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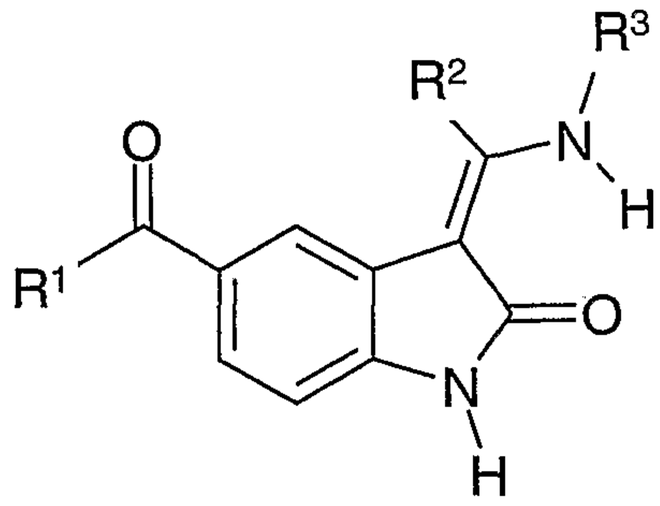
(54) Titre : NOUVELLES 5-ACYLINDOLINONES CONTENANT ARYLE, LEUR PRODUCTION ET LEUR UTILISATION EN TANT QUE MEDICAMENT

(54) Title: NOVEL ARYL-CONTAINING 5-ACYLINDOLINONES, THE PRODUCTION THEREOF AND THEIR USE AS MEDICAMENTS

(I)



(57) Abrégé/Abstract:
The invention relates to aryl-containing 5-acylindolinones of general formula (I) in which R^1 to R^3 are defined as in Claims 1 to 7, the tautomers, enantiomers, diastereomers, mixtures and salts thereof, all of which having valuable pharmacological properties, particularly an inhibitory effect upon protein kinases, particularly an inhibitory effect upon the activity of glycogen synthase kinase (GSK-3).

ABSTRACT

The invention relates to aryl-containing 5-acylindolinones of general formula (I) in which R^1 to R^3 are defined as in Claims 1 to 7, the tautomers, enantiomers, diastereomers, mixtures and salts thereof, all of which having valuable pharmacological properties, particularly an inhibitory effect upon protein kinases, particularly an inhibitory effect upon the activity of glycogen synthase kinase (GSK-3).

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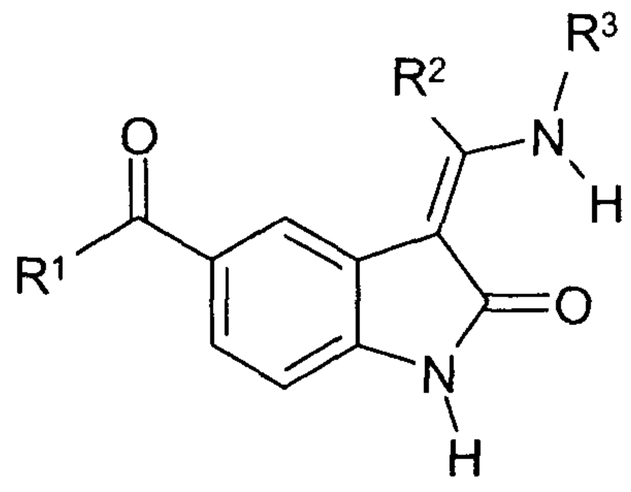
Novel aryl-containing 5-acylindolinones, the production thereof and their use as medicaments

The present invention relates to new aryl-containing 5-acylindolinones of general formula



(I),

the tautomers, the enantiomers, the diastereomers, the mixtures thereof and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases, which have valuable pharmacological properties, for example an inhibiting effect on protein kinases, particularly an inhibiting effect on the activity of glycogen-synthase-kinase (GSK-3), the preparation thereof, the use thereof for the prevention or treatment of diseases or conditions associated with an altered GSK-3 activity, particularly type I and type II diabetes mellitus, diabetes associated disorders such as diabetic neuropathy, degenerative neurological diseases such as Alzheimer's disease, stroke, neurotraumatic injuries, bipolar disorders, pharmaceutical compositions containing a compound of general formula (I) or a physiologically acceptable salt thereof and processes for the preparation thereof.

In the above formula I

R^1 denotes a straight-chain or branched C_{1-5}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or

an aryl group optionally substituted by a fluorine, chlorine or bromine atom,

while by an aryl group is meant a phenyl or naphthyl group,

R^2 denotes a C_{1-7}-alkyl or C_{3-7}-cycloalkyl group,

a 5- or 6-membered heteroaryl group with one to three heteroatoms selected from the group N, S and O, optionally substituted by one or two fluorine, chlorine, bromine or iodine atoms or one or two nitro, cyano, amino, C_{1-3}-alkyl or C_{1-3}-alkoxy groups, while both the heteratoms and the substituents may be identical or different,

a phenyl group wherein two adjacent carbon atoms are linked together through a methylenedioxy, ethylenedioxy or difluoromethylenedioxy group,

a phenyl group, to which another phenyl ring or a 5- or 6-membered heteroaromatic ring with one to three heteroatoms selected from the group N, S and O, while the heteratoms may be identical or different, is anellated, and while the bicyclic group may be substituted by one or two fluorine, chlorine, bromine or iodine atoms or one or two nitro, cyano, amino, C_{1-3}-alkyl or C_{1-3}-alkoxy groups and the substituents may be identical or different,

or

a phenyl group which may be substituted by one to three fluorine, chlorine, bromine or iodine atoms or by one to three C_{1-3}-alkyl, nitro, cyano, amino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkyl-carbonylamino, phenylcarbonylamino, C_{1-3}-alkylsulphonylamino, arylsulphonylamino, trifluoromethyl, C_{1-3} alkylsulphonyl, carboxy, C_{1-3}-alkoxy, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyloxy, C_{1-3}-alkoxy-carbonyl, C_{1-3}-alkylaminocarbonyl, hydroxy-carbonyl-C_{1-3}-alkyl-aminocarbonyl, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-amino-carbonyl-C_{1-3}-alkoxy, C_{1-3}-alkyl-amino-carbonyl-C_{1-3}-alkoxy, carboxy-C_{1-3}-alkoxy, C_{1-3}-alkyloxy-carbonyl-C_{1-3}-alkoxy, carboxy-C_{1-3}-alkyl, C_{1-3}-alkoxy-carbonyl-C_{1-3}-alkyl, C_{1-3}-alkoxy-carbonylamino-C_{1-3}-alkyl, amino-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl, C_{1-3}-alkyl-

carbonylamino-C_{1-3}-alkyl, phthalimido, pyrrolyl or mono- or di-(C_{1-3}-alkyl)-pyrrolyl groups, while the substituents are identical or different, and

R^3 denotes a phenyl, naphthyl or heteroaryl group as hereinbefore defined which may be mono-, di- or trisubstituted

by a fluorine, chlorine, bromine or iodine atom,

by a cyano, hydroxy, carboxy, C_{1-3}-alkoxy, C_{1-3}-alkoxycarbonyl or di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkoxy group,

by a C_{1-3}-alkyl group which may be substituted by a hydroxycarbonyl, C_{1-3}-alkoxy-carbonyl or heteroaryl) group,

by a C_{1-3}-alkyl group which is substituted by a 3- to 7-membered cyclcoalkyleneimino group, while a benzene ring may be fused to the cyclo-alkyleneimino group via two adjacent carbon atoms,

by an amino-C_{1-3}-alkyl group which may be substituted at the nitrogen atom by one or two C_{1-3}-alkyl, phenyl-C_{1-3}-alkyl or C_{1-4}-alkoxy-carbonyl groups, while the substituents are identical or different,

by a C_{1-3}-alkyl-carbonyl-amino group which may be substituted at the nitrogen atom by a C_{1-3}-alkyl group or a C_{2-3}-alkyl group terminally substituted by a di-(C_{1-3}-alkyl)-amino group and in the alkyl moiety by a di-(C_{1-3}-alkyl)-amino, piperazinyl or 4-(C_{1-3}-alkyl)-piperazin-1-yl group,

by a C_{2-3}-alkyl-aminocarbonyl group terminally substituted in the alkyl moiety by a di-(C_{1-3}-alkyl)-amino group which may additionally be substituted at the nitrogen atom by a C_{1-3}-alkyl group,

or by a heteroaryl group,

while the substituents may be identical or different,

while the above-mentioned alkyl groups may be straight-chain or branched,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

Unless otherwise stated, by a 5-membered heteroaryl group is preferably meant a furanyl, thiophenyl, pyrrolyl, pyrazolyl, thiazolyl, imidazolyl, oxazolyl, triazolyl or thiadiazolyl group, and by a 6-membered heteroaryl group is meant a pyridinyl, pyrimidinyl, pyridazinyl or pyrazinyl group.

By an aryl group is meant, unless otherwise stated, a phenyl or naphthyl group; the phenyl group is preferred.

Preferred compounds of general formula I are those wherein

R^2 and R^3 are as hereinbefore defined and

R^1 denotes a methyl, ethyl, n-propyl, isopropyl, n-pentyl, trifluoromethyl or phenyl group,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

Particularly preferred compounds of general formula I are those wherein

R^1 denotes a methyl, ethyl, n-propyl, isopropyl, n-pentyl or phenyl group,

R^2 denotes a C_{1-7}-alkyl group,

a phenyl group wherein two adjacent carbon atoms are linked together through a methylenedioxy, ethylenedioxy or difluoromethylenedioxy group, or

a phenyl group which may be substituted by one or two fluorine, chlorine, bromine or iodine atoms or by one or two C_{1-3}-alkyl, nitro, cyano, amino, C_{1-3}-alkylcarbonylamino, phenylcarbonylamino, C_{1-3}-alkylsulphonylamino, trifluoromethyl, carboxy, C_{1-3}-alkoxy, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyloxy, C_{1-3}-alkoxy-carbonyl, C_{1-3}-alkylaminocarbonyl, hydroxycarbonyl-C_{1-3}-alkyl-aminocarbonyl, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkylaminocarbonyl, carboxy-C_{1-3}-alkyl, C_{1-3}-alkoxy-carbonyl-C_{1-3}-alkyl, amino-C_{1-3}-alkyl or C_{1-3}-alkyl-carbonylamino-C_{1-3}-alkyl groups, while the substituents are identical or different, and

R^3 denotes a phenyl group which may be mono- or disubstituted

by a fluorine, chlorine or bromine atom,

by a cyano, hydroxy, carboxy, C_{1-3}-alkoxy, C_{1-3}-alkoxycarbonyl or di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkoxy group,

by a C_{1-3}-alkyl group which may be substituted by a hydroxycarbonyl, C_{1-3}-alkoxy-carbonyl or imidazolyl group,

by a C_{1-3}-alkyl group which is substituted by a 3- to 7-membered cyclcoalkyleneimino group, while a benzene ring may be fused to the cycloalkyleneimino group via two adjacent carbon atoms,

by an amino-C_{1-3}-alkyl group which may be substituted at the nitrogen atom by one or two C_{1-3}-alkyl, benzyl or C_{1-4}-alkoxy-carbonyl groups, while the substituents are identical or different,

by a C_{1-3}-alkyl-carbonyl-amino group which may be substituted at the nitrogen atom by a C_{1-3}-alkyl group or a C_{2-3}-alkyl group terminally substituted by a di-(C_{1-3}-alkyl)-amino group and in the alkyl moiety by a di-(C_{1-3}-alkyl)-amino, piperazinyl or 4-(C_{1-3}-alkyl)-piperazin-1-yl group,

by a C_{2-3}-alkyl-aminocarbonyl group terminally substituted in the alkyl moiety by a di-(C_{1-3}-alkyl)-amino group which may additionally be substituted at the nitrogen atom by a C_{1-3}-alkyl group,

or by an imidazolyl group

while the substituents may be identical or different,

but particularly those compounds wherein

R^1 denotes a methyl group,

R^2 denotes an ethyl, propyl, butyl or pentyl group,

a phenyl group wherein two adjacent carbon atoms are linked together through a methylenedioxy, ethylenedioxy or difluoromethylenedioxy group, or

a phenyl group which may be substituted by one or two fluorine, chlorine, bromine atoms or by one or two C_{1-3}-alkyl, cyano, C_{1-3}-alkoxy, carboxy-C_{1-3}-alkyl, C_{1-3}-alkoxy-carbonyl-C_{1-3}-alkyl, amino-C_{1-3}-alkyl or C_{1-3}-alkyl-carbonylamino-C_{1-3}-alkyl groups, while the substituents are identical or different, and

R^3 denotes a phenyl group which may be monosubstituted

by a fluorine, chlorine or bromine atom,

by a cyano, carboxy, C_{1-3}-alkoxy or C_{1-3}-alkoxycarbonyl group,

by a C_{1-3}-alkyl group which may be substituted by a hydroxycarbonyl or C_{1-3}-alkoxy-carbonyl group,

by a C_{1-3}-alkyl group which is substituted by a 3- to 7-membered cyclcoalkyleneimino group,

by an amino-C_{1-3}-alkyl group which may be substituted at the nitrogen atom by one or two C_{1-3}-alkyl or C_{1-4}-alkoxy-carbonyl groups, while the substituents are identical or different,

by a C_{1-3}-alkyl-carbonyl-amino group which may be substituted at the nitrogen atom by a C_{1-3}-alkyl group or a C_{2-3}-alkyl group terminally substituted by a di-(C_{1-3}-alkyl)-amino group and in the alkyl moiety by a di-(C_{1-3}-alkyl)-amino or 4-(methyl)-piperazin-1-yl group,

or by a C_{2-3}-alkyl-aminocarbonyl group terminally substituted in the alkyl moiety by a di-(C_{1-3}-alkyl)-amino group which may additionally be substituted at the nitrogen atom by a C_{1-3}-alkyl group,

or may be disubstituted by a hydroxy and a di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl group, while the substituents may be identical or different,

while the above-mentioned alkyl groups may be straight-chain or branched,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

Most particularly preferred compounds of general formula I are those wherein

R^1 denotes a methyl group,

R^2 denotes a phenyl group wherein two adjacent carbon atoms are linked together through a methylenedioxy or ethylenedioxy group, or

a phenyl group which may be substituted by one or two methoxy groups, and

R^3 denotes a phenyl group which is substituted

by a cyano group or

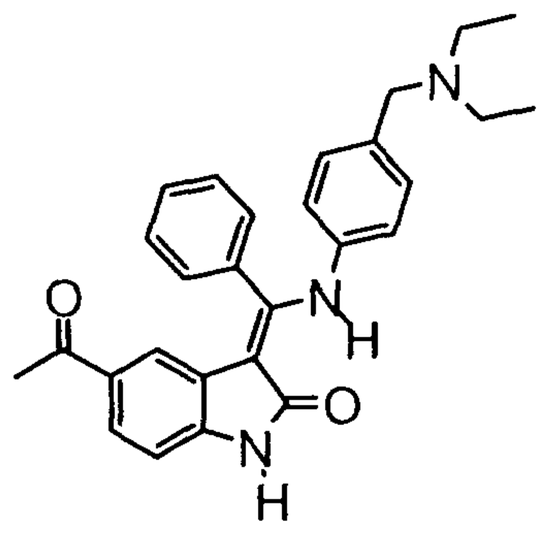
by an amino-C_{1-3}-alkyl group which may be substituted at the nitrogen atom by one or two C_{1-3}-alkyl groups, while the substituents may be identical or different,

while the above-mentioned alkyl groups may be straight-chain or branched,

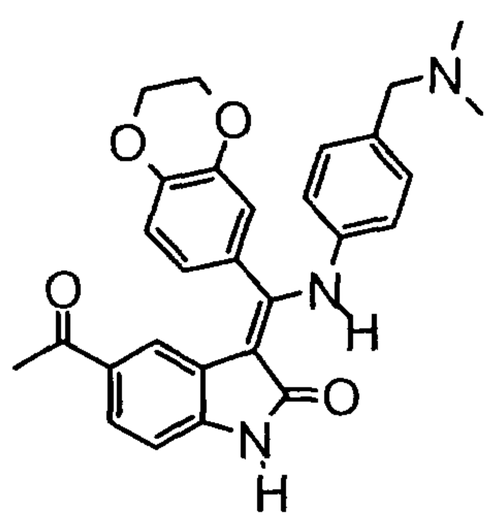
the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof;

particular mention should be made of the following compounds of general formula I:

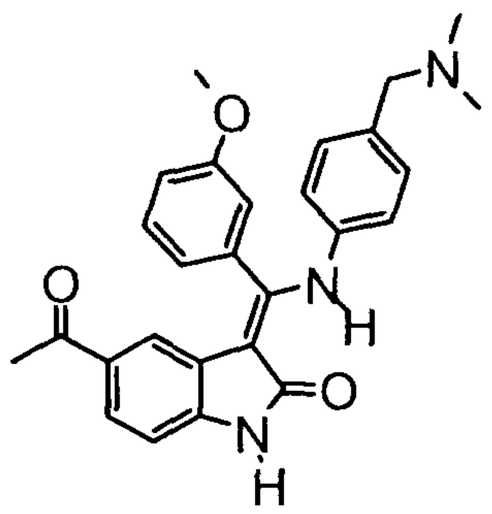
(a) 5-acetyl-3-{[4-(diethylaminomethyl)-phenylamino]-phenyl-methylidene}-2-indolinone



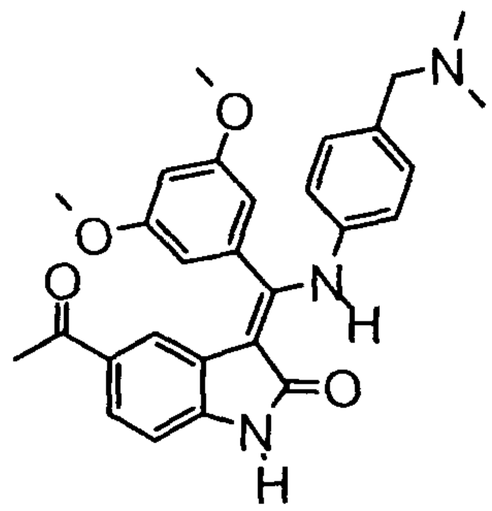
(b) 5-acetyl-3-{[4-(dimethylamino-methyl)-phenylamino]-(2,3-dihydro-benzo[1,4]-dioxin-6-yl)-methylidene}-2-indolinone



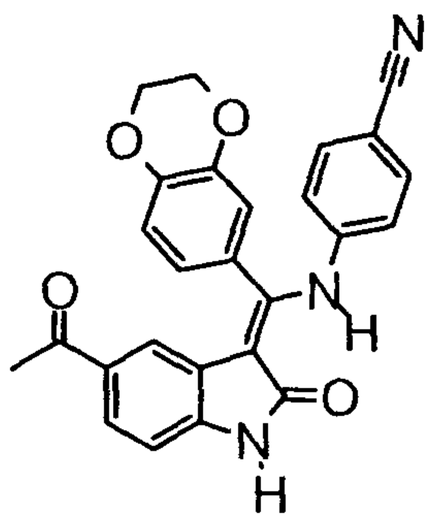
(c) 5-acetyl-3-{[4-(dimethylaminomethyl)-phenylamino]-(3-methoxy-phenyl)-methylidene}-2-indolinone



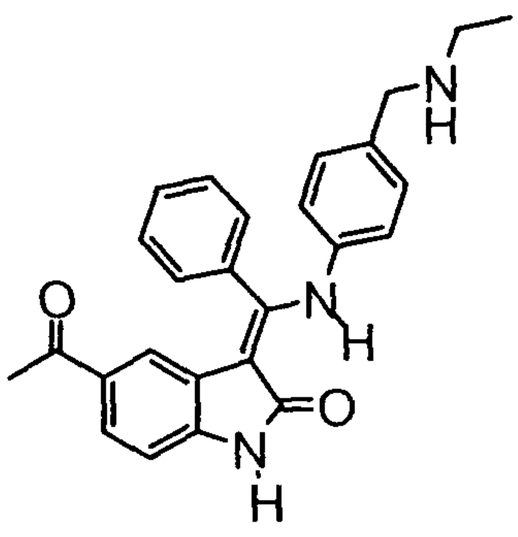
(d) 5-acetyl-3-{[4-(dimethylaminomethyl)-phenylamino]-(3,5-dimethoxy-phenyl)-methylidene}-2-indolinone



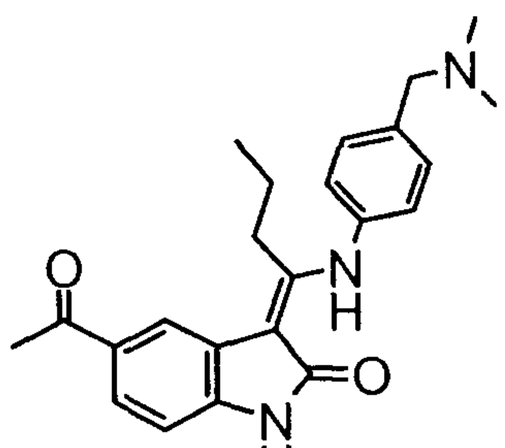
(e) 5-acetyl-3-[(4-cyano-phenylamino)-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-methylidene]-2-indolinone



