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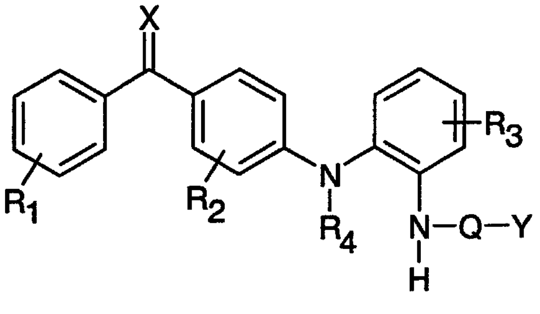
(54) Title: AMINOBENZOPHENONES AS INHIBITORS OF IL-1β AND TNF-α



(I)

(57) Abstract: The present invention relates to a compound of general formula (I) wherein R_1, R_2, and R_3 represents one or more, same or different substituents selected from the group consisting of halogen, hydroxy, mercapto, trifluoromethyl, amino, $(C_1\text{-}C_3)$alkyl, $(C_2\text{-}C_3)$olefinic group, $(C_1\text{-}C_3)$alkoxy, $(C_1\text{-}C_3)$alkylthio, $(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_3)$alkoxycarbonyl, cyano, -CONH_2, phenyl, or nitro; further R_2 can be hydrogen, and R_3 can be carboxy and carbamoyl; R_4 represents hydrogen, $(C_1\text{-}C_3)$alkyl, or allyl; X represents oxygen or sulphur; Q represents -(CO)-, -(CS)-, or a bond; Y represents $(C_5\text{-}C_{15})$alkyl; $(C_2\text{-}C_{15})$olefinic group; $(C_3\text{-}C_{10})$monocyclic hydrocarbon group; or phenyl; any of which may be optionally substituted by one or more, same or different substituents selected from the group consisting of the formula R_5 defined below; $(C_1\text{-}C_4)$alkyl substituted by one or more substituents selected for the group R_5; or a group of the formula $\text{-(Z-O)}_n\text{-Z}$, wherein Z is a $(C_1\text{-}C_3)$alkyl, n is an integer > 1; and no continuous linear sequence of atoms in the group Y exceeds 15; R_5 represents halogen, hydroxy, mercapto, trifluoromethyl, amino, $(C_1\text{-}C_3)$alkoxy, $(C_1\text{-}C_3)$alkylthio, $(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_3)$alkoxycarbonyl, cyano, azido, nitro, -COOH, -CONH_2, -CONHR', or COONR'R' wherein R' represents $(C_1\text{-}C_3)$alkyl; or a pharmaceutically acceptable salt thereof, or a hydrate or solvate thereof. The compounds are valuable in the human and veterinary therapy.

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AMINOBENZOPHENONES AS INHIBITORS OF IL-1β AND TNF-α

FIELD OF THE INVENTION

This invention relates to a hitherto unknown class of compounds which shows anti-inflammatory effects, to pharmaceutical preparations containing these compounds, to dosage units of such preparations, and to their use in the treatment and prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis and atopic dermatitis, uveitis, septic shock, AIDS, and acne.

BACKGROUND OF THE INVENTION

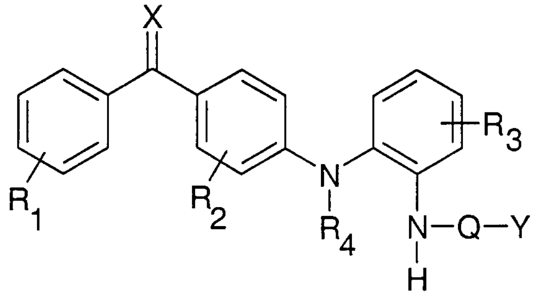
Previously, a series of closely related aminobenzophenones (e.g. 4-(2-amino-4-nitrophenylamino)benzophenone) have been described (Hussein, F.A. *et al*, Iraqi J. Sci., 22, 54-66 (1981)). However, there is no description of their uses. PCT/DK98/00008 discloses aminobenzophenone inhibitors of interleukin 1β (IL-1β) and tumour necrosis factor a (TNF-α) secretion *in vitro*, said compounds being potentially useful for treatment of inflammatory diseases in which the production of cytokines is involved in the pathogenesis, e.g. asthma, rheumatoid arthritis, psoriasis, contact dermatitis, and atopic dermatitis. Furthermore the compounds of PCT/DK98/00008 was tested *in vivo* for anti-inflammatory properties in the 12-*O*-tetradecanoylphorbol-13-acetate (TPA) induced murine chronic skin inflammation model, (De Young, L.M. et al, Agents Actions, 26, 335-341 (1989); Carlson, R.P. et al, Agents Actions, 17, 197-204 (1985); Alford, J.G. et al, Agents Action, 37, (1992); Stanley, P.L. et al, Skin Pharmacol, 4, 262-271 (1991)). In this chronic skin inflammation model the compounds had the same potency compared to the reference compound hydrocortisone.

The purpose of the present invention is to provide further pharmacologically active aminobenzophenone derivatives and related compounds.

This purpose is achieved with the novel aminobenzophenone derivatives according to the general formula I that are found to be potent inhibitors of interleukin 1β (IL-1β) and tumour necrosis factor α (TNF-α) secretion *in vitro*, making them potentially useful for treatment of inflammatory diseases, in which the secretion and regulation of cytokines or more specifically interleukin 1β (IL-1β) and tumour necrosis factor α (TNF-α) are involved in the pathogenesis. The inhibition or down regulation of the cytokines is possibly due to an inhibition of MAP kinases.

SUMMARY OF THE INVENTION

The compounds of the present invention are represented by the general formula I below



I

wherein

R_1, R_2, and R_3 represents one or more, same or different substituents selected from the group consisting of halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_2-C_3) olefinic group, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)-alkoxycarbonyl, cyano, -$CONH_2$, phenyl, or nitro; further R_2 can be hydrogen, and R_3 can be carboxy and carbamoyl;

R_4 represents hydrogen, (C_1-C_3)alkyl, or allyl;

X represents oxygen or sulphur;

Q represents -(CO)-, -(CS)-, or a bond;

Y represents (C_5-C_{15})alkyl; (C_2-C_{15})olefinic group; (C_3-C_{10})monocyclic hydrocarbon group; or phenyl; any of which may be optionally substituted by one or more, same or different substituents selected from the group consisting of the formula R_5 defined below; (C_1-C_4)alkyl substituted by one or more substituents selected from the group R_5; or a group of the formula -$(Z\text{-}O)_n$-Z, wherein Z is a (C_1-C_3)alkyl, n is an integer > 1; and no continuous linear sequence of atoms in the group Y exceeds 15;

R_5 represents halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, azido, nitro, -COOH, -$CONH_2$, -CONHR', or -COONR'R' wherein R' represents (C_1-C_3)alkyl;

or a salt thereof with a pharmaceutically acceptable acid, a hydrate or a solvate thereof.

In compounds of formula I R_1 preferably represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, (C_1-C_2)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy, (C_1-C_3)alkoxycarbonyl, cyano, or -CONH$_2$;

R_2 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy.

R_3 represents one or more, same or different substituents selected from the group consisting of hydrogen, halogen, hydroxy, trifluoromethyl, (C_1-C_3)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy, (C_1-C_3)alkoxycarbonyl, cyano, carboxy, or -CONH$_2$.

R_4 represents hydrogen, (C_1-C_2)alkyl, or allyl;
X represents oxygen or sulphur;
Q represents -(CO)-, or a bond.

Y represents (C_5-C_{10})alkyl; (C_2-C_{10})alkenyl; (C_3-C_8)cycloalkyl; (C_5-C_8)cycloalkene group; or phenyl; any of which may be optionally substituted by one or more, same or different substituents selected from the group consisting of the formula R_5 defined below; (C_1-C_4)alkyl substituted by one or more substituents with the formula R_5; or a group of formula $-(Z-O)_n-Z$, wherein Z is a (C_1-C_3)alkyl, n is an integer > 1; and no continuous linear sequence of atoms in the group Y exceeds 9;

R_5 represents halogen, hydroxy, amino, (C_1-C_2)alkoxy, (C_1-C_4)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, azido, -COOH, -CONH$_2$, -CONHR', or -CONR'R' wherein R' represents (C_1-C_2)alkyl.

More preferably R_1 represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, methyl, or methoxy; R_2 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, methyl, or methoxy; R_3 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, methyl, or methoxy; R_4 represents hydrogen; X represents oxygen; Q represents -(CO)-, or bond; Y represents (C_5-C_7)alkyl; (C_2-C_4)alkenyl; any of which may be optionally substituted by one or more, same or different substituents selected from the group consisting of the formula R_5, (C_1-C_4)alkyl, substituted by one or more substituents with the formula R_5, and a group of formula $-CH_2-O-CH_2-CH_2-O-CH_3$; R_5 preferably represents fluoro, chloro, bromo, hydroxy, amino, (C_1-C_2)alkoxycarbonyl, -COOH, $-CONH_2$, $CON(CH_3)_2$.

It is preferred that Q does not represent -(CO)- in compounds of the formula I where Y is $-CF_3$.

The phenyl group of R_1 and R_2 may optionally be substituted, e.g. with hydroxy; amino; nitro; cyano; halogen, preferably fluoro, chloro, or bromo; methyl; or methoxy.

Specific compounds of formula I are:
N-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 101),
2′-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]octananilide (Compound 102),
4-Bromo-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]butananilide (Compound 103),
Ethyl 2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]succinanilate (Compound 104),
2-(2-Methoxy-ethoxy)-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]acetanilide (Compound 105),
N,N-dimethyl-*N′*-2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenylsuccinamide (Compound 106),
2-Hydroxy-2′-[3-chloro-4-(2-methoxybenzoyl)-phenylamino]acetanilide (Compound 107),
2-Hydroxy-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]acetanilide (Compound 108),
2-Hydroxy-2′-[3-fluoro-4-(2-methylbenzoyl)-phenylamino]acetanilide (Compound 109),
2-Amino-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]acetanilide (Compound 110),
Ethyl 2-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]anilino]acetate (Compound 111),
2-Chloro-4-[2-(6-hydroxyhexylamino)phenylamino]-2′-methylbenzophenone (Compound 112),
2-Chloro-4-[2-(3-hydroxypropylamino)phenylamino]-2′-methylbenzophenone (Compound 113),
5′-Bromo-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]hexananilide (Compound 114),
5′-Bromo-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]but-3-eneanilide (Compound 115),
5′-Bromo-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-4-methylpentananilide (Compound 116),
2′-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]-2-methylpentananilide (Compound 117),

N-[5-Bromo-2-[3-chloro-4-(4-ethoxy-2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 118),

N-[5-Bromo-2-[3-ethoxy-4-(2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 119),

N-[5-Bromo-2-[3-chloro-4-(2,3-dimethylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 120),

N-[5-Bromo-2-[3-chloro-4-(4-*n*-butyl-2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 121),

N-[5-Bromo-2-[3-chloro-4-(4-chloro-2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound122),

N-[5-Bromo-2-[3-fluoro-4-(2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 123),

N-[5-Bromo-2-[3-chloro-4-(2,4,5-trimethylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 124),

N-[5-Bromo-2-[3-chloro-4-(4-fluoro-2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 125),

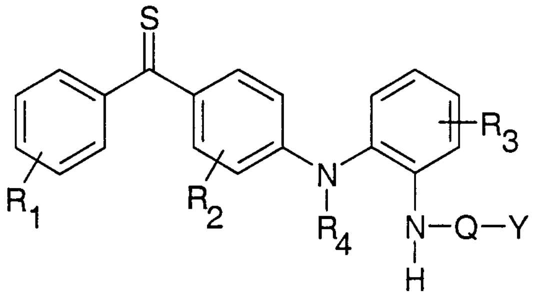
N-[5-Bromo-2-[3-chloro-4-(2,5-dimethylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 126),

N-[5-Bromo-2-[3-fluoro-4-(4-methoxy-2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 127),

N-[5-Bromo-2-[3-chloro-4-(3-chloro-2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound128),

and salts thereof with pharmaceutically acceptable acids, hydrates and solvates.

