(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 November 2013 (14.11.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/167177 A1

(51) International Patent Classification:
C07D 243/12 (2006.01) *A61K 31/4196* (2006.01)
C07D 249/12 (2006.01) *A61K 31/551* (2006.01)
C07D 487/04 (2006.01) *A61P 25/28* (2006.01)

(21) International Application Number:
PCT/EP2012/058500

(22) International Filing Date:
9 May 2012 (09.05.2012)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicants *(for all designated States except US)*: **UNIVERSITA' DEGLI STUDI DI MILANO** [IT/IT]; Via Festa del Perdono, 7, I-20122 Milano (IT). **FONDAZIONE ITALIANA SCLEROSI MULTIPLA - FISM ONLUS** [IT/IT]; Via Operai, 40, I-16149 Genova (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ABBRACCHIO, Maria Pia** [IT/IT]; Via Balzaretti, 9, I-20133 Milano (IT). **BATTAGLIA, Mario Alberto** [IT/IT]; Via Operai, 40, I-16149 Genova (IT). **EBERINI, Ivano** [IT/IT]; Via Balzaretti, 9, I-20133 Milano (IT). **FUMAGALLI, Marta** [IT/IT]; Via Balzaretti, 9, I-20133 Milano (IT). **PARRAVICINI, Chiara** [IT/IT]; Via Balzaretti, 9, I-20133 Milano (IT). **SENSI, Cristina** [IT/IT]; Via Balzaretti, 9, I-20133 Milano (IT). **ZARATIN, Paola** [IT/IT]; Via Operai, 40, I-16149 Genova (IT).

(74) Agents: **LONG, Giorgio** et al.; Jacobacci & Partners S.p.A., Via Senato, 8, I-20121 Milano (IT).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2013/167177 A1

(54) Title: GPR17 RECEPTOR MODULATORS.

(57) Abstract: The present invention relates to chemical compounds acting through GPR17 receptor for use in the treatment of diseases, in particular for use in chronic and/or acute neurodegenerative diseases, preferably Multiple Sclerosis, inflammatory diseases, pathologies involving the immune system, cardiovascular diseases, renal diseases.

Description

"GPR17 receptor modulators"

The present inventions generally relates to chemical compounds acting through GPR17 receptor for use in the treatment of diseases, in particular for use in chronic and/or acute neurodegenerative diseases, preferably Multiple Sclerosis, inflammatory diseases, pathologies involving the immune system, cardiovascular diseases, renal diseases.

Background

The seven-helix transmembrane G protein-coupled receptor (GPCR) family, encompassing more than 1,000 putative members, is crucially involved in cell-to-cell communication, in the response to environmental factors and hormones, and in the regulation of key cellular functions such as growth, differentiation and death. Due to such central roles, the malfunctioning of GPCRs (or of their signaling cascades) is associated to disease. A large majority of currently marketed drugs (including widely utilized anti-hypertensive, anti-thrombotic, anti-psychotic, anti-asthmatic and anti-ulcer drugs) indeed act through GPCRs.

Among all GPCRs, GPR17, is located at intermediate phylogenetic position between known purinergic P2Y and cysteinyl-leukotrienes (cysLTs) receptors (CysLTRs). Already characterized P2Y receptors and CysLTRs are

activated, respectively, by extracellular nucleotides (Abbracchio et al., 2006) or cysLTs (Brink et al. 2003), two distinct families of inflammatory molecules acting as "danger signals" (Lecca et al., 2008), that sense damage in tissues and activate local reparative processes. These endogenous signaling molecules and their receptors mediate immune responses and ischemic/inflammatory conditions, including stroke and several currently incurable neurodegenerative diseases (Abbracchio et al., 2009).

GPR17 signals through G(i) and inhibition of adenylyl cyclase and it has been previously shown that GPR17 responds to both uracil nucleotides and cysLTs (Ciana et al. 2006; Lecca et al., 2008; Pugliese et al. 2009). By employing a variety of *in vivo* rodent models of acute and chronic nervous system degenerative disorders, GPR17 has been validated as a novel target for the design of new drugs of potential use in human diseases characterized by neuronal and myelin dysfunction, including stroke, brain and spinal cord trauma and multiple sclerosis (Lecca et al. 2008; Ceruti et al. 2009; Chen et al. 2009). In a rat brain focal ischemia model, the selective *in vivo* knock down of GPR17 by anti-sense technology or P2Y/CysLTRs antagonists reduced progression of ischemic damage (WO2006/045476). Moreover, the involvement of GPR17 in the transition from oligodendrocyte precursors to mature oligodendrocytes expressing a myelinating phenotype has

been demonstrated (Lecca et al., 2008; Chen et al. 2009; Fumagalli et al., 2011). These mature oligodendrocytes are able to repair a myelinic damage, by restoring the damaged myelinic envelope en-wrapping neuronal axons. All the published experimental data on GPR17 have been obtained using already available agonists and, in most cases, antagonists that have been purposely developed for other GPCRs.

Multiple Sclerosis (MS) is a chronic progressive disorder. It is an inflammatory disease in which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms. MS is one of the central nervous system pathology with the largest diffusion. It affects about 1.3 million persons in the world, of which 400.000 in Europe. This incidence is worsened by the fact that MS affects still young peoples, who need chronic treatments, with a strong social and economical impact. The pharmacological treatments currently available are symptomatic and are not able to counteract MS progression. Immunomodulators are actually used and revealed a certain grade of effectiveness in acute treatments. However, they fail to solve the pathology. Moreover, all of the currently available therapeutics display significant side effects, both local and systemic.

Given the role played by GPR17 in the myelination process (Lecca et al. 2008, Chen et al. 2009; Fumagalli et al., 2011) and in the reduction of ischemic damage progression, there is the strong need to identify molecules capable to specifically bind said GPR17 receptor to be used as novel therapeutics in ischemia and MS or in any other condition characterized by demyelination. It is worth to note that for many of the conditions characterized by demyelination, such as schizophrenia, depression, Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis and Huntington's Disease, no curative therapy are currently available. Up to now, only non specific compounds have been tested on GPR17. In particular, CysLTRs antagonists have been used, selected from Montelukast, Pranlukast, Zafirlukast. These compounds are commercially available for asthma therapy. Alternatively, P2Y receptor antagonist have been used. Among these, Cangrelor and Ticagrelor. Ticagrelor has been approved by EMEA and FDA as a platelet aggregation inhibitor.

Rational drug development is a process to develop lead molecules, not by randomly screening thousands of molecules in the blind hope of finding one that shows the desired activity, but rather by deducing the active site of the target and devising a chemical that interacts with that site in the appropriate manner.

A crystallographic structure of GPR17 is not available so far. However, the crystallographic structures of the human CXC chemokine receptor type 4 (CXCR4) (Wu et al. 2010) is known and it is of particular interest for the purpose of the here claimed invention. In fact, the G protein-coupled chemokine receptor CXCR4 has been demonstrated to be phylogenetically and structurally very close to GPR17. CXCR4 crystallographic structure revealed a consistent homodimer with an interface including helices V and VI that may be involved in regulating signaling (Wu et al. 2010). The location and shape of the ligand-binding sites differ from other G protein-coupled receptors and are closer to the extracellular surface.

Here we describe families of compounds specifically able to interact with GPR17 receptor. Compounds and pharmaceutically acceptable salts thereof are useful in the treatment of pathological conditions such as stroke, heart disease, heart failure, high blood pressure, neurodegenerative diseases selected from, for example, Huntington's Disease, motor neuron diseases, leukodystrophies and MS.

Detailed description

The present invention is directed to families of compounds able to interact with GPR17 binding site, thus ameliorating a panel of pathologic phenotypes, in particular chronic and/or acute neurodegenerative

diseases, preferably Multiple Sclerosis, pathologies involving the immune system, cardiovascular diseases, renal diseases.

Figure description

Figure 1A: cys configuration in the chains of a panel of GPCRs, among which GPR17 and CXCR4.

Figure 1B: alignment proposed for a panel of GPCRs.

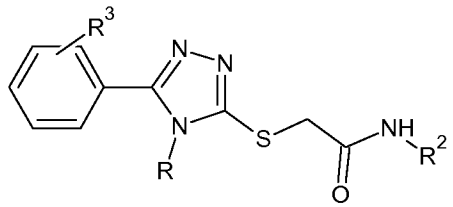
A 3-D molecular model of GPR17 embedded in a solvated phospholipids bilayer and refined by molecular dynamics simulations has been obtained (Parravicini et al. 2008). The molecular dynamics simulations indicate that GPR17 nucleotide binding pocket is similar to that described for the other P2Y receptors, although only one of the three basic residues that have been typically involved in ligand recognition is conserved (Arg255). The binding pocket is enclosed between the helical bundle and covered at the top by EL2. Driving interactions are H-bonds and salt bridges between the 6.55 and 6.52 residues and the phosphate moieties of the ligands. An "accessory" binding site in a region formed by the EL2, EL3 and the Nt was also found.

Following the disclosure of the crystallographic structure of the CXCR4 receptor, the GPR17 binding site model has been implemented. By comparing CXCR4 crystallographic structure with the *in silico* modeled GPR17 receptor previously obtained by using the above mentioned multiple template approach (Parravicini et al., 2010), in which the

extracellular loops of the receptor were modeled making reference to the most similar parts of all the class-A GPCRs crystallized so far (Eberini et al., 2011), the authors selected the CXCR4 crystallographic structure as the best template to model each domain of GPR17 receptor. Figure 1 shows the alignment of a panel of GPCRs available as templates, among which CXCR4: in Figure 1A, the values in each column represent the percentage of the chain's residues which are paired with identical residues in the chains of each row; Figure 1B shows the resulting phylogenetic tree. As suggested by the alignment, the best template for GPR17 is considered to be CXCR4.

