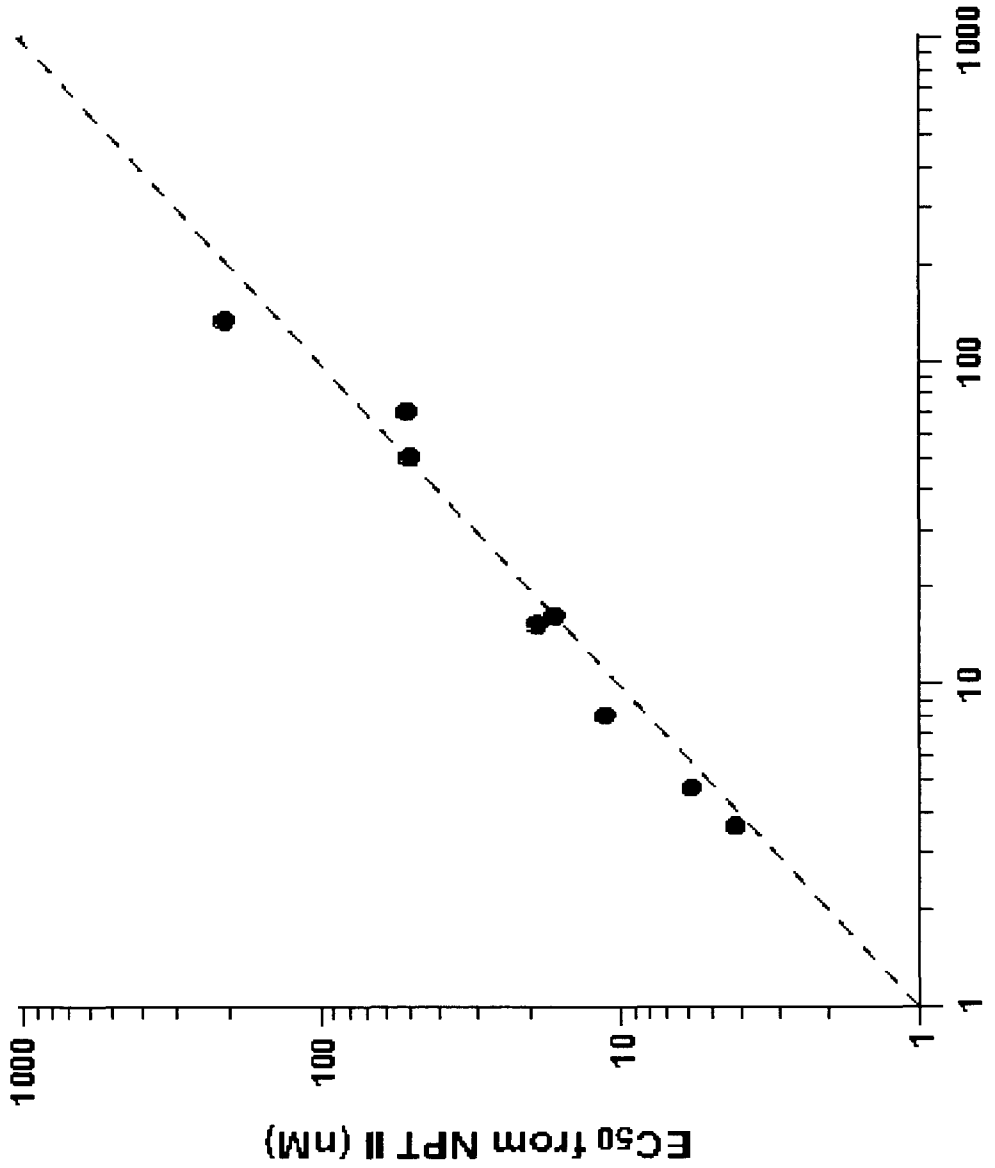

EC50 from NPT II (nM)
1000
100
10
1
EC50 from real-time RT-PCR (nM)
1
10
100
1000

