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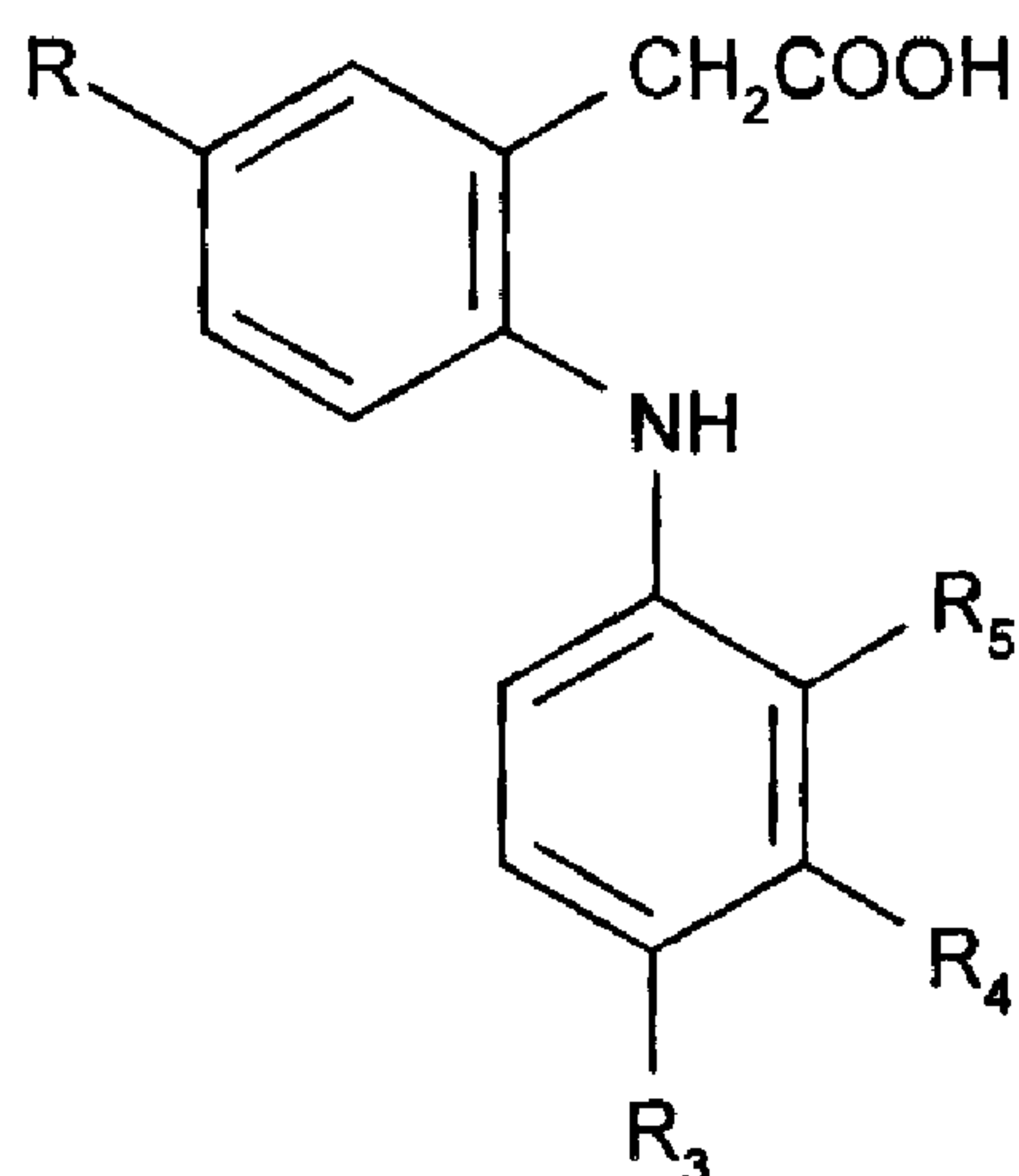
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(54) Titre : DERIVES D'ACIDE PHENYLACETIQUE

(54) Title: PHENYLACETIC ACID DERIVATIVES



(I)

(57) Abrégé/Abstract:

Compounds of formula (I) pharmaceutically acceptable salts thereof; and pharmaceutically acceptable esters thereof; which are useful for the treatment of COX-2 dependent disorders.

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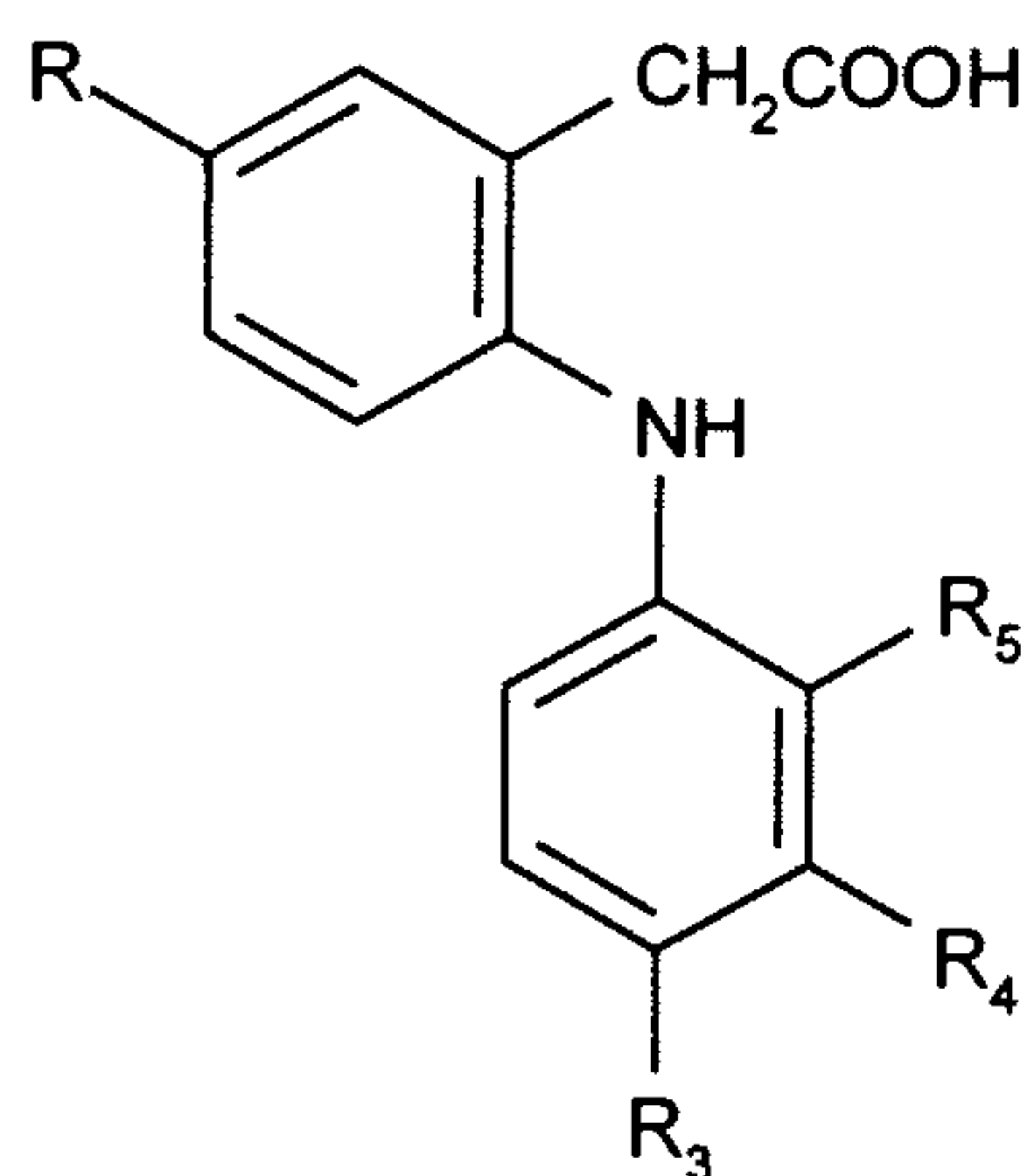
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(I)

(57) Abstract: Compounds of formula (I) pharmaceutically acceptable salts thereof; and pharmaceutically acceptable esters thereof; which are useful for the treatment of COX-2 dependent disorders.

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PHENYLACETIC ACID DERIVATIVES

The invention relates to phenylacetic acids and derivatives as defined herein which are particularly potent and selective cyclooxygenase-2 (COX-2) inhibitors, methods for
5 preparation thereof, pharmaceutical compositions comprising said compounds, methods of selectively inhibiting COX-2 activity and of treating conditions in mammals which are responsive to COX-2 inhibition using said compounds or pharmaceutical compositions comprising said compounds of the invention.

The present invention provides novel phenylacetic acids and derivatives which inhibit
10 COX-2 without significantly inhibiting cyclooxygenase-1 (COX-1). The invention thus provides novel non-steroidal anti-inflammatory agents which are surprisingly free of undesirable side effects usually associated with the classical non-steroidal anti-inflammatory agents, such as gastrointestinal and renal side effects.

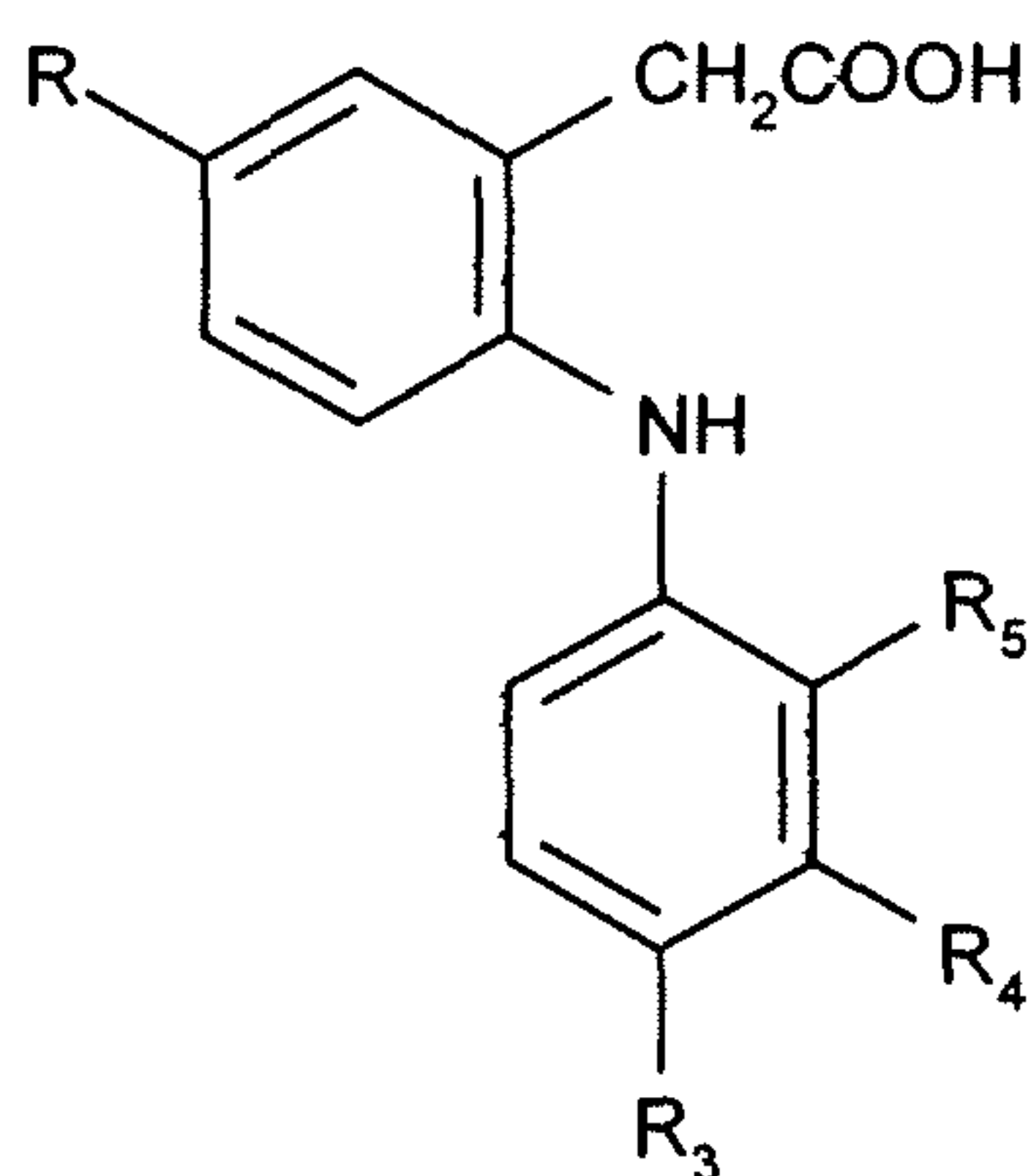
The compounds of the present invention are thus particularly useful or may be
15 metabolically converted to compounds which are particularly useful as selective COX-2 inhibitors. They are thus particularly useful for the treatment of COX-2 dependent disorders in mammals, including inflammation, pyresis, pain, osteoarthritis, rheumatoid arthritis, dysmenorrhea, migraine headache, cancer (such as of the digestive tract, e.g., colon cancer and melanoma), cancer pain, acute pain, chronic pain, neurodegenerative diseases (such as
20 multiple sclerosis, Parkinson's disease and Alzheimer's disease), cardiovascular disorders (such as atherosclerosis, coronary artery disease and arteriosclerosis), osteoporosis, gout, acute gout, asthma, lupus and psoriasis while substantially eliminating undesirable gastrointestinal ulceration associated with conventional cyclooxygenase (COX) inhibitors. The compounds of the invention are also UV absorbers, in particular, UV-B absorbers, and
25 are useful for blocking or absorbing UV radiation, for instance, for the treatment and prevention of sunburn, e.g., in suntan products.

Ocular applications of the compounds of the invention include the treatment of ocular inflammation, wet age-related macular degeneration, ocular pain including pain associated with ocular surgery, such as PRK or cataract surgery, of ocular allergy, of photophobia of
30 various etiology, of elevated intraocular pressure (in glaucoma) by inhibiting the production of trabecular meshwork inducible glucocorticoid response protein and of dry eye disease.

The compounds of the present invention are useful for the treatment of neoplasia particularly neoplasia that produce prostaglandins or express COX, including both benign and cancerous tumors, growths and polyps, in particular, epithelium cell-derived neoplasia. Compounds of the present invention are, in particular, useful for the treatment of liver, bladder, pancreatic, ovarian, prostate, cervical, lung and breast cancer and, especially gastrointestinal cancer, e.g., cancer of the colon, and skin cancer, e.g., squamous cell or basal cell cancers and melanoma, as indicated above.

The term "treatment" as used herein is to be understood as including both therapeutic and prophylactic modes of therapy, e.g., in relation to the treatment of neoplasia, therapy to prevent the onset of clinically or pre-clinically evident neoplasia, or for the prevention of initiation of malignant cells or to arrest or reverse the progression of pre-malignant to malignant cells, as well as the prevention or inhibition of neoplasia growth or metastasis. In this context, the present invention is, in particular, to be understood as embracing the use of compounds of the present invention to inhibit or prevent development of skin cancer, e.g., squamous or basal cell carcinoma consequential to UV light exposure, e.g., resulting from chronic exposure to the sun. The compounds may be used in humans or in other mammals.

In a first aspect of the invention there is provided a compound of formula (I)



(I)

wherein

R is methyl or ethyl;

R₃ is halo or C₁-C₆ alkyl;

R₄ is C₁-C₆ alkyl;

R₅ is halo;

the above mentioned C₁-C₆ alkyl at R₃ and R₄ being optionally substituted by one or more halo groups;

- 5 pharmaceutically acceptable salts thereof; and pharmaceutically acceptable esters thereof.

Preferably in compounds of formula (I), R₃ is halo, methyl or ethyl. More preferably it is halo. Alternatively preferably it is chloro.

- 10 Preferably in compounds of formula (I), R₄ is C₁-C₃ alkyl, optionally substituted by one or more halo groups. More preferably it is methyl, ethyl, isopropyl or trifluoromethyl. Yet more preferably it is methyl. Alternatively preferably it is trifluoromethyl.

Preferably in compounds of formula (I), R₅ is chloro or fluoro.

- 15 Yet more preferably both R₃ and R₅ are independently selected from chloro and fluoro.

Preferably the compound is selected from the following list of compounds:

- 5-methyl-2-(2',4'-dichloro-3'-methylanilino)phenylacetic acid
 5-ethyl-2-(2',4'-dichloro-3'-methylanilino)phenylacetic acid
 20 5-methyl-2-(2'-fluoro-3'-trifluoromethyl-4'-ethylanilino)phenylacetic acid
 5-ethyl-2-(2'-fluoro-3'-trifluoromethyl-4'-ethylanilino)phenylacetic acid
 5-methyl-2-(2'-fluoro-3'-trifluoromethyl-4'-methylanilino)phenylacetic acid
 5-ethyl-2-(2'-fluoro-3'-trifluoromethyl-4'-methylanilino)phenylacetic acid
 5-methyl-2-(2'-fluoro-3'-methyl-4'chloroanilino)phenylacetic acid
 25 5-ethyl-2-(2'-fluoro-3'-methyl-4'chloroanilino)phenylacetic acid
 5-methyl-2-(2'-fluoro-3'-ethyl-4'chloroanilino)phenylacetic acid
 5-ethyl-2-(2'-fluoro-3'-ethyl-4'chloroanilino)phenylacetic acid
 5-methyl-2-(2',4'-dichloro-3'-ethylanilino)phenylacetic acid
 5-ethyl-2-(2',4'-dichloro-3'-ethylanilino)phenylacetic acid
 30 5-ethyl-2-(2'-fluoro-3'-isopropyl-4'chloroanilino)phenylacetic acid
 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetic acid diethylamine salt
 sodium 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetate
 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetic acid tromethamine salt

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calcium 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetate monohydrate

Lysine 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetate monohydrate

choline 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetate monohydrate

5 Potassium 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetate.

In a second aspect, the invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) in combination with one or more pharmaceutically acceptable carriers.

10 In a third aspect, the invention provides a method of treating cyclooxygenase-2 (COX-2) dependent disorders in mammals which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I).

In a fourth aspect, the invention provides a method of selectively inhibiting COX-2 activity in a mammal without substantially inhibiting cyclooxygenase-1 activity which comprises
15 administering to a mammal in need thereof an effective COX-2 inhibiting amount of a compound of formula (I).