Thanks to this model, compounds able to interact with GPR17 receptor in an optimized manner, both from a geometric and from an energetic point of view, have been identified.

In one embodiment, the present invention is related to compounds of formula (I)

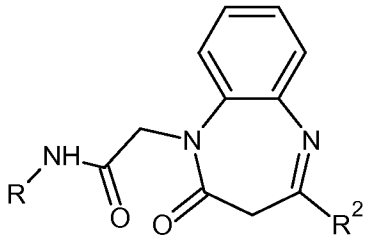


(I)

wherein R is H, a linear or branched C1-C4 alkyl, a linear or branched C1-C4 alkyl phenyl optionally substituted, a phenyl optionally substituted; R^2 is H, a linear or branched C1-C4 alkyl, a saturated or unsaturated mono, bi

or tricycle having from 3 to 16 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S; R^3 is H, a linear or branched C1-C4 alkyl or $NHC(O)R^1$, wherein R^1 is a linear or branched C1-C4 alkyl, a saturated or unsaturated mono, bi or tricycle having from 3 to 16 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S.

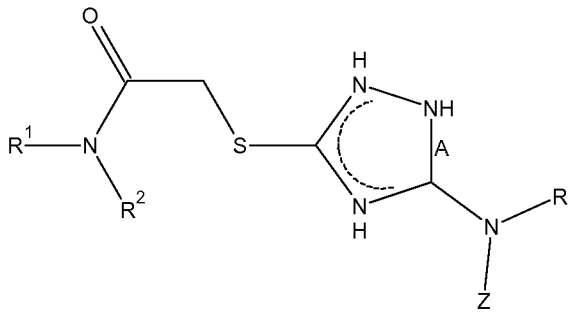
In a second embodiment, the present invention is related to compounds of formula (II)



(II)

wherein R^2 is H, a C1-C4 linear or branched alkyl, a linear or branched C1-C4 alkyl phenyl optionally substituted, a saturated or unsaturated mono, bi or tricycle having from 3 to 16 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S and R is H, a C1-C4 linear or branched alkyl phenyl optionally substituted, a saturated or unsaturated mono, bi or tricycle having from 3 to 16 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S.

In a third embodiment, what we claim are compounds of formula (III)

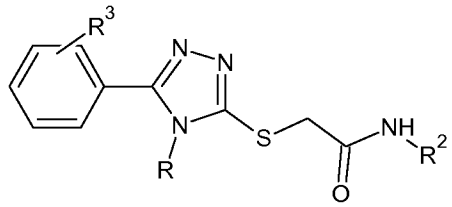


(III)

wherein R^1 and R^2 are independently H or an optionally substituted phenyl, or R^1 and R^2 form with the N to which they are linked a saturated or unsaturated mono, bi or tricycle having from 3 to 16 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S; A is a bond or a C; the dotted line represents localized or delocalized double bonds; R is H, C1-C4 aryl, optionally substituted heteroaryl, optionally substituted metylphenyl, $-CH_2C(O)R^3$, $-CH_2C(O)NR^4R^5$; R^3 is chosen from optionally substituted alkyl, optionally substituted saturated or unsaturated 3-8 membered cycle eventually containing from 1 to 4 heteroatoms selected from N, O, S, optionally substituted aryl eventually containing from 1 to 4 heteroatoms selected from N, O, S; R^4 is chosen from H, optionally substituted alkyl, optionally substituted saturated or unsaturated 3-8 membered cycle eventually containing from 1 to 4 heteroatoms selected from N, O, S,

optionally substituted aryl eventually containing from 1 to 4 heteroatoms selected from N, O, S; R^5 is chosen from H, optionally substituted alkyl, optionally substituted saturated or unsaturated 3-8 membered cycle eventually containing from 1 to 4 heteroatoms selected from N, O, S, optionally substituted aryl eventually containing from 1 to 4 heteroatoms selected from N, O, S; R^4 and R^5 taken together with the nitrogen to which they are attached can form an optionally substituted saturated or unsaturated 3-8 membered cycle eventually containing from 1 to 4 heteroatoms selected from N, O, S; Z is H or forms a bicycle with said 5 or 6 membered ring comprising 3 N by closing on a N on said cycle, or, when A is C, by closing on said C, wherein said second ring formed by Z is preferably a 5 membered ring and it is open to fusion.

In the first embodiment, compounds of formula (I)



(I)

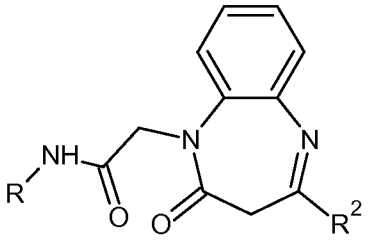
are preferably selected from the group wherein R is selected from the group comprising H, methyl, ethyl, phenyl, benzyl; R^2 is selected from the group comprising H, naphthalene, phenyl, preferably 4Cl-phenyl, benzimidazole, preferably 2-methylbenzimidazole; R^3 is preferably selected from the group comprising H, 4-methyl,

4-NHC(O)R^1, wherein R^1 is phenyl or phenyl mono, bi o tri substituted, wherein said substituents on said phenyl are independently selected from C1-C4 linear or branched alkyl, acetyl, C1-C4 alkoxy, carboxy C1-C4 alkyl, F, Cl, Br, I, triphluoromethyl, nitro, CN.

Preferably, R is H or methyl; R^2 is H, naphthalene, phenyl, preferably 4Cl-phenyl, benzimidazole, preferably 2-methylbenzimidazole; R^3 is H, 4-methyl, 4-NHC(O)R^1, wherein R^1 is phenyl, preferably 4Cl-phenyl.

Preferably, the compound is selected from N-Phenyl-2-(5-m-tolyl-2*H*-[1,2,4]triazol-3-ylsulfanyl)-acetamide, 2-(5-m-tolyl-2*H*-[1,2,4]triazol-3-ylsulfanyl)-acetamide, N-naphthalen-1-yl-2-(5-m-tolyl-2*H*-[1,2,4]triazol-3-ylsulfanyl)-acetamide, N-Thiazol-2-yl-2-(5-p-tolyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide, N-(2-Methyl-3*H*-benzoimidazol-5-yl)-2-(5-phenyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide, N-[4-[5-[[2-[(4-chlorophenyl)amino]-2-oxoethyl]thio]-4-methyl-4H-1,2,4-triazol-3-yl]phenyl]-benzamide. In a most preferred embodiment, said compound is N-[4-[5-[[2-[(4-chlorophenyl)amino]-2-oxoethyl]thio]-4-methyl-4H-1,2,4-triazol-3-yl]phenyl]-benzamide.

In the second embodiment, compounds of formula (II)



(II)

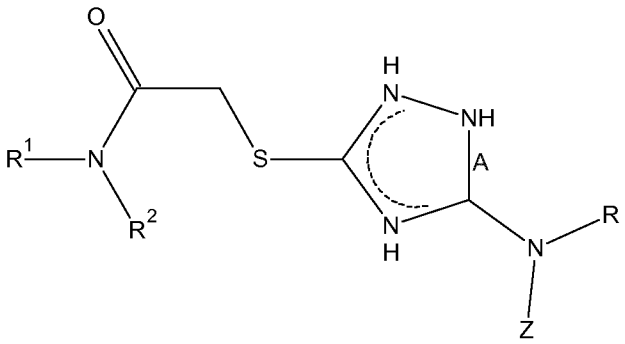
are preferably selected from the groups wherein R^2 is H, phenyl, or a phenyl mono, bi o tri substituted, wherein said substituents on said phenyl are independently selected from methyl, ethyl, methylethyl, acetyl, methoxy, ethoxy, F, Cl, Br, I, carboxyethyl, trifluoromethyl, methylthio, dimetylamino; R is H, phenyl, benzyl, phenylethyl, phenylpropyl, a phenyl mono, bi o tri substituted, wherein said substituents on said phenyl are independently selected from methyl, ethyl, methylethyl, acetyl, methoxy, ethoxy, F, Cl, Br, I, carboxyethyl, trifluoromethyl, methylthio, dimetylamino, or R is 1,3-benzodioxol-5-yl-2,3-dihydro, 2,3-dihydro-1,4-benzodioxin-6-yl, 2-furanylmethyl, cyclohexan.

In a preferred embodiment, R^2 is phenyl and R is 2,4 dimethoxyphenyl, benzyl, 2,3-dimethylphenyl or 2,6-dimethylphenyl.

Preferably, the compound is selected from the group comprising N-(2,4-dimethoxyphenyl)-2,3-dihydro-2-oxo-4-phenyl-1H-1,5-Benzodiazepine-1-acetamide, N-Benzyl-2-(2-oxo-4-phenyl-2,3-dihydro-benzo[b][1,4]diazepin-1-yl)-acetamide, N-(2,3-dimethyl-phenyl)-2-(2-oxo-4-phenyl-2,3-

dihydro-benzo[b][1,4]diazepin-1-yl)-acetamide, N-(2,6-Dimethyl-phenyl)-2-(2-oxo-4-phenyl-2,3-dihydro-benzo[b][1,4]diazepin-1-yl)-acetamide. The more preferred compound is N-(2,4-dimethoxyphenyl)-2,3-dihydro-2-oxo-4-phenyl-1H-1,5-Benzodiazepine-1-acetamide.