FIG. 3

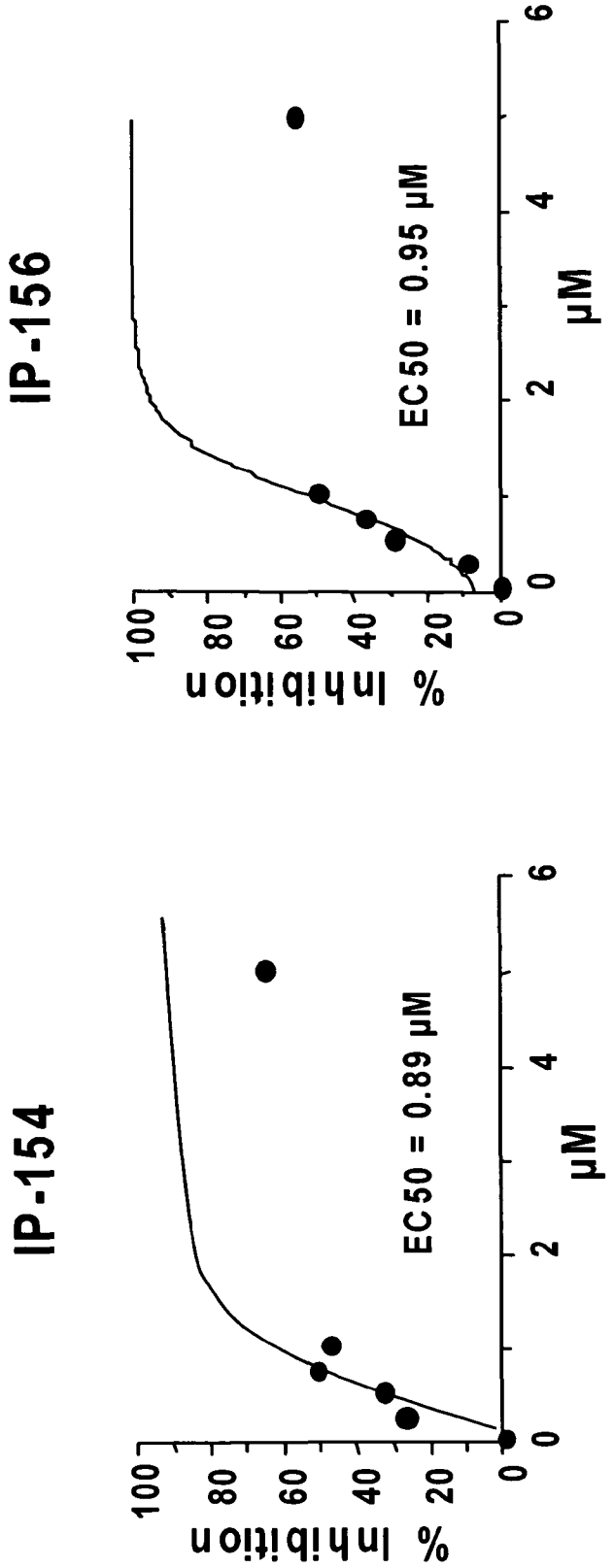

IP-156
% Inhibition
EC50 = 0.95 µM
µM
IP-154
% Inhibition
EC50 = 0.89 µM
µM

FIG. 4A

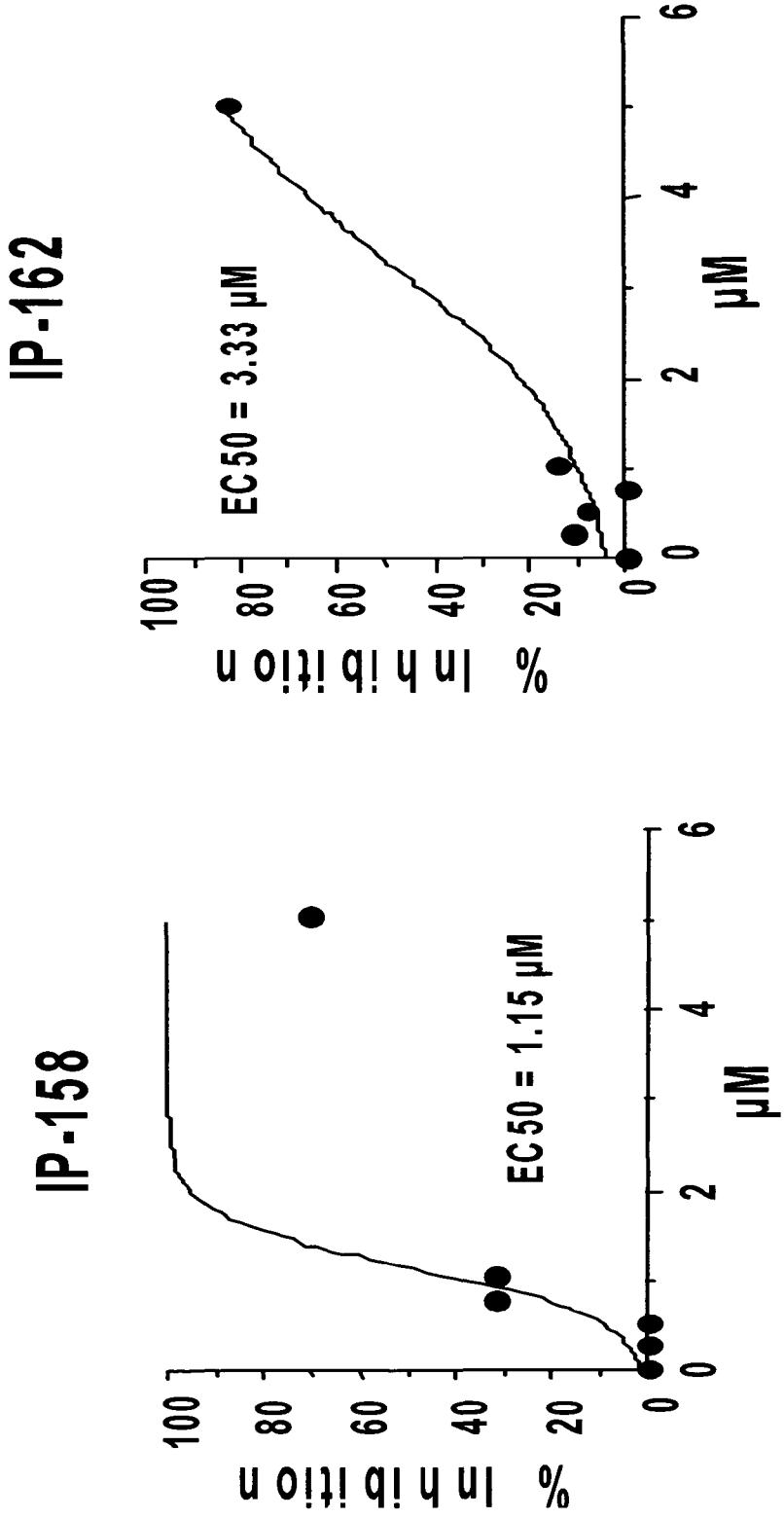

IP-162
EC50 = 3.33 µM
% Inhibition
µM
0
2
4
6
20
40
60
80
100
IP-158
EC50 = 1.15 µM
% Inhibition
µM
0
2
4
6
20
40
60
80
100

FIG. 4B

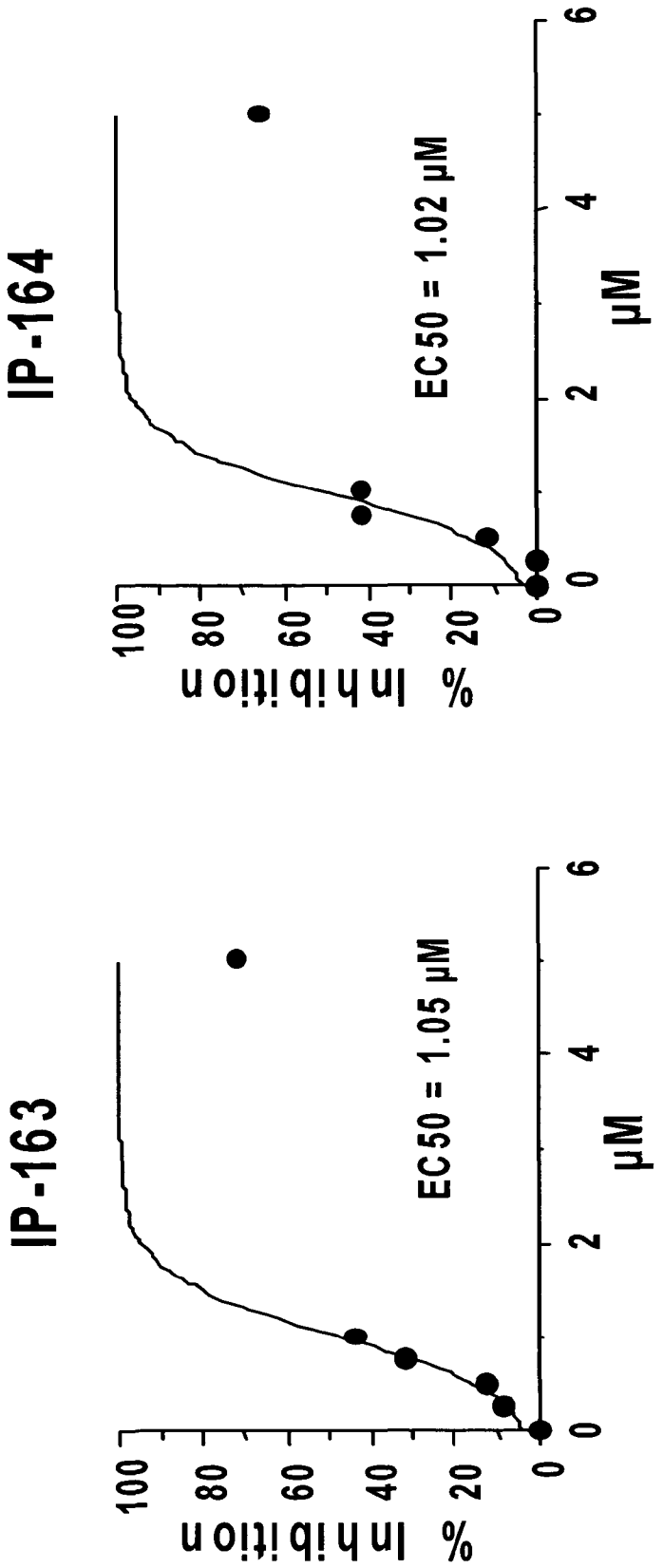
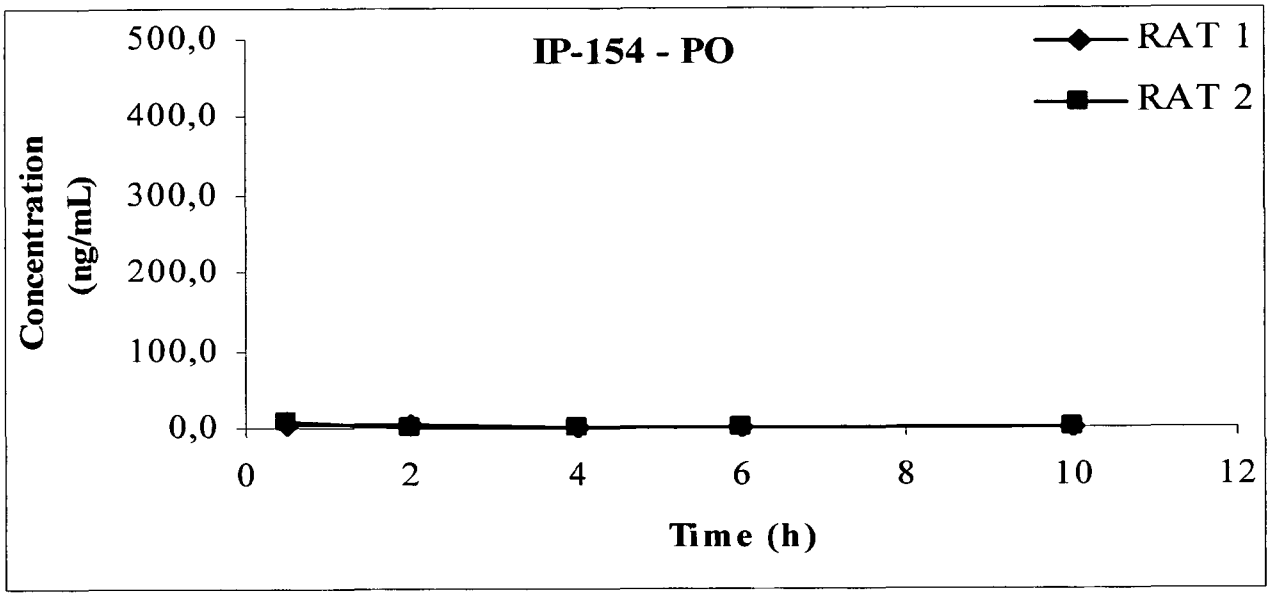