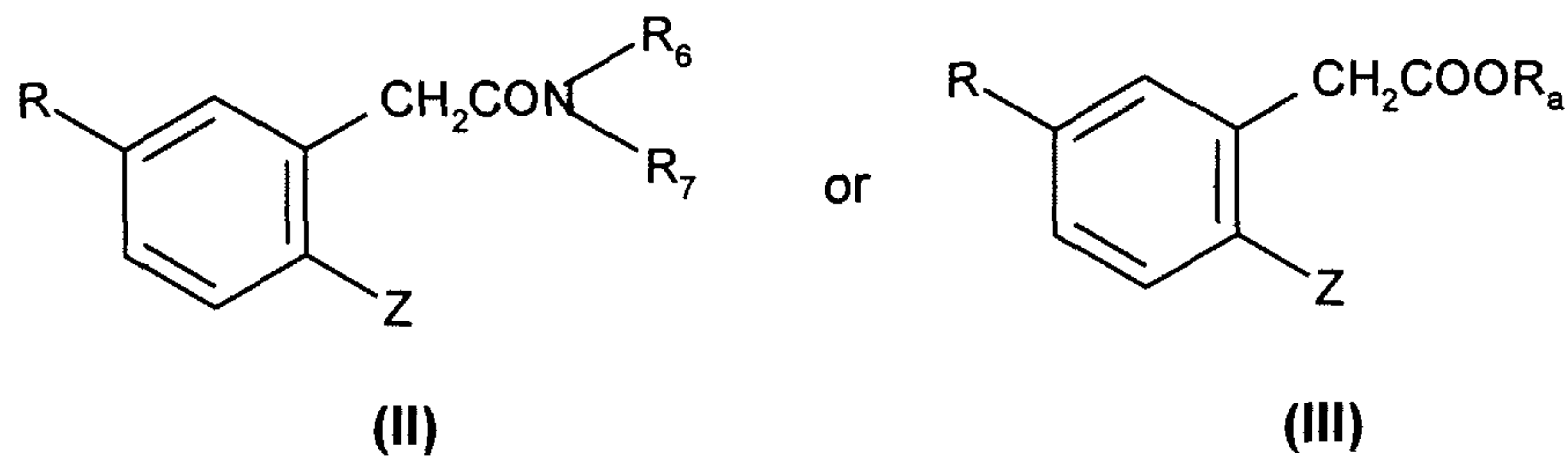
In a fifth aspect, the invention provides a method of treating rheumatoid arthritis, osteoarthritis, dysmenorrhea, pain, tumors or inflammation in mammals which comprises administering to a mammal in need thereof a correspondingly effective amount of a
20 compound of formula (I).

In a sixth aspect, the invention provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment of rheumatoid arthritis, osteoarthritis, dysmenorrhea, pain, tumors or inflammation.

25 In a seventh aspect, the invention provides a compound of formula (I) for use in the treatment of a COX-2 dependent disorder.

In an eighth aspect, the invention provides a method for the preparation of a compound of formula (I) as described herein which comprises the step of:

(a) coupling a compound of formula (II) or (III)



wherein

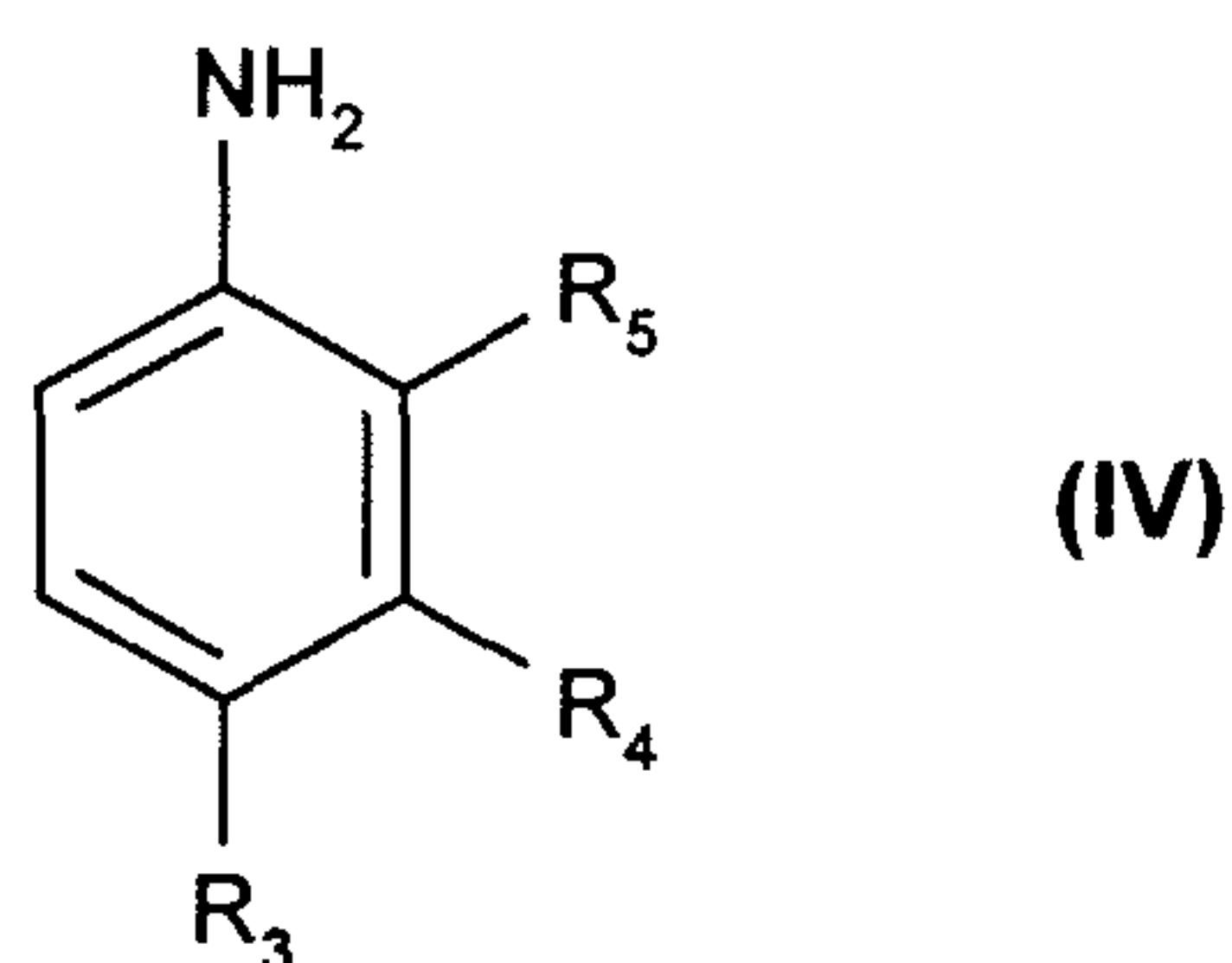
Z is bromo or iodo;

5 R has meaning as defined above;

R_a is hydrogen, an alkali metal cation or lower alkyl, preferably isopropyl; and

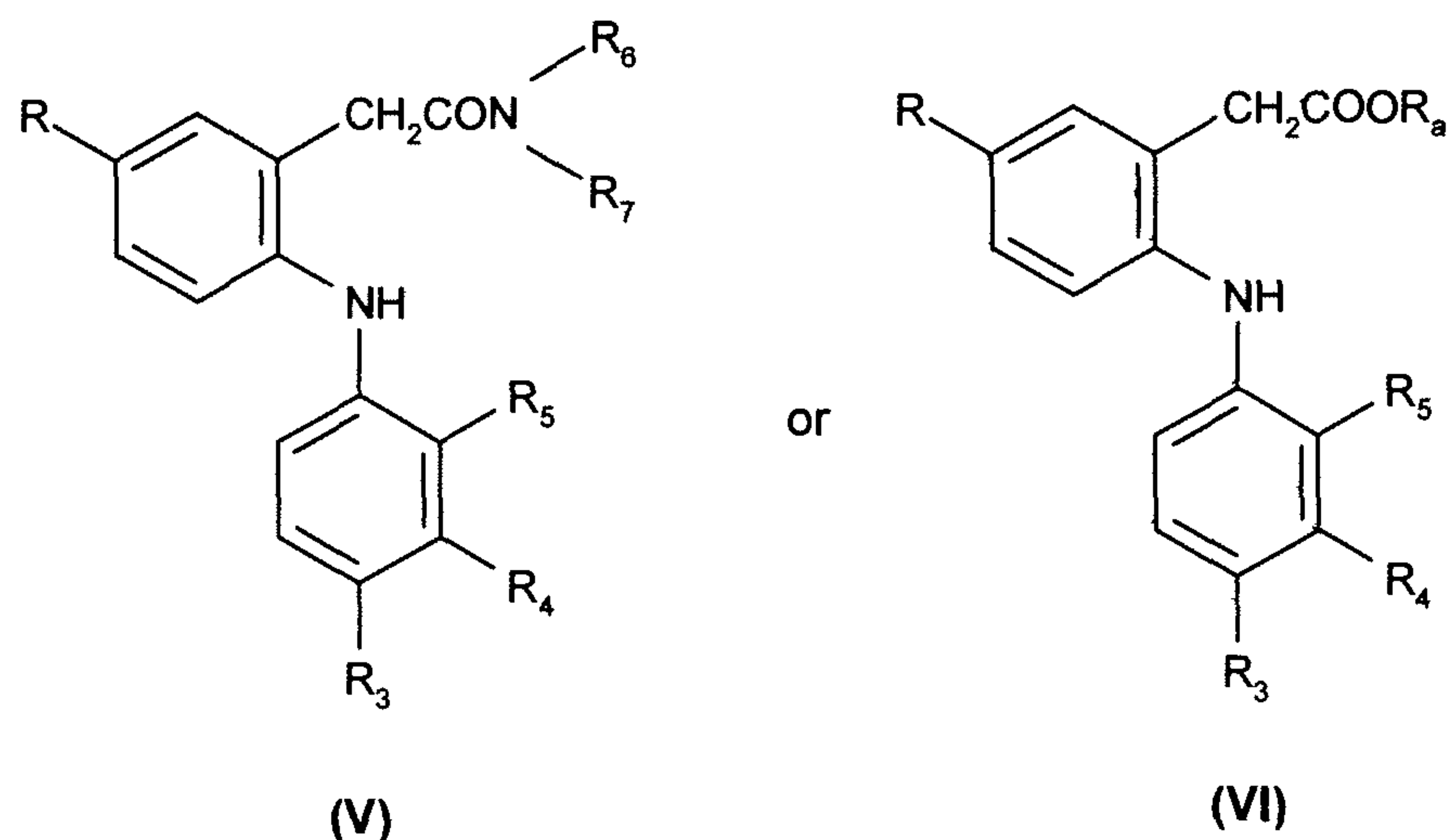
R_6 and R_7 are lower alkyl; or R_6 and R_7 , together with the nitrogen atom, represent morpholino, piperidino or pyrrolidino;

with a compound of formula (IV)



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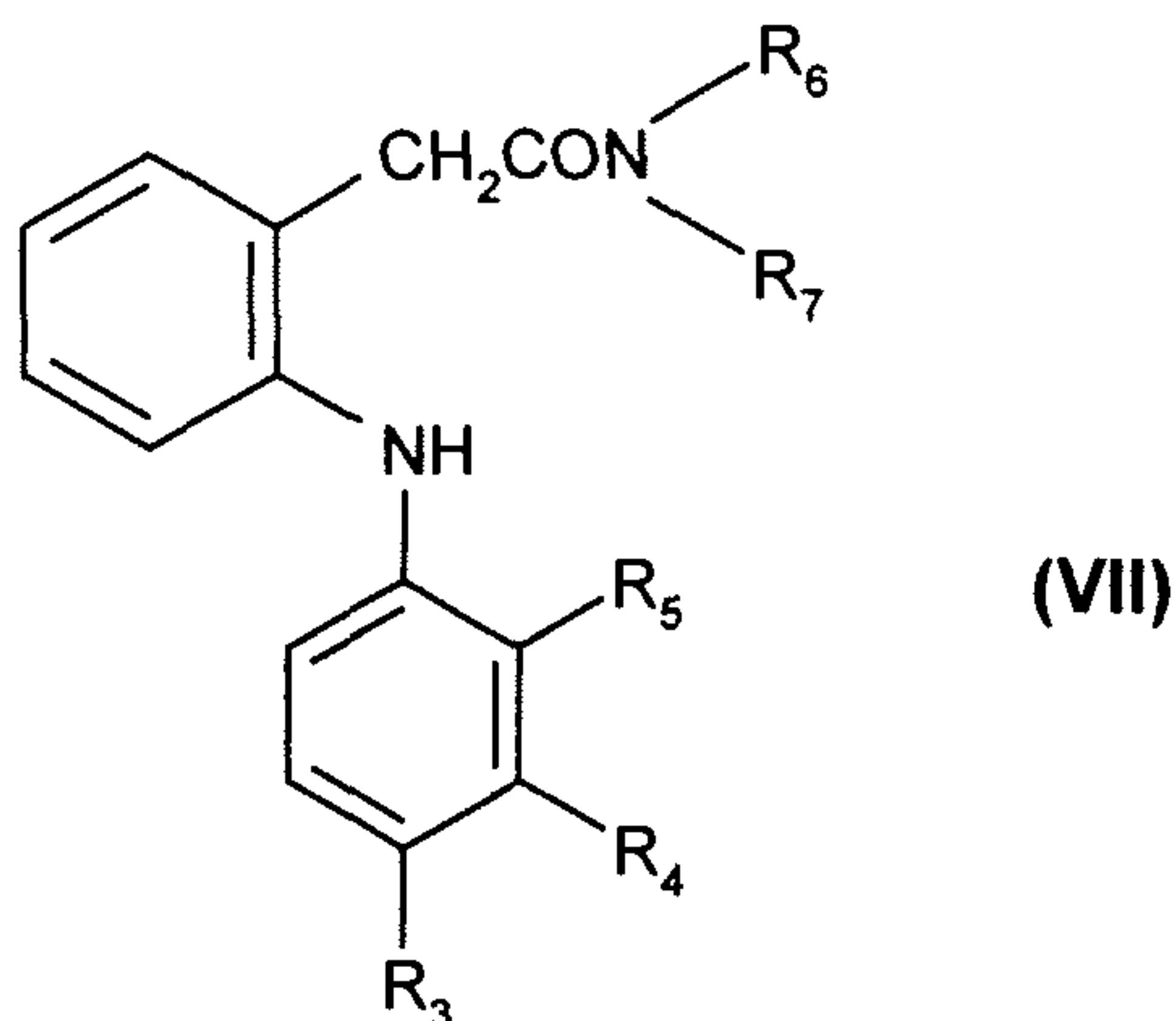
wherein R_3 - R_5 have meaning as defined above in the presence of copper and cuprous iodide to obtain a compound of formula (V) or (VI)



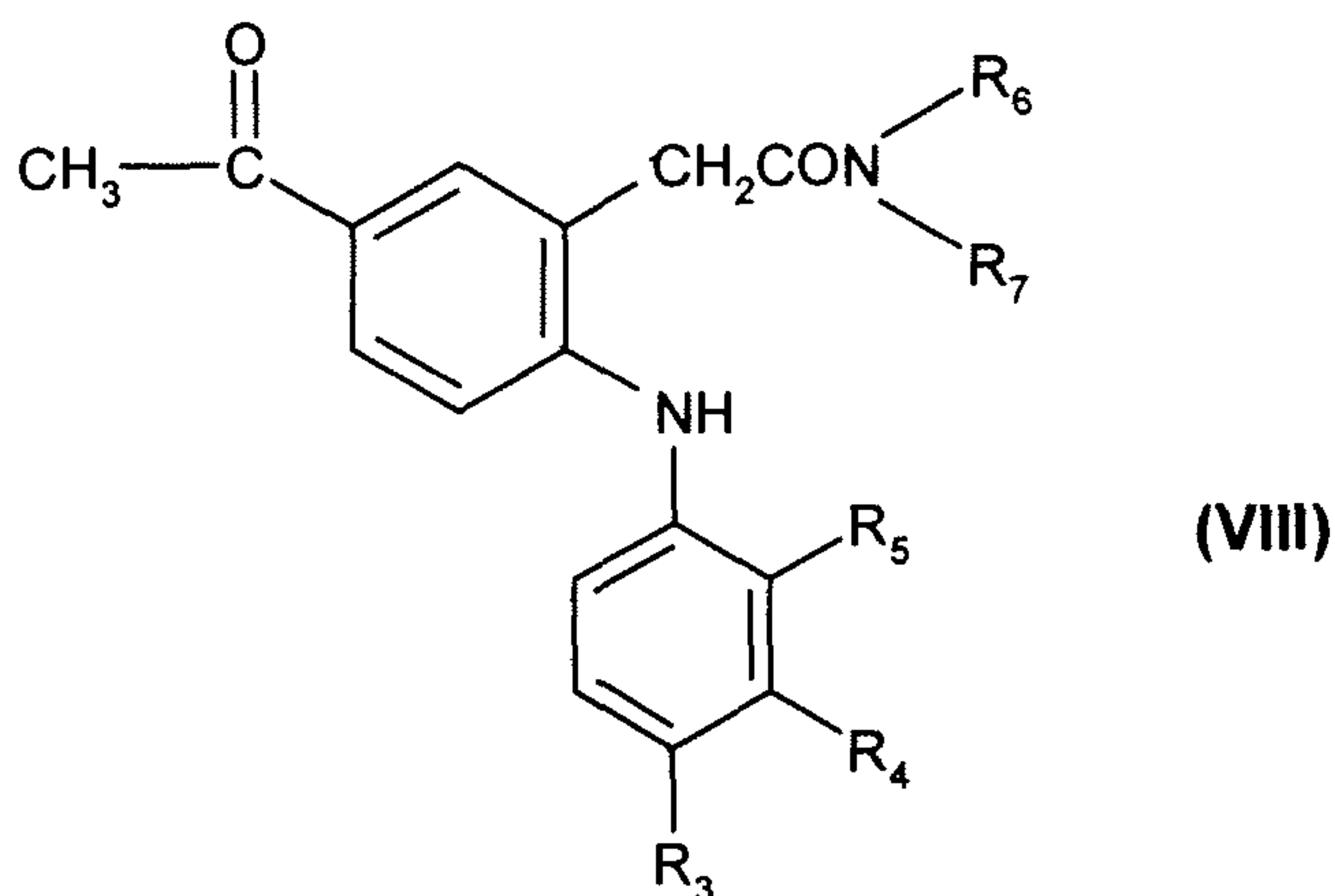
and hydrolyzing the resulting compound of formula (V) or (VI) to a compound of formula (I); or

15

(b) condensing a compound of formula (VII)

