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(54) Title: ALPHA-AMINOAMIDE DERIVATIVES USEFUL AS ANTI-INFLAMMATORY AGENTS

(57) Abstract: Methods of using certain a-aminoamide derivatives as anti-inflammatory agents. The anti-inflammatory agents of the invention are able to reduce or even stop inflammatory s conditions substantially without side effects.
α-AMINOAMIDE DERIVATIVES USEFUL AS ANTI-INFLAMMATORY AGENTS

FIELD OF THE INVENTION:

The invention relates to α-aminoamide derivatives, a chemical class of sodium channel blockers, which are useful as anti-inflammatory agents. Particularly, the invention relates to their use as therapeutic anti-inflammatory agents and to pharmaceutical compositions containing them.

BACKGROUND OF THE INVENTION

Inflammation produces profound changes in the excitability of primary afferent neurons innervating the inflamed tissue. These changes underlie the initiation and maintenance of chronic inflammatory state. Studies have shown that post-translational modification or abnormal expression of sodium channels in dorsal root ganglion (DRG) neurons occurs after tissue inflammation.

Inflammation and inflammation-induced tissue damage is believed to happen in multiple and diverse ways. In one example, sodium channels are substantially up-regulated in inflamed tissues. Carrageenan injection into the plantar surface of the rat hind paw, used as an animal model of inflammation, induces edema, hyperthermia and hyperalgesia. Although sodium channel blockers may be effective in neuropathic pain relief, not all exert an evident anti-inflammatory action. In fact, two sodium channel blockers, cromolyn and mexiteline, were able to reverse the mechanical hyperalgesia without any effect on swelling and stiffness of the inflamed joint induced by carrageenan. Hence, these findings indicate that the analgesic activity of sodium channel blockers is not necessarily related to an anti-inflammatory property.

At the same time, however, inflammatory mediators such as substance P and calcitonin gene-related peptide (CGRP), which are involved in nociceptive transmission, increase in DRG neurons following inflammation. Substance P plays an important role in the induction of neurogenic inflammation and it has been shown to exert potent pro-inflammatory action such as vasodilatation, increased capillary permeability, and the secretion of prostaglandin E₂.

PCT patent publications WO90/14334, WO94/22808, WO97/05102, WO 97/0511 and WO 99/35215, the text of which are incorporated by reference herein, disclose substituted benzylaminopropionamide compounds active on the central nervous system and useful as anti-

U.S. Patent No. 3,549,690 to Leigh et al. further describes carboxylic acid derivatives of the following general formula:

\[
\begin{array}{c}
\text{aryl} - Y - \text{aryl} - \text{CH}_2 - X - CR^1R^2\text{COOH}
\end{array}
\]

which lower the concentration of cholesterol and/or triglycerides in blood serum and which possess anti-inflammatory activity. U.S. Patent No. 6,548,507 to Bountra et al. relates to the use of sodium channel antagonists for the treatment of diseases mediated by, or exacerbated by, neuronal apoptosis, in particular sensory neuronal apoptosis.

**SUMMARY OF THE INVENTION**

Despite the large number of available anti-inflammatory agents, however, the use of such anti-inflammatory agents is limited by severe side effects and/or modest activity in some inflammation conditions. For example, adverse side effects in the gastrointestinal tract are commonly induced by certain levels of classical anti-inflammatory drugs like indomethacin, a non-steroidal anti-inflammatory drug (NSAID). Similarly, COX-2 inhibitors only partially reduce inflammatory disorders. Thus, there is still a clear need to develop new compounds with better therapeutic index in treating inflammatory disorders. The present invention provides rapid and highly effective methods for treating a variety of inflammatory disorders from body organs and systems by utilizing, in vivo, certain α-aminoamide compounds of the invention in a therapy which is a superior alternative to existing treatments.

In an embodiment, the invention includes treating one or more inflammatory disorders in a patient in need thereof by administering an effective amount of at least one α-aminoamide compound of formula (I):
wherein:

- A is a \(-(CH_2)_n\)-X- group, wherein n is an integer of 0 to 5, X is CH_2, -O-, -S- or -NH-;
- s is 1 or 2;
- R is a furyl, thieryl, or pyridyl ring or a phenyl ring, optionally substituted by one or two substituents independently selected from halogen, hydroxy, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl;
- R_1 is hydrogen or C_1-C_6 alkyl or C_3-C_7 cycloalkyl;
- R_2 and R_3 are independently selected from hydrogen; C_1-C_4 alkyl, optionally substituted by hydroxy or phenyl; phenyl, optionally substituted by one or two substituents independently selected from C_1-C_6 alkyl, halogen, hydroxy, C_1-C_6 alkoxy or trifluoromethyl; or R_2 and R_3, taken with the carbon atom which they are linked to, form a C_3-C_6 cycloalkyl ring; and
- R_4, R_5 are, independently, hydrogen, C_1-C_6 alkyl or C_3-C_7 cycloalkyl; or R_4 and R_5, taken together with the nitrogen atom they are linked to, form a 5-7 atom saturated heterocyclic ring;

or isomers, mixtures, and pharmaceutically acceptable salts thereof.

The alkyl and alkoxy groups can be branched or can be straight chain groups.

In an embodiment of the invention, when n is 1, s is 1, X is O, R_1, R_2, R_4 and R_5 are H and R_3 is CH_3, R is not an m-fluoro-substituted phenyl ring.

