

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 July 2010 (22.07.2010)

PCT

(10) International Publication Number
WO 2010/081823 A1

(51) International Patent Classification:

A61K 31/55 (2006.01) A61K 31/554 (2006.01)
A61K 31/551 (2006.01) A61K 45/06 (2006.01)
A61K 31/5513 (2006.01) A61P 27/16 (2006.01)
A61K 31/553 (2006.01)

(21) International Application Number:

PCT/EP2010/050348

(22) International Filing Date:

13 January 2010 (13.01.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/144,204 13 January 2009 (13.01.2009) US
61/166,839 6 April 2009 (06.04.2009) US

(71) Applicant (for all designated States except US): **PROTEOSYS AG** [DE/DE]; Carl-Zeiss-Str. 51, 55129 Mainz (DE).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **SCHRATTENHOLZ, André** [DE/DE]; Frauenlobstr. 93a, 55118 Mainz (DE).

(74) Agent: **WEIB, Wolfgang**; Weickmann & Weickmann, Postfach 860 820, 81635 München (DE).

(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, RO, RS, RU, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (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, 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))

(54) Title: PIRENZEPINE AS OTOPROTECTIVE AGENT

(57) Abstract: The present invention generally relates to the otoprotective activity of condensed diazepinones, e.g. condensed benzodiazepines such as pirenzepine or compounds which are metabolized to condensed benzodiazepinones such as olanzapine. These compounds are suitable as medicaments for the prevention and/or treatment of otic diseases, e.g. diseases associated with loss of hearing.



WO 2010/081823 A1

Pirenzepine as otoprotective agent

Description

5

The present invention generally relates to the otoprotective activity of condensed diazepinones, e.g. condensed benzodiazepinones such as pirenzepine or compounds which are metabolized to condensed benzodiazepinones such as olanzapine. These compounds are suitable as
10 medicaments for the prevention and/or treatment of otic diseases, e.g. diseases associated with loss of hearing.

Pirenzepine (5,11-dihydro-11[(4-methyl-1-piperazinyl)-acetyl]-6H-pyrido-[2,3-b]-[1,4] benzodiazepine-6-one), is a topical antiulcerative M1 muscarinic
15 antagonist, that inhibits gastric secretion at lower doses than are required to affect gastrointestinal motility, salivary, central nervous system, cardiovascular, ocular, and urinary function. It promotes the healing of duodenal ulcers and due to its cytoprotective action is beneficial in the prevention of duodenal ulcer recurrence. It also potentiates the effect of
20 other antiulcer agents such as cimetidine and ranitidine. It is generally well tolerated by patients. The M1 muscarinic effect of pirenzepine is thought to be an explanation for this and a variety of additional effects in other indications, listed below.

25 WO 2006/008118 and WO 2006/008119 describe that pirenzepine and related compounds are inhibitors of PARP and SIR2. The use of these compounds as cytoprotective, particularly neuroprotective agents, is disclosed. The contents of these documents is herein incorporated by reference.

30

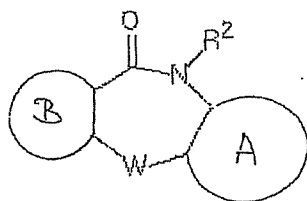
The administration of ototoxic agents or noise trauma may mediate apoptosis and/or necrosis of sensoric cells due to oxidative stress (Henderson et al., Ear Hear. 27 (2006), 1-19). In early stages of apoptosis a

- 2 -

massive activation of PARP-1 was detected (Yu et al., Science 297 (2002), 259-263). Further, it was found that PARP-1 activation causes a translocation of AIF (Apoptosis Inducing Factor) from the mitochondriae to the nucleus and an AIF-mediated PARP-1 dependent caspase-independent apoptosis (Yu et al., (2002), supra). PARP-1 hyperactivity is also associated with necrotic cell death (Virag and Szabo, Pharmacol Rev. 54 (2002), 375-429). Further it could be shown that the PARP-1 inhibitor 3-aminobenzamide alleviates cochlear dysfunctions induced by transient ischemia or acoustic trauma (Tabuchi et al., Ann. Otol. Rhinol. Laryngol. 110 (2001), 118-121; Tabuchi et al., J. Exp. Med. 200 (2003), 1995-2002).

According to the present invention it was found that pirenzepine and related compounds show significant otoprotective activity against administration of ototoxic drugs.