Compounds of formula I wherein X=S according to the formula Ia below are also generally preferred



Ia

in which R_1, R_2, R_3, R_4, Q, and Y have the above meanings.

Specific compounds of formula Ia are:

N-[2-[3-Chloro-4-(2-methyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound 129),
2'-[3-Chloro-4-(2-methyl(thiobenzoyl))-phenylamino]octananilide (Compound 130),
4-Bromo-2'-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]butananilide (Compound 131),
Ethyl 2'-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]succinanilate (Compound 132),
2-(2-Methoxy-ethoxy)-2'-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]acetanilide (Compound 133),
N,N-dimethyl-*N'*-2-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]phenylsuccinamide (Compound 134),
2-Hydroxy-2'-[3-chloro-4-(2-methoxy(thiobenzoyl))-phenylamino]acetanilide (Compound 135),
2-Hydroxy-2'-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]acetanilide (Compound 136),
2-Hydroxy-2'-[3-fluoro-4-(2-methyl(thiobenzoyl))-phenylamino]acetanilide (Compound 137),
2-Amino-2'-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]acetanilide (Compound 138),
Ethyl 2-[2-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]anilino]acetate (Compound 139),
2-Chloro-4-[2-(6-hydroxyhexylamino)phenylamino]-2'-methyl(thiobenzophenone) (Compound 140),
2-Chloro-4-[2-(3-hydroxypropylamino)phenylamino]-2'-methyl(thiobenzophenone) (Compound 141),
5'-Bromo-2'-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]hexananilide (Compound 142),
5'-Bromo-2'-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]but-3-eneanilide (Compound 143),
5'-Bromo-2'-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]-4-methylpentananilide (Compound 144),
2'-[3-Chloro-4-(2-methyl(thiobenzoyl))-phenylamino]-2-methylpentananilide (Compound 145),
N-[5-Bromo-2-[3-chloro-4-(4-ethoxy-2-methyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound 146),
N-[5-Bromo-2-[3-ethoxy-4-(2-methyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound 147),
N-[5-Bromo-2-[3-chloro-4-(2,3-dimethyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound 148),

N-[5-Bromo-2-[3-chloro-4-(4-*n*-butyl-2-methyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound 149),
N-[5-Bromo-2-[3-chloro-4-(4-chloro-2-methyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound150),
N-[5-Bromo-2-[3-fluoro-4-(2-methyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound 151),
N-[5-Bromo-2-[3-chloro-4-(2,4,5-trimethyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound 152),
N-[5-Bromo-2-[3-chloro-4-(4-fluoro-2-methyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound 153),
N-[5-Bromo-2-[3-chloro-4-(2,5-dimethyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound 154),
N-[5-Bromo-2-[3-fluoro-4-(4-methoxy-2-methyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound 155),
N-[5-Bromo-2-[3-chloro-4-(3-chloro-2-methyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound156),
and salts thereof with pharmaceutically acceptable acids, hydrates and solvates.

Further preferred compounds of general formula I are compounds wherein R_1, R_2, and R_3 represent one substituent. R_1 and R_2 preferably being in the ortho position.

The compounds of formula I and Ia can be used in the form of their salts which are formed with pharmaceutically acceptable inorganic or organic acids, such as hydrochloric, hydrobromic and hydroiodic acid, phosphoric acid, sulphuric acid, nitric acid, p-toluenesulphonic acid, methanesulphonic acid, formic acid, acetic acid, propionic acid, citric acid, tartaric acid, succinic acid, benzoic acid, maleic acid, these examples being considered as non-limiting for the invention.

As used in the specification, unless specified to the contrary, the following terms have the meaning indicated:

"Alkyl" refers to any univalent group derived from an alkane by removal of a hydrogen atom from any carbon atom, and includes the subclasses of normal alkyl (*n*-alkyl), and primary, secondary and tertiary alkyl groups respectively, and having the number of carbon atoms specified, including for example $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_5)$alkyl, (C_5)alkyl, $(C_6\text{-}C_{10})$alkyl, $(C_6\text{-}C_{15})$alkyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and t-butyl. Alkane refers to an acyclic branched or unbranched hydrocarbon having the general formula C_nH_{2n+2}, and therefore consisting entirely of hydrogen atoms and saturated carbon atoms.

"Olefinic group" refers to a straight or branched acyclic hydrocarbon having one or more carbon-carbon double bonds of either E or Z stereochemistry where applicable, and having the number of carbon atoms specified. The term includes, for example, (C_2-C_{15})olefinic group, preferably a (C_2-C_{15})alkenyl; (C_2-C_3)olefinic group, preferably a (C_2-C_3)alkenyl; vinyl; allyl; 1- butenyl; 2-butenyl; and 2-methyl-2-propenyl. Olefinic groups having only one carbon-carbon double bond, herein called alkenyl, are preferred

"Alkoxy" refers broadly to a radical of the formula -OR, where R is alkyl as defined above, for example (C_1-C_3)alkoxy, (C_1-C_2)alkoxy, methoxy, ethoxy, n-propoxy, and the like.

"(C_1-C_3)alkylthio" refers broadly to a radical of the formula -SR, where R is alkyl as defined above and includes methylthio, ethylthio, n-propylthio, and 2-propylthio.

"(C_1-C_6)alkylamino" refers broadly to a radical of the formula -NHR or $-NR_2$, where R is alkyl as defined above having from 1-6 carbon atoms and includes, for example, methylamino, dimethylamino, di-(n-propyl)amino, and n-butyl(ethyl)amino.

"(C_1-C_3)alkoxycarbonyl" refers broadly to a radical of the formula -COOR, where R is alkyl as defined above and includes methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, and i-propoxycarbonyl.

"(C_3-C_{10})monocyclic hydrocarbon group" includes the saturated cycloalkanes and unsaturated cyclic olefins, such as cycloalkenes having one endocyclic double bond, and having from 3-10 carbon atoms, and includes, for example, (C_3-C_8)cycloalkyl, cyclopropyl, cyclopentyl, cyclohexyl, and cyclooctyl, (C_3-C_{10})cycloalkene group, and (C_3-C_8)cycloalkene group. Specific examples are cycloprop-2-enyl, cyclobut-2-enyl, cyclopent-2-enyl, cyclohex-3-enyl, and cyclonon-4-enyl.

"Amino" means the group $-NH_2$.

Carbamoyl" refers to any one of the groups $-CONH_2$, -CONHR, and -CONRR' where R and R' represent alkyl as defined above.

"Carboxy" refers to a radical of the formula -COOH.

"Halogen" means the same or different of fluoro, chloro, bromo, and iodo; fluoro, chloro, and bromo being preferred.

Pharmacological methods

To study the effect of the compound of the present invention in vitro the inhibition of the IL-1β and TNF-α secretion was measured using the following procedure:

Cytokine production was measured in the media from lipopolysaccharide (LPS) stimulated peripheral blood mononuclear cells. The mononuclear cells were isolated from human peripheral blood by Lymphoprep® (Nycomed, Norway) fractionation and suspended in RPMI 1640 (growth medium) with foetal calv serum (FCS, 2%), at a concentration of 5 x 10^5 cells/ml. The cells were incubated in 24-well tissue culture plates in 1 ml aliquots. Test compounds were dissolved in dimethylsulfoxide (DMSO, 10 mM) and were diluted with the medium. Compounds were added to the cells for 30 minutes, then LPS (1 mg/ml final concentration) was added. The plates were incubated for 18 hours, and the concentration of IL-1ß and TNF-α in the medium was determined by enzyme-linked immunosorbent assays. The median inhibitory concentrations (IC_{50}) of the compounds were calculated. The results are shown in Table 1 below.

The compounds of the present invention also show similar activities in the ability to inhibit PMN (polymorphonuclear) superoxide secretion which is also indicative of potentially useful anti-inflammatory drugs. The compounds were tested using the following procedure. Human polymorphonuclear (PMN) granulocytes were isolated from human blood by dextran sedimentation, Lymphoprep® fractionation, and hypotonic lysis of contaminating erythrocytes. Superoxide anion generation was measured as the superoxide dismutase inhibitable reduction of ferricytochrome C (Madhu, S.B. et al, Inflammation, 16, 241, (1992)). The cells were suspended in Hank's balanced salt solution, and incubated for 10 minutes at 37°C with test compounds. The cells were primed by the addition of TNF-α (3 ng/ml final concentration) for 10 minutes, and then ferricytochrome C, (final concentration 750µg/ml), bovine serum albumin (BSA, final concentration 1 mg/ml) and formylmethionyl-leucyl-phenylalanine (fMLP, final concentration 10^{-7} M) were added for 3 minutes. The cells were chilled on ice, and were spun down. The optical densities in the cell-free supernatant was measured in a spectrophotometer. The median inhibitory concentration (IC_{50}) of the compounds was calculated. The results are shown in Table 1.

Table 1.	Inhibition of cytokines and PMN-superoxide production in vitro by compounds of the present invention.		
	The median inhibition concentration (IC_{50}, nM) of		
Comp. No.;	IL-1β	TNF-α	PMN-superoxide
101	200	25	63
102	6.3	6.3	5.0
ref. a)	13	7.1	5.0

ref. a): 4-(2-Aminophenylamino)-2-chloro-2′-methylbenzophenone, compound 106 disclosed in PCT/DK98/00008.