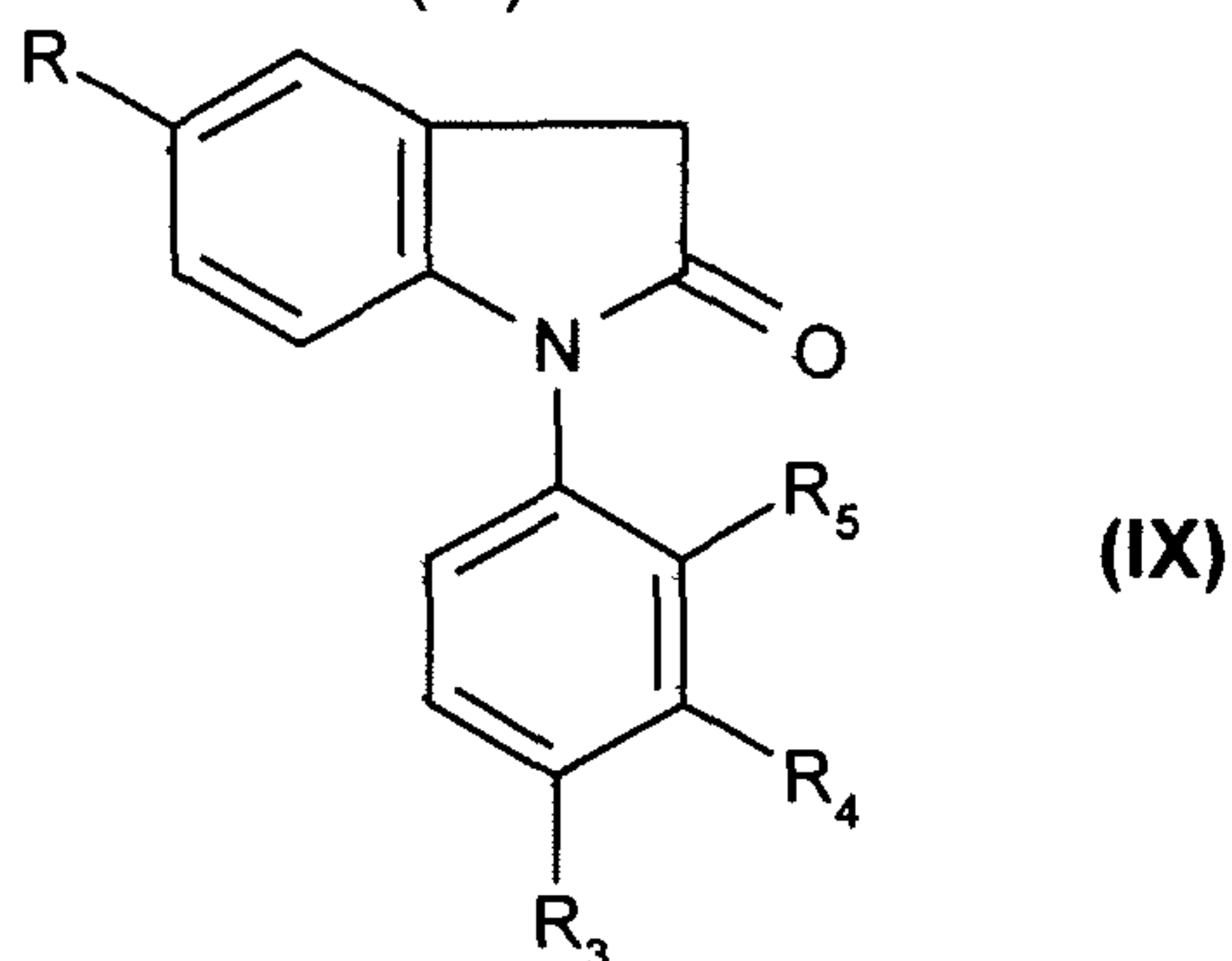


wherein R_3 - R_7 have meaning as defined herein, with a reactive functional derivative of an acid, e.g., acetic acid, such as acetyl chloride, in a Friedel-Crafts acylation to reaction to obtain, e.g., a compound of the formula (VIII)



wherein R_3 - R_7 have meaning as defined herein, which is in turn hydrogenolyzed and then hydrolyzed to obtain a compound of formula (I), wherein R represents, e.g., ethyl; or

(c) hydrolyzing a lactam of formula (IX)



wherein R and R_3 - R_5 have meaning as defined herein, with a strong base; and in above processes, if desired, temporarily protecting any interfering reactive groups and then isolating the resulting compound of the invention; and, if desired, converting any resulting

compound into another compound of the invention; and/or if desired converting a free carboxylic acid of the invention into a pharmaceutically acceptable ester derivative thereof; and/or if desired, converting a resulting free acid into a salt or a resulting salt into the free acid or into another salt.

5 In starting compounds and intermediates, which are converted to the compounds of the invention in a manner described herein, functional groups present, such as amino, hydroxy and carboxyl groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected hydroxy, amino and carboxyl groups are those that can be converted under mild conditions into free amino, hydroxy and
10 carboxyl groups without other undesirable side reactions taking place. For example, hydroxy protecting groups are preferably benzyl or substituted benzyl groups, or acyl groups, such as pivaloyl.

The preparation of compounds of formulae (V) and (VI) according to process (a) is carried out under conditions of a modified Ullmann condensation for the preparation of
15 diarylamines, e.g., in the presence of copper powder and copper (I) iodide and potassium carbonate, optionally in an inert high boiling solvent, such as nitrobenzene, toluene, xylene or *N*-methylpyrrolidone, at elevated temperature, e.g., in the range of 100-200°C, preferably at reflux temperature, according to general methodology described by Nohara, *Chem Abstr*, Vol. 94, p. 15402x (1951); and Moser et al., *J Med Chem*, Vol. 33, p. 2358 (1990). When
20 Z is bromo, the condensation is carried out in the presence of an iodide salt, e.g., potassium iodide.

Hydrolysis of the resulting ortho-anilinophenylacetamides of formula (V) is carried out in aqueous alkali hydroxide, e.g., in 6 N NaOH in the presence of an alcohol, e.g., ethanol, propanol and butanol, at elevated temperature, such as reflux temperature of the reaction
25 mixture.

The hydrolysis of esters of formula (VI) is carried out according to methods known in the art, e.g., under basic conditions as described above for the compounds of formula (V) or alternatively under acidic conditions, e.g., using methanesulfonic acid.

The starting materials of formula (II) or (III) are generally known or can be prepared
30 using methodology known in the art, e.g. as described by Nohara in Japanese patent application No. 78/96,434 (1978); U.S. Patent No. 6,291,523 and as illustrated herein.

For example, the corresponding anthranilic acid is converted to the ortho-diazonium derivative followed by treatment with an alkali metal iodide in acid, e.g., sulfuric acid, to obtain the 2-iodobenzoic acid or lower alkyl ester thereof. Reduction to the corresponding benzyl alcohol, e.g., with diborane or lithium aluminum hydride for the ester, conversion of
5 the alcohol first to the bromide and then to the nitrile, hydrolysis of the nitrile to the acetic acid and conversion to the *N,N*-dialkylamide according to methodology known in the art yields a starting material of formula (II).

Alternatively, e.g., the starting material of formula (II), wherein Z is Br and R is cyclopropyl can be prepared by first condensing according to the method outlined in
10 *J Am Chem Soc*, Vol. 123, p. 4155 (2001), e.g., 2-bromo-5-iodobenzoic acid methyl ester with cyclopropyl bromide in the presence of indium trichloride to obtain 2-bromo-5-cyclopropylbenzoic acid methyl ester which is converted as described above to the corresponding 2-bromo-5-cyclopropylphenylacetamide of formula (II).

Furthermore, the starting materials of formula (II), wherein R is, e.g., ethyl, can be
15 prepared by Friedel-Crafts acetylation of oxindole with, e.g., acetyl chloride in the presence of aluminum chloride, reduction of the resulting ketone by, e.g., catalytic hydrogenolysis, followed by hydrolytic cleavage of the resulting 5-ethyloxindole to the ortho amino-phenylacetic acid. Diazotization in the presence of, e.g., potassium iodide yields the ortho iodo-phenylacetic acid which is converted to an amide of formula (II).

20 Esters of formula (III) are prepared from the corresponding acids according to esterification methods known in the art.

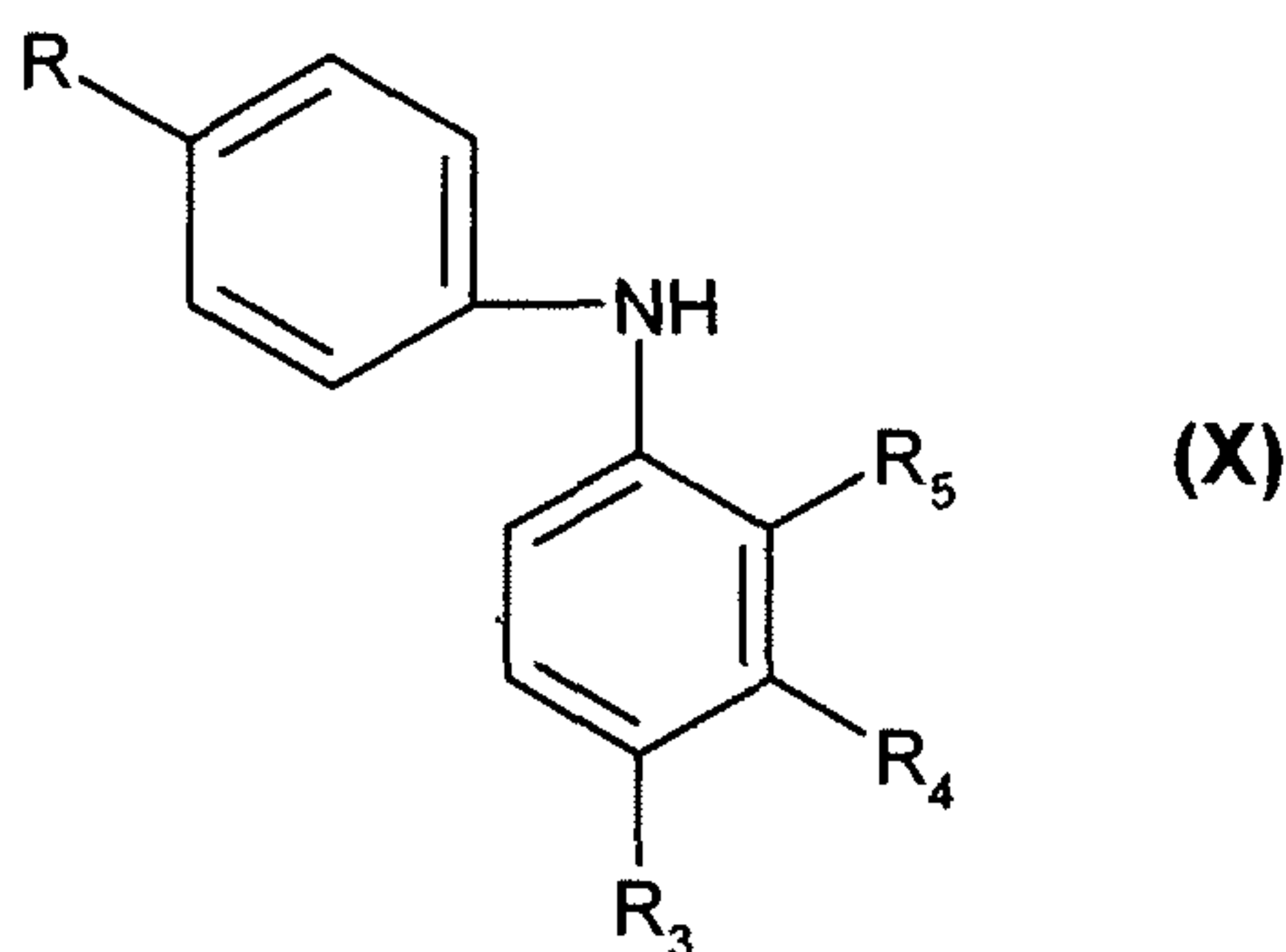
The anilines of formula (IV) are either known in the art or are prepared according to methods well-known in the art, and as illustrated herein.

The preparation of, e.g., 5-ethyl or 5-*n*-propyl substituted compounds according to
25 process (b) is carried out under conditions of Friedel-Crafts acylation, e.g., in the presence of aluminum chloride in an inert solvent, such as 1,2-dichloroethane, followed by hydrogenolysis, e.g., using palladium on charcoal catalyst, preferably in acetic acid as solvent, at room temperature and about 3 atmospheres pressure.

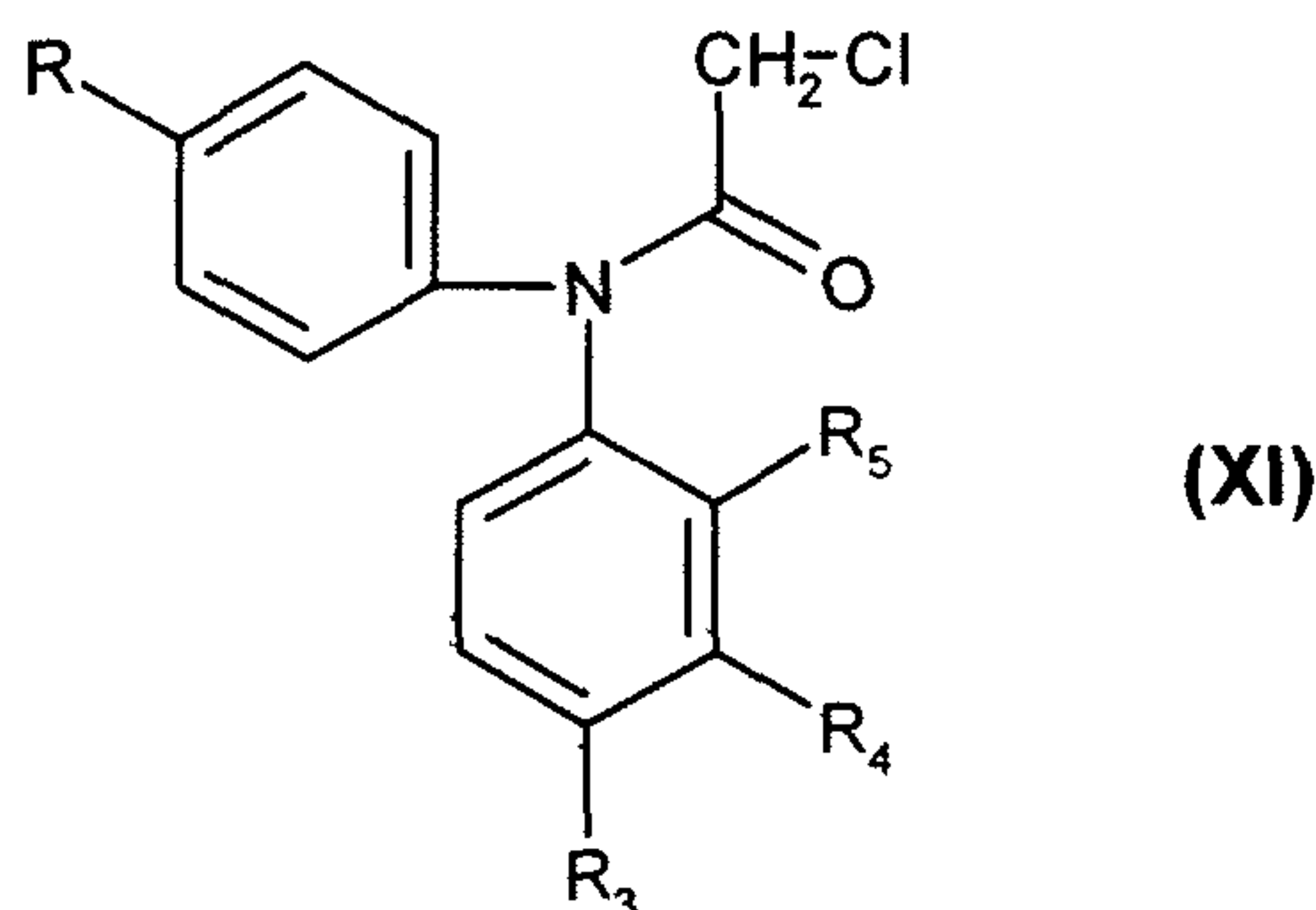
The starting materials of formula (VII) are prepared generally as described under
30 process (a) starting with an amide of formula (II) in which R represents hydrogen, e.g., as described in Moser et al. (1990), *supra*.

The preparation of the compounds of the invention according to process (c) can be carried out under conditions known in the art for the hydrolytic cleavage of lactams, preferably with a strong aqueous base, such as aqueous sodium hydroxide, optionally in the presence of an organic water miscible solvent, such as methanol at elevated temperature in the range of about 50-100°C, as generally described in U.S. Patent No. 3,558,690.

The oxindole starting materials of formula (IX) are prepared by *N*-acylation of a diarylamine of the formula (X)



wherein R and R₁-R₅ have meaning as defined above, with a haloacetyl chloride, preferably chloroacetyl chloride, advantageously at elevated temperature, e.g., near 100°C, to obtain a compound of the formula (XI)



wherein R and R₃-R₅ have meaning as defined hereinabove. Cyclization of a compound of formula (XI) is carried out under conditions of Friedel-Crafts alkylation in an inert solvent, such as dichlorobenzene, in the presence of Friedel-Crafts catalysts, e.g., aluminum chloride and ethylaluminum dichloride, at elevated temperature, e.g., at 120-175°C.

The starting amines of formula (X) can be prepared by an Ullmann condensation and other methods known in the art, e.g., a Buchwald coupling reaction.

Esters of the carboxylic acids of formula (I) are prepared by condensation of the carboxylic acid, in the form of a salt or in the presence of a base, with a halide (bromide or chloride) corresponding to the esterifying alcohol, such as benzyl chloroacetate, according to

methodology well-known in the art, e.g., in a polar solvent, such as *N,N*-dimethylformamide, and if required further modifying the resulting product. For example, if the esterification product is itself an ester, such can be converted to the carboxylic acid, e.g., by hydrogenolysis of a resulting benzyl ester. Also if the esterification product is itself a halide, such can for instance be converted to the nitrooxy derivative by reaction with, e.g., silver nitrate.

For example, the compounds of formula (Ia) are preferably prepared by condensing a salt of a carboxylic acid of formula (I) above with a compound of formula



wherein

X is a leaving group; and

R_b is a carboxy-protecting group;

to obtain a compound of formula (Ia) in carboxy-protected form, and subsequently removing the protecting group R_b.

The esterification can be carried under esterification conditions known in the art, e.g., in a polar solvent, such as *N,N*-dimethylformamide, at a temperature range of room temperature to about 100°C, preferably at a range of 40-60°C, e.g., according to the procedure described in U.S. Patent No. 5,291,523.

