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(54) Title: USE OF (HALOBENZYLOXY)BENZYLAMINO-PROPANAMIDES FOR THE MANUFACTURE OF MEDICAMENTS ACTIVE AS SODIUM AND/OR CALCIUM CHANNEL SELECTIVE MODULATORS

(57) Abstract: The invention relates to the use of selected (R) -2-[(halobenzyloxy)benzylamino]-propanamides and the pharmaceutically acceptable salts thereof for the manufacture of medicament, that are selectively active assodium and/or calcium channel modulators and therefore useful in preventing, alleviating and curing a wide range of pathologies, including, pain, migraine, periferal diseases, cardiovascular diseases, inflammatory processes affecting all body systems, disorders affecting skin and related tissues, disorders of the respiratory system, disorders of the immune and endocrinological systems, gastrointestinal, urogenital, metabolic and seizure disorders, where the above mechanisms have been described as playing a pathological role.

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**USE OF (HALOBENZYLOXY) BENZYLAMINO-PROPANAMIDES FOR THE
MANUFACTURE OF MEDICAMENTS ACTIVE AS SODIUM AND/OR CALCIUM
CHANNEL SELECTIVE MODULATORS**

5 The present invention relates to the use of a
(halobenzoyloxy)benzylamino-propanamide selected from:

(R)-2-[4-(2-fluorobenzoyloxy)benzylamino]propanamide and

(R)-2-[4-(2-chlorobenzoyloxy)benzylamino]-N-

methypropanamide

10 and the pharmaceutically acceptable salts thereof, for the
manufacture of a medicament selectively active as sodium
and/or calcium channel modulator useful in preventing,
alleviating and curing a wide range of affections where said
mechanism(s) play(s) a pathological role, including, pain,
15 migraine, cardiovascular, inflammatory, urogenital,
metabolic and gastrointestinal diseases, characterized in
that said medicament is substantially free from any MAO
inhibitory effect or exhibits a significantly reduced MAO
inhibitory effect at dosages that are therapeutically
20 effective in preventing, alleviating and/or curing said
affections.

A further aspect of the invention relates to a method
of selective treatment of the above said affections, which
method comprises administering to a patient in need thereof
25 a therapeutically effective amount of the above listed (R)-
(halobenzoyloxy)benzylamino-propanamides wherein the
therapeutic activity of said compounds is substantially free
from any MAO inhibitory side effect or exhibits
significantly reduced MAO inhibitory side effect.

30 **BACKGROUND OF THE INVENTION**

Chemical background

Substituted benzylaminopropionamide derivatives active on
the central nervous system and useful as anti-epileptic, anti-
Parkinson, neuroprotective, antidepressant, and antispastic

hypnotic agents are disclosed in International Patent Applications Publ. No. WO90/14334, WO94/22808, WO97/05102, and WO 97/05111 (see also Pevarello P. et al. "Synthesis and anticonvulsant activity of a new class of 2-
5 [(arylalkyl)amino]alkanamide derivatives", *J. Med. Chemistry*, 1998, 41, 579-590). Moreover, International Patent Applications Publ. No. WO 99/26614, WO99/35123 and WO99/35125 disclose substituted alpha aminoamide derivatives active on the central nervous system and useful as analgesic agents.

10 WO 03/020273 discloses pharmaceutical compositions comprising selected α -aminoamide derivatives and gabapentin, pregabalin or tiagabine.

WO 04/062655 discloses the use of certain α -aminoamide derivatives for the manufacture of medicaments for the
15 treatment of head pain conditions.

WO 05/018627 discloses α -aminoamide derivatives as anti-inflammatory agents.

WO 04/066987 discloses method of treating gastrointestinal tract disorders using sodium channel
20 modulators.

WO 04/066990 discloses method of treating lower urinary tract disorders using sodium channel modulators.

PCT/EP/2005/000514 discloses α -aminoamide derivatives useful in the treatment of lower urinary tract disorders.

25

Biological background

It is well known that sodium channels play an important role in the neuronal network by transmitting electrical impulses rapidly throughout cells and cell networks, thereby
30 coordinating higher processes ranging from locomotion to cognition. These channels are large transmembrane proteins, which are able to switch between different states to enable selective permeability for sodium ions. For this process an

action potential is needed to depolarize the membrane, and hence these channels are voltage-gated. In the past few years a much better understanding of sodium channels and drugs interacting with them has been developed.

5 It has become clear that a number of drugs having an unknown mechanism of action actually act by modulating sodium channel conductance, including local anesthetics, class I antiarrhythmics and anticonvulsants. Neuronal sodium channel blockers have found application with their use in
10 the treatment of epilepsy (phenytoin and carbamazepine), bipolar disorder (carbamazepine, lamotrigine), preventing neurodegeneration, and in reducing neuropathic pain. Various anti-epileptic drugs that stabilize neuronal excitability are effective in neuropathic pain (gabapentin, pregabalin).

15 In addition, an increase in sodium channel expression or activity has been observed in several models of inflammatory pain, suggesting a role of sodium channels in inflammatory pain.

Calcium channels are membrane-spanning, multi-subunit
20 proteins that allow entry of calcium ions into cells from the extracellular fluid. Commonly, calcium channels are voltage dependent and are referred to as voltage sensitive calcium channels (VSCC). VSCCs are found throughout the mammalian nervous system, where they regulate such varied
25 activities as cellular excitability, transmitter release, intracellular metabolism, neurosecretory activity and gene expression. All "excitable" cells in animals, such as neurons of the central nervous system (CNS), peripheral nerve cells, and muscle cells, including those of skeletal
30 muscles, cardiac muscles and venous and arterial smooth muscles, have voltage dependent calcium channels. Calcium channels have a central role in regulating intracellular calcium ions levels that are important for cell viability and function. Intracellular calcium ion concentrations are
35 implicated in a number of vital processes in animals, such

as neurotransmitter release, activation of second messengers and signal transduction systems, muscle contraction, pacemaker activity, and secretion of hormones. It is believed that calcium channels are relevant in certain disease states. A number of compounds useful in treating various cardiovascular diseases in mammals, including humans, are thought to exert their beneficial effects by modulating functions of voltage dependant calcium channels present in cardiac and/or vascular smooth muscle. Compounds with activity against calcium channels have also been used for the treatment of pain. In particular, N-type calcium channels (Cav2.2), responsible for the regulation of neurotransmitters, are thought to play a significant role in nociceptive transmission, as shown in several pharmacological studies. This hypothesis has been validated in the clinic by Ziconotide, a peptide derived from the venom of the marine snail, *Conus Magus*. A limitation in the therapeutic use of this peptide is that it has to be administered intrathecally in humans (Bowersox S. S. and Luther R. *Toxicon*, 1998, 36, 11, 1651-1658).

All together these findings indicate that compounds with sodium and/or calcium channel blockade have a high therapeutic potential in preventing, alleviating and curing a wide range of pathologies, including pain, migraine, cardiovascular, urogenital, metabolic and gastrointestinal diseases, where the above mechanisms have been described as playing a pathological role.

