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(54) Title: AMIDE DERIVATIVES AND THEIR USE AS CHLORIDE CHANNEL BLOCKERS

(57) Abstract: The present invention relates to novel amide derivatives useful as chloride channel blockers. In other aspects the invention relates to the use of these compounds in a method for therapy, such as for the treatment of bone metabolic diseases, diseases responsive to modulation of the mast cell or basophil activity, diseases responsive to inhibition of angiogenesis, or sickle cell anaemia, and to pharmaceutical compositions comprising the compounds of the invention.

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AMIDE DERIVATIVES AND THEIR USE AS CHLORIDE CHANNEL BLOCKERS

TECHNICAL FIELD

The present invention relates to novel amide derivatives useful as chloride channel blockers.

In other aspects the invention relates to the use of these compounds in a method for therapy, such as for the treatment of bone metabolic diseases, diseases responsive to modulation of the mast cell or basophil activity, diseases responsive to inhibition of angiogenesis, or sickle cell anaemia, and to pharmaceutical compositions comprising the compounds of the invention.

BACKGROUND ART

Chloride channels serve a wide variety of specific cellular functions and contribute to the normal function of i.a. skeletal and smooth muscle cells. Chloride channels are probably found in every cell, from bacteria to mammals. Their physiological tasks range from cell volume regulation to stabilization of the membrane potential, transepithelial or transcellular transport and acidification of intracellular organelles.

WO 97/45400, WO 98/47879, WO 00/20378 and WO 00/24707 (all NeuroSearch A/S) describe compounds, such as substituted phenyl derivatives, active as chloride channel blockers.

However, there is a strong interest in the provision of more effective and selective compounds with fewer side effects for the treatment of patients with an osteoclast related bone disease, such as osteoporosis.

Also, there is a strong interest in the provision of more effective and selective compounds with fewer side effects for the treatment of patients with diseases responsive to modulation of the mast cell or basophil activity, diseases responsive to inhibition of angiogenesis, or sickle cell anaemia.

SUMMARY OF THE INVENTION

It is an object of the invention to provide novel compounds which act as chloride channel blockers.

A further object of the invention is the provision of compounds with a better selectivity. A still further object is the provision of compounds with a better potency.

A further object of the invention is the provision of compounds that act on cell or tissue specific chloride channels, such as such as chloride channels of osteoclasts. A still further object of the invention is the provision of compounds that act on cell or tissue specific chloride channels, such as such as chloride channels of mast cells or basophils. A further object is the provision of compounds that act on specific groups or subtypes of chloride channels.

A still further object is the provision of compounds with more optimal pharmacodynamic properties such as kinetic behaviour, bioavailability, solubility and efficacy.

In its first aspect, the invention provides a compound of general formula I,

$$\text{A-L-B} \quad \text{(I)}$$

or a pharmaceutically acceptable salt thereof, wherein A, L, and B are as defined below

In its second aspect, the invention provides a pharmaceutical composition, comprising a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

In a further aspect, the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to the blockade of chloride channels.

In a still further aspect, the invention relates to a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to blockade of chloride channels, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

Amide derivatives

In its first aspect, the invention provides a compound of general formula I,

$$\text{A-L-B} \quad \text{(I)}$$

or a pharmaceutically acceptable salt thereof, wherein
one of A or B represents

- a ring system selected from the group consisting of:

    phenyl, pyridyl, naphthyl, pyrolidinyl, and cyclohexanyl;

  which ring system is either substituted with
  two neighbouring fluoro;
  or with a substituent selected from the group consisting of:

    tetrazolyl, and -COOR^a;
    wherein R^a represents hydrogen;

  and which ring system is optionally further substituted with one or more substituents independently selected from the group consisting of:

    - halo, alkyl, and
    - phenyl optionally substituted with -CO-NR^{b}R^c;
      wherein R^b and R^c independently of each other represent alkyl; **or**

- -CH(COOR^a)-R^d;
  wherein R^a represents hydrogen;
  R^d represents phenyl optionally with one or more substituents independently selected from the group consisting of:

  - halo and trifluoromethyl;

the other of A or B represents a ring system selected from the group consisting of:

phenyl, thienyl, indolyl, and naphthyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, nitro, amino, and alkoxy;

L represents

-NH-CO-, -NH-SO$_2$-, -NH-CO-CH$_2$-, -N-CO-CH$_2$-O-, or -CO-.

In one embodiment, one of A or B represents substituted phenyl, substituted pyridyl, substituted naphthyl, substituted pyrolidinyl or substituted cyclohexanyl.

In a second embodiment, one of A or B represents a ring system substituted with two neighbouring fluoro.

In a further embodiment, one of A or B represents a ring system substituted with tetrazolyl.

In a still further embodiment, one of A or B represents a ring system substituted with -COOR^a.

In a further embodiment, the ring system is further substituted with one or more halo.

In a still further embodiment, the ring system is further substituted with one or more alkyl.

In a further embodiment, the ring system is further substituted with one or more phenyl optionally substituted with -CO-NR^{b}R^c.

In a still further embodiment, one of A or B represents -CH(COOR^a)-R^d.

In a further embodiment, the other of A or B represents optionally substituted phenyl, optionally substituted thienyl, optionally substituted indolyl or optionally substituted naphthyl.

In a still further embodiment, the other of A or B represents a ring system substituted with one or more halo.

In a further embodiment, the other of A or B represents a ring system substituted with one or more trifluoromethyl.

In a still further embodiment, the other of A or B represents a ring system substituted with one or more nitro.

In a further embodiment, the other of A or B represents a ring system substituted with one or more amino.

In a still further embodiment, the other of A or B represents a ring system substituted with one or more alkoxy.

In a further embodiment, L represents -NH-CO-.

In a still further embodiment, L represents -NH-SO$_2$-.

In a further embodiment, L represents -NH-CO-CH$_2$-.

In a still further embodiment, L represents -N-CO-CH$_2$-O-.

In a further embodiment, L represents -CO-.

In a special embodiment the compound of the invention is
4-Chloro-2-(3-chloro-benzoylamino)-benzoic acid;
3-Bromo-6-(3-chloro-benzoylamino)-benzoic acid;
3-Chloro-*N*-(2,3-difluoro-phenyl)-benzamide;
5-Bromo-2-[2-(2-chloro-phenyl)-acetylamino]-benzoic acid;
5-Bromo-2-[2-(3-chloro-phenyl)-acetylamino]-benzoic acid;
2-Chloro-2-[2-(2-chloro-phenyl)-acetylamino]-benzoic acid;
4-Chloro-*N*-(2,3-difluoro-phenyl)-benzamide;
3-Bromo-6-(4-chloro-benzoylamino)-benzoic acid;
4-Chloro-2-(4-chloro-benzoylamino)-benzoic acid;
4-Chloro-3-(3-chloro-benzoylamino)-benzoic acid;
2-Chloro-*N*-(2,3-difluoro-phenyl)-benzamide;
4-Chloro-2-(4-chloro-benzenesulfonylamino)-benzoic acid;
4-Chloro-2-[(thiophene-2-carbonyl)-amino]-benzoic acid;
4-Bromo-2-[(thiophene-2-carbonyl)-amino]-benzoic acid;
4-Chloro-3-(4-chloro-benzoylamino)-benzoic acid;
4-Chloro-2-(2-chloro-benzoylamino)-benzoic acid;

