Our Ref 331726

FORM 1

AUSTRALIA
Patents Act

637623

APPLICATION FOR A STANDARD PATENT

F.HOFFMANN-LA ROCHE AG of 124 Grenzacherstrasse, CH-4002 Basel, Switzerland hereby applies for the grant of a standard patent for an invention entitled

Aromatic carboxylic amides

which is described in the accompanying complete specification.

Details of basic application:

Country	Number	Date
Switzerland	2818/89	28 July 1989

The address for service is:

ARTHUR S. CAVE & CO.
Patent & Trade Mark Attorneys
Level 10, 10 Barrack Street
SYDNEY NSW 2000

DATED this 25th day of July, 1990

F.HOFFMANN-LA ROCHE AG
By Its Patent Attorneys
ARTHUR S. CAVE & CO.

J.G. SIELY, FIPAA

TO:
The Commissioner of Patents
COMMONWEALTH OF AUSTRALIA

FEE: $318.00

4041W/gs

AUSTRALIA
CONVENTION
STANDARD
& PETTY PATEN
DECLARATION

COMMONWEALTH OF AUSTRALIA

THE PATENTS ACT 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made for a patent for an invention entitled:

RAN 4060/153

Title of Invention

Aromatic Carboxylic Amides

Full name(s) and address(es) of Declarant(s)

I Fridolin Klausner

of 187 Baselmattweg, 4123 Allschwil, Switzerland

do solemnly and sincerely declare as follows:-

Full name(s) of Applicant(s)

1. I am authorised by

F.HOFFMANN-LA ROCHE AG

of 124-184 Grenzacherstrasse, CH-4002 Basle, Switzerland

the applicant(s) for the patent to make this declaration on its/their behalf.

2. The basic application(s) as defined by Section 141 of the Act was/were made

Basic Country(ies) in Switzerland

Priority Date(s) on July 28, 1989

Basic Applicant(s) by [X] F.HOFFMANN-LA ROCHE AG

[ ] the inventor(s) cited in paragraph 3.

3.

Full name(s) and address(es) of inventor(s)

1) Michael Klaus, 6 Am Hellenrain, 7858 Weil/Rhein, Federal Republic of Germany.

2) Peter Mohr, 9 Martinsgasse, 4051 Basle, Switzerland

(respectively) is/are the actual inventor(s) of the invention and the facts upon which the applicant(s) is/are entitled to make the application are as follows:

Set out how Applicant(s) derive title from actual inventor(s) e.g. The Applicant(s) is/are the assignee(s) of the invention from the inventor(s)

( ) the inventor(s) have assigned the invention to Hoffmann-La Roche Inc., Nutley, USA, who have re-assigned all their rights for Australia to the Applicant.

(X) the Applicant is the assignee of the invention from the inventor(s).

4. The basic application(s) referred to in paragraph 2 of this Declaration was/were the first application(s) made in a Convention country in respect of the invention(s) the subject of the application.

Declared at Basle, this 15th day of June, 19 90

To:

The Commissioner of Patents,
COMMONWEALTH OF AUSTRALIA

Fridolin Klausner
Signature of Declarant(s)

AU9059892

(12) PATENT ABRIDGMENT (11) Document No. AU-B-59892/90
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 637623

(54) Title
AROMATIC CARBOXYLIC AMIDES

International Patent Classification(s)
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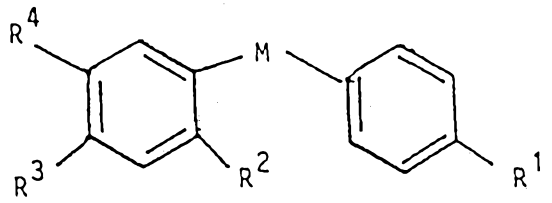
(57) Claim

1. Compounds of the general formula



I

wherein R^1 represents halogen or OR^5; R^2 represents hydrogen, lower-alkyl, lower-alkoxy or halogen; R^3 and R^4 each independently represent lower-alkyl or taken together represent alkylene, with 3-5 C atoms in a straight-chain, which may be substituted by lower-alkyl; R^5 signifies hydrogen, acyl, lower-alkoxycarbonyl or lower-alkyl, which can be substituted by amino, mono-alkylamino, di-alkylamino or a residue -N-Het; -N-Het signifies a 5-8-membered, saturated or unsaturated monocyclic heterocycle attached via a N atom and optionally containing another hetero atom; and M signifies -CONH- or -NHCO.

Our Ref: 331726

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AUSTRALIA
Patents Act

FORM 10

COMPLETE SPECIFICATION

(ORIGINAL)

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority:
Related Art:

Applicant(s): F.HOFFMANN-LA ROCHE AG
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Patent & Trade Mark Attorneys
Level 10, 10 Barrack Street
SYDNEY NSW 2000

Complete specification for the invention entitled

"Aromatic carboxylic amides".