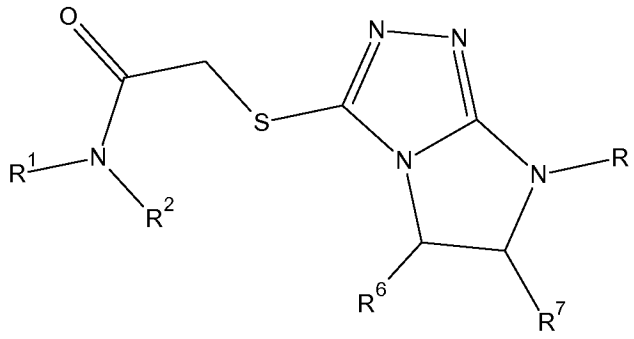
In a third embodiment, the compounds of formula (III)



(III)

are preferably selected from the group wherein R^1 and R^2 are independently H or an optionally substituted phenyl, or R^1 and R^2 are closed to form with the N to which are linked a 1,2,3,4-tetrahydroquinoline, a 1,2,3,4-tetrahydroisoquinoline, a pirrolidine, a piperidine or a piperazine optionally substituted; A is C and the 6 members ring is an aromatic ring; Z forms a bicycle with said 6 membered ring by closing on A, wherein said second ring formed by Z is a 5 membered ring open to fusion, preferably said 5 membered ring is fused with an optionally substituted phenyl forming a tricycle, preferably said tricycle is a 5*H*-[1,2,4]triazino[5,6-*b*]indole optionally substituted; R is H or C1-C4 aryl.

In a preferred embodiment, wherein A is a bond and said ring containing 3 N is a 5 membered ring, said compounds of formula (III) are selected from the group of formula (III)A



(III)A

wherein R^1 is H and R^2 is an optionally substituted phenyl, or R^1 and R^2 are closed to form with the N to which are linked a pirrolidine, an optionally substituted pirrolidine, preferably 2-(2,3-dihydro-1,4-benzodioxin-6-yl)-1-pyrrolidinyl, a phenothiazine, an optionally substituted pyridine, a piperidine, an optionally substituted piperidine, preferably a 2-methyl piperidine, a 4-piperidine carboxyester, preferably a 4-piperidine-carboxyethylester, a 4-piperidinecarboxamide, a 3-methylpiperidine, a 4-methyl piperidine, or a 4-phenylmethylpiperidine or a 3-piperidine carboxylic acid or a 4-piperidine carboxylic acid, or a 4-piperidine carboxamide-N-phenyl, or a 3,5-dimethylpiperidine, or a 2,6-dimethylpiperidine, or a 4,5-dihydro-5-phenyl-1H-pyrazol-1-yl, a 4,5-dihydro-5-(4-methoxyphenyl)-3-phenyl-1H-pyrazol-1-yl, a 2-chloro-10*H*-phenothiazin-10-yl, a 6,7-

dihydrothieno[3,2-c]pyridin-5(4H)-yl, a 4-morpholine, an optionally substituted 4-morpholine, preferably a 2,6-dimethyl-4-morpholine, or a 2-methylmorpholine, an indoline, an optionally substituted indoline, preferably a 1-[2,3-dihydro-5-(1-piperidinylsulfonyl)-1H-indol-1-yl], an isoquinoline, a 1,2,3,4-tetrahydroisoquinoline, a 1,2,3,4-tetrahydroquinoline, a 3,4-dihydro-2-methyl-1(2H)-quinoline, a 1-[3-(2-benzofuranyl)-5-(2-furanyl)-4,5-dihydro-1H-pyrazol-1-yl], a 2H-1,5-benzodiazepin-2-one-4-trifluoromethyl, a 2,3-dihydroindol-1-yl, a 2,3-dimethyl-1*H*-indol-1 yl, a 1-[4-[(3,5-dimethyl-4-isoxazolyl)sulfonyl]-1-piperazinyl], a benzothiazine, a piperazine, an optionally substituted piperazine, preferably a 4-nitrophenylpiperazine or a 2-nitrophenylpiperazine, or a 4-(2-piridinyl)1-piperazine, or a 4-(2-fluorophenil)sulfonyl-1-piperazine or a 4-phenylsulphonil-1-piperazine, or a 3-methylphenyl-1 piperazine, or a 4-(2-methoxyphenyl)piperazine or a 4-phenylpiperazine or a 4-methylphenylpiperazine or a 4-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]-1-piperazine, a 3-trifluoromethylphenyl-1-piperazine, or a 2-fluorophenyl-1-piperazine, a piperidinecarboxamide-N-phenyl, a 1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-yl, a 4,5-dihydro-3-(2-naphthalenyl)-5-phenyl-1H-pyrazol-1-yl, a 4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-1-piperazinyl, a pyrrolidone, a 2(1H)quinoxalinone, a [2,3,dihydro-5(1-

piperidinylsulfonyl)1H-indol-1 y l] , a 3 , 4-dihydro-2(1H)isoquinolinyl, a 3,4-dihydro-2-methyl-1(2H)quinoline, a 3,4-dihydro-6(1-pyrrolidinylsulfonyl)1(2H)quinoline, a 10,11-dihydro-5H-dibenz[b,f]azepin-5-yl, a hexahydro-1H-azepin-1-yl, preferably R^1 and R^2 are closed to form with the N to which are linked an indoline, a 1,2,3,4-tetrahydroisoquinoline, a 1,2,3,4-tetrahydroquinoline, a piperidine, a pirrolidine; R is H, optionally substituted benzyl or $-CH_2C(O)NR^4R^5$; R^4 is H; R^5 is an optionally substituted phenyl or an optionally substituted cycloexane or R^4 and R^5 form with the nitrogen to which they are attached a pyrrolidine; R^6 and R^7 are independently H or an optionally substituted phenyl, or R^6 and R^7 close to form a saturated or unsaturated cycle having from 3 to 8 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S. In a preferred embodiment, R^6 and R^7 are closed in a cycle forming a tricycle, preferably selected from a 4*H*-[1,2,4]triazolo[5,1-*f*]purine-6,8(5*H*,7*H*)-dione, preferably a 5,7-dimethyl-4*H*-[1,2,4]triazolo[5,1-*f*]purine-6,8(5*H*,7*H*)-dione or a 4*H*-[1,2,4]triazolo[1,5-*a*]benzimidazole.

Preferably, the compound is selected from the group comprising 3-[[2-(2,3-dihydro-1H-indol-1-yl)-2-oxoethyl]thio]-N-(2-methylphenyl)-9H-1,2,4-Triazolo[4,3-a]benzimidazole-9-acetamide, 2-[9-(4-Chloro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-

(3,4-dihydro-1H-isoquinolin-2-ethanone, 2-(9-Benzyl-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl)-1-pyrrolidin-1-yl-ethanone, 2-[9-(4-Chloro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-pyrrolidin-1-yl-ethanone, 2-[3-(2-Oxo-2-piperidin-1-yl-ethylsulfanyl)-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-9-yl]-1-pyrrolidin-1-yl-ethanone, 2-(9-Benzyl-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl)-1-(2,3-dihydro-indol-1-yl)-ethanone, 2-(9-Benzyl-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl)-1-piperidin-1-yl-ethanone, 2-[9-(4-Methyl-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-(4-methyl-piperidin-1-yl)-ethanone, 2-{3-[2-(3,4-Dihydro-2H-quinolin-1-yl)-2-oxo-ethylsulfanyl]-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-9-yl}-1-pyrrolidin-1-yl-ethanone, 2-[9-(2-Chloro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-pyrrolidin-1-yl-ethanone, 2-{3-[2-(2,3-Dihydro-indol-1-yl)-2-oxo-ethylsulfanyl]-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-9-yl}-1-pyrrolidin-1-yl-ethanone, 1-(2,3-Dihydro-indol-1-yl)-2-[9-(4-methyl-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-ethanone, 2-{3-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-2-oxo-ethylsulfanyl]-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-9-yl}-1-pyrrolidin-1-yl-ethanone, 1-(3,4-dihydro-2H-quinolin-1-yl)-2-[9-(4-fluoro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl, 2-[9-

(2-Fluoro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-pyrrolidin-1-yl-ethanone, N-Cyclohexyl-2-[3-(2-oxo-2-pyrrolidin-1-yl-ethylsulfanyl)-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-9-yl]-acetamide, 2-[9-(4-Fluoro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-pyrrolidin-1-yl-ethanone, 2-(9-Benzyl-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl)-1-(3,5-dimethyl-piperidin-1-yl)-ethanone, 2-[9-(4-Methyl-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-(3-methyl-piperidin-1-yl)-ethanone, 2-[9-(4-Methyl-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-N-(2-piperidin-1-yl-phenyl)-acetamide, 2-(9-Benzyl-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl)-N-(2-piperidin-1-yl-phenyl)-acetamide. In a preferred embodiment, said compound is 3-[[2-(2,3-dihydro-1H-indol-1-yl)-2-oxoethyl]thio]-N-(2-methylphenyl)-9H-1,2,4-Triazol[4,3-a]benzimidazole-9-acetamide.

The synthetic processes to prepare an exemplificative compound for each one of the claimed families are reported in Examples 1-3 that follow.

For the compound family (I), the proper aryl carboxylate is reacted with hydrazine to obtain an hydrazide which is then reacted with the proper isothiocyanate to give an aryl-4*H*-1,2,4-triazol-3-thiol. Finally the thiol is

reacted with the proper 2-chloroacetamide thus providing the desired product (I).

