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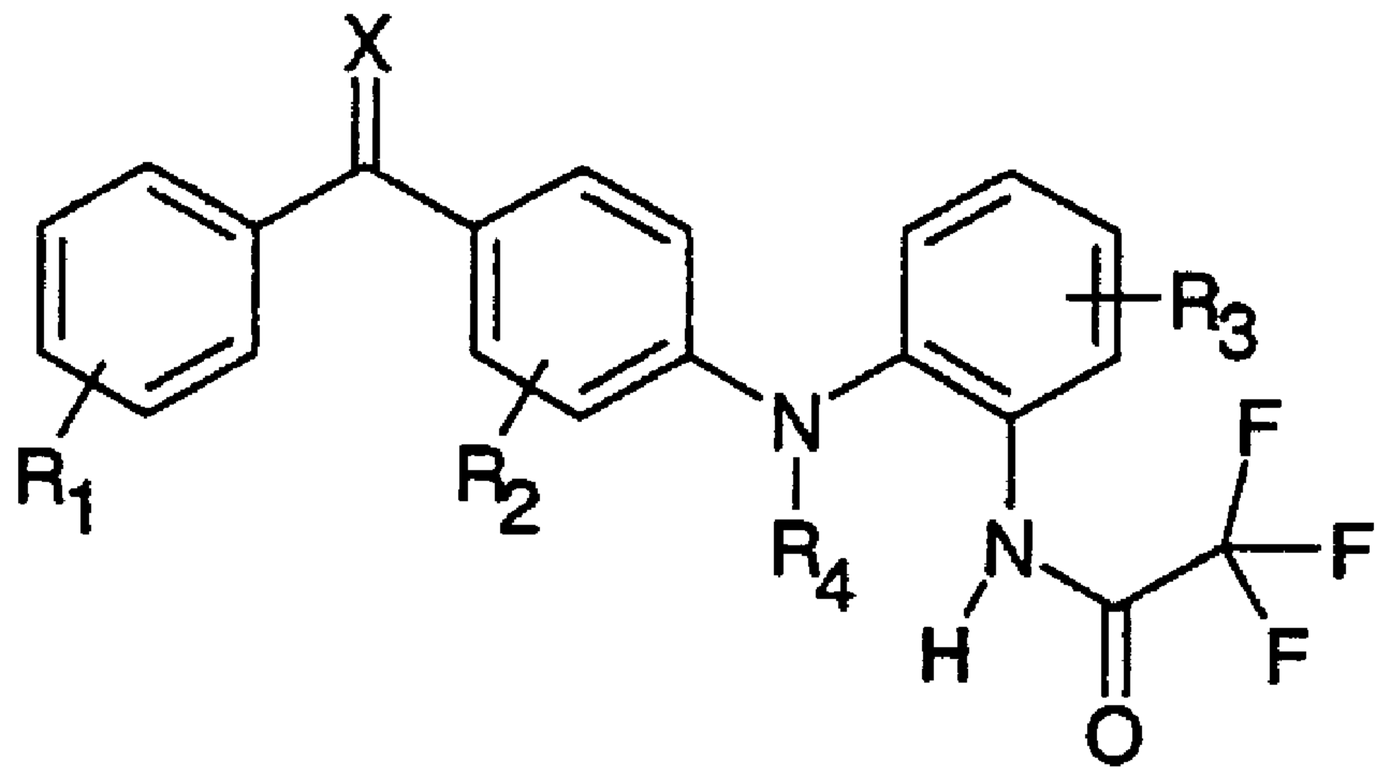
(54) Titre : AMINOBENZOPHENONES COMME INHIBITEURS D'IL-1β ET DE TNF-α
(54) Title: AMINOBENZOPHENONES AS INHIBITORS OF IL-1β AND TNF-α



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(57) Abrégé/Abstract:
The present invention relates to compounds of formula (I) wherein R_1 and R_2 independently represent 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, carbamoyl, phenyl, or nitro; R_2 further being represented by hydrogen; R_3 represents hydrogen, 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, phenyl, cyano, carboxy or carbamoyl; R_4 represents hydrogen, $(C_1$-$C_3)$alkyl, or allyl; X represents oxygen or sulphur; with the proviso that formula (I) does not comprise the compound 2,2,2-trifluoro-N-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-phenyl]acetamide wherein R_1 is a 2-methyl, R_2 is 2-chloro, R_3 and R_4 is hydrogen, and X is oxygen; and a salt thereof with a pharmaceutically acceptable acid, a hydrate or a solvate thereof. The compounds are valuable in the human and veterinary therapy.

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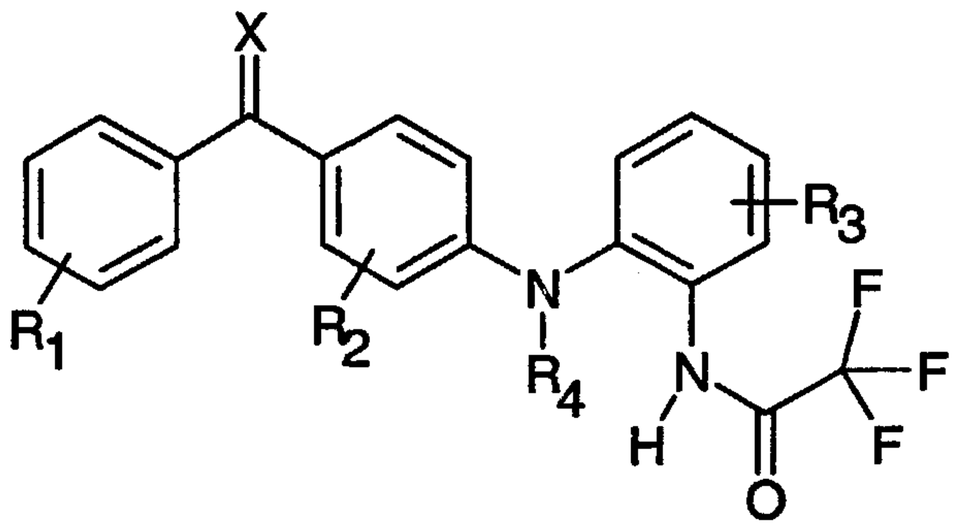
(54) Title: AMINOBENZOPHENONES AS INHIBITORS OF IL-1β AND TNF-α