The salt of the acid of formula (I) is preferably an alkali metal salt, e.g., the sodium salt which may be prepared *in situ*.

Leaving group X is preferably halo, e.g., chloro or bromo, or lower alkylsulfonyloxy, e.g., methanesulfonyloxy.

Carboxy-protecting group R_b is preferably benzyl.

The resulting benzyl esters can be converted to the free acids of formula (Ia) preferably by hydrogenolysis with hydrogen in the presence of, e.g., Pd/C catalyst in acetic acid at atmospheric pressure or under Parr hydrogenation at a temperature ranging from room temperature to about 50°C.

The invention includes any novel starting materials and processes for their manufacture.

Finally, compounds of the invention are either obtained in the free form, or as a salt thereof if salt forming groups are present.

The acidic compounds of the invention may be converted into metal salts with pharmaceutically acceptable bases, e.g., an aqueous alkali metal hydroxide, advantageously
5 in the presence of an ethereal or alcoholic solvent, such as a lower alkanol. Resulting salts may be converted into the free compounds by treatment with acids. These or other salts can also be used for purification of the compounds obtained. Ammonium salts are obtained by reaction with the appropriate amine, e.g., diethylamine, and the like.

Compounds of the invention having basic groups can be converted into acid addition
10 salts, especially pharmaceutically acceptable salts. These are formed, e.g., with inorganic acids, such as mineral acids, e.g., sulfuric acid, a phosphoric or hydrohalic acid; or with organic carboxylic acids, such as (C₁-C₄)alkanecarboxylic acids which, e.g., are unsubstituted or substituted by halogen, e.g., acetic acid, such as saturated or unsaturated dicarboxylic acids, e.g., oxalic, succinic, maleic or fumaric acid, such as hydroxycarboxylic
15 acids, e.g., glycolic, lactic, malic, tartaric or citric acid, such as amino acids, e.g., aspartic or glutamic acid; or with organic sulfonic acids, such as (C₁-C₄)alkylsulfonic acids, e.g., methanesulfonic acid; or arylsulfonic acids which are unsubstituted or substituted, e.g., by halogen. Preferred are salts formed with hydrochloric acid, methanesulfonic acid and maleic acid.

20 In view of the close relationship between the free compounds and the compounds in the form of their salts, whenever a compound is referred to in this context, a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

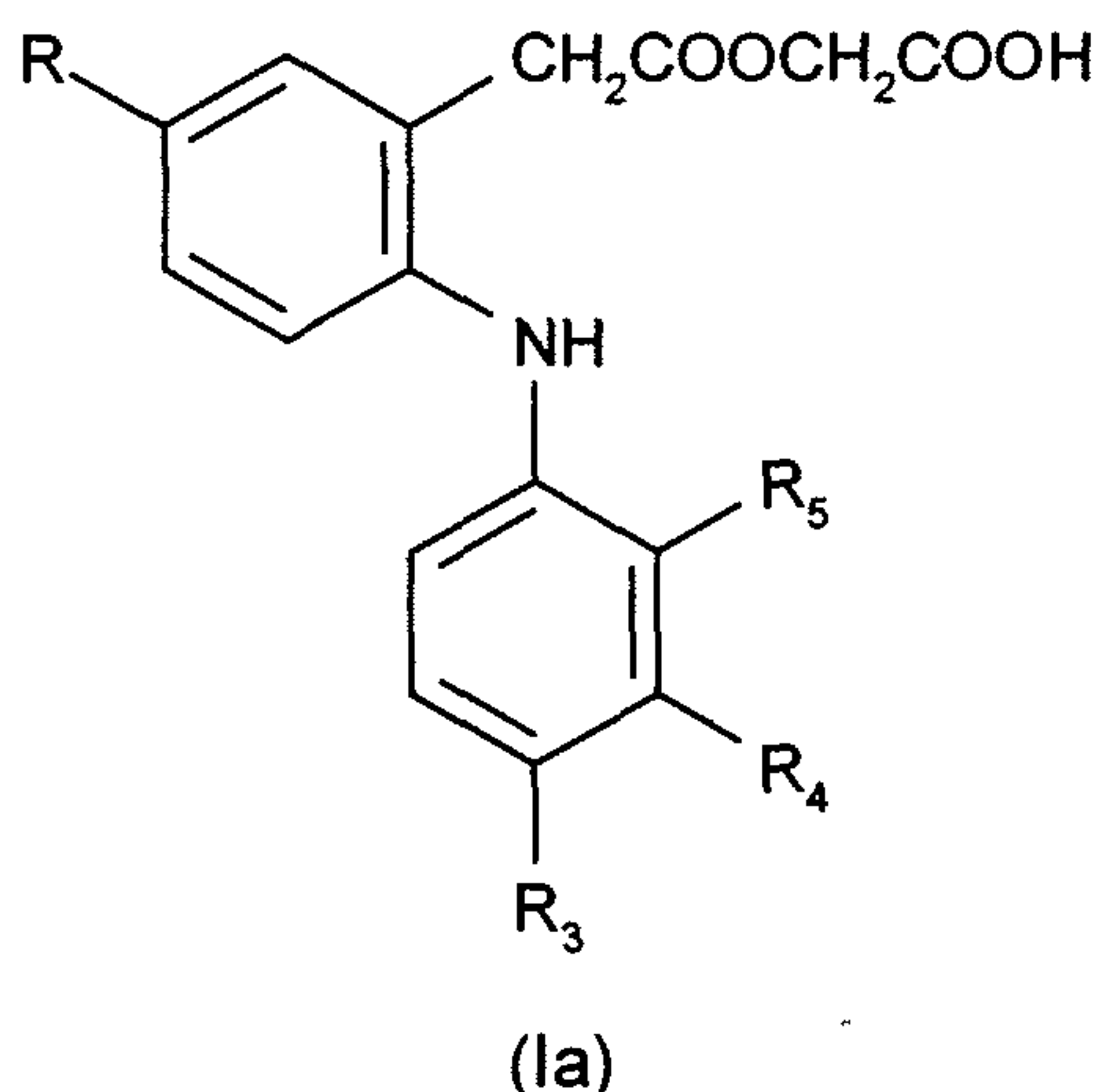
The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

25

The general definitions used herein have the following meaning within the scope of the present invention, unless otherwise indicated.

Pharmaceutically acceptable esters are preferably prodrug ester derivatives which are convertible by solvolysis or under physiological conditions to the free carboxylic acids of,
30 e.g., formula (I). Such esters are, e.g., lower alkyl esters, such as the methyl or ethyl ester;

carboxy-lower alkyl esters, such as the carboxymethyl ester; nitrooxy- or nitrosooxy-lower alkyl esters, such as the 4-nitrooxybutyl or 4-nitrosooxybutyl ester; and the like. Preferred are the phenylacetoxycetic acids of formula (Ia)



wherein R, R₃, R₄ and R₅ have meaning as defined hereinabove for compounds of formula (I); and pharmaceutically acceptable salts thereof.

Pharmaceutically acceptable salts represent metal salts, such as alkaline metal salts, e.g., sodium, potassium, magnesium or calcium salts; as well as ammonium salts, which are formed, e.g., with ammonia and mono- or di-alkylamines, such as diethylammonium salts; and with amino acids, such as arginine and histidine salts.

A lower alkyl group contains up to 6 carbon atoms, preferably 1-4 carbon atoms, may be straight chain or branched and represents, e.g., methyl, ethyl, propyl, butyl, isopropyl, isobutyl and the like, preferably methyl or ethyl. Lower alkoxy is methoxy, ethoxy and the like.

Halo is preferably chloro, bromo or fluoro, advantageously chloro or fluoro.

The compounds of the invention are useful as selective COX-2 inhibitors or as prodrugs thereof. The selective COX-2 inhibitors and prodrugs thereof of the invention are particularly useful for the treatment of, e.g., inflammation, pyresis, pain, osteoarthritis, dysmenorrhea, rheumatoid arthritis and other conditions responsive to the inhibition of COX-2 and are typically substantially free of undesirable gastrointestinal side effects associated with conventional non-steroidal anti-inflammatory agents.

The above-cited properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, e.g., rats, mice, dogs, monkeys and isolated cells or enzyme preparations of human and non-human origin. Said compounds can be applied *in vitro* in the form of solutions, e.g., aqueous solutions, and *in vivo* advantageously orally, topically or
5 parenterally, e.g., intravenously. The dosage *in vitro* may range from about 10^{-5} - 10^{-9} molar concentrations. The dosage *in vivo* may range, depending on the route of administration, between about 0.1 mg/kg and 100 mg/kg.

The biological properties can be demonstrated in tests well-known in the art, e.g., as described in U.S. Patent No. 6,291,523, and as described herein.

10 COX-2 inhibition is determined in an enzymatic *in vitro* assay using a commercially available kit (Cayman Chemical Company).

The test compound (stock solution in DMSO diluted with buffer to various concentrations) is pre-incubated with 30-50 units of purified recombinant human COX-2 and hemactin (1 μ M) for 30 minutes at 25°C, followed by incubation with 100 μ M arachidonic
15 acid and the colorimetric substrate TMPD (*N,N,N',N'*-tetramethyl-*p*-phenylenediamine) for 5-7 minutes at 25°C, followed by colorimetric detection of oxidized TMPD at 590 nm. The COX-2 activity in the presence of test compound is compared to COX-2 activity for control without test compound.

COX inhibition is also determined *in vitro* using cellular assays for inhibition of both
20 COX-1 and COX-2.

Cellular assays for testing COX inhibitors are well-known in the art and based on the fact that the COX enzyme (prostaglandin H synthase) catalyzes the rate limiting step in prostaglandin synthesis from arachidonic acid. Two enzymes mediate the reaction: COX-1 is a constitutive form of the enzyme whereas COX-2 is induced in response to various
25 growth factors and cytokines.

In vitro COX-1 and COX-2 inhibition is determined in the cell-based assays in order to assess the *in vitro* activity and selectivity for COX-2 inhibition, using a prostaglandin E₂ immunoassay (Cayman PGE₂ Kit). The cells utilized are HEK-293 EBNA cells that have been transfected and have a stable expression of either recombinant human COX-1 or
30 recombinant human COX-2, respectively. Cells are plated out into 96-well plates in which the assay is performed. Both cell lines are pre-treated with compound dilutions for

30 minutes at 37°C, then arachidonic acid (1 μ M) is added as exogenous substrate. The supernatant is harvested 15 minutes later and the production of PGE₂ is measured by immunoassay. For IC₅₀ determinations, compounds are tested at 5-9 concentrations in singlet, duplicate or quadruplicate replicates at each concentration (highest concentration 5 30 μ M). The mean inhibition of PGE₂ (compared to cells not treated with compound) for each concentration is calculated, a plot is made of mean % inhibition versus log compound concentration, and the IC₅₀ value calculated using a 4-parameter logistic fit. The relative effects on each enzyme are compared to assess selectivity for inhibition of COX-2.

In vitro COX-1 and COX-2 inhibition is also determined in human whole blood where 10 COX-1 is constitutively expressed in platelets and COX-2 expression is induced in mononuclear cells by treatment with lipopolysaccharide (LPS) (10 μ g/mL). For this assay heparinized human blood is divided into two aliquots: one for measuring TxB₂ production (a surrogate indicator of COX-1 activity) and a second for measuring PGE₂ production (a surrogate for COX-2 activity). The blood samples are pretreated with test compounds for 15 one hour before stimulation. Compounds are tested in a final concentration range from 0.1 nM to 300 μ M using half log increases in concentrations. To measure inhibition of thromboxane B₂ (TxB₂) generation, A23187 (50 μ M) is added, and the blood incubated for one hour. PGE₂ production is measured after the addition of LPS (10 μ g/mL) followed by overnight incubation. After incubation with A23187 or LPS the samples are centrifuged at 20 250 x g for 10 minutes at 4°C to collect serum. The amounts PGE₂ and TxB₂ present in the serum are measured using a chemiluminescence enzyme immunoassay from Assay Designs Inc. (Ann Arbor, MI). The levels of prostaglandin in each sample are normalized to the percent inhibition caused by each concentration of the test compound. The percent inhibition data for each donor is pooled and fitted to a 4-parameter logistic function using a 25 regression.

IC₅₀ values for compounds of formula (I) in the COX-2 inhibition assays are as low as about 0.10 μ M or even lower. Preferred are compounds for which the ratio of IC₅₀ values for COX-1 and COX-2 inhibition is above 50, advantageously in the range of about 100-1000 or higher. For example, the following IC₅₀ values were observed based on the above described 30 assay, average values being taken where more than one assay was performed:

Example	COX-2_Blood IC50 [μ M] (Avg)	COX-1_Blood IC50 [μ M] (Avg)
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5a	0.1	155
5e	0.073	126
5i	0.295	129
5k	0.165	183
5m	0.17	127

The inhibition of prostaglandin-E₂ production produced by COX-2 is determined *in vivo* in the lipopolysaccharide (LPS)-challenged subcutaneous air pouch model in the rat. See *Advances in Inflammation Research*, Raven Press (1986); *J. Med. Chem.*, Vol. 39, p. 1846 (1996); *J. Pathol.*, Vol. 141, pp. 483-495; and *J. Pathol.*, Vol. 134, pp. 147-156.

Female Lewis rats are anesthetized and then dorsal air pouches are prepared by subcutaneous injection of 10 mL of air through a sterile 0.45 micron syringe-adapted filter. Six or 7 days after preparation, the air pouches are injected with LPS (5 µg per pouch) suspended in sterile phosphate buffered saline. Compounds for evaluation are administered by gavage one hour prior to or two or more hours after LPS challenge. The pouch contents are harvested five hours after LPS challenge and PGE₂ levels present in the pouch fluids are measured by enzyme immunoassay. Illustrative of the invention, the compound of Example 4(j) inhibits PGE₂ formation by about 50% at 1 mg/kg p.o.

Anti-inflammatory activity is determined using the carrageenan-induced rat paw edema assay following a modification of the procedure of Offerness et al., described in: *Nonsteroidal Antiinflammatory Drugs*, Lombardino, Ed., John Wiley & Sons, pp. 116-128 (1986).

Sprague Dawley rats (200-225 g) are fasted overnight, then orally dosed with the compound dissolved in 0.5% methylcellulose. After one hour, a 0.1 mL volume of 1% carrageenan in saline is injected into the sub-plantar region of the left hind paw which causes an inflammatory response. At three hours post-carrageenan, the rats are euthanized and both hind paws are cut off at the paw hair line and weighed on an electronic balance. The amount of edema in the inflamed paw is determined by subtracting the weight of the

non-inflamed paw (right) from the weight of the inflamed paw (left). The percent inhibition by the compound is determined for each animal as the percent paw weight gained as compared to the control average.

5 The gastric tolerability assay is used to assess gross ulceration in the rat, measured four hours after oral administration of the test compound. The test is carried out as follows:

Male Sprague Dawley rats are fasted overnight, administered compound in 0.5% methylcellulose vehicle by gavage and sacrificed by carbon dioxide inhalation four hours later. The stomachs are removed and gross gastric lesions counted and measured to give the total lesion length per rat. Each experiment contains the following groups (5-6 rats per
10 group): vehicle control, test compounds and diclofenac as a reference compound.

Data are calculated as the mean number of ulcers in a group, the mean length of ulcers (mm) in the group and as the ulcer index (UI).

$$\text{UI} = \text{mean length of ulcers in a group} \times \text{ulcer incidence}$$

15 where ulcer incidence is the fraction of animals in the group with lesions (100% incidence is 1).

Illustrative of the invention, the compounds of the Examples are essentially free of any gastric ulcerogenic effect at 30 mg/kg p.o.

Intestinal tolerability can be determined by measuring the effect on intestinal permeability. Lack of increase in permeability is indicative of intestinal tolerability.

20 The method used is a modification of a procedure by Davies et al., *Pharm. Res.*, Vol. 11, pp. 1652-1656 (1994) and is based on the fact that excretion of orally administered ⁵¹Cr-EDTA, a marker of small intestinal permeability, is increased by NSAIDs. Groups of male Sprague Dawley rats (≥12 per group) are administered a single, oral dose of test compound or vehicle by gastric intubation. Immediately following compound dose, each rat
25 is administered ⁵¹Cr-EDTA (5 μCi per rat) by gastric intubation. The rats are placed in individual metabolic cages and given food and water *ad libitum*. Urine is collected over a 24-hour period. Twenty-four hours after administration of ⁵¹Cr-EDTA the rats are sacrificed. To quantify compound effect on intestinal permeability, the excreted ⁵¹Cr-EDTA measured in the urine of compound-treated rats is compared to the excreted ⁵¹Cr-EDTA measured in the
30 urine of vehicle-treated rats. Relative permeability is determined by calculating the activity

present in each urine sample as a percent of the administered dose after correcting for background radiation.

The analgesic activity of the compounds of the invention is determined using the complete Freund's adjuvant (CFA)-induced hyperalgesia as measured in the rat. Fifty μ l of CFA is injected into the left hind paw. Nociceptive thresholds are determined prior to 24 hrs following CFA injection using standard paw-pressure apparatus (Analgesymeter, Ugo Basile, Milan). The end point is taken as paw withdrawal or struggling. Compounds are dissolved in 0.5% methylcellulose and administered orally, and further nociceptive threshold measurements are made at 1, 3 and 6h following drug administration. In each experiment groups of 6 animals received either vehicle or one dose of compound. The results are calculated as percentage reversal of predose hyperalgesia. The dose at which 30% inhibition of the predose hyperalgesia is achieved (D30) for each compound is calculated to give an overall estimate of potency.

The anti-arthritic effect of the compounds of the invention can be determined in the well-known chronic adjuvant arthritis test in the rat.

Ocular effects can be demonstrated in well-known ophthalmic assay methods. Similarly anti-tumor activity can be demonstrated in well-known anti-tumor animal tests.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal, topical and parenteral administration to mammals, including man, to inhibit COX-2-activity, and for the treatment of COX-2 dependent disorders, and comprise an effective amount of a pharmacologically active compound of the invention, either alone or in combination with other therapeutic agents, and one or more pharmaceutically acceptable carriers.

More particularly, the pharmaceutical compositions comprise an effective COX-2 inhibiting amount of a selective COX-2 inhibiting compound of the invention which is substantially free of COX-1 inhibiting activity and of side effects attributed thereto.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral

application. Preferred are tablets and gelatin capsules comprising the active ingredient together with

a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

5 b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

10 d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or

e) absorbents, colorants, flavors and sweeteners.

Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said
15 compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, preferably about 1-50%, of the active
20 ingredient.

Tablets may be either film coated or enteric coated according to methods known in the art.