Many papers and patents describe sodium channel and/or calcium channel modulators or antagonists for treating and/or modulating a plethora of disorders. Several local anesthetics, antiarrhythmics, antiemetics, antihypertensive, mood stabilizers, agents for the treatment of unipolar depression, cardiovascular diseases, urinary incontinence, diarrhea, inflammation, stroke, epilepsy, neurodegenerative conditions, nerve cell death,

anticonvulsants, neuropathic pain, migraine, acute hyperalgesia and inflammation, renal disease, allergy, asthma, bronchospasm, dysmenorrhea, esophageal spasm, glaucoma, urinary tract disorders, gastrointestinal motility disorders, premature labour, obesity are able to modulate these channels.

A selection of references is reported below:

C. Alzheimer describes in Adv. Exp. Med. Biol. 2002, 513, 161-181, sodium and calcium channels as targets of neuroprotective substances.

Vanegas e Schaible (Pain 2000, 85, 9-18) discuss effects of antagonists of calcium channels upon spinal mechanisms of pain, hyperalgesia and allodynia.

U.S. Patent 5,051,403 relates to a method of reducing neuronal damage associated with an ischemic condition, such as stroke, by administration of binding/inhibitory omega-conotoxin peptide wherein the peptide is characterized by specific inhibition of voltage-gated calcium channel currents selectively in neuronal tissues.

U.S. Patent 5,587,454 relates to compositions and methods of producing analgesia particularly in the treatment of pain and neuropathic pain.

U.S. Patent 5,863,952 relates to calcium channel antagonists for the treatment of ischaemic stroke.

U.S. Patent 6,011,035 relates to calcium channel blockers, useful in the treatment of conditions such as stroke and pain.

U.S. Patent 6,117,841 relates to calcium channel blockers and their use in the treatment of stroke, cerebral ischemia, pain, head trauma or epilepsy.

U.S. Patent 6,362,174 relates to N-type calcium channel blockers in the treatment of stroke, cerebral ischemia, pain, epilepsy, and head trauma.

U.S. Patent 6,380,198 concerns the use of the calcium channel blocker flunarizine for the topical treatment of

glaucoma.

U.S. Patent 6,420,383 and U.S. Patent 6,472,530 relate to novel calcium channel blockers, useful for treating and preventing a number of disorders such as hypersensitivity, allergy, asthma, bronchospasm, dysmenorrhea, esophageal spasm, glaucoma, premature labor, urinary tract disorders, gastrointestinal motility disorders and cardiovascular disorders.

U.S. Patent 6,458,781 relates to compounds that act to block calcium channels and their use to treat stroke, cerebral ischemia, pain, head trauma or epilepsy.

U.S. Patent 6,521,647 relates to the the use of calcium channel blockers in the treatment of renal disease in animals, especially chronic renal failure.

WO 97/10210 relates to tricyclic heterocyclic derivatives, and their use in therapy, in particular as calcium channel antagonists, e.g. for the treatment of ischaemia, in particular ischaemic stroke.

WO 03/018561 relates to quinoline compounds as N-type calcium channel antagonists and methods of using such compounds for the treatment or prevention of pain or nociception.

WO 03/057219 relates to sodium channel blockers useful as agents for treating or modulating a central nervous system disorder, such as neuropathic pain, inflammatory pain, inflammation-related pain or epilepsy.

Monoamine oxidase (MAO) is an enzyme present in the outer mitochondrial membrane of neuronal and non-neuronal cells. Two isoforms of MAO exist: MAO-A and MAO-B. MAO enzymes are responsible for the oxidative deamination of endogenous and xenobiotic amines, and have a different substrate preference, inhibitor specificity, and tissue distribution. For MAO-A serotonin, noradrenaline and adrenaline are preferential substrates, and clorgyline is a selective MAO-A inhibitor; whereas MAO-B prefers β -

phenylethylamine as a substrate, and is selectively inhibited by selegiline. Dopamine, tyramine and tryptamine are oxidized by both MAO-A and MAO-B, in particular in human brain dopamine is deaminated by 80% by MAO-B.

5 MAO inhibition allows endogenous and exogenous substrates to accumulate and may thereby, when almost fully inhibited (>90%), alter the dynamics of regular monoamine transmitters. MAO regulate the concentrations in the brain of the most important neurotransmitters such as
10 noradrenaline, serotonin and dopamine which are related to emotion, anxiety and movement. Thus, MAO activity is thought to be closely linked to various psychiatric and neurological disorders such as depression, anxiety and Parkinson's disease (PD) and aging in general.

15 MAO-A inhibitors are mainly used in psychiatry for the treatment of major, refractory and atypical depression as a consequence of their ability to increase the reduced serotonin and noradrenalin brain levels. More recently, MAO-A inhibitors have been used to treat patients with anxiety
20 disorders such as social phobia, panic disorders, post-traumatic stress disorders and obsessive compulsive disorders.

MAO-B inhibitors are mainly used in neurology for the treatment of PD.

25 There is also recent evidence and interest in the role of MAO-B in other pathological conditions such as Alzheimer disease (AD). So far no evidence have been reported on MAO-B involvement in the metabolism of co-transmitters, such as colecystokinin, substance P, somatostatin and neurotensin,
30 which are involved in the modulation of pain sensation. For this reason there is no scientific rationale for the use of MAO-B inhibitors in pain syndromes.

Adverse drug reactions during clinical practice with MAO inhibitors have been reported. First generation of non-
35 selective and irreversible MAO inhibitors, such as

tranylcypromide and phenelzine, have serious side effects, including hepatotoxicity, orthostatic hypotension and most importantly hypertensive crisis that occurs following the ingestion of foods containing tyramine (Cooper AJ.-Tyramine and irreversible monoamine oxidase inhibitors in clinical practice.- *Br J Psych Suppl* 1989:38-45).

When these non-selective and irreversible MAO inhibitors are used, a strict tyramine-reduced diet must be observed. The pressor sensitivity towards tyramine is normalized 4 weeks after cessation of tranylcypromide therapy and more than 11 weeks after cessation of phenelzine therapy.

Selegiline, a selective and irreversible MAO-B inhibitor, especially when used in combination with levodopa in patients with PD, can cause anorexia/nausea, dry mouth, dyskinesia and orthostatic hypotension, the latter being most problematic (Volz H.P. and Gleiter C.H.- Monoamine oxidase inhibitors. A perspective on their use in the elderly.- *Drugs Aging* 13 (1998), pp. 341-355).

In monotherapy, anorexia/nausea, musculoskeletal injuries, and cardiac arrhythmias occurred more often in patients receiving selegiline compared with those receiving placebo. Apart from these adverse effects, increased rates of elevated serum AST and ALT levels were noted.

The most frequently reported adverse effect of moclobemide, a selective and reversible MAO-A inhibitor, are sleep disturbances, increased anxiety, restlessness, and headache.

The combination of selective serotonin reuptake inhibitors (SSRIs) and moclobemide has good efficacy in cases of refractory depression, but has created controversy as to whether toxic side effects, such as serotonergic syndrome, result from this combination (Baumann P.- Pharmacokinetic-pharmacodynamic relationship of the selective serotonin reuptake inhibitors. *Clin Pharmacokinet*

31 (1996), pp 444-469). Because of cardiac arrhythmias and increased liver enzyme levels, electrocardiogram and laboratory values should be checked regularly.