IP-164
EC50 = 1.02 µM
% Inhibition
µM
0
20
40
60
80
100
0
2
4
6
IP-163
EC50 = 1.05 µM
% Inhibition
µM
0
20
40
60
80
100
0
2
4
6

FIG. 4C


IP-154 - PO
RAT 1
RAT 2
Concentration (ng/mL)
500,0
400,0
300,0
200,0
100,0
0,0
0
2
4
6
8
10
12
Time (h)

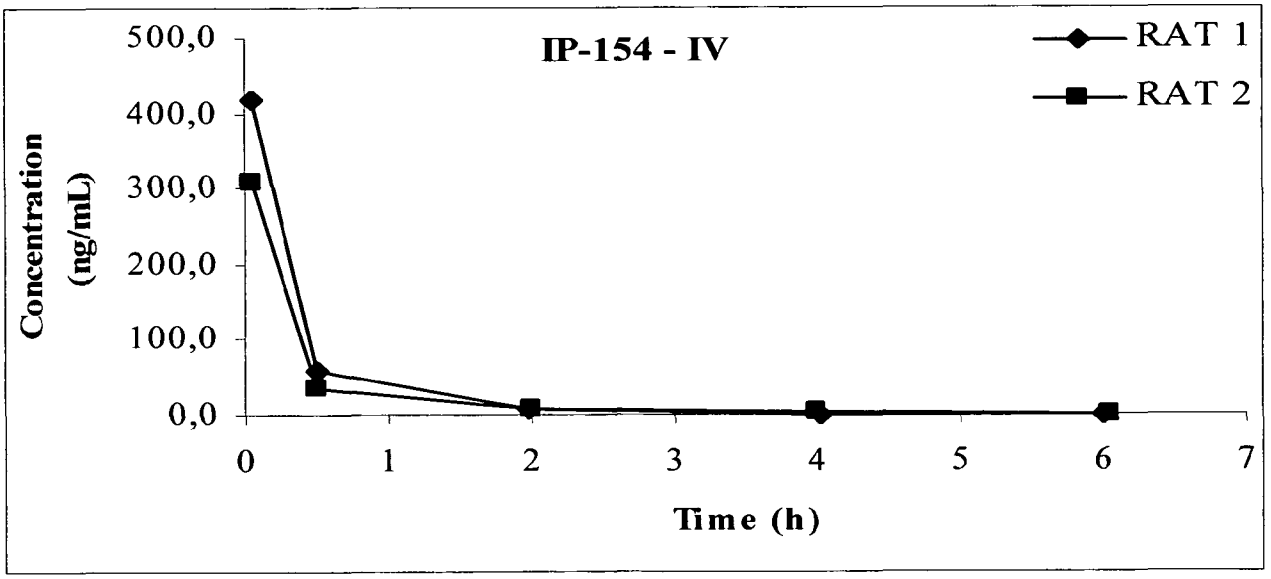
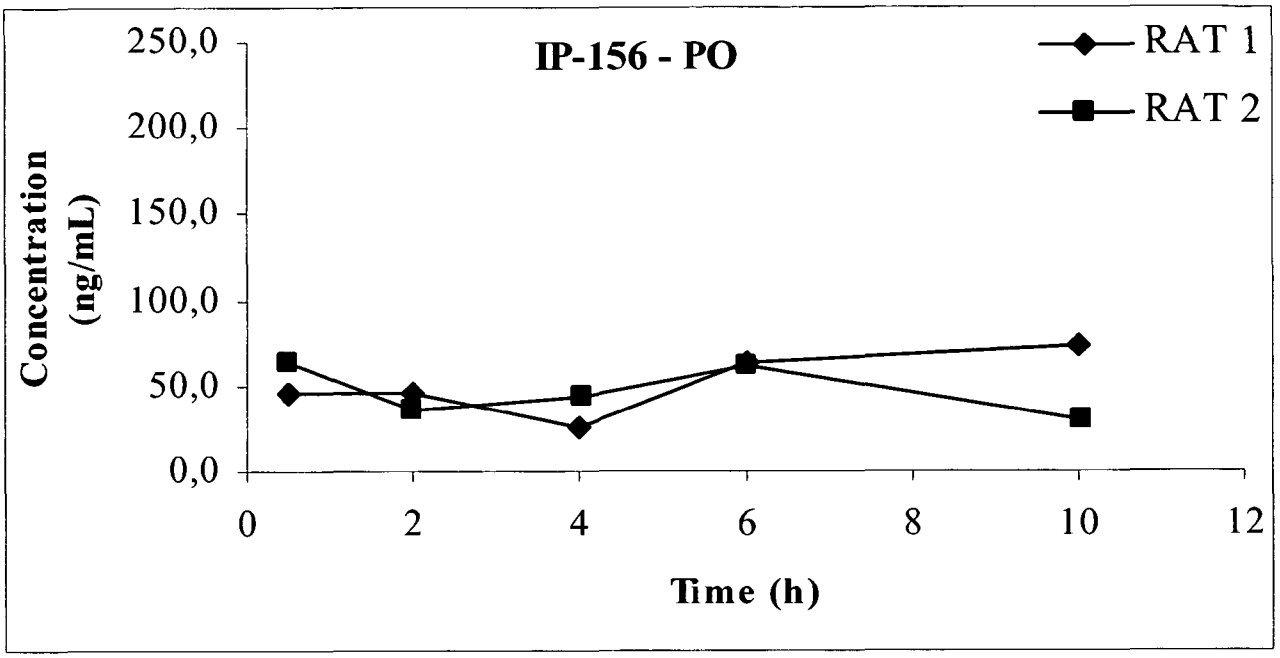

IP-154 - IV
RAT 1
RAT 2
Concentration (ng/mL)
500,0
400,0
300,0
200,0
100,0
0,0
0
1
2
3
4
5
6
7
Time (h)

FIG. 5A


IP-156 - PO
RAT 1
RAT 2
Concentration (ng/mL)
250,0
200,0
150,0
100,0
50,0
0,0
0
2
4
6
8
10
12
Time (h)