Suitable formulations for transdermal application include an effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable
25 pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

30 Suitable formulations for topical application, e.g., to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, e.g., for

delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for dermal application, e.g., for the treatment of skin cancer, e.g., for prophylactic use in sun creams, lotions, sprays and the like. In this regard it is noted that compounds of the present invention are capable of absorbing UV rays in the range of 290-320 nm while allowing
5 passage of tanning rays at higher wavelengths. They are thus particularly suited for use in topical, including cosmetic, formulations well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives. Formulations suitable for topical application can be prepared, e.g., as described in U.S. Patent No. 4,784,808. Formulations for ocular administration can be prepared, e.g., as described in
10 U.S. Patent Nos. 4,829,088 and 4,960,799.

The compounds of the invention may be used alone or in conjunction with other therapeutic agents. For example, suitable additional active agents for use in relation to the treatment of neoplasia (malignant and benign) include, e.g., the anti-neoplastic agents or radioprotective agents recited in International Patent Application WO 98/16227 and the like.
15 Other suitable additional therapeutic agents include analgesic agents, such as NSAIDs, oxycodone, codeine, paracetamol, ibuprofen, tramadol, levorphanol, propoxyphene, ketorolac, pentazocine, meperidine and the like; muscle relaxants, e.g. benzothiadiazoles e.g. Sirdalud®; also anti-platelet agents, such as aspirin, clopidogrel, ticlopidine and the like; also bisphosphonates, such as zoledronate, pamidronate, risedronate, alendronate and the
20 like; also statins, such as fluvastatin, atorvastatin, lovastatin, simvastatin, rosuvastatin, pitavastatin, pravastatin and the like; also antacids; proton pump inhibitors e.g. omeprazole, esomeprazole; calcilytics; calcitonin, e.g. oral calcitonin; an anti-IL-1beta IgG1/kappa antibody; antihypertensives, e.g. ACE inhibitors, angiotensin II blockers, renin inhibitors.

In conjunction with another active ingredient, a compound of the invention may be
25 administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

The dosage of active compound administered is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of
30 administration. A unit dosage for oral administration to a mammal of about 50-70 kg may contain between about 5 mg and 500 mg, of the active ingredient.

The present invention also relates to methods of using the compounds of the invention and their pharmaceutically acceptable salts, or pharmaceutical compositions thereof, in mammals for inhibiting COX-2 and for the treatment of conditions as described herein, e.g., inflammation, pain, rheumatoid arthritis, osteoarthritis, dysmenorrheal, tumors
5 and other COX-2-dependent disorders.

Particularly, the present invention relates to a method of selectively inhibiting COX-2 activity in a mammal without substantially inhibiting COX-1 activity, which comprises administering to a mammal in need thereof an effective COX-2 inhibiting amount of a compound of the invention.

10 Thus, the present invention also relates to a method of treating COX-2 dependent disorders in mammals, which comprises administering to a mammal in need thereof an effective COX-2 inhibiting amount of a compound of the invention.

More particularly, the present invention relates to a method of treating COX-2 dependent disorders in mammals while substantially eliminating undesirable side effects
15 associated with COX-1 inhibiting activity which comprises administering to a mammal in need thereof an effective COX-2 inhibiting amount of a selective COX-2 inhibiting compound of the invention which is substantially free of COX-1 inhibiting activity.

More specifically, such relates to a method of, e.g., treating rheumatoid arthritis, osteoarthritis, pain, dysmenorrheal, gout or inflammation in mammals without causing
20 undesirable gastrointestinal ulceration, which method comprises administering to a mammal in need thereof a correspondingly effective amount of a compound of the invention.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Celsius. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably
25 between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g., microanalysis and spectroscopic characteristics, e.g., MS, IR and NMR. Abbreviations and tradenames used are those conventional in the art. Typical are those given below

- BOC: *t*-butoxycarbonyl
 COD: cyclooctadiene
 DMAP: 4-dimethylamino-pyridine
 DME: 1,2-Dimethoxyethane
 5 DSC: differential scanning calorimetry
 DMF: *N,N*-dimethylformamide
 dppp: diphenylphosphinopropane
 EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
 HOAt: 1-hydroxy-7-azabenzotriazole
 10 LAH: lithium aluminum hydride
 NMM: *N*-methylmorpholine
 Selectfluor™: 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane *bis*(tetrafluoroborate)
 THF: tetrahydrofuran
 TLC: thin layer chromatography

15

EXAMPLES

Example 1

Aniline Starting Materials

A. 2,4-Dichloro-3-methylaniline

20 2,4-Dichloro-3-methylaniline is prepared by reduction of 2,4-dichloro-3-methylnitrobenzene according to the procedure outlined in *Tetrahedron*, Vol. 53, No. 17, p. 6145 (1997).

B. 2,4-Dichloro-3-ethylaniline

25 To a solution of 2,4-dichloroaniline (42.0 g, 260 mmol) in AcOH (40.0 mL) is added Ac₂O (80 mL). The reaction mixture is warmed up to 50 °C and stirred at this temperature for 1 hour. The reaction is cooled to room temperature and poured into ice water (500 mL). A solid precipitated and the mixture is stirred for additional 1 hour at room temperature. The solid is filtered and washed with water, hexanes and air dried to give *N*-(2,4-dichlorophenyl) acetamide.

30 To a solution of *N*-(4-chloro-2-fluorophenyl) acetamide (30.0 g, 147 mmol) in THF (300 mL) at -70 °C is added dropwise (keeping the reaction temperature below -60°C) *n*-BuLi (2.0 M in cyclohexane, 147 mL, 294 mmol). The reaction is stirred between -60 to -70 °C for

2 hours and 1,1,1-trifluoro-2-iodoethane (46.2 g, 220 mmol) is added dropwise at -70 °C. The reaction mixture is stirred at this temperature for additional 1.5 hours before 3N HCl (108 mL) solution is added slowly. The mixture is allowed to warm up to room temperature and extracted with EtOAc (200 mL x 3). The organic layers are combined washed with
5 water, brine and then dried over MgSO₄. The solvents are removed and the residue is stirred in ether and hexanes (1:2, 120 mL) for 1 hour. A solid precipitate is filtered to give *N*-(2,4-dichloro-3-iodophenyl) acetamide.

To a solution of *N*-(2,4-dichloro-3-iodophenyl) acetamide (40.0 g, 121 mmol) in MeOH (100 mL) is added concentrated HCl (50 mL). The mixture is stirred and heated at
10 reflux for 18 hours. The mixture is cooled and the solvents were removed under reduced pressure (water bath below 45 °C). The residue is cooled with an ice bath and 3N NaOH solution was added to adjust the pH to between 9 and 10. The mixture is extracted with ether and dried over MgSO₄. The solvents were removed and the residue is purified through a flash chromatographic column with a gradient of hexanes/ether to give 2,4-dichloro-3-
15 iodoaniline.

To a solution of 2,4-dichloro-3-iodoaniline (9.0 g, 31 mmol) in DME/water (180 mL/60 mL) is added vinyl triboroxine pyridine complex (5.0 g, 20.8 mmol) and K₂CO₃ (8.5 g, 62.0 mmol). The reaction mixture is stirred and N₂ is bubbled in for 15 min. Tetrakis(triphenylphosphine) palladium(0) (1.8 g, 1.6 mmol) is added at room temperature
20 and N₂ is bubbled in for additional 20 min. The reaction mixture is heated to 80 °C and stirred for 18 hours, when the GC-MS showed the reaction is complete. The mixture is filtered and washed with ether (400 mL) and water (50 mL). The organic layer is separated and washed with brine and dried over MgSO₄. The solvents were removed and the residue is purified through a flash chromatographic column with a gradient of hexanes/ether to give
25 2,4-dichloro-3-vinyaniline.

To a solution of 2,4-dichloro-3-vinyaniline (4.9 g, 26 mmol) in EtOAc (60 mL) is added 10% Pd/C (0.50 g). The pressure flask is filled with H₂ at 55 psi and shaken for 2 hrs. Excess H₂ is removed and the mixture is filtered through a pad of celite. The solvent is removed and the resulting mixture is purified through a flash chromatographic column with a
30 gradient of hexanes/ether to give 2,4-dichloro-3-ethylaniline.

C. 2-Fluoro-4-methyl-3-trifluoroaniline

To a solution of 2-fluoro-3-trifluoromethylaniline (5.0 g, 28 mmol) in DMF (25 mL) is added a solution of NBS (5.0 g, 28 mmol) in DMF (25 mL). After 2.5 h, the reaction is partitioned between ether and saturated aqueous NaCl. The separated organic phase is

washed twice with fresh saturated aqueous NaCl, dried over Na₂SO₄, and concentrated under reduced pressure to give 4-bromo-2-fluoro-3-trifluoromethylaniline as an oil.

The bromide above (10.0 g, 38.8 mmol), trimethylboroxine (4.9 g, 38.8 mmol), K₂CO₃ (16.1 g, 116 mmol), and palladium tetrakis(triphenyl)phosphine (4.5 g, 3.9 mmol) are heated under a nitrogen atmosphere. A second aliquot of trimethylboroxine (4.9 g, 38.8 mmol) is added to consume the starting bromide. After 18 h, the cooled reaction is partitioned between EtOAc and saturated aqueous NaCl. The separated organic layer is washed with fresh brine (3x), dried with Na₂SO₄, and concentrated under reduced pressure. The residue is purified by flash chromatography (Et₂O/hexanes) to give the title aniline.

10 D. 2-Fluoro-4-ethyl-3-trifluoroaniline

4-Bromo-2-fluoro-3-trifluoromethylaniline described above (5.0 g, 19.4 mmol) and tributylvinyltin chloride (7.1 g, 20.4 mmol) are added to anhydrous DMF (100 mL). The solution is degassed with N₂, palladium tetrakis(triphenyl)phosphine (1.5 g, 1.3 mmol) is added, and the reaction is heated at 120 °C for 18 hours. After cooling, the reaction mixture is partitioned between Et₂O and saturated aqueous NaCl. The separated ether layer is washed with fresh saturated aqueous NaCl (2x), dried with Na₂SO₄, and concentrated under reduced pressure. The residue is purified by flash chromatography eluting with 5, then 10, then 20% EtOAc in hexanes to give the desired product, 2-fluoro-3-trifluoromethyl-4-vinylaniline.

20 2-Fluoro-3-trifluoromethyl-4-vinylaniline prepared above (4.0 g, 19.4 mmol) is dissolved in EtOH and degassed with N₂, and 10% Pd on charcoal (0.5 g) is added. The mixture is placed in a Parr apparatus and treated with H₂ at room temperature. The reaction is flushed with N₂ and filtered. The filter pad is washed with fresh EtOH and the filtrates are combined. Concentrated HCl (6.5 mL) is added to the cooled filtrate (0 °C) before removal of the volatiles under reduced pressure. The resulting white solid is washed with Et₂O and collected by filtration to give 4-ethyl-2-fluoro-3-trifluoromethylaniline hydrochloride.

25 The free aniline is prepared from the hydrochloride salt by partitioning between Et₂O and a saturated aqueous NaHCO₃ solution. The separated organic layer is washed with brine, dried (Na₂SO₄) and concentrated *in vacuo* to give 4-ethyl-2-fluoro-3-trifluoromethylaniline as an oil.

30 E. 4-Chloro-2-fluoro-3-methylaniline

To 6-chloro-2-fluoro-3-methylbenzoic acid (10 g, 53 mmol) is added CH₂Cl₂ (60 mL), DMF (0.5 mL) and oxalyl chloride (9.25 mL, 106 mmol). The reaction mixture is allowed to stir until it reaches homogeneity and is then concentrated *in vacuo*. The residue is poured onto a 50:50 mixture of ice and 36% ammonium hydroxide to yield 6-chloro-2-fluoro-3-methylbenzamide.

The 6-chloro-2-fluoro-3-methylbenzamide prepared above is dissolved in MeOH. Sodium methoxide (16.1 g, 298 mmol) is added and the reaction is heated to reflux. NBS (21.2 g, 119 mmol) is then added portionwise as a solid and the reaction mixture is stirred at reflux an additional 2 hours. After cooling, volatiles are removed under reduced pressure and the residue is diluted with EtOAc and water. The organic phase is separated and the water layer is extracted with fresh EtOAc (3 x). The combined organic layers are dried (MgSO₄), filtered and concentrated *in vacuo* to give *N*-6-chloro-2-fluoro-3-methyl-phenyl)carbamic acid methyl ester.

The carbamate prepared above is dissolved in MeOH (220 mL) and water (22 mL). Potassium hydroxide (31 g, 560 mmol) is added and the reaction heated at reflux for 12 hours. After cooling the reaction to room temperature, the MeOH is removed under reduced pressure and the residue is diluted with water and extracted with CH₂Cl₂ (3 x). The combined organic layers are dried (MgSO₄), filtered and concentrated *in vacuo*. The residue is purified by flash chromatography using 10% EtOAc in hexane to give 6-chloro-2-fluoro-3-methylaniline.

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The carbamate prepared above is dissolved in MeOH (220 mL) and water (22 mL). Potassium hydroxide (31 g, 560 mmol) is added and the reaction heated at reflux for 12 hours. After cooling the reaction to room temperature, the MeOH is removed under reduced pressure and the residue is diluted with water and extracted with CH₂Cl₂ (3 x). The combined organic layers are dried (MgSO₄), filtered and concentrated *in vacuo*. The residue is purified by flash chromatography using 10% EtOAc in hexane to give 6-chloro-2-fluoro-3-methylaniline.

F. 4-Chloro-2-fluoro-3-ethylaniline

To a solution of 4-chloro-2-fluoroaniline (50.0 g, 344 mmol) in AcOH (30 mL) is added Ac₂O (60 mL) and the reaction is stirred at room temperature for 2 hours. The mixture is poured into ice water (500 mL) to give a solid precipitate. The mixture is stirred for an additional 1 hour at room temperature. The solid is filtered and washed with water and hexanes, then air dried to give *N*-(4-chloro-2-fluorophenyl) acetamide.

To a solution of *N*-(4-chloro-2-fluorophenyl) acetamide (10.0 g, 53.3 mmol) and diisopropylamine (7.5 mL, 53.3 mmol) in THF (300 mL) at -78 °C is added dropwise *n*-BuLi (2.5 M in hexanes, 42.6 mL, 106.6 mmol) keeping the reaction temperature below -60 °C. After 2 hours, iodoethane (12.4 g, 80 mmol) is added dropwise at -78 °C. The reaction mixture is stirred at -78 °C for additional 1.5 hours. A 1N solution of aqueous HCl is added slowly until a pH between 4 and 5 is reached. The mixture is extracted with EtOAc (200 mL x 3) and the organic layers are combined washed with water and brine, then dried over MgSO₄. The solvent is removed under reduced pressure and the solid residue is stirred in ether and hexane (1:4, 80 mL) for 1 hour. The filtered solid is dried to give *N*-(4-chloro-3-ethyl-2-fluorophenyl) acetamide.

To a solution of *N*-(4-chloro-3-ethyl-2-fluorophenyl) acetamide (11.0 g, 51.0 mmol) in MeOH (80 mL) is added concentrated HCl (40 mL) before heating at reflux for 16 hours. The solvent is removed from the cooled reaction under reduced pressure maintaining the water bath below 45 °C. The residue is cooled with an ice bath before a 3N NaOH solution is added to adjust pH between 9 and 10. The mixture is extracted with ether and dried over MgSO₄. The solvent is removed and the residue is purified through a flash chromatography using a gradient of ether/hexanes to give 4-chloro-3-ethyl-2-fluoroaniline.

Similarly prepared is:

4-chloro-3-methyl-2-fluoroaniline.

G. 4-Chloro-2-fluoro-3-isopropylaniline

To a solution of *N*-(4-chloro-2-fluorophenyl) acetamide prepared above (12.0 g, 64 mmol) in THF (300 mL) at -78 °C is added dropwise *n*-BuLi (2.0 M in cyclohexane, 64 mL, 128 mmol) keeping the reaction temperature below -60 °C. The reaction mixture is stirred between -60 to -70 °C for 2 hours and 1,1,1-trifluoro-2-iodoethane (20.1 g, 96 mmol) is added dropwise at -78 °C. The mixture is stirred at this temperature for additional 3 hrs. Then a 1N HCl (200 mL) solution is added slowly at -78 °C. The mixture is allowed to warm to room temperature and extracted with EtOAc (200 mL x 3). The combined organic layers are washed with water and brine, then dried over MgSO₄. The solvent is removed and the residue is stirred in ether and hexanes (1:2, 120 mL) for 1 hour. The solid is filtered to give *N*-(4-chloro-2-fluoro-3-iodophenyl) acetamide.

To a mixture of *N*-(4-chloro-2-fluoro-3-iodophenyl) acetamide (20.0 g, 64 mmol) in MeOH (80 mL) is added concentrated HCl (60 mL). The mixture is stirred at reflux for 18 hours before cooling to room temperature and removal of the solvent under reduced pressure while maintaining the water bath below 45 °C. The residue is cooled with an ice bath and a 1N NaOH solution is added to adjust the pH between 9 and 10. The aqueous phase is extracted with ether and dried over MgSO₄. The solvent is removed and the residue is purified through a flash chromatographic column with a gradient of hexanes/ether to give 4-chloro-2-fluoro-3-iodoaniline.

To a solution of 4-chloro-2-fluoro-3-iodoaniline (13.5 g, 50 mmol) in ~~DME~~/water (150 mL/50 mL) is added 2-propeneboronic acid (6.4 g, 74.6 mmol) and K₂CO₃ (20.6 g, 150 mmol). Nitrogen gas is bubbled in for 15 min before tetrakis(triphenylphosphine) palladium(0) (2.8 g, 2.5 mmol) is added at room temperature. Nitrogen is bubbled in for additional 20 minutes before the reaction mixture is heated to 80 °C for 18 hours. The mixture is filtered through a pad of celite and washed with ether (400 mL) and water (50 mL). The organic layer is separated and washed with brine and dried over MgSO₄. The solvent is removed and the residue is purified through a flash chromatographic column with a gradient of hexanes/ether to give 4-chloro-3-isopropene-2-fluoroaniline.

To a solution of 4-chloro-3-isopropene-2-fluoroaniline (4.5 g, 24.2 mmol) in EtOAc (50 mL) is added 10% Pt/C (0.45 g). The pressure flask is filled with H₂ at 50 psi and shaken at room temperature for 4 hrs. The excess H₂ is removed and the mixture is filtered through a pad of celite. The solvent is removed and the resulting mixture is purified through a flash chromatographic column with a gradient of hexanes/ether to give 4-chloro-3-isopropane-2-fluoroaniline.