Pharmaceutically acceptable salts of the compounds of the invention include, for example, acid addition salts with inorganic acids, e.g., nitric, hydrochloric, hydrobromic, sulfuric and phosphoric acids and the like, or organic acids, e.g., acetic, propionic, glycolic, lactic, oxalic, malonic, malic, tartaric, citric, succinic, benzoic, cinnamic, mandelic, methanesulfonic, p-toluenesulfonic and salicylic acids, and the like.
Some of the compounds of formula (I) can have asymmetric carbon atoms, and therefore can exist either as racemic mixtures or as individual optical isomers (enantiomers). Accordingly, the term “pharmacologically acceptable salts” of the β-aminoamide of formula (I) is also meant to include within its scope all the possible isomers and their mixtures, and any pharmacologically acceptable metabolite, bioprecursor and/or pro-drug, i.e., a compound which has a structural formula different from the one of the β-aminoamide of formula (I), and yet is directly or indirectly converted in vivo into a compound having formula (I), upon administration to a mammal, particularly a human being.

Preferred compounds of formula (I) include those wherein A is a group chosen from -CH₂-, -CH₂-CH₂-, -CH₂-S-, -CH₂-CH₂-S-, and -(CH₂)ₙ-O-, wherein n is an integer of 1 to 5;

- s is 1 or 2;
- R is a phenyl ring, optionally substituted by one or two substituents independently selected from a halogen, trifluoromethyl, a methoxy, or a thienyl ring;
- R₁ is hydrogen or C₁-C₄ alkyl;
- one of R₂ and R₃ is hydrogen and the other is C₁-C₄ alkyl, optionally substituted by hydroxy or phenyl, optionally substituted by one or two halogen atoms, or R₂ and R₃ are both methyl, or together they can from with the atom they are linked to a cyclopropyl or a cyclopentyl ring; and
- R₄, R₅ are hydrogen or C₁-C₄ alkyl, or, together with the nitrogen they are linked to, form a pyrrolidine or piperidine ring, and the pharmacologically acceptable salts thereof.

Examples of specific compounds of formula (I) - which can be used singly or in combination with other compounds of formula (I) - in an effective amount for treating one or more inflammatory disorders in a patient include, but are not limited to:

2-(4-Benzylxoybenzylamino)-propanamide;
2-[4-(2-Methoxybenzylxoy)-benzylamino]-propanamide;
2-[4-(2-Fluorobenzylxoy)-benzylamino]-propanamide;
(S)-(+)2-[4-(2-Fluorobenzyloxy)-benzylamino]-propanamide;
2-[4-(2-Fluorobenzyloxy)-benzylamino]-2-methyl-propanamide;
(S)-(+)2-[4-(3-Fluorobenzyloxy)-benzylamino]-propanamide, methanesulfonate;
2-[4-(2-Fluorobenzyloxy)-benzylamino]-N-methyl-propanamide;
N-{2-[4-(2-Fluorobenzyloxy)-benzylamino]}-propionyl-pyrrolidine;
2-[4-(3-Methoxybenzyloxy)-benzylamino]-propanamide;
2-[4-(3-Cyanobenzyloxy)-benzylamino]-propanamide;
2-[4-(3-Fluorobenzyloxy)-benzylamino]-propanamide;
(S)-(+)2-[4-(3-Fluorobenzyloxy)-benzylamino]-propanamide;
2-[4-(3-Fluorobenzyloxy)-benzylamino]-2-methyl-propanamide;
2-[4-(3-Fluorobenzyloxy)-benzylamino]-N-methyl-propanamide;
N-{2-[4-(3-Fluorobenzyloxy)-benzylamino]}-propionyl-pyrrolidine;
2-[4-(4-Fluorobenzyloxy)-benzylamino]-propanamide;
2-[4-(3-Fluorobenzyloxy)-benzylamino]-2-methyl-propanamide;
2-[4-(2-Chlorobenzyloxy)-benzylamino]-propanamide;
2-[4-(3-Chlorobenzyloxy)-benzylamino]-propanamide;
2-(4-Benzzyloxybenzylamino)-3-hydroxy-propanamide;
2-[4-(2-Fluorobenzyloxy)-benzylamino]-3-hydroxy-propanamide;
2-[4-(3-Fluorobenzyloxy)-benzylamino]-3-hydroxy-propanamide;
2-[4-(2-Chlorobenzyloxy)-benzylamino]-3-hydroxy-N-methyl-propanamide;
2-[4-(3-Chlorobenzyloxy)-benzylamino]-3-hydroxy-N-methyl-propanamide;
2-[4-(2-Chlorobenzyloxy)-benzylamino]-3-hydroxy-N-methyl-propanamide;
2-[4-(3-Cyanobenzyloxy)-benzylamino]-3-hydroxy-N-methyl-propanamide;
2.4-(3-Cyanobenzyloxy)-benzylamino]-2-methyl-3-hydroxy-N-methyl-propanamide;
2.4-(3-Chlorobenzyloxy)-phenylethylamino]-propanamide;
2.4-[2-(3-Fluorophenyl)-ethoxy]benzylamino]-propanamide;
2.4-[2-(3-Fluorophenyl)-ethyl]benzylamino]-propanamide;
2.4-[N-(4-Benzylxybenzyl)-N-methylamino]-propanamide;
2.4-[4-(3-Chlorobenzyloxy)-phenylethyl]-amino]-propanamide;
2.4-[4-Benzylthiobenzylamino]-propanamide;
2.4-[4-(2-Fluorobenzylthio)-benzylamino]-propanamide;
2.4-[4-(3-Fluorobenzylthio)-benzylamino]-propanamide;
2.4-(3-Phenylpropoxy]-benzylamino]-propanamide;
2.4-(4-Phenylbutyloxy]-benzylamino]-propanamide;
2.4-(5-Phenylpentxyloxy]-benzylamino]-propanamide;
2-(4-Benzylxybenzylamino)-3-phenyl-N-methyl-propanamide;
2-(4-Benzylxybenzylamino)-3-methyl-N-methyl-butanamide;
2.4-(4-Benzylxybenzylamino)-2-phenyl-acetamide;
2.4-(2-Fluorobenzyloxy)-benzylamino]-2-phenyl-acetamide;
2.4-(3-Fluorobenzyloxy)-benzylamino]-2-phenyl-acetamide;
2.4-(2-Fluorobenzyloxy)-benzyl-N-methylamino]-2-phenyl-acetamide;
2.4-(3-Fluorobenzyloxy)-benzyl-N-methylamino]-2-phenyl-acetamide;
2.4-(3-Chlorobenzyloxy)-benzylamino]-2-phenyl-acetamide;
2.4-(2-Fluorobenzyloxy)-benzylamino]-2-(2-fluorophenyl)-acetamide;
2.4-(2-Fluorobenzyloxy)-benzylamino]-2-(3-fluorophenyl)-acetamide;
2.4-(3-Fluorobenzyloxy)-benzylamino]-2-(2-fluorophenyl)-acetamide;
2.4-(3-Fluorobenzyloxy)-benzylamino]-2-(3-fluorophenyl)-acetamide;
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2-[4-(3-Chlorobenzyloxy)-benzylamino]-2-(3-fluorophenyl)-acetamide;