The following statement is a full description of this invention, including the best method of performing it known to me:-

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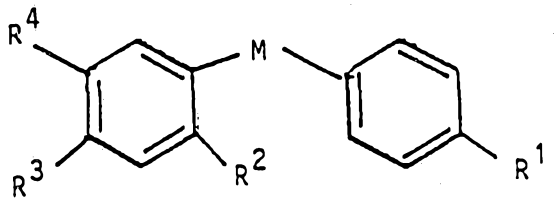
The present invention is concerned with novel aromatic carboxamides of the general formula



I

wherein R^1 represents hydrogen, halogen or OR^5; R^2 represents hydrogen, lower-alkyl, lower-alkoxy or halogen; R^3 and R^4 each independently represent lower-alkyl or taken together represent alkylene with 3-5 C atoms in a straight-chain; R^5 signifies hydrogen, acyl, lower-alkoxycarbonyl or lower-alkyl, which can be substituted by amino, mono-alkylamino, di-alkylamino or a residue -N-Het; -N-Het signifies a 5-8-membered, saturated or unsaturated monocyclic heterocycle attached via a N atom; and M signifies -CONH- or -NHCO-.

The invention is also concerned with a process for the manufacture of the compounds of formula I, pharmaceutical preparations based on the compounds of formula I, the compounds of formula I as medicaments, especially in the treatment and prophylaxis of neoplasms, dermatoses and ageing of the skin, rheumatic and immunological disorders, as well as the use of the compounds of formula I in the manufacture of pharmaceutical preparations for the treatment and prophylaxis of such disorders.

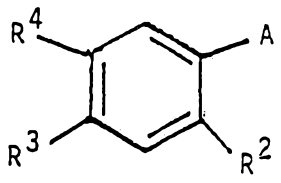
Grn/31.5.90

The term "lower" relates to groups with 1-6 C atoms. Alkyl and alkoxy groups can be straight-chain or branched, such as methyl, ethyl, propyl, isopropyl, butyl, sec.-butyl or tert.-butyl and, respectively, methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec.-butoxy and tert.-butoxy. Examples of acyl groups are alkanoyl groups, preferably lower-alkanoyl groups such as acetyl, propionyl, butyryl, pivaloyl and caproyl; or aroyl groups such as benzoyl, p-nitrobenzoyl and toluoyl; or aralkanoyl groups such as phenylacetyl.

Preferred heterocyclic residues -NHet are those of the formula -NY in which Y is $-CH_2-$, -CH=, -O-, -S-, -SO-, $-SO_2-$ or $-NR^6-$ and R^6 is hydrogen, lower-alkyl or acyl and in which 3-6 C atoms are arranged between N and Y. Piperidino, pyrrolidino, morpholino, piperazino, N-methylpiperazino, thiomorpholino, thiomorpholino 4-oxide, thiomorpholino 4,4-dioxide as well as imidazolino and pyrrolo are examples of such residues. An alkylene residue with 3-5 C atoms in a straight chain represented by R^3 and R^4 together can have branchings, examples of such alkylene residues being 1,3-propylene, 1,4-butylene and 1,5-pentylene and lower-alkyl-substituted derivatives thereof such as the residues $-C(CH_3)_2-CH_2-C(CH_3)_2-$, $-C(CH_3)_2-CH_2CH_2-C(CH_3)_2-$ and $-CH_2CH_2-C(CH_3)_2-CH_2CH_2-$.

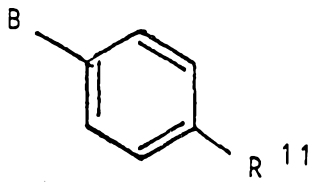
Hydrogen, hydroxy, fluorine, morpholinoethoxy and N-methylpiperidinoethoxy are preferred residues R^1.

The compounds of formula I can be obtained by reacting a compound of the general formula



II

with a compound of the general formula



III

wherein either A signifies a carboxyl group or a reactive derivative thereof and B signifies an amino group or A signifies an amino group and B signifies a carboxyl group or a reactive derivative thereof and R^{11} signifies a residue R^1 in which an amino group which may be present is in protected form, whereupon an amino protecting group which may be present is cleaved off.

The reaction of a compound II with a compound III can be carried out according to methods known per se for the acylation of amines. Preferably, a compound of formula II in which A represents a carboxylic acid halide group, e.g. the group -COCl, is reacted with a compound of formula III in which B is $-NH_2$ to give a compound of formula I in which M is -CONH- or an amine of formula II is reacted with a carboxylic acid halide of formula III to give a compound of formula I in which M is -NH-CO-.

These acylations are conveniently carried out in the presence of a base, e.g. an organic base such as pyridine.