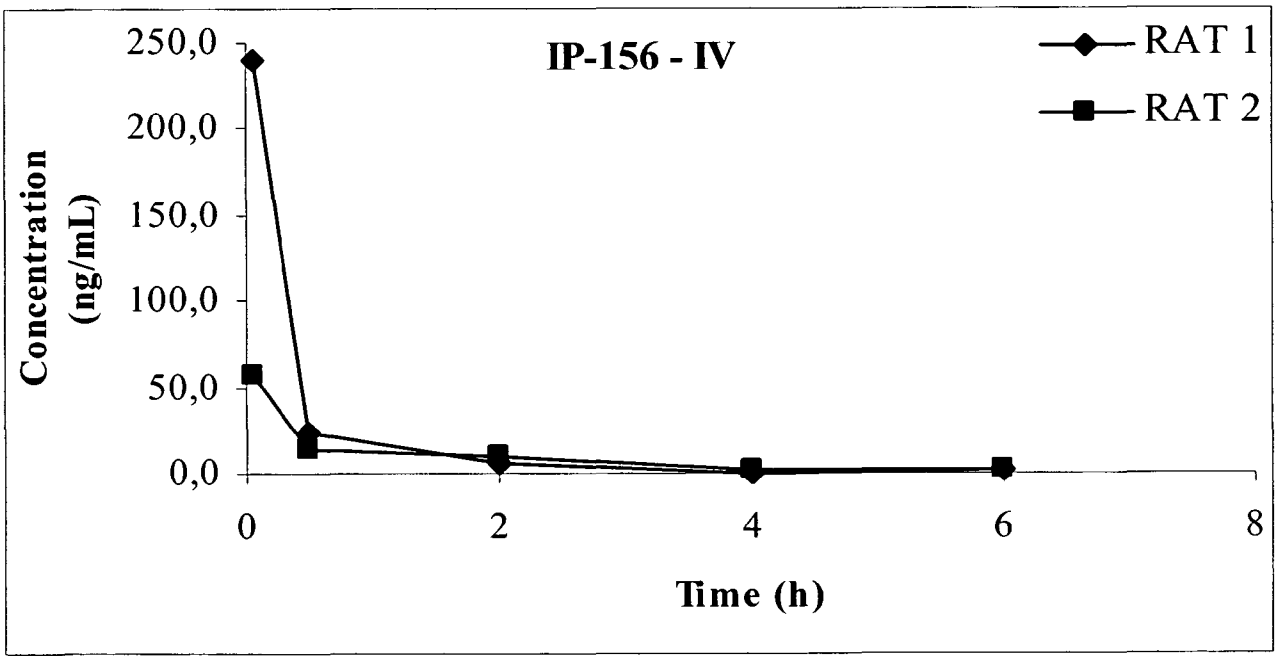
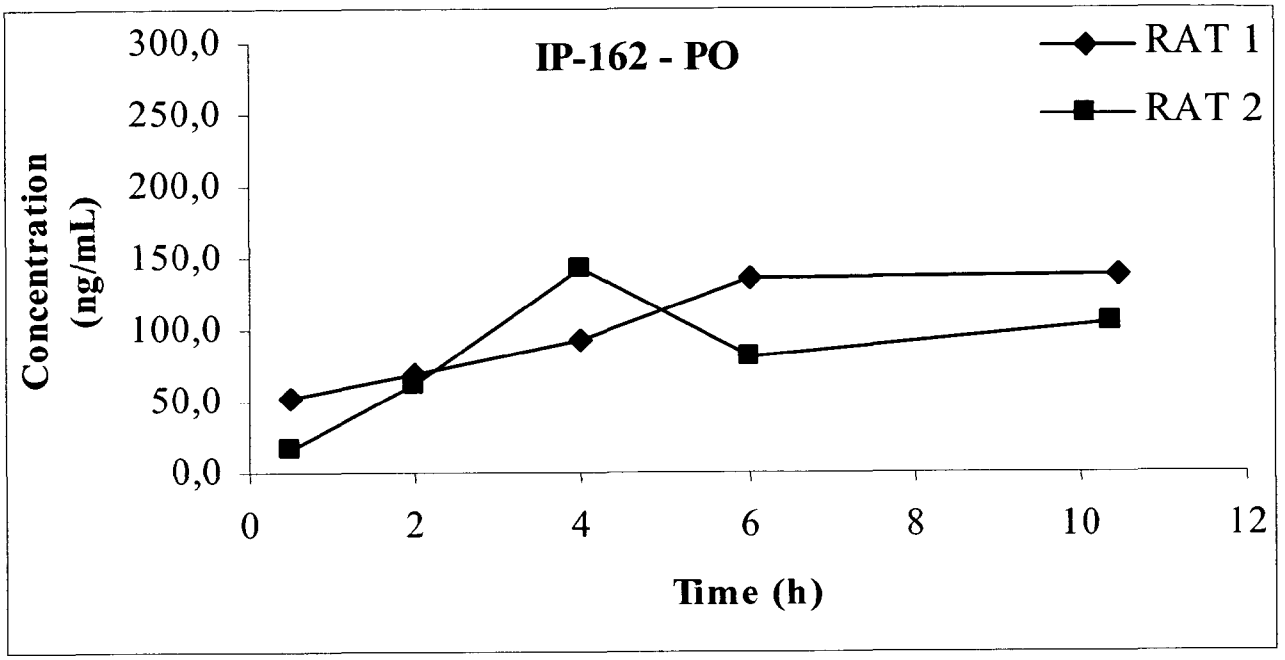

IP-156 - IV
RAT 1
RAT 2
Concentration (ng/mL)
250,0
200,0
150,0
100,0
50,0
0,0
0
2
4
6
8
Time (h)

FIG. 5B


IP-162 - PO
RAT 1
RAT 2
Concentration (ng/mL)
300,0
250,0
200,0
150,0
100,0
50,0
0,0
0
2
4
6
8
10
12
Time (h)