Thus, a first aspect of the present invention relates to the use of a compound of formula I



(I)

wherein A and B are five- or six-membered rings optionally containing at least one heteroatom selected from N, S and O, wherein the rings are optionally mono- or polysubstituted with halo, e.g. F, Cl, Br, or I, C₁-C₄-(halo)-alkyl, C₁-C₄-(halo)-alkoxy, amino, C₁-C₄-alkyl-amino, or di(C₁-C₄-alkyl) amino, W is S, O, NR¹ or CHR¹

R¹ is hydrogen, Y or COY,

R² is hydrogen or C₁-C₄-(halo)-alkyl, and

Y is C₁-C₆ (halo)alkyl, or C₃-C₈ cyclo-(halo)-alkyl, wherein the alkyl or cycloalkyl group is optionally substituted with a five- or six-membered ring

- 3 -

optionally containing at least one heteroatom selected from N, S and O, and wherein the ring is optionally mono- or poly-substituted with halo, C₁-C₄-(halo)alkyl, C₁-C₄(halo)alkoxy, amino, C₁-C₄-alkyl amino, di(C₁-C₄-alkyl)amino or Z,

- 5 wherein Z is a C₁-C₆ (halo) alkyl group ω-substituted with a group N(R₄)₂, wherein each R₄ is independently hydrogen, C₁-C₈ alkyl, or CO-C₁-C₈-alkyl or wherein both R₄ together form a five- or six-membered ring optionally containing at least one further heteroatom selected from N, S and O, wherein the ring is optionally mono- or polysubstituted with halo, C₁-C₄(halo)-
10 alkyl and C₁-C₄(halo) alkoxy,
or of a salt or derivative thereof for the manufacture of an otoprotective medicament.

The term „(halo)alkyl“ according to the present invention relates to an alkyl
15 group which optionally contains at least one halo, e.g. F, Cl, Br or I substituent up to perhalogenation.

The term „salt“ preferably refers to pharmaceutically acceptable salts of compounds of Formula I with suitable cations and/or anions. Examples of
20 suitable cations are alkaline metal cations such as Li⁺, Na⁺ and K⁺, alkaline earth metal cations such as Mg⁺ and Ca⁺ as well as suitable organic cations, e.g. ammoniums or substituted ammonium cations. Examples of pharmaceutically acceptable anions are inorganic anions such as chloride, sulfate, hydrogen sulfate, phosphate or organic cations such as acetate,
25 citrate, tartrate, etc.

Derivatives of compounds of Formula I are any molecules which are converted under physiological conditions to a compound of Formula I, e.g. esters, amides etc. of compounds of Formula I or molecules which are
30 products of metabolization reactions of a compound of Formula I.

Preferably, the compounds of Formula I are used for the prevention or treatment of otic PARP-1 associated disorders, i.e. otic disorders which are

- 4 -

caused by and/or accompanied by excitotoxicity and/or apoptosis, in particular mitochondrial apoptosis and/or calcium-related cell stress. For example, these disorders are selected from dysfunctions of middle or inner ear, e.g. cochlear disorders associated with partial or complete loss of hearing, particularly at higher frequency. Preferably, the invention refers to loss of hearing caused by aging, by noise trauma, e.g. by acute or chronic noise trauma, and/or by administration of ototoxic compounds, e.g. administration of chemotherapeutic agents, particularly platinum compounds such as cis-platinum or carboplatinum in cancer therapy or administration of antibiotics, such as aminoglycosides.

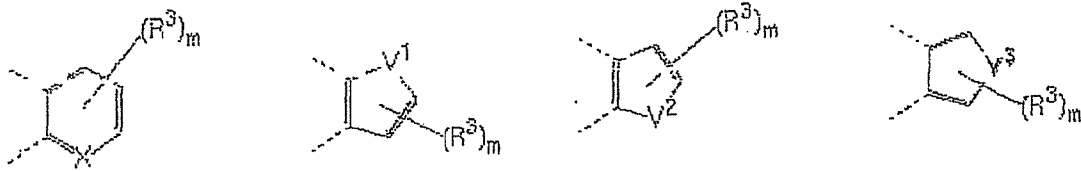
It was found that compounds of formula I prevent an irreversible loss of auditory sensory cells, e.g. outer or inner hair cells, which may be caused by and/or accompanied by aging, noise or toxic compounds.

For therapeutic applications, the compounds of Formula I may be used alone or together with other medicaments, e.g. together with other otoprotective medicaments such as other PARP-1 inhibitors and/or anti-excitatory medicaments such as memantine.

Particularly, the compounds of formula I may be administered to a subject who is under treatment with medicaments having ototoxic side effects, e.g. platinum compounds or aminoglycosides, in order to reduce and/or abolish the ototoxic side effects of such compounds.

Surprisingly, it was found that administration of the compounds of formula I does not negatively affect the cytotoxic anti-tumor activity of chemotherapeutic agents, e.g. cis-platinum.