Conventional amino protecting groups such as the phthaloyl group, the benzyloxycarbonyl group and the tert.-butoxycarbonyl group come into consideration as amino protecting groups. The cleavage of these protecting groups can be effected with conventional agents. A phthaloyl group can be cleaved off by treatment with hydrazine; a benzyloxycarbonyl group can be cleaved off by catalytic hydrogenation; and a tert.-butoxycarbonyl group can be cleaved off by treatment with acids, e.g. dilute hydrochloric acid or trifluoroacetic acid.

The compounds of formulae II and III which are used as starting materials for the manufacture of the compounds of formula I, insofar as they are not known or described hereinafter, can be prepared in analogy to known methods or the methods described hereinafter.

The compounds of formula I are pharmacodynamically valuable compounds. They can be used for the topical and systemic therapy of benign and malignant neoplasms, of premalignant lesions and also for the systemic and topical prophylaxis of the said conditions.

Furthermore, they are suitable for the topical and systemic therapy of acne, psoriasis and other dermatoses which are accompanied by an intensified or pathologically altered cornification, and also of inflammatory and allergic dermatological conditions as well as of light--damaged (aged) skin. Further, the compounds of formula I can also be used for the control of mucous membrane disorders with inflammatory or degenerative or metaplastic changes. The antineoplastic activity of the compounds of formula I can be investigated using the test procedure described hereinafter.

Female Sprague-Dawley rats are held under temperature--controlled and light-controlled conditions with free access to drinking water and feed. At the age of 50 days 12 mg of 7,12-dimethylbenz(a)anthracene are administered to each rat by means of a stomach tube. After a period of about 4 months, in which on average 3.6 to 4 mammary tumours have developed per rat, the treatment is commenced. The test substance is admixed with normal feed in a 25% spray-dried formulation. The following parameters are measured weekly: body weight, average number of tumours and average tumour volume per animal. The volumes are calculated according to the formula $\frac{D}{2} \cdot d^2$ in which D is the largest diameter of the tumour ellipsoid and d is the smallest diameter of the tumour ellipsoid.

The values obtained with the compound of Example 3 in this test procedure after a test period of 10 weeks are presented in Table I:

Table I

Dosage [mg/kg/day] p.o.	Change in the average number of tumours per rat [%]	Change in the average tumour volume per rat [%]
50	+50	+840
100	+35	+475
200	+16	+193
Control group	+78	+875

The compounds of formula I can also be used for the treatment of inflammatory, allergic, rheumatic and immunological disorders of the widest variety of organs. Examples of such disorders are: primary-chronic polyarthritis, spondylarthritis ancylopoetica, osteoarthritides, arthritides and arthroses; eczemas, atopic dermatitis, allergic rhinitis, bronchial asthma; autoimmune disorders such as e.g. lupus erythematosus, Reiter's syndrome.

The compounds of formula I can accordingly be used as medicaments, e.g. in the form of pharmaceutical preparations.

The preparations can be administered enterally, parenterally or topically. Preparations in the form of tablets, capsules, dragees, syrups, suspensions, solutions and suppositories are suitable e.g. for parenteral administration. Preparations in the form of infusion solutions or injection solutions are suitable for parenteral administration.

The dosages in which the preparations are administered can vary according to the mode of use and route of use as well as according to the requirements of the patients.

In the case of oral administration of the compounds in accordance with the invention there come into consideration in the case of adults dosages of about 0.1-100 mg/kg, preferably 0.5-50 mg/kg, per day.

The preparations can be administered in one dosage or several dosages. Capsules containing about 5-500 mg of active ingredient are a preferred administration form.

The preparations can contain inert or also pharmacodynamically active additives. Tablets or granulates e.g. can contain a series of binding agents, filler materials, carrier substances or diluents. Liquid preparations can be present, for example, in the form of a sterile solution which is miscible with water. Capsules can additionally contain a filler material or thickening agent in addition to the active ingredient. Furthermore, there can also be present flavour-improving additives as well as the substances usually used as preserving, stabilizing, moisture-retaining and emulsifying agents, further also salts for varying the osmotic pressure, buffers and other additives.

The previously mentioned carrier substances and diluents can consist of organic or inorganic substances, e.g. of water, gelatine, lactose, starch, magnesium stearate, talc, gum arabic, polyalkylene glycols and the like. It is a prerequisite that all adjuvants used in the manufacture of the preparations are non-toxic.

For topical use the active ingredients are conveniently used in the form of salves, tinctures, creams, solutions, lotions, sprays, suspensions and the like. Salves and creams as well as solutions are preferred. These preparations intended for topical use can be prepared by mixing the process products as active ingredients with non-toxic, inert, solid or liquid carriers which are usual in such preparations and which are suitable for topical treatment.

For topical use there are suitable conveniently about 0.1-5%, preferably 0.3-2%, solutions as well as about 0.1-5%, preferably about 0.3-2%, salves or creams.

If desired, an antioxidant, e.g. tocopherol, N-methyl--γ-tocopheramine as well as t-butyl-hydroxyanisole or t-butyl-hydroxytoluene, can be admixed with the preparations.