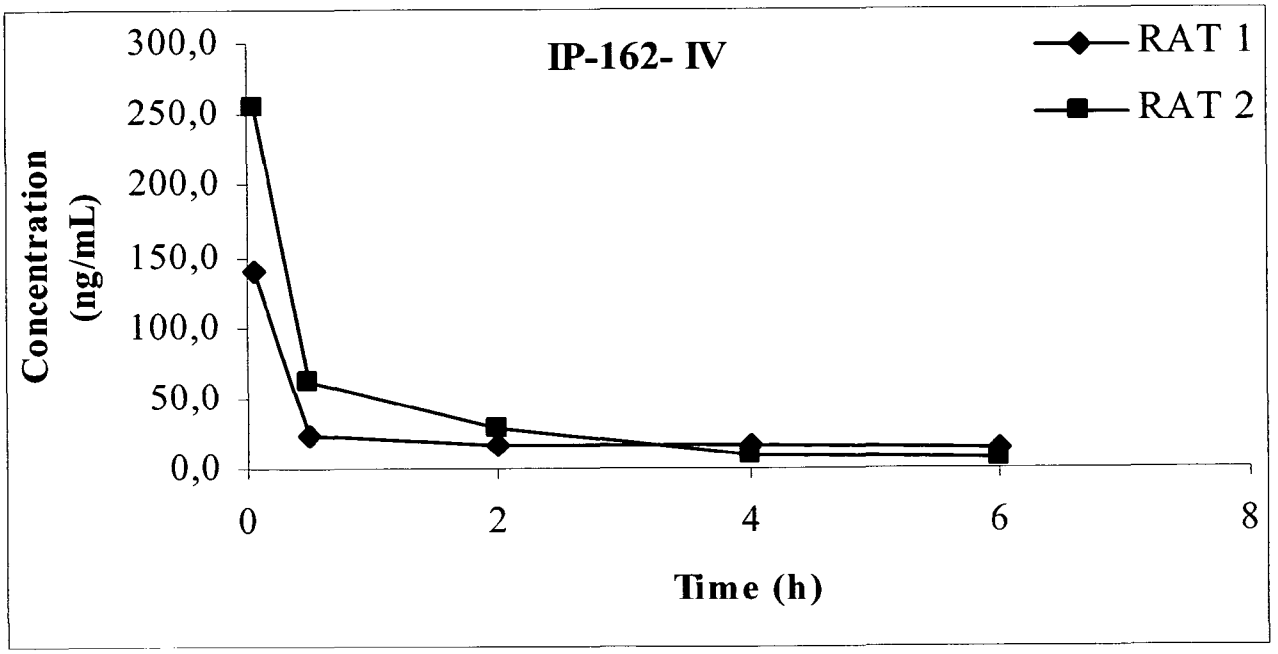
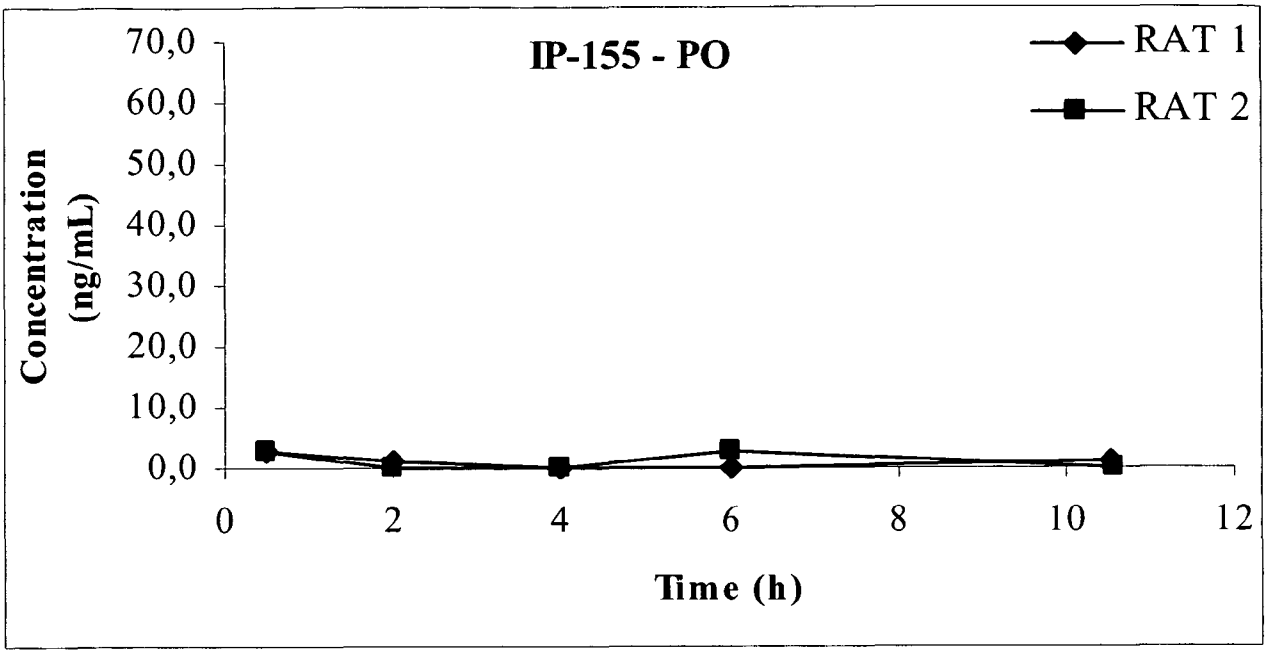

IP-162- IV
RAT 1
RAT 2
Concentration (ng/mL)
300,0
250,0
200,0
150,0
100,0
50,0
0,0
0
2
4
6
8
Time (h)

FIG. 5C


IP-155 - PO
RAT 1
RAT 2
Concentration (ng/mL)
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
0
2
4
6
8
10
12
Time (h)

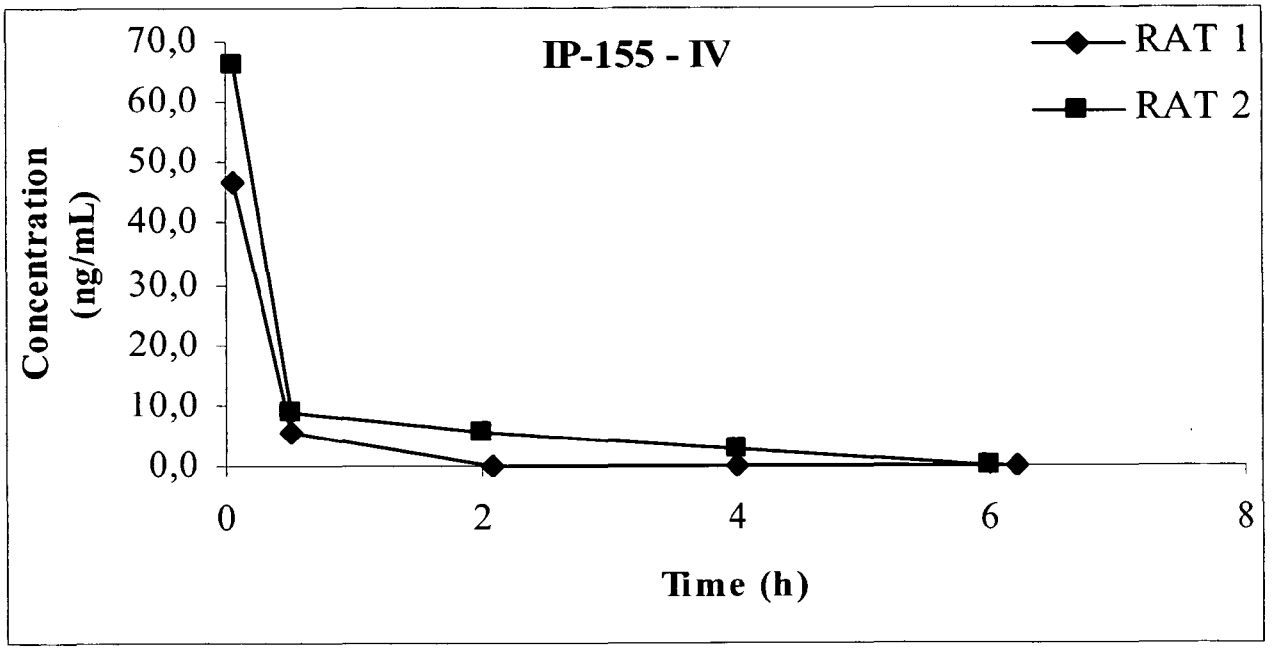
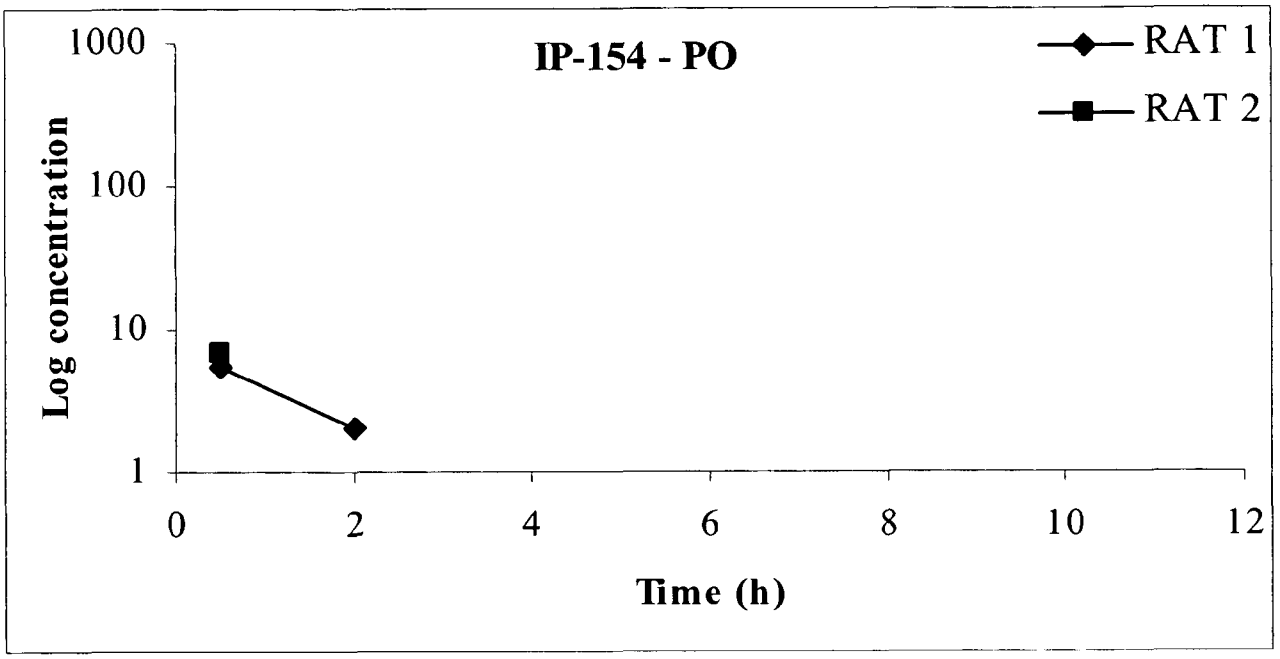