(I)

(57) Abstract: The present invention relates to compounds of formula (I) wherein R_1 and R_2 independently represent 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, carbamoyl, phenyl, or nitro; R_2 further being represented by hydrogen; R_3 represents hydrogen, 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, phenyl, cyano, carboxy or carbamoyl; R_4 represents hydrogen, $(C_1\text{-}C_3)$alkyl, or allyl; X represents oxygen or sulphur; with the proviso that formula (I) does not comprise the compound 2,2,2-trifluoro-*N*-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-phenyl]acetamide wherein R_1 is a 2-methyl, R_2 is 2-chloro, R_3 and R_4 is hydrogen, and X is oxygen; and a salt thereof with a pharmaceutically acceptable acid, a hydrate or a 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

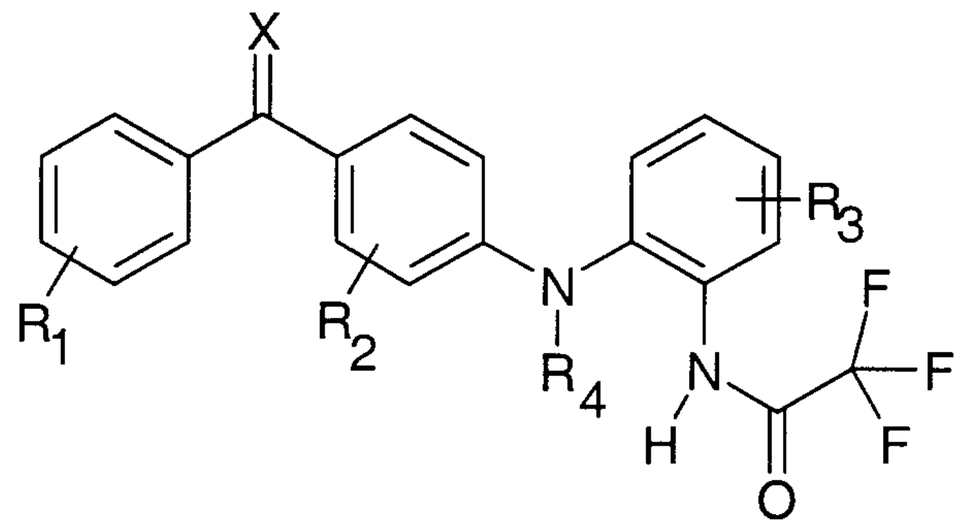
Previously, a series of closely related aminobenzophenones (e.g. 4-(2-amino-4-nitro-phenylamino)benzophenone) have been described (Hussein, F.A. *et al*, Iraqi J. Sci., 22, 54-66 (1981)). However, there is no description of their uses. PCT/DK98/00008 discloses aminobenzophenone inhibitors of interleukin 1β (IL-1β) and tumour necrosis factor a (TNF-α) secretion *in vitro*, said inhibitors 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 by providing novel aminobenzophenone derivatives according to the general formula I that are 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



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wherein R_1 and R_2 independently represent 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, carbamoyl, phenyl, or nitro; R_2 further being represented by hydrogen;

R_3 represents hydrogen, halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, phenyl, cyano, carboxy, or carbamoyl;

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

X represents oxygen or sulphur;

with the proviso that formula I does not comprise the compound 2,2,2-Trifluoro-*N*-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]acetamide wherein R_1 is 2-methyl, R_2 is 2'-chloro, R_3 and R_4 is hydrogen, and X is oxygen,

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

DETAILED DESCRIPTION OF THE INVENTION

Preferred embodiments of the invention

In compounds of the invention it is preferred that 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)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, fluoro, chloro, bromo, 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; and X represents oxygen.

More preferred are compounds of formula I 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 fluoro, chloro, bromo, hydroxy, methyl, or methoxy; R_4 represents hydrogen or (C_1-C_2)alkyl.

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.

Even more preferred are compounds of formula I wherein R_1 is in the 2-position and represents 2-methyl; wherein R_2 is in the 2-position and represents 2-chloro or 2-methyl; wherein R_3 is in the 4-position and represents 4-Br or 4-F; and wherein R_4 is hydrogen.

Specific compounds of the invention are:

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-phenyl]acetamide (Compound 101),
2,2,2-Trifluoro-*N*-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-5-fluoro-phenyl]acetamide (Compound 102),
2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(2,3-dimethylbenzoyl)-phenylamino]phenyl]acetamide (Compound 103),

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(4-*n*-butyl-2-methylbenzoyl)-phenylamino]-phenyl]acetamide (Compound 104),

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(4-chloro-2-methylbenzoyl)-phenylamino]-phenyl]acetamide (Compound 105),

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-fluoro-4-(2-methylbenzoyl)-phenylamino]phenyl]-acetamide (Compound 106),

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(2,4,5-trimethylbenzoyl)-phenylamino]phenyl]-acetamide (Compound 107),

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(4-fluoro-2-methylbenzoyl)-phenylamino]-phenyl]acetamide (Compound 108),

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(2,5-dimethylbenzoyl)-phenylamino]phenyl]-acetamide (Compound 109),

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(3-chloro-2-methylbenzoyl)-phenylamino]-phenyl]acetamide (Compound 110),

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-fluoro-4-(4-methoxy-2-methylbenzoyl)-phenylamino]-phenyl]acetamide (Compound 111),

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(4-ethoxy-2-methylbenzoyl)-phenylamino]-phenyl]acetamide (Compound 112),

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-ethoxy-4-(2-methylbenzoyl)-phenylamino]phenyl]-acetamide (Compound 113),

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

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-C_3)alkyl, methyl, ethyl, n-propyl, isopropyl. 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_3)olefinic group, preferably a (C_2-C_3)alkenyl, preferably a vinyl; or allyl. 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.

"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.

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.

The compounds 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.

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-1β 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.

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 Hanks' 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 formyl-methionyl-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
comp. 101	32	6.3	13
comp. 102	6.3	3.2	25
ref. a)	13	7.1	5.0
ref. b)	20	4.0	13

ref. a): 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone, compound 106 disclosed in PCT/DK98/00008. ref. b): 2,2,2-Trifluoro-*N*-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-phenyl]acetamide, compound 181 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, thus making them potentially useful in the treatment of inflammatory diseases.