Example 1

2 g of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2--naphthalenecarboxylic acid were treated with 15 ml of thionyl chloride and heated at reflux for 1 hour. After distilling of the excess thionyl chloride, the residue was dissolved in 10 ml of tetrahydrofuran and added dropwise while stirring to a solution of 0.9 g of aniline in 20 ml of pyridine. After stirring at room temperature for half an hour the reaction mixture was poured on to ice-water, extracted with ethyl acetate, the organic phase was washed with 2N hydrochloric acid and water, dried and evaporated. The orange-coloured oil was crystallized from hexane and gave 1.8 g of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2--naphthalenecarboxanilide in colourless crystals, m.p. 144-146°C.

Example 2

In analogy to Example 1, from 2 g of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenecarboxylic acid and 1 g of 4-fluoroaniline there were prepared 1.7 g of 4'-fluoro-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2--naphthalenecarboxanilide in colourless crystals, m.p. 163-165°C (from ethyl acetate/hexane).

Example 3

In analogy to Example 1, 52.5 g of 5,6,7,8-tetrahydro--5,5,8,8-tetramethyl-2-naphthalenecarboxylic acid were converted by reaction with 200 ml of thionyl chloride into

the acid chloride and, after dissolution in 200 ml of tetrahydrofuran, added dropwise to a solution of 48.8 g of 4-[2-(4-amino-phenoxy)ethyl]morpholine in 400 ml of pyridine while cooling slightly. The temperature should not rise above 30°C. After stirring at room temperature for 1 hour the reaction mixture was poured on to ice--water, extracted with ethyl acetate, the organic phase was washed with ice-cold 2N hydrochloric acid, dried and evaporated. The crystalline crude product was purified by filtration over a silica gel column (eluting agent hexane/ethyl acetate 1:4, then ethyl acetate, then ethyl acetate/ethanol = 1:1) and recrystallized from hexane/ethyl acetate. There were obtained 52 g of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-4'-(2-morpholinoethoxy)-2--naphthalenecarboxanilide in white crystals, m.p. 134-136°C.

The 4-[2-(4-amino-phenoxy)ethyl]morpholine used as the starting material was prepared as follows:

19 g of sodium hydride (50% suspension in mineral oil) were washed twice with absolute pentane, dried and suspended in 130 ml of dimethylformamide. A solution of 42.5 g of 4-aminophenol in 250 ml of dimethylformamide was added dropwise thereto while cooling with ice and the mixture was stirred at 0°C for a further hour. Thereafter, a solution of 100 g of 4-(2-chloroethyl)-morpholine in 250 ml of dimethylformamide was added dropwise thereto. After heating to 70°C for 1 hour the reaction mixture was poured on to ice-water, extracted with ethyl acetate, the organic phase was washed with water, dried and evaporated. The thus-obtained dark brown oil was purified by filtration over a silica gel column (eluting agent ethyl acetate) and, after drying in a high vacuum, gave 66 g of 4-[2-(4-aminophenoxy)ethyl]morpholine as a slightly brownish oil.

Example 4

In analogy to Example 1, from 2 g of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenecarboxylic acid and 0.95 g of 4-aminophenol there were obtained, after recrystallization from hexane/ethyl acetate, 2.1 g of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-4'-hydroxy-2--naphthalenecarboxanilide in beige crystals, m.p. 216-218°C.

Example 5

In analogy to Example 1, from 4 g of 1,1,3,3-tetramethyl-5-indanecarboxylic acid and 1.7 g of aniline there were obtained, after recrystallization from hexane/ethyl acetate, 3.3 g of 1,1,3,3-tetramethyl-5-indanecarboxanilide in white crystals, m.p. 137-138°C.

Example 6

In analogy to Example 1, from 4 g of 1,1,3,3-tetramethyl-5-indanecarboxylic acid and 2 g of 4-fluoroaniline there were obtained, after recrystallization from hexane/ethyl acetate, 2.1 g of 4'-fluoro-1,1,3,3-tetramethyl-5--indanecarboxanilide, m.p. 155-156°C.

Example 7

In analogy to Example 3, the reaction of 5.7 g of 1,1,3,3-tetramethyl-5-indanecarboxylic acid with 5.8 g of 4-[2-(4-aminophenoxy)ethyl]morpholine gave, after recrystallization from hexane/ethyl acetate, 5.2 g of 1,1,3,3-tetramethyl-4'-(2-morpholinoethoxy)-5-indanecarboxanilide in white crystals, m.p. 131-133°C.

Example 8

In analogy to Example 1, from 4 g of 1,1,3,3-tetramethyl-5-indanecarboxylic acid and 1.9 g of 4-aminophenol there were obtained, after recrystallization from hexane/ethyl acetate, 2.3 g of 4'-hydroxy-1,1,3,3-tetramethyl-5--indanecarboxanilide, m.p. 196-197°C.