Example 2**2-Iodophenylacetic Acid Ester and Phenylacetamide Starting Materials**

Prepared according to, e.g., *J Med Chem*, Vol. 33, pp. 2358-2368 (1990),
U.S. Patent No. 6,291,523 and International Application WO 99/11605, starting from the
5 corresponding benzoic acid or 2-indolinone, are, for instance:

N,N-dimethyl-5-methyl-2-iodophenylacetamide;

N,N-dimethyl-5-ethyl-2-iodophenylacetamide;

Example 3**5-Ethyl-2-(2'-fluoro-4'-methyl-3'-trifluoromethylanilino)phenylacetic acid *N,N*-dimethyl
10 amide.**

A mixture of *N,N*-dimethyl-5-ethyl-2-iodophenylacetamide (2.0 g, 6.3 mmol), 2-fluoro-
methyl-3-trifluoromethylaniline (2.4 g, 12.6 mmol), copper (0.2 g, 3.2 mmol), cuprous iodide
(0.6 g, 3.2 mmol), and K₂CO₃ (0.9 g, 6.3 mmol) in xylenes (6.0 mL) are heated at reflux for
24 h. After cooling, the crude reaction mixture is diluted with EtOAc and filtered through
15 Celite®. The filtrate is concentrated under reduced pressure. The residue is purified by
flash chromatography, eluting with hexanes, then up to 25% EtOAc/hexane mixtures to give
the target compound 5-ethyl-2-(2'-fluoro-4'-methyl-3'-trifluoromethylanilino)phenylacetic acid
N,N-dimethyl amide.

Similarly prepared are:

20 5-Methyl-2-(2'-fluoro-4'-methyl-3'-trifluoromethylanilino)phenylacetic acid *N,N*-dimethyl amide.

5-Methyl-2-(2'-fluoro-4'-bromo-3'-trifluoromethylanilino)phenylacetic acid *N,N*-dimethyl amide.

5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetic acid *N,N*-dimethyl amide.

5-Ethyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetic acid *N,N*-dimethyl amide.

5-Methyl-2-(2',4'-dichloro -3'-ethylanilino)phenylacetic acid *N,N*-dimethyl amide.

25 5-Ethyl-2-(2',4'-dichloro -3'-ethylanilino)phenylacetic acid *N,N*-dimethyl amide.

5-Methyl-2-(2'-fluoro-4'-chloro-3'-methylanilino)phenylacetic acid *N,N*-dimethyl amide.

5-Ethyl-2-(2'-fluoro-4'-chloro-3'-methylanilino)phenylacetic acid *N,N*-dimethyl amide.

5-Methyl-2-(2'-fluoro-4'-chloro-3'-ethylanilino)phenylacetic acid *N,N*-dimethyl amide.

5-Ethyl-2-(2'-fluoro-4'-chloro-3'-ethylanilino)phenylacetic acid *N,N*-dimethyl amide.

5-Ethyl-2-(2'-fluoro-4'-chloro-3'-isopropylanilino)phenylacetic acid *N,N*-dimethyl amide.

Example 4

5-Methyl-2-(2'-fluoro-4'-ethyl-3'-trifluoromethylanilino)phenylacetic acid *N,N*-dimethyl amide.

5-Methyl-2-(2'-fluoro-4'-bromo-3'-trifluoromethylanilino)phenylacetic acid *N,N*-dimethyl amide prepared by method outlined in example 3 (0.8 g, 1.7 mmol), Pd(PPh₃)₄ (0.1 g, 0.09 mmol), and vinyl tributylstannane (0.6 g, 1.9 mmol) in DMF (5 mL) is heated to 120 °C under nitrogen overnight. After cooling, the reaction is portioned between EtOAc and saturated aqueous solution of NaCl. The separated organic layer is washed twice with fresh saturated aqueous solution of NaCl. The EtOAc layer is dried and concentrated under reduced pressure. The residue is purified by flash chromatography to give 5-Methyl-2-(2'-fluoro-4'-vinyl-3'-trifluoromethylanilino)phenylacetic acid *N,N*-dimethyl amide.

The above styrene is reduced under conditions outlined in . The styrene is dissolved in *i*-PrOH and toluene and degassed for 10 minutes. Then Cs₂CO₃ (22 mg, 0.07 mmol), [Ir(cod)Cl]₂ (44 mg, 0.07 mmol), and dppp (27 mg, 0.07 mmol) are added and the reaction is heated to 80 °C over night. The cooled solution is concentrated in vacuo and the residue purified by flash chromatography eluting with 10, then 20, then 30% EtOAc/hexanes to give the title 5-methyl-2-(2'-fluoro-4'-ethyl-3'-trifluoromethylanilino)phenylacetic acid *N,N*-dimethyl amide.

Example 5

5a) 5-Ethyl-2-(2'-fluoro-4'-methyl-3'-trifluoromethylanilino)phenylacetic acid

A solution of the above 5-ethyl-2-(2'-fluoro-4'-methyl-3'-trifluoromethylanilino)phenylacetic acid *N,N*-dimethyl amide described in Example 3 (0.9 g, 2.4 mmol) in EtOH (25 mL) and 4N NaOH (12 mL) is heated to 80 °C overnight. After cooling, the reaction is concentrated under reduced pressure and diluted with ice cold EtOAc. The pH of the aqueous layer is adjusted to 1-2 with ice cold 2.5 N HCl. The separated organic layer is dried with Na₂SO₄ and concentrated to a solid. The solid is

purified by trituration with an Et₂O/hexane mixture to give the title acid, 5-ethyl-2-(2'-fluoro-4'-methyl-3'-trifluoromethylanilino)phenylacetic acid.

MS m/z 356 (ES⁺), 354 (ES⁻)

CHN found C 60.47, H 4.47, N 3.73

5 Similarly prepared are:

5b) 5-Methyl-2-(2'-fluoro-4'-methyl-3'-trifluoromethylanilino)phenylacetic acid.

MS m/z 342 (ES⁺), 340 (ES⁻)

CHN found C 59.56, H 4.36, N 3.91

5c) 5-Methyl-2-(2'-fluoro-4'-ethyl-3'-trifluoromethylanilino)phenylacetic acid.

10 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.13 (t, *J*=7.3 Hz, 3 H), 2.27 (s, 3 H), 2.63 - 2.70 (m, 2 H), 3.56 (s, 2 H), 6.87 (t, *J*=8.6 Hz, 1 H), 7.02 - 7.09 (m, 2 H), 7.12 (s, 1 H), 7.43 (s, 1 H).

MS m/z 356 (ES⁺), 354 (ES⁻)

5d) 5-Ethyl-2-(2'-fluoro-4'-ethyl-3'-trifluoromethylanilino)phenylacetic acid.

15 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.17 (t, *J*=7.5 Hz, 3 H), 1.26 (t, *J*=7.5 Hz, 3 H), 2.59 (q, *J*=7.5 Hz, 2 H), 2.89 (q, *J*=7.1 Hz, 2 H), 3.75 (d, *J*=22.7 Hz 1 H), 3.83 (d, *J*=22.7 Hz, 1 H), 6.52 (d, *J*=8.1 Hz, 1 H), 7.06 (d, *J*=8.1 Hz, 1 H), 7.23 (s, 1 H), 7.50 (d, *J*=8.3 Hz, 1 H), 7.79 (t, *J*=7.8 Hz, 1 H).

MS m/z 370 (ES⁺), 368 (ES⁻)

20 5e) 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetic acid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.29 (s, 3 H), 2.41 (s, 3 H), 3.51 (s, 2 H), 6.51 (d, *J*=8.8 Hz, 1 H), 7.07 - 7.22 (m, 4 H), 12.46 (s, 1 H)

MS m/z 324, 326, 328 (ES⁺), 322, 324, 326 (ES⁻)

5f) 5-Ethyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetic acid.

25 MS m/z 338, 340, 342 (ES⁺), 336, 338, 340 (ES⁻)

CHN found C 59.97, H 4.71, N 4.12

5g) 5-Methyl-2-(2',4'-dichloro -3'-ethylanilino)phenylacetic acid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.14 (t, *J*=7.5 Hz, 3 H), 2.29 (s, 3 H), 2.88 (q, *J*=7.5 Hz, 2 H), 3.52 (s, 2 H), 6.52 (d, *J*=9.0 Hz, 1 H), 7.07 - 7.18 (m, 4 H), 7.25 (s, 1 H), 12.49 (br. s., 1 H)

CHN found C 60.53, H 5.19, N 3.98

5 5h) 5-Ethyl-2-(2',4'-dichloro-3'-ethylanilino)phenylacetic acid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.11 - 1.22 (m, 6 H), 2.52 - 2.63 (m, 4 H), 2.88 (q, *J*=7.5 Hz, 2 H), 3.54 (s, 2 H), 6.55 (d, *J*=9.0 Hz, 1 H), 7.11 - 7.15 (m, 3 H), 7.18 (s, 1 H), 7.26 (s, 1 H), 12.50 (br. s., 1 H)

CHN found C 61.39, H 5.22, N 4.24

10 5i) 5-Methyl-2-(2'-fluoro-4'-chloro-3'-methylanilino)phenylacetic acid.

MS *m/z* 308 (ES⁺), 306 (ES⁻)

CHN found C 62.16, H 4.79, N 4.49

5j) 5-Ethyl-2-(2'-fluoro-4'-chloro-3'-methylanilino)phenylacetic acid.

MS *m/z* 322 (ES⁺), 320 (ES⁻)

15 CHN found C 63.20, H 5.22, N 4.32

5k) 5-Methyl-2-(2'-fluoro-4'-chloro-3'-ethylanilino)phenylacetic acid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.15 (t, *J*=7.5 Hz, 3 H), 2.27 (s, 3 H), 2.72 (qd, *J*=7.5, 2.1 Hz, 2 H), 3.54 (s, 2 H), 6.55 (t, *J*=9.0 Hz, 1 H), 6.98 - 7.07 (m, 3 H), 7.10 (s, 1 H), 7.30 (br. s., 1 H), 12.35 (br. s., 1 H)

20 MS *m/z* 322 (ES⁺), 320 (ES⁻)

CHN found C 63.54, H 5.28, N 4.38

5l) 5-Ethyl-2-(2'-fluoro-4'-chloro-3'-ethylanilino)phenylacetic acid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.12 - 1.20 (m, 6 H), 2.57 (q, *J*=7.7 Hz, 2 H), 2.68 - 2.76 (m, 2 H), 3.56 (s, 2 H), 6.58 (t, *J*=9.0 Hz, 1 H), 7.00 (dd, *J*=9.0, 1.5 Hz, 1 H), 7.04 - 7.10 (m, 2 H), 7.13 (s, 1 H), 7.31 (s, 1 H), 12.36 (s, 1 H)

25

CHN found C 64.20, H 5.61, N 4.37

5m) 5-Ethyl-2-(2'-fluoro-4'-chloro-3'-isopropylanilino)phenylacetic acid.

^1H NMR (400 MHz, CDCl_3) δ ppm 1.23 (t, $J=7.7$ Hz, 3 H), 1.37 (dd, $J=7.0$, 1.3 Hz, 6 H), 2.62 (q, $J=7.7$ Hz, 2 H), 3.46 - 3.60 (m, 1 H), 3.68 (s, 2 H), 6.72 (t, $J=8.8$ Hz, 1 H), 6.92 (dd, $J=8.8$, 1.8 Hz, 1 H), 7.07 - 7.14 (m, 2 H), 7.23 (d, $J=8.1$ Hz, 1 H)

CHN found C 65.08, H 6.16, N 3.84

5

Example 6

6a) 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetic acid diethylamine salt

10 A suspension of 600 mg 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetic acid (1.85 mmoles) in 6 ml tert. Butyl methyl ether (TBME) is heated to 40°C. 137 mg diethylamine (1.85 mmoles) are dropwise added. The resulting slightly cloudy solution is clarified via hot filtration through a Whatman glasfiber filter. The filter is rinsed with 2 ml TBME of 40°C. The filtrate is allowed to cool slowly.

15 The solution is seeded at 30°C and crystallization takes place. The suspension is stirred for ca. 15 h at room temperature and then for 2 h at 0°C. The slurry is filtered and the filter cake washed with 4.5 ml TBME of 0°C. The crystals are dried for 4 h at 50°C and ca. 10 mbar to yield a white powder, m.p. 115-116°C.

6b) sodium 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetate

20

A suspension of 400 mg 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetic acid (1.23 mmoles) in 4 ml acetone is heated to 50°C. The resulting almost clear solution is clarified via hot filtration through a Whatman glasfiber filter. The filter is rinsed with 2 ml acetone of 50°C. 165 mg 30 % aqueous natriumhydroxide solution (1.23 mmoles) are added at 50 °C.

25 The solution is allowed to cool to room temp. and seeded at ca. 25°C. Crystallization takes then very slowly place. The suspension is stirred for ca. 15 h at room temperature and then for 2 h at 0°C. After filtration only 97 mg wet crystals are obtained. The crystals and the mother liquor are combined and 6 ml isopropylacetate are added dropwise under stirring.

30 The thick suspension is filtered and the solid washed with isopropylacetate. The salt is dried first for 2 h at 50°C / ca. 10 mbar and then for 16 h at 80°C and ca. 10 mbar to yield the salt as a white powder, m.p. 254-255°C.

Water assay: 2.31% m/m

6c) 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetic acid tromethamine salt

A suspension of 1.30 g 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetic acid (4.01 mmoles) in 13 ml acetone is heated to 55°C.

- 5 The resulting almost clear solution is clarified via hot filtration through a Whatman glasfiber filter. The filter is rinsed with 2.6 ml acetone of 50°C. A solution of 0.487 g tromethamine (Trisma base) (4.01 mmoles) in 1 ml water is added dropwise at 50°C. The dropping funnel is rinsed with 0.5 ml water. The solution is allowed to cool to room temp. and seeded at ca. 40°C°C. Crystallization takes then place. The suspension is stirred for ca. 15 h at room
- 10 temperature and then for 2 h at 0°C. The slurry is filtered and the solid washed with 6 ml acetone. The salt is dried first for 2 h at 50°C / ca. 10 mbar and then for 16 h at 80°C and ca. 10 mbar to yield the salt as a white powder, m.p. 156-157°C, DSC 162.0°C, melting enthalpy 132 J/g.

15 Prinicipal X-ray diffraction peaks:

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
4.371	20.19907	360	66.7
13.276	6.66382	525	97.2
13.719	6.44934	312	57.8
14.443	6.12802	316	58.5
14.943	5.9239	356	65.9
15.663	5.65321	318	58.9
16.948	5.22734	403	74.6
17.739	4.99598	304	56.3
22.832	3.89177	464	85.9
23.707	3.75003	389	72
24.877	3.57629	323	59.8
25.868	3.44143	217	40.2
26.596	3.34886	540	100

6d) calcium 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetate monohydrate

- 20 A suspension of 1.30 g 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetic acid (4.01 mmoles) in 13 ml acetone is heated to 55°C. 0.535 g 30 % aqueous sodium hydroxide solution (4.01 mmoles) are added. The resulting almost clear solution is clarified via filtration at 50°C through a Whatman glasfiber filter. The filter is rinsed with 3.9 ml acetone of 50°C. Then a solution of 0.51 g calciumchloride (4.41 mmoles) in 1 ml water is added dropwise at 50°C. The dropping funnel is rinsed with 0.5 ml water. The resulting thick suspension is

allowed to cool to room temperature. Further 7 ml water are added at 25°C The mixture is stirred at r.t. for 1 h and filtered. The filter cake is washed with 20 ml acetone/water 2:1 v/v and then with 5 ml acetone. the crystallisate is dried for 2 h at 50°C / ca. 10 mbar and then for 16 h at 80°C and ca. 10 mbar. As the salt is still contaminated with some natriumchloride the crystals are suspended in 13.5 ml water and 1.5 ml acetone and the suspension stirred for 1 h at r.t. After filtration the filter cake is washed with 8 ml water/acetone 9:1 v/v in 4 portions. The salt is dried first for 2 h at 50°C / ca. 10 mbar and then for 16 h at 80°C and ca. 10 mbar to yield a white powder, m.p. 278-279°C, DSC 147.1 / 224.2°C, melting enthalpy 121 / 2 J/g.

10 Water assay: 2.63% m/m

Principal X-ray diffraction peaks:

Angle 2-Theta °	d value Angstrom	Intensity %
6.273	14.07919	100
10.622	8.32204	30.7
11.106	7.96028	34.8
13.38	6.61206	33.7
14.348	6.16798	25.5
16.473	5.37693	48.2
18.634	4.75806	29.2
21.394	4.15001	34.7
23.887	3.72226	27.8
24.498	3.63067	23.5
25.395	3.5045	19

15 **6e) Lysine 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetate monohydrate**

A suspension of 400 mg 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetic acid (1.23 mmoles) in 4ml acetone is heated to 50°C. The resulting almost clear solution is clarified via hot filtration through a Whatman glasfiber filter. The filter is rinsed with 4 ml acetone of 50°C.

20 A solution of 184 mg lysine (1.23 mmoles) in 1 ml water is added dropwise. The resulting thick suspension is kept for 30 min. at 50°C and then allowed to cool to room temperature. The mixture is further stirred at ca. 25°C over night and filtered. The filter cake is washed with 6 ml acetone. The crystals are dried first for 2 h at 50°C / ca. 10 mbar and then for 16 h at 80°C and ca. 10 mbar to yield a white powder, m.p. 162-163°C.

25 Water assay :3.80 % m/m

6f) choline 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetate monohydrate

- 5 A suspension of 400 mg 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetic acid (1.23 mmoles) in 4ml acetone is heated to 50°C. 305 mg choline solution 50% in water (1.23 mmoles) are added. The resulting almost clear solution is clarified via hot filtration through a Whatman glasfiber filter. The filter is rinsed with 2 ml acetone of 50°C. 6 ml tert. Butyl methyl ether (TBME) are slowly added at 40°C to the filtrate. The slightly cloudy solution is allowed
- 10 to cool and seeded at 25°C. Crystallization takes then very slowly place. The mixture is stirred over night at r.t. After 16h, 12 ml additional TBME are added dropwise. The thick suspension is stirred further for 2 h at 25°C and filtered.
- The solid is washed with 6 ml TBME/acetone 9/1 v/v and dried for 4 h at 50°C and ca 10 mbar to yield a white powder, m.p. 105-106°C.
- 15 Water assay :4.55 % m/m

6g) Potassium 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetate

- A suspension of 5-Methyl-2-(2',4'-dichloro -3'-methylanilino)phenylacetic acid (15.42 mmoles) in acetone is heated to reflux temperature and allow to stir for 10 min at ca. 55°C.
- 20 The resulting solution is slightly cooled to 50 °C and filtered hot over Whatman glasfiber filter. The filter is washed with acetone at 50°C. The filtrate is heated to 50°C and a mixture of potassium hydroxide 45% (14.65 mmoles) (0.95 eq.) and water is dropwise added over ca. 15 min. The dropping funnel is rinsed with water and acetone. The resulting suspension is stirred at 50°C for 30 min. The slurry is then allowed to cool to 25°C over ca. 2hours. The
- 25 suspension is stirred over night at room temperature and filtered. The filter cake is washed in three portions. The crystals are dried first for 3 h at 50°C / 10 mbar and then further for 17 h at 80°C / 10 mbar to yield a white powder, m.p. 315-317°C., 326.9°C, melting enthalpy 29 J/g.