In the compounds of Formula I, the cyclic groups A and B are preferably selected from



wherein X is N or CR₃,

V1, V2 or V3 are selected from -O-, -S-, and NR₆,

R₃ is in each case independently halo, C₁-C₄-(halo)-alkyl, C₁-C₄-(halo)-alkyl,

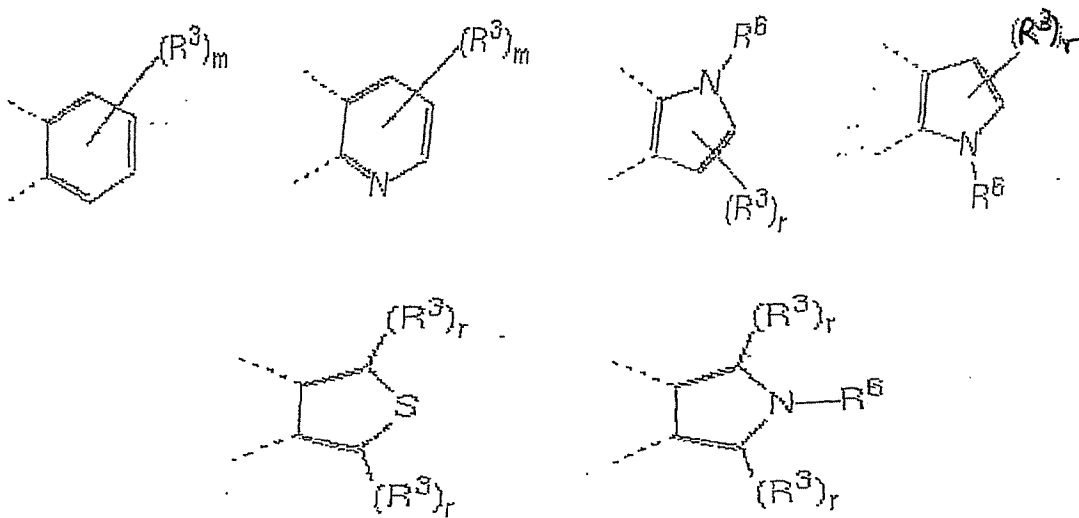
5 C₁-C₄-(halo)-alkoxy, amino, C₁-C₄-alkyl-amino, or di(C₁-C₄-alkyl) amino,

m is an integer of 0-2, and

R₆ is hydrogen or C₁-C₄-(halo)alkyl.

More preferably, the cyclic group A is selected from

10



wherein R₃ is defined as above,

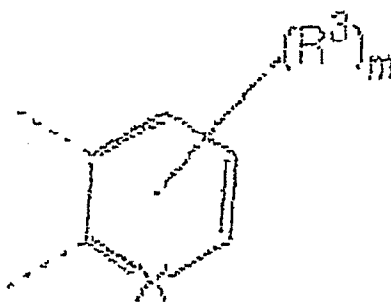
m is an integer of 0-2,

15 r is an integer of 0-1 and

R₆ is hydrogen or methyl.

More preferably, the cyclic group B is selected from

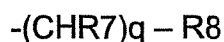
- 6 -



wherein X, R3 and m are as defined above

In one embodiment, R1 is Y. In this case Y is preferably C₃-C₆ cyclo(halo)-alkyl, e.g. cyclopropyl, cyclobutyl or cyclopentyl.

5 In a further embodiment, R1 is COY and Y is selected from

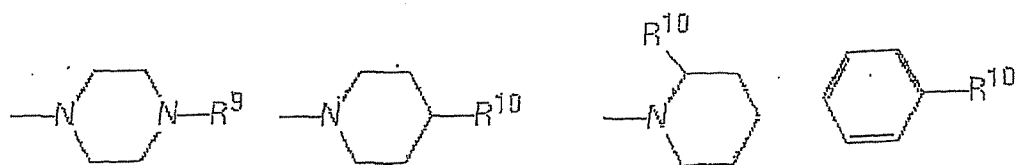


wherein R7 is hydrogen, halo or C₁-C₄-(halo)alkyl,

10 q is an integer of 1-4, and preferably 1 and

R8 is a five- or six-membered ring optionally containing at least one heteroatom, wherein the ring is optionally mono- or polysubstituted with C₁-C₄-(halo)alkyl or a ω -amino-substituted alkyl group Z as defined above.

15 In this embodiment, R8 is preferably selected from



wherein R9 is hydrogen or C₁-C₄-(halo)alkyl and R10 is a ω -amino-substituted alkyl group Z as defined above.

20

R9 is preferably a methyl group. The ω -amino-substituted alkyl group Z is preferably a C₁-C₄ (halo)alkyl group having a terminal amino group which is substituted with at least one C₁-C₆ alkyl group, e.g. a diethylamino, or di-

- 7 -

isobutylamino group, or with a CO (C₁-C₆) alkyl group and with hydrogen or a C₁-C₂ alkyl group.

Specific examples of compounds of Formula I are pirenzepine and related
5 compounds as disclosed in FR 1,505,795, U.S. Patents 3406168, 3660380,
4021557, 4210648, 4213984, 4213985, 4277399, 4308206, 4317823,
4335250, 4424222, 4424226, 4724236, 4863920, 5324832, 5620978,
6316423, otenzepad and related compounds as disclosed in US 3406168,
5324832 and 5712269, AQ-RA741 and related compounds as disclosed in
10 U.S. Patents 5,716,952, 5,576,436 and 5,324,832, viramune and related
compounds as disclosed in EP-A-0429987, and U.S. Patents 5366972,
5705499, BIBN 99 and related compounds as disclosed in U.S. Patents
6,022,683 and 5,935,781, DIBD, telenzepine and related compounds as
disclosed in EP-A-0035519, and U.S. Patent 4381301 and salts or
15 derivatives thereof. The above documents are herein incorporated by
reference.