3-Bromo-6-(2-chloro-benzoylamino)-benzoic acid;
4-Chloro-2-[2-(3-chloro-phenyl)-acetylamino]-benzoic acid;
2-(4-nitro-benzoylamino)-benzoic acid methyl ester;
4-Chloro-2-(4-nitro-benzoylamino)-benzoic acid methyl ester;
4-Chloro-2-[(1*H*-indole-2-carbonyl)-amino]-benzoic acid;
4-Chloro-2-[(1*H*-indole-3-carbonyl)-amino]-benzoic acid;
2-(4-Nitro-benzoylamino)-benzoic acid;
2-(4-Bromo-benzoylamino)-benzoic acid;
2-(4-Amino-benzoylamino)-benzoic acid;
2-(4-Chloro-benzenesulfonylamino)-3,5-dibromo-benzoic acid;
Thiophene-2-carboxylic acid (2,3-difluoro-phenyl) amide;
4-Chloro-*N*-(2,3-difluoro-phenyl)-benzenesulfonamide;
5-Bromo-2-[(1*H*-indole-3-carbonyl)-amino]-benzoic acid;
5-Bromo-2-[(1*H*-indole-2-carbonyl)-amino]-benzoic acid;
3,5-Dibromo-6-[(1*H*-indole-2-carbonyl)-amino]-benzoic acid;
2-(4-Chloro-benzoylamino)-3,5-dibromo-benzoic acid;
3,5-Dibromo-2-[2-(2-chloro-phenyl)-acetylamino]-benzoic acid;
3,5-Dibromo-2-(2-chloro-benzoylamino)-benzoic acid;
3,5-Dibromo-2-[2-(3-chloro-phenyl)-acetylamino]-benzoic acid;
3,5-Dibromo-2-[2-(4-chloro-phenyl)-acetylamino]-benzoic acid;
2-[2-(4-Chloro-phenyl)-acetylamino]-nicotinic acid;
4-Chloro-2-[2-(4-chloro-phenyl)-acetylamino]-benzoic acid;
5-Bromo-2-[2-(4-chloro-phenyl)-acetylamino]-benzoic acid;
4-Chloro-2-[(5-chloro-1*H*-indole-2-carbonyl)-amino]-benzoic acid;
5-Bromo-2-[(5-chloro-1*H*-indole-2-carbonyl)-amino]-benzoic acid;
2-[2-(3-Chloro-phenyl)-acetylamino]-nicotinic acid;
2-[2-(2-Chloro-phenyl)-acetylamino]-nicotinic acid;
3,5-Dibromo-2-(3-chloro-benzoylamino)-benzoic acid;
4-Chloro-2-(2,4-dichloro-benzoylamino)-benzoic acid;
3,5-Dibromo-2-[(thiophene-2-carbonyl)-amino]-benzoic acid;
4′-(2-Chloro-benzoylamino)-3′-(1*H*-tetrazol-5-yl)-biphenyl-4-carboxylic acid dimethylamide;
2-Chloro-*N*-[5-chloro-2-(1*H*-tetrazol-5-yl)-phenyl]-benzamide;
Thiophene-2-carboxylic acid [4′-dimethylcarbamoyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-amide;
Thiophene-2-carboxylic acid [5-chloro-2-(1*H*-tyetrazol5-yl)-phenyl]-amide;
3-Bromo-6-(2,4-dichloro-benzoylamino)-benzoic acid;
2-(3-Chloro-benzoylamíno)-nicotinic acid;
4-Chloro-2-(3,4-dichloro-benzoylamino)-benzoic acid;

5-Bromo-(3,4-dichloro-benzoylamino)-benzoic acid;
3,5-Dibromo-2-(3,4-dichloro-benzoylamino)-benzoic acid;
3,6-Dibromo-2-(2,4-dichloro-benzoylamino)-benzoic acid;
2-(3,4-Dichloro-benzoylamino)-nicotinic acid;
5-Bromo-2-[2-(2,4-dichloro-phenoxy)-acetylamino]-benzoic acid;
5-Chloro-2-[2-(2,4-dichloro-phenyl)-acetylamino]-benzoic acid;
5-Bromo-2-[2-(2,4-dichloro-phenyl)-acetylamino]-benzoic acid;
3,5-Dibromo-2-[2-(2,4-dichloro-phenyl)-acetylamino]-benzoic acid;
3,5-Dibromo-2-[2-(5-chloro-1*H*-indole-2-carbonyl)-amino]-benzoic acid;
4′-(2-Bromo-benzoylamino)-3′-(1*H*-tetrazol-5-yl)-biphenyl-4-carboxylic acid dimethylamide;
2-Bromo-*N*-[5-chloro-2-(1*H*-tetrazol-5-yl)-phenyl]-benzamide;
5-Bromo-2-(2-bromo-benzoylamino)-benzoic acid;
4-Chloro-2-(2-bromo-benzoylamino)-benzoic acid;
5-Iodo-3-(2,4-dichloro-benzoylamino)-benzoic acid;
5-Iodo-2-(2-chloro-benzoylamino)-benzoic acid;
5-Iodo-2-(2-bromo-benzoylamino)-benzoic acid;
5-Iodo-2-(thiophene-2-yl)-benzoic acid;
5-Iodo-2-(2-fluoro-benzoylamino)-benzoic acid;
5-Methyl-2-(2-fluoro-benzoylamino)-benzoic acid;
5-Chloro-2-(2-fluoro-benzoylamino)-benzoic acid;
5-Bromo-2-(2-fluoro-benzoylamino)-benzoic acid;
5-Bromo-2-(2,6-difluoro-benzoylamino)-benzoic acid;
5-Iodo-2-[(naphthalene-1-carbonyl)-amino]-benzoic acid;
5-Chloro-2-[(naphthalene-1-carbonyl)-amino]-benzoic acid;
5-Bromo-2-[(naphthalene-1-carbonyl)-amino]-benzoic acid;
5-Iodo-2-(2,6-difluoro-benzoylamino)-benzoic acid;
5-Iodo-2-(2,3-difluoro-benzoylamino)-benzoic acid;
5-Chloro-2-(2,3-difluoro-benzoylamino)-benzoic acid;
5-Bromo-2-(2,3-difluoro-benzoylamino)-benzoic acid;
5-Methyl-2-(2,6-dichloro-benzoylamino)-benzoic acid;
5-Chloro-2-(2,6-dichloro-benzoylamino)-benzoic acid;
5-Bromo-2-(2,6-dichloro-benzoylamino)-benzoic acid;
5-Iodo-2-(2,4-difluoro-benzoylamino)-benzoic acid;
5-Chloro-2-(2,4-difluoro-benzoylamino)-benzoic acid;
5-Bromo-2-(2,4-difluoro-benzoylamino)-benzoic acid;
5-Iodo-2-(2,6-dimethoxy-benzoylamino)-benzoic acid;
5-Bromo-2-(2-fluoro-4-trifluoromethyl-benzoylamino)-benzoic acid;
5-Chloro-2-(2-fluoro-4-trifluoromethyl-benzoylamino)-benzoic acid;

5-Iodo-2-(2-fluoro-4-trifluoromethyl-benzoylamino)-benzoic acid;
5-Chloro-2-(2-bromo-benzoylamino)-benzoic acid;
5-Chloro-2-(2,6-dimethoxy-benzoylamino)-benzoic acid;
5-Bromo-2-(2,6-dimethoxy-benzoylamino)-benzoic acid;
5-Iodo-2-(2-methyl-benzoylamino)-benzoic acid;
5-Bromo-2-(2-methyl-benzoylamino)-benzoic acid;
5-Chloro-2-(2,5-difluoro-benzoylamino)-benzoic acid;
5-Bromo-2-(2,5-difluoro-benzoylamino)-benzoic acid;
5-Methyl-2-(2,6-dimethoxy-benzoylamino)-benzoic acid;
5-Iodo-2-(2,5-difluoro-benzoylamino)-benzoic acid;
5-Chloro-2-(2,4-dichloro-benzoylamino)benzoic acid;
1-(2-Chloro-benzoyl)-pyrrolidine-2-carboxylic acid;
1-(2-Fluoro-benzoyl)-pyrrolidine-2-carboxylic acid;
1-(2-Bromo-benzoyl)-pyrrolidine-2-carboxylic acid;
1-(2,6-Dichloro-benzoyl)-pyrrolidine-2-carboxylic acid;
2-(2-Chloro-benzoylamino)-cyclohexane carboxylic acid;
2-(2-Fluoro-benzoylamino)-cyclohexane carboxylic acid;
2-(2-Bromo-benzoylamino)-cyclohexane carboxylic acid;
2-(2,6-Dichloro-benzoylamino)-cyclohexane carboxylic acid;
(2-Chloro-benzoylamino)-(4-fluoro-phenyl)-acetic acid;
(2-Fluoro-benzoylamino)-(4-fluoro-phenyl)-acetic acid;
(2-Bromo-benzoylamino)-(4-fluoro-phenyl)-acetic acid;
(2,6-Dichloro-benzoylamino)-(4-fluoro-phenyl)-acetic acid;
(2-Chloro-benzoylamino)-(3-trifluoromethyl-phenyl)-acetic acid;
(2-Fluoro-benzoylamino)-(3-trifluoromethyl-phenyl)-acetic acid;
(2-Bromo-benzoylamino)-(3-trifluoromethyl-phenyl)-acetic acid;
(2,6-Dichloro-benzoylamino)-(3-trifluoromethyl-phenyl)-acetic acid;
5-Chloro-2-(2-trifluoromethyl-benzoylamino)-benzoic acid;
5-Bromo-2-(2-trifluoromethyl-benzoylamino)-benzoic acid;
5-Iodo-2-(4-ethoxy-benzoylamino)-benzoic acid;
5-Chloro-2-(4-ethoxy-benzoylamino)-benzoic acid;
5-Bromo-2-(4-ethoxy-benzoylamino)-benzoic acid;
3-(2-Chloro-benzoylamino)-naphthalene-2-carboxylic acid;
5-Chloro-2-(2-iodo-benzoylamino)-benzoic acid;
5-Bromo-2-(2-iodo-benzoylamino)-benzoic acid;
3-(2-Bromo-benzoylamino)-naphthalene-2-carboxylic acid;
5-Iodo-2-(2-trifluoromethyl-benzoylamino)-benzoic acid;
5-Iodo-2-(2-iodo-benzoylamino)-benzoic acid;
or a pharmaceutically acceptable salt thereof.