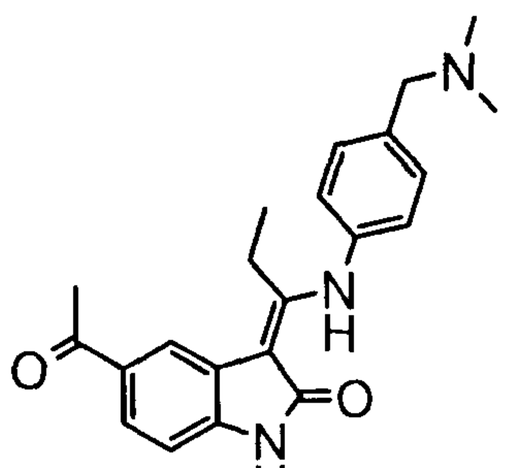
(f) 5-acetyl-3-{[4-(ethylaminomethyl)-phenylamino]-phenyl-methylidene}-2-indolinone



(g) 5-acetyl-3-[1-(4-(dimethylaminomethyl)-phenylamino)-butylidene)-2-indolinone



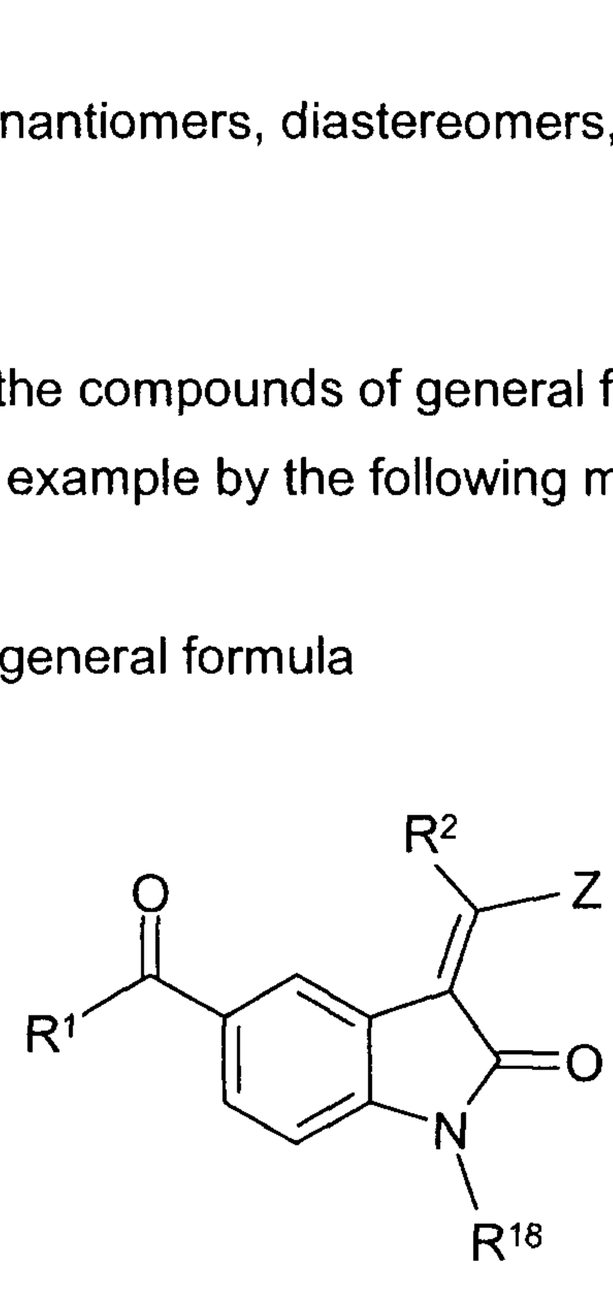
(h) 5-acetyl-3-[1-(4-(dimethylaminomethyl)-phenylamino)-propylidene)-2-indolinone



as well as the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

According to the invention the compounds of general formula I are obtained by methods known *per se*, for example by the following methods:

a) reacting a compound of general formula



(II),

wherein R^1 and R^2 are as hereinbefore defined,

R^{18} denotes a hydrogen atom or a protective group for the nitrogen atom of the lactam group and

Z denotes a leaving group such as e.g. a halogen atom, a hydroxy, alkoxy, alkylsulphonyl, alkyl-arylsulphonyl, trialkylsilyloxy or aryl-alkoxy group, e.g. a chlorine or bromine atom, a methoxy, ethoxy, methanesulphonyl, toluenesulphonyl, trimethylsilyloxy or benzyloxy group,

with an amine of general formula

$$R^3\text{-}NH_2 \qquad (III),$$

wherein R^3 is as hereinbefore defined,

while any hydroxy, amino or imino groups optionally contained in the groups R^2 and/or R^3 may be temporarily protected by suitable protective groups;

and if necessary subsequently cleaving any protective group used for the nitrogen atom of the lactam or imino group.

A protective group for the nitrogen atom of the lactam group may be for example an acetyl, benzoyl, ethoxycarbonyl, tert.butyloxycarbonyl or benzyloxycarbonyl group and

The reaction is expediently carried out in a solvent such as dimethylformamide, toluene, acetonitrile, tetrahydrofuran, dimethylsulphoxide, methylene chloride or mixtures thereof, optionally in the presence of an inert base such as triethylamine, N-ethyl-diisopropylamine or sodium hydrogen carbonate at temperatures between 20 and 175°C, while any protective group used may simultaneously be cleaved.

If Z in a compound of general formula II denotes a halogen atom, then the reaction is preferably carried out in the presence of an inert base at temperatures between 20 and 120°C.

If Z in a compound of general formula II denotes a hydroxy, alkoxy or arylalkoxy group, then the reaction is preferably carried out at temperatures between 20 and 200°C.

If any protecting group used subsequently has to be cleaved, this is conveniently carried out either hydrolytically in an aqueous or alcoholic solvent, e.g. in methanol/water, ethanol/water, isopropanol/water, tetrahydrofuran/water, dioxane/water, dimethylformamide/water, methanol or ethanol in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide, at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C,

or advantageously by transamidation with an organic base such as ammonia, butylamine, dimethylamine or piperidine in a solvent such as methanol, ethanol, dimethylformamide and mixtures thereof or in an excess of the amine used at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C.

b) in order to prepare a compound of formula I which contains an aminocarbonyl group: reacting a compound which contains a carboxy group with the corresponding amine to produce the corresponding aminocarbonyl compound;

c) in order to prepare a compound of formula I which contains a carbonylamino group: reacting a compound which contains an amino group with the corresponding acid chloride to produce the carbonylamino compound;

d) in order to prepare a compound of formula I which contains an aminomethyl group: hydrogenating a compound which contains a cyano group to produce the corresponding aminomethyl derivative;

e) in order to prepare a compound of formula I which contains an amino group: reducing a compound which contains a nitro group.

Then any protective groups optionally used during the reaction may be cleaved and/or

the compounds of general formula I thus obtained may be resolved into their enantiomers and/or diastereomers and/or

the compounds of formula I obtained may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts thereof with inorganic or organic acids or bases.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the cis/trans mixtures obtained may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically

active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+) or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)-or (-)-menthyloxycarbonyl.

Furthermore, the compounds of formula I may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulphonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Moreover, if the new compounds of formula I contain a carboxy group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The compounds of general formulae II to III used as starting materials are either known from the literature or may be obtained by methods known from the literature (cf. Examples I to VII).

As already mentioned hereinbefore, the compounds according to the invention of general formula I and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly an inhibiting effect on the enzyme GSK-3.

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine kinase which exists in two isoforms, GSK-3α and GSK-3β. GSK-3 phosphorylates and inactivates not only glycogen synthase, a key enzyme of the insulin-dependent regulation of glycogen synthesis (Embi et al., Eur. J. Biochem. 107, 519-527, (1980)), but also a number of other regulatory proteins *in vitro*. These proteins include the microtubule associated protein Tau, elongation initiation factor 2b (eIF2b), β-catenin, axin, ATP-citratelyase, heat-shock-factor 1, c-jun, c-myc, c-myb, CREB and CEBPα. These different substrates imply a role for GSK-3 in numerous fields of cell metabolism, proliferation, differentiation and development.

Type 2 diabetes is characterised by insulin resistance in various tissues such as skeletal muscle, liver and fatty tissue and by altered secretion of insulin from the pancreas. The storage of glycogen in liver and muscle is of great importance for maintaining the glucose equilibrium. In type 2 diabetes the activity of glycogen synthase is reduced and thus the rate of glycogen synthesis is reduced. It has also been shown that GSK-3 is expressed to a greater extent in type 2 diabetic muscle and hence a reduced GSK-3 activity is associated with a reduced rate of glycogen synthesis (Nikoulina et al., diabetes 49, 263-271, (2000)). Inhibition of the GSK-3 activity stimulates glycogen synthase, thus intensifies glycogen synthesis and leads eventually to a reduction in the glucose levels. GSK-3 inhibition is therefore of therapeutic relevance for the treatment of type 1 and type 2 diabetes and also diabetic neuropathy.

Alzheimer's disease is characterised in that the microtubule-associated protein Tau is present in excessively strongly phosphorylated form (Cohen & Frame, Nature Reviews: Molecular Cell Biology, 2, 1-8, (2001)). GSK-3 phosphorylates many of these phosphorylations sites of Tau in vitro, thereby preventing binding to microtubules. As a result, Tau is available for increased filament assembly, which is at the root of Alzheimer's disease and other neurological diseases of neuronal degeneration. It has been shown that GSK-3 inhibitors such as insulin or lithium bring about partial dephosphorylation of Tau in neuronal cells (Cross et al., J. Neurochem.

77, 94-102 (2001)). GSK-3 inhibition may therefore be of therapeutic relevance for the treatment of degenerative neurological diseases such as Alzheimer's disease.

Inhibitors of GSK-3 activity may thus be of therapeutical and /or preventive benefit for a number of diseases where it is useful to inhibit GSK-3, such as diabetes and diabetes-associated diseases, chronic neurodegenerative diseases and dementias, such as Alzheimer's disease, Parkinson's syndrome, Pick`s disease, dementia in subcortical arteriosclerotic encephalopathy (SAE), Huntington's chorea, multiple sclerosis, infectious diseases (meningoencephalitis, syphilis, brain abscess, Creutzfeldt-Jakob disease, AIDS), dementia complex with Lewy bodies, neurotraumatic diseases such as acute stroke, schizophrenia, manic depression, brain haemorrhage, alopecia, obesity, atherosclerotic cardiovaskular diseases, high blood pressure, PCO syndrome, metabolic syndrome, ischaemia, cancer, leuko-penia, Down's syndrome, inflammations, immunodeficiency.

A new study (Sato, N. et al., Nature Medicine 10, 55-63 (2004)) shows that GSK-3 inhibitors may acquire the pluripotence of stem cells, which may open up new possibilities in the field of regenerative therapies using stem cells.

<u>Determining the GSK-3 activity</u>

The effect of substances on the GSK-3 activity was carried out according to the following test method, based on the phosphorylation of a 26mer peptide (YRRAAVPPSPSLSRHSSFHQpSEDEEE) from glycogen synthase, the sequence of which contains the phosphorylation sites for GSK-3 and the prephosphorylation of which is indicated by (pS).

The test substance is dissolved in DMSO/water. GSK3β (University of Dundee, UK) dissolved in 10 mM MOPS (morpholinopropanesulphonic acid), 0.05 mM EDTA, 0.005% Brij, 2.5 % glycerol, 0.05 % mercaptoethanol, pH 7.0, is combined with 10 µM [^{33}P]-ATP, 0.25 µM of 26mer peptide and incubated with the dissolved substance in 50 mM tris, 10 mM $MgCl_2$, 0.1 % mercaptoethanol, pH 7.5, at ambient temperature. The reaction was stopped by the addition of 75 mM phosphoric acid.

The reaction mixture was transferred onto Phosphocellulose filter plates (Millipore) and filtered to dryness and washed twice with 75 mM phosphoric acid. The phosphorylation was determined by measuring the radioactivity on the filter in a scintillation counter (Topcount, Packard). The ability of a substance to inhibit GSK-3 is determined by comparing the signal of a reaction mixture containing various concentrations of the substance with the signal of the reaction mixture without any substance. The IC_{50} values are calculated by non-linear regression analysis using GraphPad Prism software.

Typical IC_{50} values for the substances investigated were between 0.0001 µM and 1 µM.

Determining glycogen synthesis

This test serves to investigate the effect of test substances on glycogen synthesis in cells.

C3A hepatoma cells (ATCC) are seeded at a density of 100000 cells/ml in 96-well plates and grown to confluence as a monolayer in the medium. The medium is removed and the cells are washed several times with PBS and then incubated in KRBH buffer (134 mM NaCl, 3.5 mM KCl, 1.2 mM KH_2PO_4, 0.5 mM $MgSO_4$, 1.5 mM $CaCl_2$, 5 mM $NaHCO_3$, 10 mM HEPES, pH 7.4) with 0.1 % BSA and 0.5 mM glucose for 60 min at 37°C. Test substance and 0.2 µCi D-[$U^{14}C$]glucose (Amersham) are added and the cells are incubated for a further 60 min under the same conditions. After the removal of the incubation buffer the cells are washed several times with cold PBS and then lysed for 10 min at 37°C and 10 min at ambient temperature with 1 M NaOH. The cell lysates are transferred onto filter plates and the glycogen is precipitated by incubating for 2 h with cold ethanol (70%) on ice. The precipitates are washed several times with ethanol and filtered to dryness. The glycogen synthesised is determined by measuring the radioactivity (14C-glucose incorporated) on the filter plates in a scintillation counter (Topcount, Packard).

The ability of a substance to stimulate glycogen synthesis is determined by comparing the signal of a reaction mixture containing various concentrations of the substance with the signal of the reaction mixture without any substance.

Oral glucose tolerance test

Fasted db/db mice 7 to 9 weeks old (Janvier, France) are weighed and blood is taken from the tip of the tail. This blood is used for the first measurement of glucose on the basis of which the animals are randomised and divided into groups. The test substance to be tested may be given either orally or i.p. as a suspension in 0.5 % Natrosol. 30 minutes after the administration of the substance the animals are given orally 2 g/kg glucose in a volume of 0.1 ml/100 g body weight dissolved in NaCl solution. Subsequently, the glucose values are determined from the tail blood using a glucometer (Ultra OneTouch, Lifescan) at specific time intervals [30, 60, 120 and 180 minutes after oral administration of the glucose].
For example, compound 1.051 exhibits a significant activity in the oral glucose tolerance test.

The compounds prepared according to the invention are well tolerated as, for example, after oral administration of 10 mg/kg of the compound of Example 1.051 to mice no changes were observed in the animals' behaviour.

The compounds according to the invention may also be used in combination with other active substances. Therapeutic agents which are suitable for such a combination include, for example, antidiabetic agents such as metformin, sulphonylureas (e.g. glibenclamide, tolbutamide, glimepiride), nateglinide, repaglinide, thiazolidinediones (e.g. rosiglitazone, pioglitazone), PPAR-gamma-agonists (e.g. GI 262570) and antagonists, PPAR-gamma/alpha modulators (e.g. KRP 297), alpha-glucosidase inhibitors (e.g. acarbose, voglibose), DPP-IV inhibitors, alpha2-antagonists, insulin and insulin analogues, GLP-1 and GLP-1 analogues (e.g. exendin-4) or amylin. The list also includes SGLT2-inhibitors such as T-1095, inhibitors of protein tyrosinephosphatase 1, substances that affect deregulated glucose production in the liver, such as e.g. inhibitors of glucose-6-phosphatase, or fructose-1.6-bisphosphatase, glycogen phosphorylase, glucagon receptor antagonists and inhibitors of phosphoenol pyruvate carboxykinase, pyruvate dehydrokinase, lipid lowering agents such as for example HMG-CoA-reductase inhibitors (e.g. simvastatin, atorvastatin), fibrates (e.g. bezafibrate, fenofibrate),

nicotinic acid and the derivatives thereof, PPAR-alpha agonists, PPAR-delta agonists, ACAT inhibitors (e.g. avasimibe) or cholesterol absorption inhibitors such as, for example, ezetimibe, bile acid-binding substances such as, for example, cholestyramine, inhibitors of ileac bile acid transport, HDL-raising compounds such as CETP inhibitors or ABC1 regulators or active substances for treating obesity, such as sibutramine or tetrahydrolipostatin, dexfenfluramine, axokine, antagonists of the cannabinoid1 receptor, MCH-1 receptor antagonists, MC4 receptor agonists, NPY5 or NPY2 antagonists or ß3-agonists such as SB-418790 or AD-9677 and agonists of the 5HT2c receptor.

In addition, combinations with drugs for influencing high blood pressure such as e.g. A-II antagonists or ACE inhibitors, diuretics, ß-blockers, Ca-antagonists and others or combinations thereof are suitable.

Generally speaking, GSK-3 inhibitors may be administered in various ways: by oral, transdermal, intranasal or parenteral route or, in special cases, by intrarectal route. The preferred method of administration is by oral route daily, possibly several times a day. GSK-3 inhibitors are effective over wide dosage range. Thus, the dosage may be between 0.001 and 100 mg/kg, for example.

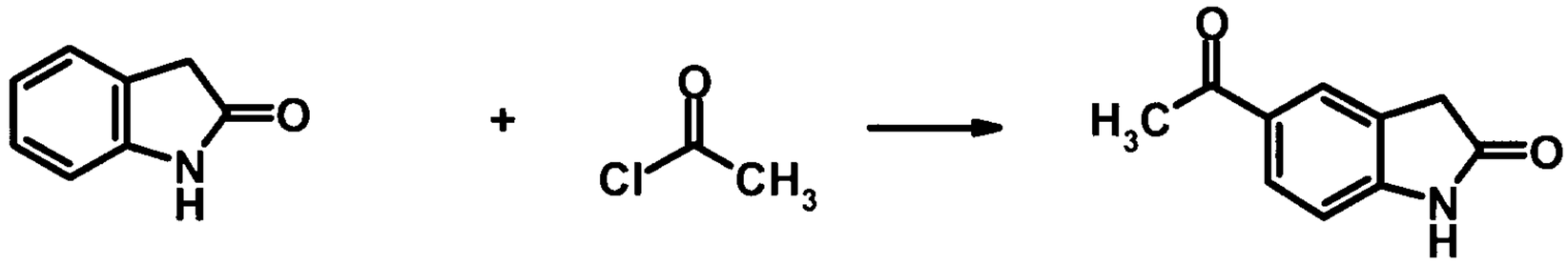
For this purpose, the compounds of formula I prepared according to the invention may be formulated, optionally together with other active substances, with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

The Examples that follow are intended to illustrate the invention:

Preparation of the starting compounds:

Example I

5-acetyl-2-indolinone



171 g (1.28 mol) aluminium chloride in 500 ml 1,2-dichloroethane are cooled in the ice bath. Then 78 g (1.1 mol) acetylchloride are added dropwise, so that the temperature does not exceed10°C. After 1 h, 71.3 g (0.53 mol) 2-indolinone (1,3-dihydro-indol-2-one) are added in 4 batches and the temperature is kept at 10-12°C. The reaction mixture is left overnight to warm up slowly to ambient temperature. Then the solution is slowly added to 1 kg ice with vigorous stirring. The slurry is diluted with 1 l water and stirred for another 30 min. Then the precipitate is suction filtered.

Yield: 80.9 g (86.3 % of theory)

R_f = 0.36 (silica gel, ethyl acetate/cyclohexane/methanol 9:9:2)

$C_{10}H_9NO_2$ (MG = 175.19)

Mass spectrum: m/z = 174 $(M-H)^-$

The following compounds are prepared analogously to Example I:

(1) 5-propionly-2-indolinone

Prepared from 2-indolinone and propionyl chloride

Yield: 72 % of theory

R_f = 0.44 (silica gel, methylene chloride/methanol 9:1)

$C_{11}H_{11}NO_2$ (MW = 189.22)

Mass spectrum: m/z = 188 $(M-H)^-$

(2) 5-butyryl-2-indolinone

Prepared from 2-indolinone and butyric acid chloride (butyryl chloride)

Yield: 68 % of theory

$C_{12}H_{13}NO_2$ (MW = 203.24)

Mass spectrum: m/z = 202 $(M-H)^-$

(3) 5-isobutyryl-2-indolinone

Prepared from 2-indolinone and isobutyryl chloride

Yield: 13 % of theory

$C_{12}H_{13}NO_2$ (MW = 203.24)

Mass spectrum: m/z = 202 $(M-H)^-$

(4) 5-hexanoyl-2-indolinone

Prepared from 2-indolinone and hexanoic acid chloride

Yield: 88 % of theory

R_f = 0.51 (silica gel, ethyl acetate/cyclohexane/methanol 9:9:2)

$C_{14}H_{17}NO_2$ (MW = 231.30)

Mass spectrum: m/z = 230 $(M-H)^-$

(5) 5-benzoyl-2-indolinone

Prepared from 2-indolinone and benzoic acid chloride

Yield: 80 % of theory

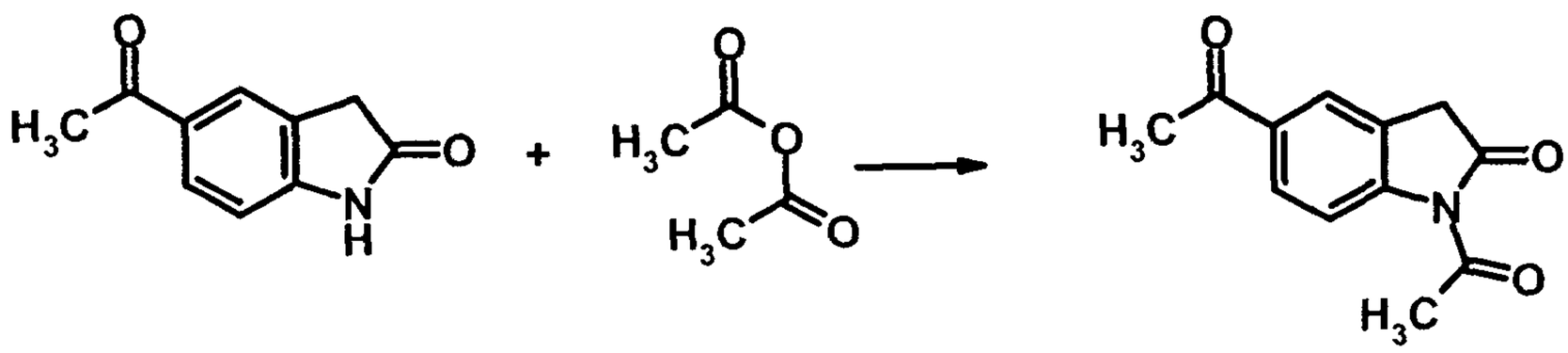
R_f = 0.46 (silica gel, methylene chloride/methanol 9:1)

$C_{15}H_{11}NO_2$ (MW = 237.26)

Mass spectrum: m/z = 236 $(M-H)^-$

Example II

1.5-diacetyl-2-indolinone



48.9 g (0.279 mol) 5-acetyl-2-indolinone are stirred in 400 ml acetic anhydride in an oil bath at 140 °C for 2 h. During this time the starting material dissolves.
Then the reaction mixture is left to cool, evaporated down, the precipitate is removed by suction filtering, washed with ether and the product is dried.