IP-155 - IV
RAT 1
RAT 2
Concentration (ng/mL)
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
0
2
4
6
8
Time (h)

FIG. 5 D


IP-154 - PO
RAT 1
RAT 2
Log concentration
1000
100
10
1
0
2
4
6
8
10
12
Time (h)

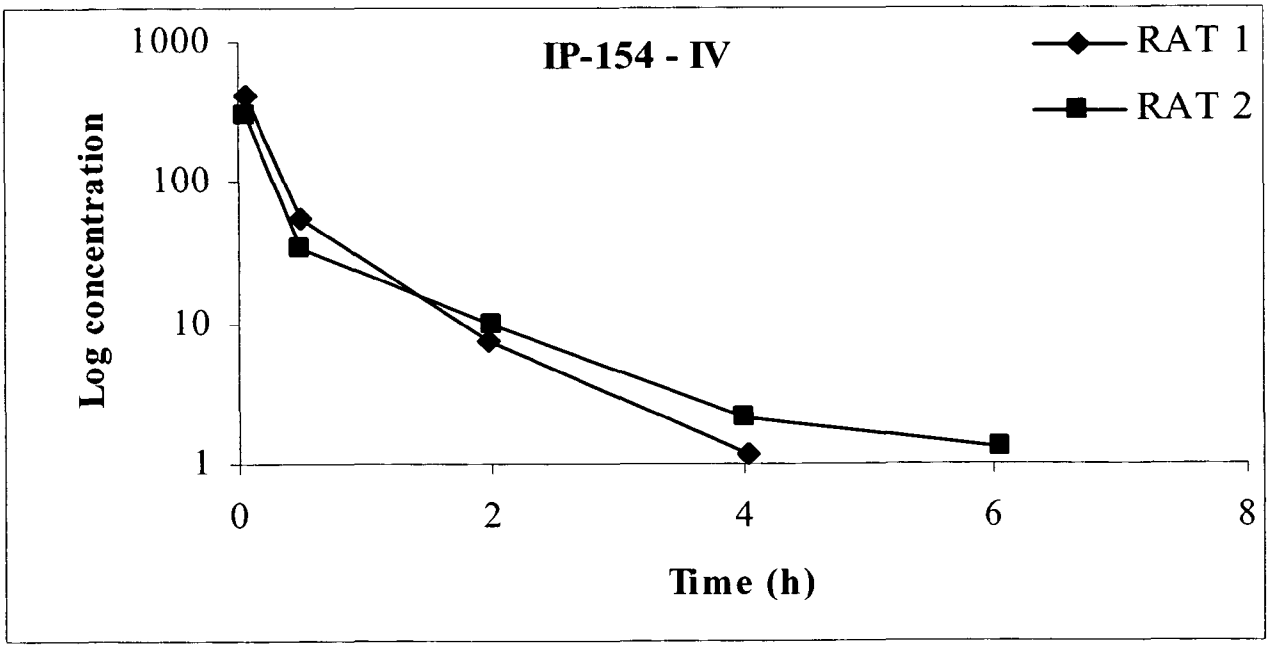
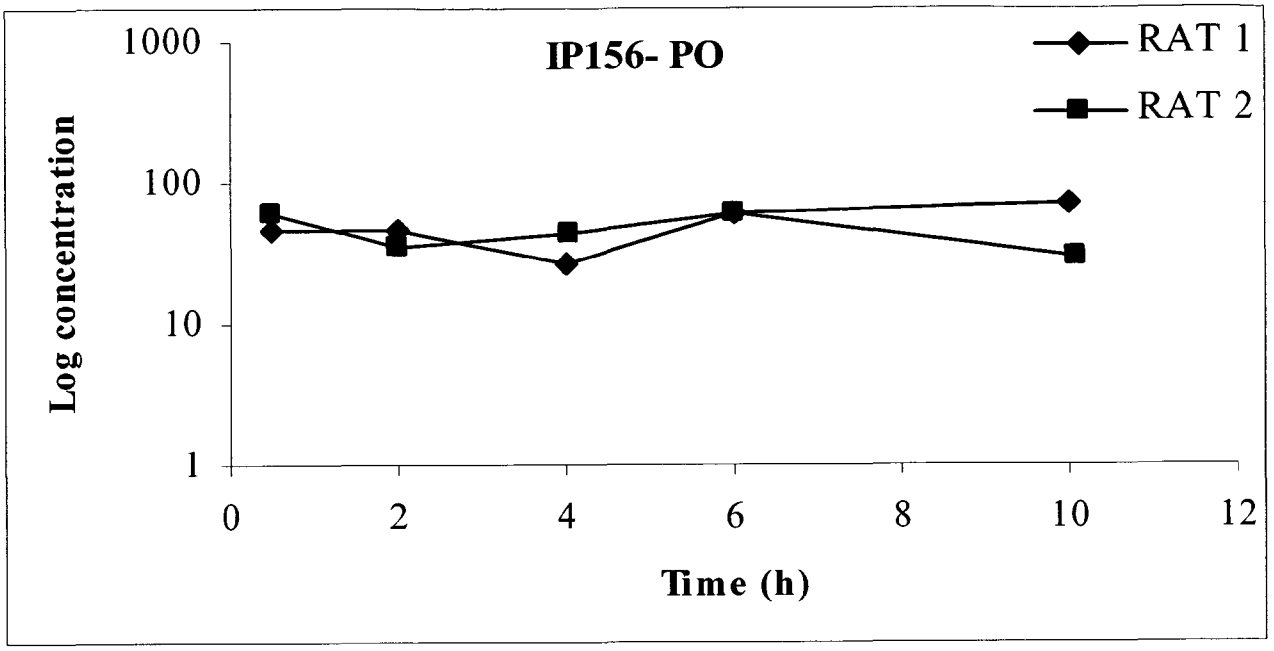

IP-154 - IV
RAT 1
RAT 2
Log concentration
1000
100
10
1
0
2
4
6
8
Time (h)

FIG. 6A


IP156- PO
RAT 1
RAT 2
Log concentration
1000
100
10
1
0
2
4
6
8
10
12
Time (h)