Any combination of two or more of the embodiments described herein is considered within the scope of the present invention.

Definition of Substituents

In the context of this invention halo represents fluoro, chloro, bromo or iodo atom.

Alkyl means a straight chain or branched chain of one to six carbon atoms, including but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and hexyl; methyl, ethyl, propyl and isopropyl are preferred groups.

Alkoxy is O-alkyl, wherein alkyl is as defined above.

Amino is NH_2 or NH-alkyl or N-$(alkyl)_2$, wherein alkyl is as defined above.

Steric Isomers

The chemical compounds of the present invention may exist in (+) and (-) forms as well as in racemic forms. The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e.

physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulphonate derived from benzensulphonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulphonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

Examples of pharmaceutically acceptable cationic salts of a chemical compound of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the zinc, the aluminium, the lithium, the choline, the lysine, and the ammonium salt, and the like, of a chemical compound of the invention containing an anionic group. Such cationic salts may be formed by procedures well known and described in the art.

In the context of this invention the “onium salts” of N-containing compounds are also contemplated as pharmaceutically acceptable salts (aza-onium salts). Preferred aza-onium salts include the alkyl-onium salts, in particular the methyl- and the ethyl-onium salts; the cycloalkyl-onium salts, in particular the cyclopropyl-onium salts; and the cycloalkylalkyl-onium salts, in particular the cyclopropyl-methyl-onium salts.

Methods of Preparation

The compounds of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of a compound of the invention.

While a compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising a compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof. In a further embodiment, the invention provides pharmaceutical compositions comprising more than one compound/prodrug of the invention, such as two different compounds/prodrugs of the invention.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, pulmonal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of sustained release systems include semipermeable matrices of solid hydrophobic polymers containing the compound of the invention, which matrices may be in form of shaped articles, e.g. films or microcapsules.

The chemical compound of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The chemical compound of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a chemical compound of the invention or a pharmaceutically acceptable salt of a chemical compound of the invention.

For preparing pharmaceutical compositions from a chemical compound of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term “preparation” is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The chemical compound according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations, intended for conversion shortly before use to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. In addition to the active component such preparations may comprise colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the chemical compound of the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Compositions suitable for topical administration in the mouth include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration and continuous infusion are preferred compositions.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

A therapeutically effective dose refers to that amount of active ingredient, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED_{50}

and LD_{50}, may be determined by standard pharmacological procedures in cell cultures or experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by the ratio LD_{50}/ED_{50}. Pharmaceutical compositions exhibiting large therapeutic indexes are preferred.

The dose administered must of course be carefully adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 μg/kg i.v. and 1 μg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 μg/kg to about 10 mg/kg/day i.v., and from about 1 μg/kg to about 100 mg/kg/day p.o.

Biological Activity

The compounds of the present invention are useful as blockers of chloride channels, such as chloride channels of osteoclasts. In a further embodiment, the compounds of the present invention are useful as blockers of chloride channels of mast cells and basophils. For measuring the activity of the compounds, various in vitro and in vivo methods, such as various osteoclast inhibition assays known in the art can be used.

Methods of Therapy

Compounds that are active as chloride channels blockers are likely to be useful in the treatment of a number of diseases, disorders and conditions, including bone metabolic diseases. Further, compounds that are active as chloride channel blockers are likely to be useful in the treatment of diseases responsive to modulation of the mast cell or basophil activity, diseases responsive to inhibition of angiogenesis, or sickle cell anaemia.

Thus in a further aspect, the compounds of the invention are considered useful for the treatment, prevention or alleviation of a disease, disorder or condition responsive to the blockade of chloride channels.

In a special embodiment, the disease or a disorder or a condition is a bone metabolic disease, such as an osteoclast related bone disease. In a further embodiment, the disease or a disorder or a condition is an osteoclast related bone disease, such as osteoporosis, postmenopausal osteoporosis, secondary osteoporosis, osteolytic breast cancer bone metastasis, osteolytic cancer invation, and Paget's disease of bone.

In a further special embodiment, the disease or a disorder or a condition is responsive to modulation of the mast cell or basophil activity. In a still further embodiment, the disease or a disorder or a condition is responsive to modulation of mast cell or basophil production or secretion of histamine, neutral proteases or tryptases (such as chymotryptases and carboxypeptidases), leukotrienes (such as LTC4, and LTB4), prostaglandins (such as PGD2), TXA2, PAF, or cytokines (such as IL-4 and TNF-α). In a further embodiment, the disorder or disease that is responsive to modulation of the mast cell or basophil activity is a disorder or disease that is responsive to modulation of mast cell or basophil production or secretion of histamine. In a still further embodiment, the disorder or disease that is responsive to modulation of the mast cell or basophil activity is allergic bronchopulmonary aspergillosis (ABPA), allergic rhinitis, allergic skin disease, allergic skin reaction, drug induced allergic skin reaction, anaphylaxis, asthma, atherosclerosis, atopic dermatitis (AD), bronchial asthma, cancer, chronic obstructive pulmonary disease (COPD), Chrohn's disease, contact dermatitis, dilated cardiomyopathy, fatal asthma, graft rejection, hypersensitivity pneumonitis, ischemic hearth disease, pulmonary fibrosis, rheumatoid arthritis, systemic sclerosis, urticaria, or uveoretinitis. In a special embodiment, the disorder or disease that is responsive to modulation of the mast cell or basophil activity is allergic bronchopulmonary aspergillosis (ABPA), allergic rhinitis, allergic skin disease, allergic skin reaction, drug induced allergic skin reaction, asthma, bronchial asthma, fatal asthma or chronic obstructive pulmonary disease (COPD). In a further special embodiment, the disorder or disease is asthma, bronchial asthma, fatal asthma or chronic obstructive pulmonary disease (COPD). In a further special embodiment, the disorder or disease is COPD. In a still further special embodiment, the disorder or disease is asthma.

In a further special embodiment, the disease or a disorder or a condition is responsive to inhibition of angiogenesis. In a special embodiment, the diseases, disorders or conditions that are responsive to inhibition of angiogenesis are selected from:

- diseases, disorders or conditions that involve the proliferation of tumor cells, such as cancer, prostate cancer, lung cancer, breast cancer, bladder cancer, renal cancer, colon cancer, gastric cancer, pancreatic cancer, ovarian cancer, melanoma, hepatoma, sarcoma and lymphoma;

- ophthalmic angiogenesis related diseases, disorders or conditions, such as exudative macular degeneration, age-related mucular degeneration (AMD), retinopathy, diabetic retinopathy, proliferative diabetic retinopathy, diabetic macular edema (DME), ischemic retinopathy (e.g. retinal vain or artery occlusion), retinopathy of prematurity, neovascular glaucoma, and corneal neovascularization; and
- rheumatoid arthritis, and psoriasis.

In a special embodiment, the disease, disorder or condition to be treated is a preneoplastic disease state. In a further embodiment, the treatment is an anti-metastatic treatment. In a still further embodiment, the disease, disorder or condition to be prevented is metastatic cancer. In a further embodiment, the disease, disorder or condition to be prevented or alleviated is DME.

In the context of this invention, "age-related macular degeneration" (AMD) includes dry AMD (non-exudative AMD) and wet AMD (exudative AMD).

In a still further embodiment, the disease, disorder or condition responsive to the blokade of chloride channels is sickle cell anaemia, brain oedema following ischaemia or tumors, diarrhea, hypertension, diuretic hypertension, glaucoma, or ulcers.

It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge. When administered in combination with compounds known in the art for treatment of the diseases, the dosis regimen may be reduced.