Yield: 56.0 g (92.4 % of theory)

R_f = 0.41 (silica gel, methylene chloride/methanol 50:1)

$C_{12}H_{11}NO_3$ (MW = 217.223)

Mass spectrum: m/z = 216 $(M-H)^-$

The following compounds are prepared analogously to Example II:

(1) 1-acetyl-5-propionly-2-indolinone

Prepared from 5-propionly-2-indolinone and acetic anhydride

Yield: 79 % of theory

R_f = 0.68 (silica gel, methylene chloride/methanol 9:1)

$C_{13}H_{13}NO_3$ (MW = 231.25)

Mass spectrum: m/z = 232 $(M+H)^+$

(2) 1-acetyl-5-benzoyl-2-indolinone

Prepared from 5-benzoyl-2-indolinone and acetic anhydride

Yield: 89 % of theory

R_f = 0.60 (silica gel, methylene chloride/methanol 30:1)

$C_{17}H_{13}NO_3$ (MW = 279.294)

Mass spectrum: m/z = 278 $(M-H)^-$

(3) 1-acetyl-5-hexanoyl-2-indolinone

Prepared from 5-hexanoyl-2-indolinone and acetic anhydride

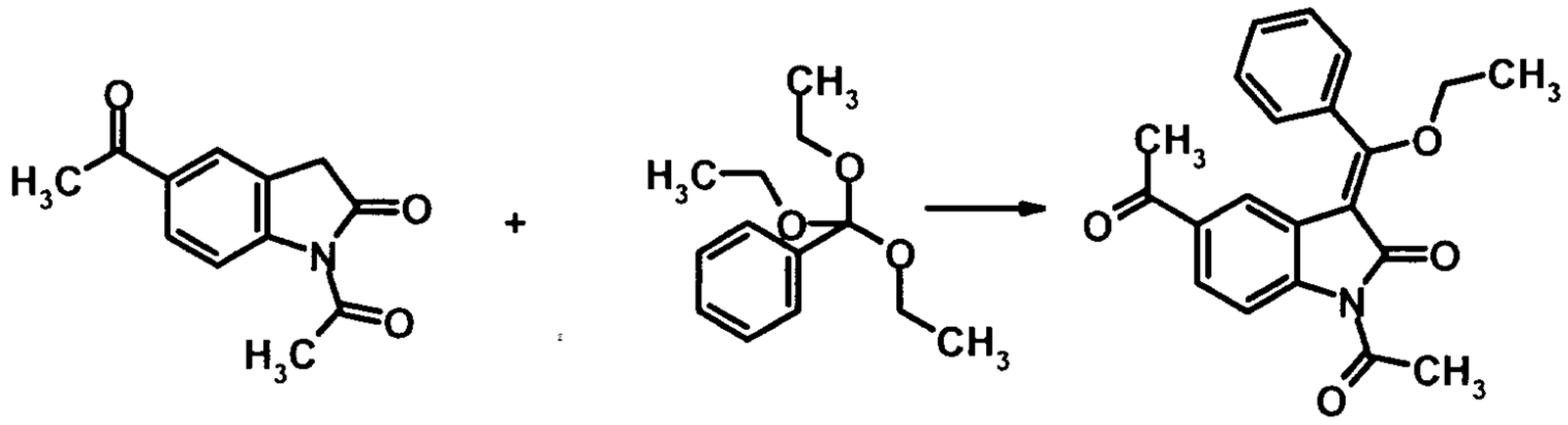
R_f = 0.74 (silica gel, methylene chloride/methanol 30:1)

$C_{16}H_{19}NO_3$ (MW = 273.33)

Mass spectrum: m/z = 272 $(M-H)^-$

Example III

1.5-diacetyl-3-(ethoxy-phenyl-methylidene)-2-indolinone



32.6 g (150 mmol) 1,5-diacetyl-2-indolinone are suspended in 100 ml triethyl orthobenzoate and stirred overnight with 150 ml acetic anhydride at 110 °C. Then a further 50 ml triethyl orthobenzoate are added and the mixture is stirred for a further 24 h. Then it is evaporated down and the resulting precipitate is suction filtered, washed and dried.

Yield: 38 g (72.5 % of theory)

R_f = 0.60 (silica gel, methylene chloride/methanol 30:1)

$C_{21}H_{19}NO_4$ (MW = 349.384)

Mass spectrum: m/z = 350 $(M+H)^+$

The following compounds are prepared analogously to Example III:

(1) 1-acetyl-5-hexanoyl-3-(ethoxy-phenyl-methylidene)-2-indolinone

Prepared from 1-acetyl-5-hexanoyl-2-indolinone and triethyl orthobenzoate

Yield: 29 % of theory

R_f = 0.72 (silica gel, methylene chloride/methanol 30:1)

$C_{25}H_{27}NO_4$ (MW = 405.491)

Mass spectrum: m/z = 428 $(M+Na)^+$

(2) 1-acetyl-5-benzoyl-3-(ethoxy-phenyl-methylidene)-2-indolinone

Prepared from 1-acetyl-5-benzoyl-2-indolinone and triethyl orthobenzoate

Yield: 65 % of theory

R_f = 0.72 (silica gel, methylene chloride/methanol 30:1)

$C_{26}H_{21}NO_4$ (MW = 411.455)

Mass spectrum: m/z = 412 $(M+H)^+$

(3) 1,5-diacetyl-3-(1-methoxy-propylidene)-2-indolinone

Prepared from 1,5-diacetyl-2-indolinone and trimethyl orthopropionate

Yield: 80 % of theory

R_f = 0.50 (silica gel, methylene chloride/methanol 50:1)

$C_{16}H_{17}NO_4$ (MW = 287.311)

Mass spectrum: m/z = 288 $(M+H)^+$

(4) 1,5-diacetyl-3-(1-methoxy-butylidene)-2-indolinone

Prepared from 1,5-diacetyl-2-indolinone and trimethyl orthobutyrate

Yield: 71 % of theory

R_f = 0.53 (silica gel, methylene chloride/methanol 50:1)

$C_{17}H_{19}NO_4$ (MW = 301.337)

Mass spectrum: m/z = 302 $(M+H)^+$

(5) 1,5-diacetyl-3-(1-methoxy-pentylidene)-2-indolinone

Prepared from 1,5-diacetyl-2-indolinone and trimethyl orthovalerate

Yield: 66 % of theory

R_f = 0.60 (silica gel, methylene chloride/methanol 50:1)

$C_{18}H_{21}NO_4$ (MW = 315.364)

Mass spectrum: m/z = 316 $(M+H)^+$

(6) 1,5-diacetyl-3-(1-methoxy-2-methyl-propylidene)-2-indolinone

Prepared from 1,5-diacetyl-2-indolinone and 1.1.1-trimethoxy-2-methylpropane

Yield: 40 % of theory

R_f = 0.71 (silica gel, ethyl acetate:cyclohexane:methanol 9:9:2)

$C_{17}H_{19}NO_4$ (MW = 301.337)

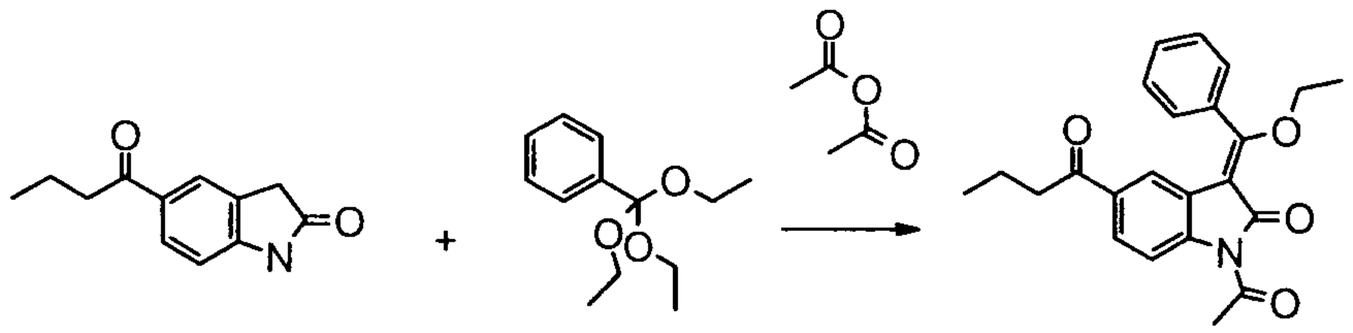
Mass spectrum: m/z = 302 $(M+H)^+$

(7) 1,acetyl-5-propionyl-3-(1-methoxy-propylidene)-2-indolinone

Prepared from 1-acetyl-5-propionyl-2-indolinone and trimethyl orthopropionate

Example IV

1-acetyl-5-butyryl-3-(ethoxy-phenyl-methylidene)-2-indolinone



10 g (49 mmol) 5-butyryl-2-indolinone (Ex. I.2) in 200 ml acetic anhydride are stirred for 5 h at 130 °C. Then 35 ml triethyl orthobenzoate are added and the mixture is stirred for a further 4 h at 100 °C. It is then evaporated down and the resulting precipitate is suction filtered, washed and dried.

Yield: 11.5 g (62 % of theory)

R_f = 0.79 (silica gel, ethyl acetate/cyclohexane/methanol 9:9:2)

$C_{23}H_{23}NO_4$ (MW = 377.438)

Mass spectrum: m/z = 378 $(M+H)^+$

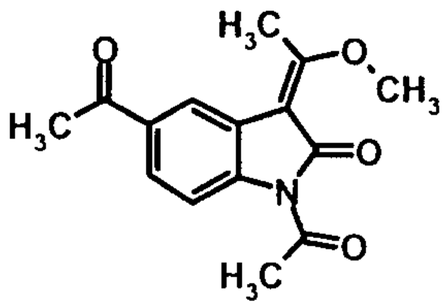
The following compounds are prepared analogously to Example IV:

(1) 1-acetyl-5-isobutyryl-3-(ethoxy-phenyl-methylidene)-2-indolinone

Prepared from 5-isobutyryl-2-indolinone, acetic anhydride and triethyl orthobenzoate

R_f = 0.55 (silica gel, ethyl acetate/cyclohexane/methanol 9:9:2)

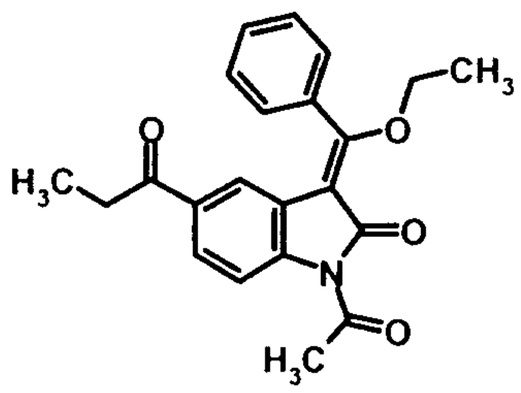
(2) 1,5-diacetyl-3-[1-methoxy-ethylidene]-2-indolinone



Prepared from 5-acetyl-2-indolinone, acetic anhydride and trimethyl orthoacetate

R_f = 0.40 (silica gel, methylene chloride/methanol 50 :1)

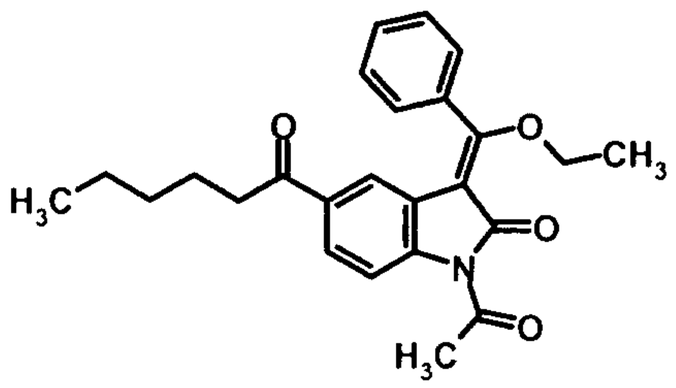
(3) 1-acetyl-5-propionyl-3-(ethoxy-phenyl-methylidene)-2-indolinone



Prepared from 5-propionyl-2-indolinone, acetic anhydride and triethyl orthobenzoate

R_f = 0.79 (silica gel, ethyl acetate/cyclohexane/methanol 9:9:2)

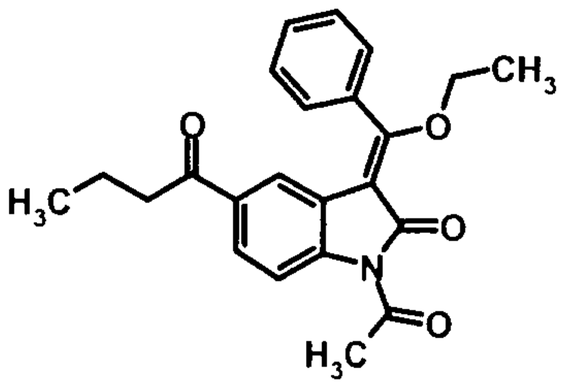
(4) 1-acetyl-5-hexanoyl-3-(ethoxy-phenyl-methylidene)-2-indolinone



Prepared from 5-hexanoyl-2-indolinone, acetic anhydride and triethyl orthobenzoate

R_f = 0.72 (methylene chloride/methanol 30 :1)

(5) 1-acetyl-5-butyryl-3-(ethoxy-phenyl-methylidene)-2-indolinone

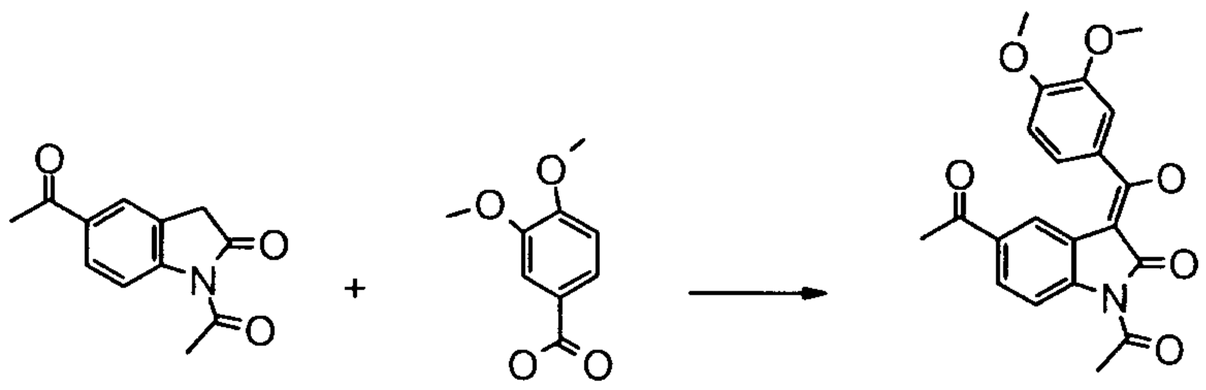


Prepared from 5-butyryl-2-indolinone, acetic anhydride and triethyl orthobenzoate

R_f = 0.79 (silica gel, ethyl acetate/cyclohexane/methanol 9:9:2)

Example V

1,5-diacetyl-3-[(3.4-dimethoxy-phenyl)-hydroxy-methylidene]-2-indolinone



4.3 g (20 mmol) 1,5-diacetyl-2-indolinone (Ex. II) are stirred overnight together with 4 g of 3,4-dimethoxybenzoic acid, 7.1 g TBTU (O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate) and 14 ml triethylamine in 80 ml DMF (dimethylformamide) at ambient temperature. Then the mixture is poured onto 300 ml ice water with 10 ml of conc. hydrochloric acid and the precipitate formed is suction filtered. The residue is washed with a little methanol and then with ether.

Yield: 6.2 g (81.3 % of theory)

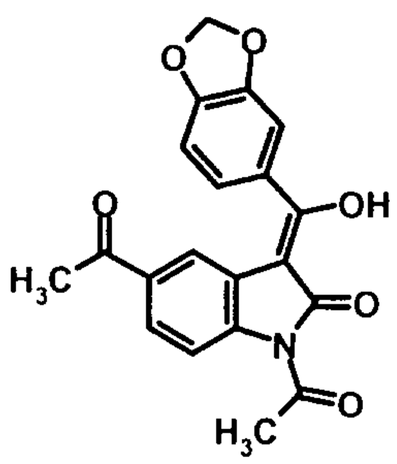
R_f = 0.85 (silica gel, methylene chloride/methanol 9:1)

$C_{21}H_{19}NO_6$ (MW = 381.382)

Mass spectrum: m/z = 381 $(M)^+$

The following compounds are prepared analogously to Example V:

(1) 1,5-diacetyl-3-[(benzo[1,3]dioxol-5-yl)-hydroxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-2-indolinone and piperonylic acid (benzo[1,3]dioxole-5-carboxylic acid)

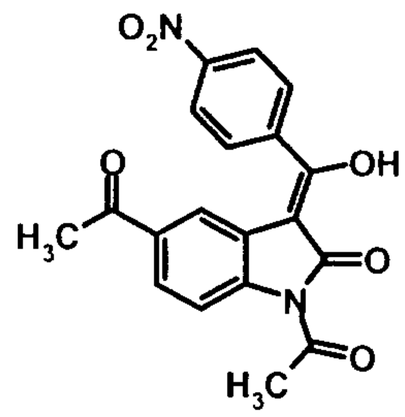
Yield: 60 % of theory

R_f = 0.70 (silica gel, methylene chloride/methanol 9:1)

$C_{20}H_{15}NO_6$ (MW = 365.339)

Mass spectrum: m/z = 366 $(M+H)^+$

(2) 1,5-diacetyl-3-[(4-nitro-phenyl)-hydroxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-2-indolinone and 4-nitrobenzoic acid

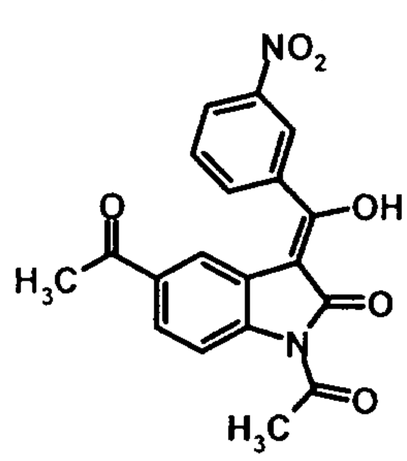
Yield: 82 % of theory

R_f = 0.38 (silica gel, methylene chloride/methanol 9:1)

$C_{19}H_{14}N_2O_6$ (MW = 366.328)

Mass spectrum: m/z = 367 $(M+H)^+$

(3) 1,5-diacetyl-3-[(3-nitro-phenyl)-hydroxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-2-indolinone and 3-nitrobenzoic acid

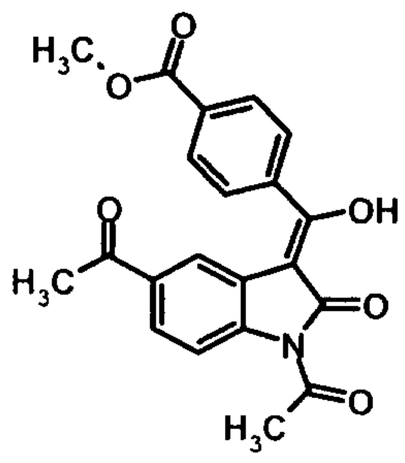
Yield: 75 % of theory

R_f = 0.38 (silica gel, methylene chloride/methanol 9:1)

$C_{19}H_{14}N_2O_6$ (MW = 366.328)