Further preferred compounds are 7-azabicyclo-[2.2.1]-heptane and heptene
compounds such as a tiotropium bromide as disclosed in US Patents
20 5,817,679, 6,060,473, 6,077,846, 6,117,889, 6,255,490, 6,403,584,
6,410,583, 6,537,524, 6,579,889, 6,608,055, 6,627,644, 6,635,658,
6,693,202, 6,699,866 and 6,756,392, heterocyclic compounds, e.g.
pyrrolidinones, tetrahydropyridines, isoxazocarboxamides, thienopyrane
carboxamides, or benzopyranes, such as alvameline tartrate and related
25 compounds disclosed in US Patents 6,306,861, 6,365,592, 6,403,594,
6,486,163, 6,528,529, 6,680,319, 6,716,857 and 6,759,419,
metocloproamide and related compounds as disclosed in US Patent
3,177,252 and QNB and related compounds as disclosed in US Patent
2,648,667 and salts and derivatives thereof. The above documents are
30 herein incorporated by reference.

Further, the invention encompasses compounds which are metabolized to
give diaryl diazepinones according to Formula I such as clozapine and

olenzepine.

The compounds as indicated above are preferably administered to a subject in need thereof, e.g. a human subject, as a pharmaceutical composition, which may contain pharmaceutically acceptable carriers, diluents and/or adjuvants. The pharmaceutical composition may be administered in the form of a tablet, capsule, solution suspension, etc. The medicament may be administered according to any known means, wherein oral and intravenous administration is particularly preferred. Alternatively, the medicament may be directly administered to the ear.

The present application has applications in human and veterinary medicine, particularly in human medicine.

Furthermore, the present invention shall be explained by the following Figures and Examples.

Figure legends

Fig. 1 shows Otoprotection by pirenzepine (PSY 310).

In cultivated cochlea, a loss of sensory or hair cells was induced by administering cis-platin (5 μ M).

(A): Inner hair cells (IHC) and (B): Outer hair cells (OHC).

Left: Comparison of hair cell protection (preserved fraction) in wild-type (+/+) heterozygous (+/-) and homozygous (-/-) PARP-1 knock out mice.

Right: Addition of pirenzepine caused dosis dependent protection of sensory cells. The preserved cell fraction is significantly increased compared to controls.

Fig.2 shows Otoprotection by LS 75 (PSY 3101).

In cultivated cochlea, a loss of sensory or hair cells was induced by administering cis-platin (5 μ M).

5

(A): Inner hair cells (IHC) and (B): Outer hair cells (OHC).

Left: Comparison of hair cell protection (preserved fraction) in wild-type (+/+) heterozygous (+/-) and homozygous (-/-) PARP-1 knock out mice.

10

Right: Addition of LS 75 caused dosis dependent protection of sensory cells. The preserved cell fraction is significantly increased compared to controls.

Fig. 3 shows the survival rate of cis-platin (1.4 μ M) treated cancer cell lines (germ cell tumors 2101 Ep and NT2) without (black bars) or with simultaneous administration (grey bars) of 10 μ M PSY 301 (pirenzepine) or PSY 3103 (LS 75) compared to control (DMSO: 0.1 %).

15

Examples

20

Example 1

Otic protectivity of compounds PSY 310 (Pirenzepine) and PSY 3103 (LS 75)

25

1. Materials and Methods

Intact cochlea of post-natal mice were cultivated up to 7 days (Unsworth and Lelkes, Nat. Med. 4 (1998), 901-907) in simulated microgravity.

30

The otic protectivity of the test compounds PSY 310 and PSY 3101 in the presence of ototoxic agents was tested. Neomycin (an aminoglycoside antibiotic) and cis-platinum (a chemotherapeutic agent) were added in three different concentrations to the cultivate organ over a time period of 48 hours.

- 10 -

The test compounds were added in six different amounts of 0.1 to 100 μ M respectively.

2. Results

5

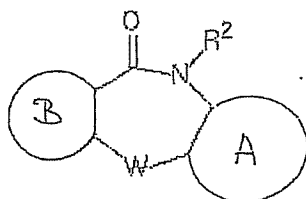
The results are shown in Fig. 1 and 2. Administration of pirenzepine and LS 75 resulted in a dose-dependent increase of the preserved fraction of inner and outer hair cells from the ototoxic effect of cis-platinum.

10

Fig. 3 shows that administration of pirenzepine and LS 75 does not reduce the (desired) cytotoxic effect of cis-platinum on germ cell tumor cell lines Ep 2101 and NT2.