Use of the compounds of the invention may be combined with the use of one or more additional drugs.

Use of the compounds of the invention may be combined with the use of other bone metabolism controlling compounds for the treatment of bone metabolic disease. Such known bone metabolism controlling compounds include bisphophonates such as etidronate, pamidronate, or clodronate optionally combined with calcium; oestrogen-receptor active compounds such as oestrogen i.e. oestradiol and ethyloestradiol, calcitonin, 1,25-dihydroxyvitamine D and metabolites thereof, fluoride, growth hormone, parathyroid hormone, triiodo-thyrosine, collagen degrading enzymes such as protease inhibitors, or cancer therapeutic agents.

Further, use of the compounds of the invention may be combined with the use of one or more additional drugs useful for the treatment, prevention or alleviation of a disease responsive to inhibition of angiogenesis, such as compounds useful for anti-metastatic treatment. Such additional drugs include cytotoxic compounds, antimitotic compounds, and antimetabolites.

Examples of cytotoxic compounds (including cytotoxic alkylating agents) include carmustine (BCNU), fotemustin, temozolomide (temodal), ifosfamide, and cyclofosfamide.

Examples of antimitotic compounds include paclitaxel (taxol) and docetaxel.

An example of antimetabolites includes methotrexat.

Furthermore, the compounds of the invention may be combined or administered in combination with other treatments or therapies. Examples of other treatments or therapies include radiotherapy and surgery.

The treatment of the diseases and disorder can be in chronical or long term treatment as well as a treatment of sudden crisis in the disease and disorder.

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

Example 1

4-Chloro-2-(3-chloro-benzoylamino)-benzoic acid

3-Chloro-benzoylchloride (0.509 g, 2.91 mmol) in benzene (7 ml) was added 2-amino-4-chloro-benzoic acid, the mixture was heated at 90 °C for 4 hours. The product was isolated by filtration washed with water, and the title compound was crystallized from ethyl alcohol. Yield 0.37 g, Mp. 208-209 °C.

The following compounds were made analogously;
3-Bromo-6-(3-chloro-benzoylamino)-benzoic acid; Mp. 240.7-241.2 °C;
3-Chloro-*N*-(2,3-difluoro-phenyl)-benzamide; Mp. 127.5-128.5 °C;
5-Bromo-2-[2-(2-chloro-phenyl)-acetylamino]-benzoic acid; Mp. 226-227°C;
5-Bromo-2-[2-(3-chloro-phenyl)-acetylamino]-benzoic acid; Mp. 205-206°C;
2-Chloro-2-[2-(2-chloro-phenyl)-acetylamino]-benzoic acid; Mp. 201-202°C;
4-Chloro-*N*-(2,3-difluoro-phenyl)-benzamide;
3-Bromo-6-(4-chloro-benzoylamino)-benzoic acid; Mp. 226-227 °C;
4-Chloro-2-(4-chloro-benzoylamino)-benzoic acid; Mp. 233-234 °C;
4-Chloro-3-(3-chloro-benzoylamino)-benzoic acid; Mp. 267-268 °C;
2-Chloro-*N*-(2,3-difluoro-phenyl)-benzamide; Mp. 85-86 °C;
4-Chloro-2-(4-chloro-benzenesulfonylamino)-benzoic acid; Mp. 204-205 °C;
4-Chloro-2-[(thiophene-2-carbonyl)-amino]-benzoic acid; Mp. 248-249 °C;
4-Bromo-2-[(thiophene-2-carbonyl)-amino]-benzoic acid; Mp. 250-251 °C;
4-Chloro-3-(4-chloro-benzoylamino)-benzoic acid; Mp. 260 °C (decomp.);

4-Chloro-2-(2-chloro-benzoylamino)-benzoic acid; Mp. 197-198 °C;
3-Bromo-6-(2-chloro-benzoylamino)-benzoic acid; Mp. 208-209 °C;
4-Chloro-2-[2-(3-chloro-phenyl)-acetylamino]-benzoic acid; Mp 175-176 °C
2-(4-Nitro-benzoylamino)-benzoic acid methyl ester; Mp. 156-157 °C;
4-Chloro-2-(4-nitro-benzoylamino)-benzoic acid methyl ester; Mp. > 280 °C;
4-Chloro-2-[(1*H*-indole-2-carbonyl)-amino]-benzoic acid; Mp. > 280 °C;
4-Chloro-2-[(1*H*-indole-3-carbonyl)-amino]-benzoic acid;
2-(4-Nitro-benzoylamino)-benzoic acid; Mp. 211-212 °C;
2-(4-Bromo-benzoylamino)-benzoic acid; Mp 193-194 °C;
2-(4-Amino-benzoylamino)-benzoic acid; Mp. 205-206 °C;
2-(4-Chloro-benzenesulfonylamino)-3,5-dibromo-benzoic acid; Mp. 196-198 °C;
Thiophene-2-carboxylic acid (2,3-difluoro-phenyl) amide; Mp. 97-99 °C;
4-Chloro-*N*-(2,3-difluoro-phenyl)-benzenesulfonamide; Mp. 105-107 °C;
5-Bromo-2-[(1*H*-indole-3-carbonyl)-amino]-benzoic acid; Mp. > 270 °C;
5-Bromo-2-[(1*H*-indole-2-carbonyl)-amino]-benzoic acid; Mp. > 270 °C;
3,5-Dibromo-6-[(1*H*-indole-2-carbonyl)-amino]-benzoic aicd; Mp. > 260 °C;
2-(4-Chloro-benzoylamino)-3,5-dibromo-benzoic acid; Mp. 201-202 °C;
3,5-Dibromo-2-[2-(2-chloro-phenyl)-acetylamino]-benzoic acid; Mp. 183-184 °C;
3,5-Dibromo-2-(2-chloro-benzoylamino)-benzoic acid; Mp. 190-191 °C;
3,5-Dibromo-2-[2-(3-chloro-phenyl)-acetylamino]-benzoic acid; Mp. 182-183 °C;
3,5-Dibromo-2-[2-(4-chloro-phenyl)-acetylamino]-benzoic acid; Mp. 218-219 °C;
2-[2-(4-Chloro-phenyl)-acetylamino]-nicotinic acid; Mp. 126-127 °C;
4-Chloro-2-[2-(4-chloro-phenyl)-acetylamino]-benzoic acid; Mp. 210-211 °C;
5-Bromo-2-[2-(4-chloro-phenyl)-acetylamino]-benzoic acid; Mp. 211-212 °C;
4-Chloro-2-[(5-chloro-1*H*-indole-2-carbonyl)-amino]-benzoic acid; Mp. 280 °C;
5-Bromo-2-[(5-chloro-1*H*-indole-2-carbonyl)-amino]-benzoic acid; Mp. >270 °C;
2-[2-(3-Chloro-phenyl)-acetylamino]-nicotinic acid; Mp. 168-169 °C;
2-[2-(2-Chloro-phenyl)-acetylamino]-nicotinic acid; Mp. 107-108 °C;
3,5-Dibromo-2-(3-chloro-benzoylamino)-benzoic acid; Mp. 167-168 °C;
4-Chloro-2-(2,4-dichloro-benzoylamino)-benzoic acid; Mp. 222-223 °C;
3,5-Dibromo-2-[(thiophene-2-carbonyl)-amino]-benzoic acid; Mp. 192-193 °C;
4′-(2-Chloro-benzoylamino)-3′-(1*H*-tetrazol-5-yl)-biphenyl-4-carboxylic acid dimethylamide; Mp.240-241 °C;
2-Chloro-*N*-[5-chloro-2-(1*H*-tetrazol-5-yl)-phenyl]-benzamide; Mp. 193-195 °C;
Thiophene-2-carboxylic acid [4′-dimethylcarbamoyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-amide; Mp. 221-222 °C;
Thiophene-2-carboxylic acid [5-chloro-2-(1*H*-tyetrazol5-yl)-phenyl]-amide; 245-246 °C;
3-Bromo-6-(2,4-dichloro-benzoylamino)-benzoic acid; Mp. 247-248 °C;
2-(3-Chloro-benzoylamino)-nicotinic acid; Mp. 156-157 °C;