Principial X-ray diffraction peaks:

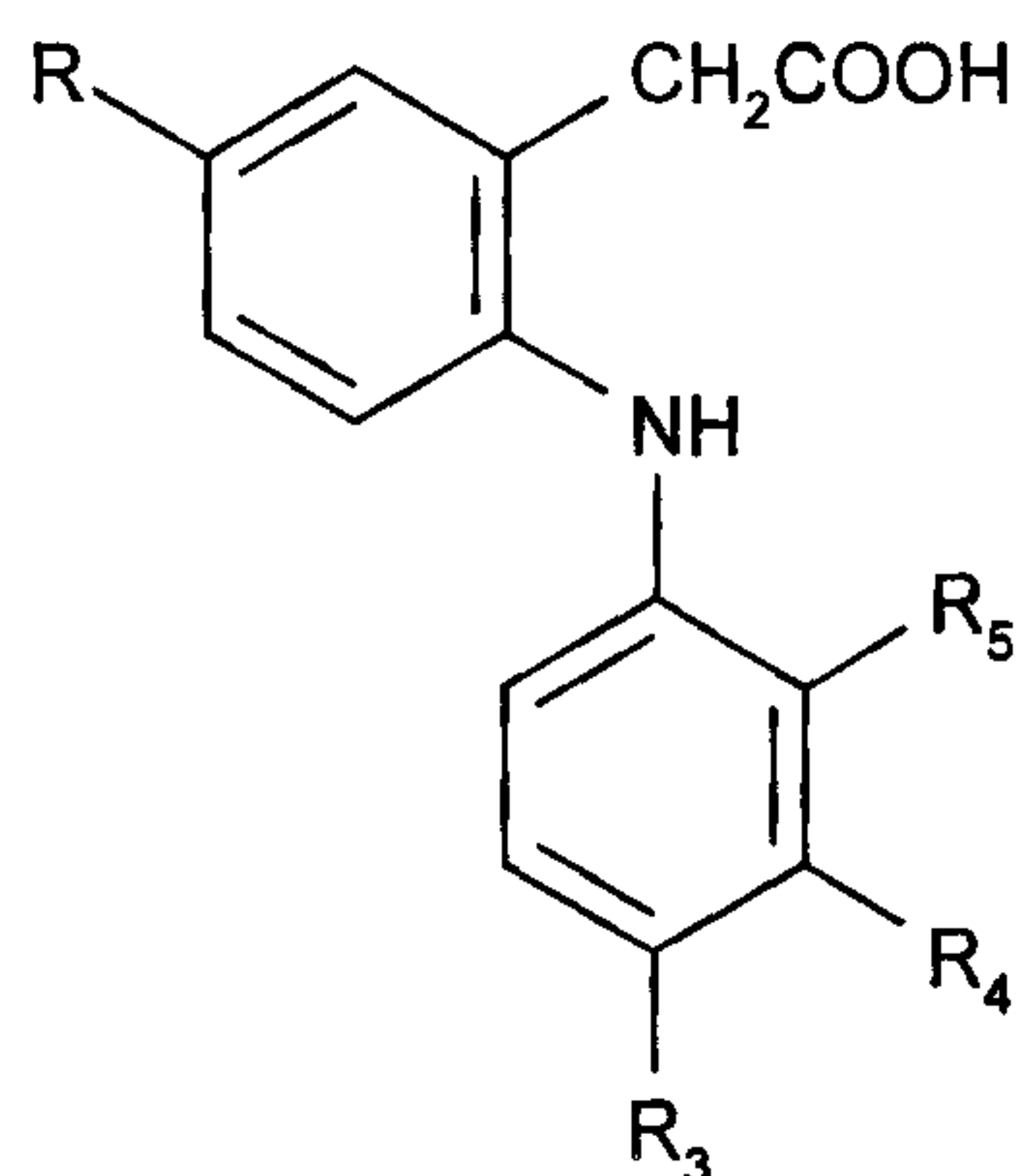
Angle 2-Theta °	d value Angstrom	Intensity %
6.263	14.10146	100
10.932	8.08664	38.2
12.602	7.01831	24.7
13.614	6.49915	25.2

14.689	6.02592	22.6
16.669	5.31402	26.9
18.904	4.69055	31.7
21.442	4.14078	14.9
21.958	4.04458	17.3
22.829	3.89219	15.7
24.24	3.66874	22.6
25.114	3.40963	25.8
26.698	3.33632	36.4
26.988	3.30112	19.8
28.026	3.1812	33.1
29.173	3.05867	13.8

21489-11042

CLAIMS:

1. A compound of formula (I):



(I),

- 5 or a pharmaceutically acceptable salt or ester thereof,

wherein:

R is methyl or ethyl;

R₃ is halo;

R₄ is C₁-C₆ alkyl; and

- 10 R₅ is halo;

the above mentioned C₁-C₆ alkyl at R₄ being optionally substituted by one or more halo groups.

2. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, wherein R₄ is methyl or ethyl.

- 15 3. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt or ester thereof, wherein R₃ and R₅ are each independently chloro or fluoro.

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4. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is 5-methyl-2-(2',4'-dichloro-3'-methylanilino)phenylacetic acid.
5. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is 5-ethyl-2-(2',4'-dichloro-3'-methylanilino)phenylacetic acid.
- 5 6. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is 5-methyl-2-(2'-fluoro-3'-trifluoromethyl-4'-ethylanilino)phenylacetic acid.
7. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is 5-ethyl-2-(2'-fluoro-3'-trifluoromethyl-4'-ethylanilino)phenylacetic acid.
10
8. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is 5-methyl-2-(2'-fluoro-3'-trifluoromethyl-4'-methylanilino)phenylacetic acid.
9. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is 5-ethyl-2-(2'-fluoro-3'-trifluoromethyl-4'-methylanilino)phenylacetic acid.
15
10. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is 5-methyl-2-(2'-fluoro-3'-methyl-4'chloroanilino)phenylacetic acid.
- 20 11. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is 5-ethyl-2-(2'-fluoro-3'-methyl-4'chloroanilino)phenylacetic acid.
12. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is 5-methyl-2-(2'-fluoro-3'-ethyl-4'chloroanilino)phenylacetic acid.
25

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13. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is 5-ethyl-2-(2'-fluoro-3'-ethyl-4'chloroanilino)phenylacetic acid.

14. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is 5-methyl-2-(2',4'-dichloro-3'-ethylanilino)phenylacetic acid.

5 15. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is 5-ethyl-2-(2',4'-dichloro-3'-ethylanilino)phenylacetic acid.

16. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is 5-ethyl-2-(2'-fluoro-3'-isopropyl-4'chloroanilino)phenylacetic acid.

10 17. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is 5-methyl-2-(2',4'-dichloro-3'-methylanilino)phenylacetic acid diethylamine salt.

18. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is sodium 5-methyl-2-(2',4'-dichloro-3'-
15 methylanilino)phenylacetate.

19. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is 5-methyl-2-(2',4'-dichloro-3'-methylanilino)phenylacetic acid tromethamine salt.

20. A compound according to claim 1, or a pharmaceutically acceptable salt
20 or ester thereof, which is calcium 5-methyl-2-(2',4'-dichloro-3'-methylanilino)phenylacetate monohydrate.

21. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is lysine 5-methyl-2-(2',4'-dichloro-3'-methylanilino)phenylacetate monohydrate.

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22. A compound according to claim 1, or a pharmaceutically acceptable salt or ester thereof, which is choline 5-methyl-2-(2',4'-dichloro-3'-methylanilino)phenylacetate monohydrate.

23. A compound according to any one of claims 1 to 22, or a
5 pharmaceutically acceptable salt or ester thereof, for use in the treatment of a COX-2 dependent disorder.

24. A compound according to any one of claims 1 to 22, or a pharmaceutically acceptable salt or ester thereof, for use in selectively inhibiting COX-2 activity without substantially inhibiting cyclooxygenase-1 activity.

10 25. A compound according to any one of claims 1 to 22, or a pharmaceutically acceptable salt or ester thereof, for use in treating rheumatoid arthritis, osteoarthritis, dysmenorrhea, pain, a tumor or inflammation.

26. A pharmaceutical composition comprising a compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt or ester thereof, in combination
15 with one or more pharmaceutically acceptable carriers.

27. The pharmaceutical composition according to claim 26 for use in treating a cyclooxygenase-2 (COX-2) dependent disorder.

28. The pharmaceutical composition according to claim 26 for use in selectively inhibiting COX-2 activity without substantially inhibiting cyclooxygenase-1
20 activity.

29. The pharmaceutical composition according to claim 26 for use in treating rheumatoid arthritis, osteoarthritis, dysmenorrhea, pain, a tumor or inflammation.

30. Use of a compound according to any one of claims 1 to 22, or a
25 pharmaceutically acceptable salt or ester thereof, in the manufacture of a medicament for treating a COX-2 dependent disorder.

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31. Use of a compound according to any one of claims 1 to 22, or a pharmaceutically acceptable salt or ester thereof, in the manufacture of a medicament for selectively inhibiting COX-2 activity without substantially inhibiting cyclooxygenase-1 activity.

5 32. Use of a compound according to any one of claims 1 to 22, or a pharmaceutically acceptable salt or ester thereof, in the manufacture of a medicament for the treatment of rheumatoid arthritis, osteoarthritis, dysmenorrhea, pain, tumors or inflammation.

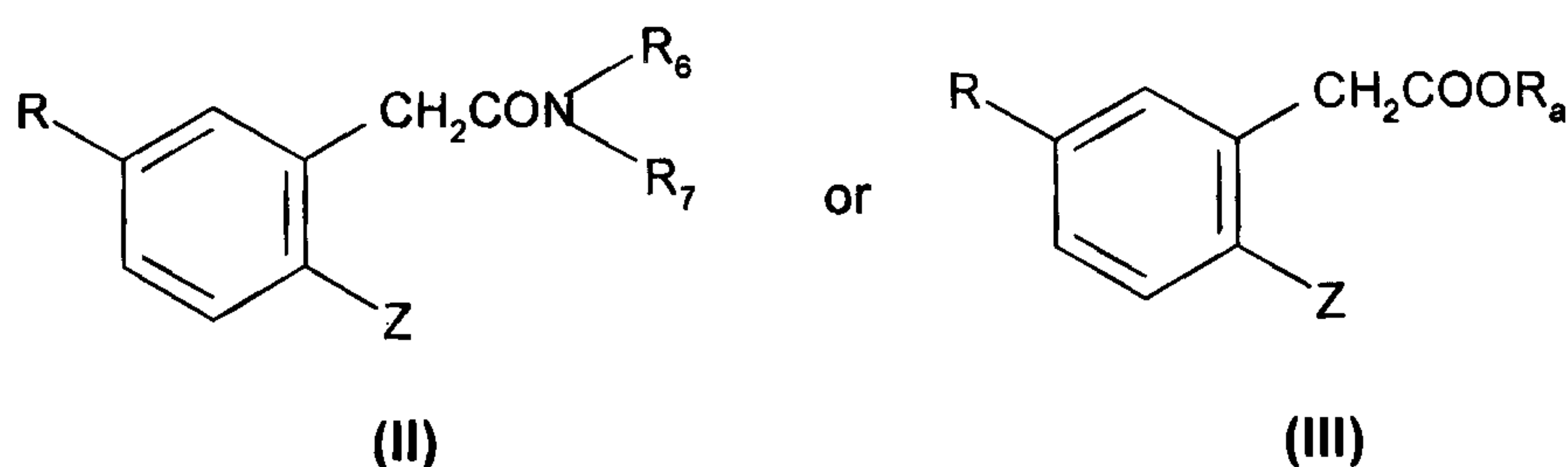
33. Use of a compound according to any one of claims 1 to 22, or a
10 pharmaceutically acceptable salt or ester thereof, for treating a COX-2 dependent disorder.

34. Use of a compound according to any one of claims 1 to 22, or a pharmaceutically acceptable salt or ester thereof, for selectively inhibiting COX-2 activity without substantially inhibiting cyclooxygenase-1 activity.

15 35. Use of a compound according to any one of claims 1 to 22, or a pharmaceutically acceptable salt or ester thereof, for the treatment of rheumatoid arthritis, osteoarthritis, dysmenorrhea, pain, tumors or inflammation.

36. A method for the preparation of a compound of formula (I) of claim 1 which comprises the step of:

20 (a) coupling a compound of formula (II) or (III)



wherein

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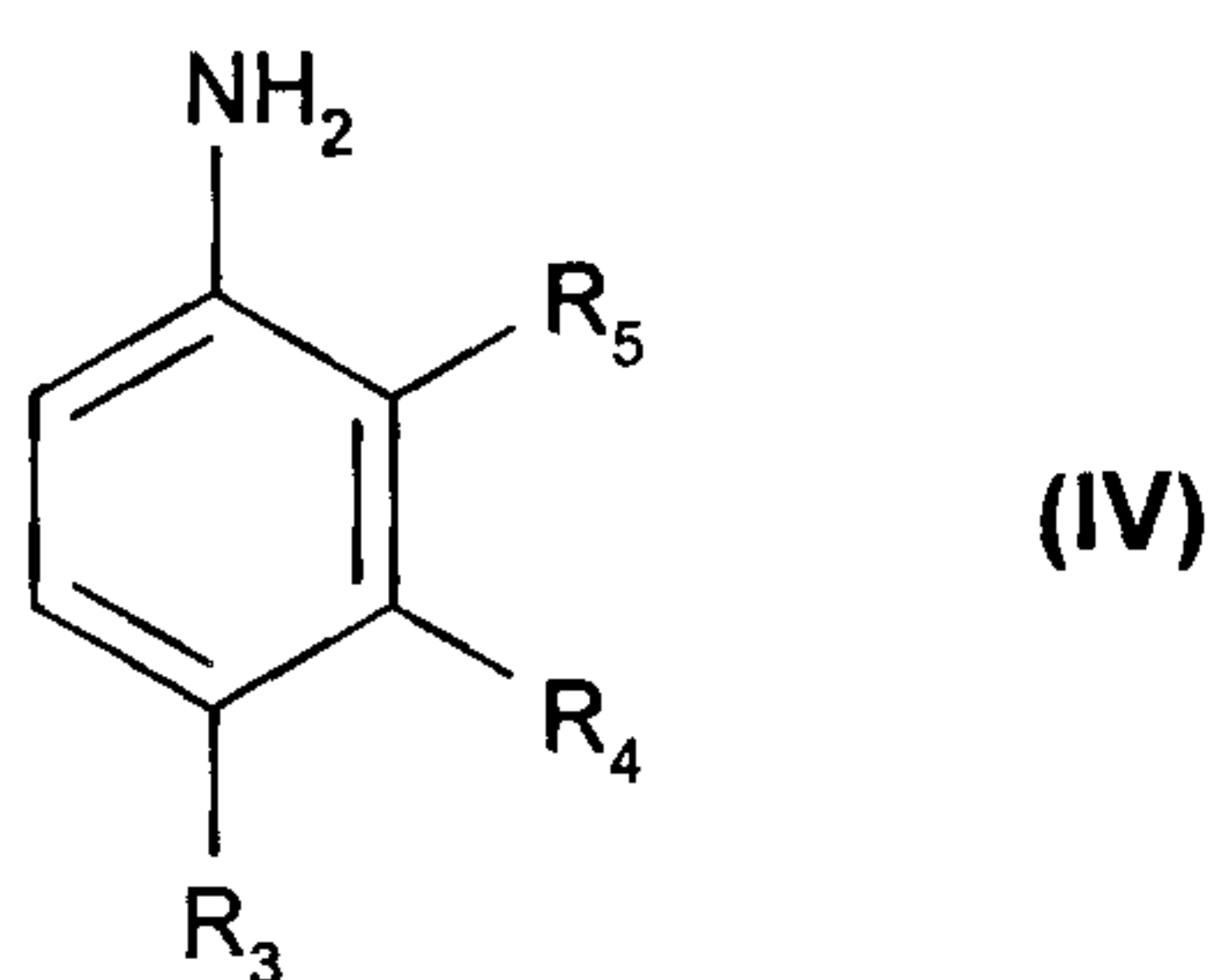
Z is bromo or iodo;

R has meaning as defined above;

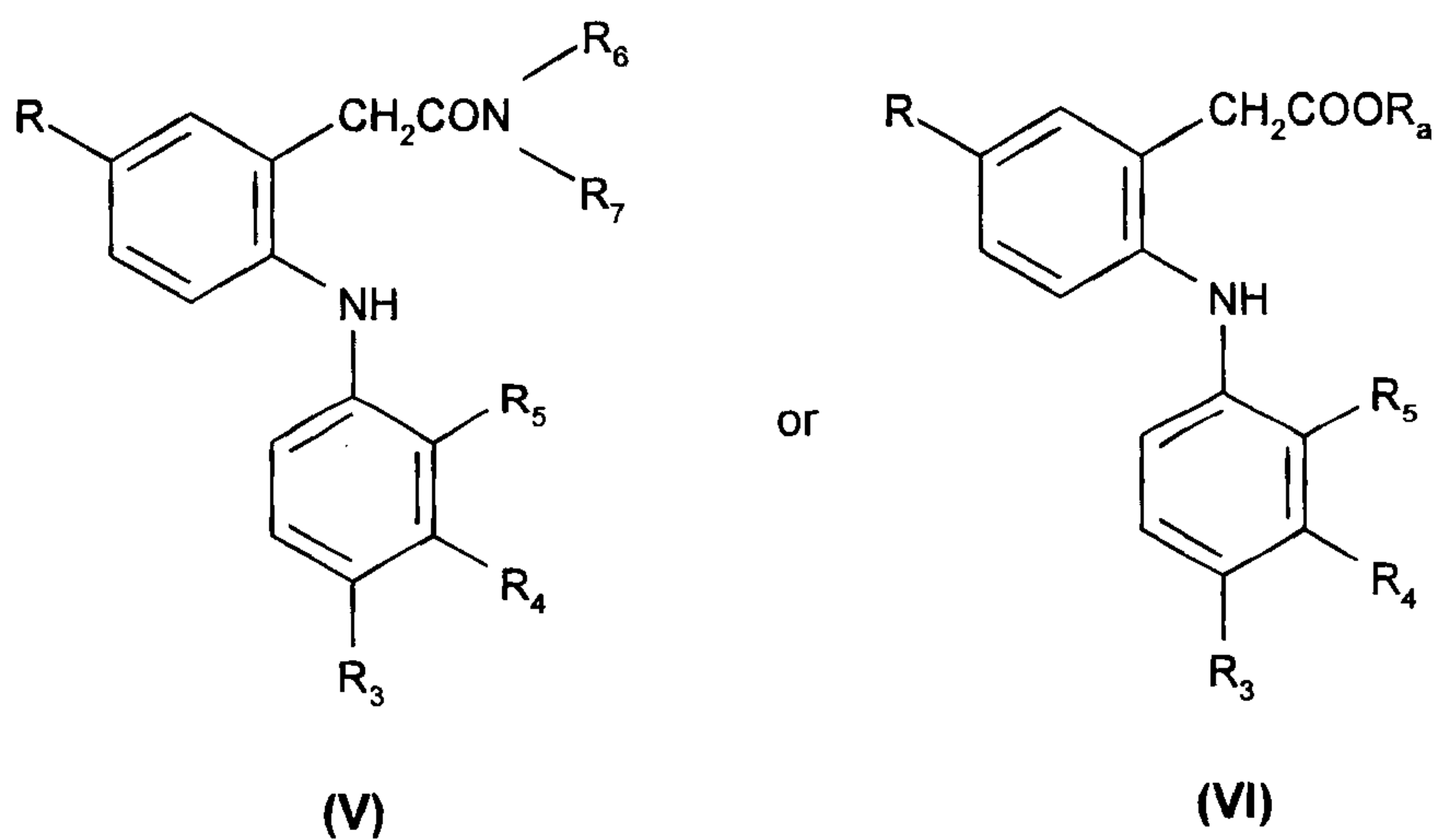
R_a is hydrogen, an alkali metal cation or lower alkyl; and