2-(4-(2-Thienyloxy)-benzylamino)-propanamide;

or isomers, mixtures, and pharmaceutically acceptable salts thereof.

A preferred compound of formula (I), which can be used singly, or in combination with other compounds of formula (I), in an effective amount for treating one or more inflammatory disorders in a patient is (S)-(+)2-[4-(2-Fluorobenzyloxy)-benzylamino]-propanamide, or a pharmaceutically acceptable salt thereof.

In one embodiment the patient being treated is a mammal, including humans, in need of alleviation, prevention, or inhibition of symptoms of one or more inflammatory disorders.

Particularly, the mammal in need of the above mentioned treatment is administered a dose of an α-aminoamide of formula (I) as above defined which ranges from about 0.3 to about 100 mg/kg of body weight per day. “Treatment” as used herein includes any care by procedures or applications to a mammal, and particularly a human, that are intended to a) prevent the disease or disorder from occurring in a subject that may be predisposed to the disease/disorder, but has not yet been diagnosed with having it; b) inhibiting the disease/disorder, or condition, i.e., arresting its development; or c) relieving the disease/disorder, or condition, i.e., causing regression of the disease/disorder, or condition.

Inflammatory conditions in a mammal, including humans, can thus be inhibited, alleviated and prevented. Examples of inflammation conditions in mammals which can be treated by administering one or more α-aminoamide compounds of formula (I) include, but are not limited to: arthritic conditions such as alkyllosing spondylitis, cervical arthritis, fibromyalgia, gut, juvenile rheumatoid arthritis, lumbosacral arthritis, osteoarthritis, osteoporosis, psoriatic arthritis, rheumatic disease, rheumatoid arthritis, eczema, psoriasis, dermatitis and inflammatory conditions such as sunburn; inflammatory eye conditions such as uveitis and conjunctivitis; lung disorders in which inflammation is involved such as asthma and bronchitis; conditions of gastro-intestinal tract including ulcers, gingivitis, Crohn’s disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, celiac disease, regional ileitis, peptic ulceration, pyresis, and other damage to the GI tract, for example, by Helicobacter pylori; visceral inflammation such as bladder irritation and cystitis; inflammatory neurological
disorders of the central or peripheral nervous system; multiple sclerosis; inflammatory neuropathies and neurological complication of AIDS, inflammation associated with autoimmune diseases, to trauma including trauma generated by surgery, infections, metabolic disorders, and tumors.

In another aspect, the invention includes an α-aminoamide of formula (I) administered as the active agent of a pharmaceutically acceptable composition having anti-inflammatory activity which can be prepared by conventional procedures known in the art, for instance by mixing the active agent with a pharmaceutically acceptable, therapeutically inert organic and/or inorganic carrier or excipient materials.

DETAILED DESCRIPTION OF THE INVENTION

A preferred compound of formula (I), used in an effective amount for treating one or more inflammatory disorders in a patient is (S)-(+)2-[4-(2-fluorobenzyloxy)-benzylamino]-propanamide. The compounds of formula (I), and the pharmaceutically acceptable salts thereof, may be obtained by well known processes as described in the international applications cited above.

Combination therapy” (or “co-therapy”) includes the administration of an alpha-aminoamide compound of formula (I) of the invention and at least a second agent as part of a specific treatment regimen intended to provide the beneficial effect from the co-action of these therapeutic agents. Benefits of such combinations include reduction of the dose of conventional inflammatory agents (i.e., other than the agents of the present invention) with consequent reduction of the side-effects of such conventional agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination selected). “Combination therapy” may, but generally is not, intended to encompass the administration of two or more of these therapeutic agents as part of separate monotherapy regimens that incidentally and arbitrarily result in the combinations contemplated by the present invention. “Combination therapy” is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of
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these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule having a fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally.

Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not narrowly critical. “Combination therapy” also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies (e.g., surgery or radiation treatment.) Where the combination therapy further comprises a non-drug treatment, the non-drug treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and non-drug treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the non-drug treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

The α-aminoamide compositions of the invention can be administered in a variety of dosage forms, e.g., orally, in the form of tablets, troches, capsules, sugar or film coated tablets, liquid solutions, emulsions or suspensions; rectally, in the form of suppositories; parenterally, e.g., by intramuscular or intravenous injection or infusion; and transdermally in the form of a patch, ointment, emulsion, lotion, solution, gel, cream and nasal spray.