4-Chloro-2-(3,4-dichloro-benzoylamino)-benzoic acid; Mp. 168-170 °C;
5-Bromo-(3,4-dichloro-benzoylamino)-benzoic acid; Mp. 191-193 °C;
3,5-Dibromo-2-(3,4-dichloro-benzoylamino)-benzoic acid; Mp. 228-230 °C;
3,6-Dibromo-2-(2,4-dichloro-benzoylamino)-benzoic acid; Mp. 164-165 °C;
2-(3,4-Dichloro-benzoylamino)-nicotinic acid; Mp. 240-241 °C;
5-Bromo-2-[2-(2,4-dichloro-phenoxy)-acetylamino]-benzoic acid; Mp. 174-176 °C;
5-Chloro-2-[2-(2,4-dichloro-phenyl)-acetylamino]-benzoic acid; Mp. 224-225 °C;
5-Bromo-2-[2-(2,4-dichloro-phenyl)-acetylamino]-benzoic acid; Mp. 232-233 °C;
3,5-Dibromo-2-[2-(2,4-dichloro-phenyl)-acetylamino]-benzoic acid; Mp. 211-212 °C;
3,5-Dibromo-2-[2-(5-chloro-1*H*-indole-2-carbonyl)-amino]-benzoic acid; Mp.>250 °C;
4′-(2-Bromo-benzoylamino)-3′-(1*H*-tetrazol-5-yl)-biphenyl-4-carboxylic acid dimethylamide; Mp. 250-252 °C;
2-Bromo-*N*-[5-chloro-2-(1*H*-tetrazol-5-yl)-phenyl]-benzamide; Mp. 207-208 °C;
5-Bromo-2-(2-bromo-benzoylamino)-benzoic acid; Mp. 204-205 °C;
4-Chloro-2-(2-bromo-benzoylamino)-benzoic acid; Mp. 200-201 °C;
5-Iodo-3-(2,4-dichloro-benzoylamino)-benzoic acid; Mp 214-216 °C;
5-Iodo-2-(2-chloro-benzoylamino)-benzoic acid; Mp. 197-198 °C;
5-Iodo-2-(2-bromo-benzoylamino)-benzoic acid; Mp. 192-193 °C;
5-Iodo-2-(thiophene-2-yl)-benzoic acid; Mp. 212-213 °C;
5-Iodo-2-(2-fluoro-benzoylamino)-benzoic acid; Mp. 226-228 °C;
5-Methyl-2-(2-fluoro-benzoylamino)-benzoic acid; Mp. 159-160 °C;
5-Chloro-2-(2-fluoro-benzoylamino)-benzoic acid; Mp. > 170 °C;
5-Bromo-2-(2-fluoro-benzoylamino)-benzoic acid; Mp. 223-234 °C;
5-Bromo-2-(2,6-difluoro-benzoylamino)-benzoic acid; Mp. 234-235 °C;
5-Iodo-2-[(naphthalene-1-carbonyl)-amino]-benzoic acid; Mp. 221-222 °C;
5-Chloro-2-[(naphthalene-1-carbonyl)-amino]-benzoic acid; Mp. 225-226 °C;
5-Bromo-2-[(naphthalene-1-carbonyl)-amino]-benzoic acid; Mp. 226-227 °C;
5-Iodo-2-(2,6-difluoro-benzoylamino)-benzoic acid; Mp. 199-200 °C;
5-Iodo-2-(2,3-difluoro-benzoylamino)-benzoic acid; Mp. 220-221 °C;
5-Chloro-2-(2,3-difluoro-benzoylamino)-benzoic acid; Mp. 214-215 °C;
5-Bromo-2-(2,3-difluoro-benzoylamino)-benzoic acid; Mp. 212-213 °C;
5-Methyl-2-(2,6-dichloro-benzoylamino)-benzoic acid; Mp. > 250 °C;
5-Chloro-2-(2,6-dichloro-benzoylamino)-benzoic acid; Mp. 221-222 °C;
5-Bromo-2-(2,6-dichloro-benzoylamino)-benzoic acid; Mp. > 250 °C;
5-Iodo-2-(2,4-difluoro-benzoylamino)-benzoic acid; Mp. 237-238 °C;
5-Chloro-2-(2,4-difluoro-benzoylamino)-benzoic acid; Mp. 231-232 °C;
5-Bromo-2-(2,4-difluoro-benzoylamino)-benzoic acid; Mp. 245-246 °C;
5-Iodo-2-(2,6-dimethoxy-benzoylamino)-benzoic acid; Mp. 235-236 °C;
5-Bromo-2-(2-fluoro-4-trifluoromethyl-benzoylamino)-benzoic acid; Mp. 222-223 °C;

5-Chloro-2-(2-fluoro-4-trifluoromethyl-benzoylamino)-benzoic acid; Mp. 215-216 °C;
5-Iodo-2-(2-fluoro-4-trifluoromethyl-benzoylamino)-benzoic acid; Mp. 228-229 °C;
5-Chloro-2-(2-bromo-benzoylamino)-benzoic acid; Mp. 201-202 °C;
5-Chloro-2-(2,6-dimethoxy-benzoylamino)-benzoic acid; Mp. 175-176 °C;
5-Bromo-2-(2,6-dimethoxy-benzoylamino)-benzoic acid; Mp. 197-198 °C;
5-Iodo-2-(2-methyl-benzoylamino)-benzoic acid; Mp. 192-193 °C;
5-Bromo-2-(2-methyl-benzoylamino)-benzoic acid; Mp. 139-140 °C;
5-Chloro-2-(2,5-difluoro-benzoylamino)-benzoic acid; Mp. 171-172 °C;
5-Bromo-2-(2,5-difluoro-benzoylamino)-benzoic acid; Mp. 169-170 °C;
5-Methyl-2-(2,6-dimethoxy-benzoylamino)-benzoic acid; Mp. 183-184 °C;
5-Iodo-2-(2,5-difluoro-benzoylamino)-benzoic acid; Mp. 230-231 °C;
5-Chloro-2-(2,4-dichloro-benzoylamino)benzoic acid; Mp. 182-183 °C;
1-(2-Chloro-benzoyl)-pyrrolidine-2-carboxylic acid; Mp. 147-150 °C;
1-(2-Fluoro-benzoyl)-pyrrolidine-2-carboxylic acid; Oil;
1-(2-Bromo-benzoyl)-pyrrolidine-2-carboxylic acid; Mp. 151-152 °C;
1-(2,6-Dichloro-benzoyl)-pyrrolidine-2-carboxylic acid; Mp. 190-194 °C;
2-(2-Chloro-benzoylamino)-cyclohexane carboxylic acid; Mp. 198-202 °C;
2-(2-Fluoro-benzoylamino)-cyclohexane carboxylic acid; Mp. 190-191 °C;
2-(2-Bromo-benzoylamino)-cyclohexane carboxylic acid; Mp. 230-231 °C;
2-(2,6-Dichloro-benzoylamino)-cyclohexane carboxylic acid; Mp. 227-228 °C;
(2-Chloro-benzoylamino)-(4-fluoro-phenyl)-acetic acid; Mp.173-178 °C;
(2-Fluoro-benzoylamino)-(4-fluoro-phenyl)-acetic acid; Mp. 89-139 °C;
(2-Bromo-benzoylamino)-(4-fluoro-phenyl)-acetic acid; Mp. 177-178 °C;
(2,6-Dichloro-benzoylamino)-(4-fluoro-phenyl)-acetic acid; Mp. 243-245 °C;
(2-Chloro-benzoylamino)-(3-trifluoromethyl-phenyl)-acetic acid; Mp. 121-136 °C;
(2-Fluoro-benzoylamino)-(3-trifluoromethyl-phenyl)-acetic acid; Mp. 94-105 °C;
(2-Bromo-benzoylamino)-(3-trifluoromethyl-phenyl)-acetic acid; Mp. 147-151 °C;
(2,6-Dichloro-benzoylamino)-(3-trifluoromethyl-phenyl)-acetic acid;
5-Chloro-2-(2-trifluoromethyl-benzoylamino)-benzoic acid;
5-Bromo-2-(2-trifluoromethyl-benzoylamino)-benzoic acid; Mp. 151-152 °C;
5-Iodo-2-(4-ethoxy-benzoylamino)-benzoic acid; Mp. 252-253 °C;
5-Chloro-2-(4-ethoxy-benzoylamino)-benzoic acid; Mp. 221-222 °C;
5-Bromo-2-(4-ethoxy-benzoylamino)-benzoic acid; Mp. 224-225 °C;
3-(2-Chloro-benzoylamino)-naphthalene-2-carboxylic acid; Mp. > 260 °C;
5-Chloro-2-(2-iodo-benzoylamino)-benzoic acid; Mp. 196-197.5 °C;
5-Bromo-2-(2-iodo-benzoylamino)-benzoic acid; Mp. 188-189 °C;
3-(2-Bromo-benzoylamino)-naphthalene-2-carboxylic acid; Mp. 225-226 °C;
5-Iodo-2-(2-trifluoromethyl-benzoylamino)-benzoic acid; Mp. 179-180 °C;
5-Iodo-2-(2-iodo-benzoylamino)-benzoic acid; Mp. 206-207 °C.