5 R₆ and R₇ are lower alkyl; or R₆ and R₇, together with the nitrogen atom, represent morpholino, piperidino or pyrrolidino;

with a compound of formula (IV)



wherein R₃-R₅ have meaning as defined above in the presence of copper and cuprous iodide to obtain a compound of formula (V) or (VI)

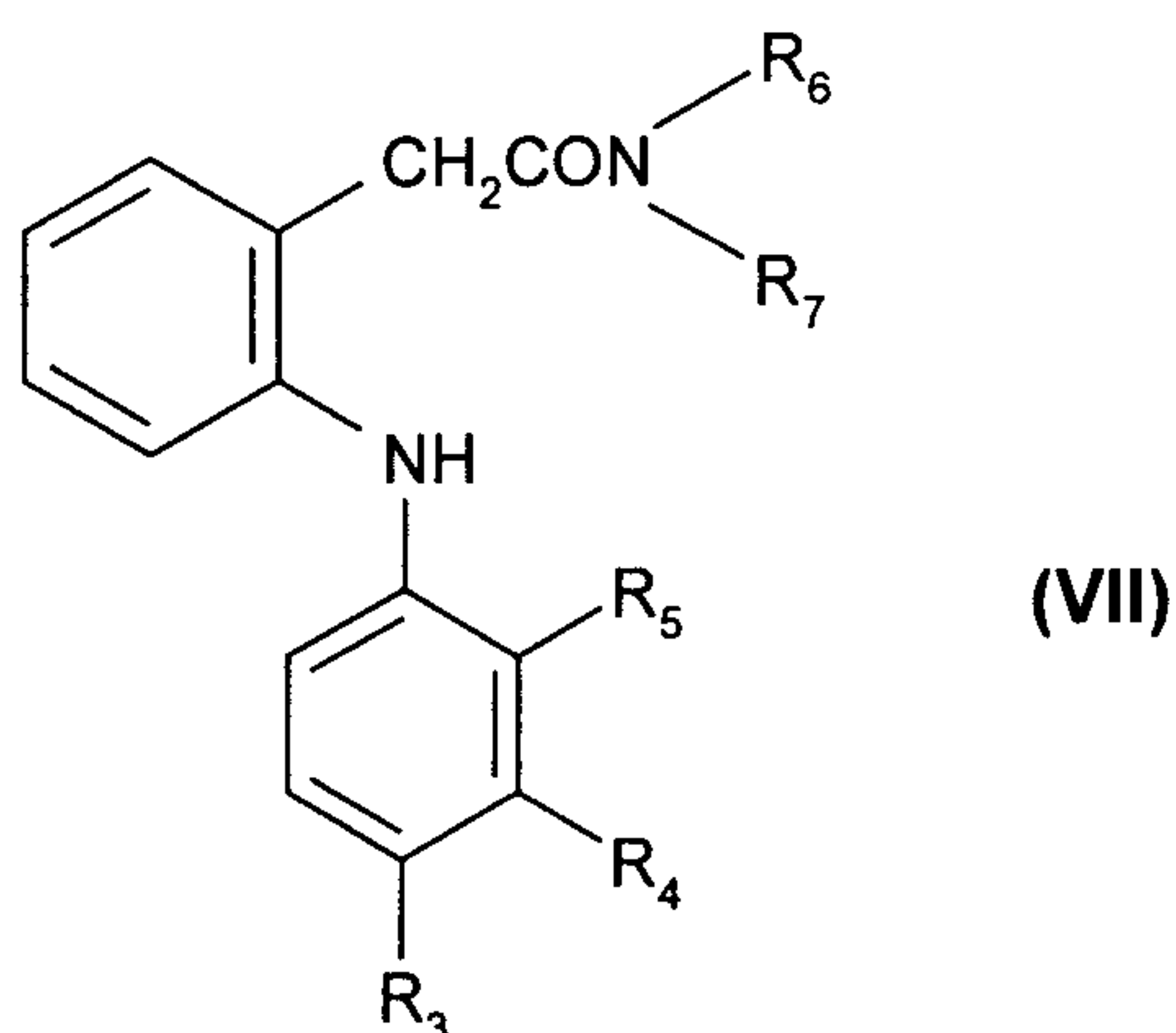


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and hydrolyzing the resulting compound of formula (V) or (VI) to a compound of formula (I); or

(b) condensing a compound of formula (VII)

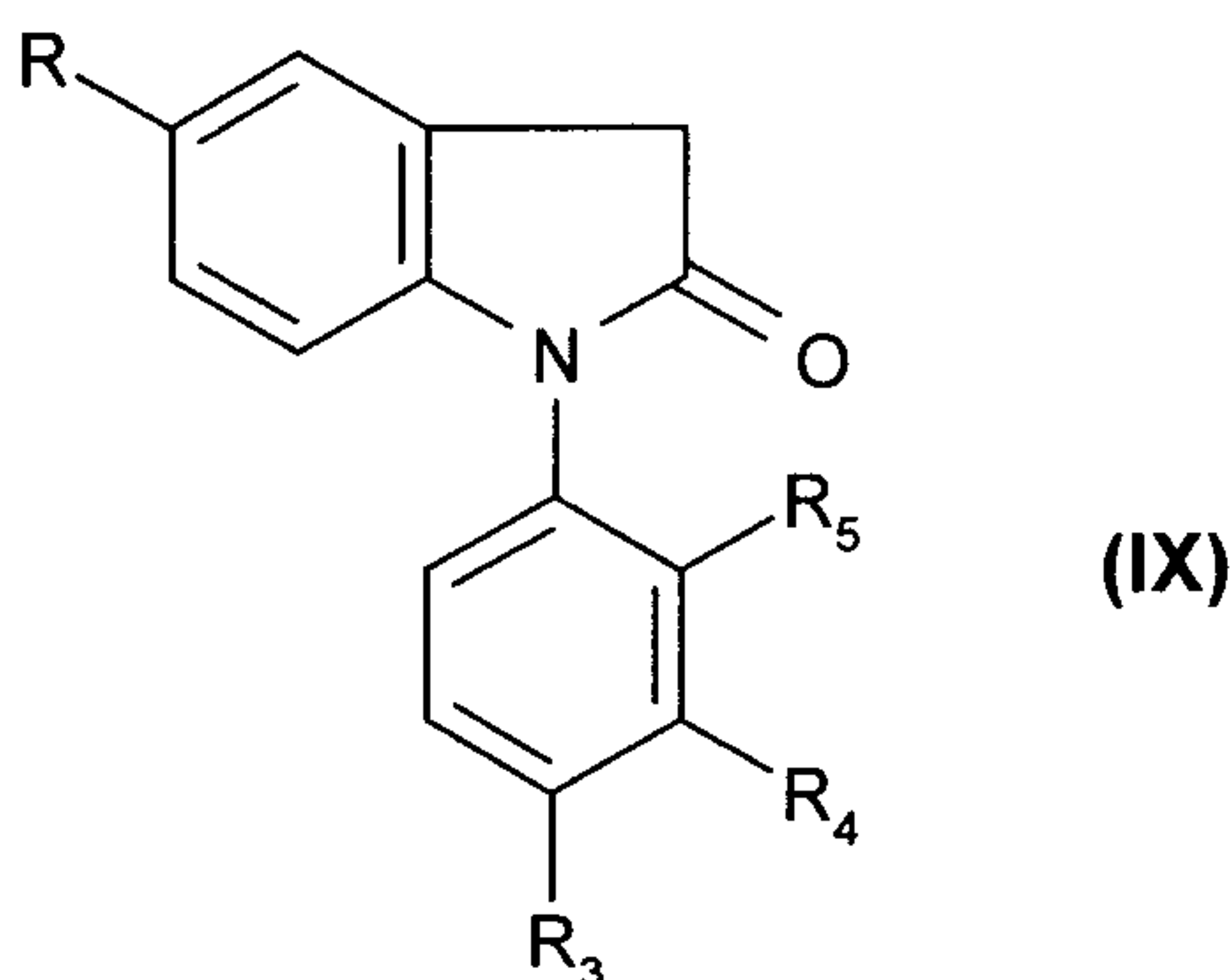
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wherein R_3 - R_7 have meaning as defined herein, with a reactive functional derivative of an acid, in a Friedel-Crafts acylation,

which is in turn hydrogenolyzed and then hydrolyzed to obtain a compound of formula (I); or

(c) hydrolyzing a lactam of formula (IX)



wherein R and R_3 - R_5 have meaning as defined herein, with a strong base; and in above processes, if desired, temporarily protecting any interfering reactive groups and then isolating the resulting compound of formula (I); and, if desired, converting any resulting compound of formula (I) into another compound of formula (I); and/or if desired converting a free carboxylic acid into a pharmaceutically acceptable ester derivative thereof; and/or if desired, converting a resulting free acid into a salt or a resulting salt into the free acid or into another salt.

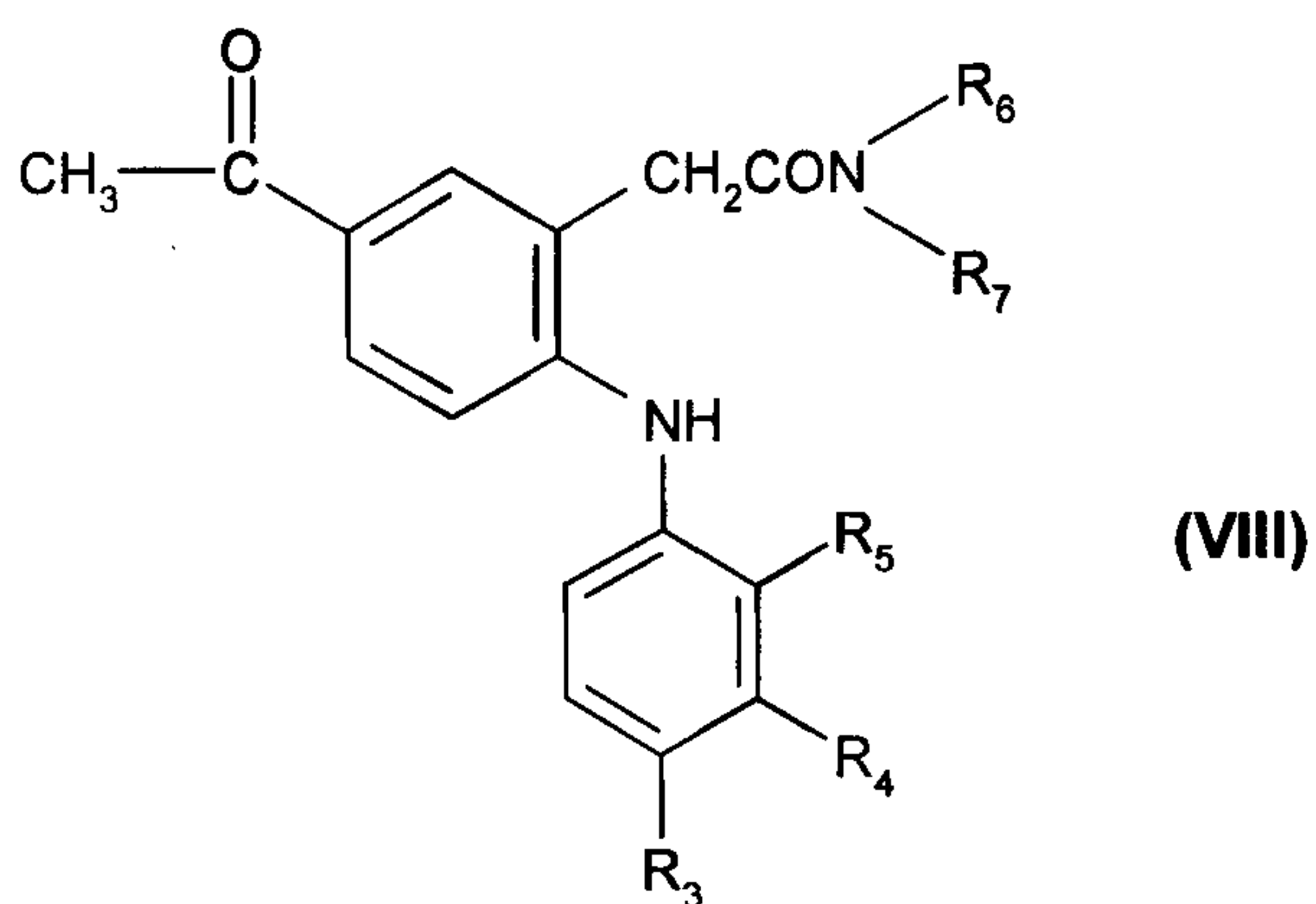
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37. The method according to claim 36, wherein the lower alkyl of R_a in (a) is isopropyl.

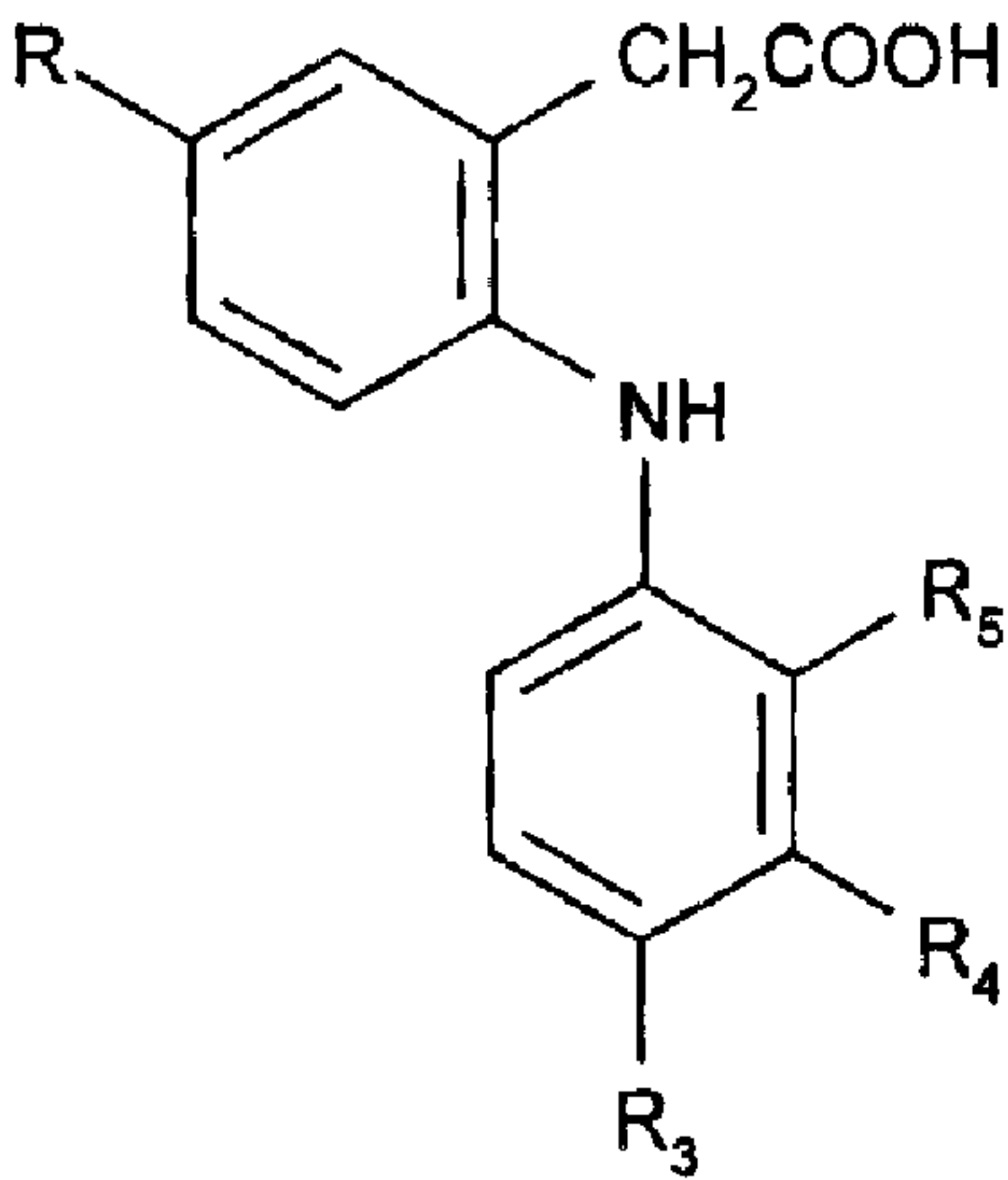
38. The method according to claim 36, wherein the acid in (b) is acetic acid.

39. The method according to claim 36, wherein the reactive functional
5 derivative of an acid in (b) is acetyl chloride.

40. The method according to claim 38 or 39, wherein the Friedel-Crafts acylation results in a compound of the formula (VIII)



wherein R_3 - R_7 have meaning as defined herein.



(I)