Mass spectrum: m/z = 367 $(M+H)^+$

(4) 1,5-diacetyl-3-[(4-methoxycarbonyl-phenyl)-hydroxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-2-indolinone and monomethyl terephthalate

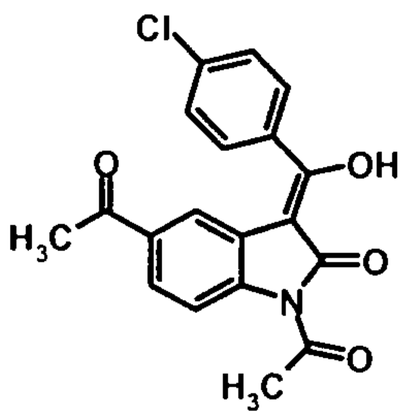
Yield: 71 % of theory

R_f = 0.41 (silica gel, methylene chloride/methanol 30:1)

$C_{21}H_{17}NO_6$ (MW = 379.366)

Mass spectrum: m/z = 380 $(M+H)^+$

(5) 1,5-diacetyl-3-[(4-chloro-phenyl)-hydroxy-methylidene]-2-indolinone



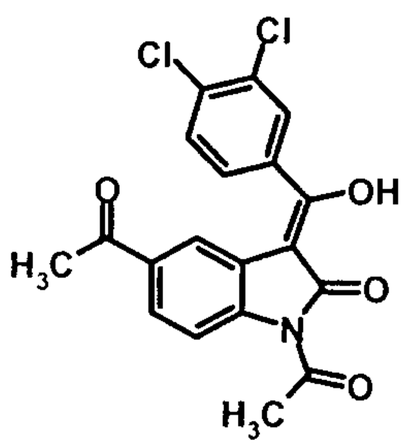
Prepared from 1,5-diacetyl-2-indolinone and 4-chlorobenzoic acid

Yield: 87 % of theory

$C_{19}H_{14}ClNO_4$ (MW = 355.776)

Mass spectrum: m/z = 356/358 $(M+H)^+$

(6) 1,5-diacetyl-3-[(3,4-dichloro-phenyl)-hydroxy-methylidene]-2-indolinone



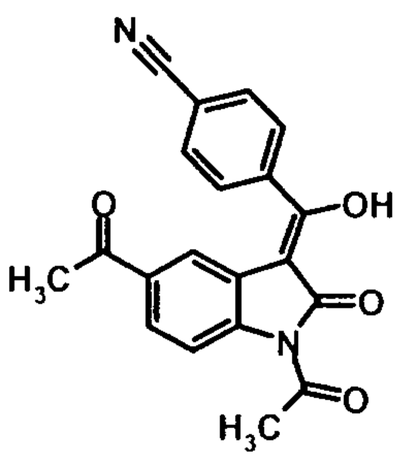
Prepared from 1,5-diacetyl-2-indolinone and 3,4-dichlorobenzoic acid

Yield: 83 % of theory

$C_{19}H_{13}Cl_2NO_4$ (MW = 390.221)

Mass spectrum: m/z = 390/392/394 $(M+H)^+$

(7) 1,5-diacetyl-3-[(4-cyano-phenyl)-hydroxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-2-indolinone and 4-cyanobenzoic acid

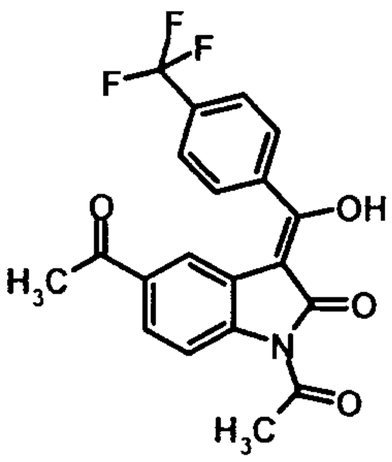
Yield: 71 % of theory

R_f = 0.32 (silica gel, methylene chloride/methanol 9:1)

$C_{20}H_{14}N_2O_4$ (MW = 346.341)

Mass spectrum: m/z = 347 $(M+H)^+$

(8) 1,5-diacetyl-3-[(4-trifluoromethyl-phenyl)-hydroxy-methylidene]-2-indolinone



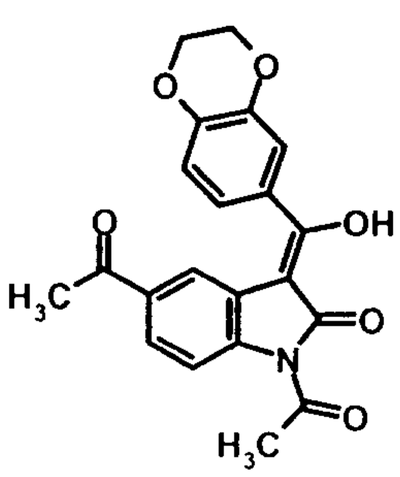
Prepared from 1,5-diacetyl-2-indolinone and 4-trifluoromethyl-benzoic acid

Yield: 83 % of theory

$C_{20}H_{14}F_3NO_4$ (MW = 389.328)

Mass spectrum: m/z = 390 $(M+H)^+$

(9) 1,5-diacetyl-3-[(2,3-dihydro-benzo-[1,4]dioxin-6-yl)-hydroxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-2-indolinone and 2,3-dihydro-1.4-benzodioxine-6-carboxylic acid

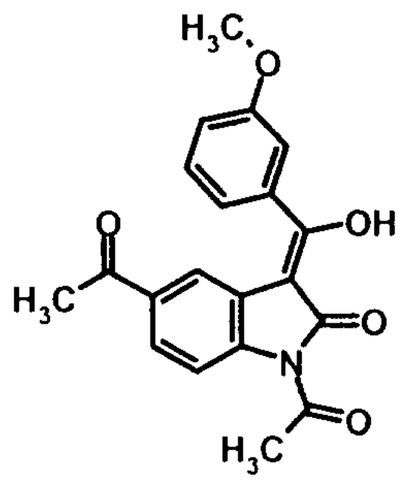
Yield: 90 % of theory

R_f = 0.75 (silica gel, methylene chloride/methanol 9:1)

$C_{21}H_{17}NO_6$ (MW = 379.366)

Mass spectrum: m/z = 380 $(M+H)^+$

(10) 1,5-diacetyl-3-[(3-methoxy-phenyl)-hydroxy-methylidene]-2-indolinone

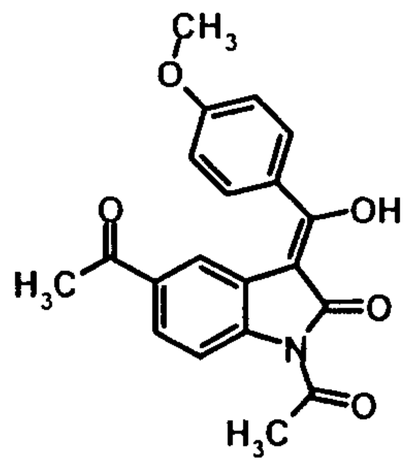


Prepared from 1,5-diacetyl-2-indolinone and 3-methoxybenzoic acid

Yield: 70 % of theory

R_f = 0.67 (silica gel, methylene chloride/methanol 9:1)

(11) 1,5-diacetyl-3-[(4-methoxy-phenyl)-hydroxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-2-indolinone and 4-methoxybenzoic acid

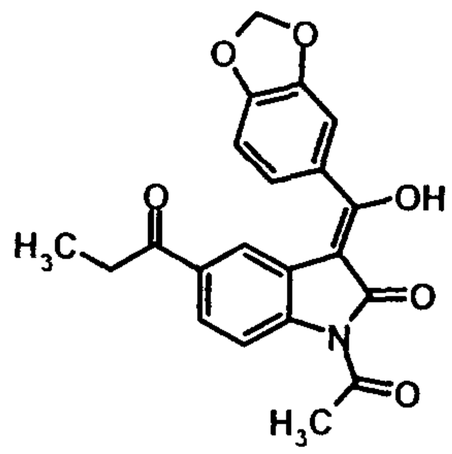
Yield: 59 % of theory

R_f = 0.39 (silica gel, methylene chloride/methanol 9:1)

$C_{20}H_{17}NO_5$ (MW = 351.356)

Mass spectrum: m/z = 350 $(M-H)^-$

(12) 1-diacetyl-5-propionyl-3-[(benzo[1,3]dioxol-5-yl)-hydroxy-methylidene]-2-indolinone



Prepared from 1-acetyl-5-propionyl-2-indolinone and piperonylic acid (benzo[1,3]-dioxole-5-carboxylic acid)

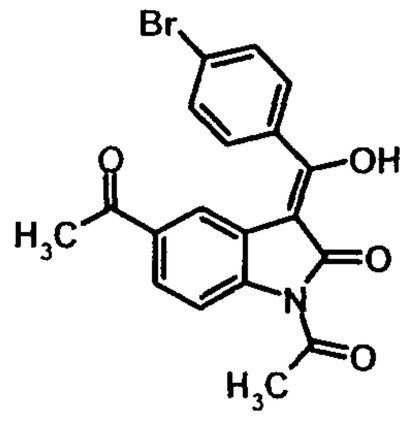
Yield: 67 % of theory

R_f = 0.49 (silica gel, methylene chloride/methanol 30:1)

$C_{21}H_{17}NO_6$ (MW = 379.366)

Mass spectrum: m/z = 380 $(M+H)^+$

(13) 1,5-diacetyl-3-[(4-bromophenyl)-hydroxy-methylidene]-2-indolinone



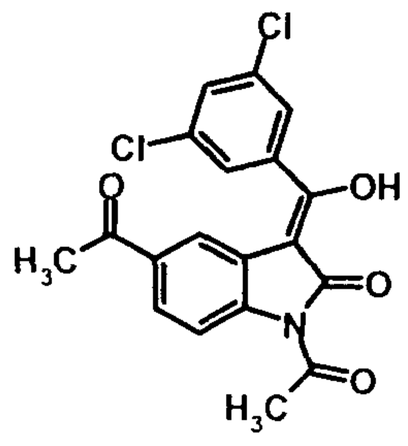
Prepared from 1,5-diacetyl-2-indolinone and 4-bromobenzoic acid

Yield: 89 % of theory

$C_{19}H_{14}BrNO_4$ (MW = 400.227)

Mass spectrum: m/z = 400/402 $(M+H)^+$

(14) 1,5-diacetyl-3-[(3,5-dichloro-phenyl)-hydroxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-2-indolinone and 3,5-dichlorobenzoic acid

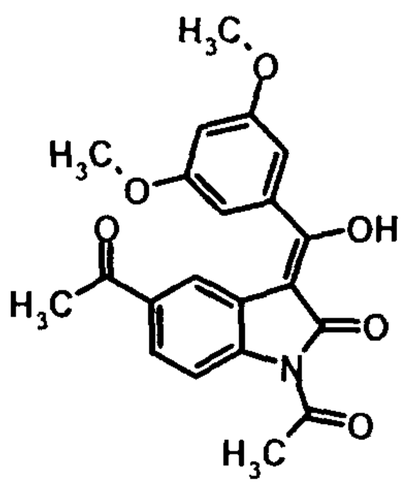
Yield: 79 % of theory

R_f = 0.26 (silica gel, methylene chloride/methanol 30:1)

$C_{19}H_{13}Cl_2NO_4$ (MW = 390.221)

Mass spectrum: m/z = 390/392/394 $(M+H)^+$

(15) 1,5-diacetyl-3-[(3,5-dimethoxyphenyl)-hydroxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-2-indolinone and 3,5-dimethoxybenzoic acid

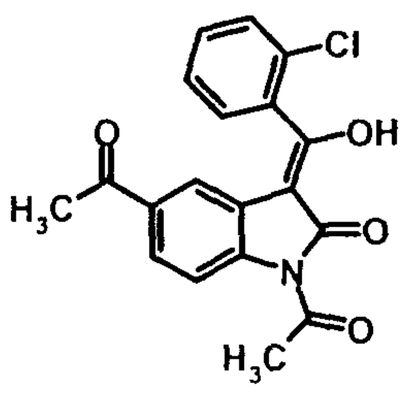
Yield: 83 % of theory

R_f = 0.37 (silica gel, methylene chloride/methanol 30:1)

$C_{21}H_{19}NO_6$ (MW = 381.382)

Mass spectrum: m/z = 382 $(M+H)^+$

(16) 1,5-diacetyl-3-[(2-chloro-phenyl)-hydroxy-methylidene]-2-indolinone



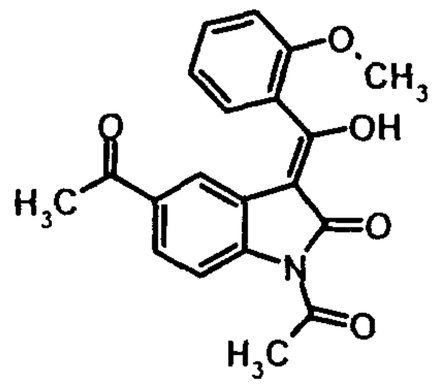
Prepared from 1,5-diacetyl-2-indolinone and 2-chlorobenzoic acid

Yield: 96 % of theory

$C_{19}H_{14}ClNO_4$ (MW = 355.776)

Mass spectrum: m/z = 356/358 $(M+H)^+$

(17) 1,5-diacetyl-3-[(2-methoxy-phenyl)-hydroxy-methylidene]-2-indolinone



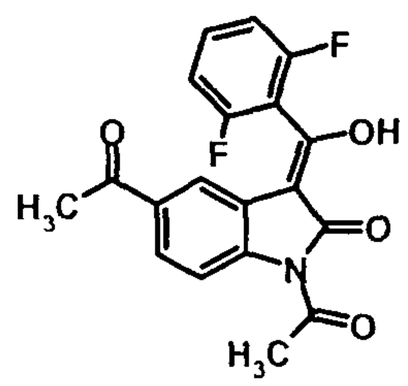
Prepared from 1,5-diacetyl-2-indolinone and 2-methoxybenzoic acid

Yield: 27 % of theory

$C_{20}H_{17}NO_5$ (MW = 351.356)

Mass spectrum: m/z = 352 $(M+H)^+$

(18) 1,5-diacetyl-3-[(2,6-difluoro-phenyl)-hydroxy-methylidene]-2-indolinone



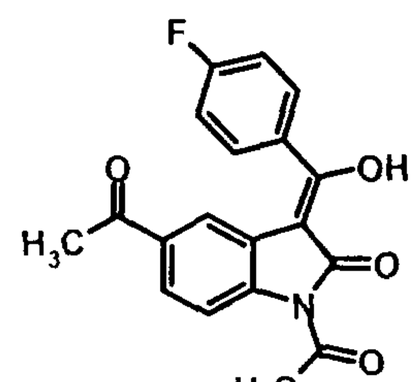
Prepared from 1,5-diacetyl-2-indolinone and 2,6-difluorobenzoic acid

Yield: 52 % of theory

$C_{19}H_{13}F_2NO_4$ (MW = 357.311)

Mass spectrum: m/z = 358 $(M+H)^+$

(19) 1,5-diacetyl-3-[(4-fluorophenyl)-hydroxy-methylidene]-2-indolinone



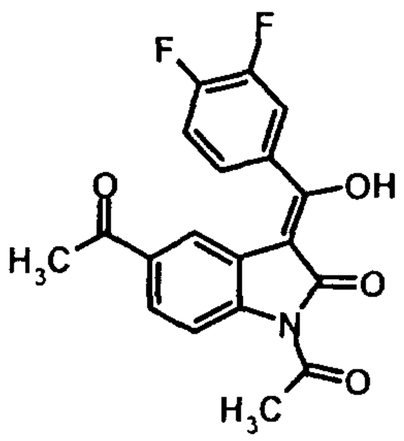
Prepared from 1,5-diacetyl-2-indolinone and 4-fluorobenzoic acid

Yield: 77 % of theory

$C_{19}H_{14}FNO_4$ (MW = 339.321)

Mass spectrum: m/z = 338 $(M-H)^-$

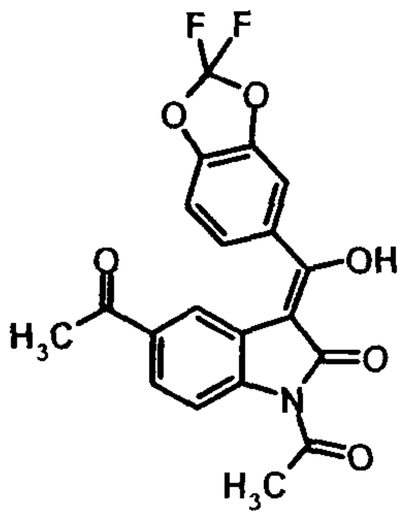
(20) 1,5-diacetyl-3-[(3,4-difluoro-phenyl)-hydroxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-2-indolinone and 3,4-difluorobenzoic acid

Yield: 91 % of theory

(21) 1,5-diacetyl-3-[(2,2-difluoro-benzo[1,3]dioxol-5-yl)-hydroxy-methylidene]-2-indolinone



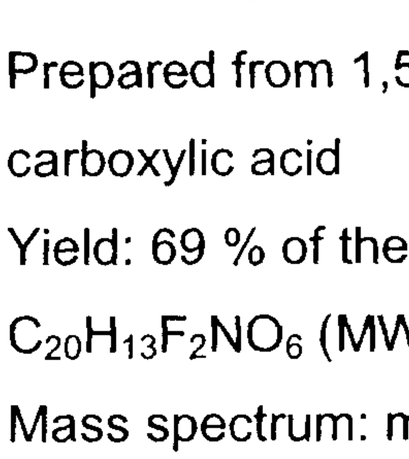
Prepared from 1,5-diacetyl-2-indolinone and 2,2-difluoro-benzo[1,3]dioxole-5-carboxylic acid

Yield: 69 % of theory

$C_{20}H_{13}F_2NO_6$ (MW = 401.32)

Mass spectrum: m/z = 402 $(M+H)^+$

(22) 1,5-diacetyl-3-[(4-(2-methoxycarbonyl-ethyl)-phenyl)-hydroxy-methylidene]-2-indolinone



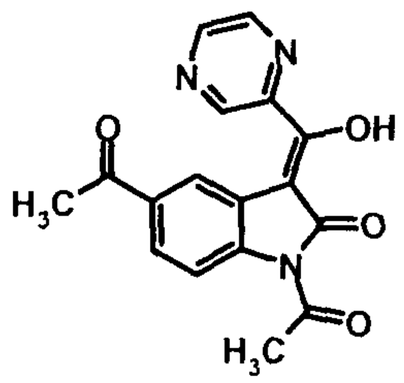
Prepared from 1,5-diacetyl-2-indolinone and 4-(2-methoxycarbonyl-ethyl)-benzoic acid

Yield: 23 % of theory

$C_{23}H_{21}NO_6$ (MW = 407.42)

Mass spectrum: m/z = 408 $(M+H)^+$

(23) 1,5-diacetyl-3-[(pyrazin-2-yl)-hydroxy-methylidene]-2-indolinone



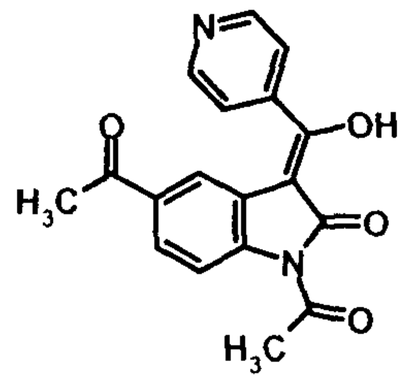
Prepared from 1,5-diacetyl-2-indolinone and pyrazine-2-carboxylic acid

Yield: 57 % of theory

$C_{17}H_{13}N_3O_4$ (MW = 323.311)

Mass spectrum: m/z = 324 $(M+H)^+$

(24) 1,5-diacetyl-3-[(pyridin-4-yl)-hydroxy-methylidene]-2-indolinone



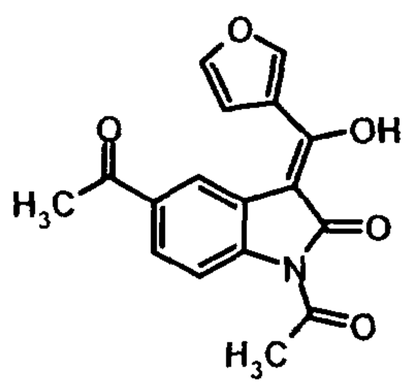
Prepared from 1,5-diacetyl-2-indolinone and isonicotinic acid (pyridine-4-carboxylic acid)

Yield: 87 % of theory

$C_{18}H_{14}N_2O_4$ (MW = 322.323)

Mass spectrum: m/z = 323 $(M+H)^+$

(25) 1,5-diacetyl-3-[(furan-3-yl)-hydroxy-methylidene]-2-indolinone



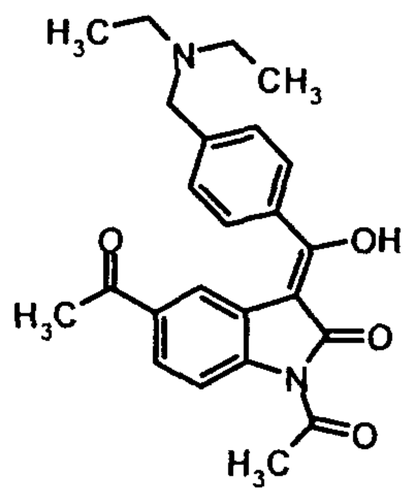
Prepared from 1,5-diacetyl-2-indolinone and furan-3-carboxylic acid