Claims

- 5 1. Use of a compound of formula I



10 wherein A and B are a five- or six-membered ring optionally containing at least one heteroatom selected from N, S and O, wherein the ring is optionally mono- or polysubstituted with halo, C₁-C₄-(halo)-alkyl, C₁-C₄-(halo)-alkoxy, amino, C₁-C₄-alkyl-amino, or di(C₁-C₄-alkyl) amino,

W is S, O, NR₁ or CHR₁

R₁ is hydrogen, Y or COY,

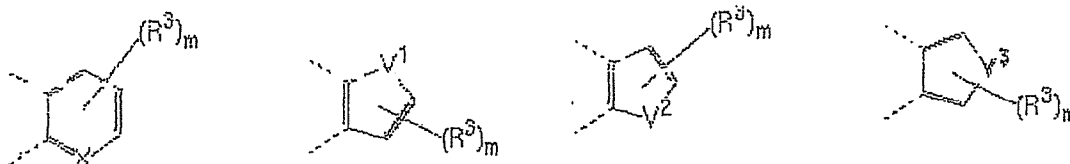
R₂ is hydrogen or C₁-C₄-(halo)-alkyl, and

15 Y is C₁-C₆ (halo)alkyl, or C₃-C₈ cyclo-(halo)-alkyl, wherein the alkyl or cycloalkyl group is optionally substituted with a five- or six-membered ring optionally containing at least one heteroatom selected from N, S and O, wherein the ring is optionally mono- or poly-substituted with halo, C₁-C₄-(halo)alkyl, C₁-C₄(halo)alkoxy, amino, C₁-C₄-alkyl amino, di(C₁-C₄-alkyl)amino or Z,

20 wherein Z is a C₁-C₆ (halo) alkyl group ω-substituted with a group N(R₄)₂, wherein each R₄ is independently hydrogen, C₁-C₈ alkyl, or CO-C₁-C₈-alkyl or wherein both R₄ together form a five- or six-membered ring optionally containing at least one further heteroatom selected from N, S and O, wherein the ring is optionally mono- or polysubstituted with halo, C₁-C₄(halo)-alkyl and C₁-C₄(halo) alkoxy,

25 or of a salt or derivative thereof for the manufacture of an otoprotective medicament.

2. The use of claim 1 for the manufacture of a medicament for the prevention or treatment of otic PARP-1-associated disorders.
- 5 3. The use of claim 1 or 2 for the manufacture of a medicament for the prevention or treatment of cochlear disorders associated with partial or complete loss of hearing particularly at higher frequency.
- 10 4. The use of any of claims 1-3 for the manufacture of a medicament for the prevention or treatment of loss of hearing caused by aging, by noise trauma and/or by administration of ototoxic compounds.
- 15 5. The use of claim 4 for the manufacture of a medicament for the prevention or treatment of loss of hearing caused by administration of chemotherapeutic agents, particularly platinum compounds such as cisplatin, or carboplatinum, or antibiotics, particularly aminoglycoside antibiotics.
- 20 6. The use of any one of claims 1-5 for administration to a subject who is under treatment of medicaments having ototoxic side effects.
7. The use of any of claims 1-6 wherein the cyclic groups A and B are selected from



wherein X is N or CR₃,

V1, V2 or V3 are selected from -O-, -S-, and NR₆,

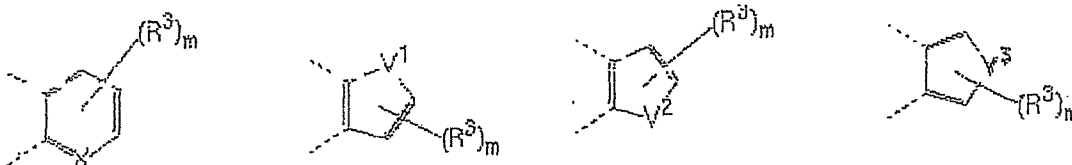
R₃ is halo, C₁-C₄-(halo)-alkyl, C₁-C₄-(halo)-alkoxy, amino, C₁-C₄-alkyl-amino, or di(C₁-C₄-alkyl) amino,

30 m is an integer of 0-2, and

- 13 -

R6 is hydrogen or C₁-C₄-(halo)alkyl.

8. The use of claim 7, wherein the cyclic groups A and B are selected from



wherein R₃ is defined as in claim 6,

m is an integer of 0-2,

r is an integer of 0-1 and

R₆ is hydrogen or methyl.

10

9. The use of any one of claims 1-8 wherein R₁ is Y and Y is C₃-C₈-cyclo(halo)alkyl.

10. The use of any one of claims 1-8 wherein R₁ is COY and Y is selected from

15

-(CHR₇)_q - R₈

wherein R₇ is hydrogen, halo or C₁-C₄-(halo)alkyl,

20

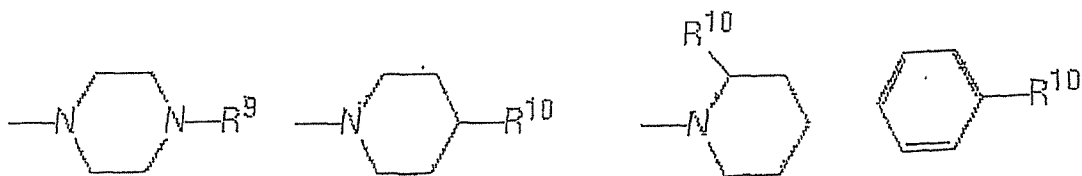
q is an integer of 1-4, and preferably 1 and

R₈ is a five- or six-membered ring optionally containing at least one heteroatom, wherein the ring is optionally mono- or polysubstituted with C₁-C₄-(halo)alkyl or a ω-amino-substituted alkyl group Z as defined in claim 1.