Many types of physiologic changes that occur with aging affect the pharmacodynamics and pharmacokinetics of MAO inhibitors. Indeed, pharmacokinetic variables in the elderly are markedly different from those in younger patients. These variables including absorption, distribution, metabolism and excretion have to be taken into account to avoid or minimize certain adverse effects and drug-drug interactions. Elderly patients are generally more susceptible to side effects, including adverse drug reactions. Hypertensive crisis may occur more frequently in elderly, because the cardiovascular system of the elderly is compromised by age.

The use of sympathomimetic drugs in combination with MAO inhibitors may also elevate blood pressure. In addition, compared with placebo, phenelzine was associated with a significantly higher incidence of drowsiness, tremor, dyskinesia, diarrhea, micturition difficulties, orthostatic effects, and adverse dermatological effects. It is interesting to note that in the elderly, headache is reported with a higher frequency during treatment with moclobemide (Volz H.P. and Gleiter C.H.- Monoamine oxidase inhibitors. A perspective on their use in the elderly. *Drugs Aging* 13 (1998), pp. 341-355).

MAO inhibitors are sometimes prescribed for depression. Because of the potential risk of suicide, adverse drug reactions and toxicity due to overdose are important factors to consider when choosing an antidepressant. In addition, when MAO inhibitors are used in high dosage, adverse cardiovascular effects seem to increase considerably; and because, with most available drugs, MAO selectivity is lost with such high doses, tyramine can induce potentially dangerous hypertensive reactions. Acute overdose with MAO inhibitors causes agitation, hallucinations, hyperpyrexia,

hyperreflexia and convulsions. Abnormal blood pressure is also a toxic sign, so that gastric lavage and maintenance of cardiopulmonary function may be required. Overdose of traditional non-selective and irreversible MAO inhibitors are considerably dangerous and sometimes fatal (Yamada and Richelson, 1996. Pharmacology of antidepressants in the elderly. In: David JR, Snyder L., editors. Handbook of pharmacology of aging. Boca Raton: CRC Press 1996).

In the treatment of the affections wherein sodium and calcium channels mechanism(s) play(s) a pathological role and, in particular, of pain syndromes (either of neuropathic or inflammatory type) inhibition of MAO enzymes is of no benefits. The most clinically active anti-nociceptive drugs are devoid of MAO inhibition. On the contrary, MAO inhibitory side effects may impose at least two types of negative limitations.

- 1) Dietary: eating food with high tyramine content may cause severe, even life threatening increase of systemic blood pressure (the so called "cheese-effect").
- 2) Pharmacological: pain is often treated with a combination of drugs such as opioid derivatives and tricyclic antidepressant. With MAO inhibitors such association is dangerous as it may cause the serotonergic syndrome (agitation, tremors, hallucination, hyperthermia and arrhythmias).

Thus, eliminating or significantly reducing MAO inhibitory activity in medicaments active as sodium and/or calcium channel modulators useful in preventing, alleviating and curing a wide range of pathologies where said mechanism(s) play(s) a pathological role, (such as pain, migraine, cardiovascular, inflammatory, urogenital, metabolic and gastrointestinal diseases) is an unexpected and substantial therapeutic improvement versus compounds of similar efficacy but with the above mentioned side effects. Said improvement is particularly desirable for the

medicaments active as sodium and/or calcium channel modulators useful, in particular, for the treatment of pain syndromes.

5 Taken into account these findings on MAO inhibitors and, in particular, lacking any evidence for a MAO-B role in pathological affections like pain, migraine, cardiovascular, inflammatory, urogenital, metabolic and gastrointestinal diseases, compounds indicated in these above conditions should not possess MAO-B inhibitory
10 activity, which if present may increment undesired adverse events.

Medicaments which are "selectively active as sodium and/or calcium modulators" or a useful for the "selective treatment" of pathological affections, disorders or diseases
15 wherein the sodium and/or calcium channel mechanism(s) play(s) a pathological role should be preferred. With this expression are intended medicaments which, when administered to a patient in need thereof in amounts that are effective in the treatment of the above said affections wherein the
20 above said mechanism(s) play(s) pathological role, do not exhibit any MAO inhibitory activity or exhibit a significantly reduced MAO inhibitory activity, thus resulting in avoidance of side effects due to accumulation of endogenous and exogenous monoamine transmitters.

25 It is a primary object of this invention the use of selected (halobenzyloxy)-benzylamino-propanamides for the manufacture of medicaments active as sodium and/or calcium channel modulators for the treatment of pathologies where the above said mechanism(s) play(s) a pathological role,
30 said medicaments being substantially free from any MAO-B inhibitory activity or having significantly reduced MAO inhibitory activity and, therefore, having a reduced potential for unwanted side effects. Said use provides an improved selective resource for the prevention, alleviation
35 and/or cure of the above said pathological affections.

DESCRIPTION OF THE INVENTION

The object of the present invention relates to the use of a (R)-2-[(halobenzyloxy)benzylamino]-propanamide selected from:

5 (R)-2-[4-(2-fluorobenzyloxy)benzylamino]propanamide, and
(R)-2-[4-(2-chlorobenzyloxy)benzylamino]-N-methylpropanamide
and the pharmaceutically acceptable salts thereof for the
manufacture of a medicament selectively active as sodium
and/or calcium channel modulator useful in preventing,
10 alleviating and/or curing affections where said mechanism(s)
play(s) a pathological role, characterized in that said
medicament is substantially free from any MAO inhibitory
effect or exhibits a significantly reduced MAO inhibitory
effect at dosages that are therapeutically effective in
15 preventing, alleviating and/or curing said affections.

Said diseases include, but are not limited to pain,
migraine, cardiovascular, inflammatory, urogenital,
metabolic and gastrointestinal diseases and seizure
disorders. According to a further aspect of this invention,
20 the affections that can be prevented, alleviated or cured
with the above mentioned compounds and the pharmaceutically
acceptable salts thereof preferably consist in pain
syndromes (either of neuropathic and/or inflammatory type)
and/or migraine, and/or urogenital and/or gastrointestinal
25 diseases and/or seizure disorders.

These compounds have sodium and/or calcium channel
modulating activity with an unexpected selectivity profile
when compared to other derivatives of the same chemical
class which are active as sodium and/or calcium channel
30 modulators and, in particular, when compared to the
corresponding S-isomers. Indeed, it has been shown, through
predictive pharmacological tests, that the ratio between the
doses of the invention compounds active as sodium and/or
calcium channel modulators and the doses of the same
35 products active as MAO-B enzyme inhibitors decreases in an

unexpected and significant manner.

In this description and claims, the expression "sodium and/or calcium channel modulator(s)" means compounds able to block sodium and/or calcium currents in a voltage dependent
5 manner.

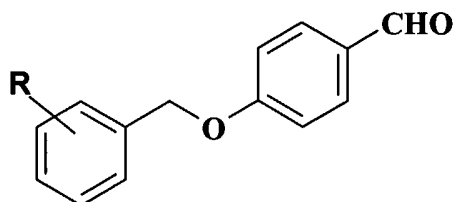
The compound (R)-2-[4-(2-fluorobenzyloxy)benzylamino]propanamide is mentioned as a single isomer or racemate mixture in EP 1045830 B1 (and WO 99/35125) without any specific information about its
10 preparation and characterization.