Yield: 73 % of theory

$C_{17}H_{13}NO_5$ (MW = 311.297)

Mass spectrum: m/z = 312 $(M+H)^+$

(26) 1,5-diacetyl-3-[(4-diethylaminomethyl-phenyl)-hydroxy-methylidene]-2-indolinone



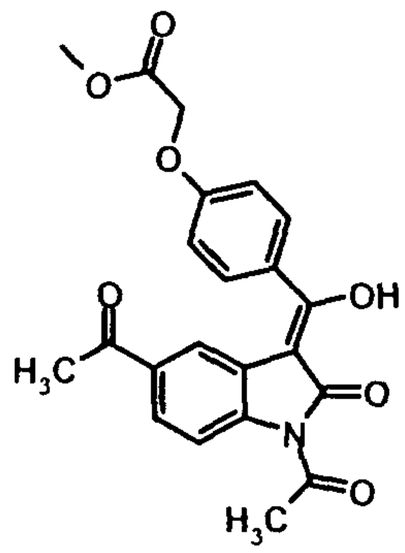
Prepared from 1,5-diacetyl-2-indolinone and 4-diethylaminomethyl-benzoic acid

Yield: 10 % of theory

$C_{24}H_{26}N_2O_4$ (MW = 406.486)

Mass spectrum: m/z = 407 $(M+H)^+$

(27) 1,5-diacetyl-3-[(4-methoxycarbonylmethoxy-phenyl)-hydroxy-methylidene]-2-indolinone



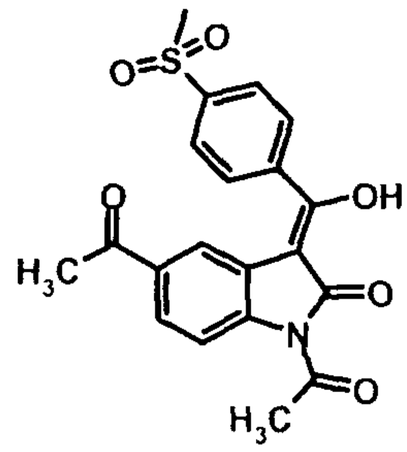
Prepared from 1,5-diacetyl-2-indolinone and 4-methoxycarbonyl-methoxy-benzoic acid

Yield: 43 % of theory

$C_{22}H_{19}NO_7$ (MW = 409.39)

Mass spectrum: m/z = 410 $(M+H)^+$

(28) 1,5-diacetyl-3-[(4-methylsulphonyl-phenyl)-hydroxy-methylidene]-2-indolinone



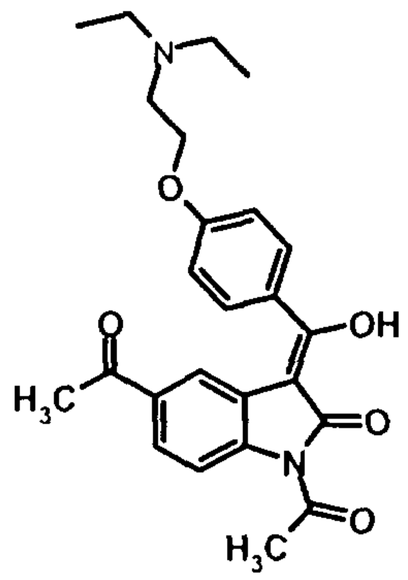
Prepared from 1,5-diacetyl-2-indolinone and 4-methylsulphonyl-benzoic acid

Yield: 25 % of theory

$C_{20}H_{17}NO_6S$ (MW = 399.418)

Mass spectrum: m/z = 400 $(M+H)^+$

(29) 1,5-diacetyl-3-[(4-(2-diethylamino-ethoxy)-phenyl)-hydroxy-methylidene]-2-indolinone



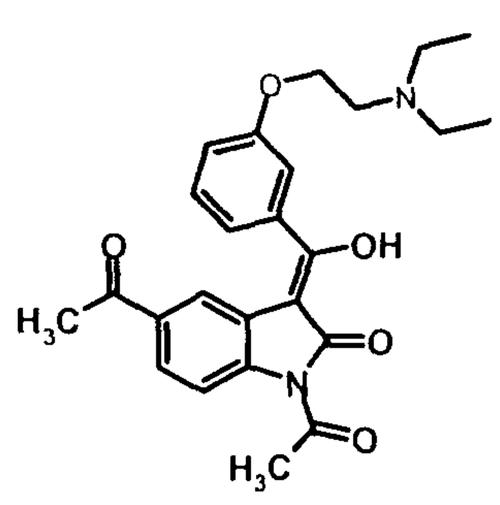
Prepared from 1,5-diacetyl-2-indolinone and 4-diethylamino-ethoxy-benzoic acid

Yield: 27 % of theory

$C_{25}H_{28}N_2O_5$ (MW = 436.500)

Mass spectrum: m/z = 437 $(M+H)^+$

(30) 1,5-diacetyl-3-[(3-(2-diethylamino-ethoxy)-phenyl)-hydroxy-methylidene]-2-indolinone



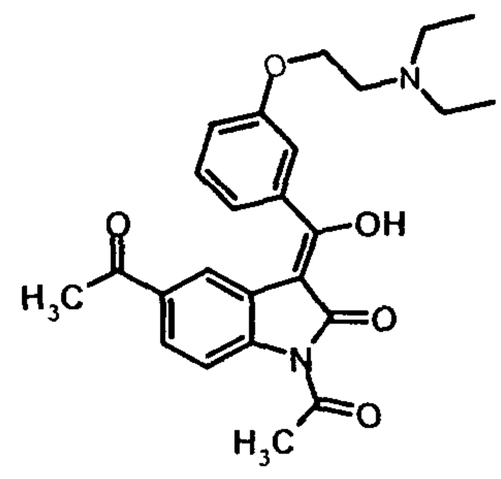
Prepared from 1,5-diacetyl-2-indolinone and 3-diethylamino-ethoxy-benzoic acid

Yield: 43 % of theory

$C_{25}H_{28}N_2O_5$ (MW = 436.500)

Mass spectrum: m/z = 437 $(M+H)^+$

(31) 1,5-diacetyl-3-[(3-(2-diethylamino-ethoxy)-phenyl)-hydroxy-methylidene]-2-indolinone



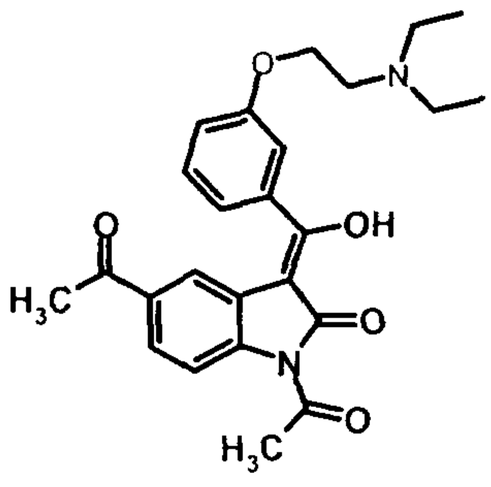
Prepared from 1,5-diacetyl-2-indolinone and 3-diethylamino-ethoxy-benzoic acid

Yield: 43 % of theory

$C_{25}H_{28}N_2O_5$ (MW = 436.500)

Mass spectrum: m/z = 437 $(M+H)^+$

(31) 1,5-diacetyl-3-[(3-(2-diethylamino-ethoxy)-phenyl)-hydroxy-methylidene]-2-indolinone



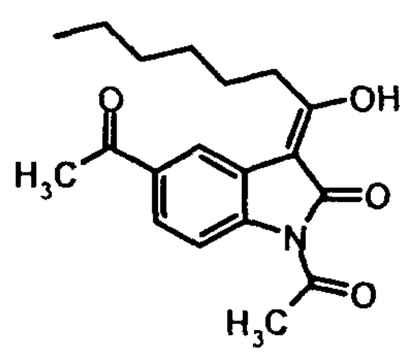
Prepared from 1,5-diacetyl-2-indolinone and 3-diethylamino-ethoxy-benzoic acid

Yield: 43 % of theory

$C_{25}H_{28}N_2O_5$ (MW = 436.500)

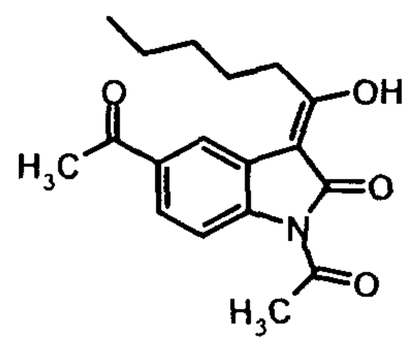
Mass spectrum: m/z = 437 $(M+H)^+$

(32) 1,5-diacetyl-3- (1-hydroxy-heptylidene)-2-indolinone



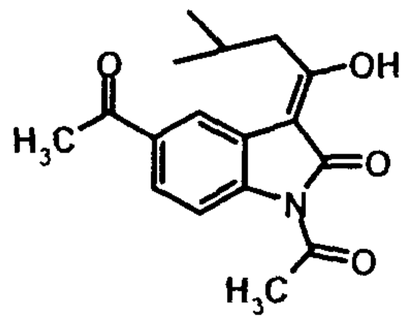
Prepared from 1,5-diacetyl-2-indolinone and heptanoic acid

(33) 1,5-diacetyl-3- (1-hydroxy-hexylidene)-2-indolinone



Prepared from 1,5-diacetyl-2-indolinone and hexanoic acid

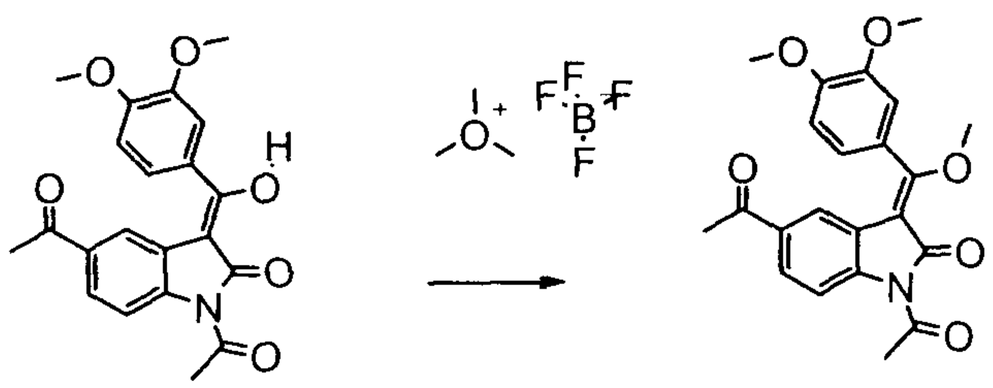
(34) 1,5-diacetyl-3- (1-hydroxy-3-methyl-butylidene)-2-indolinone



Prepared from 1,5-diacetyl-2-indolinone and isovaleric acid

Example VI

1,5-diacetyl-3-[(3,4-dimethoxy-phenyl)-methoxy-methylidene]-2-indolinone



4.0 g (10.5 mmol) 1,5-diacetyl-3-[(3,4-dimethoxy-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V) are suspended in 100 ml methylene chloride and combined with 3.1 g (21 mmol) trimethyloxonium tetrafluoroborate as well as 7.2 ml Hünig base (ethyldiisopropylamine) at ambient temperature. The solution is stirred for 3 h, then a further 1.55 g trimethyloxonium tetrafluoroborate and 3.5 ml Hünig base are added and the mixture is stirred overnight. After the same amount of reagent has been added again and the mixture has been stirred for a further 5 h, the reaction is washed three times with water, the organic phase is dried over sodium sulphate, filtered and concentrated by rotary evaporation. The residue is chromatographed through a silica gel column with methylene chloride/methanol 9:1, the corresponding fractions are combined and concentrated by rotary evaporation.

Yield: 1.6 g (37 % of theory)

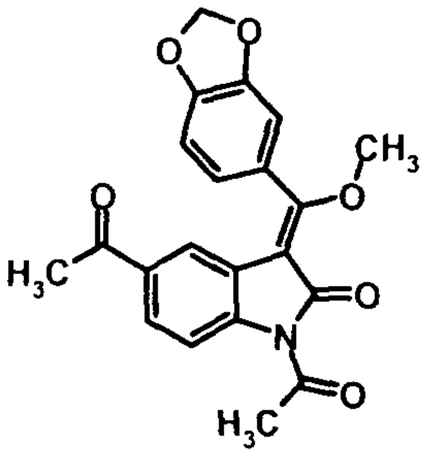
R_f = 0.78 (silica gel, methylene chloride/methanol 50:1)

$C_{22}H_{21}NO_6$ (MW = 395.409)

Mass spectrum: m/z = 396 $(M+H)^+$

The following compounds are prepared analogously to Example VI:

(1) 1,5-diacetyl-3-[(benzo[1,3]dioxol-5-yl)-methoxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-3-[(benzo[1,3]dioxol-5-yl)-hydroxy-methylidene]-2-indolinone (Ex. V.1)

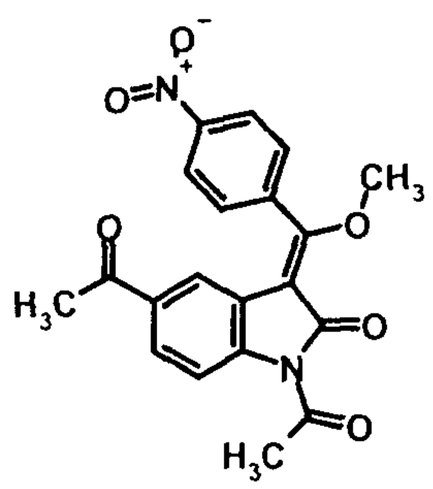
Yield: 85 % of theory

R_f = 0.55 (silica gel, methylene chloride/methanol 30:1)

$C_{21}H_{17}NO_6$ (MW = 379.366)

Mass spectrum: m/z = 380 $(M+H)^+$

(2) 1,5-diacetyl-3-[(4-nitro-phenyl)-methoxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-3-[(4-nitro-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.2)

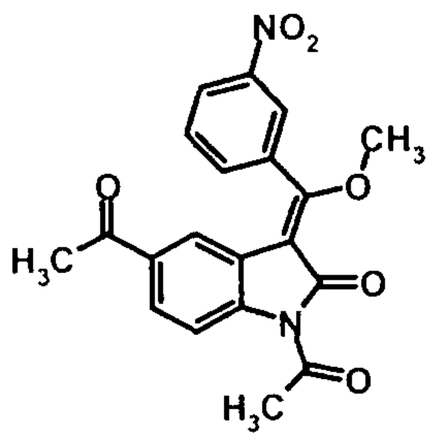
Yield: 82 % of theory

R_f = 0.55 (silica gel, methylene chloride/methanol 30:1)

$C_{20}H_{16}N_2O_6$ (MW = 380.354)

Mass spectrum: m/z = 381 $(M+H)^+$

(3) 1,5-diacetyl-3-[(3-nitro-phenyl)-methoxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-3-[(3-nitro-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.3)

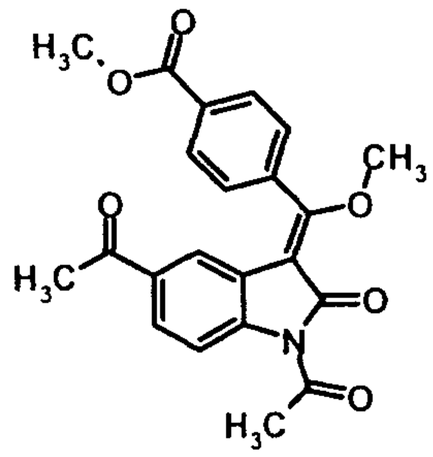
Yield: 43 % of theory

R_f = 0.44 (silica gel, methylene chloride/methanol 9:1)

$C_{20}H_{16}N_2O_6$ (MW = 380.354)

Mass spectrum: m/z = 381 $(M+H)^+$

(4) 1,5-diacetyl-3-[(4-methyloxycarbonyl-phenyl)-methoxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-3-[(4-methyloxycarbonyl-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.4)

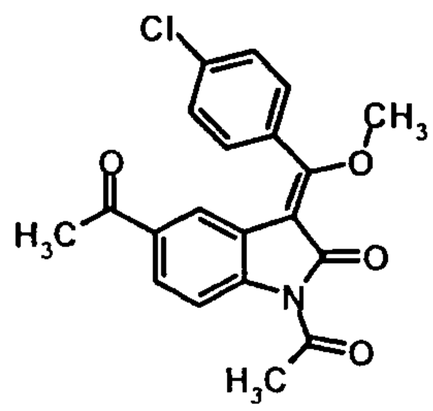
Yield: 52 % of theory

R_f = 0.56 (silica gel, methylene chloride/methanol 30:1)

$C_{22}H_{19}NO_6$ (MW = 393.393)

Mass spectrum: m/z = 394 $(M+H)^+$

(5) 1,5-diacetyl-3-[(4-chloro-phenyl)-methoxy-methylidene]-2-indolinone



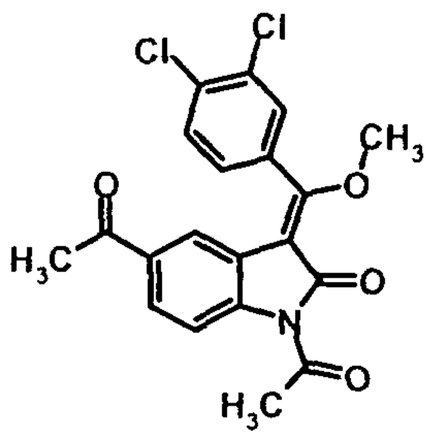
Prepared from 1,5-diacetyl-3-[(4-chloro-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.5)

Yield: 65 % of theory

$C_{20}H_{16}ClNO_4$ (MW = 369.802)

Mass spectrum: m/z = 370/372 $(M+H)^+$

(6) 1,5-diacetyl-3-[(3,4-dichloro-phenyl)-methoxy-methylidene]-2-indolinone



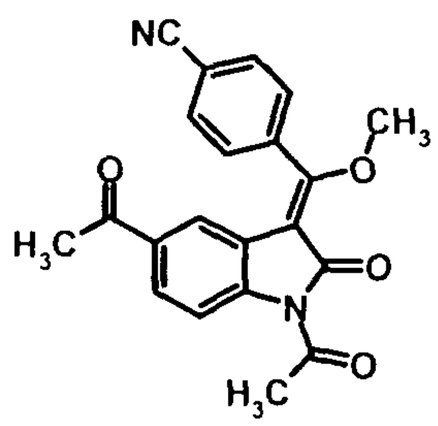
Prepared from 1,5-diacetyl-3-[(3,4-dichloro-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.6)

Yield: 72 % of theory

$C_{20}H_{15}Cl_2NO_4$ (MW = 404.247)

Mass spectrum: m/z = 404/406/408 $(M+H)^+$

(7) 1,5-diacetyl-3-[(4-cyano-phenyl)-methoxy-methylidene]-2-indolinone



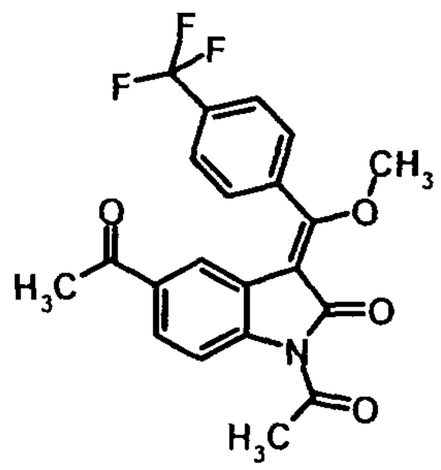
Prepared from 1,5-diacetyl-3-[(4-cyano-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.7)

Yield: 53 % of theory

$C_{21}H_{16}N_2O_4$ (MW = 360.367)

Mass spectrum: m/z = 361 $(M+H)^+$

(8) 1,5-diacetyl-3-[(4-trifluoromethyl-phenyl)-methoxy-methylidene]-2-indolinone



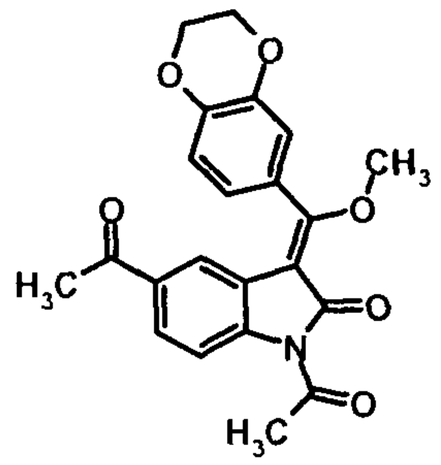
Prepared from 1,5-diacetyl-3-[(4-trifluoromethyl-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.8)

Yield: 37 % of theory

$C_{21}H_{16}F_3NO_4$ (MW = 403.354)

Mass spectrum: m/z = 404 $(M+H)^+$

(9) 1,5-diacetyl-3-[(2,3-dihydro-benzo-[1,4]dioxin-6-yl)-methoxy-methylidene]-2-indolinone