Example 9

2.5 g of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2--naphthylamine were dissolved in 50 ml of pyridine and treated at room temperature with a solution of 1.7 g of benzoyl chloride in 20 ml of tetrahydrofuran. After stirring at room temperature for two hours the reaction mixture was poured on to ice-water and, after acidification with 3N hydrochloric acid, extracted with ethyl acetate. The oil obtained after drying and evaporating the organic phase was crystallized from hexane/ethyl acetate and gave 3 g of N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl--2-naphthyl)benzamide in white crystals, m.p. 146-148°C.

Example 10

In analogy to Example 9, by reacting 5.9 g of 5,6,7,8--tetrahydro-5,5,8,8-tetramethyl-2-naphthylamine with 4-fluorobenzoyl chloride, obtained from 4 g of 4-fluorobenzoic acid and 15 ml of thionyl chloride, there were obtained, after recrystallization from hexane/ethyl acetate, 6.3 g of p-fluoro-N-(5,6,7,8-tetrahydro-5,5,8,8--tetramethyl-2-naphthyl)benzamide, m.p. 160-162°C.

Example 11

6.1 g of p-(2-morpholinoethoxy)benzoic acid were covered with 100 ml of thionyl chloride and heated at

reflux for 1 hour. After evaporating the excess thionyl chloride the residue was suspended in 100 ml of tetrahydrofuran and added dropwise to a solution of 4.9 g of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylamine in 150 ml of pyridine. After stirring at room temperature for 20 hours the reaction mixture was poured on to ice-water and extracted with ethyl acetate. After repeatedly washing the organic phase with water, drying over sodium sulphate and evaporating the solvent there was obtained a crystalline crude product which was purified by filtration over a silica gel column (eluting agent hexane/ethyl acetate = 1:1, then ethyl acetate) and crystallization from hexane/ethyl acetate. There were obtained 8.6 g of p-(2-morpholinoethoxy)-N-(5,6,7,8-tetrahydro-5,5,8,8--tetramethyl-2-naphthyl)benzamide, m.p. 130-132°C.

The p-(2-morpholinoethoxy)benzoic acid used as the starting material was prepared as follows:

10 g of methyl 4-hydroxybenzoate and 20.5 g of 4-(2-chloroethyl)morpholine were dissolved in 100 ml of dimethylformamide and, after the addition of 38 g of potassium carbonate, heated to 100°C for 1 hour. The reaction mixture obtained was poured on to ice-water, extracted with ethyl acetate, dried and evaporated. The oily, slightly brown residue was saponified with potassium hydroxide in water/ethanol and, after acidification and recrystallization from hexane/ethyl acetate, gave 7.3 g of p-(2-morpholinoethoxy)benzoic acid in beige crystals, m.p. 112-114°C.

Example 12

In analogy to Example 9, from 1 g of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylamine and 1 g of p-acetoxybenzoyl chloride there were obtained, after

recrystallization from hexane/ethyl acetate, 1.5 g of p-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-carbamoyl]phenyl acetate, m.p. 186-188°C.

Hydrolysis of this compound with potassium hydroxide/water/ethanol gave, after recrystallization from hexane/ethyl acetate, 1.1 g of p-hydroxy-N-(5,6,7,8-tetrahydro--5,5,8,8-tetramethyl-2-naphthyl)benzamide, m.p. 204-206°C.

Example 13

In analogy to Example 9, from 2.5 g of 1,1,3,3-tetramethyl-5-indanamine and 1.9 g of benzoyl chloride there were obtained, after recrystallization from hexane/ethyl acetate, 2.7 g of N-(1,1,3,3-tetramethyl-5-indanyl)-benzamide, m.p. 167-169°C.

Example 14

In analogy to Example 9, from 5.5 g of 1,1,3,3-tetramethyl-5-indanamine and 4 g of 4-fluorobenzoyl chloride there were obtained, after recrystallization from hexane/ethyl acetate, 5.5 g of p-fluoro-N-(1,1,3,3-tetramethyl-5--indanyl)benzamide, m.p. 167-169°C.

Example 15

In analogy to Example 11, from 4 g of p-(2-morpholino-ethoxy)benzoic acid and 3.1 g of 1,1,3,3-tetramethyl-5--indanamine there were obtained, after recrystallization from hexane/ethyl acetate, 4.6 g of p-(2-morpholino-ethoxy)-N-(1,1,3,3-tetramethyl-5-indanyl)benzamide, m.p. 134-136°C.

Example 16

In analogy to Example 12, from 2 g of 1,1,3,3-tetramethyl-5-indanamine and 2.2 g of p-acetoxybenzoyl chloride there were obtained, after recrystallization from hexane/ethyl acetate, 2.7 g of p-[1,1,3,3-tetramethyl-5--indanoyl]carbamoyl]phenyl acetate, m.p. 196-198°C.

Hydrolysis of this compound gave 2.2 g of p-hydroxy-N--(1,1,3,3-tetramethyl-5-indanyl)benzamide, m.p. 185-187°C.