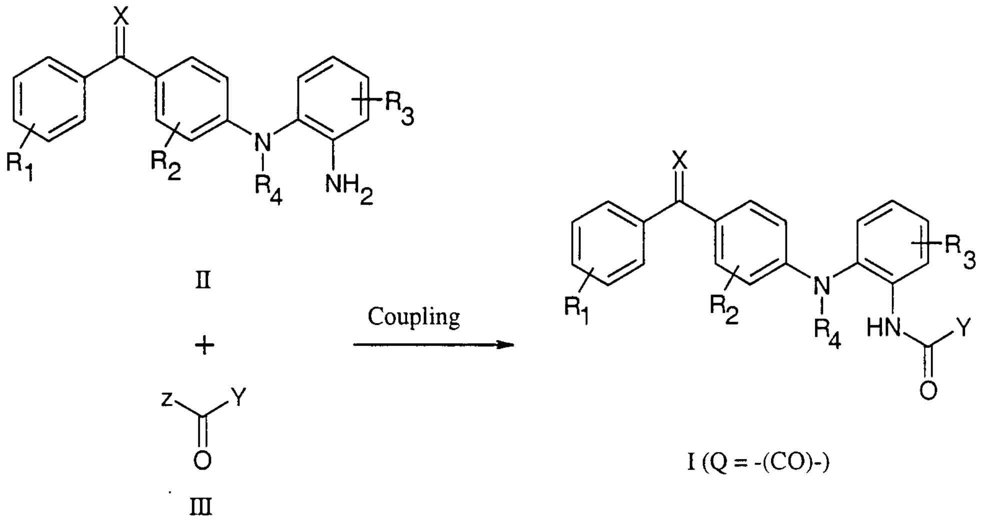
These results show that the compounds of the present invention are able to inhibit the production of IL-1β, TNF-α and PMN-superoxide, and showing a pharmacological activity comparable to a reference compound, thus making them potentially useful in the treatment of inflammatory diseases.

To study the compounds of the present invention *in vivo* the 12-*O*-tetradecanoylphorbol-13-acetate (TPA) induced murine chronic skin inflammation model can be used (De Young, L.M. et al, Agents Actions, 26, 335-341 (1989); Carlson, R.P. et al, Agents Actions, 17, 197-204 (1985); Alford, J.G. et al, Agents Action, 37, (1992); Stanley, P.L. et al, Skin Pharmacol, 4, 262-271 (1991)), cf. description of method in PCT/DK98/00008 hereby incorporated by reference. These results show that the compounds of the present invention are of the same potency compared to known reference compounds, e.g. hydrocortisone with its known side effects, whereas the compounds of the present invention are well tolerated and are non-toxic. Some members of the present class of compounds show a very low absorption, thus making them especially useful in the treatment of various dermatological diseases. In general, they may be administered by e.g. oral, intravenous, intranasal, topically or transdermal routes.

Method of preparation

The compounds of the present invention can be prepared in a number of ways well known to those skilled in the art of organic synthesis. The compounds of the present invention can be synthesised using the methods outlined below, together with methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below.

The novel compounds of formula I and Ia may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of experiment and work-up procedures, are chosen to be conditions of standard for that reaction, which should be readily recognised by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the educt molecule must be compatible with the reagents and reactions proposed. Not all compounds of formula I falling into a given class may be compatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods can be used.



Z: OH, Cl, YCOO

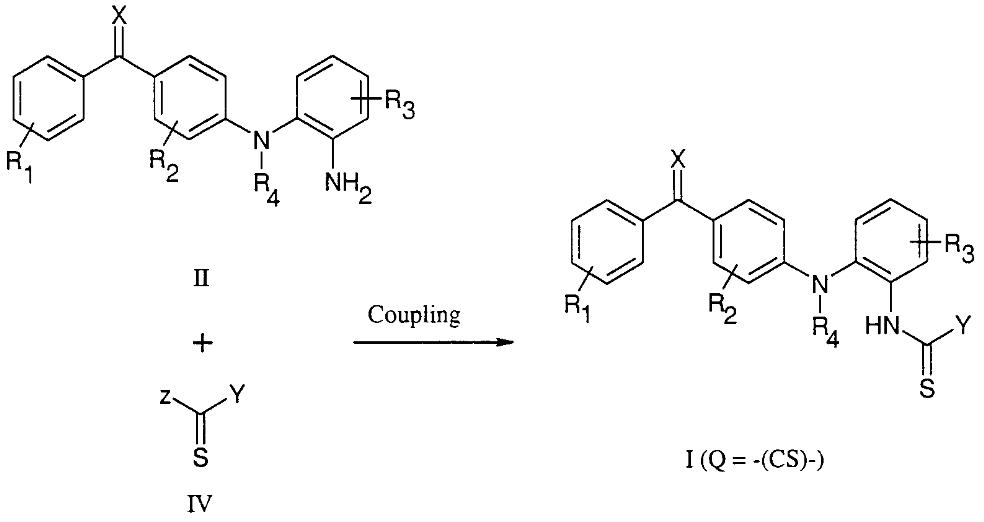
and R_1, R_2, R_3, R_4, X, and Y have the above meanings.

Scheme 1

Compounds according to the present invention in which Q represents -(CO)- may be prepared by a process comprising coupling of an amine of the formula II with an acid of the formula III or an activated derivative thereof, as shown in scheme 1, where R_1, R_2, R_3, R_4, X, and Y are as defined in general formula I, except that any substituents or functional group which are potentially reactive in the coupling reaction may themselves be protected before the coupling reaction is performed and subsequently removed.

The coupling reaction or condensation is carried out using any of the many methods for the formation of amide bonds known to one skilled in the art of organic synthesis. These methods include, but are not limited to, the use of standard coupling procedures such as mixed carbonic anhydride (isobutyl chloroformate) method, carbodiimide (N,N-dimethylaminopropyl-N^I-ethyl carbodiimide (EDC), dicyclohexyl carbodiimide, diisopropyl carbodiimide) method, active ester (pentafluorophenyl ester, p-nitrophenyl ester, N-hydroxysuccinic imido ester) method, cabonyldiimidazole method, azide method, phosphorous reagents such as BOP-Cl, azide method , conversion of an acid of formula III to an acid chloride. Some of these methods (especially carbodiimide) can be enhanced by the addition of 1-hydroxybenzotriazole (HOBt).

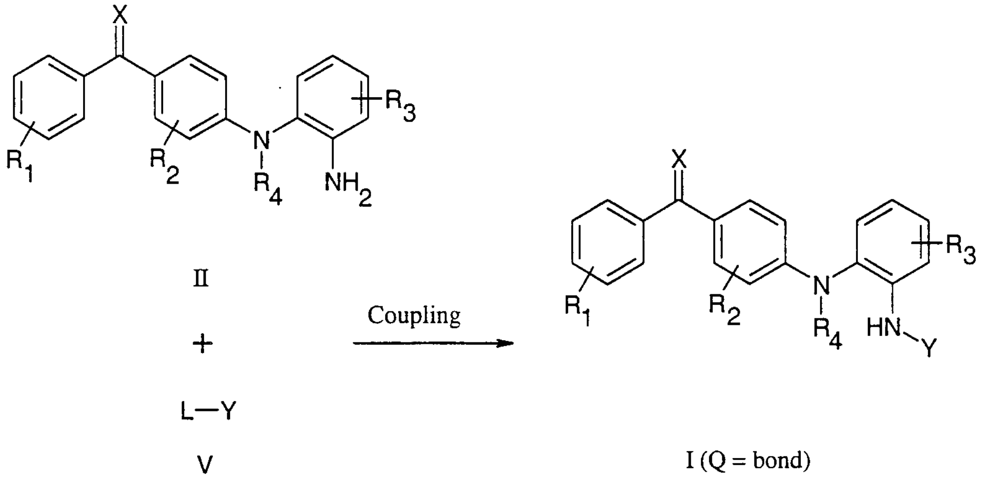
Compounds according to the present invention in which C=X and Q simultaneusly represents -(CS)- may be prepared from compounds of the invention in which C=X or Q, or both represents -(CO)- by a process using an appropiate thiocarbonylating agent such as phosphorous pentasulfide (P_4S_{10}), or Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide) or the like. Alternatively, compounds according to the present invention in which Q represents -(CS)- may be prepared by a process comprising coupling of an amine of the formula II with a thioacylating agent of the formula IV, as shown in scheme 2, where R_1, R_2, R_3, R_4, X, and Y are as defined in general formula I, except that any substituents or functional group which are potentially reactive in the coupling reaction may themselves be protected before the coupling reaction is performed and subsequently removed. Examples of such thioacylating agents are, but are not limited too, thionoesters, dithioesters and N-thioacylazoles (derived from imidazole, triazole, benzimidazole and benzotriazole).



and R_1, R_2, R_3, R_4, X, and Y have the above meanings.

Scheme 2

Compounds according to the present invention in which Q represents a bond may be prepared by a process comprising coupling of an amine of the formula II with an alkylating agent of the formula V , as shown in scheme 3, where R_1, R_2, R_3, R_4, X, and Y are as defined in general formula I, except that any substituents or functional group which are potentially reactive in the coupling reaction may themselves be protected before the coupling reaction is performed and subsequently removed.



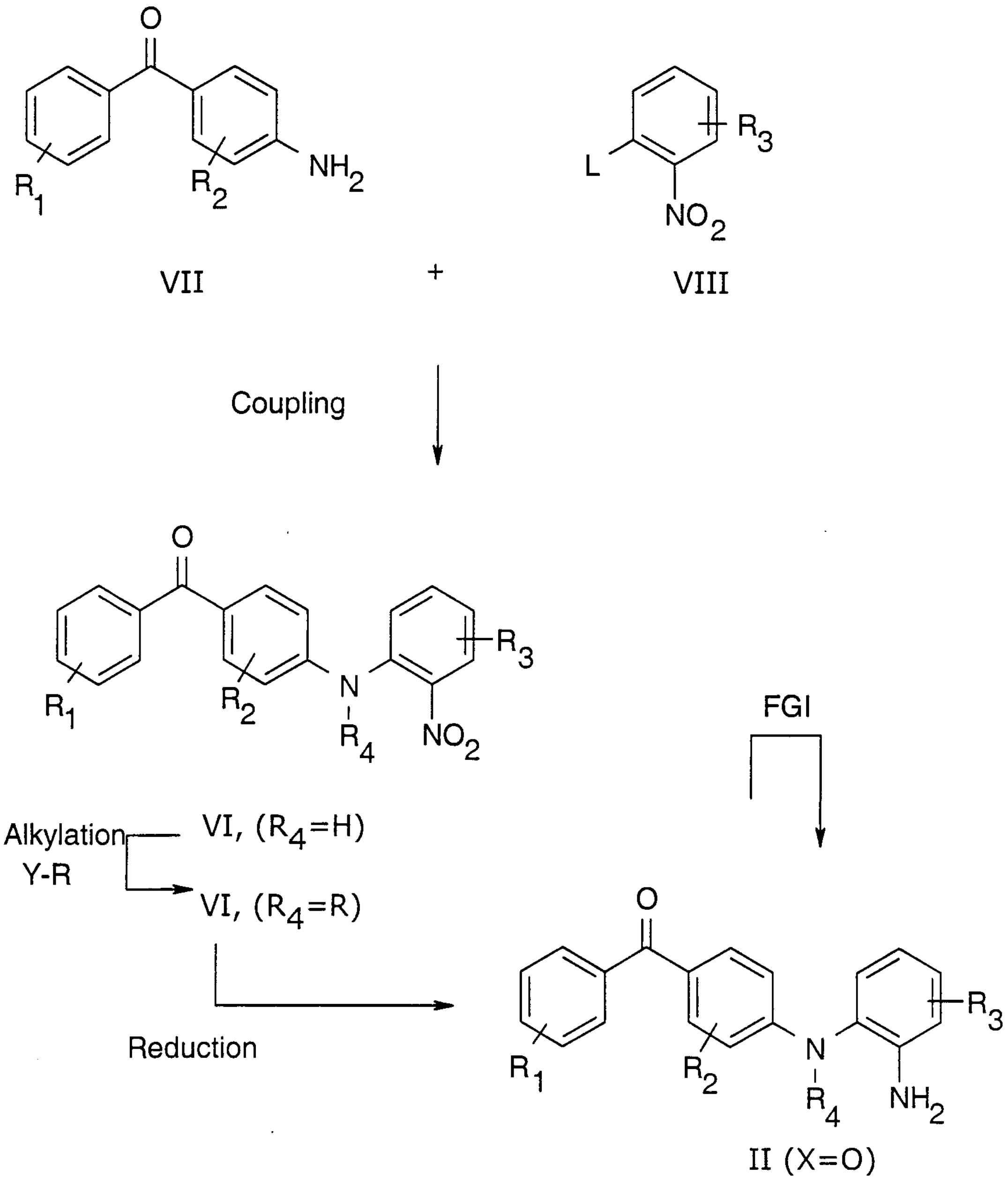
L: I, Br, Cl, OTs

and R_1, R_2, R_3, R_4, X, and Y have the above meanings.