Prepared from 11,5-diacetyl-3-[(2,3-dihydro-benzo-[1,4]dioxin-6-yl)-hydroxy-methylidene]-2-indolinone (Ex. V.9)

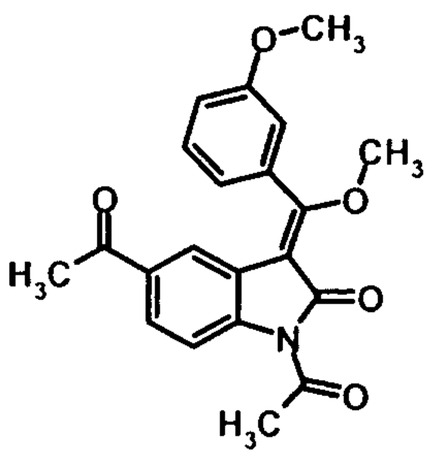
Yield: 52 % of theory

R_f = 0.82 (silica gel, methylene chloride/methanol 9:1)

$C_{22}H_{19}NO_6$ (MW = 393.393)

Mass spectrum: m/z = 394 $(M+H)^+$

(10) 1,5-diacetyl-3-[(3-methoxy-phenyl)-methoxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-3-[(3-methoxy-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.10)

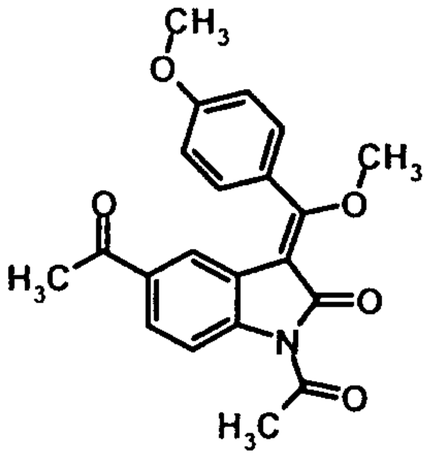
Yield: 48 % of theory

R_f = 0.40 (silica gel, methylene chloride/methanol 9:1)

$C_{21}H_{19}NO_5$ (MW = 365.383)

Mass spectrum: m/z = 366 $(M+H)^+$

(11) 1,5-diacetyl-3-[(4-methoxy-phenyl)-methoxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-3-[(4-methoxy-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.11)

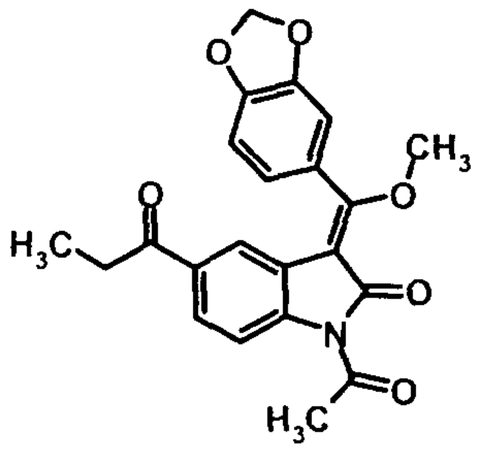
Yield: 85 % of theory

R_f = 0.35 (silica gel, methylene chloride/methanol 30:1)

$C_{21}H_{19}NO_5$ (MW = 365.383)

Mass spectrum: m/z = 366 $(M+H)^+$

(12) 1-diacetyl-5-propionyl-3-[(benzo[1,3]dioxol-5-yl)-methoxy-methylidene]-2-indolinone



Prepared from 1-diacetyl-5-propionyl-3-[(benzo[1,3]dioxol-5-yl)-hydroxy-methylidene]-2-indolinone (Ex. V.12)

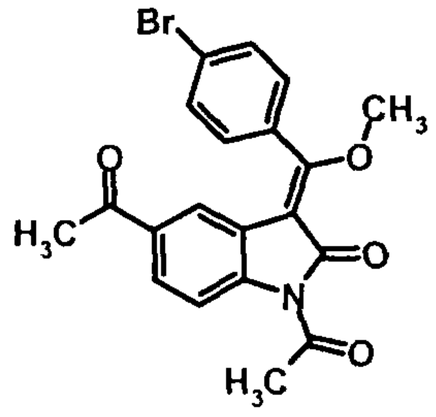
Yield: 98 % of theory

R_f = 0.63 (silica gel, methylene chloride/methanol 30:1)

$C_{22}H_{19}NO_6$ (MW = 393.393)

Mass spectrum: m/z = 394 $(M+H)^+$

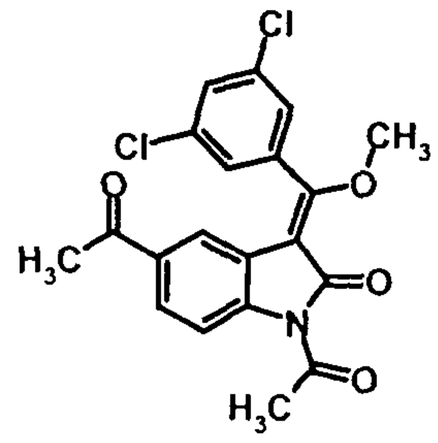
(13) 1,5-diacetyl-3-[(4-bromophenyl)-methoxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-3-[(4-bromophenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.13)

Yield: 48 % of theory

(14) 1,5-diacetyl-3-[(3,5-dichloro-phenyl)-methoxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-3-[(3,5-dichloro-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.14)

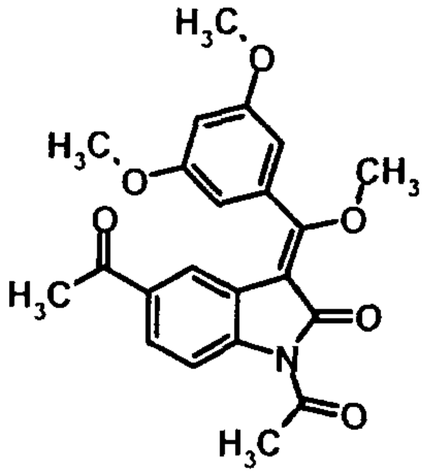
Yield: 44 % of theory

R_f = 0.86 (silica gel, methylene chloride/methanol 30:1)

$C_{19}H_{13}Cl_2NO_4$ (MW = 390.221)

Mass spectrum: m/z = 388/390/392 (Cl2, $M+H)^+$

(15) 1,5-diacetyl-3-[(3,5-dimethoxy-phenyl)-methoxy-methylidene]-2-indolinone



Prepared from 1,5-diacetyl-3-[(3,5-dimethoxy-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.15)

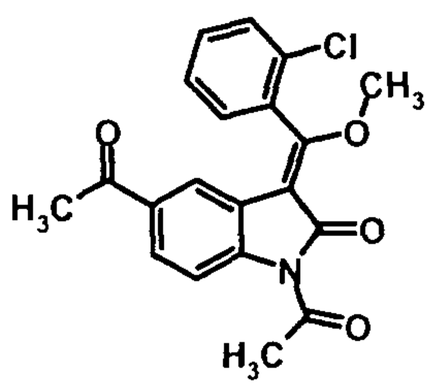
Yield: 74 % of theory

R_f = 0.65 (silica gel, methylene chloride/methanol 30:1)

$C_{22}H_{21}NO_6$ (MW = 395.409)

Mass spectrum: m/z = 396 $(M+H)^+$

(16) 1,5-diacetyl-3-[(2-chloro-phenyl)-methoxy-methylidene]-2-indolinone



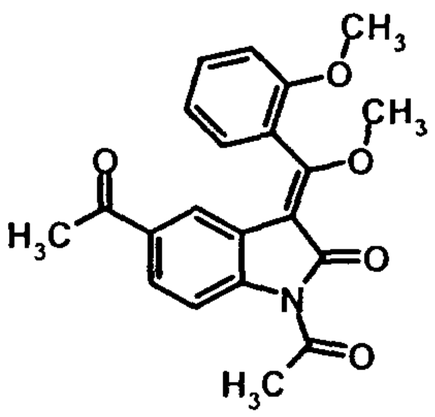
Prepared from 1,5-diacetyl-3-[(2-chloro-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.16)

Yield: 54 % of theory

$C_{20}H_{16}ClNO_4$ (MW = 369.802)

Mass spectrum: m/z = 370/372 $(M+H)^+$

(17) 1,5-diacetyl-3-[(2-methoxy-phenyl)-methoxy-methylidene]-2-indolinone



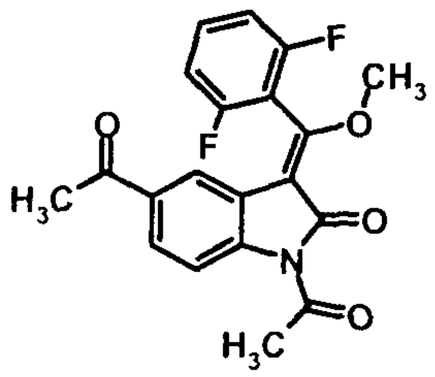
Prepared from 1,5-diacetyl-3-[(2-methoxy-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.17)

Yield: 56 % of theory

$C_{21}H_{19}NO_5$ (MW = 365.383)

Mass spectrum: m/z = 366 $(M+H)^+$

(18) 1,5-diacetyl-3-[(2,6-difluoro-phenyl)-methoxy-methylidene]-2-indolinone



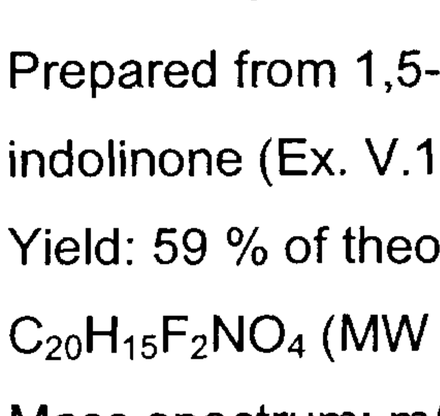
Prepared from 1,5-diacetyl-3-[(2,6-difluoro-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.18)

Yield: 59 % of theory

$C_{20}H_{15}F_2NO_4$ (MW = 3371.337)

Mass spectrum: m/z = 372 $(M+H)^+$

(19) 1,5-diacetyl-3-[(4-fluorophenyl)-methoxy-methylidene]-2-indolinone



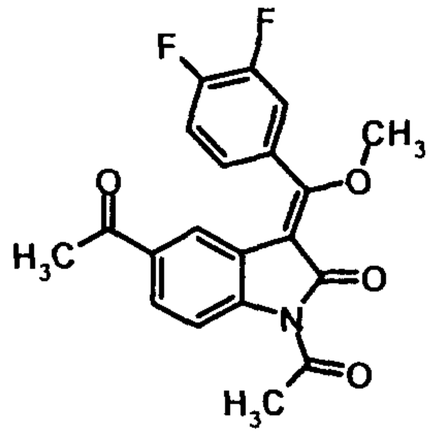
Prepared from 1,5-diacetyl-3-[(4-fluorophenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.19)

Yield: 88 % of theory

$C_{20}H_{16}FNO_4$ (MW = 353.347)

Mass spectrum: m/z = 354 $(M+H)^+$

(20) 1,5-diacetyl-3-[(3,4-difluoro-phenyl)-methoxy-methylidene]-2-indolinone



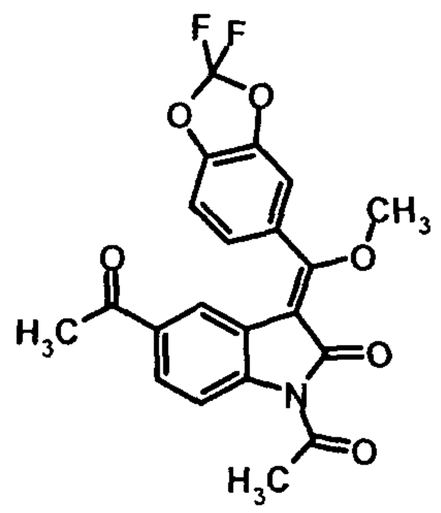
Prepared from 1,5-diacetyl-3-[(3,4-difluoro-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.20)

Yield: 23 % of theory

$C_{20}H_{15}F_2NO_4$ (MW = 371.334)

Mass spectrum: m/z = 372 $(M+H)^+$

(21) 1,5-diacetyl-3-[(2,2-difluoro-benzo[1,3]dioxol-5-yl)-methoxy-methylidene]-2-indolinone



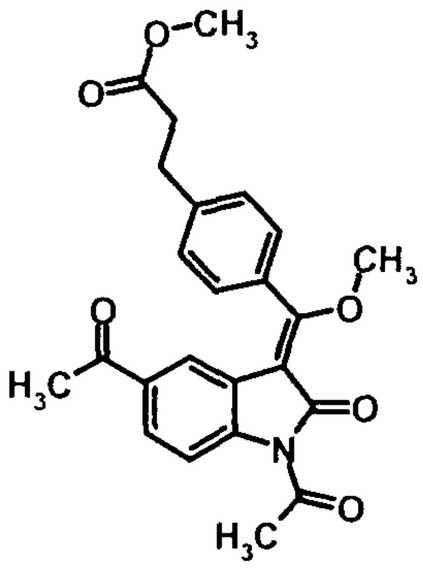
Prepared from 1,5-diacetyl-3-[(2,2-difluoro-benzo[1,3]dioxol-5-yl)-hydroxy-methylidene]-2-indolinone (Ex. V.21)

Yield: 6 % of theory

$C_{21}H_{15}F_2NO_6$ (MW = 415.346)

Mass spectrum: m/z = 416 $(M+H)^+$

(22) 1,5-diacetyl-3-[(4-(2-methoxycarbonyl-ethyl)-phenyl)-methoxy-methylidene]-2-indolinone



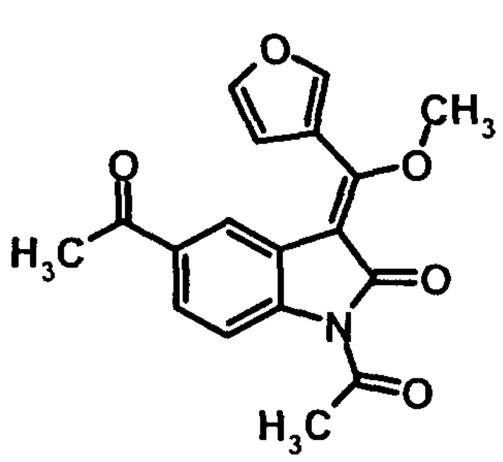
Prepared from 1,5-diacetyl-3-[(4-(2-methoxycarbonyl-ethyl)-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.22)

Yield: 63 % of theory

$C_{24}H_{23}NO_6$ (MW = 421.447)

Mass spectrum: m/z = 422 $(M+H)^+$

(23) 1,5-diacetyl-3-[furan-3-yl-methoxy-methylidene]-2-indolinone



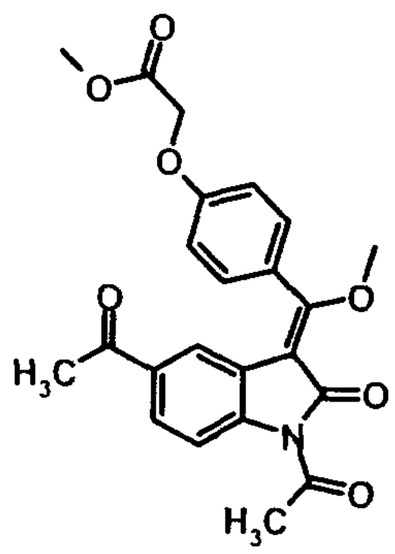
Prepared from 1,5-diacetyl-3-[furan-3-yl-hydroxy-methylidene]-2-indolinone (Ex. V.25)

Yield: 59 % of theory

$C_{18}H_{15}NO_5$ (MW = 325.324)

Mass spectrum: m/z = 326 $(M+H)^+$

(24) 1,5-diacetyl-3-[(4-methoxycarbonylmethoxy-phenyl)-methoxy-methylidene]-2-indolinone



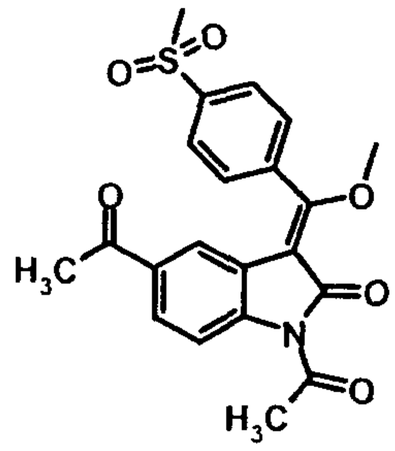
Prepared from 1,5-diacetyl-3-[(4-methoxycarbonylmethoxy-phenyl)-hydroxy-methylidene]-2-indolinone

Yield: 24 % of theory

$C_{23}H_{21}NO_7$ (MW = 423.415)

Mass spectrum: m/z = 424 $(M+H)^+$

(25) 1,5-diacetyl-3-[(4-methylsulphonyl-phenyl)-methoxy-methylidene]-2-indolinone



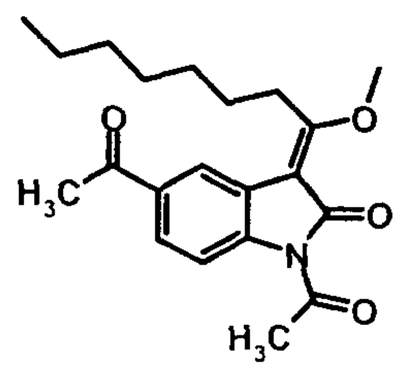
Prepared from 1,5-diacetyl-3-[(4-methylsulphonyl-phenyl)-hydroxy-methylidene]-2-indolinone (Ex. V.28)

Yield: 20 % of theory

$C_{21}H_{19}NO_6S$ (MW = 413.445)

Mass spectrum: m/z = 414 $(M+H)^+$

(26) 1,5-diacetyl-3-(1-methoxy-octylidene)-2-indolinone



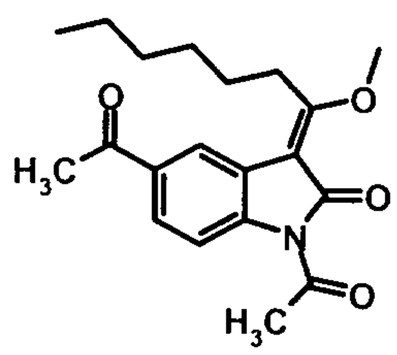
Prepared from 1,5-diacetyl-3-(1-hydroxyl-octylidene)-2-indolinone (Ex. VIII)

Yield: 82 % of theory

$C_{21}H_{27}NO_4S$ (MW = 357.443)

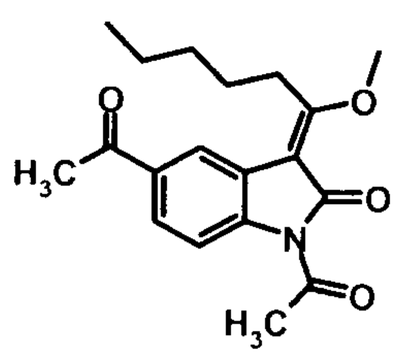
Mass spectrum: m/z = 358 $(M+H)^+$

(27) 1,5-diacetyl-3-(1-methoxy-heptylidene)-2-indolinone



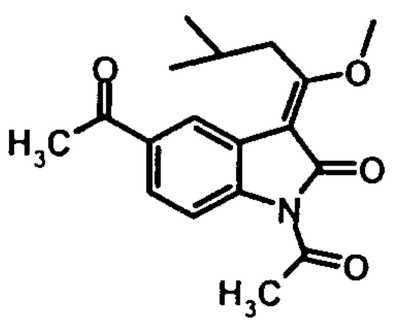
Prepared from 1,5-diacetyl-3- (1-hydroxy-heptylidene)-2-indolinone (Ex. V.32)

(28) 1,5-diacetyl-3-(1-methoxy-hexylidene)-2-indolinone



Prepared from 1,5-diacetyl-3- (1-hydroxy-hexylidene)-2-indolinone (Ex. V.33)

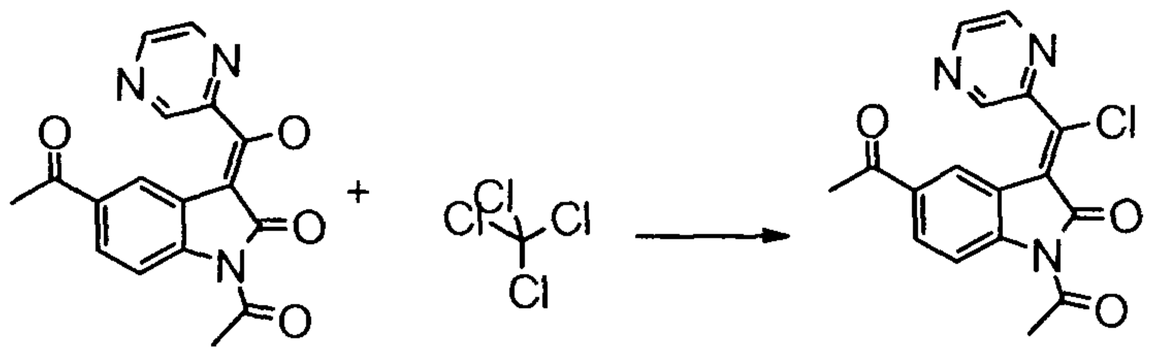
(29) 1,5-diacetyl-3-(1-methoxy-3-methyl-butylidene)-2-indolinone



Prepared from 1,5-diacetyl-3- (1-hydroxy-3-methyl-butylidene)-2-indolinone (Ex. V.34)

Example VII

1,5-diacetyl-3-[chloro-(pyrazin-2-yl)-methylidene]-2-indolinone



1.2 g (3.7 mmol) 1,5-diacetyl-3-[pyrazin-2-yl-hydroxy-methylidene]-2-indolinone (Ex. V.23) are dissolved in 50 ml dioxane and refluxed with 2 ml carbon tetrachloride and 2 g triphenylphosphine for 5 h. Then the mixture is left to cool and evaporated down. The residue is chromatographed through a silica gel column with methylene chloride/methanol 25:1, the corresponding fractions are combined and concentrated by rotary evaporation.