For the compound family (II) the proper [(2-aminophenyl)amino]methyl 3-oxopropanoate is heated in xylene at reflux to give 1,3-dihydro-2H-1,5-benzodiazepin-2-one, which is then reacted with the proper 2-chloroacetamide to give the desired product (II).

For the compound family (III) the proper heteroaryl thiol is reacted with the proper 2-chloroacetamide to give product (III).

Said families of compounds possess a high affinity for GPR17, significantly higher with respect to endogenous ligands and are not related to ligands known to interact with said receptor, namely agonists and antagonists of P2Y receptor and CysLTRs.

The docking energy evaluated for the here claimed compounds on GPR17 is significantly better than the docking energy evaluated for any other of the compounds tested, as explained in the examples that follow.

The compounds of the present invention revealed useful in treating a variety of pathological conditions associated with GPR17, in particular Multiple Sclerosis and pathologies involving the immune system, cardiovascular diseases, renal diseases.

The methods and techniques for preparing medicaments of a compound of the present invention are well-known in the

art. Exemplary pharmaceutical formulations and routes of delivery are described below. One of skill in the art will appreciate that any one or more of the compounds described herein, including the many specific embodiments, are prepared by applying standard pharmaceutical manufacturing procedures. Such medicaments can be delivered to the subject by using delivery methods that are well-known in the pharmaceutical arts.

Is an object of the present invention a compound selected from the group comprising compounds of formula (I), (II), and (III), as above defined, for use in the treatment of disorders involving GPR17 activation, in particular to treat chronic and/or acute neurodegenerative diseases, inflammatory diseases, pathologies involving the immune system, cardiovascular diseases, renal diseases. Said disorders are selected from the group consisting of Huntington's Disease, Machado-Joseph disease, Spinal and Bulbar muscular Atrophy (SBMA), Dentatorubral Pallidoluysian Atrophy (DRPLA), Fragile X syndrome, Fragile XE mental retardation, Friedreich ataxia, myotonic dystrophy, Spinocerebellar ataxias (types 8, 10 and 12), spinal muscular atrophy (Werdnig-Hoffman disease, Kugelberg-Welander disease), Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Pick's disease, and spongiform encephalopathies, age-related memory impairment, agyrophilic grain dementia,

corticobasal degeneration, conditions due to developmental dysfunction of the cerebrovasculature, dementia - multi infarct, dementia - subcortical, dementia with Lewy bodies, dementia of human immunodeficiency virus (HIV), dementia lacking distinct histology, dyskinesias (Paroxysmal), dystonias, essential tremor, fronto-temporal dementia, motor neuron diseases, multiple system atrophy, multiple sclerosis and other demyelinating conditions (e.g., leukodystrophies), vascular dementia.

In a preferred embodiment, said compounds are used in ischemia, cerebral trauma and MS.

In a further preferred embodiment, compounds selected from the group of compounds of formula (I), (II) and (III) as above defined are used in the treating of a demyelinizing disease, selected from MS, schizophrenia, depression, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, SLA or of a neuro-inflammatory disease.

In a further embodiment, said compounds are used in cerebral, cardiac and renal ischemia.

In some embodiments of the present invention, the compositions are administered alone, while in some other embodiments, the compositions are preferably present in a pharmaceutical formulation comprising at least one active ingredient/agent, as defined above, together with a solid support or alternatively, together with one or more pharmaceutically acceptable carriers and optionally other

therapeutic agents. Each carrier must be "acceptable" in the sense that it is compatible with the other ingredients of the formulation and not injurious to the subject.

Contemplated formulations include those suitable for oral and parenteral administration and also include subcutaneous, intramuscular, intravenous and intradermal. In some embodiments, formulations are conveniently presented in unit dosage form and are prepared by any method known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association (*e.g.*, mixing) the active ingredient with carriers and then if necessary shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets, wherein each preferably contains a predetermined amount of the active ingredient; as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. In other embodiments, the active ingredient is presented as a bolus, electuary, or paste, *etc.*

In some embodiments, tablets comprise at least one active ingredient and optionally one or more accessory

agents/carriers are made by compressing or molding the respective agents. In preferred embodiments, compressed tablets are prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (*e.g.*, povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (*e.g.*, sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets are made by molding in a suitable machine a mixture of the powdered compound (*e.g.*, active ingredient) moistened with an inert liquid diluent. Tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

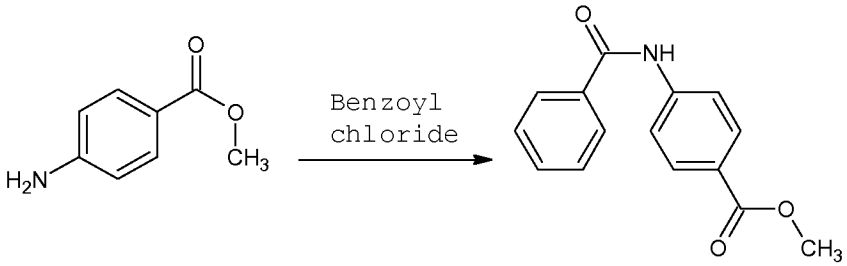
Formulations suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may

include suspending agents and thickening agents, and liposomes or other micro particulate systems which are designed to target the compound to blood components or one or more organs. In some embodiments, the formulations are presented/formulated in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents. It also is intended that the agents, compositions and methods of this invention be combined with other suitable compositions and therapies.

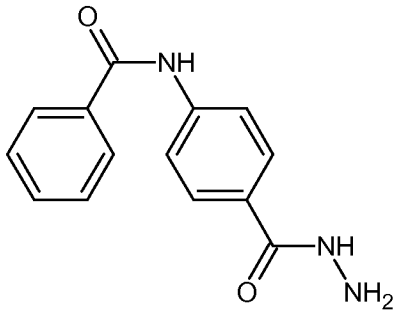
Examples:

Example 1. Synthesis of N-[4-[5-[[2-[(4-chlorophenyl)amino]-2-oxoethyl]thio]-4-methyl- 4H-1,2,4-triazol-3-yl]phenyl]-benzamide of formula (I)



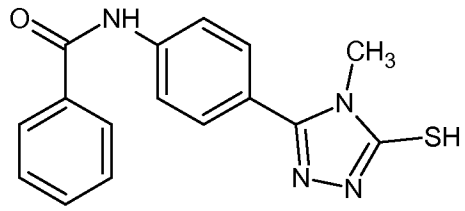
a) b)

To a solution of a) in DCM/water and KOH was added a solution of an equimolar amount of benzoyl chloride in DCM, to give product b) that was then reacted with $NH_2NH_2*H_2O$ in EtOH thus obtaining the *N*-[4-(hydrazinylcarbonyl)phenyl]benzamide) c).



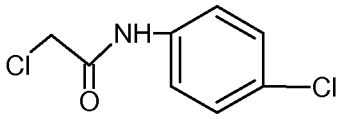
c)

c) was then reacted with MeNCS in EtOH in the presence of KOH, then acidified with HCl thus obtaining the *N*-[4-(4-methyl-5-sulfanyl-4*H*-1,2,4-triazol-3-yl)phenyl]benzamide d)



d)

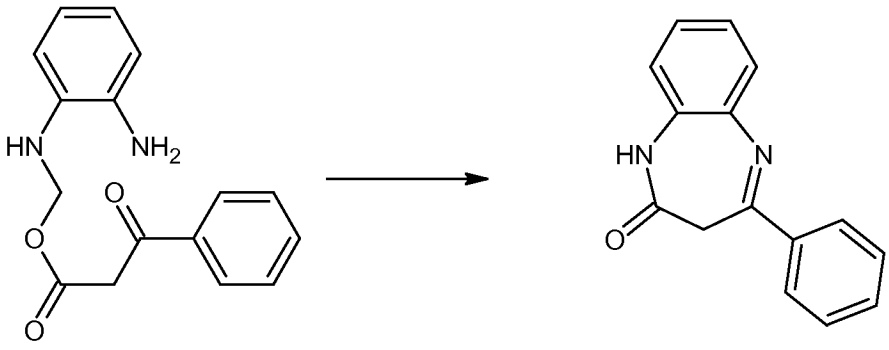
by reacting d) with 2-chloro-*N*-(4-chlorophenyl)acetamide e)in EtOH, KOH and TEA



e)

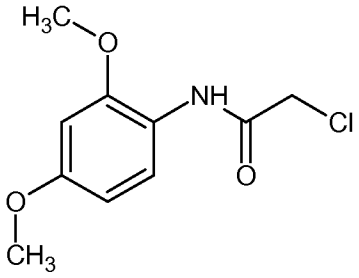
the desired product *N*-[4-[5-[[2-[(4-chlorophenyl)amino]-2-oxoethyl]thio]-4-methyl-4*H*-1,2,4-triazol-3-yl]phenyl]-benzamide has been obtained.

Example 2. Synthesis of 1H-1,5-N-(2,4-dimethoxyphenyl)-2,3-dihydro-2-oxo-4-phenyl benzodiazepine-1-acetamide of formula (II)



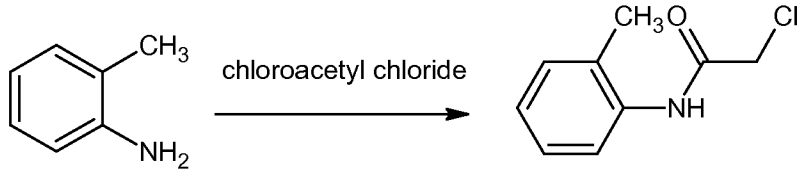
a) b)

[(2-aminophenyl)amino]methyl 3-oxo-3-phenylpropanoate a) has been reacted in xylene at 140°C to give 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one b) that was then reacted with 2-chloro-*N*-(2,4-dimethoxyphenyl)acetamide c) in K_2CO_3, DMF to give the desired product which is 1H-1,5-N-(2,4-dimethoxyphenyl)-2,3-dihydro-2-oxo-4-phenyl benzodiazepine-1-acetamide. The 2-chloro-*N*-(2,4-dimethoxyphenyl)acetamide has been obtained by reacting 2,4-dimetoxybenzenamine with chloroacetyl chloride in MeCN at reflux.