Example 17

1.77 g of 6,7,8,9-tetrahydro-7,7-dimethyl-5H-benzocycloheptene-2-carboxylic acid were treated with 1.17 ml of $SOCl_2$ and heated to reflux for 3/4 hour. The excess reagent was removed under reduced pressure and the crude acid chloride was dried briefly in a high vacuum. It was then dissolved in 20 ml of abs. pyridine and added dropwise under an argon atmosphere at 0°C to a solution of 0.97 g of 4-aminophenol in 16 ml of abs. pyridine. The mixture was left to react at room temperature for 20 minutes and then poured on to ice/conc. HCl. The mixture was then extracted with ethyl acetate, washed with 1N HCl, 10% sodium carbonate solution and saturated NaCl solution, dried over Na_2SO_4, boiled with active charcoal and filtered. The filtrate was concentrated under reduced pressure until the product began to crystallize and there were obtained 1.98 g of 6,7,8,9-tetrahydro-7,7--dimethyl-5H-benzocycloheptene-2-carboxylic acid (4-hydroxy)anilide as brownish crystals of melting point 175-176°C.

The educt can be prepared as follows:

A mixture of 11.4 g of K_2CO and 3.40 g of KOH dissolved in 30 ml of H_2O was added to 16.3 g of $Ca(OCl)_2$ in 60 ml of H_2O. The mixture was stirred intensively for 1/4 hour and then filtered. 6.49 g of 6,7,8,9-tetrahydro-7,7-dimethyl-5H-benzocyclohepten-2-yl methyl ketone were added to the filtrate (calcium hypochlorite) and the mixture was heated slowly. A strongly exothermic reaction occurred at 70°C and this allowed the temperature to rise to 100°C. After cooling the mixture was acidified cautiously with 50 ml of 3N HCl and the precipitated acid was filtered off. After washing with H_2O and drying in a high vacuum there were obtained 5.48 g of 6,7,8,9-tetrahydro-7,7-dimethyl-5H-benzocycloheptene-2-carboxylic acid as white crystals of melting point 166-171°C.

Example 18

In analogy to Example 17, but using 4-fluoroaniline as the amine component, there was manufactured 6,7,8,9-tetrahydro-7,7-dimethyl-5H-benzocycloheptene-2-carboxylic acid (4-fluoro)anilide as white crystals of melting point 178-179°C.

Example 19

In analogy to Example 17, but using aniline as the amine component, there was manufactured 6,7,8,9-tetrahydro-7,7-dimethyl-5H-benzocycloheptene-2-carboxylic acid anilide as white crystals of melting point 146-147°C.

Example 20

In analogy to Example 17, from 4-aminophenol and 6,7,8,9-tetrahydro-9,9-dimethyl-5H-benzocycloheptene-2--carboxylic acid there was manufactured 6,7,8,9-tetra-

hydro-9,9-dimethyl-5H-benzocycloheptene-2-carboxylic acid (4-hydroxy)anilide as white crystals of melting point 147-148°C.

The starting material can be prepared as follows:

The Grignard compound was prepared under an argon atmosphere from 4.00 g of 2-bromo-6,7,8,9-tetrahydro-9,9--dimethyl-5H-benzocycloheptene (EP-A2-0315071) and 456 mg of Mg shavings in 20 ml of absolute tetrahydrofuran. After carrying out the metallation a vigorous CO_2 stream was introduced at -10°C. The mixture was hydrolyzed with dil. HCl, extracted with ether and washed with a small amount of water. The acid was then purified by extraction in 1N NaOH, acidification to pH 1 (HCl) and re-extraction in ether. After washing with water, drying over Na_2SO_4 and evaporating there were obtained 2.64 g of 6,7,8,9--tetrahydro-9,9-dimethyl-5H-benzocycloheptene-2-carboxylic acid as colourless crystals of melting point 155-156°C.

Example 21

In analogy to Example 17, from 4-fluoroaniline and 6,7,8,9-tetrahydro-9,9-dimethyl-5H-benzocycloheptene-2--carboxylic acid there was manufactured 6,7,8,9-tetrahydro-9,9-dimethyl-5H-benzocycloheptene-2-carboxylic acid (4-fluoro)anilide as colourless crystals of melting point 135-136°C.

Example 22

In analogy to Example 17, starting from 3-ethyl--6,7,8,9-tetrahydro-7,7-dimethyl-5H-benzocyclohepten-2-yl methyl ketone and using 4-aminophenol as the amine component there was manufactured 3-ethyl-6,7,8,9-tetrahydro-7,7-dimethyl-5H-benzocycloheptene-2-carboxylic acid

(4-hydroxy)anilide as colourless crystals of melting point 197-198°C.

The starting material can be synthesized from the building bricks ethylbenzene, 3,3-dimethylglutaric anhydride and acetyl chloride (see EP-A2-0315071).