The compound (R)-2-[4-(2-chlorobenzyloxy)benzylamino]-N-methylpropanamide is disclosed in the form of the respective salt with methanesulfonic acid in EP 0400495 B1 (and WO 90/14334).

15 It is also an object of this invention to provide a method for selectively preventing, alleviating and/or curing pathological affections where sodium and/or calcium channel mechanism(s) play(s) a pathological role, which method comprises administering to a patient in need thereof a
20 therapeutically effective amount of a (R)-2-[(halobenzyloxy)benzylamino]-propanamide selected from: (R)-2-[4-(2-fluorobenzyloxy)benzylamino]propanamide and (R)-2-[4-(2-chlorobenzyloxy)benzylamino]-N-methylpropanamide and the pharmaceutically acceptable salts thereof, wherein
25 the therapeutic activity of said compound is substantially free from any MAO inhibitory side effect or exhibits significantly reduced MAO inhibitory side effect.

According to a further aspect of the above said method of this invention, the pathological affections where the
30 sodium or calcium channel mechanism(s) play(s) a pathological role include pain, migraine, cardiovascular, inflammatory, urogenital, methabolic and gastrointestinal diseases and seizure disorders; preferably, said pathological affections comprise pain syndromes either of
35 neuropathic or inflammatory type.

The compounds of the invention and the salts thereof can be obtained by a process comprising the reaction of compounds of general formula **I**

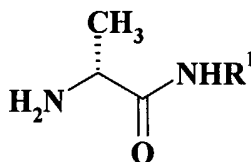


5

I

wherein R represents a 2-fluoro or 2-chloro substituent with a compound of formula **II**

10

**II**

wherein R¹ represents hydrogen, when R in the compound of formula **II** represents a 2-fluoro substituent, or a methyl group, when R in the compound of formula **II** represents a 2-chloro substituent.

15

Compounds **I**, and **II** are commercially available compounds.

The reaction of a compound of formula **I** with the compound of formula **II** to give the corresponding (R)-2-[(halobenzyloxy)benzylamino]-propanamide, is a reductive amination reaction, which can be carried out according to well known methods. According to a preferred embodiment of the invention, it may be performed under nitrogen atmosphere, in a suitable organic solvent, such as an alcohol, e.g. a lower alkanol, in particular methanol, or in acetonitrile, or in tetrahydrofuran, at a temperature ranging from about 0°C to about 80°C, in the presence of a

20

25

reducing agent, the most appropriate being sodium borohydride or sodium cyanoborohydride. Occasionally Titanium IV isopropylate and molecular sieves can be added to the reaction mixture for facilitating the reaction.

5 **PHARMACOLOGY**

The compounds of the invention are voltage dependent blockers of the calcium and/or sodium channels as demonstrated by fluorescence calcium influx assay and electrophysiological studies.

10 The sodium channel modulating activity of the selective (R)-2-[(halobenzyloxy)benzylamino]-propanamides was measured through electrophysiological assays using the two electrodes voltage clamp (TEVC) technique in isolated *Xenopus* oocytes expressing the Na channel Nav 1.3.

15 The N-type calcium channel modulating activity of the (R)-2-[(halobenzyloxy)benzylamino]-propanamides was measured through a fluorescence based calcium influx assay.

The MAO-B blocking activity of the above compounds was measured by using an in-vitro enzyme activity assay.

20 The *in-vivo* activity of the above compounds as analgesics was assessed through a mice formalin test.

The selectivity of the compounds of this invention has been evaluated by comparison with other 2-[(halobenzyloxy)benzylamino]-propanamide derivatives that
25 are known to be active as analgesics, according to EP 1045830 B1, in particular, in comparison with the respective (S)-isomers and with both the (R) and (S) isomer of 2-[4-(3-chlorobenzyloxy)benzylamino]propanamide.

30 These comparison tests show that while the (R)-isomers of this invention have substantially the same degree of analgesic activity as the comparison compounds, their activity as MAO-B blockers is at least 40-90 fold lower than that of the comparison compounds.

35 In addition, the ratio between the doses of the R-isomers of this invention, active as Na⁺ and/or Ca⁺

modulators and the doses of the same products active as MAO-B enzyme inhibitors is much lower than that of the comparison compounds, thus providing a further confirmation of their selective profile.

5 Such substances also exhibit "use-dependency" when the sodium channels are blocked i.e. maximum blockage of the sodium channels is only achieved after repeated stimulation of the sodium channel. Consequently, the substances preferably bind to sodium channels which are multiply
10 activated. As a result the substances are capable of activity preferentially in those regions of the body which are pathologically over-stimulated, as illustrated by patch-clamp experiments which show that the compounds according to the invention block the electrically stimulated sodium
15 channel in a "use-dependent" manner.

As a consequence of these mechanisms the compounds of the invention are active in vivo when orally administered in the range of 0.1 to 100 mg/kg in the formalin animal model of persistent pain.

20 In view of the above described mechanisms of action, the compounds of the present invention are particularly useful in the selective treatment or prevention of neuropathic pain. Neuropathic pain syndromes include, and are not limited to: diabetic neuropathy; sciatica; non-
25 specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; neuralgia, such as post-herpetic neuralgia and trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions; spinal cord, nerve root
30 peripheral nerve and central pain pathways compressions.

The compounds of the invention are also useful for the selective treatment of chronic pain. Chronic pain includes, and is not limited to, chronic pain caused by inflammation or an inflammatory-related condition, osteoarthritis,
35 rheumatoid arthritis or as sequela to disease, acute injury

or trauma and includes upper back pain or lower back pain (resulting from systematic, regional or primary spine disease (such as radiculopathy), bone pain (due to osteoarthritis, osteoporosis, bone metastasis or unknown reasons), pelvic pain, spinal cord injury-associated pain, cardiac chest pain, non-cardiac chest pain, central post-stroke pain, myofascial pain, cancer pain, AIDS pain, sickle cell pain, geriatric pain or pain caused by headache, temporomandibular joint syndrome, gout, fibrosis or thoracic outlet syndromes, pain related to surgery and *sequaelae* of surgery.

The compounds of the invention are also useful in the selective treatment of acute pain (caused by acute injury, illness, sports-medicine injuries, carpal tunnel syndrome, burns, musculoskeletal sprains and strains, musculotendinous strain, cervicobrachial pain syndromes, dyspepsis, gastric ulcer, duodenal ulcer, dysmenorrhea, endometriosis or surgery (such as open heart or bypass surgery), post operative pain, kidney stone pain, gallbladder pain, gallstone pain, obstetric pain or dental pain.

The compounds of the invention are also useful in the selective treatment of migraine, and others headaches, transformed migraine or evolutive headache, cluster headache, tension headache as well as secondary headache disorders, such as the ones derived from infections, metabolic disorders or other systemic illnesses and other acute headaches, paroxysmal hemicrania and the like, resulting from a worsening of the above mentioned primary and secondary headaches.