CLAIMS:

1. A chemical compound represented by general formula (I)

$$\text{A-L-B} \quad \text{(I)}$$

or a pharmaceutically acceptable salt thereof, wherein

one of A or B represents

- a ring system selected from the group consisting of:
  phenyl, pyridyl, naphthyl, pyrolidinyl, and cyclohexanyl;
  which ring system is either substituted with
  two neighbouring fluoro;
  or with a substituent selected from the group consisting of:
  tetrazolyl, and -COOR^a;
  wherein R^a represents hydrogen;
  and which ring system is optionally further substituted with one or more substituents independently selected from the group consisting of:
  - halo, alkyl, and
  - phenyl optionally substituted with -CO-NR^{b}R^c;
    wherein R^b and R^c independently of each other represent alkyl; **or**
- -CH(COOR^a)-R^d;
  wherein R^a represents hydrogen;
  R^d represents phenyl optionally with one or more substituents independently selected from the group consisting of:
  - halo and trifluoromethyl;

the other of A or B represents a ring system selected from the group consisting of:
phenyl, thienyl, indolyl, and naphthyl;
which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:
halo, trifluoromethyl, nitro, amino, and alkoxy;

L represents
-NH-CO-, -NH-SO$_2$-, -NH-CO-CH$_2$-, -N-CO-CH$_2$-O-, or -CO-.

2. The compound of claim 1, being
4-Chloro-2-(3-chloro-benzoylamino)-benzoic acid;
3-Bromo-6-(3-chloro-benzoylamino)-benzoic acid;
3-Chloro-*N*-(2,3-difluoro-phenyl)-benzamide;

5-Bromo-2-[2-(2-chloro-phenyl)-acetylamino]-benzoic acid;
5-Bromo-2-[2-(3-chloro-phenyl)-acetylamino]-benzoic acid;
2-Chloro-2-[2-(2-chloro-phenyl)-acetylamino]-benzoic acid;
4-Chloro-*N*-(2,3-difluoro-phenyl)-benzamide;
3-Bromo-6-(4-chloro-benzoylamino)-benzoic acid;
4-Chloro-2-(4-chloro-benzoylamino)-benzoic acid;
4-Chloro-3-(3-chloro-benzoylamino)-benzoic acid;
2-Chloro-*N*-(2,3-difluoro-phenyl)-benzamide;
4-Chloro-2-(4-chloro-benzenesulfonylamino)-benzoic acid;
4-Chloro-2-[(thiophene-2-carbonyl)-amino]-benzoic acid;
4-Bromo-2-[(thiophene-2-carbonyl)-amino]-benzoic acid;
4-Chloro-3-(4-chloro-benzoylamino)-benzoic acid;
4-Chloro-2-(2-chloro-benzoylamino)-benzoic acid;
3-Bromo-6-(2-chloro-benzoylamino)-benzoic acid;
4-Chloro-2-[2-(3-chloro-phenyl)-acetylamino]-benzoic acid;
2-(4-Nitro-benzoylamino)-benzoic acid methyl ester;
4-Chloro-2-(4-nitro-benzoylamino)-benzoic acid methyl ester;
4-Chloro-2-[(1*H*-indole-2-carbonyl)-amino]-benzoic acid;
4-Chloro-2-[(1*H*-indole-3-carbonyl)-amino]-benzoic acid;
2-(4-Nitro-benzoylamino)-benzoic acid;
2-(4-Bromo-benzoylamino)-benzoic acid;
2-(4-Amino-benzoylamino)-benzoic acid;
2-(4-Chloro-benzenesulfonylamino)-3,5-dibromo-benzoic acid;
Thiophene-2-carboxylic acid (2,3-difluoro-phenyl) amide;
4-Chloro-*N*-(2,3-difluoro-phenyl)-benzenesulfonamide;
5-Bromo-2-[(1*H*-indole-3-carbonyl)-amino]-benzoic acid;
5-Bromo-2-[(1*H*-indole-2-carbonyl)-amino]-benzoic acid;
3,5-Dibromo-6-[(1*H*-indole-2-carbonyl)-amino]-benzoic acid;
2-(4-Chloro-benzoylamino)-3,5-dibromo-benzoic acid;
3,5-Dibromo-2-[2-(2-chloro-phenyl)-acetylamino]-benzoic acid;
3,5-Dibromo-2-(2-chloro-benzoylamino)-benzoic acid;
3,5-Dibromo-2-[2-(3-chloro-phenyl)-acetylamino]-benzoic acid;
3,5-Dibromo-2-[2-(4-chloro-phenyl)-acetylamino]-benzoic acid;
2-[2-(4-Chloro-phenyl)-acetylamino]-nicotinic acid;
4-Chloro-2-[2-(4-chloro-phenyl)-acetylamino]-benzoic acid;
5-Bromo-2-[2-(4-chloro-phenyl)-acetylamino]-benzoic acid;
4-Chloro-2-[(5-chloro-1*H*-indole-2-carbonyl)-amino]-benzoic acid;
5-Bromo-2-[(5-chloro-1*H*-indole-2-carbonyl)-amino]-benzoic acid;
2-[2-(3-Chloro-phenyl)-acetylamino]-nicotinic acid;

2-[2-(2-Chloro-phenyl)-acetylamino]-nicotinic acid;
3,5-Dibromo-2-(3-chloro-benzoylamino)-benzoic acid;
4-Chloro-2-(2,4-dichloro-benzoylamino)-benzoic acid;
3,5-Dibromo-2-[(thiophene-2-carbonyl)-amino]-benzoic acid;
4′-(2-Chloro-benzoylamino)-3′-(1*H*-tetrazol-5-yl)-biphenyl-4-carboxylic acid dimethylamide;
2-Chloro-*N*-[5-chloro-2-(1*H*-tetrazol-5-yl)-phenyl]-benzamide;
Thiophene-2-carboxylic acid [4′-dimethylcarbamoyl-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-amide;
Thiophene-2-carboxylic acid [5-chloro-2-(1*H*-tyetrazol5-yl)-phenyl]-amide;
3-Bromo-6-(2,4-dichloro-benzoylamino)-benzoic acid;
2-(3-Chloro-benzoylamíno)-nicotinic acid;
4-Chloro-2-(3,4-dichloro-benzoylamino)-benzoic acid;
5-Bromo-(3,4-dichloro-benzoylamino)-benzoic acid;
3,5-Dibromo-2-(3,4-dichloro-benzoylamino)-benzoic acid;
3,6-Dibromo-2-(2,4-dichloro-benzoylamino)-benzoic acid;
2-(3,4-Dichloro-benzoylamino)-nicotinic acid;
5-Bromo-2-[2-(2,4-dichloro-phenoxy)-acetylamino]-benzoic acid;
5-Chloro-2-[2-(2,4-dichloro-phenyl)-acetylamino]-benzoic acid;
5-Bromo-2-[2-(2,4-dichloro-phenyl)-acetylamino]-benzoic acid;
3,5-Dibromo-2-[2-(2,4-dichloro-phenyl)-acetylamino]-benzoic acid;
3,5-Dibromo-2-[2-(5-chloro-1*H*-indole-2-carbonyl)-amino]-benzoic acid;
4′-(2-Bromo-benzoylamino)-3′-(1*H*-tetrazol-5-yl)-biphenyl-4-carboxylic acid dimethylamide;
2-Bromo-*N*-[5-chloro-2-(1*H*-tetrazol-5-yl)-phenyl]-benzamide;
5-Bromo-2-(2-bromo-benzoylamino)-benzoic acid;
4-Chloro-2-(2-bromo-benzoylamino)-benzoic acid;
5-Iodo-3-(2,4-dichloro-benzoylamino)-benzoic acid;
5-Iodo-2-(2-chloro-benzoylamino)-benzoic acid;
5-Iodo-2-(2-bromo-benzoylamino)-benzoic acid;
5-Iodo-2-(thiophene-2-yl)-benzoic acid;
5-Iodo-2-(2-fluoro-benzoylamino)-benzoic acid;
5-Methyl-2-(2-fluoro-benzoylamino)-benzoic acid;
5-Chloro-2-(2-fluoro-benzoylamino)-benzoic acid;
5-Bromo-2-(2-fluoro-benzoylamino)-benzoic acid;
5-Bromo-2-(2,6-difluoro-benzoylamino)-benzoic acid;
5-Iodo-2-[(naphthalene-1-carbonyl)-amino]-benzoic acid;
5-Chloro-2-[(naphthalene-1-carbonyl)-amino]-benzoic acid;
5-Bromo-2-[(naphthalene-1-carbonyl)-amino]-benzoic acid;