Yield: 400 mg (40 % of theory)

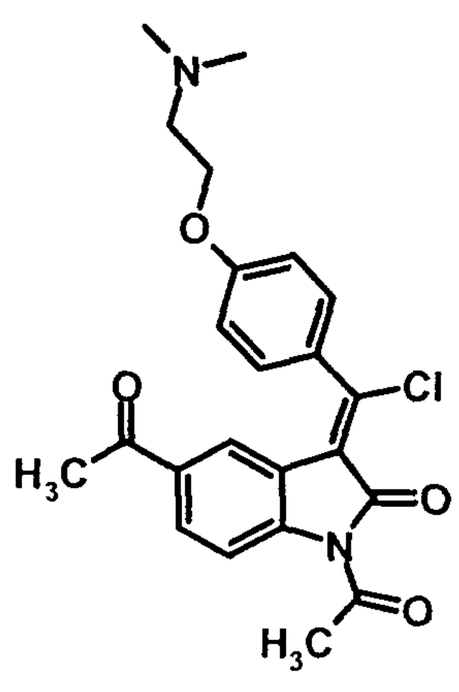
R_f = 0.70 (silica gel, methylene chloride/methanol 30:1)

$C_{17}H_{12}ClN_3O_3$ (MW = 341.756)

Mass spectrum: m/z = 342/344 $(M+H)^+$ (CL)

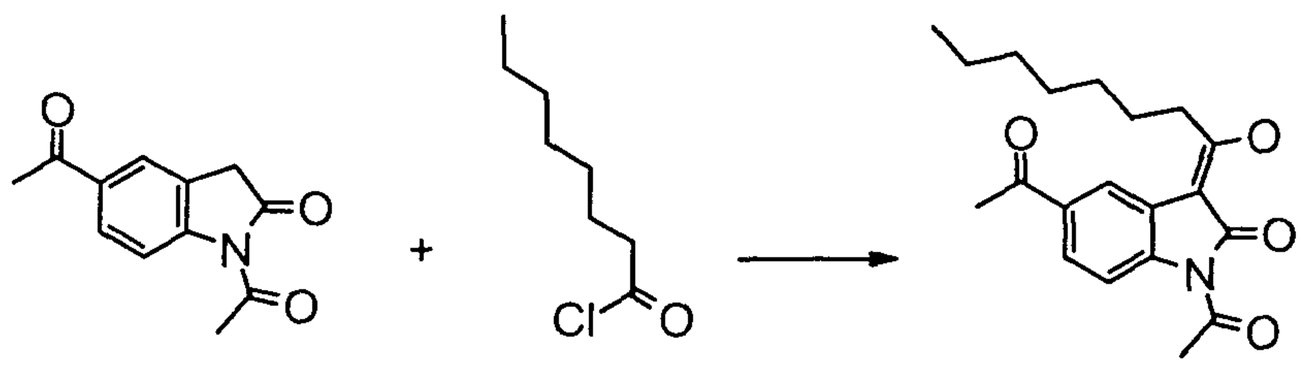
The following compounds are prepared analogously to Example VII:

(1)1,5-diacetyl-3-[chloro-(4-(2-dimethylamino-ethoxy)-phenyl)-methylidene]-2-indolinone



Example VIII

1,5-diacetyl-3-(1-hydroxy-octylidene)-2-indolinone



4.3 g (20 mmol) 1,5-diacetyl-2-indolinone (Ex. II) are dissolved in 20 ml of dimethylformamide and 490 mg dimethylaminopyridine (DMAP) and 6 ml triethylamine are added and the mixture is cooled in the ice bath. 3.8 ml (22 mmol) octanoic acid chloride in 20 ml of dimethylformamide are added to this solution and the mixture is stirred for a further 10 min. Then the reaction mixture is added to 150 ml methylene chloride and 150 ml 1 N hydrochloric acid. The organic phase is separated off, dried over sodium sulphate and concentrated by rotary evaporation. The residue is chromatographed through a silica gel column with methylene chloride/methanol 95:5.

Yield: 740 mg (11 % of theory)

$C_{20}H_{25}NO_4$ (MW = 343.417)

Mass spectrum: m/z = 344 $(M)^+$

Preparation of the end compounds:

Eluant:

A: methylene chloride/methanol 9:1

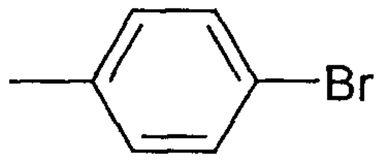
B: methylene chloride/methanol 4:1

C: methylene chloride/methanol/conc. ammonia 9:1:0.1

D: methylene chloride/methanol 30:1

E: methylene chloride/methanol/triethylamine 9:1:0.1

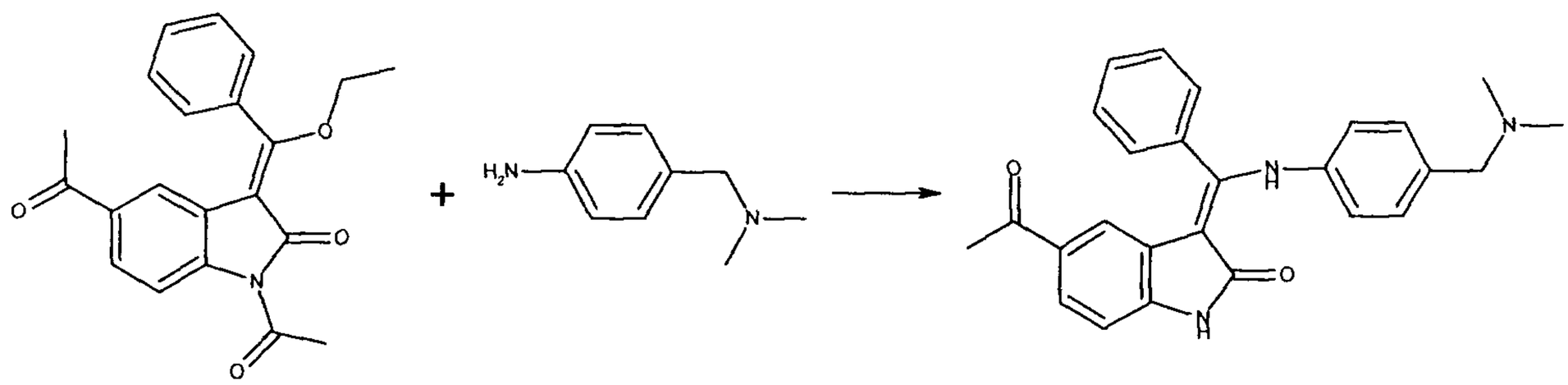
In the formulae in the Table the bond drawn free always represents the bond of the relevant group at the point of attachment in the molecule. The entry " $-CH_3$" in the Table thus denotes a methyl group and the entry



denotes a 4-bromophenyl group .

Example 1

5-acetyl-3-[(4-dimethylaminomethylphenylamino)-phenyl-methylidene]-2-indolinone



200 mg (0.57 mmol) 1,5-diacetyl-3-[ethoxy-phenyl-methylidene]-2-indolinone (Ex. III) are suspended in 5 ml of dimethylformamide and stirred with 86 mg (0.57 mmol) 4-dimethylaminomethyl-phenylamine at an ambient temperature of 80°C for about 5 h. The acetyl-protected intermediate product is combined with 2 ml of conc. ammonia without being purified and stirred overnight at ambient temperature. Then the

mixture is evaporated down and the residue is chromatographed through a silica gel column with methylene chloride/methanol 9:1 as eluant.

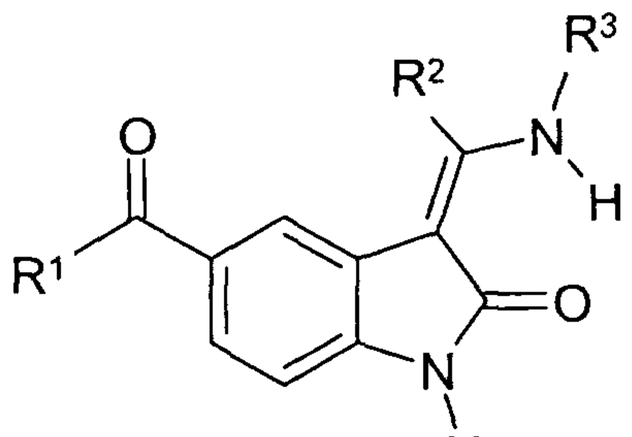
Yield: 100 mg (42 % of theory)

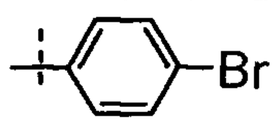
R_f = 0.27 (silica gel, methylene chloride/methanol 9:1)

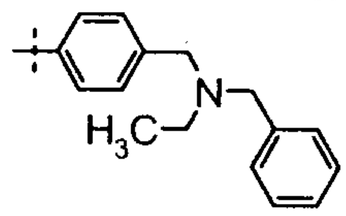
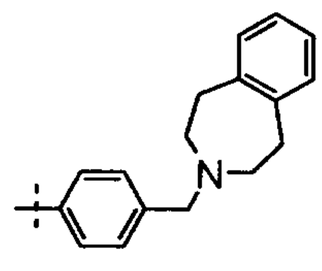
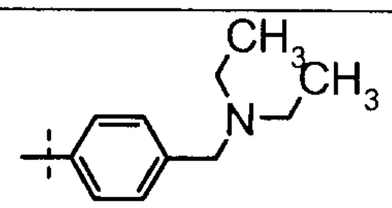
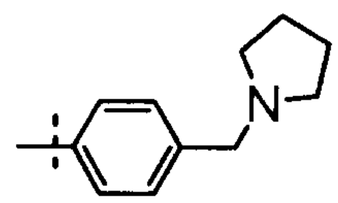
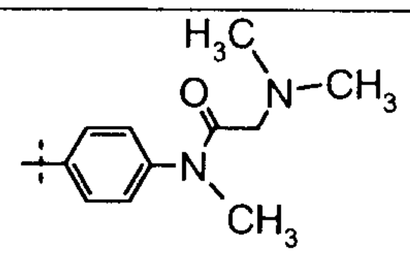
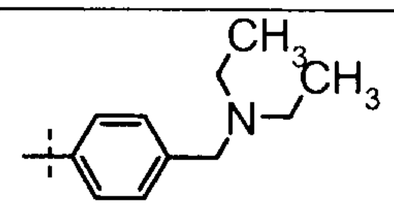
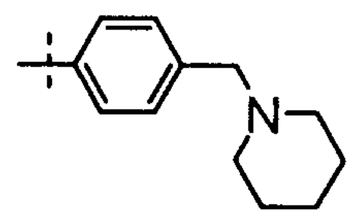
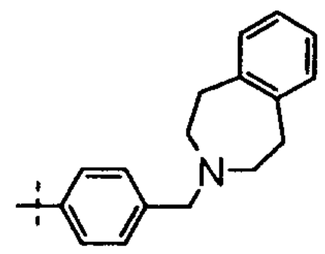
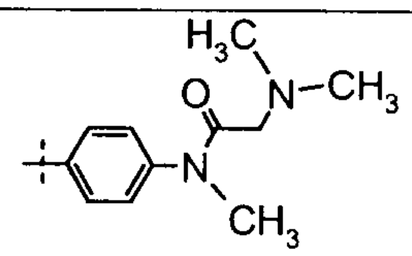
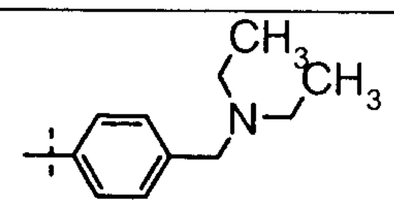
$C_{26}H_{25}N_3O_2$ (MW = 411.502)

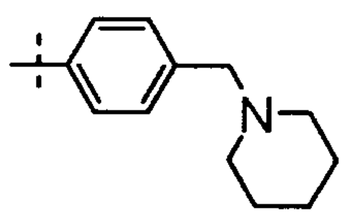
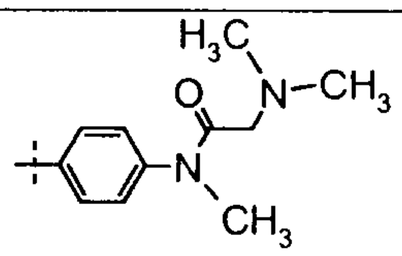
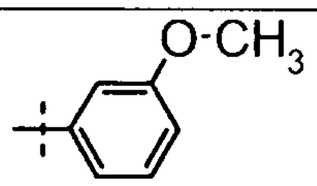
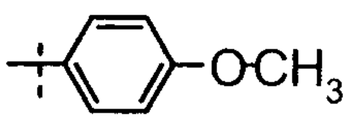
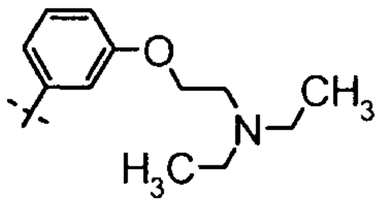
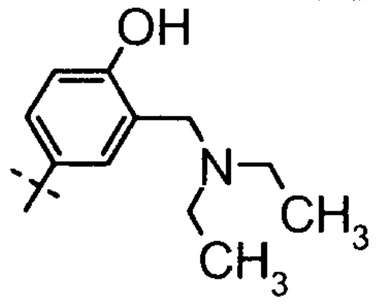
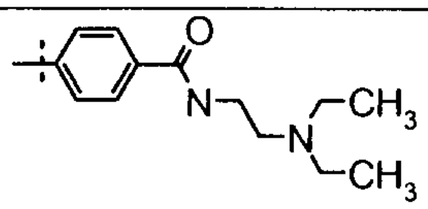
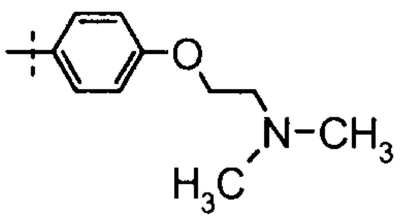
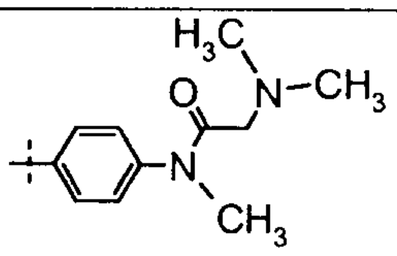
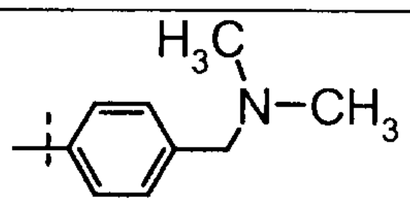
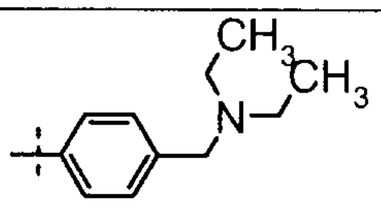
Mass spectrum: m/z = 412 $(M+H)^+$

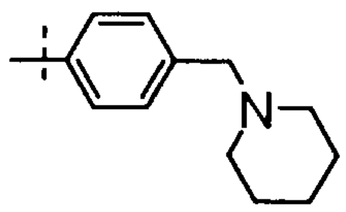
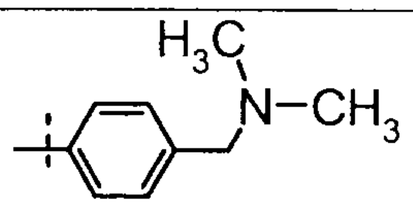
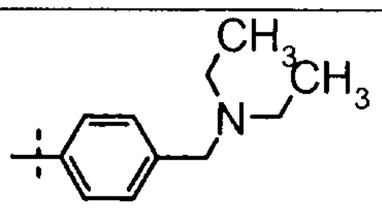
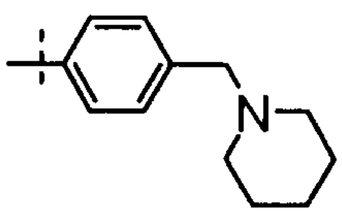
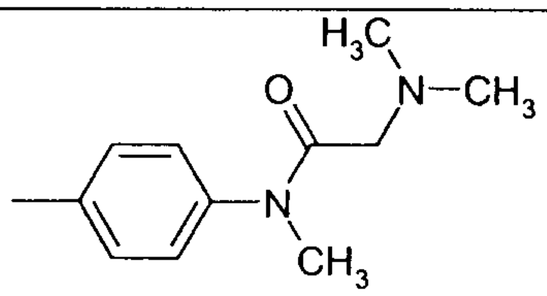
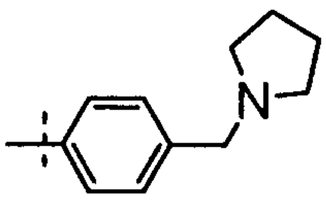
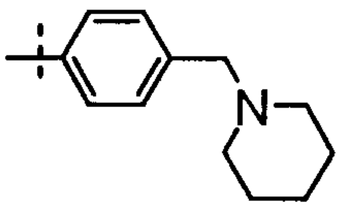
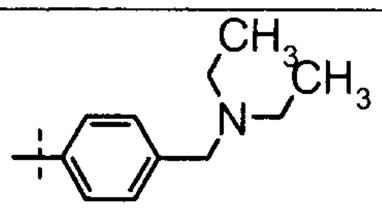
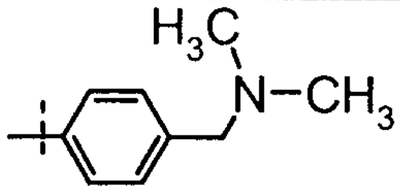
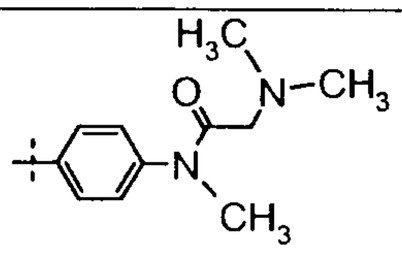
The following compounds of formula I are prepared analogously to Example 1:

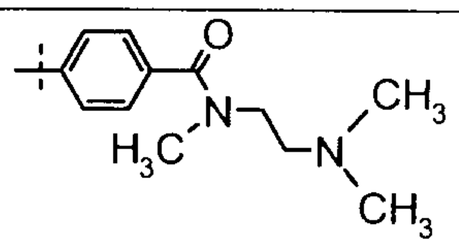
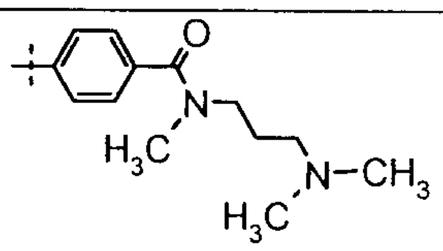
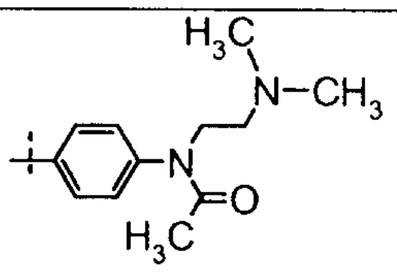
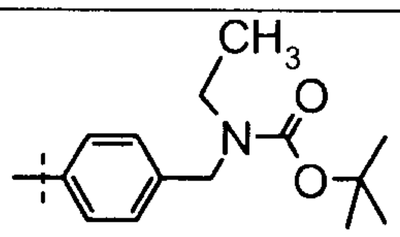
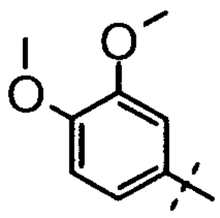
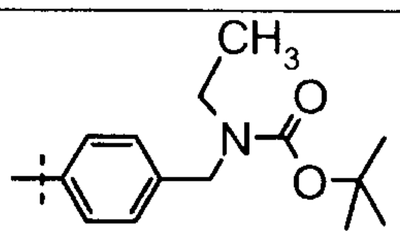
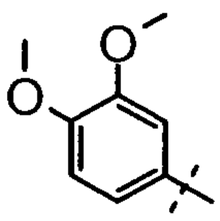
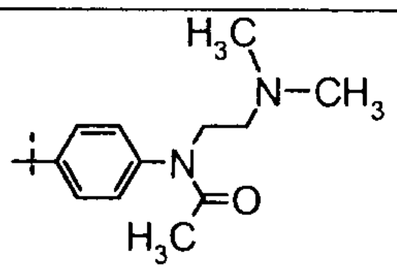
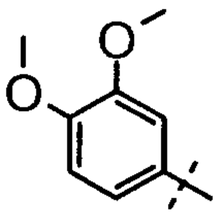
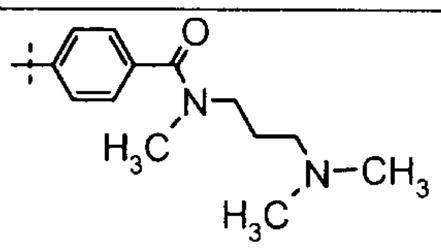
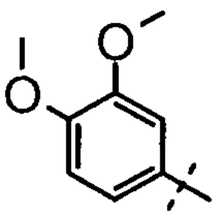
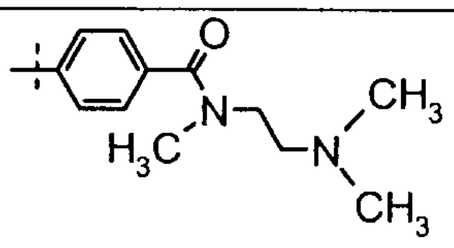
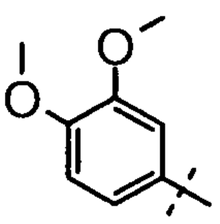
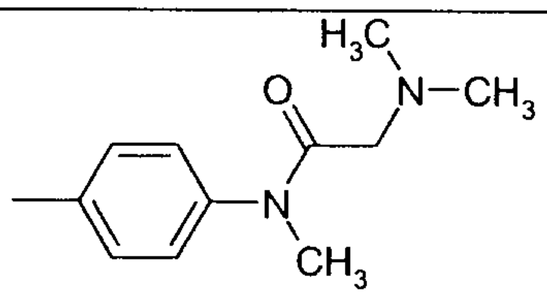