Scheme 3

Typically alkylating agents of the general formula V include, but are not limited to, iodides(L=I), bromides(L=Br), chlorides(L=Cl) and sulfonates(L=OSO_2R, where R represents methyl, trifluoromethyl or 4-methylphenyl).

Compounds accordingly to the present invention with the general formula II(X=O) may be prepared by several methods known to those skilled in the art of organic synthesis. One useful sequence is shown in scheme 4 were the key process comprising coupling of an amine of the formula VII with an fluoride, chloride, bromide, iodide, or triflate with the formula VIII, as shown in Scheme 4, where R_1, R_2, R_3, and, R_4 are as defined in general formula I, to give a coupled product with the general formula VI, except that any substituents or functional group which are potentially reactive in the coupling reaction may themselves be protected before the coupling reaction is performed and subsequently removed. This compound VI may then be reduced to the corresponding amine with the general formula II by treatment with standard reducing agents. Examples of such reducing agents include, but are not limited to, stannous chloride dihydrate; hydrogen, ammonium formiate, or hydrazine hydrate and a catalytic amount of palladium on carbon.



L: Br, I, OSO_2CF_3, or F and Cl

Y:Cl, Br, I, OSO_2CF_3 , OSO_2CH_3, or OTs

FGI: Functional group interconversion

and R_1, R_2, R_3, R_4, and Y have the above meanings.

Scheme 4

The coupling reaction is carried out using any of the methods for the formation of diphenylamines known to one skilled in the art of organic synthesis. The preferred method is the nucleophilc aromatic substiution method which comprising coupling of an amine with an arylfluoride or arylchloride in the presence of a base, in an suitable solvent. Especially potassium-*tert*-butoxide (KO*t*-Bu), sodium-*tert*-butoxide (NaO*t*-Bu), sodium hydrid (NaH), and potassium hydride (KH) have proven to be the best bases in this process, but other bases may be used as well.

The reaction is typically performed at ambient temperature (20-25 °C) in dipolar aprotic solvents like dimethylsulfoxide (DMSO), dimethylformamide (DMF), or *N*-methylpyrrolidone (NMP) under an inert atmosphere like argon or nitrogen.

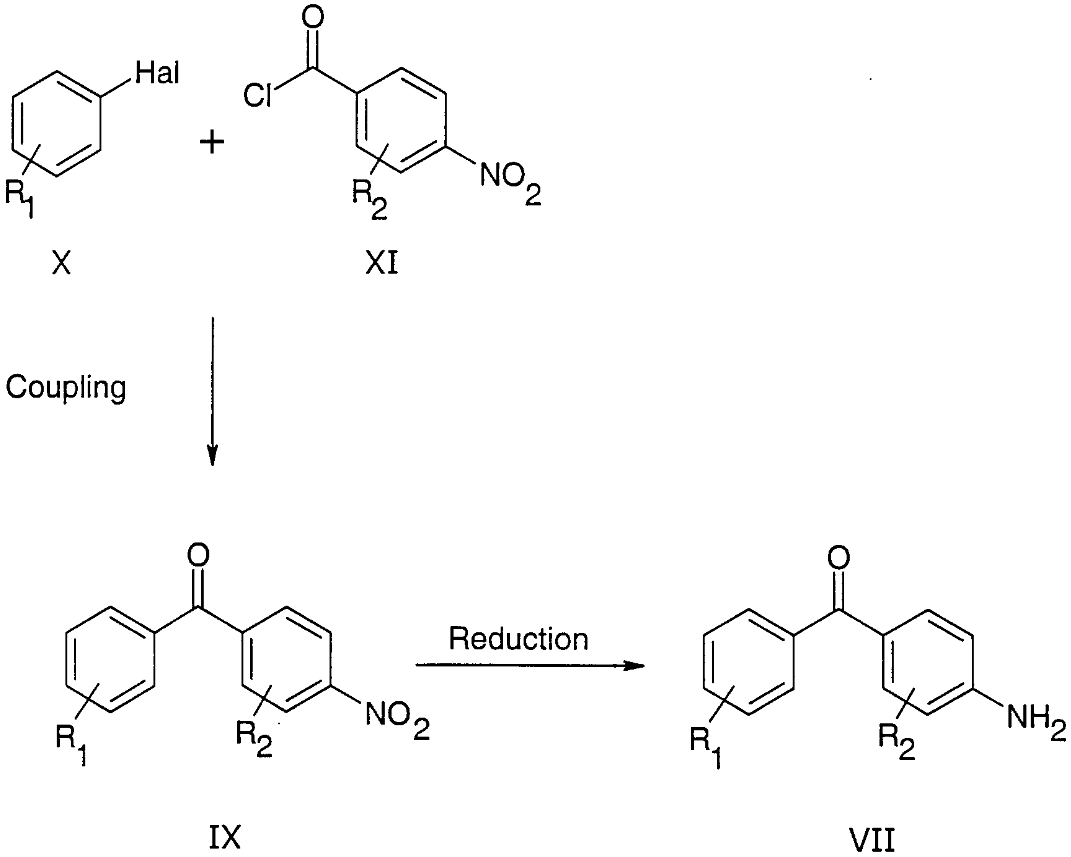
Alternatively, the coupling reaction can be done by the palladium catalysed amination method which comprising coupling of an amine with an arylhalogenide (iodide, bromide, triflate, or in some cases chloride) in the presence of a base, a suitable Pd source, and a suitable phosphine ligand in an inert solvent.

The palladium compound used in the process is not particularly limited, and as specific examples are palladium(II) acetate, palladium(II) chloride, palladium(II) bromide, dichlorobis(triphenylphosphine)palladium(II), tetrakis(triphenylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0). The preferred ligand include, but are not limited to, racemic or non-racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (hereinafter referred to as BINAP), tri-o-tolylphosphine, tri-tert-butylphosphine, 1,1'-bis(diphenylphosphino)-ferrocene, bis[(2-diphenylphosphino)phenyl]ether (DPEphos), 2-dicyclohexylphosphanyl-2'-dimethylaminobiphenyl, 2-(di-*tert*-butylphosphino)biphenyl, and 9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene (Xantphos). The amount of palladium and ligand used in this process is typically in the range 0.1 to 10 % by mole relative to the amount of the aromatic halide (or triflate) used. Especially sodium-*tert*-butoxide (NaO*t*-Bu) and caesium carbonate (Cs_2CO_3) have proven to be the best bases in this process, but other bases may be used as well. The reaction is typically performed at elevated temperature (80-120 °C) in inert solvents like 1,4-dioxane, toluene, benzene and tetrahydrofurane under an inert atmosphere like argon or nitrogen.

Compounds according to the present invention in which R_4 is not hydrogen may be prepared by a process comprising coupling of an amine of the formula VI (R_4= H) with an alkylating agent, as shown in scheme 4, where R_1, R_2, R_3, and, R_4 are as defined in general formula I, except that any substituents or functional group which are potentially reactive in the coupling reaction may themselves be protected before the coupling reaction is performed and subsequently removed.

Typically alkylating agents of the general formula R-Y include, but are not limited to, iodides (Y=I), bromides (Y=Br), chlorides (Y=Cl) and sulfonates ($Y=OSO_2R'$, where R' represents methyl, trifluoromethyl or 4-methylphenyl).

Compounds according to the present invention may in special cases be prepared by a simple functional group interconversion (FGI), meaning a standard process, known to those skilled in the art of organic synthesis, where a functional group in compounds with the general formula I (or any other intermediate described herein) is transformed into a different functional group in one or more synthetic steps, leading to a new compound with the general formula I. Examples of such processes are, but are not limited to, hydrolysis of an ester to give an acid under basic conditions; deprotection of an methylether to give an phenol by treatment with e.g. borontribromide (BBr_3); and catalytic hydrogenation of an olefin to give an saturated hydrocarbon.



hal: Br, I

and R_1 and R_2 have the above meanings.

SCHEME 5

Compounds accordingly to the present invention with the general formula VII may be prepared by several methods known to those skilled in the art of organic synthesis. One useful sequence is shown in Scheme 5. The key step comprises coupling of a bromide (or iodide) with the general formula X with an acid chloride with the general formula XI to afford the benzophenone with the general formula IX. This compound IX may then be reduced to the corresponding amine with the general formula VII by treatment with standard reducing agents. Examples of such reducing agents include, but are not limited to, stannous chloride dihydrate; hydrogen, ammonium formiate, or hydrazine hydrate and a catalytic amount of palladium on carbon. The coupling reaction is done by transforming the bromide (X) into a reactive organometallic intermediate, e.g. by treatment with butyllithium to afford the lithium derivative or by treatment with magnesium to afford the magnesium derivative. The reactivity of this intermediate is then modulated by transmetallation to e.g. zinc, by treatment with $ZnCl_2$, $ZnBr_2$, or ZnI_2. This organozinc compound is then coupled with the acid chloride, with the general formula XI, under the influence of a palladium(0) complex in catalytic amount. Examples of such catalyst include but are not particularly limited to tetrakis(triphenylphosphine)palladium(0), tetrakis(triphenylarsine)-palladium(0), dichlorobis(triphenylphosphine)palladium(II), or benzylchlorobis(triphenylphosphine)palladium(II).

It may be more advantageous in some cases to alter the sequence of the processes described above. The described sequence of processes is not considered as being limited for the preparation of the compounds of the present invention with the general formula I and alteration of the reaction sequence is an obvious alternative for those skilled in the art of organic synthesis.

The present compounds are intended for use in pharmaceutical compositions which are useful in the treatment of the above mentioned diseases.

The amount required of a compound of formula I and Ia (hereinafter referred to as the active ingredient) for therapeutic effect will, of course, vary both with the particular compound, the route of administration and the mammal under treatment. A suitable dose of a compound of formula I for systemic treatment is 0.1 to 200 mg/kg bodyweight, the most preferred dosage being 0.2 to 50 mg/kg of mammal bodyweight, administered one or more times daily.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. Conveniently, the active ingredient comprises from 0.1% to 100% by weight of the formulation. Conveniently, dosage units of a formulation contain between 0.07 mg and 1 g of the active ingredient. For topical administration, the active ingredient preferably comprises from 1% to 20% by weight of the formulation but the active ingredient may comprise as much as 50% w/w.