25

11. The use of claim 10 wherein R₈ is selected from

- 14 -



wherein R⁹ is hydrogen or C₁-C₄(halo)alkyl and R¹⁰ is a ω -amino-substituted alkyl group Z as defined in claim 1.

- 5
12. The use of any one of claims 1-11 wherein the compound of Formula I is selected from pirenzepine LS-75, otenzepad, AQ-RA741, viramune, BIBN 99, DIBD, telenzepine and salts or derivatives thereof.
 13. The use of any one of claims 1-12 for use in human medicine.

Figure 1

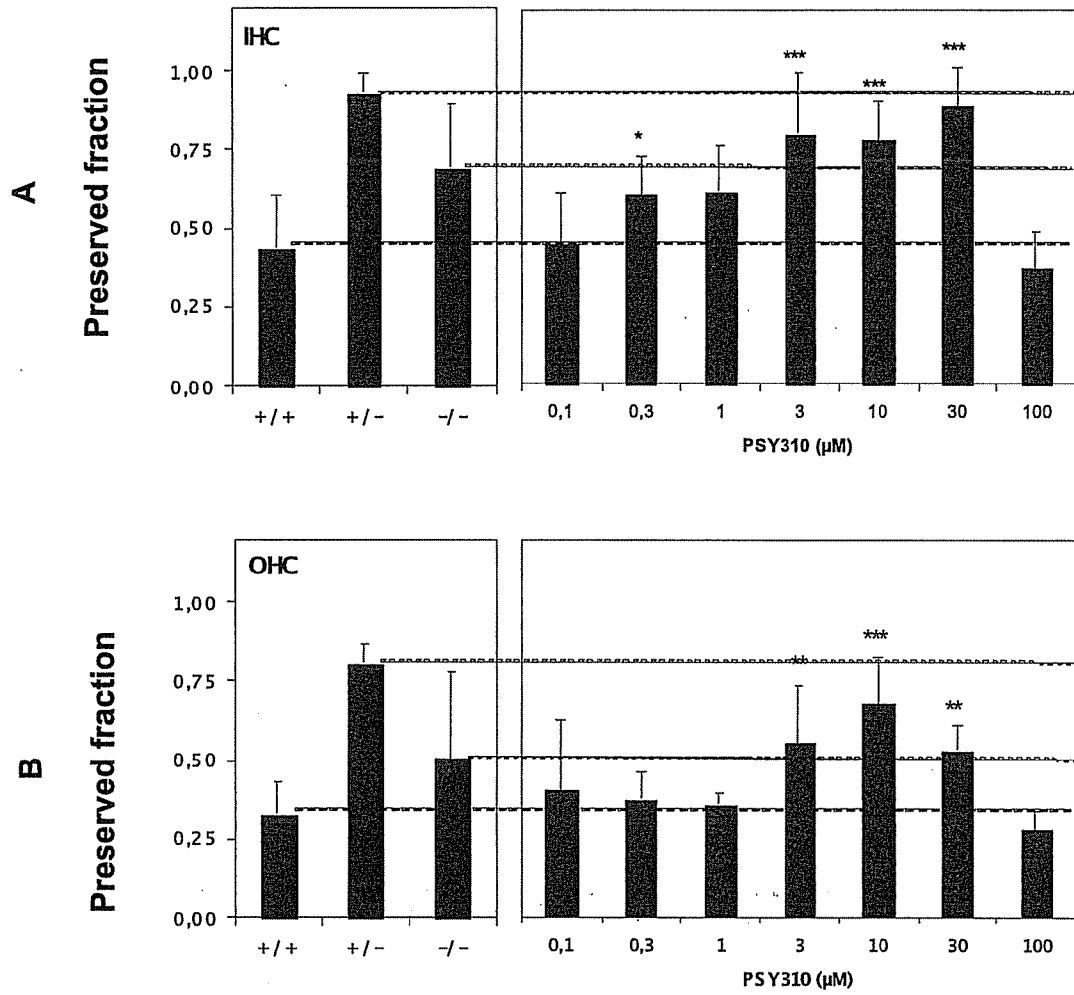


Figure 2

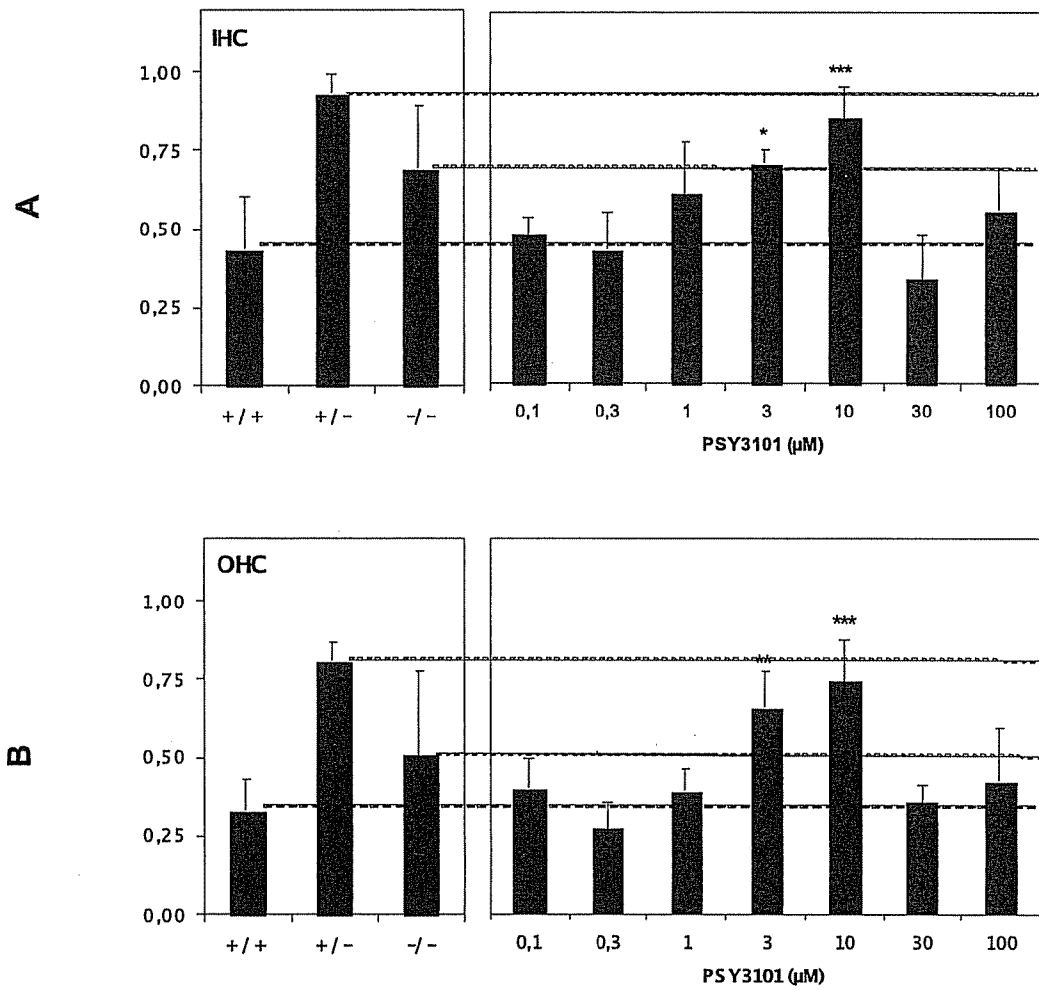
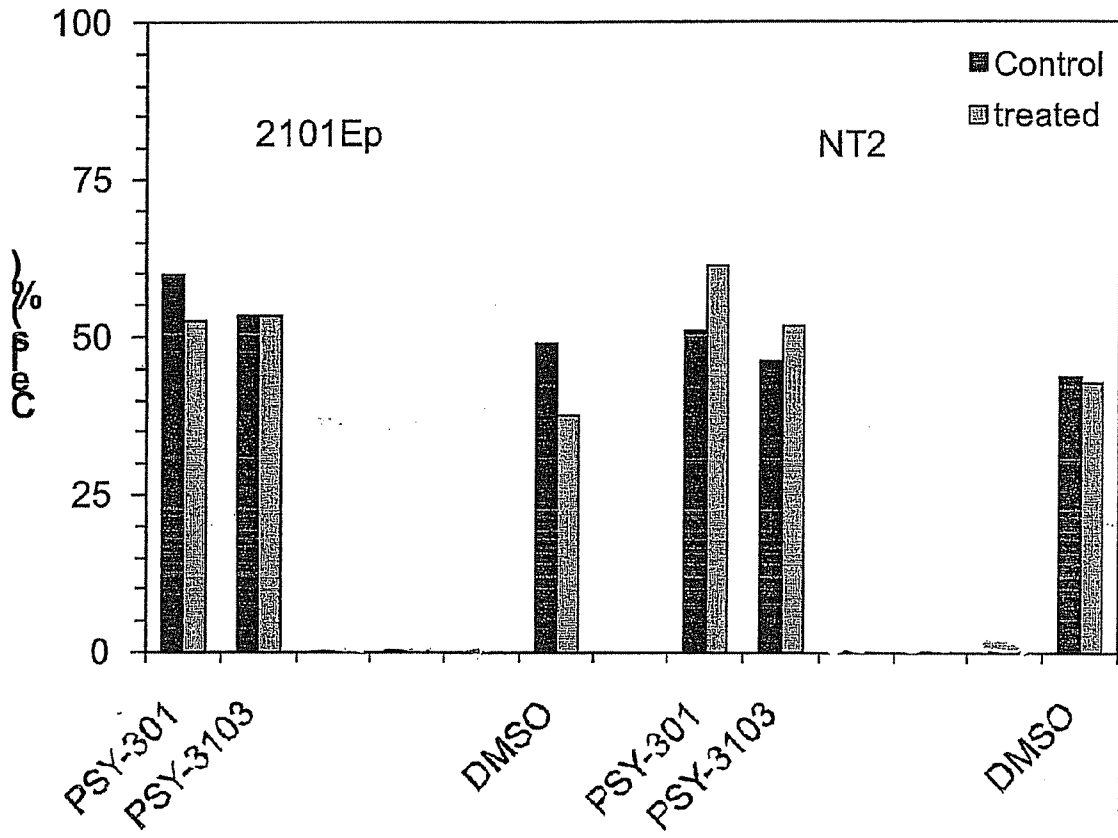