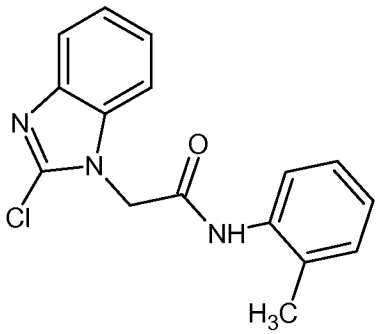


c)

Example 3. Synthesis of 3-[[2-(2,3-dihydro-1H-indol-1-yl)-2-oxoethyl]thio]-N-(2-methylphenyl)-9H-1,2,4-Triazol[4,3-a]benzimidazole-9-acetamide of formula (III)

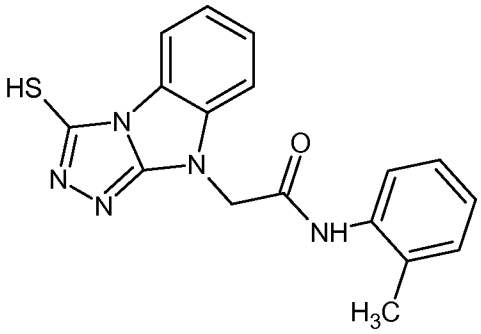


a) b)



d)

a) was reacted in MeCN with chloroacetyl chloride at reflux to give b) which was then reacted with 2-chloro-1*H*-benzimidazole in K_2CO_3, DMF to give d). d) was then reacted with $NH_2NH_2*H_2O$ in EtOH to give e) that, reacted with 2-chloro-1-(1,3-dihydro-2*H*-isoindol-2-yl)ethanone, lead to the obtainment of the desired 3-[[2-(2,3-dihydro-1H-indol-1-yl)-2-oxoethyl]thio]-N-(2-methylphenyl)-9H-1,2,4-Triazol[4,3-a]benzimidazole-9-acetamide.



e)

Example 4, Molecular database preparation

The Asinex Platinum Collection (http://www.asinex.com/download-zone.html) is a lead-like structural library containing approx. 130,000 in-house synthesized compounds.

The SD file containing all the structures was downloaded and a single low-energy conformation for each putative ligand contained in the Asinex SD file was produced.

Example 5, Molecular docking

The *in silico* screening was carried out with a molecular docking approach. 1,000 conformations were generated for each ligand by sampling their rotable bonds. The selected placement methodology was carried out by superposing triplets of ligand atoms and triplets of receptor site points. Before scoring all the generated poses, duplicate complexes were removed. The accepted poses were scored according to the London dG scoring, which estimates the free energy of binding of the ligand from a given pose.

All the ligands contained in the Platinum library were screened according to the above procedure. The 15 top

scoring compounds were resubmitted to the same docking procedure, keeping for each one of them 300 poses. The estimated binding affinity and the ligand efficiency were calculated, and the pKi was computed through the binding free energy estimated with the London dG scoring function. Data related to the docking energy obtained for a panel of compound tested *in silico* on the CXCR4 structural model are reported in Table 1. In the first section of the table, data referred to compounds belonging to the three family of compounds here claimed are reported. In the second section, data referred to compounds that do not share the claimed structures are reported. For this second group of compounds, the docking energy is considerably higher than that observed for the first group of compound, meaning a low affinity for the receptor.

Table 1

Compound	Docking score
Compounds of formula (I)	
N-[4-[5-[[2-[(4-chlorophenyl)amino]-2-oxoethyl]thio]-4-methyl-4H-1,2,4-triazol-3-yl]phenyl]-benzamide	-32.569
N-Phenyl-2-(5-m-tolyl-2H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	-7,295
2-(5-m-Tolyl-2H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	-9,987
N-Naphthalen-1-yl-2-(5-m-tolyl-2H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	-18,409
N-Thiazol-2-yl-2-(5-p-tolyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	-14,440
N-(2-Methyl-3H-benzoimidazol-5-yl)-2-(5-phenyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide	-5,990
Compounds of formula (II)	
1H-1,5-N-(2,4-dimethoxyphenyl)-2,3-dihydro-2-oxo-4-phenyl benzodiazepine-1-acetamide	-32.200
N-Benzyl-2-(2-oxo-4-phenyl-2,3-dihydro-benzo[b][1,4]diazepin-1-yl)-acetamide	-8,498
N-(2,3-Dimethyl-phenyl)-2-(2-oxo-4-phenyl-2,3-dihydro-benzo[b][1,4]diazepin-1-yl)-acetamide	-29.188
N-(2,6-Dimethyl-phenyl)-2-(2-oxo-4-phenyl-2,3-dihydro-benzo[b][1,4]diazepin-1-yl)-acetamide	-24,581
Compounds of formula (III)	
3-[[2-(2,3-dihydro-1H-indol-1-yl)-2-oxoethyl]thio]-N-(2-methylphenyl)-9H-1,2,4-Triazol[4,3-a]benzimidazole-9-acetamide	-35.597
2-[9-(4-Chloro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-	-24.021

ylsulfanyl]-1-(3,4-dihydro-1H-isoquinolin-2-ethanone	
2-(9-Benzyl-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl)-1-pyrrolidin-1-yl-ethanone	-23,531
2-[9-(4-Chloro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-pyrrolidin-1-yl-ethanone	-22,275
1-(3,4-Dihydro-2H-quinolin-1-yl)-2-(6,8-dimethyl-9H-1,3,4,9-tetraaza-fluoren-2-ylsulfanyl)-ethanone	-21,426
2-[3-(2-Oxo-2-piperidin-1-yl-ethylsulfanyl)-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-9-yl]-1-pyrrolidin-1-yl-ethanone	-21,251
2-(9-Benzyl-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl)-1-(2,3-dihydro-indol-1-yl)-ethanone	-20,713
2-(9-Benzyl-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl)-1-piperidin-1-yl-ethanone	-20,700
2-[9-(4-Methyl-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-(4-methyl-piperidin-1-yl)-ethanone	-19,385
2-{3-[2-(3,4-Dihydro-2H-quinolin-1-yl)-2-oxo-ethylsulfanyl]-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-9-yl}-1-pyrrolidin-1-yl-ethanone	-17,248
2-[9-(2-Chloro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-pyrrolidin-1-yl-ethanone	-17,126
2-{3-[2-(2,3-Dihydro-indol-1-yl)-2-oxo-ethylsulfanyl]-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-9-yl}-1-pyrrolidin-1yl-ethanone	-14,847

1-(2,3-Dihydro-indol-1-yl)-2-[9-(4-methyl-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-ethanone	-13,766
2-{3-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-2-oxo-ethylsulfanyl]-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-9-yl}-1-pyrrolidin-1yl-ethanone	-13,030
1-(3,4-Dihydro-2H-quinolin-1-yl)-2-[9-(4-fluoro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl	-12,962
2-[9-(2-Fluoro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-pyrrolidin-1-yl-ethanone	-12,758
N-Cyclohexyl-2-[3-(2-oxo-2-pyrrolidin-1-yl-ethylsulfanyl)-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-9-yl]-acetamide	-12,439
2-[9-(4-Fluoro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-pyrrolidin-1-yl-ethanone	-12,181
2-(9-Benzyl-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl)-1-(3,5-dimethyl-piperidin-1-yl)-ethanone	-11,970
2-[9-(4-Methyl-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-(3-methyl-piperidin-1-yl)-ethanone	-10,300
2-[9-(4-Methyl-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-N-(2-piperidin-1-yl-phenyl)-acetamide	-8,359
2-(9-Benzyl-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl)-N-(2-piperidin-1-yl-phenyl)-acetamide	-23.545
Other compounds	

Benzenesulfonamide, 4-chloro-N-[(5,6-dihydro-6-oxo-1,3-dioxolo[4,5-g]quinolin-7-yl)methyl]-N-[(tetrahydro-2-furanyl)methyl]-	208.559
Propanamide,N-[4-[[2-[(8,9,10,11 tetrahydro[1]benzothieno[3,2-e]-1,2,4-triazolo[4,3-c]pyrimidin-3-yl)thio]acetyl]amino]phenyl]	223.048
Acetamide,N-(5-methyl-3-isoxazolyl)-2-[(8,9,10,11-tetrahydro-5-methyl[1]benzothieno[3,2-e]-1,2,4-triazolo[4,3-c]pyrimidin-3-yl)thio]-	253.290
Acetamide,N-[4-(1,1-dimethylethyl)-2-thiazolyl]-2-[(5-ethyl-8,9,10,11-tetrahydro[1]benzothieno[3,2-e]-1,2,4-triazolo[4,3-c]pyrimidin-3-yl)thio]-	253.916

Bibliography

Abbracchio MP (2006) EMBO J 25:4615.

Abbracchio MP, Burnstock G, Boeynaems JM, Barnard EA, Boyer JL, Kennedy C, Knight GE, Fumagalli M, Gachet C, Jacobson KA, Weisman GA (2006) Pharmacol Rev. 58(3):281-341.