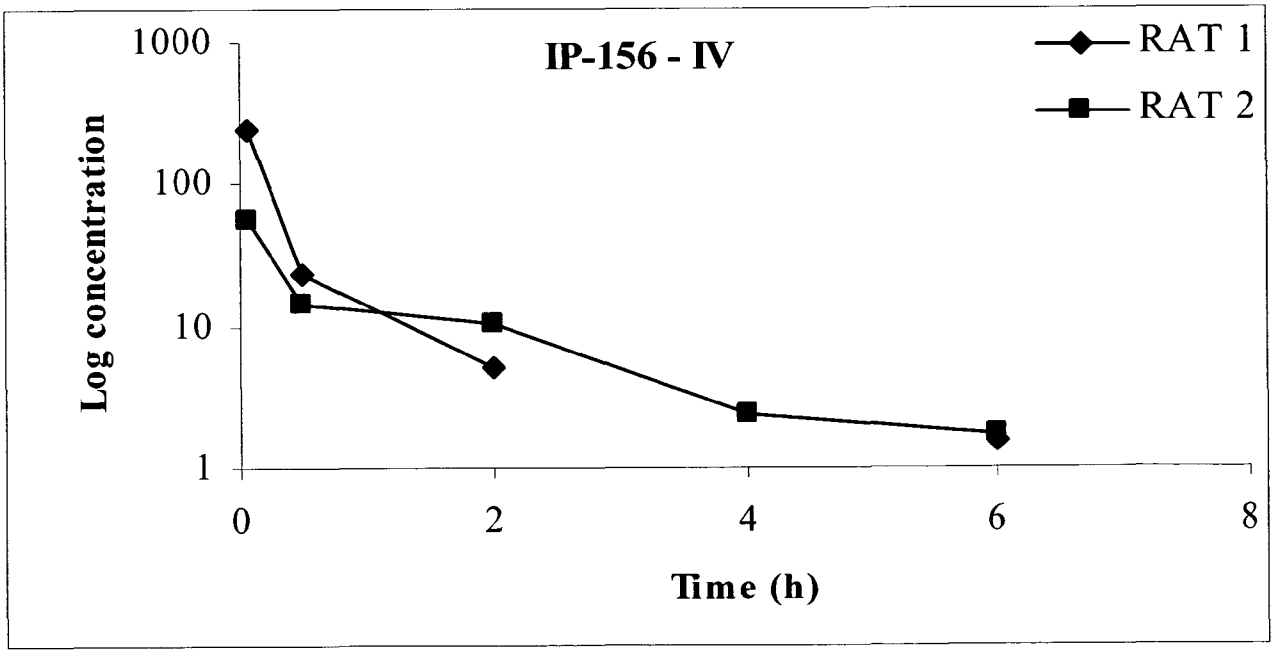
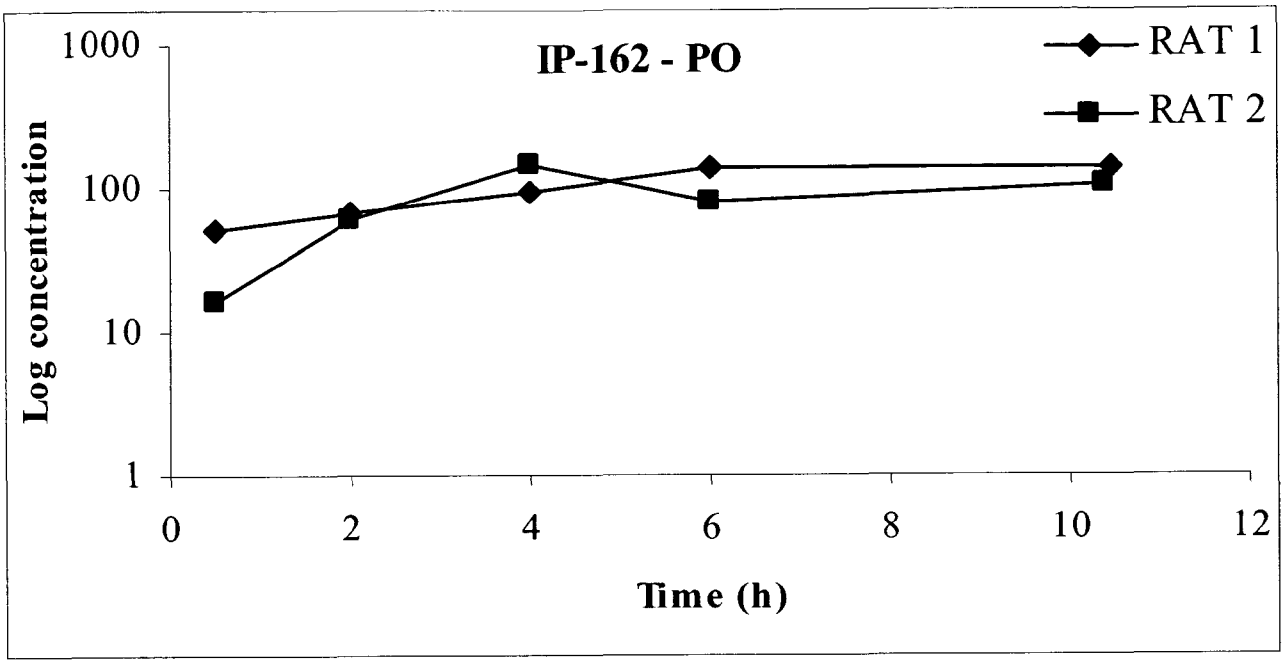

IP-156 - IV
RAT 1
RAT 2
Log concentration
1000
100
10
1
0
2
4
6
8
Time (h)

FIG. 6B


IP-162 - PO
RAT 1
RAT 2
Log concentration
1000
100
10
1
0
2
4
6
8
10
12
Time (h)