Suitable pharmaceutically acceptable, therapeutically inert organic and/or inorganic carrier or excipient materials useful in the preparation of such composition include, for example, water, gelatin, gum arabic, lactose, starch, cellulose, magnesium stearate, talc, vegetable oils, polyalkylene glycols and the like. The α-aminoamide compositions of formula
(I) can be sterilized and may contain further components, well known to those skilled in the art, 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.

Additionally, the solid oral forms can contain, together with the active agent, 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; binding agents, e.g., starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g., a starch, alginic acid, alginates or sodium starch glycolate; effervesing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. The pharmaceutical preparations may be manufactured in any known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film-coating processes.

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

The liquid dispersion for oral administration may be e.g., syrups, emulsions and suspension. The syrups may further contain as a carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as a carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethyl-cellulose, or polyvinyl alcohol. The suspensions or solutions for intramuscular injections may contain, together with the active compound, a 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 a carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, or isotonic saline solutions.

The suppositories may contain, together with the active agent, a pharmaceutically acceptable carrier, e.g., cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.
Compositions including α-aminoamides of formula (I) are generally in the form of a dose unit containing, for example, 21 to 7000 mg of active ingredient per unit dosage form. Suitable treatment is given 1 or 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 including an α-aminoamide of formula (I) can contain, per dosage unit, e.g., capsule, tablet, powder injection, teaspoonful, suppository and the like, from about 21 to 7000 mg of the active agent.

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 inflammatory condition or 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.

The advantages derived from the uses and the methods of the invention as above defined are many, and include the possibility to prevent and treat basically all types of inflammation disorders.

Surprisingly, the use of the α-aminoamides of formula (I) as set forth herein does not show relevant adverse side effects at gastrointestinal levels that are commonly induced by classical anti-inflammatory drugs, e.g., NSAIDs like indomethacin, and COX-2 inhibitors, that only partially reduce them.

The following EXAMPLES are presented in order to more fully illustrate the preferred embodiments of the invention. These EXAMPLES should in no way be construed as limiting the scope of the invention, as defined by the appended claims.

EXAMPLES

EXAMPLE 1. Paw edema carrageenan-induced inflammation

The anti-inflammatory activity of the α-aminoamide compounds of formula (I) have proven effective in a rat model of inflammation induced by carrageenan injection. The α-
aminoamide compounds disclosed herein have been found to be active in inhibiting the paw edema formation after injection of carrageenan and the *in vitro* substance P (SP) release, and are therefore deemed to be useful as anti-inflammatory agents generally.

The potential anti-inflammatory effect of (S)-(+)\textsuperscript{-}2-[4-(2-fluorobenzyl oxy)-benzylamino]-propanamide ("compound A") was investigated in the rat model of inflammatory acute pain induced by subplantar injection of carrageenan. Intraplantar injection of carrageenan elicit a time-dependent increase in paw volume.

**Procedure:**

Male Wistar rats of 175-200 grams were used. The left hind paw was injected with 100 μl of carrageenan (2 % w/v in saline). Compound A (30 mg/kg), indomethacin (5 mg/kg), or control vehicle (such as distilled water) were orally administered 1 h before carrageenan injection. The paw volume was measured with a plethysmometer (Ugo Basile) immediately before (basal) and 1, 2, 3, 4 and 5h after the carrageenan injection.

**Results:**

In the control group carrageenan injection resulted in a time-related increase in ipsilateral hindpaw volume of 1.02 ml at 5 h after carrageenan injection. Compound A (30 mg/kg) prevented paw edema formation at all time points considered. Notably, the inhibition was maximal at 4 h after carrageenan injection with a 40 % reduction of edema vs. the control vehicle. Similarly, indomethacin (5 mg/kg) was able to prevent paw edema formation yielding an inhibition of about 50 % at the same time point. Data are reported in Table 1.
TABLE 1:

Effect of Compound A (30 mg/kg po) and indomethacin (5 mg/kg po) on volume of paw edema (ml) induced by carrageenan.

<table>
<thead>
<tr>
<th></th>
<th>60'</th>
<th>120'</th>
<th>180'</th>
<th>240'</th>
<th>300'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Vehicle</td>
<td>0.35 ± 0.03</td>
<td>0.54 ± 0.04</td>
<td>0.72 ± 0.03</td>
<td>0.92 ± 0.03</td>
<td>1.02 ± 0.04</td>
</tr>
<tr>
<td>Compound A 30 mg/Kg</td>
<td>0.19 ± 0.03</td>
<td>0.32± 0.03</td>
<td>0.44*** ± 0.03</td>
<td>0.56*** ± 0.04</td>
<td>0.70*** ± 0.05</td>
</tr>
<tr>
<td>Indomethacin 5 mg/Kg</td>
<td>0.29 ± 0.04</td>
<td>0.31± 0.04</td>
<td>0.38*** ± 0.05</td>
<td>0.45*** ± 0.05</td>
<td>0.57*** ± 0.07</td>
</tr>
</tbody>
</table>

Data are expressed as mean Δml ± s.e. of 13/15 rats and represent the volume difference in paw edema at different time points after carrageenan injection with respect to the basal paw volume measured before treatment. Data are evaluated by two-way analysis of variance followed by Bonferroni test. * p<0.05; ***p<0.001 vs. vehicle

EXAMPLE 2. Determination of substance P (SP) release from rat spinal cord synaptosomes

Procedure:

Male adult Sprague-Dawley rats were used. Following decapitation, the spinal cord was removed and homogenized in sucrose buffer 0.32 M, pH 7.4. Samples were centrifuged at 12000 g for 20 minutes and the synaptosomal fraction was resuspended in physiological buffer. SP release from spinal cord superfused synaptosomes was induced by KCl (35 mM) and measured by RIA
method (see Lee CM. et al. (1980) "The development and application of a novel N-terminal