The compounds of the invention are also useful in the selective treatment of peripheral diseases such as tinnitus, muscle spasm, muscular sclerosis, and other disorders, including, and not limited to cardiovascular diseases (such as cardiac arrhythmia, cardiac infarction or angina pectoris, hypertension, cardiac ischemia) endocrine

disorders (such as acromegaly or diabetes insipidus), diseases in which the pathophysiology of the disorder involves excessive or hypersecretory or otherwise inappropriate cellular secretion of an endogeneous substance
5 (such as catecholamine, a hormone or a growth factor).

The compounds of the invention are also useful in the selective treatment of liver disease, such as inflammatory liver disease, for example chronic viral hepatitis B, chronic viral hepatitis C, alcoholic liver injury, primary
10 biliary cirrhosis, autoimmune hepatitis, non-alcoholic steatohepatitis and liver transplant rejection.

The compounds of the invention inhibit inflammatory processes affecting all body systems. Therefore are useful in the selective treatment of inflammatory processes of the
15 muscular-skeletal system of which the following is a list of examples but it is not comprehensive of all target disorders: arthritic conditions such as alkylosing spondylitis, cervical arthritis, fibromyalgia, gut, juvenile rheumatoid arthritis, lumbosacral arthritis, osteoarthritis,
20 osteoporosis, psoriatic arthritis, rheumatic disease; disorders affecting skin and related tissues: eczema, psoriasis, dermatitis and inflammatory conditions such as sunburn; disorders of the respiratory system: asthma, allergic rhinitis and respiratory distress syndrome, lung
25 disorders in which inflammation is involved such as asthma and bronchitis; chronic obstructive pulmonary disease; disorders of the immune and endocrinological systems: periarteritis nodosa, thyroiditis, aplastic anaemia, sclerodoma, myasthenia gravis, multiple sclerosis,
30 sarcoidosis, nephritic syndrome, Bechet's syndrome, polymyositis, gingivitis.

The compounds of the invention are also useful in the selective treatment of gastrointestinal (GI) tract disorders such as inflammatory bowel disorders including but
35 not limited to ulcerative colitis , Crohn's disease,

ileitis, proctitis, celiac disease, enteropathies, microscopic or collagenous colitis, eosinophilic gastroenteritis, or pouchitis resulting after proctocolectomy and post ileonatal anastomosis, and
5 irritable bowel syndrome including any disorders associated with abdominal pain and/or abdominal discomfort such as pylorospasm, nervous indigestion, spastic colon, spastic colitis, spastic bowel, intestinal neurosis, functional colitis, mucous colitis, laxative colitis and functional
10 dyspepsia; but also for treatment of atrophic gastritis, gastritis varioliforme, ulcerative colitis, peptic ulceration, pyresis, and other damage to the GI tract, for example, by *Helicobacter pylori*, gastroesophageal reflux disease, gastroparesis, such as diabetic gastroparesis; and
15 other functional bowel disorders, such as non-ulcerative dyspepsia (NUD); emesis, diarrhea, and visceral inflammation.

The compounds of the invention are also useful in the selective treatment of disorders of the genito-urinary tract
20 such as overactive bladder, prostatitis (chronic bacterial and chronic non-bacterial prostatitis), prostadynia, interstitial cystitis, urinary incontinence and benign prostatic hyperplasia, annexities, pelvic inflammation, bartolinitis and vaginitis.

25 The compounds of the invention are also useful in the selective treatment of metabolic disorders (e.g. obesity) and seizure disorders (e.g. epilepsy).

The compounds of the invention are also useful for the selective treatment of all other conditions mediated by the
30 inhibition of voltage gated sodium channels and/or voltage gated calcium channels.

It will be appreciated that the compounds of the invention may advantageously be used in conjunction with one or more other therapeutic agents. Examples of suitable
35 agents for adjunctive therapy include a 5HT_{1B/1D} agonist, such

as a triptan (e.g. sumatriptan or naratriptan); an adenosine A1 agonist; an EP ligand; an NMDA modulator, such as a glycine antagonist; a substance P antagonist (e.g. an NK1 antagonist); a cannabinoid; acetaminophen or phenacetin; a
5 5-lipoxygenase inhibitor; a leukotriene receptor antagonist; a DMARD (e.g. methotrexate); gabapentin and related compounds; a tricyclic antidepressant (e.g. amitriptyline); a neurone stabilising antiepileptic drug; a matrix metalloproteinase inhibitor; a nitric oxide synthase (NOS)
10 inhibitor, such as an iNOS or an nNOS inhibitor; an inhibitor of the release, or action, of tumor necrosis factor alpha; an antibody therapy, such as monoclonal antibody therapy; an antiviral agent, such as a nucleoside inhibitor (e.g. lamivudine) or an immune system modulator
15 (e.g. interferon); an analgesic, such as a cyclooxygenase-2 inhibitor; a local anaesthetic; a stimulant, including caffeine; an H2-antagonist (e.g. ranitidine); a proton pump inhibitor (e.g. omeprazole); an antacid (e.g. aluminium or magnesium hydroxide; an antifatulent (e.g. semethicone); a
20 decongestant (e.g. phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, epinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine); antitussive (e.g.
25 codeine, hydrocodone, carmiphen, carbetapentane, or dextramethorphan); a diuretic; or a sedating or non-sedating antihistamine. It is to be understood that the present invention include the use of a compounds according to this invention, or a pharmaceutically acceptable salt thereof in
30 combination with one or more therapeutic agents.

The compounds of the present invention are useful in human and veterinary medicine. It is to be understood that as used herein the terms "treatment" or "treating" whenever not specifically defined otherwise, include prevention,
35 alleviation and cure of a pathological affection, in

particular, they include both treatment of established symptoms and prophylactic treatment.

Accordingly, the expression "therapeutically effective" when referred to an "amount", a "dose" or "dosage" of the (R)-2-[(halobenzyloxy)benzylamino]-propanamides of this invention is intended as an "amount", a "dose" or "dosage" of any said compounds sufficient for use in both the treatment of the established symptoms and the prophylactic treatment of the above said pathological affections.

According to the use of this invention the above selectively active R-2-[(halobenzyloxy)benzylamino]-propanamides derivatives and their pharmaceutically acceptable salts can be administered as the "active ingredient" of a pharmaceutically acceptable composition which can be prepared by conventional procedures, for instance by mixing the active ingredient with pharmaceutically acceptable, therapeutically inert organic and/or inorganic carrier materials.

The composition comprising the above defined 2-[(halobenzyloxy)benzylamino]-propanamides derivatives can be administered in a variety forms, e.g. orally, in the form of tablets, troches, capsules, sugar or film coated tablets, liquid solutions, emulsions or suspensions; rectally or intravaginally, in the form of suppositories; parenterally, e.g. by intramuscular, subcutaneous or intravenous injection or infusion, locally and transdermally in form of patch and gel and cream.

Suitable pharmaceutically acceptable, therapeutically inert organic and/or inorganic carrier materials useful in the preparation of such composition include, for example, water, gelatin, gum arabic, lactose, starch, cellulose, magnesium stearate, talc, vegetable oils, cyclodextrins, polyalkyleneglycols and the like. The composition comprising the (R)-2-[(halobenzyloxy)benzylamino]-propanamides mentioned above can be sterilized and may contain further

well known components, such as, for example, preservatives, stabilizers, wetting or emulsifying agents, e.g. paraffin oil, mannide monooleate, salts to adjust osmotic pressure, buffers and the like.