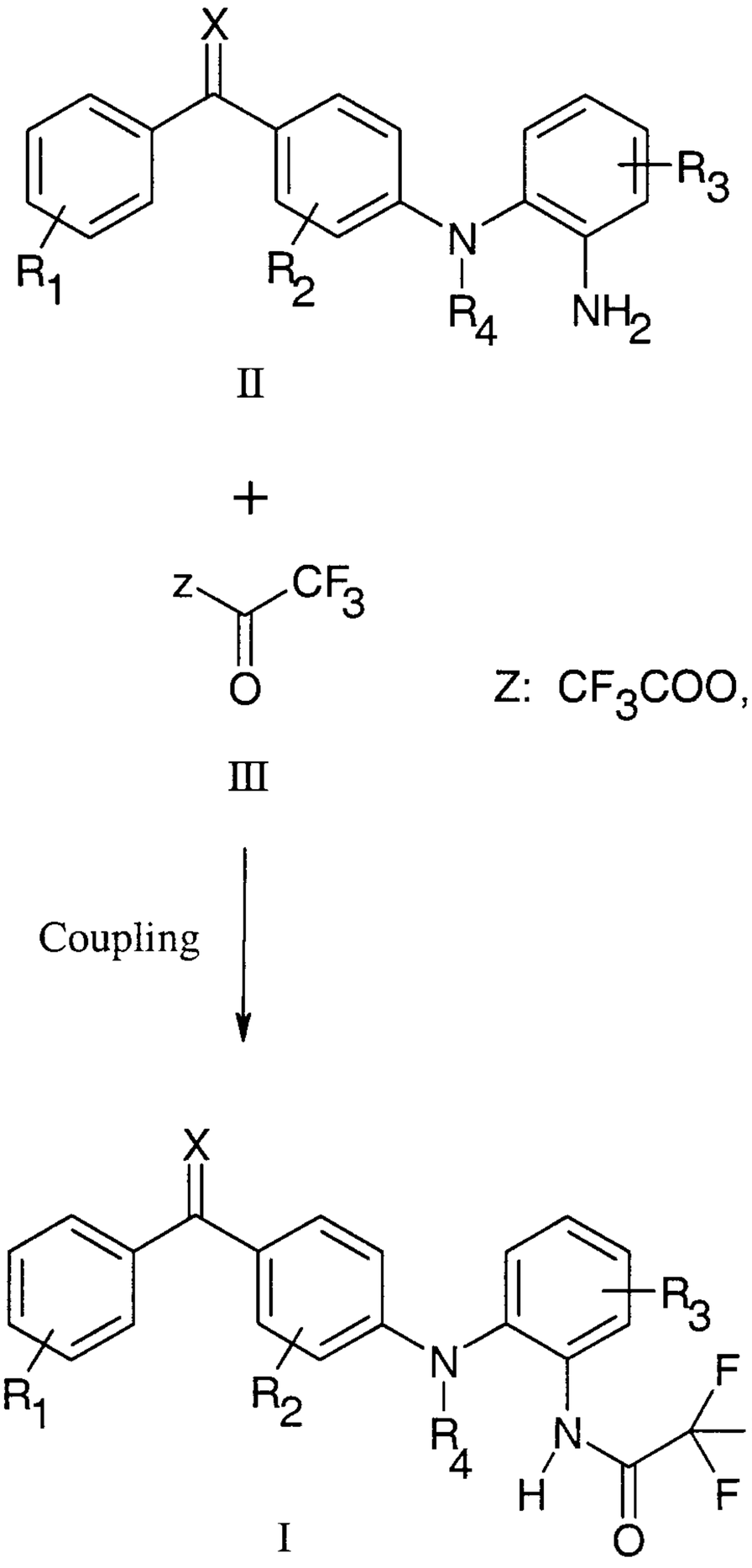
To study the compounds of the present invention *in vivo* the 12-*O*-tetradecanoylphorbol-13-acetate (TPA) induced murine chronic skin inflammation model can be used (De Young, L.M. et al, Agents Actions, 26, 335-341 (1989); Carlson, R.P. et al, Agents Actions, 17, 197-204 (1985); Alford, J.G. et al, 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 shows 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 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.



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

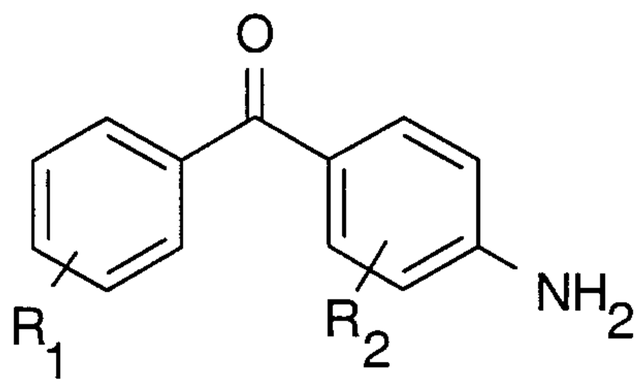
Scheme 1

Compounds according to the present invention 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; especially trifluoroacetic anhydride, as shown in scheme 1, where R_1, R_2, R_3, R_4, and X 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.

In the case where Z stand for OH, 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, use of standard

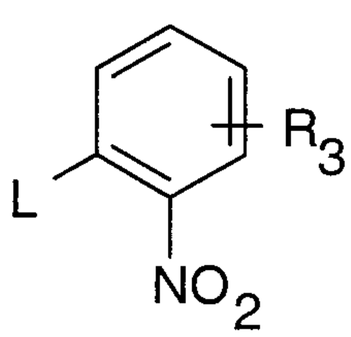
coupling procedures such as mixed carbonic anhydride (isobutyl chloroformate) method, carbodiimide (N,N-dimethylaminopropyl-N^I-ethyl carbodiimide (EDC)), dicyclohexyl carbodiimide, diisopropyl carbodiimide) method, active ester (pentafluorophenyl ester, p-nitrophenyl ester, N-hydroxysuccinic imido ester) method, cabonyldiimidazole method, azide method, phosphorous reagents such as BOP-Cl, azide method , conversion of acid (III) to an acid chloride. Some of these methods (especially carbodiimide) can be enhanced by the addition of 1-hydroxybenzotriazole (HOBt).