Formulations suitable for nasal or buccal administration may comprise 0.1% to 20% w/w. for example about 2% w/w of active ingredient.

By the term "dosage unit" is meant a unitary, i.e. a single dose which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically and chemically stable unit dose comprising either the active material as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

The formulations, both for veterinary and human medical use, of the present invention comprise an active ingredient in association with a pharmaceutically acceptable carrier therefore and optionally other therapeutic ingredient(s). The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

The formulations include those in a form suitable for oral, ophthalmic, rectal, parenteral (including subcutaneous, intramuscular and intravenous), transdermal, intra-articular, topical, nasal, or buccal administration.

The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be in the form of discrete units as capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. The active ingredient may also be administered in the form of a bolus, electuary or paste.

Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient and a carrier such as cocoa butter, or in the form of an enema.

Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredient which is preferably isotonic with the blood of the recipient.

Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the active ingredient which may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the active ingredient for both intra articular and ophthalmic administration.

Formulations suitable for topical administration, including eye treatment, include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops.

Formulations suitable for administration to the nose or buccal cavity include powder, self-propelling and spray formulations, such as aerosols and atomizers.

In addition to the aforementioned ingredients, the formulations of this invention may include one or more additional ingredients.

The compositions may further contain other therapeutically active compounds usually applied in the treatment of the above mentioned pathological conditions, for instance glucocorticoids, vitamin D's, anti-histamines, platelet activating factor (PAF) antagonists, anticolinergic agents, methyl xanthines, β-adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

The novel compounds of the invention are of value in the human and veterinary practice as systemic and topical therapeutic agents for the treatment and prevention of diseases. The novel compounds show anti-acne properties and, i.a., anti-inflammatory and cytokine regulating effects possibly due to MAP kinase inhibition, and are useful in the treatment and prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondylo-arthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, and osteoporosis.

The invention will now be further described in the following non-limiting general procedures, preparations and examples.

EXAMPLES

General procedures, preparations and Examples

Specific examples of compounds of formula I are listed in Table 2.

All melting points are uncorrected. For ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra (300 MHz) chemical shift values (δ) (in ppm) are quoted, unless otherwise specified, for deuteriochloroform and hexadeuterodimethylsulfoxide solutions relative to internal tetramethylsilane (δ 0.00) or chloroform (^1H NMR δ 7.25, ^{13}C NMR δ 76.81). The value for a multiplet (m), either defined (doublet (d), triplet (t), quartet (q)) or not at the approximate mid point is given unless a range is quoted (s singlet, b broad). The organic solvents used were anhydrous. The term "chromatography" refers to column chromatography using the flash technique and was performed on silica gel.

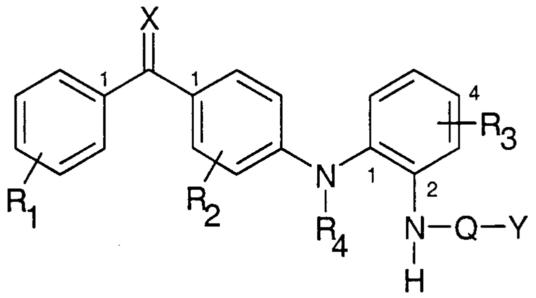
The following abbreviations have been used throughout this specification: $CDCl_3$=deuteriochloroform, DMF=*N*,*N*-dimethylformamide, DMSO-d_6=hexadeuterodimethylsulfoxide, Et_3N=triethylamine, EtOAc=ethyl acetate, Et_2O=diethylether, HMPA=hexamethylphosphorous triamide, NMM=*N*-methylmorpholine, THF=tetrahydrofurane, BOP-Cl=bis(2-oxo-3-oxazolidinyl)phosphinic chloride, TLC=thin layer chromatography.

<u>Table 2 Compounds of General formula I</u>

Comp. No. Example No.	X	R_1	R_2	R_3	R_4	Q	Y
101, Ex. 1	O	2-Me	2-Cl	H	H	-(CO)-	$-(CH_2)_2COOH$
102, Ex. 2	O	2-Me	2-Cl	H	H	-(CO)-	$-(CH_2)_6CH_3$
103, Ex. 3	O	2-Me	2-Cl	H	H	-(CO)-	$-(CH_2)_3Br$
104, Ex.4	O	2-Me	2-Cl	H	H	-(CO)-	$-(CH_2)_2COOCH_2CH_3$
105, EX.5	O	2-Me	2-Cl	H	H	-(CO)-	$-(CH_2)-O-(CH_2)_2-O-CH_3$
106, Ex.6	O	2-Me	2-Cl	H	H	-(CO)-	$-(CH_2)_2CON(CH_3)_2$
107, Ex.7	O	2-OMe	2-Cl	H	H	-(CO)-	$-CH_2OH$
108, Ex.8	O	2-Me	2-Cl	H	H	-(CO)-	$-CH_2OH$

Comp. No. Example No.	X	R_1	R_2	R_3	R_4	Q	Y
109, Ex.9	O	2-Me	2-F	H	H	-(CO)-	$-CH_2OH$
110, Ex.10	O	2-Me	2-Cl	H	H	-(CO)-	$-CH_2NH_2$
111, Ex.11	O	2-Me	2-Cl	H	H	Bond	$-CH_2COOCH_2CH_3$
112, Ex.12	O	2-Me	2-Cl	H	H	Bond	$-(CH_2)_6OH$
113, Ex.13	O	2-Me	2-Cl	H	H	Bond	$-(CH_2)_3OH$
114, Ex.14	O	2-Me	2-Cl	4-Br	H	-(CO)-	$-(CH_2)_4CH_3$
115, Ex.15	O	2-Me	2-Cl	4-Br	H	-(CO)-	$-CH_2CH{=}CH_2$
116, Ex.16	O	2-Me	2-Cl	4-Br	H	-(CO)-	$-(CH_2)_2CH(CH_3)_2$
117, Ex.17	O	2-Me	2-Cl	H	H	-(CO)-	$-CH(CH_3)(CH_2)_2CH_3$
118, Ex.18	O	2-Me, 4-OEt	2-Cl	4-Br	H	-(CO)-	$-(CH_2)_2COOH$
119, Ex.19	O	2-Me	2-OEt	4-Br	H	-(CO)-	$-(CH_2)_2COOH$
120, Ex.20	O	2-Me, 3-Me	2-Cl	4-Br	H	-(CO)-	$-(CH_2)_2COOH$
121, Ex.21	O	2-Me, 4-$(CH_2)_3CH_3$	2-Cl	4-Br	H	-(CO)-	$-(CH_2)_2COOH$
122, Ex.22	O	2-Me, 4-Cl	2-Cl	4-Br	H	-(CO)-	$-(CH_2)_2COOH$
123, Ex.23	O	2-Me	2-F	4-Br	H	-(CO)-	$-(CH_2)_2COOH$
124, Ex.24	O	2-Me, 4-Me, 5-Me	2-Cl	4-Br	H	-(CO)-	$-(CH_2)_2COOH$
125, Ex.25	O	2-Me, 4-F	2-Cl	4-Br	H	-(CO)-	$-(CH_2)_2COOH$
126, Ex.26	O	2-Me, 5-Me	2-Cl	4-Br	H	-(CO)-	$-(CH_2)_2COOH$
127, Ex.27	O	2-Me, 4-OMe	2-F	4-Br	H	-(CO)-	$-(CH_2)_2COOH$
128, Ex.28	O	2-Me, 3-Cl	2-Cl	4-Br	H	-(CO)-	$-(CH_2)_2COOH$

The numbering in Table 2 refers to the numbering in the formula below



General procedure 1

Coupling of compounds of the general formula II with compounds of the general formula III (Z=Cl) to give compounds of the general formula (I, Q=O), or a protected derivative thereof.

To a cooled (0 ^{o}C) solution of an amine (0.9 mmol), with the general formula II, and Et_3N (2.7 mmol) in CH_2Cl_2 (5 ml) was slowly added a solution of an acid chloride (1.2 mmol), with the general formula III, in CH_2Cl_2 (1 ml). The mixture was stirred at 0 ^{o}C for 2h and at RT overnight. The reaction mixture was added more CH_2Cl_2, and the solution was washed succesively with 2 M HCl, water, and brine, then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified either by crystallization or chromatography to afford the anilide with the general formula I, or a protected derivative thereof.

General procedure 2

Coupling of compounds of the general formula II with compounds of the general formula III (Z=OH) to give compounds of the general formula I (Q=O) , or a protected derivative thereof.

NMM (2.8 mmol) was added to a solution of the acid (2.8 mmol), with the general formula III (Z=O), in THF (10 ml) at -15 ^{o}C, followed by dropwise addition of isobutyl chloroformate (2.8 mmol). The mixture was stirred for 30 min, the amine (2.0 mmol) in THF (10 ml), with the general formula II, was added, and the resulting slurry was stirred at 0 ^{o}C for 1h and at RT overnight. The reaction mixture was poured into EtOAc, and the solution was washed succesively with 1 M HCl, 25% $NaHCO_3$, and brine, then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified either by crystallization or chromatography to afford the anilide, with the general formula I, or a protected derivative thereof.

General procedure 3

Alkylation of compounds of the general formula II with compounds of the general formula V to give compounds of the general formula I (Q=bond) , or a protected derivative thereof.

To a slurry of an amine (1.0 mmol), with the general formula II, K_2CO_3 (2.0 mmol), and KI (0.1 mmol) in DMF (5 ml) was added an alkylating agent (1.0 mmol), with the general formula V. The mixture was stirred for 24 h at 25 ^{o}C, or until the starting material had disappered, as seen on TLC. The reaction mixture was poured into water (100 ml) and extracted with EtOAc (3*50 ml). The combined organic extracts were whashed with brine, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by chromatography to afford the alkylated aniline, with the general formula I, or a protected derivative thereof.

General procedure 4

Coupling of compounds of the general formula II with compounds of the general formula III (Z=YCOO) to give compounds of the general formula (I, Q=O), or a protected derivative thereof.

To a solution of an amine (2.9 mmol), with the general formula II, in acetic acid (100%, 8 ml) was slowly added an acid anhydride (3.8 mmol) with the general formula III. The mixture was stirred at RT for 2h or until no more starting material was seen on TLC. The reaction mixture was added water, and the solution was stirred for 30 minutes and then extracted with EtOAc twice. The organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified either by crystallization or chromatography to afford the anilide with the general formula I, or a protected derivative thereof.

Example 1

N-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 101)

A stirred solution of 4-(2-aminophenylamino)-2-chloro-2′-methylbenzophenone (3.0 mmol) in glacial acetic acid (5.0 ml) was heated to 70 ^{o}C, then succinic anhydride (4.0 mmol) was added. The temperature was held at 100 ^{o}C for 20 min after which the reaction mixture was concentrated *in vacuo* to afford a light brown syrupy, which crystallised on standing. Trituration with a mixture of Et_2O/CH_2Cl_2 3:1 followed by filtration and washing yielded the product as white crystals.