Results:

In vitro, Compound A was very potent in reducing the evoked SP release from spinal
cord superfused synaptosomes in a concentration-related manner ranging from 0.1 to 30 μM
with an IC_{50} of 2.12 μM. SP is one of those substances referred to as cytokines, that are
mediators of inflammation. SP is a prime link in the chain of events that, after the interaction
between a noxa with tissues or cells of the host, leads to inflammatory damage and symptoms
of inflammation. The ability to inhibit release of SP is an important step in reducing
inflammation-related damage and symptoms.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than
routine experimentation, numerous equivalents to the specific procedures described herein.
Such equivalents are considered to be within the scope of the present invention and are covered
by the following claims. Various substitutions, alterations, and modifications may be made to
the invention without departing from the spirit and scope of the invention as defined by the
claims. For instance, the choice of the particular substitution to the alpha-aminoamide
compound of formula (I), or the specific dosing formulations, is believed to be a matter of
routine for a person of ordinary skill in the art with knowledge of the embodiments described
herein. Other aspects, advantages, and modifications are within the scope of the invention.
The contents of all references, issued patents, and published patent applications cited
throughout this application are hereby incorporated by reference. The appropriate components
and methods of those patents, applications and other documents may be selected for the present
invention and embodiments thereof.
CLAIMS

What is claimed is:

1. A method of treating one or more inflammatory disorders in a patient in need thereof, the method comprising administering to the patient an effective amount of at least one anti-inflammatory agent which is an alpha-aminoamide compound of formula (I),

   ![Chemical Structure](image)

   (I)

   wherein:

   - A is a -(CH₂)n-X- group, wherein n is an integer of 0 to 5, X is CH₂, -O- or -NH-;
   - s is 1 or 2;
   - R is a furyl, thienyl, or pyridyl ring or a phenyl ring, optionally substituted by one or two substituents independently selected from halogen, hydroxy, cyano, C₁-C₆ alkyl, C₁-C₆ alkoxy or trifluoromethyl;
   - R₁ is hydrogen or C₁-C₆ alkyl or C₃-C₇ cycloalkyl;
   - R₂ and R₃ are independently selected from hydrogen; C₁-C₄ alkyl, optionally substituted by hydroxy or phenyl; phenyl, optionally substituted by one or two substituents independently selected from C₁-C₆ alkyl, halogen, hydroxy, C₁-C₆ alkoxy or trifluoromethyl; or R₂ and R₃, taken with the carbon atom which they are linked to, form a C₃-C₆ cycloalkyl ring; and
   - R₄, R₅ are, independently, hydrogen, C₁-C₆ alkyl or C₃-C₇ cycloalkyl; or R₄ and R₅, taken together with the nitrogen atom they are linked to, a 5-7 atom saturated heterocyclic ring;

   or isomers, mixtures, and pharmaceutically acceptable salts or esters thereof.

2. The method of claim 1, wherein A is selected from -CH₂-, -CH₂-CH₂-, -CH₂-S-, -CH₂-CH₂-S- or -(CH₂)ₙ-OR; n is an integer from 0 to 5; s is 1 or 2; R is a phenyl ring, optionally substituted by one or two substituents independently selected from halogen, trifluoromethyl, a methoxy, or a thienyl ring; R₁ is hydrogen or C₁-C₄ alkyl; one of R₂ and R₃ is hydrogen and the other is C₁-C₄ alkyl, optionally substituted by hydroxy or phenyl, or phenyl, optionally substituted by one or two halogen atoms, or R₂ and R₃ are both methyl or together they can from with the atom they are linked to a cyclopropyl or
a cyclopentyl ring; and R₄, R₅ are hydrogen or C₁-C₄ alkyl or together with the nitrogen they are linked to, the form pyrrolidine or piperidine ring.

3. The method of claim 1, wherein said patient is a mammal.

4. The method of claim 3, wherein said mammal is a human.

5. The method of claim 3, wherein said mammal is administered a dose of the medicament ranging from about 0.3 to about 100 mg/kg body weight per day.

6. The method of claim 1, wherein said one or more inflammatory disorders are selected from the group consisting of: alkylosing spondylitis; cervical arthritis; fibromyalgia; gut; juvenile rheumatoid arthritis; lumbosacral arthritis; osteoarthritis; osteoporosis; psoriatic arthritis; rheumatic disease; rheumatoid arthritis; eczema; psoriasis; dermatitis; sunburn; inflammatory eye conditions; uveitis; conjunctivitis; inflammatory lung disorders; asthma; bronchitis; ulcers; gingivitis; Crohn’s disease; atrophic gastritis; gastritis varialoformae; ulcerative colitis; celiac disease; regional ileitis; peptic ulceration; pyrosis; inflammation of the GI tract due to Helicobacter pylori; visceral inflammation; bladder irritation; cystitis; inflammatory neurological disorders of the central or peripheral nervous system; multiple sclerosis; inflammatory neuropathies; neurological complication of AIDS, and other diseases or disorders associated with inflammation.