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 2 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 2, 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.



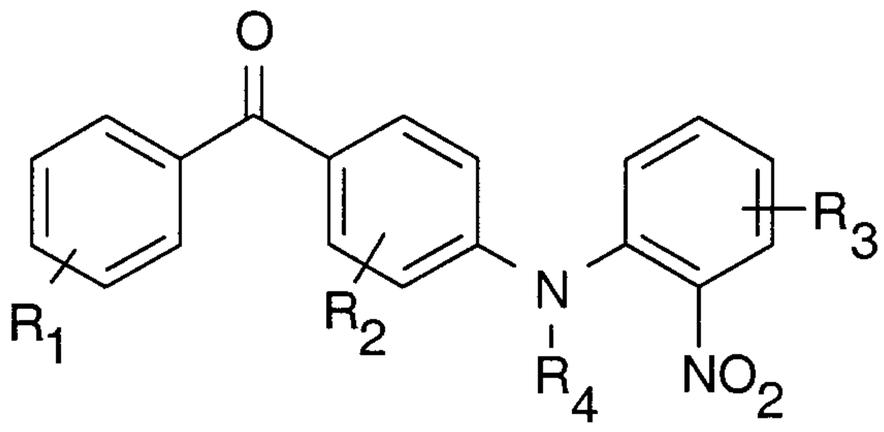
VII

+



VIII

Coupling



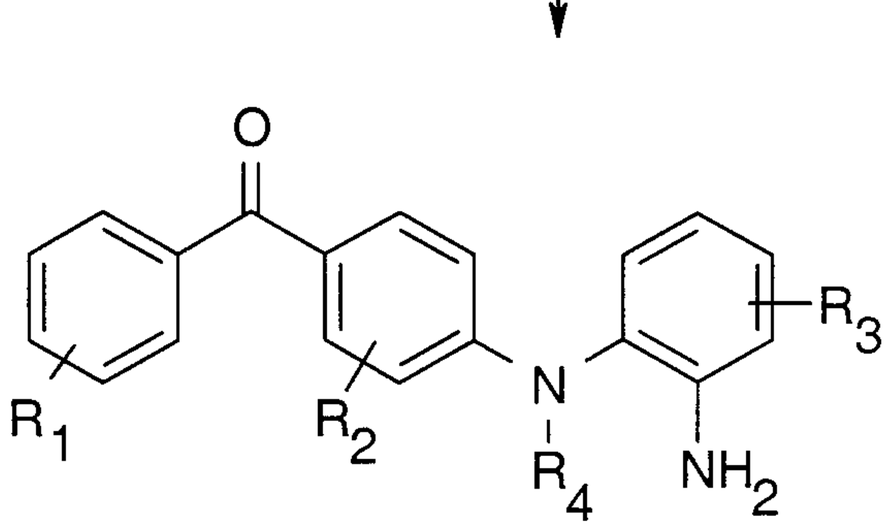
Alkylation
Y-R

VI, (R_4=H)

VI, (R_4=R)

Reduction

FGI



II (X=O)

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, and R_4 have the above meanings.

Scheme 2

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 ^{o}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

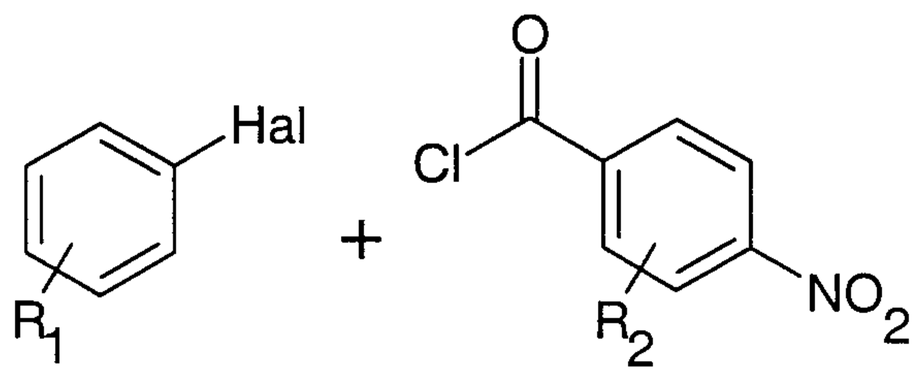
palladium(II) acetate, palladium(II) chloride, palladium(II) bromide, dichlorobis(triphenylphosphine)palladium(II), tetrakis(triphenylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0). The preferred ligand include, but are not limited to, racemic or non-racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (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 ^{o}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 2, 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).

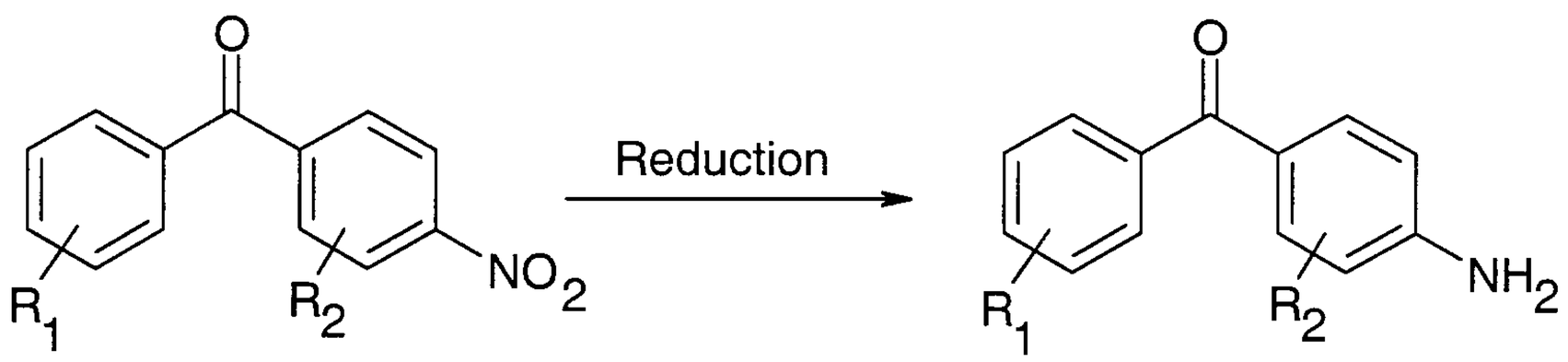
Compounds according to the present invention may in special cases be prepared by a simple functional group interconversion (FGI), meaning a standard process, known to those skilled in the art of organic synthesis, where a functional group in compounds with the general formula I (or any other intermediate 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.