Example 23

The following compounds can be manufactured in analogy to Example 1:

6,7,8,9-Tetrahydro-7,7-dimethyl-4'-[2-(4-methyl-piperazino)ethoxy]-(5H)-benzocycloheptene-2-carboxanilide;

6,7,8,9-tetrahydro-4'-hydroxy-5,5-dimethyl-5H-benzo-cycloheptene-2-carboxanilide;

4'-[2-[bis(2-methoxyethyl)amino]ethoxy]-6,7,8,9-tetra-hydro-6,6,8,8-tetramethyl-5H-benzocycloheptene-2-carbox-anilide;

5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-4'-[2-(4-methyl-piperazino)ethoxy]-2-naphthalenecarboxanilide;

1,1,3,3-tetramethyl-4'-(2-dimethylaminoethoxy)-5--indanecarboxanilide.

Example 24

The following compounds can be manufactured in analogy to Example 9:

p-Fluoro-N-(6,7,8,9-tetrahydro-7,9,9-trimethyl-5H--benzocyclohepten-2-yl)benzamide;

p-(2-imidazoloethoxy)-N-(5,6,7,8-tetrahydro-5,5,8,8--tetramethyl-2-naphthyl)benzamide;

p-(2-morpholinoethoxy)-N-(6,7,8,9-tetrahydro-7,7--dimethyl-5H-benzocyclohepten-2-yl)benzamide;

6,7,8,9-tetrahydro-7,7-dimethyl-4'-[2-(4-methyl-piperazino)ethoxy]-(5H)-2-benzocycloheptenecarboxanilide.

Example A

Hard gelatine capsules can be manufactured as follows:

Ingredients		mg/capsule
1.	Spray-dried powder containing 75% of compound I	200
2.	Sodium dioctylsulphosuccinate	0.2
3.	Sodium carboxymethylcellulose	4.8
4.	Microcrystalline cellulose	86.0
5.	Talc	8.0
6.	Magnesium stearate	1.0
	Total	300

The spray-dried powder, which is based on the active ingredient, gelatine and microcrystalline cellulose and which has an average particle size of the active ingredient of < 1μ (measured by means of autocorrelation spectroscopy), is moistened with an aqueous solution of sodium carboxymethylcellulose and sodium dioctylsulphosuccinate and kneaded. The resulting mass is granulated, dried and sieved, and the granulate obtained is mixed with microcrystalline cellulose, talc and magnesium stearate. The powder is filled into size O capsules.

Example B

Tablets can be manufactured as follows:

Ingredients		mg/tablet
1.	Compound I as a finely milled powder	500
2.	Powd. lactose	100
3.	White maize starch	60
4.	Povidone K30	8

5.	White maize starch	112
6.	Talc	16
7.	Magnesium stearate	4
	Total	800

The finely milled substance is mixed with lactose and a portion of the maize starch. The mixture is moistened with an aqueous solution of Povidone K30 and kneaded, and the resulting mass is granulated, dried and sieved. The granulate is mixed with the remaining maize starch, talc and magnesium stearate and pressed to tablets of suitable size.

Example C

Soft gelatine capsules can be manufactured as follows:

Ingredients		mg/capsule
1.	Compound I	50
2.	Triglyceride	450
	Total	500

10 g of compound I are dissolved in 90 g of medium-chain triglyceride with stirring, inert gasification and exclusion from light. This solution is processed as a capsule fill mass to soft gelatine capsules containing 50 mg of active ingredient.

Example D

A lotion can be manufactured as follows:

Ingredients

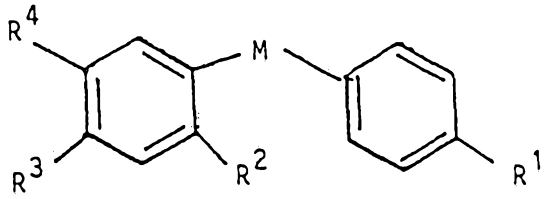
1.	Compound I, finely milled	3.0 g
2.	Carbopol 934	0.6 g

3.	Sodium hydroxide	q.s. ad pH 6
4.	Ethanol, 94%	50.0 g
5.	Demineralized water	ad 100.0 g

The active ingredient is incorporated into the 94% ethanol/water mixture under protection from light. Carbopol 934 is stirred in until gelling is complete and the pH value is adjusted with sodium hydroxide.

The claims defining the invention are as follows:

1. Compounds of the general formula



I

wherein R^1 represents halogen or OR^5; R^2 represents hydrogen, lower-alkyl, lower-alkoxy or halogen; R^3 and R^4 each independently represent lower-alkyl or taken together represent alkylene, with 3-5 C atoms in a straight-chain, which may be substituted by lower-alkyl; R^5 signifies hydrogen, acyl, lower-alkoxycarbonyl or lower-alkyl, which can be substituted by amino, mono-alkylamino, di-alkylamino or a residue -N-Het; -N-Het signifies a 5-8-membered, saturated or unsaturated monocyclic heterocycle attached via a N atom and optionally containing another hetero atom; and M signifies -CONH- or -NHCO.