7. A method of treating one or more inflammatory disorders in a patient in need thereof, the method comprising administering to the patient an effective amount of at least one anti-inflammatory agent selected from the group consisting of: 2-(4-Benzylxoybenzylamino)-propanamide;

2-[4-(2-Methoxybenzyloxy)-benzylamino]-propanamide;

2-[4-(2-Fluorobenzyloxy)-benzylamino]-propanamide;

(S)-(+)2-[4-(2-Fluorobenzyloxy)-benzylamino]-propanamide;

2-[4-(2-Fluorobenzyloxy)-benzylamino]-2-methyl-propanamide;

(S)-(+)2-[4-(3-Fluorobenzyloxy)-benzylamino]-propanamide, methanesulfonate;

2-[4-(2-Fluorobenzyloxy)-benzylamino]-N-methyl-propanamide;

N-{2-[4-(2-Fluorobenzyloxy)-benzylamino]}-propionyl-pyrrolidine;

2-[4-(3-Methoxybenzyloxy)-benzylamino]-propanamide;

2-[4-(3-Cyanobenzyloxy)-benzylamino]-propanamide;

2-[4-(3-Fluorobenzyloxy)-benzylamino]-propanamide;
26204-502

2-[(4-(3-Fluorobenzyl)oxy)-benzylamino]-2-methyl-propanamide;
2-[(4-(3-Fluorobenzyl)oxy)-benzylamino]-N-methyl-propanamide;
N-[(4-(3-Fluorobenzyl)oxy)-benzylamino]-propionyl-pyrrolidine;
2-[(4-(Fluorobenzyl)oxy)-benzylamino]-propanamide;
2-[(4-(3-Fluorobenzyl)oxy)-benzylamino]-2-methyl-propanamide;
2-[(4-(2-Chlorobenzyl)oxy)-benzylamino]-propanamide;
2-[(4-(3-Chlorobenzyl)oxy)-benzylamino]-propanamide;
2-(4-Benzyloxybenzylamino)-3-hydroxy-propanamide;
2-[(4-(2-Fluorobenzyl)oxy)-benzylamino]-3-hydroxy-propanamide;
2-[(4-(3-Fluorobenzyl)oxy)-benzylamino]-3-hydroxy-propanamide;
2-(4-Benzyloxybenzylamino)-3-hydroxy-N-methyl-propanamide;
2-[(4-(2-Fluorobenzyl)oxy)-benzylamino]-3-hydroxy-N-methyl-propanamide;
2-[(4-(3-Fluorobenzyl)oxy)-benzylamino]-3-hydroxy-N-methyl-propanamide;
2-[(4-(2-Chlorobenzyl)oxy)-benzylamino]-3-hydroxy-N-methyl-propanamide;
2-[(4-(3-Cyanobenzyl)oxy)-benzylamino]-3-hydroxy-N-methyl-propanamide;
2-[(4-(3-Cyanobenzyl)oxy)-benzylamino]-2-methyl-3-hydroxy-N-methyl-propanamide;
2-[(4-(3-Chlorobenzyl)oxy)-phenylethylamino]-propanamide;
2-[(4-[(2-(3-Fluorophenyl)ethoxy]benzylamino)-propanamide;
2-[(4-[(2-(3-Fluorophenyl)ethyl]benzylamino)-propanamide;
2-[(N-(4-Benzyloxybenzy)-N-methylamino]-propanamide;
2-[(4-[(3-Chlorobenzyl)oxy]-phenylethyl]-amino]-propanamide;
2-[(4-Benzylthiobenzylamino]-propanamide;
2-[(4-(2-Fluorobenzylthio)-benzylamino]-propanamide;
2-[(4-(3-Fluorobenzylthio)-benzylamino]-propanamide;
2-[(4-(3-Phenylpropoxy)-benzylamino]-propanamide;
2-[(4-(4-Phenylbutyloxy)-benzylamino]-propanamide;
2-[(4-(5-Phenylpentyloxy)-benzylamino]-propanamide;
2-(4-Benzyloxybenzylamino)-3-phenyl-N-methyl-propanamide;
2-(4-Benzyloxybenzylamino)-3-methyl-N-methyl-butanamide;
2-(4-Benzyloxybenzylamino)-2-phenyl-acetamide;
2-[4-(2-Fluorobenzyloxy)-benzylamino]-2-phenyl-acetamide;
2-[4-(3-Fluorobenzyloxy)-benzylamino]-2-phenyl-acetamide;

2-[4-(2-Fluorobenzyloxy)-benzyl-N-methylamino]-2-phenyl-acetamide;
2-[4-(3-Fluorobenzyloxy)-benzyl-N-methylamino]-2-phenyl-acetamide;
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2-[4-(2-Fluorobenzyloxy)-benzylamino]-2-(2-fluorophenyl)-acetamide;
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2-[4-(3-Fluorobenzyloxy)-benzylamino]-2-(2-fluorophenyl)-acetamide;
2-[4-(3-Fluorobenzyloxy)-benzylamino]-2-(3-fluorophenyl)-acetamide;
2-[4-(3-Chlorobenzyloxy)-benzylamino]-2-(3-fluorophenyl)-acetamide;
2-(4-(2-Thienyloxy)-benzylamino)-propanamide;

or isomers, mixtures, and pharmaceutically acceptable salts thereof.

8. The method of any one of claims 1 or 7, wherein the α-aminoamide is (S)-(+)2-[4-(2-fluorobenzyloxy)-benzylamino]-propanamide.