5 For example, the solid oral forms may contain, together with the active ingredient, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; 10 binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disgregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as 15 lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film-coating processes. 20

The oral formulations comprise sustained release formulations that can be prepared in conventional manner, for instance by applying an enteric coating to tablets and granules.

25 The liquid dispersion for oral administration may be e.g. syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

30 Suspensions and emulsions may contain as a carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspensions or solutions for intramuscular injections may contain, together with the active compound, a 35 pharmaceutically acceptable carrier, e.g. sterile water,

olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusion may contain as carrier, for example, sterile water or, preferably, they may be in the form of sterile, aqueous, isotonic saline solutions.

The suppositories may contain, together with the active ingredient, a pharmaceutically acceptable carrier, e.g. cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactants or lecithin.

Suitable treatment is given 1, 2 or 3 times daily, depending upon clearance rate. Accordingly, the desired dose may be presented in a single dose or as divided doses administered at appropriate intervals, for example two to four or more sub-doses per day.

The pharmaceutical compositions comprising the selectively active (R)-2-[(halobenzoyloxy)benzylamino]propanamides mentioned above will contain, per dosage unit, e.g., capsule, tablet, powder injection, teaspoonful, suppository and the like from about 1 to about 2500 mg of the active ingredient, preferably from 5 to 1000 mg, most preferably from 10 to 200 mg of the active ingredient.

Optimal therapeutically effective doses to be administered may be readily determined by those skilled in the art and will vary, basically, with the strength of the preparation, with the mode of administration and with the advancement of the condition or with the type of disorder treated. In addition, factors associated with the particular subject being treated, including subject age, weight, diet and time of administration, will result in the need to adjust the dose to an appropriate therapeutically effective level. In general therapeutically effective daily dosages of the invention compounds in patient in need of the selective treatment of the above mentioned affections wherein the sodium and/or calcium channel mechanism(s) play(s) a

pathological role range from 0.05 to 100 mg/kg, preferably from 0.1 to 50 mg/kg, most preferably 0.5 to 10 mg/kg of body weight.

The following Examples further illustrate the invention.

Example 1

(R)-2-[4-(2-fluorobenzoyloxy)benzylamino]propanamide

To 50 ml of dry methanol with bubbling in (R) alaninamide hydrochloride (1.37 g, 11 mmol), 4-(2-fluorobenzoyloxy)benzaldehyde (2.3 g 10 mmol), triethylamine (1,12 g, 11 mmol) and 1g of 3-Å molecular sieves were added and the mixture was stirred for 4 h at 40 °C. The temperature was then lowered to 10 °C and sodium borohydride (0.19 g, 5 mmol) was added in 15'. The reaction mixture was stirred for 6h at room temperature, then it was filtered and evaporated to dryness under vacuo. The residue was taken up with water and toluene at 60 °C, and the organic phase was washed twice with warm water and dried at the same temperature with anhydrous sodium sulphate. The solution was filtered, and gradually cooled at 10 °C. The precipitate was filtered, washed with a small amount of cooled toluene and dried under vacuum to give 2,69 g (89.0% yield) of white crystals.

25

Example 2

(R)-2-[4-(2-fluorobenzoyloxy)benzylamino]propanamide methanesulfonate

To a solution of (R)-2-[4-(2-fluorobenzoyloxy)benzylamino]-propanamide (2.5 g, 8.3 mmol) in 40 ml of ethyl acetate, the stoichiometric amount of methanesulfonic acid (0.80 g) diluted in 10 ml of ethyl acetate was added under stirring at room temperature. After 1h the white crystals were filtered, washed with 5 ml of ethyl acetate and dried in a vacuum oven to give 3.26 g

35

(98.8% yield) of the title compound: m.p. 240-241 °C

¹H-NMR (DMSO-d₆) δ: 1.39 (d, J = 6.9 Hz, 3H, CH₃CH), 2.30 (s, 3H, CH₃SO₃⁻), 3.71 (q, J = 6.9 Hz, 1H, CH₃CH), 4.01 (m, 2H, ArCH₂-NH), 5.15 (s, 2H, ArCH₂O), 7.08 (m, 2H, H₃, H₅), 7.1-7.6 (m, 6H, H₃', H₄', H₅', H₆', H₂, H₆), 7.63, 7.89 (2s, 2H, CONH₂), 9.0 (br s, 2H, NH₂⁺); MS m/z 302 (M⁺), 258, 230, 215, 109.

Anal. (C₁₇H₁₉FN₂O₂·CH₃SO₃H) C, H, F, N, S.

10 Analogously were prepared:

(R)-2-[4-(2-chlorobenzyloxy)benzylamino]-N-methylpropanamide methanesulfonate

15 ¹H-NMR (DMSO-d₆) δ: 1.40 (d, J = 7.0 Hz, 3H, CH₃CH), 2.30 (s, 3H, CH₃SO₃⁻), 2.65 (d, J = 4.5 Hz, 3H, CONHCH₃), 3.70 (q, J = 7.0 Hz, 1H, CH₃CH), 4.01 (s, 2H, ArCH₂-NH), 5.17 (s, 2H, ArCH₂O), 7.08 (m, 2H, H₃, H₅), 7.3-7.7 (m, 6H, H₃', H₄', H₅', H₆', H₂, H₆), 7.63, 7.89 (2s, 2H, CONH₂), 9.0 (br s, 2H, NH₂⁺); MS m/z 332 (M⁺), 274, 246, 231, 125.

Anal. (C₁₈H₂₁ClN₂O₂·CH₃SO₃H) C, H, Cl, N, S.

(R)-2-[4-(3-chloro-benzyloxy)benzylamino]propanamide methanesulfonate

25

¹H-NMR (DMSO-d₆) δ: 1.39 (d, J = 6.8 Hz, 3H, CH₃CH), 2.29 (s, 3H, CH₃SO₃⁻), 3.70 (q, J = 6.8 Hz, 1H, CH₃CH), 4.01 (s, 2H, ArCH₂-NH), 5.15 (s, 2H, ArCH₂O), 7.06 (m, 2H, H₃, H₅), 7.3-7.6 (m, 6H, H₂', H₄', H₅', H₆', H₂, H₆), 7.64-7.91 (2s, 2H, CONH₂), 8.96 (br s, 2H, NH₂⁺); MS m/z 318 (M⁺), 274, 246, 231, 125.

Anal. (C₁₇H₁₉ClN₂O₂·CH₃SO₃H) C, H, Cl, N, S.

Example 3

In vitro* MAO-B enzyme activity assay**Membrane preparations (crude mitochondrial fraction):***

male Wistar rats (Harlan, Italy - 175-200 g) were sacrificed
5 under light anaesthesia and brains were rapidly removed and
homogenized in 8 vol. of ice-cold 0.32 M sucrose buffer
containing 0.1 M EDTA, pH 7.4. The crude homogenate was
centrifuged at 2220 rpm for 10 min and the supernatant
recovered. The pellet was homogenized and centrifuged again
10 and the two supernatants were pooled and centrifuged at 9250
rpm for 10 min, +4°C. The pellet was resuspended in fresh
buffer and centrifuged at 11250 rpm for 10 min, +4°C. The
resulting pellet was stored at -80°C until use.