Abbracchio MP, Burnstock G, Verkhratsky A, Zimmermann H (2009) Trends Neurosci. 32(1):19-29.

Brink C (2003) Adv Exp Med Biol 525:7.

Calleri E, Ceruti S, Cristalli G, Martini C, Temporini C, Parravicini C, Volpini R, Daniele S, Caccialanza G, Lecca D, Lambertucci C, Trincavelli ML, Marucci G, Wainer IW, Ranghino G, Fantucci P, Abbracchio MP, Massolini G (2010) J Med Chem 53:3489.

Ceruti S, Villa G, Genovese T, Mazzon E, Longhi R, Rosa P, Bramanti P, Cuzzocrea S, Abbracchio MP (2009) Brain 132:2206.

Chen Y, Wu H, Wang S, Koito H, Li J, Ye F, Hoang J, Escobar SS, Gow A, Arnett HA, Trapp BD, Karandikar NJ, Hsieh J, Lu QR (2009) Nat Neurosci 12:1398.

Ciana P, Fumagalli M, Trincavelli ML, Verderio C, Rosa P, Lecca D, Ferrario S, Parravicini C, Capra V, Gelosa P, Guerrini U, Belcredito S, Cimino M, Sironi L, Tremoli E, Rovati GE, Martini C, Eberini I, Daniele S, Parravicini C,

Sensi C, Trincavelli ML, Martini C, Abbracchio MP (2011) J Comput Aided Mol Des 25:743:752.

Fumagalli M, Daniele S, Lecca D, Lee PR, Parravicini C, Fields RD, Rosa P, Antonucci F, Verderio C, Trincavelli ML, Bramanti P, Martini C, Abbracchio MP (2011) J Biol Chem. 286(12):10593-604.

Lecca D, Trincavelli ML, Gelosa P, Sironi L, Ciana P, Fumagalli M, Villa G, Verderio C, Grumelli C, Guerrini U, Tremoli E, Rosa P, Cuboni S, Martini C, Buffo A, Cimino M, Abbracchio MP (2008) PLoS One 3:e3579.

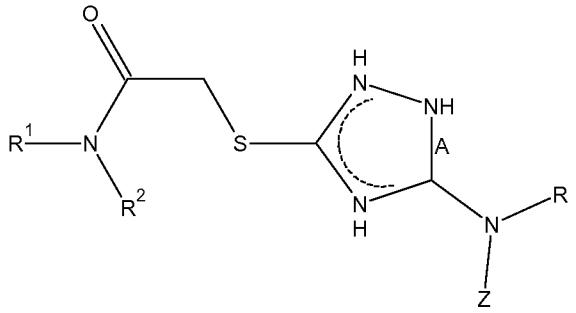
Pugliese AM, Trincavelli ML, Lecca D, Coppi E, Fumagalli M, Ferrario S, Failli P, Daniele S, Martini C, Pedata F, Abbracchio MP (2009) Am J Physiol Cell Physiol 297:C1028.

Wojciechowski M, Lesyng B (2004) J. Phys. Chem. B 108:18368.

Wu B, Chien EY, Mol CD, Fenalti G, Liu W, Katritch V, Abagyan R, Brooun A, Wells P, Bi FC, Hamel DJ, Kuhn P, Handel TM, Cherezov V, Stevens RC (2010) Science 330:1066.

CLAIMS

1. Compounds of formula (III)



(III)

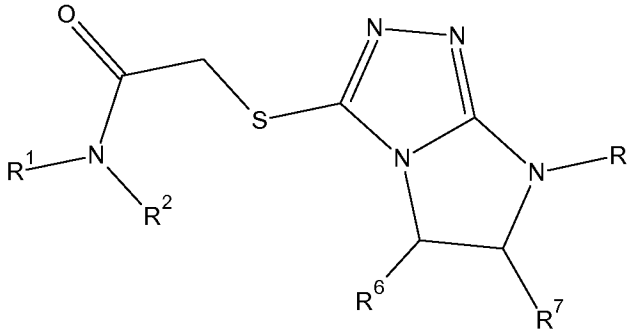
wherein R^1 and R^2 are independently H or an optionally substituted phenyl, or R^1 and R^2 form with the N to which they are linked a saturated or unsaturated mono, bi or tricycle having from 3 to 16 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S; A is a bond or a C; the dotted line represents localized or delocalized double bonds; R is H, C1-C4 aryl, optionally substituted heteroaryl, optionally substituted benzyl, $-CH_2C(O)R^3$, $-CH_2C(O)NR^4R^5$; R^3 is chosen from optionally substituted alkyl, optionally substituted saturated or unsaturated 3-8 membered cycle eventually containing from 1 to 4 heteroatoms selected from N, O, S, optionally substituted aryl eventually containing from 1 to 4 heteroatoms selected from N, O, S; R^4 is chosen from H, optionally substituted alkyl, optionally substituted saturated or unsaturated 3-8 membered cycle

eventually containing from 1 to 4 heteroatoms selected from N, O, S, optionally substituted aryl eventually containing from 1 to 4 heteroatoms selected from N, O, S; R^5 is chosen from H, optionally substituted alkyl, optionally substituted saturated or unsaturated 3-8 membered cycle eventually containing from 1 to 4 heteroatoms selected from N, O, S, optionally substituted aryl eventually containing from 1 to 4 heteroatoms selected from N, O, S; R^4 and R^5 taken together with the nitrogen to which they are attached can form an optionally substituted saturated or unsaturated 3-8 membered cycle eventually containing from 1 to 4 heteroatoms selected from N, O, S; Z is H or forms a bicycle with said 5 or 6 membered ring comprising 3 N by closing on a N on said cycle, or, when A is C, by closing on said C, wherein said second ring formed by Z is preferably a 5 membered ring and it is open to fusion or their pharmacologically acceptable salts to be used as a medicament.

2. The compounds for use according to claim 1, wherein R^1 and R^2 are independently H or an optionally substituted phenyl, or R^1 and R^2 are closed to form with the N to which are linked a 1,2,3,4-tetrahydroquinoline, a 1,2,3,4-tetrahydroisoquinoline, a pirrolidine, a piperidine,

a piperazine optionally substituted; A is C and the formed 6 membered ring is preferably an aromatic ring; Z forms a bicycle with said 6 membered ring by closing on A, wherein said second ring formed by Z is a 5 membered ring open to fusion, preferably said 5 membered ring is fused with an optionally substituted phenyl forming a tricycle, preferably said tricycle is a 5*H*-[1,2,4]triazino[5,6-*b*]indole optionally substituted; R is H or C1-C4 aryl.

3. The compounds for use according to claim 1, wherein A is a bond and said ring containing 3 N is a 5 membered ring and said compounds are selected from the group of formula (III)A



(III)A

wherein R1 is H and R2 is an optionally substituted phenyl, or R1 and R2 are closed to form with the N to which are linked a pirrolidine, an optionally substituted pirrolidine, preferably 2-(2,3-dihydro-1,4-benzodioxin-6-yl)-1-pyrrolidinyl, a phenothiazine, an optionally substituted pyridine, a piperidine, an optionally substituted piperidine, preferably a 2-methyl piperidine, a 4-piperidine

carboxyester, preferably a 4-piperidine-carboxyethylester, a 4-piperidinecarboxamide, a 3-methylpiperidine, a 4-methyl piperidine, or a 4-phenylmethylpiperidine or a 3-piperidine carboxylic acid or a 4-piperidine carboxylic acid, or a 4-piperidine carboxamide-N-phenyl, or a 3,5-dimethylpiperidine, or a 2,6-dimethylpiperidine, or a 4,5-dihydro-5-phenyl-1H-pyrazol-1-yl, a 4,5-dihydro-5-(4-methoxyphenyl)-3-phenyl-1H-pyrazol-1-yl, a 2-chloro-10H-phenothiazin-10-yl, a 6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl, a 4-morpholine, an optionally substituted 4-morpholine, preferably a 2,6-dimethyl-4-morpholine, or a 2-methylmorpholine, an indoline, an optionally substituted indoline, preferably a 1-[2,3-dihydro-5-(1-piperidinylsulfonyl)-1H-indol-1-yl], an isoquinoline, a 1,2,3,4-tetrahydroisoquinoline, a 1,2,3,4-tetrahydroquinoline, a 3,4-dihydro-2-methyl-1(2H)-quinoline, a 1-[3-(2-benzofuranyl)-5-(2-furanyl)-4,5-dihydro-1H-pyrazol-1-yl], a 2H-1,5-benzodiazepin-2-one-4-trifluoromethyl, a 2,3-dihydroindol-1-yl, a 2,3-dimethyl-1H-indol-1yl, a 1-[4-[(3,5-dimethyl-4-isoxazolyl)sulfonyl]-1-piperazinyl], a benzothiazine, a piperazine, an optionally substituted piperazine, preferably a 4-nitrophenylpiperazine or a 2-nitrophenylpiperazine, or a 4-(2-piridinyl)1-

piperazine, or a 4-(2-fluorophenil)sulfonyl-1-piperazine or a 4-phenylsulphonil-1-piperazine, or a 3-methylphenyl-1 piperazine, or a 4-(2-methoxyphenyl)piperazine or a 4-phenylpiperazine or a 4-methylphenylpiperazine or a 4-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]-1-piperazine, a 3-trifluoromethylphenyl-1-piperazine, or a 2-fluorophenyl-1-piperazine, a piperidinecarboxamide-N-phenyl, a 1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-yl, a 4,5-dihydro-3-(2-naphthalenyl)-5-phenyl-1H-pyrazol-1-yl, a 4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-1-piperazinyl, a pyrrolidone, a 2(1H)quinoxalinone, a [2,3,dihydro-5(1-piperidinylsulfonyl)1H-indol-1yl], a 3,4-dihydro-2(1H)isoquinolinyl, a 3,4-dihydro-2-methyl-1(2H)quinoline, a 3,4-dihydro-6(1-pyrrolidinylsulfonyl)1(2H)quinoline, a 10,11-dihydro-5H-dibenz[b,f]azepin-5-yl, a hexahydro-1H-azepin-1-yl, preferably R1 and R2 are closed to form with the N to which are linked an indoline, a 1,2,3,4-tetrahydroisoquinoline, a 1,2,3,4-tetrahydroquinoline, a piperidine, a pirrolidine; R is H, optionally substituted benzyl or -CH2C(O)NR4R5; R4 is H; R5 is an optionally substituted phenyl or an optionally substituted cycloexane or R^4 and R^5 form with the nitrogen to which they are attached a