^{13}C NMR (DMSO-d_6): δ 195.3, 173.9, 170.6, 149.3, 142.4, 139.4, 136.5, 133.5, 132.4, 131.8, 131.1, 130.7, 128.8, 126.5, 125.7, 125.3, 125.1, 124.5, 123.7, 115.3, 112.2, 30.8, 29.1, 19.8

Example 2

2′-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]octananilide (Compound 102)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2′-methylbenzophenone

Starting compound III: Octanoyl chloride

Purification: Chromatography using EtOAc/pentane 1:3 as eluant

^{13}C NMR ($CDCl_3$): δ 196.8, 172.8, 148.9, 139.2, 137.6, 135.1, 133.7, 132.8, 131.8, 131.2, 130.8, 129.5, 128.3, 126.2, 125.6, 125.4, 124.8, 124.1, 116.0, 112.4, 37.2, 31.6, 29.1, 29.0, 25.7, 22.6, 20.3, 14.0

Example 3

4-Bromo-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]butananilide (Compound 103)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2′-methylbenzophenone

Starting compound III: 4-Bromobutyryl chloride

Purification: Chromatography using CH_2Cl_2 followed by EtOAc/CH_2Cl_2 1:20 as eluant

^{13}C NMR ($CDCl_3$): δ 196.8, 171.1, 148.8, 139.1, 137.8, 135.1, 33.6, 132.5, 131.8, 131.3, 130.9, 129.6, 128.7, 126.3, 125.9, 125.4, 125.0, 123.8, 116.1, 112.5, 44.3, 33.8, 27.9, 20.4

Example 4

Ethyl 2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]succinanilate (Compound 104)

General procedure: 2

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2′-methylbenzophenone

Starting compound III: Mono ethyl succinate

Purification: Chromatography using EtOAc/pentane 1:4 and 1:2 as eluant

^{13}C NMR ($CDCl_3$): δ 196.5, 173.4, 171.0, 148.5, 139.2, 137.9, 35.0, 133.5, 133.4, 131.3, 130.8, 129.6, 128.9, 126.5, 125.4, 125.2, 124.7, 123.8, 116.5, 112.6, 61.2, 29.7, 20.4, 14.2, 14.2

Example 5

2-(2-Methoxy-ethoxy)-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]acetanilide (Compound 105)

General procedure: 2

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2′-methylbenzophenone

Starting compound III: 2-(2-Methoxyethoxy)acetic acid

Purification: Chromatography using EtOAc/pentane 1:5 as eluant

^{13}C NMR ($CDCl_3$): δ 196.4, 169.1, 148.7, 139.3, 137.7, 135.0, 33.6, 133.1, 131.2, 130.8, 130.8, 129.5, 128.6, 126.5, 125.4, 125.3, 124.5, 124.0, 116.2, 112.5, 71.5, 71.3, 70.5, 59.1, 20.4

Example 6

N,N-dimethyl-*N'*-2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenylsuccinamide (Compound 106)

General procedure: 2

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: *N,N*-Dimethylsuccinamic acid

Purification: Chromatography using EtOAc as eluant

^{13}C NMR ($CDCl_3$): δ 196.5, 172.2, 148.5, 139.4, 137.8, 134.9, 133.7, 133.5, 131.2, 130.7, 130.3, 129.6, 128.5, 126.2, 125.3, 125.3, 124.4, 122.5, 116.7, 112.5, 37.1, 35.8, 32.4, 29.6, 20.4

Example 7

2-Hydroxy-2'-[3-chloro-4-(2-methoxybenzoyl)-phenylamino]acetanilide (Compound 107)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methoxybenzophenone

Starting compound III: Acetoxyacetyl chloride

Purification of the O-acetylated derivative (I) was done by chromatography using Et_2O/pentane 1:4 as eluant. Deprotection: The protected derivative (I) (0.38 mmol) and K_2CO_3 (0.5 mmol) was stirred in MeOH (5 ml) for 1 h at ambient temperature. The reaction mixture was poured into EtOAc, and the solution was washed successively with water and brine, then dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a weakly coloured solid product.

Mp: 180.0-181.3 °C

^{13}C NMR (DMSO-d_6): δ 192.3, 170.5, 157.1, 149.7, 133.7, 133.4, 132.8, 132.4, 130.6, 129.4, 129.2, 126.8, 125.7, 125.4, 124.8, 122.2, 120.4, 114.7, 112.0, 111.7, 61.5, 55.6

Example 8

2-Hydroxy-2'-[3-chloro-4-(2-methylbenzoyl)-phenylamino]acetanilide (Compound 108)

By following the procedure of example 7, but substituting 4-(2-aminophenylamino)-2-chloro-2'-methylbenzophenone for 4-(2-aminophenylamino)-2-chloro-2'-methoxybenzophenone, the desired compound was obtained. The compound was further purified by chromatography using EtOAc/pentane 1:1 as eluant.

Mp: 127-129 °C

^{13}C NMR ($CDCl_3$): δ 197.4, 170.9, 149.0, 138.8, 138.0, 135.0, 133.5, 132.1, 131.4, 131.4, 131.2, 129.9, 128.6, 126.4, 126.2, 125.4, 125.3, 123.4, 116.1, 112.4, 62.4, 20.5

Example 9

2-Hydroxy-2′-[3-fluoro-4-(2-methylbenzoyl)-phenylamino]acetanilide (Compound 109)
By following the procedure of example 7, but substituting 4-(2-aminophenylamino)-2-fluoro-2′-methylbenzophenone for 4-(2-aminophenylamino)-2-chloro-2′-methoxybenzophenone, the desired compound was obtained. The compound was further purified by crystallization from CH_2Cl_2.

Mp: 149-150 ^{0}C

^{13}C NMR (DMSO-d_6): δ 192.8, 170.5, 164.6, 161.2, 152.6, 152.4, 140.5, 134.9, 133.4, 132.9, 130.5, 130.3, 129.8, 127.3, 126.0, 125.7, 125.4, 124.8, 122.3, 115.7, 115.5, 109.8, 100.0, 99.7, 61.5, 19.2

Example 10

2-Amino-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]acetanilide (Compound 110)
General procedure: 2
Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2′-methylbenzophenone
Starting compound III: *N*-(9-Fluorenylmethoxycarbonyl)-glycine
Purification of the FMOC-protected derivative (I) was done by chromatography using EtOAc/pentane 1:4 and 1:2. Deprotection: The protected derivative (I) (0.16 mmol) and CsF (0.33 mmol) was stirred in a mixture of CH_2Cl_2 (6 ml) and CH_3CN (2 ml) for 6 days at ambient temperature. The reaction mixture was poured into water and EtOAc and the organic phase was separated. The aqueous phase was extracted with more EtOAc. The organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product which was purified by chromatography using EtOAc/pentane 1:2 as eluant.

^{13}C NMR ($CDCl_3$): δ 196.6, 171.8, 148.8, 139.3, 137.7, 135.0, 133.6, 132.6, 131.5, 131.2, 130.8, 129.5, 128.5, 126.2, 125.7, 125.3, 124.8, 123.4, 116.1, 112.4, 44.9, 20.4

Example 11

Ethyl 2-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]anilino]acetate (Compound 111)
General procedure: 3
Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2′-methylbenzophenone
Starting compound V: Ethyl bromoacetate
Purification: Chromatography using EtOAc/pentane 1:2 as eluant

^{13}C NMR ($CDCl_3$): δ 196.5, 171.1, 149.9, 143.6, 139.4, 137.7, 135.1, 133.6, 131.2, 130.6, 129.5, 128.2, 127.8, 126.9, 125.8, 125.3, 118.4, 115.6, 112.0, 111.8, 61.4, 45.7, 20.4, 14.2

Example 12

2-Chloro-4-[2-(6-hydroxyhexylamino)phenylamino]-2'-methylbenzophenone (Compound 112).

To a solution of 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone (0.50 mmol) in HMPA (5 ml) was added 6-bromohexanol (0.76 mmol) and $NaHCO_3$ (5.0 mmol). The mixture was stirred for 24 h at 60 ^{o}C, more 6-bromohexanol (0.36 mmol) was added and stirring was continued for 6 h. The reaction mixture was poured into ice water and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography twice using EtOAc/hexane 1:2 and then Et_2O/hexane 1:4 as eluant to afford the alkylated aniline as an oil.

^{1}H NMR ($CDCl_3$): δ 7.05-7.40 (m,8H), 6.60-6.80 (m,3H), 6.53 (dd,1H), 5.49 (s,1H), 3.97 (bs,1H), 3.60 (bt,2H), 3.13 (bt,2H), 2,47 (s,3H), 1.20-1.70 (m,8H)

Example 13

2-Chloro-4-[2-(3-hydroxypropylamino)phenylamino]-2'-methylbenzophenone (Compound 113)

To a solution of 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone (10.0 mmol) in HMPA (50 ml) was added 3-bromopropanol (25.8 mmol) and $NaHCO_3$ (50 mmol). The mixture was stirred for 72 h at 60-70 ^{o}C. The reaction mixture was poured into ice water and the precipitated product was filtered off, washed with water and dried. The crude product was purified by chromatography using EtOAc/Et_2O 1:9 as eluant to afford the alkylated aniline as an oil.

^{13}C NMR (DMSO-d_6): δ 195.0, 151.0, 144.2, 139.6, 136.1, 133.6, 130.9, 130.4, 128.5, 127.0, 126.1, 125.5, 125.2, 124.6, 115.6, 114.3, 111.2, 110.6, 58.6, 39.9, 31.7, 19.6

Example 14

5'-Bromo-2'-[3-chloro-4-(2-methylbenzoyl)-phenylamino]hexananilide (Compound 114)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Hexanoyl chloride

Purification: Chromatography using EtOAc/pentane 1:4 as eluant

^{13}C NMR ($CDCl_3$): δ 196.8, 172.5, 148.3, 138.9, 137.9, 135.0, 133.5, 133.5, 131.4, 131.3, 131.1, 129.7, 129.3, 129.0, 126.3, 125.4, 118.5, 116.2, 112.7, 37.3, 31.3, 25.2, 22.4, 20.5, 13.9

Example 15

5′-Bromo-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]but-3-eneanilide (Compound 115)

General procedure: 2

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-chloro-2′-methylbenzophenone

Starting compound III: 3-Butenoic acid

Purification: Chromatography using dichloromethane as eluant

^{13}C NMR ($CDCl_3$): δ 196.9, 169.8, 148.4, 138.8, 137.8, 135.0, 133.5, 131.4, 131.1, 130.8, 130.3, 129.7, 129.1, 128.9, 126.4, 125.9, 125.4, 120.8, 118.7, 116.2, 112.6, 42.1, 20.4

Example 16

5′-Bromo-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-4-methylpentananilide (Compound 116)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-chloro-2′-methylbenzophenone

Starting compound III: 4-methyl pentanoyl chloride

Purification: Chromatography using EtOAc/pentane 1:6 as eluant

^{13}C NMR ($CDCl_3$): δ 196.7, 172.7, 148.3, 138.9, 138.0, 135.0, 133.5, 133.4, 131.4, 131.3, 131.1, 129.7, 129.4, 129.0, 126.3, 125.4, 118.5, 116.3, 112.7, 35.3, 34.3, 27.7, 22.3, 20.5

Example 17

2′-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]-2-methylpentananilide (Compound 117)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2′-methylbenzophenone

Starting compound III: 2-Methyl pentanoyl chloride

Purification: Chromatography using EtOAc/pentane 1:4 as eluant

^{13}C NMR ($CDCl_3$): δ 196.6, 176.0, 148.9, 139.2, 137.8, 135.1, 133.6, 132.6, 132.1, 131.3, 130.8, 129.6, 128.8, 126.3, 126.1, 125.4, 123.8, 115.8, 112.3, 42.0, 36.6, 20.6, 20.4, 17.9, 14.0

Example 18

N-[5-Bromo-2-[3-chloro-4-(4-ethoxy-2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 118)

By following the procedure of example 1, but substituting 4-(2-Amino-4-bromophenylamino)-2-chloro-4′-ethoxy-2′-methylbenzophenone for 4-(2-aminophenylamino)-2-chloro-2′-methylbenzophenone, the desired compound was obtained.