Figure 3



INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/050348

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	A61K31/55 A61K45/06	A61K31/551 A61P27/16
	A61K31/5513	A61K31/553
		A61K31/554
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) A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI 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 2007/056388 A2 (GEN HOSPITAL CORP [US]; KAZANTSEV ALEKSEY G [US]) 18 May 2007 (2007-05-18) page 1, line 24 - page 3, column 17 page 6, line 9 - line 24 table 1 page 17, line 9 - page 18, line 2 claims 1-5,18; figure 4	1-13
Y	TABUCHI KEIJI ET AL: "Involvement of Poly(ADP-ribose) synthetase in acoustic trauma of the cochlea." TOHOKU JOURNAL OF EXPERIMENTAL MEDICINE, vol. 200, no. 4, August 2003 (2003-08), pages 195-202, XP002573156 ISSN: 0040-8727 the whole document	1-13
----- -/--		
<input checked="" type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/>
		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	"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	
"E" earlier document but published on or after the international filing date	"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	
"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)	"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.	
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search	Date of mailing of the international search report	
15 March 2010	24/03/2010	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Hoff, Philippe	

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/050348

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WO 2006/008118 A1 (PROTEOSYS AG [DE]; SCHRATTENHOLZ ANDRE [DE]) 26 January 2006 (2006-01-26) page 1, paragraph 1 page 9, line 28 - page 10, line 10 page 26, line 21 - page 27, line 24; claims</p>	1-13
Y	<p>TABUCHI K ET AL: "Poly(adenosine diphosphate-ribose) synthetase inhibitor 3-aminobenzamide alleviates cochlear dysfunction induced by transient ischemia." THE ANNALS OF OTOTOLOGY, RHINOLOGY, AND LARYNGOLOGY FEB 2001, vol. 110, no. 2, February 2001 (2001-02), pages 118-121, XP8119895 ISSN: 0003-4894 the whole document</p>	1-13
A	<p>WO 2006/008119 A1 (PROTEOSYS AG [DE]; SCHRATTENHOLZ ANDRE [DE]) 26 January 2006 (2006-01-26) abstract; claims</p>	1-13
A	<p>KUJAWA S G ET AL: "A nicotinic-like receptor mediates suppression of distortion product otoacoustic emissions by contralateral sound" HEARING RESEARCH, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 74, no. 1-2, 1 April 1994 (1994-04-01), pages 122-134, XP024396452 ISSN: 0378-5955 [retrieved on 1994-04-01] the whole document</p>	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/050348

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007056388	A2	18-05-2007	NONE
<hr style="border-top: 1px dashed black;"/>			
WO 2006008118	A1	26-01-2006	AU 2005263577 A1 26-01-2006
			AU 2005263578 A1 26-01-2006
			CA 2573673 A1 26-01-2006
			CA 2573674 A1 26-01-2006
			EP 1768674 A1 04-04-2007
			EP 1781300 A1 09-05-2007
			WO 2006008119 A1 26-01-2006
			JP 2008506660 T 06-03-2008
			JP 2008506661 T 06-03-2008
			US 2007265251 A1 15-11-2007
<hr style="border-top: 1px dashed black;"/>			
WO 2006008119	A1	26-01-2006	AU 2005263577 A1 26-01-2006
			AU 2005263578 A1 26-01-2006
			CA 2573673 A1 26-01-2006
			CA 2573674 A1 26-01-2006
			EP 1768674 A1 04-04-2007
			EP 1781300 A1 09-05-2007
			WO 2006008118 A1 26-01-2006
			JP 2008506660 T 06-03-2008
			JP 2008506661 T 06-03-2008
			US 2007265251 A1 15-11-2007
<hr style="border-top: 1px dashed black;"/>			