9. A pharmaceutical composition having anti-inflammatory activity comprising a pharmaceutically acceptable excipient and, as an active agent, an amount of a compound as defined in claim 1 present in an amount, when administered in vivo, effective to reduce or prevent inflammation.
AMENDED CLAIMS
[received by the International Bureau on 13 January 2005 (13.01.05); original claims 1-9 replaced by new claims 1-7 (4 pages)]

1. A method of treating inflammation from one or more inflammatory disorders in a human patient in need thereof, the method comprising administering to a human patient an amount of at least one anti-inflammatory agent effective to reduce or prevent inflammation which is an alpha-aminoamide compound of formula (I),

\[
\begin{align*}
&\text{R} - A - (\text{CH}_2)_n - \text{N} - \text{CR}_2\text{R}_3\text{CONR}_4\text{R}_5 \\
&\text{R}_1
\end{align*}
\]

wherein:

- A is a -(CH₂)ₙ-X- group, wherein n is an integer of 0 to 5, X is CH₂, -O-, -S- or -NH-;
- s is 1 or 2;
- R is a furyl, thiényl, or pyridyl ring or a phenyl ring, optionally substituted by one or two substituents independently selected from halogen, hydroxy, cyano, C₁-C₆ alkyl, C₁-C₆ alkoxy or trifluoromethyl;
- R₁ is hydrogen or C₁-C₆ alkyl or C₃-C₇ cycloalkyl;
- R₂ and R₃ are independently selected from hydrogen; C₁-C₄ alkyl, optionally substituted by hydroxy or phenyl; phenyl, optionally substituted by one or two substituents independently selected from C₁-C₆ alkyl, halogen, hydroxy, C₁-C₆ alkoxy or trifluoromethyl; or R₂ and R₃, taken with the carbon atom which they are linked to, form a C₃-C₆ cycloalkyl ring; and
- R₄, R₅ are, independently, hydrogen, C₁-C₆ alkyl or C₃-C₇ cycloalkyl; or R₄ and R₅, taken together with the nitrogen atom they are linked to, a 5-7 atom saturated heterocyclic ring; or isomers, mixtures, and pharmaceutically acceptable salts or esters thereof, such that inflammation is reduced or prevented.

2. The method of claim 1, wherein A is selected from -CH₂-, -CH₂-CH₂-, -CH₂-S-, -CH₂-CH₂-S- or -(CH₂)ₙ-O-; n is an integer from 0 to 5; s is 1 or 2; R is a phenyl ring, optionally substituted by one or two substituents independently selected from halogen, trifluoromethyl, a methoxy, or a thiényl ring; R₁ is hydrogen or C₁-C₄ alkyl; one of R₂ and R₃ is hydrogen and the other is C₁-C₆ alkyl, optionally substituted by hydroxy or phenyl, or phenyl, optionally substituted by one or two halogen atoms, or R₂ and R₃ are
both methyl or together they can from with the atom they are linked to a cyclopropyl or a cyclopentyl ring; and R₄, R₅ are hydrogen or C₁-C₄ alkyl or together with the nitrogen they are linked to, the form pyrrolidine or piperidine ring.

3. The method of claim 1, wherein said patient is administered a dose of the medicament ranging from about 0.3 to about 100 mg/kg body weight per day.

4. The method of claim 1, wherein said one or more inflammatory disorders are selected from the group consisting of: alkylosing spondylitis; cervical arthritis; fibromyalgia; gut; juvenile rheumatoid arthritis; lumbosacral arthritis; osteoarthritis; osteoporosis; psoriatic arthritis; rheumatoid disease; rheumatoid arthritis; eczema; psoriasis; dermatitis; sunburn; inflammatory eye conditions; uveitis; conjunctivitis; inflammatory lung disorders; asthma; bronchitis; ulcers; gingivitis; Crohn's disease; atrophic gastritis; gastritis varialoforme; ulcerative colitis; celiac disease; regional ileitis; peptic ulceration; pyrosis; inflammation of the GI tract due to Helicobacter pylori; visceral inflammation; bladder irritation; cystitis; inflammatory neurological disorders of the central or peripheral nervous system; multiple sclerosis; inflammatory neuromyopathies; neurological complication of AIDS, and other diseases or disorders associated with inflammation.

5. A method of treating inflammation from one or more inflammatory disorders in a human patient in need thereof, the method comprising administering to a human patient an amount of at least one anti-inflammatory agent effective to reduce or prevent inflammation selected from the group consisting of:

- 2-(4-Benzylloxybenzylamino)-propanamide;
- 2-[4-(2-Methoxybenzylloxy)-benzylamino]-propanamide;
- 2-[4-(2-Fluorobenzylloxy)-benzylamino]-propanamide;
- (S)-(++)-2-[4-(2-Fluorobenzylloxy)-benzylamino]-propanamide;
- 2-[4-(2-Fluorobenzylloxy)-benzylamino]-2-methyl-propanamide;
- (S)-(++)-2-[4-(3-Fluorobenzylloxy)-benzylamino]-propanamide, methanesulfonate;
- 2-[4-(2-Fluorobenzylloxy)-benzylamino]-N-methyl-propanamide;
- N-(2-[4-(2-Fluorobenzylloxy)-benzylamino])-propionyl-pyrrolidine;
- 2-[4-(3-Methoxybenzylloxy)-benzylamino]-propanamide;
- 2-[4-(3-Cyanobenzylloxy)-benzylamino]-propanamide;
- 2-[4-(3-Fluorobenzylloxy)-benzylamino]-propanamide;
- 2-[4-(3-Fluorobenzylloxy)-benzylamino]-2-methyl-propanamide;
- 2-[4-(3-Fluorobenzylloxy)-benzylamino]-N-methyl-propanamide;
N-{2-[4-(3-Fluorobenzyloxy)-benzylamino]}-propionyl-pyrrolidine;
2-[4-(4-Fluorobenzyloxy)-benzylamino]-propanamide;
2-[4-(3-Fluorobenzyloxy)-benzylamino]-2-methyl-propanamide;
2-[4-(2-Chlorobenzyloxy)-benzylamino]-propanamide;
2-[4-(3-Chlorobenzyloxy)-benzylamino]-propanamide;
2-(4-Benzylloxybenzylamino)-3-hydroxy-propanamide;
2-[4-(2-Fluorobenzyloxy)-benzylamino]-3-hydroxy-propanamide;
2-[4-(3-Fluorobenzyloxy)-benzylamino]-3-hydroxy-propanamide;
2-(4-Benzylloxybenzylamino)-3-hydroxy-N-methyl-propanamide;
2-[4-(2-Fluorobenzyloxy)-benzylamino]-3-hydroxy-N-methyl-propanamide;
2-[4-(3-Fluorobenzyloxy)-benzylamino]-3-hydroxy-N-methyl-propanamide;
2-[4-(2-Chlorobenzyloxy)-benzylamino]-3-hydroxy-N-methyl-propanamide;
2-[4-(3-Cyanobenzyloxy)-benzylamino]-3-hydroxy-N-methyl-propanamide;
2-[4-(3-Cyanobenzyloxy)-benzylamino]-2-methyl-3-hydroxy-N-methyl-propanamide;
2-[4-(3-Chlorobenzyloxy)-phenylethylamino]-propanamide;
2-[4-[2-(3-Fluorophenyl)-ethoxy]benzylamino]-propanamide;
2-[4-[2-(3-Fluorophenyl)-ethyl]benzylamino]-propanamide;
2-[N-(4-Benzylloxybenzyl)-N-methylamino]-propanamide;
2-[4-[(3-Chlorobenzyloxy)-phenylethyl]-amino]-propanamide;
2-[4-Benzylthiobenzylamino]-propanamide;
2-[4-(2-Fluorobenzylthio)-benzylamino]-propanamide;
2-[4-(3-Fluorobenzylthio)-benzylamino]-propanamide;
2-[4-(3-Phenylpropoxy)-benzylamino]-propanamide;
2-[4-(4-Phenylbutoxy)-benzylamino]-propanamide;
2-[4-(5-Phenylpentyloxy)-benzylamino]-propanamide;
2-(4-Benzylloxybenzylamino)-3-phenyl-N-methyl-propanamide;
2-(4-Benzylloxybenzylamino)-3-methyl-N-methyl-butanamide;
2-(4-Benzylloxybenzylamino)-2-phenyl-acetamide;
2-[4-(2-Fluorobenzyloxy)-benzylamino]-2-phenyl-acetamide;
2-[4-(3-Fluorobenzyloxy)-benzylamino]-2-phenyl-acetamide;
2-[4-(2-Fluorobenzyloxy)-benzyl-N-methylamino]-2-phenyl-acetamide;
2-[4-(3-Fluorobenzyloxy)-benzyl-N-methylamino]-2-phenyl-acetamide;
2-[4-(3-Chlorobenzyloxy)-benzylamino]-2-phenyl-acetamide;
2-[4-(2-Fluorobenzyloxy)-benzylamino]-2-(2-fluorophenyl)-acetamide;
2-[4-(2-Fluorobenzyloxy)-benzylamino]-2-(3-fluorophenyl)-acetamide;
2-[4-(3-Fluorobenzyloxy)-benzylamino]-2-(2-fluorophenyl)-acetamide;
2-[4-(3-Fluorobenzyloxy)-benzylamino]-2-(3-fluorophenyl)-acetamide;
2-[4-(3-Chlorobenzyloxy)-benzylamino]-2-(3-fluorophenyl)-acetamide;
2-(4-(2-Thienyloxy)-benzylamino)-propanamide;

or isomers, mixtures, and pharmaceutically acceptable salts thereof, such that
inflammation is reduced or prevented.

6. The method of any one of claims 1 or 5, wherein the α-aminoamide is (S)-(+)2-[4-(2-
fluorobenzyloxy)-benzylamino]-propanamide.

7. A pharmaceutical composition having anti-inflammatory activity comprising a
pharmaceutically acceptable excipient and, as an active agent, an amount of a
compound as defined in claim 1 present in an amount, when administered to a human,
effective to reduce or prevent inflammation.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 A61K31/165 A61K31/381 A61P1/04 A61P13/10 A61P19/02

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 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, WPI Data, PAJ, BIOSIS, EMBASE, CHEMABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>WO 03/020273 A (MAJ ROBERTO; BENATTI LUCA (IT); FARIELLO RUGGERO (IT); NEWRON PHARM S) 13 March 2003 (2003-03-13) claim 1, 4; page 7, line 4-7; example 1-3</td>
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

**Date of the actual completion of the international search**

14 October 2004

**Date of mailing of the international search report**

04/11/2004

**Name and mailing address of the ISA**

European Patent Office, P.B. 5816 Patentlaan 2 NL-2280 HV Rijswijk, Tel: (+31-70) 340-2040, Tx: 31 651 epo nl, Fax: (+31-70) 340-3016

Authorized officer

Borst, M
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<td>WO 99/32462 A (SHAH GITA PUNJABHAI ; COX BRIAN (GB); GLAXO GROUP LTD (GB); HEALY MARK) 1 July 1999 (1999-07-01) page 23, paragraph entitled &quot;Biological Data&quot;; page 24, paragraph entitled &quot;Analgesic activity&quot;</td>
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<td>WO 99/55322 A (ASTRA PHARMA PROD ; ASHgar AZIZ (GB); KING ANNE (GB); ASTRA AB (SE)) 4 November 1999 (1999-11-04) page 1, line 1-19; example 1</td>
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<td>WO 2004/066990 A (DYNEN PHARMACEUTICALS INC ; FRASER MATTHEW OLIVER (US); THOR KARL BR) 12 August 2004 (2004-08-12) claim 1, 2, 33</td>
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INTERNATIONAL SEARCH REPORT

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

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

1. [X] Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   
   Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy: Although claims 1-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

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

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

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

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

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

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

Remark on Protest

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

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

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
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