^{13}C NMR ($CDCl_3$): δ 198.3, 179.0, 170.9, 162.2, 146.7, 142.8, 135.0, 134.5, 133.1, 131.0, 130.1, 130.0, 129.8, 129.5, 128.3, 121.7, 118.0, 116.6, 114.9, 113.7, 111.1, 63.7, 30.4, 29.1, 21.9, 14.7

Example 19

N-[5-Bromo-2-[3-ethoxy-4-(2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 119)

By following the procedure of example 1, but substituting 4-(2-Amino-4-bromophenylamino)-2-ethoxy-2′-methylbenzophenone for 4-(2-aminophenylamino)-2-chloro-2′-methylbenzophenone, the desired compound was obtained.
The compound was further purified by crystallization from mixtures of dichloromethane and *n*-hexane.

^{13}C NMR (): δ 195.3, 173.7, 170.8, 160.0, 150.1, 142.9, 134.3, 132.6, 132.2, 132.1, 129.9, 128.7, 127.5, 126.8, 126.5, 125.0, 124.5, 118.6, 114.7, 107.2, 98.1, 62.9, 30.7, 28.8, 19.2, 13.5

Example 20

N-[5-Bromo-2-[3-chloro-4-(2,3-dimethylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 120)

By following the procedure of example 1, but substituting 4-(2-Amino-4-bromophenylamino)-2-chloro-2′,3′-dimethylbenzophenone for 4-(2-aminophenylamino)-2-chloro-2′-methylbenzophenone, the desired compound was obtained. The compound was further purified by crystallization from mixtures of dichloromethane and *n*-hexane.

^{13}C NMR (): δ 195.6, 173.7, 170.7, 148.9, 140.3, 137.4, 134.2, 133.8, 133.6, 133.3, 131.6, 131.2, 127.5, 126.7, 126.6, 125.7, 125.3, 125.1, 115.7, 112.1, 30.7, 28.8, 19.6, 16.0

Example 21

N-[5-Bromo-2-[3-chloro-4-(4-*n*-butyl-2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 121)

By following the procedure of example 1, but substituting 4-(2-Amino-4-bromophenylamino)-4′-*n*-butyl-2-chloro-2′-methylbenzophenone for 4-(2-aminophenylamino)-2-chloro-2′-methylbenzophenone, the desired compound was obtained.

^{13}C NMR ($CDCl_3$): δ 199.4, 178.9, 170.9, 147.9, 147.0, 139.4, 135.1, 134.4, 133.6, 132.0, 131.9, 131.5, 130.2, 129.5, 128.4, 125.7, 122.0, 116.6, 115.2, 113.6, 35.6, 33.2, 30.4, 29.1, 22.4, 21.2, 13.9

Example 22

N-[5-Bromo-2-[3-chloro-4-(4-chloro-2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound122)

By following the procedure of example 1, but substituting 4-(2-Amino-4-bromophenylamino)-2,4′-dichloro-2′-methylbenzophenone for 4-(2-aminophenylamino)-2-chloro-2′-methylbenzophenone, the desired compound was obtained. The compound was further purified by crystallization from mixtures of dichloromethane and *n*-hexane.

^{13}C NMR (DMSO-d_6): δ 194.1, 173.7, 170.7, 148.9, 139.1, 137.9, 135.1, 133.4, 133.3, 131.2, 130.7, 130.5, 127.5, 126.7, 126.4, 125.6, 125.3, 115.8, 115.5, 112.3, 30.7, 28.8, 19.4

Example 23

N-[5-Bromo-2-[3-fluoro-4-(2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 123)

By following the procedure of example 1, but substituting 4-(2-Amino-4-bromophenylamino)-2-fluoro-2′-methylbenzophenone for 4-(2-aminophenylamino)-2-chloro-2′-methylbenzophenone, the desired compound was obtained. The compound was further purified by crystallization from mixtures of dichloromethane and *n*-hexane.

^{13}C NMR (DMSO-d_6): δ 192.8, 173.7, 170.8, 162.7, 151.3, 140.5, 134.9, 133.4, 133.1, 131.1, 130.5, 129.8, 127.5, 127.3, 126.7, 125.6, 125.4, 116.0, 115.9, 110.3, 100.6, 30.7, 28.8, 19.2

Example 24

N-[5-Bromo-2-[3-chloro-4-(2,4,5-trimethylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 124)

By following the procedure of example 1, but substituting 4′-(2-Amino-4-bromophenylamino)-2′-chloro-2,4,5-trimethylbenzophenone for 4-(2-aminophenylamino)-2-chloro-2′-methylbenzophenone, the desired compound was obtained. The compound was further purified by crystallization from mixtures of dichloromethane and *n*-hexane.

^{13}C NMR (DMSO-d_6): δ 195.2, 173.7, 170.7, 148.2, 139.7, 136.2, 134.3, 133.2, 133.1, 132.8, 132.8, 132.4, 131.5, 130.4, 127.8, 127.5, 126.7, 124.9, 115.5, 115.4, 112.3, 30.7, 28.8, 19.4, 19.2, 18.6

Example 25

N-[5-Bromo-2-[3-chloro-4-(4-fluoro-2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 125)

By following the procedure of example 1, but substituting 4-(2-Amino-4-bromophenyl-amino)-2-chloro-4′-fluoro-2′-methylbenzophenone for 4-(2-aminophenylamino)-2-chloro-2′-methylbenzophenone, the desired compound was obtained.

^{13}C NMR ($CDCl_3$): δ 197.7, 178.6, 170.9, 164.5, 147.6, 142.4, 134.3, 134.0, 133.6, 133.5, 132.0, 130.8, 129.6, 129.1, 128.0, 123.1, 118.6, 116.4, 116.1, 113.5, 112.7, 30.7, 29.1, 21.1

Example 26

N-[5-Bromo-2-[3-chloro-4-(2,5-dimethylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 126)

By following the procedure of example 1, but substituting 4-(2-Amino-4-bromophenylamino)-2-chloro-2′,5′-dimethylbenzophenone for 4-(2-aminophenylamino)-2-chloro-2′-methylbenzophenone, the desired compound was obtained. The compound was further purified by crystallization from mixtures of dichloromethane and *n*-hexane.

^{13}C NMR (DMSO-d_6): δ 195.3, 173.7, 170.7, 148.6, 139.0, 134.6, 133.3, 133.2, 133.2, 131.3, 130.9, 129.1, 127.5, 127.0, 126.7, 125.1, 115.6, 112.3, 30.7, 28.8, 20.3, 19.3

Example 27

N-[5-Bromo-2-[3-fluoro-4-(4-methoxy-2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 127)

By following the procedure of example 1, but substituting 4-(2-Amino-4-bromophenyl-amino)-2-fluoro-4′-methoxy-2′-methylbenzophenone for 4-(2-aminophenylamino)-2-chloro-2′-methylbenzophenone, the desired compound was obtained. The compound was further purified by crystallization from mixtures of dichloromethane and *n*-hexane.

^{13}C NMR (DMSO-d_6): δ 191.9, 173.7, 170.8, 162.0, 160.7, 150.4, 138.9, 133.2, 132.8, 132.1, 131.4, 131.1, 127.5, 126.7, 125.2, 117.0, 116.3, 115.6, 110.6, 110.4, 100.7, 55.2, 30.7, 28.8, 20.1

Example 28

N-[5-Bromo-2-[3-chloro-4-(3-chloro-2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound128)

By following the procedure of example 1, but substituting 4-(2-Amino-4-bromophenylamino)-2,3'-dichloro-2'-methylbenzophenone for 4-(2-aminophenylamino)-2-chloro-2'-methylbenzophenone, the desired compound was obtained. The compound was further purified by crystallization from mixtures of dichloromethane and *n*-hexane.

^{13}C NMR (DMSO-d_6): δ 193.8, 173.7, 170.7, 149.4, 142.2, 134.5, 134.2, 134.0, 133.5, 133.2, 130.9, 130.7, 127.5, 127.2, 126.7, 126.6, 125.6, 125.4, 116.0, 115.7, 112.2, 30.7, 28.8, 16.6

Example 29

Tablet containing compound 111

Compound 111 (active substance)	50 mg
Lactose	125 mg
Starch	12 mg
Methyl cellulose	2 mg
Sodium carboxymethyl cellulose	10 mg
Magnesium stearate	1 mg

The active substance, lactose and starch are mixed to a homogeneous state in a suitable mixer and moistened with a 5 per cent aqueous solution of methyl cellulose 15 cps. The mixing is continued until granules are formed. If necessary, the wet granulation is passed through a suitable screen and dried to a water content of less than 1% in a suitable drier, e.g. fluid bed or drying oven. The dried granules are passed through a 1 mm screen and mixed to a homogeneous state with sodium carboxymethyl cellulose. Magnesium stearate is added, and the mixing is continued for a short period of time. Tablets with a weight of 200 mg are produced from the granulation by means of a suitable tabletting machine.

Example 30: Formulation for injection containing compound 111.

Compound 111 (active substance)	1%
Sodium chloride	q.s.
Ethanol	10%
Water for injection to make	100%

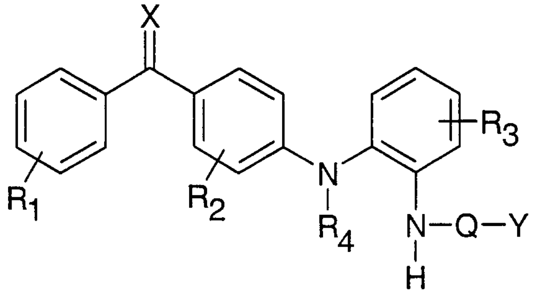
The active substance is dissolved in ethanol (10%) then water for injection made isotonic with sodium chloride is added to make 100%. The mixture is filled into ampoules and sterilized.

Example 31 Cream formulation containing compound 101

Compound 101 (10 g) was dissolved in Octyldodecyl myristate (250g) to form Part A. Methylparaben (1 g) and propylparaben (0.2 g) were dissolved in phenoxyethanol (6 g) and mixed with a 0.025 M Phosphate buffer pH = 7.5 (632,8 g) to form Part B. Cetostearyl alcohol (50 g) and ARLACEL 165® (50 g) was melted in a vessel at 70° to 80 °C. Part A was added and heated to 60-70°C. The aqueous phase was likewise heated to 60-70 °C and slowly added to the melted oil phase under high speed stirring. The homogenized components were cooled to room temperature.