5-Iodo-2-(2,6-difluoro-benzoylamino)-benzoic acid;
5-Iodo-2-(2,3-difluoro-benzoylamino)-benzoic acid;
5-Chloro-2-(2,3-difluoro-benzoylamino)-benzoic acid;
5-Bromo-2-(2,3-difluoro-benzoylamino)-benzoic acid;
5-Methyl-2-(2,6-dichloro-benzoylamino)-benzoic acid;
5-Chloro-2-(2,6-dichloro-benzoylamino)-benzoic acid;
5-Bromo-2-(2,6-dichloro-benzoylamino)-benzoic acid;
5-Iodo-2-(2,4-difluoro-benzoylamino)-benzoic acid;
5-Chloro-2-(2,4-difluoro-benzoylamino)-benzoic acid;
5-Bromo-2-(2,4-difluoro-benzoylamino)-benzoic acid;
5-Iodo-2-(2,6-dimethoxy-benzoylamino)-benzoic acid;
5-Bromo-2-(2-fluoro-4-trifluoromethyl-benzoylamino)-benzoic acid;
5-Chloro-2-(2-fluoro-4-trifluoromethyl-benzoylamino)-benzoic acid;
5-Iodo-2-(2-fluoro-4-trifluoromethyl-benzoylamino)-benzoic acid;
5-Chloro-2-(2-bromo-benzoylamino)-benzoic acid;
5-Chloro-2-(2,6-dimethoxy-benzoylamino)-benzoic acid;
5-Bromo-2-(2,6-dimethoxy-benzoylamino)-benzoic acid;
5-Iodo-2-(2-methyl-benzoylamino)-benzoic acid;
5-Bromo-2-(2-methyl-benzoylamino)-benzoic acid;
5-Chloro-2-(2,5-difluoro-benzoylamino)-benzoic acid;
5-Bromo-2-(2,5-difluoro-benzoylamino)-benzoic acid;
5-Methyl-2-(2,6-dimethoxy-benzoylamino)-benzoic acid;
5-Iodo-2-(2,5-difluoro-benzoylamino)-benzoic acid;
5-Chloro-2-(2,4-dichloro-benzoylamino)benzoic acid;
1-(2-Chloro-benzoyl)-pyrrolidine-2-carboxylic acid;
1-(2-Fluoro-benzoyl)-pyrrolidine-2-carboxylic acid;
1-(2-Bromo-benzoyl)-pyrrolidine-2-carboxylic acid;
1-(2,6-Dichloro-benzoyl)-pyrrolidine-2-carboxylic acid;
2-(2-Chloro-benzoylamino)-cyclohexane carboxylic acid;
2-(2-Fluoro-benzoylamino)-cyclohexane carboxylic acid;
2-(2-Bromo-benzoylamino)-cyclohexane carboxylic acid;
2-(2,6-Dichloro-benzoylamino)-cyclohexane carboxylic acid;
(2-Chloro-benzoylamino)-(4-fluoro-phenyl)-acetic acid;
(2-Fluoro-benzoylamino)-(4-fluoro-phenyl)-acetic acid;
(2-Bromo-benzoylamino)-(4-fluoro-phenyl)-acetic acid;
(2,6-Dichloro-benzoylamino)-(4-fluoro-phenyl)-acetic acid;
(2-Chloro-benzoylamino)-(3-trifluoromethyl-phenyl)-acetic acid;
(2-Fluoro-benzoylamino)-(3-trifluoromethyl-phenyl)-acetic acid;
(2-Bromo-benzoylamino)-(3-trifluoromethyl-phenyl)-acetic acid;

(2,6-Dichloro-benzoylamino)-(3-trifluoromethyl-phenyl)-acetic acid;
5-Chloro-2-(2-trifluoromethyl-benzoylamino)-benzoic acid;
5-Bromo-2-(2-trifluoromethyl-benzoylamino)-benzoic acid;
5-Iodo-2-(4-ethoxy-benzoylamino)-benzoic acid;
5-Chloro-2-(4-ethoxy-benzoylamino)-benzoic acid;
5-Bromo-2-(4-ethoxy-benzoylamino)-benzoic acid;
3-(2-Chloro-benzoylamino)-naphthalene-2-carboxylic acid;
5-Chloro-2-(2-iodo-benzoylamino)-benzoic acid;
5-Bromo-2-(2-iodo-benzoylamino)-benzoic acid;
3-(2-Bromo-benzoylamino)-naphthalene-2-carboxylic acid;
5-Iodo-2-(2-trifluoromethyl-benzoylamino)-benzoic acid;
5-Iodo-2-(2-iodo-benzoylamino)-benzoic acid;
or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1-2, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

4. The use of a compound according to any one of claims 1-2, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to the blockade of chloride channels.

5. The use according to claim 4, wherein the disease, disorder or condition responsive to the blockade of chloride channels is a bone metabolic disease or an osteoclast related bone disease.

6. The use according to claim 4, wherein the disease, disorder or condition responsive to the blockade of chloride channels is osteoporosis, postmenopausal osteoporosis, secondary osteoporosis, osteolytic breast cancer bone metastasis, osteolytic cancer invation, or Paget's disease of bone.

7. The use according to claim 4, wherein the disease, disorder or condition responsive to the blockade of chloride channels is a disease, disorder or condition responsive to the mast cell or basophil activity, or to inhibition of angiogenesis.

8. The use according to claim 4, wherein the disease, disorder or condition responsive to the blockade of chloride channels is allergic bronchopulmonary aspergillosis (ABPA), allergic rhinitis, allergic skin disease, allergic skin reaction, drug induced allergic skin reaction, anaphylaxis, asthma, atherosclerosis, atopic dermatitis (AD), bronchial asthma, cancer, chronic obstructive pulmonary disease (COPD), Chrohn's disease, contact dermatitis, dilated cardiomyopathy, fatal asthma, graft rejection, hypersensitivity pneumonitis, ischemic hearth disease, pulmonary fibrosis, rheumatoid arthritis, systemic sclerosis, urticaria, uveoretinitis, cancer, metastatic cancer, prostate cancer, lung cancer, breast cancer, bladder cancer, renal cancer, colon cancer, gastric cancer, pancreatic cancer, ovarian cancer, melanoma, hepatoma, sarcoma, lymphoma, exudative macular degeneration, age-related mucular degeneration (AMD), retinopathy, diabetic retinopathy, proliferative diabetic retinopathy, ischemic retinopathy (e.g. retinal vain or artery occlusion), retinopathy of prematurity, neovascular glaucoma, corneal neovascularization, rheumatoid arthritis, psoriasis, sickle cell anaemia, brain oedema following ischaemia or tumors, diarrhea, hypertension, diuretic hypertension, glaucoma, or ulcers.