Compounds according to the present invention in which C=X represents -(CS)- may be prepared from compounds of the invention (or any other intermediate described herein) in which C=X 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.



X XI

Coupling



IX VII

hal: Br, I

and R_1, and R_2 have the above meanings.

SCHEME 3

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 3. 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 transme-

tallation 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(triphenyl-phosphine)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 (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 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

The exemplified compounds I are listed in table 2. All melting points are uncorrected. For ^{1}H 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 (^{1}H 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:

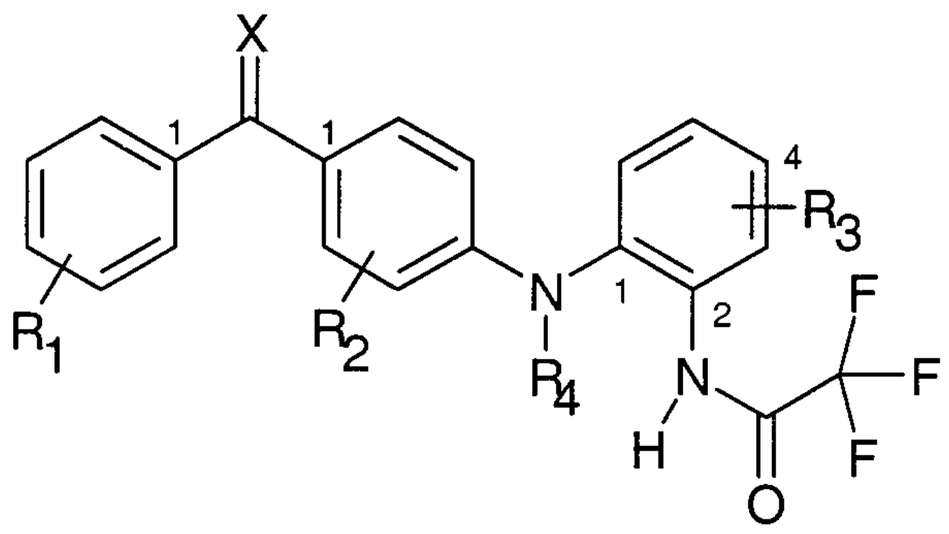
$CDCl_3$	Deuteriochloroform
DMF	*N*,*N*-Dimethylformamide
DMSO-d_6	Hexadeuterodimethylsulfoxide
Et_3N	Triethylamine
EtOAc	Ethyl acetate
Et_2O	Diethylether
HMPA	Hexamethylphosphorous triamide
NMM	*N*-Methylmorpholine
THF	Tetrahydrofurane
TLC	Thin layer chromatography
HOBt	1-Hydroxybenzotriazol
BOP-Cl	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
EDC	N,N-dimethylaminopropyl-N^I-ethyl carbodiimide

Table 2 Compounds of general formula I

Comp. No.	Example No.	X	R_1	R_2	R_3	R_4
101	1	O	2-CH_3	2-Cl	4-Br	H
102	2	O	2-CH_3	2-Cl	4-F	H
103	3	O	2-CH_3, 3-CH_3	2-Cl	4-Br	H
104	4	O	2-CH_3, 4-$(CH_2)_3CH_3$	2-Cl	4-Br	H

Comp. No.	Example No.	X	R_1	R_2	R_3	R_4
105	5	O	2-CH_3, 4-Cl	2-Cl	4-Br	H
106	6	O	2-CH_3	2-F	4-Br	H
107	7	O	2-CH_3, 4-CH_3, 5-CH_3	2-Cl	4-Br	H
108	8	O	2-CH_3, 4-F	2-Cl	4-Br	H
109	9	O	2-CH_3, 5-CH_3	2-Cl	4-Br	H
110	10	O	2-CH_3, 3-Cl	2-Cl	4-Br	H
111	11	O	2-CH_3, 4-OCH_3	2-F	4-Br	H
112	12	O	2-CH_3, 4-OCH_2CH_3	2-Cl	4-Br	H
113	13	O	2-CH_3	2-OCH_2CH_3	4-Br	H

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=$OOCCF_3$) to give compounds of the general formula I, or a protected derivative thereof.

To a cooled (0 ^oC) solution of an amine (2.0 mmol), with the general formula II, and pyridine (6.0 mmol) in CH_2Cl_2 (10 ml) was added trifluoroacetic anhydride (2.2 mmol). After stirring for 30 minuttes, the reaction mixture was poured into water and extracted with ethyl acetate twise. The organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product. This was further purified either by crystallization or chromatography to afford the anilide with the general formula I, or a protected derivative thereof.

Example 1

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-phenyl]acetamide (Compound 101)

General procedure: 1

Starting compound II: 4-[(2-Amino-4-bromo-phenyl)amino]-2-chloro-2'-methylbenzophenone

Purification: Chromatography using EtOAc/pentane 1:9 as eluant

^{13}C NMR ($CDCl_3$): δ 196.8, 155.9, 155.4, 154.9, 154.4, 147.9, 138.4, 138.3, 134.9, 133.1, 132.1, 131.5, 131.4, 130.8, 130.7, 130.5, 130.1, 127.6, 125.6, 125.5, 120.1, 117.4, 116.7, 113.5, 113.1, 20.6

Example 2

2,2,2-Trifluoro-*N*-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-5-fluoro-phenyl]acetamide (Compound 102)

General procedure: 1

Starting compound II: 4-[(2-Amino-4-fluoro-phenyl)amino]-2-chloro-2'-methylbenzophenone