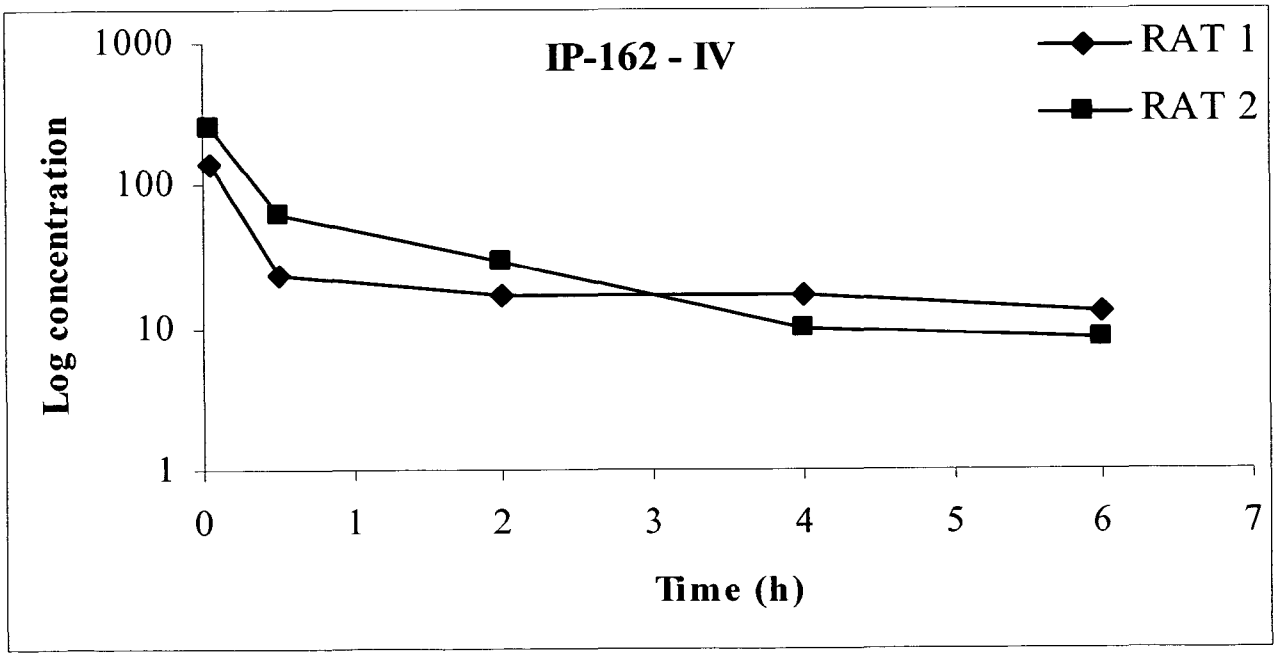
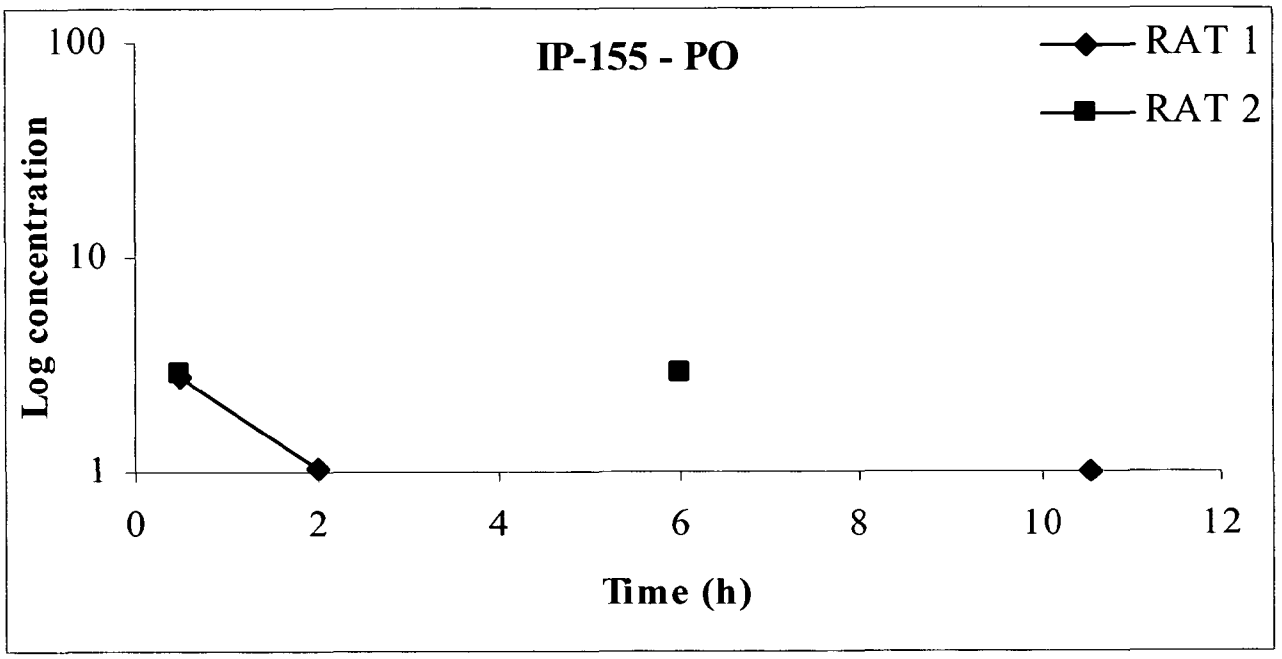

IP-162 - IV
RAT 1
RAT 2
Log concentration
1000
100
10
1
0
1
2
3
4
5
6
7
Time (h)

FIG. 6C


IP-155 - PO
RAT 1
RAT 2
Log concentration
100
10
1
0
2
4
6
8
10
12
Time (h)

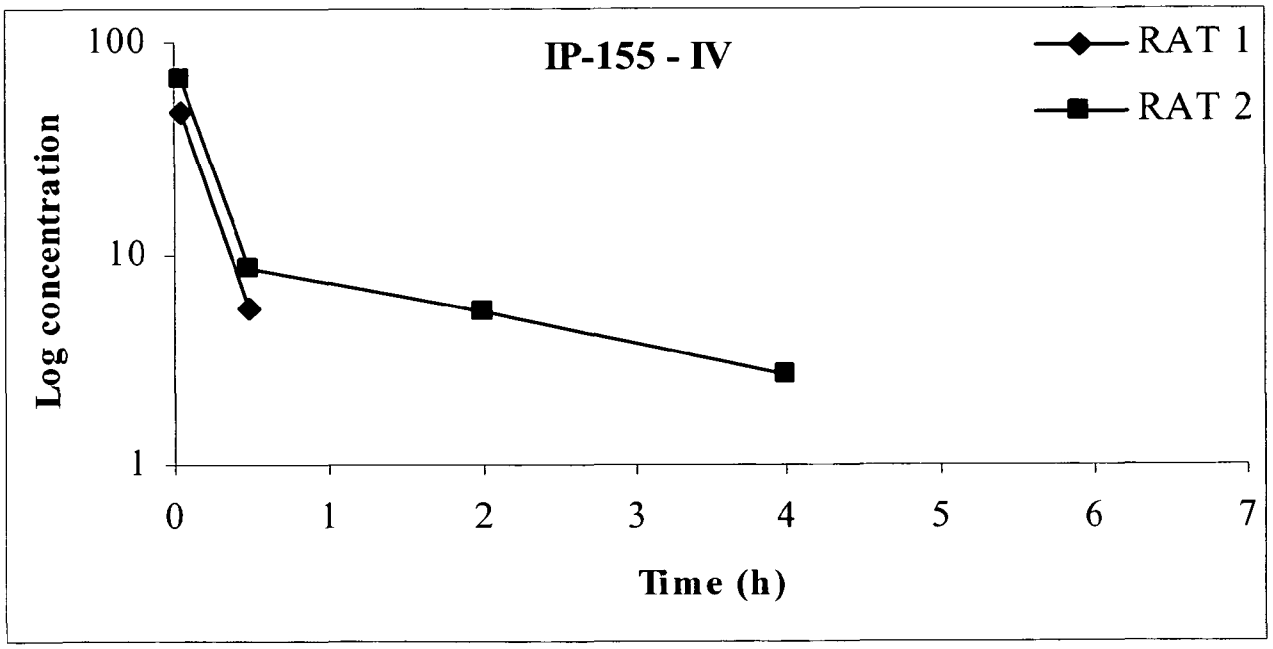

IP-155 - IV
RAT 1
RAT 2
Log concentration
100
10
1
0
1
2
3
4
5
6
7
Time (h)

FIG. 6D

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/050401

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/58 C07D401/04 C07D401/12 C07D401/06 C07D401/14
A61K31/496 A61P31/12

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)
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, BEILSTEIN 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.
A	US 2007/027160 A1 (ASSELIN MAGDA [US] ET AL) 1 February 2007 (2007-02-01) cited in the application page 49, paragraph 622; claims	1-15
A	WO 2006/088919 A (SCHERING CORP [US]; PHARMACOPEIA DRUG DISCOVERY [US]; MCGUINNESS BRIAN) 24 August 2006 (2006-08-24) cited in the application claims	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"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

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"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
25 March 2010	12/04/2010

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, Fax: (+31–70) 340–3016	Ladenburger, Claude

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/050401

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2007027160 A1	01-02-2007	NONE	
WO 2006088919 A	24-08-2006	AR 055195 A1	08-08-2007
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		EP 1856097 A2	21-11-2007
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		KR 20070107056 A	06-11-2007
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