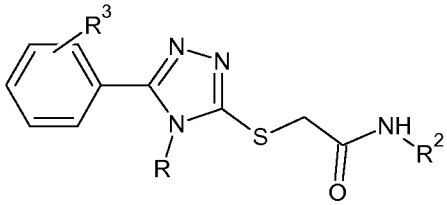
pyrrolidine; R^6 and R^7 are independently H or an optionally substituted phenyl, or R^6 and R^7 close to form a saturated or unsaturated cycle having from 3 to 8 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S; in a preferred embodiment, R^6 and R^7 are closed in a cycle forming a tricycle, preferably selected from a 4H-[1,2,4]triazolo[5,1-f]purine-6,8(5H,7H)-dione, preferably a 5,7-dimethyl-4H-[1,2,4]triazolo[5,1-f]purine-6,8(5H,7H)-dione or a 4H-[1,2,4]triazolo[1,5-a]benzimidazole.

4. The compounds for use according to any of the claims from 1 to 3 which are selected from the group comprising 3-[[2-(2,3-dihydro-1H-indol-1-yl)-2-oxoethyl]thio]-N-(2-methylphenyl)-9H-1,2,4-Triazolo[4,3-a]benzimidazole-9-acetamide, 2-[9-(4-Chloro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-(3,4-dihydro-1H-isoquinolin-2-ethanone, 2-(9-Benzyl-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl)-1-pyrrolidin-1-yl-ethanone, 2-[9-(4-Chloro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-pyrrolidin-1-yl-ethanone, 2-[3-(2-Oxo-2-piperidin-1-yl-ethylsulfanyl)-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-9-yl]-1-pyrrolidin-1-yl-ethanone, 2-(9-Benzyl-9H-

benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl)-1-(2,3-dihydro-indol-1-yl)-ethanone, 2-(9-Benzyl-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl)-1-piperidin-1-yl-ethanone, 2-[9-(4-Methyl-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-(4-methyl-piperidin-1-yl)-ethanone, 2-{3-[2-(3,4-Dihydro-2H-quinolin-1-yl)-2-oxo-ethylsulfanyl]-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-9-yl}-1-pyrrolidin-1-yl-ethanone, 2-[9-(2-Chloro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-pyrrolidin-1-yl-ethanone, 2-{3-[2-(2,3-Dihydro-indol-1-yl)-2-oxo-ethylsulfanyl]-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-9-yl}-1-pyrrolidin-1-yl-ethanone, 1-(2,3-Dihydro-indol-1-yl)-2-[9-(4-methyl-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-ethanone, 2-{3-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-2-oxo-ethylsulfanyl]-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-9-yl}-1-pyrrolidin-1-yl-ethanone, 1-(3,4-dihydro-2H-quinolin-1-yl)-2-[9-(4-fluoro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl, 2-[9-(2-Fluoro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-pyrrolidin-1-yl-ethanone, N-Cyclohexyl-2-[3-(2-oxo-2-pyrrolidin-1-yl-ethylsulfanyl)-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-9-yl]-

acetamide, 2-[9-(4-Fluoro-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-pyrrolidin-1-yl-ethanone, 2-(9-Benzyl-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl)-1-(3,5-dimethyl-piperidin-1-yl)-ethanone, 2-[9-(4-Methyl-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-1-(3-methyl-piperidin-1-yl)-ethanone, 2-[9-(4-Methyl-benzyl)-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl]-N-(2-piperidin-1-yl-phenyl)-acetamide, 2-(9-Benzyl-9H-benzo[4,5]imidazo[2,1-c][1,2,4]triazol-3-ylsulfanyl)-N-(2-piperidin-1-yl-phenyl)-acetamide.

5. Compounds of formula (I)



(I)

wherein R is H, a linear or branched C1-C4 alkyl, a linear or branched C1-C4 alkyl phenyl optionally substituted, a phenyl optionally substituted; R^2 is H, a linear or branched C1-C4 alkyl, a saturated or unsaturated mono, bi or tricycle having from 3 to 16 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S; R^3 is H, a linear or branched C1-C4 alkyl or NHC(O)R^1, wherein R^1 is a linear or branched C1-C4

alkyl, a saturated or unsaturated mono, bi or tricycle having from 3 to 16 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S or their pharmacologically acceptable salts for use as a medicament.

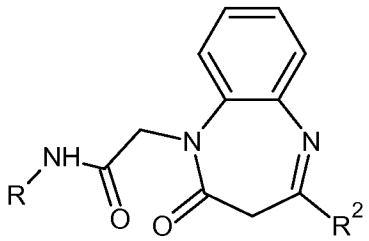
6. The compounds for use according to claim 5, wherein R is selected from the group comprising H, methyl, ethyl, phenyl, benzyl; R^2 is selected from the group comprising H, naphthalene, phenyl, preferably 4Cl-phenyl, benzimidazole, preferably 2-methylbenzimidazole; R^3 is preferably selected from the group comprising H, 4-methyl, 4-NHC(O)R^1, wherein R^1 is phenyl or phenyl mono, bi o tri substituted, wherein said substituents on said phenyl are independently selected from C1-C4 linear or branched alkyl, acetyl, C1-C4 alkoxy, carboxy C1-C4 alkyl, F, Cl, Br, I, triphluoromethyl, nitro, CN.

7. The compounds for use according to claim 5, wherein R is H or methyl; R^2 is H, naphthalene, phenyl, preferably 4Cl-phenyl, benzimidazole, preferably 2-methylbenzimidazole; R^3 is H, 4-methyl, 4-NHC(O)R^1, wherein R^1 is phenyl, preferably 4Cl-phenyl.

8. The compounds for use according to claim 5 selected from the group comprising N-Phenyl-2-(5-m-tolyl-2*H*-[1,2,4]triazol-3-ylsulfanyl)-acetamide, 2-(5-m-tolyl-

2*H*-[1,2,4]triazol-3-ylsulfanyl)-acetamide, N-naphthalen-1-yl-2-(5-m-tolyl-2*H*-[1,2,4]triazol-3-ylsulfanyl)-acetamide, N-Thiazol-2-yl-2-(5-p-tolyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide, N-(2-Methyl-3*H*-benzoimidazol-5-yl)-2-(5-phenyl-4H-[1,2,4]triazol-3-ylsulfanyl)-acetamide, N-[4-[5-[[2-[(4-chlorophenyl)amino]-2-oxoethyl]thio]-4-methyl-4H-1,2,4-triazol-3-yl]phenyl]-benzamide.

9. Compounds of formula (II)



(II)

wherein R^2 is H, a C1-C4 linear or branched alkyl, a linear or branched C1-C4 alkyl phenyl optionally substituted, a saturated or unsaturated mono, bi or tricycle having from 3 to 16 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S and R is H, a C1-C4 linear or branched alkyl phenyl optionally substituted, a saturated or unsaturated mono, bi or tricycle having from 3 to 16 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S or their

pharmacologically acceptable salts for use as a medicament.

10. The compounds for use according to claim 9 wherein R^2 is H, phenyl, or a phenyl mono, bi o tri substituted, wherein said substituents on said phenyl are independently selected from methyl, ethyl, methylethyl, acetyl, methoxy, ethoxy, F, Cl, Br, I, carboxyethyl, trifluoromethyl, methylthio, dimetylamino; R is H, phenyl, benzyl, phenylethyl, phenylpropyl, a phenyl mono, bi o tri substituted, wherein said substituents on said phenyl are independently selected from methyl, ethyl, methylethyl, acetyl, methoxy, ethoxy, F, Cl, Br, I, carboxyethyl, trifluoromethyl, methylthio, dimetylamino, or R is 1,3-benzodioxol-5-yl-2,3-dihydro, 2,3-dihydro-1,4-benzodioxin-6-yl, 2-furanylmethyl, cyclohexane.

11. The compounds for use according to claim 9 wherein R^2 is phenyl and R is 2,4 dimethoxyphenyl, benzyl, 2,3-dimethylphenyl, 2,6-dimethylphenyl.

12. The compounds for use according to claim 9 selected from the group comprising N-(2,4-dimethoxyphenyl)-2,3-dihydro-2-oxo-4-phenyl-1H-1,5-Benzodiazepine-1-acetamide, N-Benzyl-2-(2-oxo-4-phenyl-2,3-dihydro-benzo[b][1,4]diazepin-1-yl)-acetamide, N-(2,3-dimethyl-phenyl)-2-(2-oxo-4-phenyl-2,3-dihydro-

benzo[b][1,4]diazepin-1-yl)-acetamide, N-(2,6-Dimethyl-phenyl)-2-(2-oxo-4-phenyl-2,3-dihydro-benzo[b][1,4]diazepin-1-yl)-acetamide.