In vitro enzyme activity assay: the enzyme activities
15 were assessed with a radioenzymatic assay using the
selective substrate ¹⁴C-phenylethylamine (PEA) for MAO-B.

The mitochondrial pellet (500 µg protein) was
resuspended in 0.1M phosphate buffer pH 7.4 and 500 µl was
added to 50 µl of the test compound or buffer for 30 min at
20 37°C (preincubation) then the substrate (50 µl) was added.
The incubation was carried out for 10 min at 37°C (¹⁴C-PEA,
0.5 µM).

The reaction was stopped by adding 0.2 ml HCl or
perchloric acid. After centrifugation, the deaminated
25 metabolites were extracted with 3 ml of toluene and the
radioactive organic phase measured by liquid scintillation
spectrometry at 90% efficiency. Radioactivity in the eluate
indicates the production of neutral and acidic metabolites
formed as a result of MAO-B activity.

30 The enzymatic activity was expressed as nmoles of
substrate transformed/mg protein/min. The activity of MAO-B
in the sample was expressed as a percentage of control
activity in the absence of inhibitors after subtraction of
appropriate blank values.

The drug inhibition curves were obtained from at least eight different concentrations, each in duplicate (10^{-10} to 10^{-5} M) and the IC₉₀ values (the drug concentration inhibiting 90% enzyme activity) with confidence intervals determined using linear regression analysis. (aided-computer program).

To reach a significant increase in neurotransmitter levels, MAO-B enzyme activity has to be blocked at least by 90%. The IC₉₀ values for both the (R)-isomers of this invention and the comparison compounds are reported in Table I.

Example 4

Calcium influx assay

IMR32 human neuroblastoma cells constitutively possess both L and N type channels. Under differentiating conditions, IMR32 preferentially express on the membrane surface N- type calcium channels. The remaining L-type calcium channels were blocked using the selective L type blocker, nifedipine. In these experimental conditions, only N type channels can be detected.

IMR32 cells were differentiated using 1mM dibutyryl-cAMP and 2.5 μ M bromodeoxyuridine for 8 days (4 times) in 225 cm² flask, then detached, seeded at 200,000 cells/well on 96 polyllysine-coated plates and further incubated for 18-24 h in the presence of differentiating buffer before use.

The Ca²⁺ Kit Assay (Molecular Devices), based on a fluorescent calcium indicator 485-535 nm wavelength, was used.

Differentiated cells were incubated with dye loading for 30 min at 37°C then, nifedipine alone (1 μ M) or in the presence of ω -conotoxin or test compounds were added for further 15 min.

The fluorescence (485-535nm) was measured before and after (30-40 sec) the automated injection of 100 mM KCl

depolarizing solution using a Victor plate reader (Perkin Elmer).

The inhibition curves were calculated from 5 concentrations, each in triplicate, and the IC50 determined using a linear regression analysis.

The activity on N-type Calcium channel, expressed as IC50 of the (R)-isomer of this invention and the comparison compounds is reported in Table I.

10 **Example 5**

Electrophysiological assay

Experiments for the determination of the tonic block are carried out on isolated Xenopus oocytes expressing the Na channel Nav 1.3. Currents are recorded using the two electrodes voltage clamp (TEVC) technique

Oocytes preparation:

The frog (Xenopus Laevis) is anesthetized in a solution with 3-aminobenzoic acid ethyl ester (1 g/l) and, after 25 minutes, it is placed on its back on an "iced-bed". The skin and the others tissues are cut, the ovarian lobes are pulled out and kept in ND960Ca²⁺ (NaCl 96mM, KCl 2mM, MgCl2 1 mM, Hepes 10mM, pH 7.85 with NaOH)

After the removal of the oocytes, the muscle and the skin are sutured separately.

25 Ovarian lobes are reduced into clusters of 10/20 oocytes, put in tubes with collagenase solution (1 mg/ml) and kept in movement for about 1 h in an incubator.

At the end of this step, when the oocytes are well separated ones from the others, they are rinsed three times with ND960Ca²⁺ and three times with NDE (ND960Ca²⁺ + CaCl 0.9mM, MgCl2 0.9 mM, piruvate 2.5 mM, gentamicine 50 mg/l)

30 The oocytes obtained are at different stages of development. Only cells at stages V or VI are selected for RNA injection subsequent experiments.

35 The day after the preparation, the oocytes are injected

(Drummond Nanoject) with 20 ng Nav1.3 cRNA and maintained in NDE.

Starting from 48h after the mRNA injection whole cell currents are recorded using a two-microelectrode voltage clamp automated workstation.

Typical Microelectrodes have a resistance of 0.5 to 1 Mohm and are filled with KCl 3M

Control bath solution contains (mM): NaCl 98, MgCl₂ 1, CaCl₂ 1.8, HEPES 5 (pH 7.6).

Compounds are prepared in stock solutions (20mM) and dissolved to the final concentrations in the external bath solution.

Currents recording:

The current/voltage (I/V) relationship for the Nav1.3 currents expressed in oocytes was first studied in order to determine the membrane potential evoking the maximal activation. Nav1.3 showed the max activation at 0 mV, that we used as test potential (V_{test}) for tonic block studies.

The steady - state inactivation properties of the Nav1.3 currents were than studied in order to determine the membrane potentials for the resting state (V_{rest}) at which channel availability is maximal (I_{max}), and the membrane potential for the half maximal inactivation (V_½) producing half of the max current availability (I_½) respectively. This two voltage conditions were then used for the evaluation of the voltage dependence of the tonic block.

Finally a two-step protocol was used to determine the voltage dependence of the block of Nav1.3: the oocytes were clamped at -80 mV, the currents were activated by a 100 ms step pulse to 0 mV (V_{test}) from a 3000 ms preconditioning potential at -80 mV (resting, I_{max} condition) and -40 mV (depolarized, I_½ condition), respectively.

Current amplitudes in the two conditions were recorded in the absence and in the presence of different concentrations of compound (washout was made in between) in

oder to determine the concentration - inhibition curves and IC50 values for the tonic block in the depolarized (half max current availability) conditions.

The activity on Nav 1.3 sodium channel, expressed as
5 IC50 of the (R)-isomers of this invention and of the comparison compounds is reported in Table I.

Example 6

Mice Formalin Test

10 According to a modified protocol from Rosland et al., (1990) mice were injected subcutaneously (s.c.) with 20 μ l of 2.7% solution of formalin into the plantar surface of left hindpaw and placed immediately into clear PVC observation chambers (23 x 12 x 13 cm).

15 The test compound (20 mg/kg) was administered p.o. 15 min before formalin injection in a volume of 10 ml/kg body weight to groups of 10 mice per dose. Control group was treated with vehicle.

Pain behavior was quantified by counting the
20 cumulative licking time (seconds) of the injected paw with formalin. Measurements were taken during the late phase 30-40 min after formalin injection (Tjolsen et al 1992).

The analgesic effect of the compounds was calculated as the % of inhibition of the cumulative licking time respect
25 the control group.