Purification: Chromatography using EtOAc/pentane 1:7 as eluant

^{13}C NMR (DMSO-d_6): δ 195.2, 159.9, 156.7, 155.4, 154.9, 149.1, 139.2, 136.4, 133.3, 133.2, 131.3, 131.2, 131.0, 130.7, 130.3, 130.2, 128.7, 126.7, 126.3, 126.2, 125.5, 117.6, 115.0, 114.8, 114.7, 114.3, 113.9, 113.8, 111.9, 19.7

Example 3

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(2,3-dimethylbenzoyl)-phenylamino]-phenyl]acetamide (Compound 103)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-chloro-2',3'-dimethylbenzophenone

Purification: Crystallization from a mixture of ethanol and water

^{13}C NMR ($CDCl_3$): δ 197.2, 155.1, 148.0, 139.7, 138.1, 135.9, 135.3, 133.8, 132.5, 132.2, 130.7, 130.6, 130.5, 127.7, 126.9, 125.5, 125.1, 120.2, 116.8, 115.4, 113.0, 20.3, 16.5

Example 4

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(4-*n*-butyl-2-methylbenzoyl)-phenylamino]phenyl]acetamide (Compound 104)

General procedure: 1

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

Purification: Crystallization from a mixture of ethanol and water

^{13}C NMR ($CDCl_3$): δ 196.5, 155.1, 147.5, 147.2, 139.0, 135.4, 134.5, 132.7, 132.2, 131.9, 131.6, 131.1, 130.8, 130.5, 127.6, 125.5, 120.1, 116.7, 115.5, 113.2, 35.6, 33.2, 22.4, 20.9, 13.9

Example 5

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(4-chloro-2-methylbenzoyl)-phenylamino]-phenyl]acetamide (Compound 105)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2,4'-dichloro-2'-methyl-benzophenone

Purification: Crystallization from a mixture of ethanol and water

^{13}C NMR ($CDCl_3$): δ 196.5, 155.1, 147.5, 147.2, 139.0, 135.4, 134.5, 132.7, 132.2, 131.9, 131.6, 131.1, 130.8, 130.5, 127.6, 125.5, 120.1, 116.7, 115.5, 113.2, 35.6, 33.2, 22.4, 20.9, 13.9

Example 6

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-fluoro-4-(2-methylbenzoyl)-phenylamino]phenyl]-acetamide (Compound 106)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-fluoro-2'-methylbenzo-phenone

Purification: Crystallization from a mixture of ethanol and water

^{13}C NMR ($CDCl_3$): δ 194.4, 163.3, 155.1, 150.4, 139.7, 136.7, 134.0, 132.3, 131.1, 130.6, 130.4, 128.5, 128.0, 125.5, 120.5, 119.4, 115.4, 113.5, 110.7, 102.2, 20.0

Example 7

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(2,4,5-trimethylbenzoyl)-phenylamino]-phenyl]acetamide (Compound 107)

General procedure: 1

Starting compound II: 4'-(2-Amino-4-bromophenylamino)-2'-chloro-2,4,5-

trimethylbenzophenone

Example 8

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(4-fluoro-2-methylbenzoyl)-phenylamino]-phenyl]acetamide (Compound 108)

General procedure: 1

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

Example 9

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(2,5-dimethylbenzoyl)-phenylamino]phenyl]-acetamide (Compound 109)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-chloro-2',5'-dimethyl-benzophenone

Purification: Crystallization from a mixture of ethanol and water

^{13}C NMR ($CDCl_3$): δ 196.8, 155.1, 147.7, 138.3, 135.2, 135.0, 134.9, 133.1, 132.1, 131.4, 131.0, 130.6, 130.5, 130.5, 127.6, 125.5, 120.2, 116.7, 115.5, 113.1, 20.8, 20.1

Example 10

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(3-chloro-2-methylbenzoyl)-phenylamino]-phenyl]acetamide (Compound 110)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2,3'-dichloro-2'-methyl-benzophenone

^{13}C NMR ($CDCl_3$): δ 195.5, 155.1, 148.5, 141.5, 136.1, 135.6, 135.2, 134.0, 132.2, 131.6, 130.7, 130.4, 129.6, 127.8, 127.1, 126.4, 125.7, 120.4, 116.8, 115.4, 113.0, 17.1

Example 11

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-fluoro-4-(4-methoxy-2-methylbenzoyl)-phenylamino]-phenyl]acetamide (Compound 111)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-fluoro-4'-methoxy-2'-methyl-benzophenone

Purification: Crystallization from a mixture of ethanol and water

^{13}C NMR ($CDCl_3$): δ 193.3, 162.5, 161.7, 155.1, 149.7, 140.9, 133.5, 132.5, 132.3, 131.5, 130.6, 130.5, 127.8, 125.6, 120.4, 120.3, 116.9, 115.4, 110.8, 110.4, 102.2, 55.3, 21.0

Example 12

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(4-ethoxy-2-methylbenzoyl)-phenylamino]-phenyl]acetamide (Compound 112)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-chloro-4'-ethoxy-2'-methyl-benzophenone

^{13}C NMR ($CDCl_3$): δ 195.6, 161.8, 155.1, 147.2, 142.5, 134.2, 134.0, 132.1, 132.1, 132.0, 131.0, 130.5, 130.0, 127.4, 125.5, 119.8, 117.8, 116.5, 115.5, 113.3, 110.9, 63.6, 21.7, 14.7

Example 13

2,2,2-Trifluoro-*N*-[5-bromo-2-[3-ethoxy-4-(2-methylbenzoyl)-phenylamino]phenyl]-acetamide (Compound 113)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-ethoxy-2'-methyl-benzophenone

Purification: Crystallization from a mixture of ethanol and water

^{13}C NMR ($CDCl_3$): δ 197.3, 160.6, 155.1, 149.6, 141.9, 136.0, 133.4, 132.1, 131.1, 130.5, 130.3, 129.6, 127.7, 127.5, 125.5, 125.1, 121.8, 119.7, 115.5, 107.5, 98.9, 63.9, 19.9, 13.8

Example 14 Tablet containing compound 101

Compound 101 (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 15: Formulation for injection containing compound 101.