CLAIMS

1. A compound of the general formula I



I

wherein

R_1, R_2, and R_3 represents one or more, same or different substituents selected from the group consisting of halogen, hydroxy, mercapto, trifluoromethyl, amino, $(C_1\text{-}C_3)$alkyl, $(C_2\text{-}C_3)$ olefinic group, $(C_1\text{-}C_3)$alkoxy, $(C_1\text{-}C_3)$alkylthio, $(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_3)$-alkoxycarbonyl, cyano, $-CONH_2$, phenyl, or nitro; further R_2 can be hydrogen, and R_3 can be carboxy and carbamoyl;

R_4 represents hydrogen, $(C_1\text{-}C_3)$alkyl, or allyl;

X represents oxygen or sulphur;

Q represents -(CO)-, -(CS)-, or a bond;

Y represents $(C_5\text{-}C_{15})$alkyl; $(C_2\text{-}C_{15})$olefinic group; $(C_3\text{-}C_{10})$monocyclic hydrocarbon group; or phenyl; any of which may be optionally substituted by one or more, same or different substituents selected from the group consisting of the formula R_5 defined below; $(C_1\text{-}C_4)$alkyl substituted by one or more substituents selected from the group R_5; or a group of the formula $-(Z\text{-}O)_n\text{-}Z$, wherein Z is a $(C_1\text{-}C_3)$alkyl, n is an integer > 1; and no continuous linear sequence of atoms in the group Y exceeds 15;

R_5 represents halogen, hydroxy, mercapto, trifluoromethyl, amino, $(C_1\text{-}C_3)$alkoxy, $(C_1\text{-}C_3)$alkylthio, $(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_3)$alkoxycarbonyl, cyano, azido, nitro, -COOH, -$CONH_2$, -CONHR', or COONR'R' wherein R' represents $(C_1\text{-}C_3)$alkyl;

or a pharmaceutically acceptable salt thereof, or a hydrate or solvate thereof.

2. A compound according to claim 1 wherein

- R_1 represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, $(C_1$-$C_2)$alkyl, $(C_2$-$C_3)$olefinic group, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$alkoxycarbonyl, cyano, or $CONH_2$.

- R_2 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, $(C_1$-$C_3)$alkyl, $(C_2$-$C_3)$olefinic group, $(C_1$-$C_3)$alkoxy.

- R_3 represents one or more, same or different substituents selected from the group consisting of hydrogen, halogen, hydroxy, trifluoromethyl, $(C_1$-$C_3)$alkyl, $(C_2$-$C_3)$olefinic group, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$alkoxycarbonyl, cyano, carboxy, or $-CONH_2$.

- R_4 represents hydrogen, $(C_1$-$C_2)$alkyl, or allyl.

- X represents oxygen.

- Q represents -(CO)-, or a bond.

- Y represents $(C_6$-$C_{10})$alkyl; $(C_2$-$C_{10})$olefinic group; $(C_3$-$C_8)$cycloalkyl; $(C_3$-$C_8)$cycloalkene group; or phenyl; any of which may be optionally substituted by one or more, same or different substituents selected from the group consisting of the formula R_5 defined below, $(C_1$-$C_5)$alkyl substituted by one or more substituents with the formula R_5, and a group of formula $-(Z-O)_n-Z$, wherein Z is a $(C_1$-$C_3)$alkyl, n is an integer > 1; and no continuous linear sequence of atoms in the group Y exceeds 9; preferably Q-Y represents $-(CO)-(C_5)$alkyl, or $-(CS)-(C_5)$alkyl, any of which may be optionally substituted by one or more, same or different substituents represented by the formula R_5.

- R_5 represents halogen, hydroxy, amino, $(C_1$-$C_2)$alkoxy, $(C_1$-$C_4)$alkylamino, $(C_1$-$C_3)$alkoxycarbonyl, cyano, azido, -COOH, $-CONH_2$, -CONHR', or -CONR'R' wherein R' represents $(C_1$-$C_2)$alkyl.

3. A compound according to any one of the preceding claims wherein

- R_1 represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, methyl, or methoxy.

- R_2 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, methyl, or methoxy.

- R_3 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, methyl, or methoxy.

- R_4 represents hydrogen or (C_1-C_2)alkyl.

- Y represents (C_5-C_7)alkyl; or (C_2-C_4)alkenyl; any of which may be optionally substituted by one or more, same or different substituents selected from the group consisting of the formula R_5; or (C_1-C_4)alkyl substituted by one or more substituents with the formula R_5 representing fluoro, chloro, bromo, hydroxy, amino, (C_1-C_2)alkoxycarbonyl, -COOH, $-CONH_2$, or $CON(CH_3)_2$; and a group of formula $-CH_2-O-CH_2-CH_2-O-CH_3$.

4. A compound of formula I herein wherein Q does not represent -(CO)- when Y is $-CF_3$.

5. A compound according to claim 1 and selected from the group consisting of
N-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 101),
2′-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]octananilide (Compound 102),
4-Bromo-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]butananilide (Compound 103),
Ethyl 2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]succinanilate (Compound 104),
2-(2-Methoxy-ethoxy)-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]acetanilide (Compound 105),
N,N-dimethyl-*N′*-2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenylsuccinamide (Compound 106),
2-Hydroxy-2′-[3-fluoro-4-(2-methylbenzoyl)-phenylamino]acetanilide (Compound 109),
2-Amino-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]acetanilide (Compound 110),
Ethyl 2-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]anilino]acetate (Compound 111),

5′-Bromo-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]but-3-eneanilide (Compound 115),

5′-Bromo-2′-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-4-methylpentananilide (Compound 116),

N-[5-Bromo-2-[3-ethoxy-4-(2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 119),

N-[5-Bromo-2-[3-chloro-4-(2,3-dimethylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 120),

N-[5-Bromo-2-[3-chloro-4-(4-chloro-2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound122),

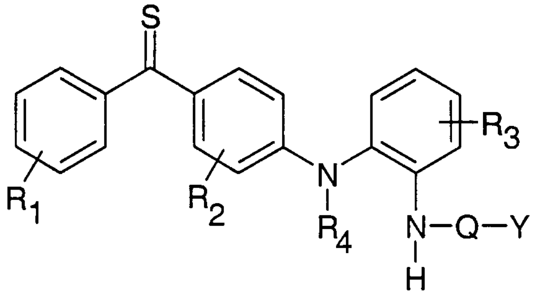
N-[5-Bromo-2-[3-fluoro-4-(2-methylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 123),

N-[5-Bromo-2-[3-chloro-4-(2,4,5-trimethylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 124),

N-[5-Bromo-2-[3-chloro-4-(2,5-dimethylbenzoyl)-phenylamino]phenyl]-succinamic acid (Compound 126),

and salts thereof with pharmaceutically acceptable acids, hydrates and solvates.

6. A compound according to claim 1 and having the general formula Ia



Ia

wherein R_1, R_2, R_3, R_4, Q, and Y have the meanings specified in claim 1.

7. A compound according to the preceding claim and selected from the group consisting of

N-[2-[3-Chloro-4-(2-methyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound 129),

2′-[3-Chloro-4-(2-methyl(thiobenzoyl))-phenylamino]octananilide (Compound 130),

4-Bromo-2′-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]butananilide (Compound 131),

Ethyl 2′-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]succinanilate (Compound 132),

2-(2-Methoxy-ethoxy)-2′-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]acetanilide

(Compound 133),
N,N-dimethyl-*N'*-2-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]phenylsuccinamide (Compound 134),
2-Hydroxy-2'-[3-fluoro-4-(2-methyl(thiobenzoyl))-phenylamino]acetanilide (Compound 137),
2-Amino-2'-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]acetanilide (Compound 138),
Ethyl 2-[2-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]anilino]acetate (Compound 139),
5'-Bromo-2'-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]but-3-eneanilide (Compound 143),
5'-Bromo-2'-[3-chloro-4-(2-methyl(thiobenzoyl))-phenylamino]-4-methylpentananilide (Compound 144),
N-[5-Bromo-2-[3-ethoxy-4-(2-methyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound 147),
N-[5-Bromo-2-[3-chloro-4-(2,3-dimethyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound 148),
N-[5-Bromo-2-[3-chloro-4-(4-chloro-2-methyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound150),
N-[5-Bromo-2-[3-fluoro-4-(2-methyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound 151),
N-[5-Bromo-2-[3-chloro-4-(2,4,5-trimethyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound 152),
N-[5-Bromo-2-[3-chloro-4-(2,5-dimethyl(thiobenzoyl))-phenylamino]phenyl]-succinamic acid (Compound 154),
and salts thereof with pharmaceutically acceptable acids, hydrates and solvates.

8. A compound according to any one of the preceding claims wherein one or both of $R_1$and R_2 represent one substituent, said substituent preferably being in the ortho position.

9. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 8 together with a pharmaceutically acceptable carrier and optionally together with a second active ingredient optionally selected from the group consisting of glucocorticoids, vitamin D's, anti-histamines, platelet activating factor (PAF) antagonists, anticolinergic agents, methyl xanthines, β-adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

10. Use of a compound according to any one of claim 1 to 8 for the preparation of a medicament for the treatment and/or prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, osteoporosis and acne.

11. A method for the treatment and/or prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, and osteoporosis, characterized in administering to patients suffering from said diseases an effective amount of one or more compounds described in any one of claims 1 - 8, optionally together or concomitantly with one or more other therapeutically active components selected from the group consisting of glucocorticoids, vitamin D's, anti-histamines, platelet activating factor (PAF) antagonists, anticolinergic agents, methyl xanthines, β-adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin), and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 00/00385

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 235/04, C07C 237/04, C07C 229/18, A61K 31/165, A61K 31/222
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)

IPC7: C07C

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 practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9832730 A1 (LEO PHARMACEUTICAL PRODUCTS LTD. A/S), 30 July 1998 (30.07.98)	1-5,8-10
A		6-7
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier 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 14 Sept 2000	Date of mailing of the international search report 10.10.2000
Name and mailing address of the International Searching Authority European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel(+31-70)340-2040, Tx 31 651 epo nl, Fax(+31-70)340-3016	Authorized officer GÖRAN KARLSSON/GH Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK00/00385

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.: 11
because they relate to subject matter not required to be searched by this Authority, namely:

see extra sheet

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.

Claim 11 is directed to a diagnostic method or to a method for treatment of the human or animal body by therapy methods practised on the human or animal body, see Rule 39.1 (iv).
Nevertheless, a search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/06/00

International application No.

PCT/DK 00/00385

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9832730 A1	30/07/98	AU 2969297 A	05/01/98
		AU 5478198 A	18/08/98
		CN 1248966 T	29/03/00
		EP 0902872 A	24/03/99
		EP 0966424 A	29/12/99
		GB 9701453 D	00/00/00
		PL 334806 A	13/03/00