As reported in Table II both (R)-isomers of this inventions showed similar (not statistically different) or better analgesic activity than the comparison compounds.

Results

30 Table 1

COMPOUND NAME (1)	MAO-B IC90 (μ M)		Nav 1.3 Dep.Curr IC50 (μ M)		Ca 2+ N-Type IC50 (μ M)	
	R isomer	S isomer	R isomer	S isomer	R isomer	S isomer
2-[4-(2-fluorobenzoyloxy)benzylamino]	2500	28.4	149	202	29.2	23

-propanamide						
2-[4-(2-chlorobenzoyloxy)benzylamino]-N-methyl-propanamide	122	2.8	38	210	8.4	30
2-[4-(3-chlorobenzoyloxy)benzylamino]-propanamide	32.3	1.64	39	79.0	20	94.0

(1) All compounds were employed in the form of salts with methanesulfonic acid.

Table 2

COMPOUND NAME (20mg/kg) (2)	FORMALIN TEST % inhibition	
	R isomer	S isomer
2-[4-(2-fluorobenzoyloxy)benzylamino]propanamide	80	79
2-[4-(2-chlorobenzoyloxy)benzylamino]-N-methyl-propanamide	49	32
2-[4-(3-chlorobenzoyloxy)benzylamino]propanamide	39	45

(2) All compounds were employed in the form of salts with
5 methanesulfonic acid

According to the terms and criteria used in this application and claims a medicament active as sodium and/or channel modulator is considered as substantially free from
10 any MAO-B inhibitory effect at dosages that are therapeutically effective in preventing, alleviating and/or curing affections where said mechanism(s) play(s) a pathological role when both the ratio between the values of IC₅₀ of Nav 1.3 and of IC₉₀ MAO-B and the ratio between the
15 values of IC₅₀ Ca²⁺N-Type and of IC₉₀ MAO-B are lower than 0.1. Similarly, a medicament active as sodium and/or calcium channel modulator is considered as exhibiting a significantly reduced MAO-B inhibitory effect at dosages that are therapeutically effective in preventing,
20 alleviating, and/or curing affections where said mechanism(s) play(s) a pathological role when both the ratio between the values of IC₅₀ Nav 1.3 and IC₉₀ MAO-B and the

ratio between the values of IC50 Ca²⁺ and IC90 MAO-B are lower than 0.5 but at least one of them is not lower than 0.1.

CLAIMS

1. The use of a (halobenzoyloxy)benzylamino-propanamide selected from:

(R)-2-[4-(2-fluorobenzoyloxy)benzylamino]propanamide, and

5 (R)-2-[4-(2-chlorobenzoyloxy)benzylamino]-N-methylpropanamide,

and the pharmaceutically acceptable salts thereof for the manufacture of a medicament selectively active as sodium and/or calcium channel modulator characterized in that said
10 medicament is substantially free from any MAO inhibitory effect or exhibits a significantly reduced MAO inhibitory effect at dosages that are therapeutically effective in preventing, alleviating and/or curing affections where the above said mechanism(s) play(s) a pathological role.

15 2. The use of a (halobenzoyloxy)benzylamino-propanamide as defined in claim 1, or a pharmaceutically acceptable salt thereof in a mixture with a suitable carrier and/or diluent and, optionally, together with other therapeutic agents, for the manufacture of a pharmaceutical composition for the
20 selective treatment of a disorder where the sodium and/or calcium channel mechanism(s) play(s) a pathological role.

3. The use of a (halobenzoyloxy)benzylamino-propanamide or a pharmaceutically acceptable salt thereof as defined in any of claims 1 and 2, for the manufacture of a medicaments
25 that is active as sodium and/or calcium channel modulator, useful in preventing, alleviating and curing a pathological affection selected from pain, migraine, periferal diseases, cardiovascular diseases, inflammatory processes affecting all body systems, disorders affecting
30 skin and related tissues, disorders of the respiratory system, disorders of the immune and endocrinological systems, gastrointestinal, urogenital, seizure and metabolic disorders characterized in that said medicament is substantially free from any MAO inhibitory effect or
35 exhibits a significantly reduced MAO inhibitory effect at

dosages that are therapeutically effective in preventing, alleviating and/or curing said pathological affection .

4. The use according to any of claims 1 to 3 which includes both treatment of established symptoms and prophylactic treatment.

5. The use according to any of claims 1 to 4 wherein the pathological affection is a pain syndrome, migraine, a urogenital and/or gastrointestinal disease and/or a seizure disorder.

10 6. The use according to any of claims 1 to 5 wherein the pathological affection, is a pain syndrome.

7. The use according to claim 6 wherein the pain syndrome is either of neuropathic or inflammatory type.

15 8. The use according to claims 5 wherein the pathological affection is migraine.

9. The use according to any of claims 1 to 8 wherein the (halobenzyloxy)benzylamino-propanamide is (R)-2-[4-(2-fluorobenzyloxy)benzylamino]propanamide and/or a pharmaceutically acceptable salt thereof.

20 10. The use according to claim 9 wherein the salt is the salt with methanesulfonic acid.

11. The use according to any of claims 1 to 10 wherein the MAO enzyme is MAO-B isoform.

25 12. The use according to any of claims 1 to 11 wherein the (halobenzyloxy)benzylamino-propanamide or the pharmaceutically acceptable salt thereof is used in conjunction with one or more other therapeutic agents.

13. (R)-2-[4-(2-fluorobenzyloxy)benzylamino]propanamide and its methanesulfonate.

30 14. A method for selectively preventing, alleviating and/or curing pathological affections where sodium and/or calcium channel mechanism(s) play(s) a pathological role, which method comprises administering to a patient in need thereof a therapeutically effective amount of a
35 (halobenzyloxy)benzylamino-propanamide selected from:

(R)-2-[4-(2-fluorobenzyloxy)benzylamino]propanamide, and
(R)-2-[4-(2-chlorobenzyloxy)benzylamino]-N-
methylpropanamide,

and the pharmaceutically acceptable salts thereof, wherein
5 the therapeutical activity of said compound is substantially
free from any MAO inhibitory side effect or exhibits
significantly reduced MAO inhibitory side effect.

10 **15.** A method as in claim 14 wherein the pathological
affection is a pain syndrome, migraine a periferal disease,
a cardiovascular disease, an inflammatory process affecting
any body system, a disorder affecting skin and related
tissues, a disorder of the respiratory system, a disorder of
the immune and endocrinological systems, a gastrointestinal,
urogenital, seizure or metabolic disorder.

15 **16.** A method as in claim 15 wherein the pathological
affection is a pain syndrome, migraine, a urogenital and/or
gastrointestinal disease and/or a seizure disorder.

17. A method as in claim 16 wherein the pathological
affection is a pain syndrome.

20 **18.** A method as in claim 17 wherein the pain syndrome
is either of neurophatic or inflammatory type.

19. A method as in claim 16 wherein the pathological
affection is migraine.

25 **20.** A method according to any of the claims 14 to 19
wherein the MAO enzyme is MAO-B isoform.

21. A method according to any of claims 14 to 20
wherein the (halobenzyloxy)benzylamino-propanamide or the
pharmaceutically acceptable salt thereof is used in
conjunction with one or more other therapeutic agents.