Compound 101 (active substance)	1%
Sodium chloride	q.s.
Ethanol	10%
Water for injection to make	100%

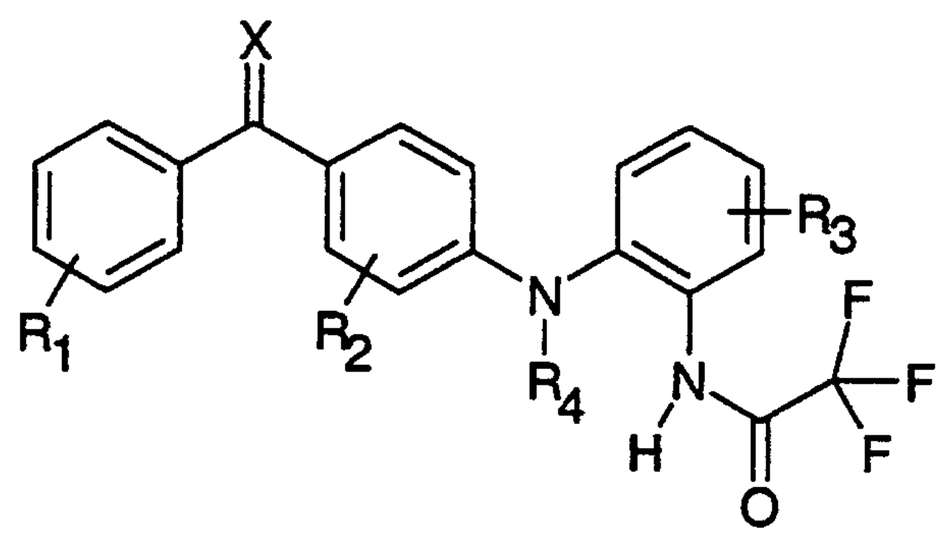
The active substance is dissolved in ethanol (10%) then water for injection made isotonic with sodium chloride is added to make 100%. The mixture is filled into ampoules and sterilized.

Example 16 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 independently 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, carbamoyl, phenyl, or nitro, provided that when R_1 represents one substituent, it is in the ortho position, and when R_1 represents more than one substituent, at least one R_1 substituent is in the ortho position; and R_2 represents one substituent in the ortho position, said substituent being 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, carbamoyl, phenyl, or nitro;

R_3 represents hydrogen, 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, phenyl, cyano, carboxy, or carbamoyl;

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

with the proviso that formula I does not comprise the compound 2,2,2-trifluoro-*N*-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-phenyl]acetamide wherein R_1 is 2-methyl, R_2 is 2-chloro, R_3 and R_4 is hydrogen, and X is oxygen;

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

2. A compound according to the preceding claim wherein independently

- R_1 represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, $(C_1\text{-}C_2)$alkyl, $(C_2\text{-}C_3)$alkenyl, $(C_1\text{-}C_3)$alkoxy, $(C_1\text{-}C_3)$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, $(C_1\text{-}C_3)$alkyl, $(C_2\text{-}C_3)$alkenyl, $(C_1\text{-}C_3)$alkoxy.

- R_3 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, $(C_1\text{-}C_3)$alkyl, $(C_2\text{-}C_3)$alkenyl, $(C_1\text{-}C_3)$alkoxy, $(C_1\text{-}C_3)$alkoxycarbonyl, cyano, carboxy, or $-CONH_2$.

- R_4 represents hydrogen, $(C_1\text{-}C_2)$alkyl, or allyl.

- X represents oxygen.

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

- 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 fluoro, chloro, bromo, hydroxy, methyl, or methoxy.

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

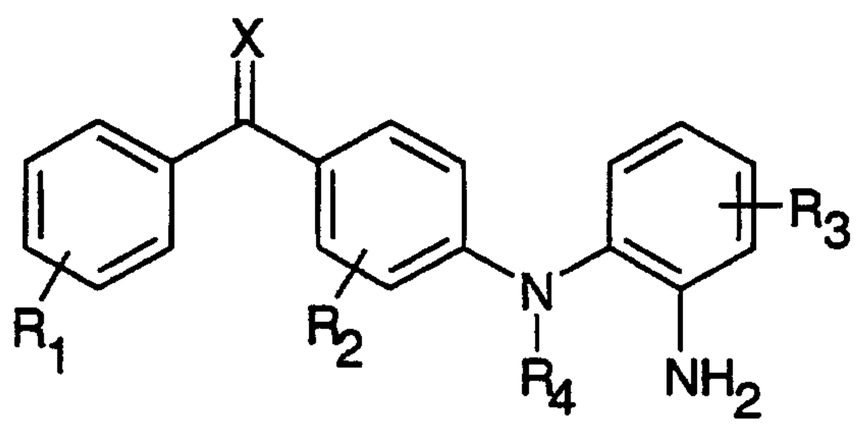
4. A compound according to any one of the preceding claims wherein R_1 is 2-methyl.

5. A compound according to any one of the preceding claims wherein R_2 is 2-Cl.

6. A compound according to claim 1 selected from the group consisting of

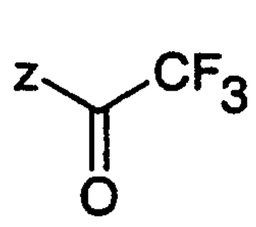
2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-phenyl]acetamide (Compound 101),
2,2,2-Trifluoro-*N*-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-5-fluoro-phenyl]acetamide (Compound 102),
2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(4-chloro-2-methylbenzoyl)-phenylamino]phenyl]acetamide (Compound 105),
2,2,2-Trifluoro-*N*-[5-bromo-2-[3-fluoro-4-(2-methylbenzoyl)-phenylamino]phenyl]acetamide (Compound 106),
2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(2,4,5-trimethylbenzoyl)-phenylamino]phenyl]acetamide (Compound 107),
2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(4-fluoro-2-methylbenzoyl)-phenylamino]phenyl]acetamide (Compound 108),
2,2,2-Trifluoro-*N*-[5-bromo-2-[3-chloro-4-(2,5-dimethylbenzoyl)-phenylamino]phenyl]acetamide (Compound 109),
2,2,2-Trifluoro-*N*-[5-bromo-2-[3-fluoro-4-(4-methoxy-2-methylbenzoyl)-phenylamino]phenyl]acetamide (Compound 111),
and salts thereof with pharmaceutically acceptable acids, hydrates and solvates.