13. The compounds for use according to any of the claim from 1 to 12, wherein said compounds are used in the treatment of disorders involving GPR17 dysfunction, said disorders being preferably selected from the group comprising chronic and/or acute neurodegenerative diseases, preferably Multiple Sclerosis, inflammatory diseases, pathologies involving the immune system, cardiovascular diseases, renal diseases.

14. A pharmaceutical composition comprising at least one compounds selected from the compounds claimed in any of the claims from 1 to 12.

15. The pharmaceutical composition according to claim 14, further comprising an additional active principle active in the treatment of chronic and/or acute neurodegenerative diseases, preferably Multiple Sclerosis, inflammatory diseases, pathologies involving the immune system, cardiovascular diseases, renal diseases.

16. The pharmaceutical composition according to claim 14 or 15 for use in the treatment of a disorder selected from the group comprising: Huntington's Disease, Machado-Joseph disease, Spinal and Bulbar muscular

Atrophy (SBMA), Dentatorubral Pallidoluysian Atrophy (DRPLA), Fragile X syndrome, Fragile XE mental retardation, Friedreich ataxia, myotonic dystrophy, Spinocerebellar ataxias (types 8, 10 and 12), spinal muscular atrophy (Werdnig-Hoffman disease, Kugelberg-Welander disease), Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Pick's disease, and spongiform encephalopathies, age-related memory impairment, agyrophilic grain dementia, corticobasal degeneration, conditions due to developmental dysfunction of the cerebrovasculature, dementia - multi infarct, dementia - subcortical, dementia with Lewy bodies, dementia of human immunodeficiency virus (HIV), dementia lacking distinct histology, dyskinesias (Paroxysmal), dystonias, essential tremor, fronto-temporal dementia, motor neuron diseases, multiple system atrophy, multiple sclerosis and other demyelinating conditions (e.g., leukodystrophies), vascular dementia.

17. The pharmaceutical composition according to any of the claims from 14 to 16 for the treatment of Multiple Sclerosis.

Figure 1A

Catene	1	2	3	4	5	6
1: GPR17		19,5	15,3	16,0	15,0	20,5
2: Rh	18,5		12,4	13,6	14,8	15,6
3: ADRB1	19,9	17,0		51,6	24,8	15,9
4: ADRB2	18,0	16,1	44,7		24,3	20,2
5: AA2AR	16,9	17,5	21,4	24,2		15,6
6: CXCR4	19,6	15,8	11,7	17,2	13,3	

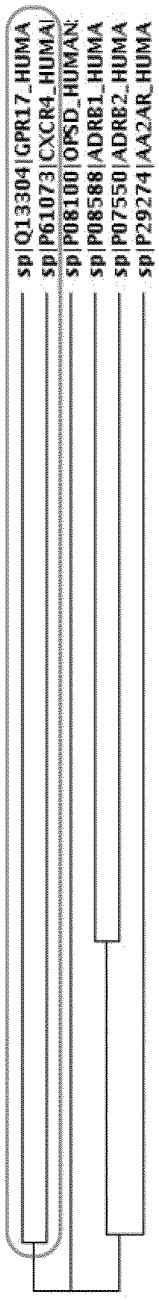

sp|Q13304|GPR17_HUMA
sp|P61073|CXCR4_HUMA
sp|P08100|OPSD_HUMAN
sp|P08588|ADRB1_HUMA
sp|P07550|ADRB2_HUMA
sp|P29274|AA2AR_HUMA

Figure 1B

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/058500

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D243/12 C07D249/12 C07D487/04 A61K31/4196 A61K31/551
A61P25/28
ADD.
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 practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/151797 A2 (UNIV MASSACHUSETTS [US]) 29 December 2010 (2010-12-29) page 19, lines 7-15; claim 23 page 37; compound 3rd claim 23 -----	1-4, 13-17
X	WO 2010/111713 A2 (ZACHARON PHARMACEUTICALS INC [US]) 30 September 2010 (2010-09-30) page 2, paragraph [0009] page 50, paragraph [00153] - page 54, paragraph [00159] claims 13, 14 figure 31Q; compound 5th ----- -/--	1-4, 13-17

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2012	16/08/2012

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	Cortés, José

1

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/111711 A2 (ZACHARON PHARMACEUTICALS INC [US]) 30 September 2010 (2010-09-30) page 2, line 33, paragraph [0010] - page 4, line 1 page 50, line 24, paragraph [00180] - paragraph [00190] claim 14 figure 36C; compound 13th	1-4, 13-17
X	WO 2010/025308 A2 (UNIVERSTIY OF SOUTHERN CALIFOR [US]) 4 March 2010 (2010-03-04) page 1, line 14 page 18, line 4 page 25; compound 15	1-4, 13-17
X	WO 2006/007864 A1 (MAX PLANCK GESELLLSCHAFT ZUR F [DE]) 26 January 2006 (2006-01-26) page 1, paragraph 1 page 84; compound 374	1-4, 13-17
X	WO 2007/061923 A2 (TAKEDA SAN DIEGO INC [US]) 31 May 2007 (2007-05-31) page 173; compound 9th page 174; compounds 1st, 2nd, 6th page 189; examples; table 1; compound 1st page 191; examples; table 1; compounds 5th, 6th claims 1, 9-11	5-8, 13-17
X	US 2011/257184 A1 (QU CHENG-KUI [US] ET AL) 20 October 2011 (2011-10-20) page 2, paragraph [0009] - paragraph [0010] page 3, paragraph [0012]; compounds #220-323 to #220-328	1,2
X	WO 2004/005323 A2 (RECEPTRON INC [US]) 15 January 2004 (2004-01-15) page 18, paragraph [00077]; table 1; compounds E5-A24 and E5-A25	1,2
X	US 5 939 462 A (CONNELL RICHARD D [US] ET AL) 17 August 1999 (1999-08-17) column 19; compounds 57, 67	1,2
X	SU 1 596 719 A1 (NII GIGIENY I PROFPATOLOGII [SU]; VOENNO MED AKADEMIYA IM S M KI [SU]) 10 September 1996 (1996-09-10) page 3, left-hand column, paragraph 5 - paragraph 10; compound 1	1,2

-/--

1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/058500

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JACOBSSON, MICAEL; GAREDAL, MAGNUS; SCHULTZ, JOHAN; KARLEN, ANDERS: "Identification of Plasmodium falciparum Spermidine Synthase Active Site Binders through Structure-Based Virtual Screening", JOURNAL OF MEDICINAL CHEMISTRY, vol. 51, no. 9, 2008, pages 2777-2786, XP002678218, ISSN: 0022-2623, DOI: 10.1021/jm7016144 page 2779; figure 4; compound 11	1,2
X	US 2009/118135 A1 (REED JOHN C [US] ET AL) 7 May 2009 (2009-05-07) page 76; compound 1st page 131; compound 3rd page 187; compound 3rd	9-12
A	WO 2006/045476 A2 (UNIV DEGLI STUDI MILANO [IT]; UNI DEGLI STUDI DI PISA [IT]) 4 May 2006 (2006-05-04) cited in the application the whole document	1-17

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/058500

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

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

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

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

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

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

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

1-4(completely); 13-17(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4(completely); 13-17(partially)

   compounds of formula (III) for use as a medicament

   ---

2. claims: 5-8(completely); 13-17(partially)

   compounds of formula (II) for use as a medicament

   ---

3. claims: 9-12(completely); 13-17(partially)

   compounds of formula (I) for use as a medicament

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/058500

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010151797 A2	29-12-2010	US 2011065704 A1	17-03-2011
		WO 2010151797 A2	29-12-2010
WO 2010111713 A2	30-09-2010	EP 2411529 A2	01-02-2012
		US 2012100609 A1	26-04-2012
		WO 2010111713 A2	30-09-2010
WO 2010111711 A2	30-09-2010	EP 2411526 A2	01-02-2012
		US 2010248365 A1	30-09-2010
		WO 2010111711 A2	30-09-2010
WO 2010025308 A2	04-03-2010	US 2011212467 A1	01-09-2011
		WO 2010025308 A2	04-03-2010
WO 2006007864 A1	26-01-2006	NONE	
WO 2007061923 A2	31-05-2007	EP 1948614 A2	30-07-2008
		JP 2009515997 A	16-04-2009
		US 2007197532 A1	23-08-2007
		US 2011070297 A1	24-03-2011
		WO 2007061923 A2	31-05-2007
US 2011257184 A1	20-10-2011	NONE	
WO 2004005323 A2	15-01-2004	AU 2003248882 A1	23-01-2004
		EP 1539219 A2	15-06-2005
		JP 2006508041 A	09-03-2006
		US 2004116346 A1	17-06-2004
		US 2004171541 A1	02-09-2004
		WO 2004005323 A2	15-01-2004
US 5939462 A	17-08-1999	AU 6144098 A	08-09-1998
		CA 2251368 A1	20-08-1998
		EP 0910565 A1	28-04-1999
		JP 2000510164 A	08-08-2000
		US 5939462 A	17-08-1999
		WO 9835957 A1	20-08-1998
SU 1596719 A1	10-09-1996	NONE	
US 2009118135 A1	07-05-2009	US 2009118135 A1	07-05-2009
		WO 2008154207 A1	18-12-2008
WO 2006045476 A2	04-05-2006	EP 1807701 A2	18-07-2007
		JP 2008516617 A	22-05-2008
		US 2009156521 A1	18-06-2009
		WO 2006045476 A2	04-05-2006