9. A method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to the blockade of chloride channels, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound according to any one of the claims 1-2, or any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00576

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C233/00 C07C235/00 C07C311/15 C07D257/04 C07D207/00
C07D209/00 C07D333/02 A61K31/165 A61K31/395 A61K31/381
A61P19/00 A61P43/00

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 C07C C07D A61K

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, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03 000245 A (POSEIDON PHARMACEUTICALS AS ;DAHL BJARNE H (DK); MADSEN LARS SIIM) 3 January 2003 (2003-01-03) the whole document ---	1-9
P,X	WO 03 000267 A (ALLEN JOANNE VICTORIA ;CAULKETT PETER WILLIAM RODNEY (GB); HARGREA) 3 January 2003 (2003-01-03) the whole document ---	1-3
X	WO 02 39987 A (DAHL BJARNE H ;NEUROSEARCH AS (DK); CHRISTOPHERSEN PALLE (DK)) 23 May 2002 (2002-05-23) the whole document --- -/--	1-9

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search
8 December 2003

Date of mailing of the international search report
12.02.2004

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GERD STRANDELL

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 24707 A (DAHL BJARNE H ;NEUROSEARCH AS (DK); CHRISTOPHERSEN PALLE (DK)) 4 May 2000 (2000-05-04) the whole document ---	1-9
X	S. R. RAHALKAR ET AL: "Potential antituberculosis drugs "synthesis of mono-N-arylamides of Quinolinic acid" INDIAN DRUGS, vol. 23, no. 10, 1986, pages 545-548, XP002264100 page 547 compounds 1-4 ---	1-3
X	FR 2 102 170 A (SOCIBRE) 7 April 1972 (1972-04-07) the whole document ---	1-3
X	FR 2 143 577 A (UGINE KUHLMANN) 9 February 1973 (1973-02-09) the whole document ---	1-3
X	DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS accession no. 1982:491971, Document 97:91971; NIPPON ZOKI PHARMACEUTICAL CO., LTD.: "Benzoylaminophenylcarboxylic acid derivatives" XP002264101 abstract & JP 57 064655 A 19 April 1982 (1982-04-19) ---	1-3
X	CA 519 684 A (ALLEN E. SMITH ET AL) 20 December 1955 (1955-12-20) column 1, line 25 -column 2, line 23 ---	1,2
X	US 4 108 632 A (HANSEN DALE J ET AL) 22 August 1978 (1978-08-22) the whole document ---	1,2
X	GB 1 162 727 A (SUMITOMO CHEMICAL COMPANY LIMITED) 27 August 1969 (1969-08-27) the whole document ---	1,2
X	DATABASE WPI Section Ch, Week 199705 Derwent Publications Ltd., London, GB; Class B03, AN 1997-048240 XP002264103 & JP 08 301760 A (SHISEIDO CO LTD), 19 November 1996 (1996-11-19) abstract --- -/--	1,2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00576

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 320 484 A (SANWA KAGAKU KENKYUSHO CO) 13 June 1973 (1973-06-13) claim 6 formula II ---	1,2
X	US 3 100 226 A (RAMAN HARVEY P ET AL) 6 August 1963 (1963-08-06) claims column 1, line 11 - line 42 ---	1,2
X	DATABASE REGISTRY ON STN INTERN. [Online] File Registry No. 444077-81-0, 443673-06-1, 443673-02-7, 402590-25-4, 392726-58-8, 311762-70-6,on on; 18705-79-8, 7595-67-7. , 16 August 2002 (2002-08-16) XP002264102 abstract ---	1,2
X	WO 98 47879 A (NEUROSEARCH AS ;PEDERSEN OVE (DK); CHRISTOPHERSEN PALLE (DK)) 29 October 1998 (1998-10-29) the whole document ---	1-9
X	WO 97 45400 A (NEUROSEARCH AS ;PEDERSEN OVE (DK); CHRISTOPHERSEN PALLE (DK)) 4 December 1997 (1997-12-04) the whole document ---	1-9
X	WO 99 07669 A (AMERICAN HOME PROD) 18 February 1999 (1999-02-18) the whole document -----	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 03/00576

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. ☒ Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

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 II Observations where unity of invention is lacking (Continuation of item 2 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 9

Claim 9 relates to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds or compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK 03/00576

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03000245 A	03-01-2003	WO 03000245 A1	03-01-2003
WO 03000267 A	03-01-2003	WO 03000267 A1	03-01-2003
WO 0239987 A	23-05-2002	AU 2349202 A	27-05-2002
		WO 0239987 A2	23-05-2002
WO 0024707 A	04-05-2000	AU 759275 B2	10-04-2003
		AU 6325999 A	15-05-2000
		BR 9914638 A	03-07-2001
		CA 2342626 A1	04-05-2000
		CN 1322194 T	14-11-2001
		WO 0024707 A1	04-05-2000
		EE 200100185 A	15-08-2002
		EP 1123274 A1	16-08-2001
		HU 0103673 A2	28-02-2002
		JP 2002528432 T	03-09-2002
		JP 2003246773 A	02-09-2003
		NO 20011956 A	20-04-2001
		NZ 510098 A	26-09-2003
		PL 347371 A1	08-04-2002
		SK 5222001 A3	09-05-2002
		TR 200101126 T2	21-09-2001
		US 2002032210 A1	14-03-2002
		US 2002037905 A1	28-03-2002
		ZA 200101824 A	05-03-2002
FR 2102170 A	07-04-1972	BE 754750 A1	12-02-1971
		FR 2102170 A2	07-04-1972
FR 2143577 A	09-02-1973	FR 2143577 A1	09-02-1973
JP 57064655 A	19-04-1982	JP 1484933 C	14-03-1989
		JP 63032064 B	28-06-1988
CA 519684 A		NONE	
US 4108632 A	22-08-1978	BR 7708500 A	15-08-1978
		FR 2374846 A1	21-07-1978
		IT 1089437 B	18-06-1985
		ZA 7707588 A	25-10-1978
GB 1162727 A	27-08-1969	DE 1667993 B1	28-10-1971
		FR 1583442 A	31-10-1969
JP 8301760 A	19-11-1996	NONE	
GB 1320484 A	13-06-1973	FR 2095112 A5	04-02-1972
		JP 48017267 B	28-05-1973
		BE 768276 A1	03-11-1971
		CH 555806 A	15-11-1974
		DE 2128381 A1	16-12-1971
		NL 7107358 A	13-12-1971
		SE 366542 B	29-04-1974
		US 3867437 A	18-02-1975
US 3100226 A	06-08-1963	FR 1270377 A	25-08-1961
		GB 900131 A	04-07-1962

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 03/00576

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9847879 A	29-10-1998	AT 226189 T	15-11-2002
		AT 248824 T	15-09-2003
		AU 735545 B2	12-07-2001
		AU 2962197 A	05-01-1998
		AU 728520 B2	11-01-2001
		AU 6919698 A	13-11-1998
		BR 9808938 A	01-08-2000
		CA 2255858 A1	04-12-1997
		CN 1118462 B	20-08-2003
		DE 69716424 D1	21-11-2002
		DE 69716424 T2	20-02-2003
		DE 69817802 D1	09-10-2003
		WO 9847879 A1	29-10-1998
		DK 977741 T3	01-12-2003
		WO 9745400 A1	04-12-1997
		EP 0906273 A1	07-04-1999
		EP 0977741 A1	09-02-2000
		JP 2000511167 T	29-08-2000
		JP 2001521532 T	06-11-2001
		NZ 332789 A	26-05-2000
		NZ 337976 A	25-05-2001
		RU 2197482 C2	27-01-2003
		SK 144799 A3	16-05-2000
		TR 9902593 T2	21-03-2000
		US 6417393 B1	09-07-2002
		US 6297261 B1	02-10-2001
		US 2002037905 A1	28-03-2002
WO 9745400 A	04-12-1997	AT 226189 T	15-11-2002
		AU 735545 B2	12-07-2001
		AU 2962197 A	05-01-1998
		AU 2962297 A	05-01-1998
		CA 2255858 A1	04-12-1997
		DE 69716424 D1	21-11-2002
		DE 69716424 T2	20-02-2003
		WO 9745400 A1	04-12-1997
		WO 9745111 A1	04-12-1997
		EP 0906273 A1	07-04-1999
		EP 0910358 A1	28-04-1999
		JP 2000511167 T	29-08-2000
		JP 2000510862 T	22-08-2000
		NZ 332789 A	26-05-2000
		US 6417393 B1	09-07-2002
		AT 248824 T	15-09-2003
		AU 728520 B2	11-01-2001
		AU 6919698 A	13-11-1998
		BR 9808938 A	01-08-2000
		CN 1118462 B	20-08-2003
		DE 69817802 D1	09-10-2003
		WO 9847879 A1	29-10-1998
		DK 977741 T3	01-12-2003
		EP 0977741 A1	09-02-2000
		JP 2001521532 T	06-11-2001
		NZ 337976 A	25-05-2001
		RU 2197482 C2	27-01-2003
		SK 144799 A3	16-05-2000
		TR 9902593 T2	21-03-2000
		US 6297261 B1	02-10-2001

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK 03/00576

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9745400 A		US 2002037905 A1	28-03-2002
WO 9907669 A	18-02-1999	AU 8684598 A	01-03-1999
		BR 9811845 A	08-08-2000
		CN 1273579 T	15-11-2000
		EP 1003712 A1	31-05-2000
		JP 2001513526 T	04-09-2001
		WO 9907669 A1	18-02-1999