7. A method of preparing a compound of formula I according to the reaction



II

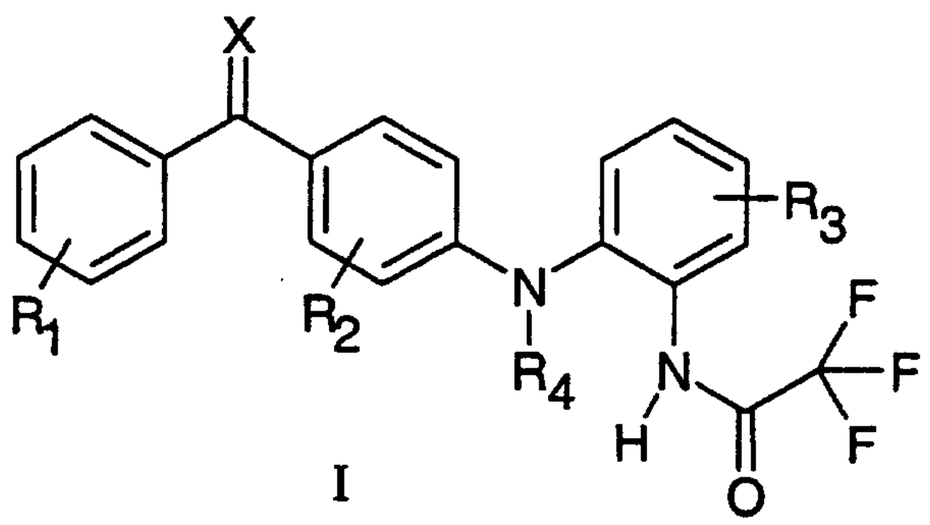
+



Z: CF_3COO, OH, Cl

III

Coupling



I

scheme

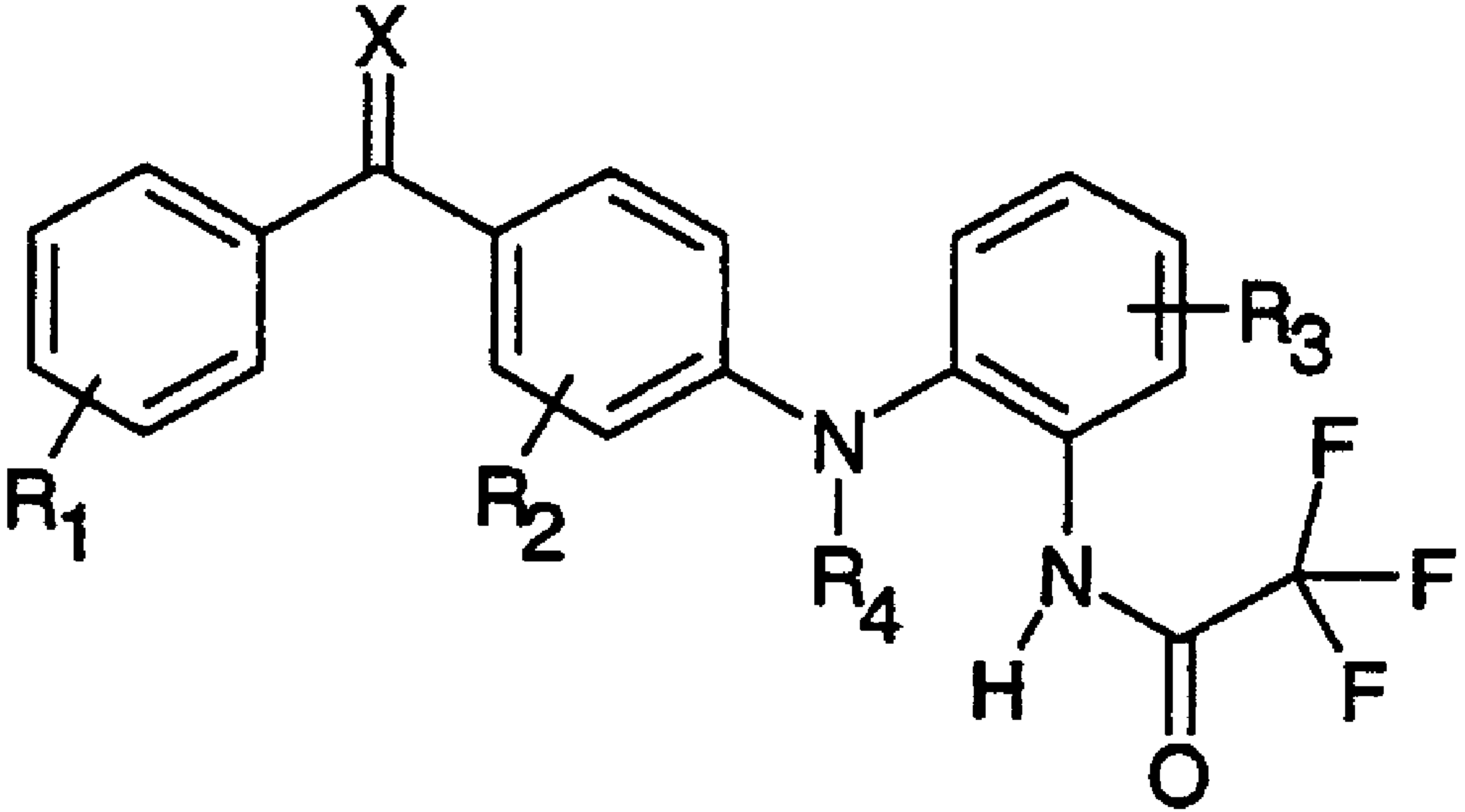
said scheme describing a process comprising coupling of an amine of the formula II with an acid of the formula III or an activated derivative thereof, especially trifluoroacetic anhydride, to obtain a compound of formula I, where R_1, R_2, R_3, R_4, and X are as defined above and where any substituents or functional group which are potentially reactive in the coupling reaction are, if necessary, protected before the coupling reaction is performed and subsequently deprotected.

8. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 6 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).

9. Use of a compound according to any one of claim 1 to 6 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.

10. 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, osteoporosis and acne, characterised in administering to a patient suffering from at least one of said diseases an effective amount of one or more compounds according to any one of claims 1 to 6 as an active ingredient alone, or if necessary together with a pharmaceutically acceptable carrier, and, optionally, 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).



I