2. Compounds in accordance with claim 1, wherein R^3 and R^4 taken together represent alkylene with 3-5 C atoms in a straight chain.

3. Compounds in accordance with claim 2, wherein R^3 and R^4 taken together represent the residue $-C(CH_3)_2-CH_2-C(CH_3)_2-$, $-C(CH_3)_2-CH_2CH_2-C(CH_3)_2-$ or $-CH_2CH_2-C(CH_3)_2-CH_2CH_2-$.

4. Compounds in accordance with claims 1-3, wherein R^1 is hydroxy, fluorine, morpholinoethoxy or N-methylpiperidinoethoxy.

5. Compounds in accordance with claims 1-4, wherein M is -CONH-.

6. 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-4'-(2--morpholinoethoxy)-2-naphthalenecarboxanilide.

7. 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-4'-hydroxy--2-naphthalenecarboxanilide.

8. The compounds 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenecarboxanilide; 4'-fluoro-5,6,7,8--tetrahydro-5,5,8,8-tetramethyl-2-naphthalenecarboxanilide; 1,1,3,3-tetramethyl-5-indanecarboxanilide; 4'-fluoro--1,1,3,3-tetramethyl-5-indanecarboxanilide; 1,1,3,3-tetramethyl-4'-(2-morpholinoethoxy)-5-indanecarboxanilide; 4'-hydroxy-1,1,3,3-tetramethyl-5-indanecarboxanilide; 6,7,8,9-tetrahydro-7,7-dimethyl-5H-benzocycloheptene-2--carboxylic acid (4-hydroxy)anilide; 6,7,8,9-tetrahydro--7,7-dimethyl-5H-benzocycloheptene-2-carboxylic acid (4-fluoro)anilide; 6,7,8,9-tetrahydro-7,7-dimethyl-5H--benzocycloheptene-2-carboxanilide.

9. Compounds in accordance with claims 1-4, wherein M is -NHCO-.

10. (5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2--naphthyl)-4-hydroxybenzamide.

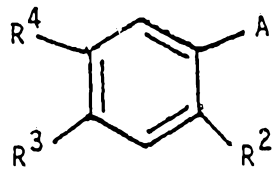
11. The compounds N-(5,6,7,8-tetrahydro-5,5,8,8--tetramethyl-2-naphthyl)benzamide; p-fluoro-N-(5,6,7,8--tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)benzamide; p-(2-morpholinomethoxy)-N-(5,6,7,8-tetrahydro-5,5,8,8--tetramethyl-2-naphthyl)benzamide.

12. The compounds N-(1,1,3,3-tetramethyl-5-indanyl)-benzamide; p-fluoro-N-(1,1,3,3-tetramethyl-5-indanyl)-

benzamide; p-(2-morpholinoethoxy)-N-(1,1,3,3-tetramethyl--5-indanyl)benzamide; p-hydroxy-N-(1,1,3,3-tetramethyl-5--indanyl)benzamide; 6,7,8,9-tetrahydro-9,9-dimethyl-5H--benzocycloheptene-2-carboxylic acid (4-hydroxy)anilide; 6,7,8,9-tetrahydro-9,9-dimethyl-5H-benzocycloheptene-2--carboxylic acid (4-fluoro)anilide; 3-ethyl-6,7,8,9-tetrahydro-7,7-dimethyl-5H-benzocyclohepten-2-carboxylic acid (4-hydroxy)anilide.

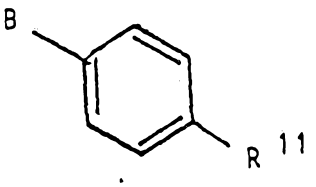
13. A process for the manufacture of the compounds of claim 1, which process comprises

reacting a compound of the general formula



II

with a compound of the general formula



III

wherein either A signifies a carboxyl group or a reactive derivative thereof and B signifies an amino group or A signifies an amino group and B signifies a carboxyl group or a reactive derivative thereof and R^{11} signifies a residue R^1 in which an amino group which may be present is in protected form.

whereupon an amino protecting group which may be present is cleaved off.

14. Compounds of formula I as defined in claim 1 whenever prepared by the process of claim 13 or by an obvious chemical equivalent thereof.

15. Pharmaceutical preparations containing a compound of formula I and usual carrier materials and adjuvants.

16. A method for the treatment of neoplasms and dermatoses, ageing skin and rheumatic and immunological disorders which comprises administering to a patient, in need of such treatment, a compound as claimed in any one of claim 1 to 12 or 14, or a preparation as claimed in claim 15.

DATED this 3rd day of March, 1993.

F. HOFFMANN-LA ROCHE AG
By Its Patent Attorneys
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