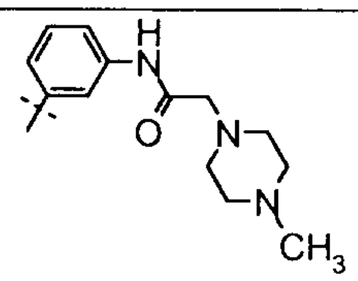
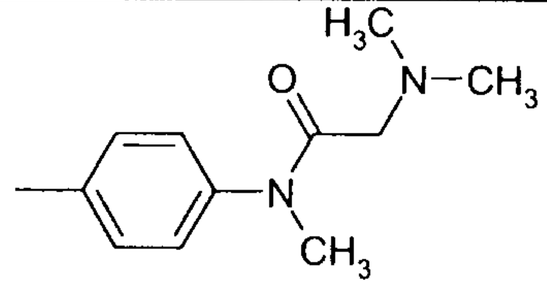
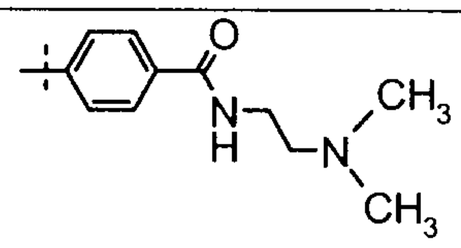
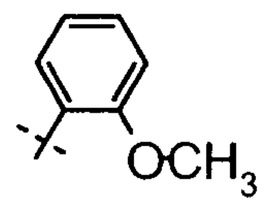
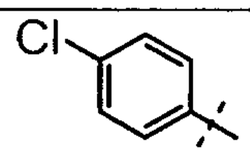
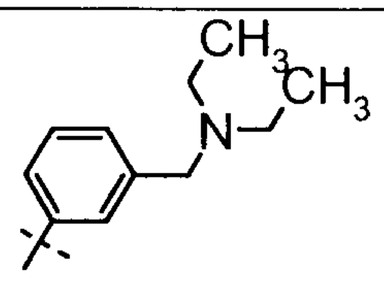
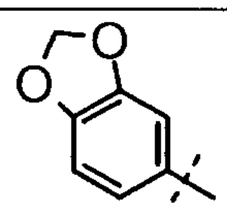
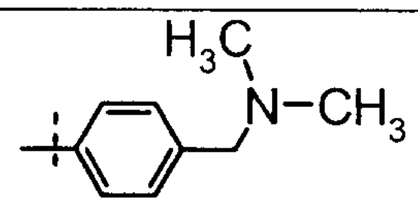
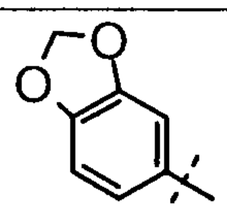
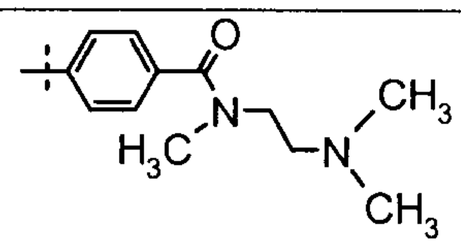
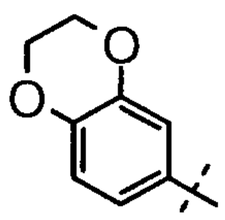
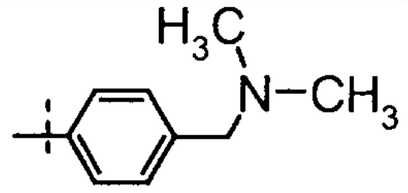
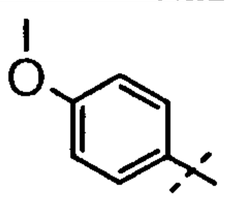
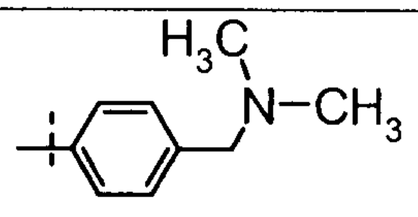
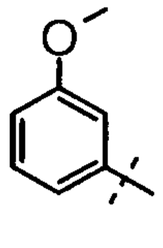
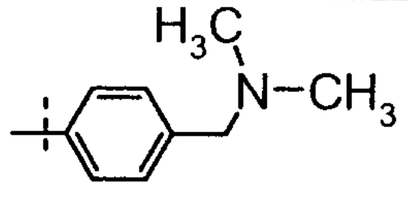
Example	R^1	R^2	R^3	Educt Yield [%]	Mass spectrum (ES) m/z	R_f value (silica gel) (eluant)
1.001	Me	Ph		III 60.5	$(M+H)^+$ = 432/434 (Br)	0.6 (EE /cyclo-hexane /MeOH 9:9:2)
1.002	Me	Ph		III 35.0	$(M+H)^+$ = 451	0.4 (A)
1.003	Me	Ph		III 56.7	$(M-H)^-$ = 387	not deter-mined

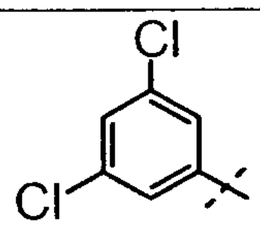
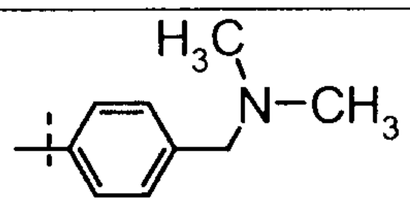
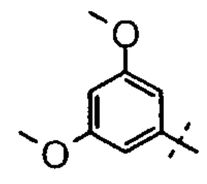
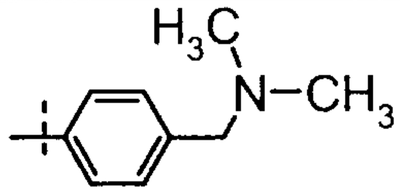
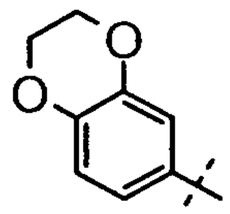
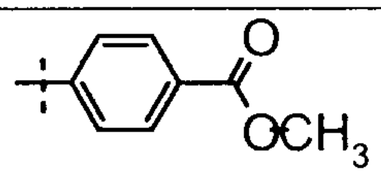
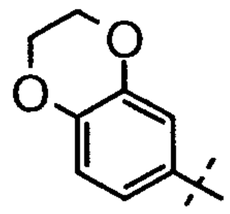
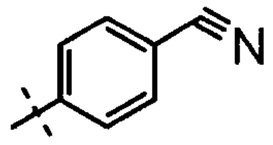
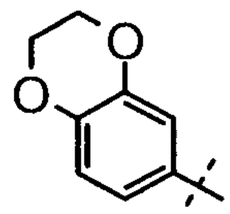
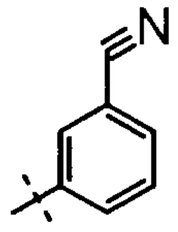
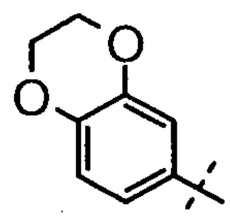
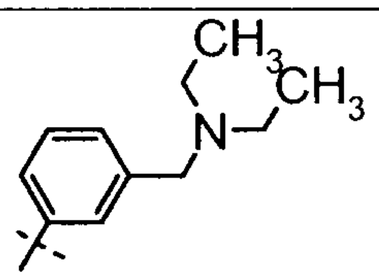
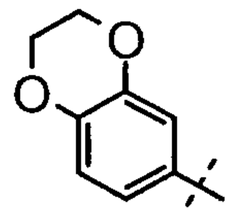
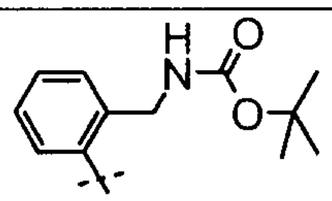
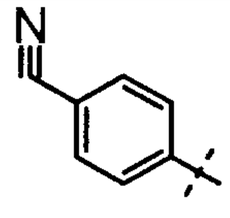
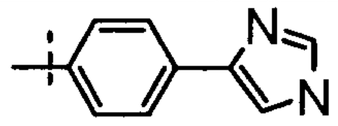
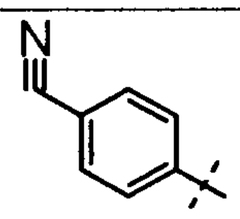
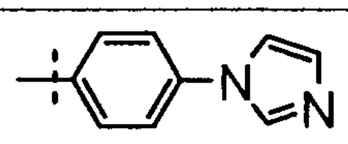
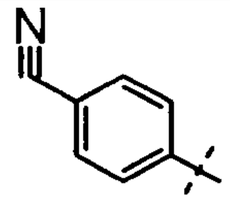
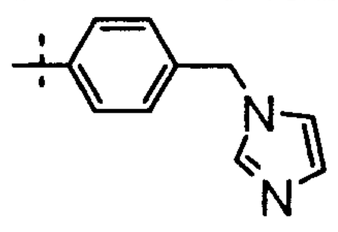
1.004	Me	Ph		III 74.9	$(M+H)^+$ = 502	0.2 (D)
1.005	Me	Ph		III 56.2	$(M+H)^+$ = 514	0.38 (A)
1.006	Me	Ph		III 47.7	$(M+H)^+$ = 440	0.3 (A)
1.007	Me	Ph		III 47.9	$(M+H)^+$ = 438	0.31 (A)
1.008	Me	Ph		III 20.5	$(M+H)^+$ = 469	0.24 (A)
1.009	Et	Ph		IV.3 55.1	$(M+H)^+$ = 454	0.3 (A)
1.010	Et	Ph		IV.3 14.6	$(M-H)^-$ = 464	0.33 (A)
1.011	Et	Ph		IV.3 24.1	$(M+H)^+$ = 528	0.33 (A)
1.012	Et	Ph		IV.3 28.0	$(M+H)^+$ = 483	0.27 (A)
1.013	n-C_5H_{11}	Ph		IV.4 53.2	$(M-H)^-$ = 494	0.32 (A)

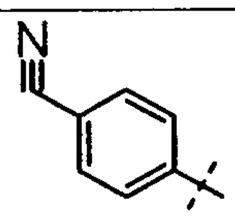
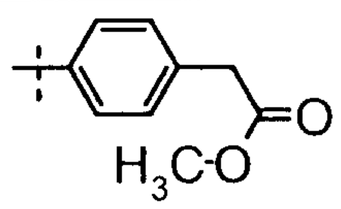
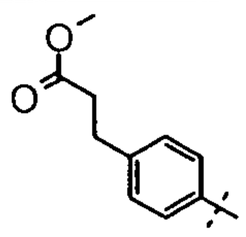
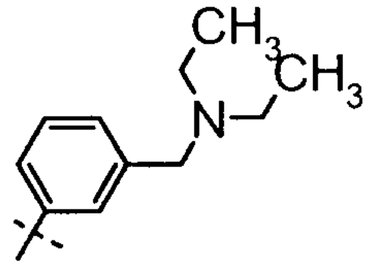
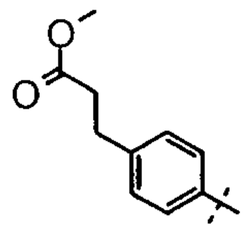
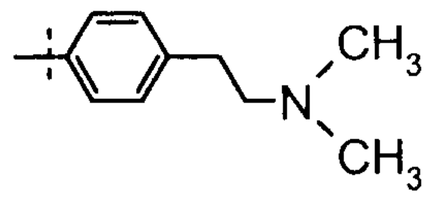
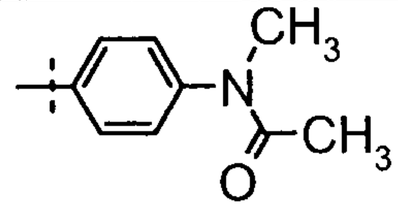
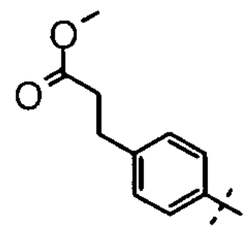
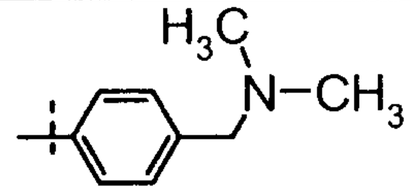
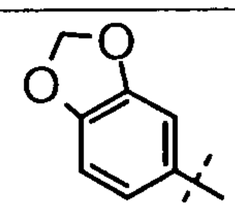
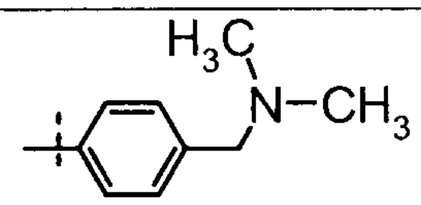
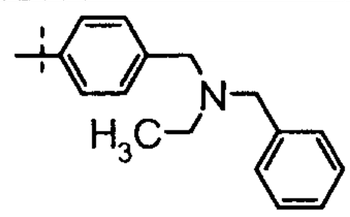
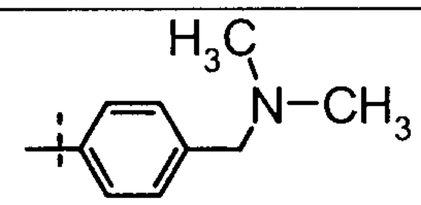
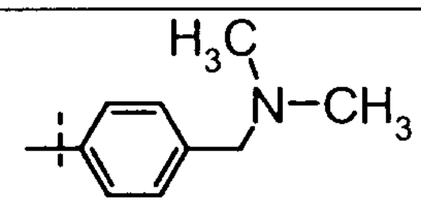
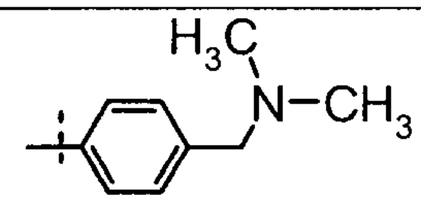
1.014	n-C_5H_{11}	Ph		IV.4 79.9	$(M-H)^-$ = 506	0.28 (A)
1.015	n-C_5H_{11}	Ph		IV.4 54.1	$(M-H)^-$ = 523	0.33 (A)
1.016	Me	Ph		III 30.8	$(M-H)^-$ = 383	0.32 (A)
1.017	Me	Ph		III 57.0	$(M-H)^-$ = 383	0.26 (A)
1.018	Me	Ph		III 53.0	$(M-H)^-$ = 468	0.19 (A)
1.019	Me	Ph		III 9.8	$(M-H)^-$ = 454	0.37 (A)
1.020	Me	Ph		III 35.5	$(M+H)^+$ = 497	0.39 (B)
1.021	Me	Ph		III 70.0	$(M-H)^-$ = 440	0.15 (A)
1.022	Ph	Ph		III.2 28.4	$(M+H)^+$ = 531	0.46 (A)
1.023	Ph	Ph		III.2 46.3	$(M+H)^+$ = 474	0.45 (A)
1.024	Ph	Ph		III.2 46.5	$(M+H)^+$ = 502	0.48 (A)

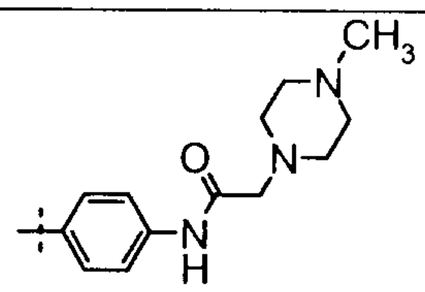
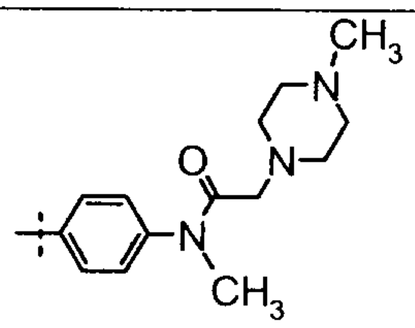
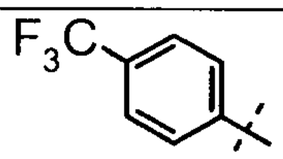
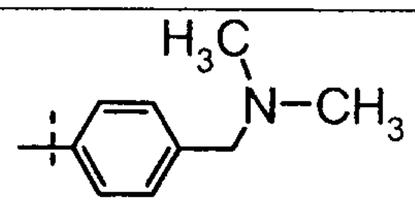
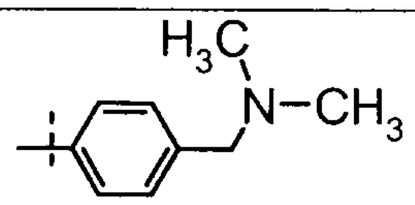
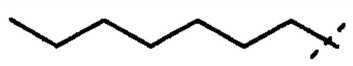
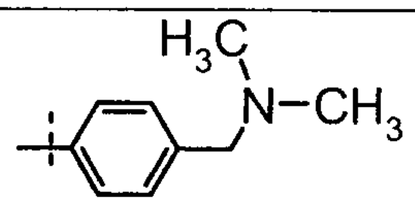
1.025	Ph	Ph		III.2 57.4	not deter-mined	0.46 (A)
1.026	n-Pr	Ph		IV.5 33.1	$(M+H)^+$ = 440	0.32 (A)
1.027	n-Pr	Ph		IV.5 32.3	$(M+H)^+$ = 468	0.34 (A)
1.028	n-Pr	Ph		IV.5 83.4	$(M+H)^+$ = 480	0.36 (A)
1.029	n-Pr	Ph		IV.5 45.6	$(M+H)^+$ = 497	0.36 (A)
1.030	i-Pr	Ph		IV.1 29.7	$(M-H)^-$ = 464	0.3 (A)
1.031	i-Pr	Ph		IV.1 44.6	$(M+H)^+$ = 480	0.25 (A)
1.032	i-Pr	Ph		IV.1 9.4	$(M+H)^+$ = 468	0.28 (A)
1.033	i-Pr	Ph		IV.1 22.9	$(M+H)^+$ = 440	0.31 (A)
1.034	i-Pr	Ph		VI.1 20.3	$(M+H)^+$ = 497	0.28 (A)

1.035	Me	Ph		III 53.1	$(M+H)^+$ = 483	0.68 (A)
1.036	Me	Ph		III 42.2	$(M+H)^+$ = 543	0.23 (B)
1.037	Me	Ph		III 33.8	$(M+H)^+$ = 483	0.6 (B)
1.038	Me	Ph		III 59.2	$(M+H)^+$ = 512	0.86 (B)
1.039	Me			VI 84.7	$(M+H)^+$ = 572	0.87 (B)
1.040	Me			VI 40.1	$(M+H)^+$ = 543	0.43 (B)
1.041	Me			VI 17.8	$(M+H)^+$ = 557	0.36 (B)
1.042	Me			VI 16.4	$(M+H)^+$ = 543	0.35 (B)
1.043	Me			VI 61.7	$(M+H)^+$ = 529	0.38 (B)

1.044	Me	Ph		III 32.1	$(M+H)^+$ = 510	0.34 (C)
1.045	Me	Ph		III 66.9	$(M+H)^+$ = 469	0.46 (C)
1.046	Me	Ph		III 60.8	$(M+H)^+$ = 483	0.32 (C)
1.047	Me	Ph		III 81.9	$(M+H)^+$ = 385	0.57 (A)
1.048	Me			VI.5 74.9	$(M+H)^+$ = 474/476 (Cl)	0.26 (A)
1.049	Me			VI.1 39.2	$(M+H)^+$ = 456	0.33 (A)
1.050	Me			VI.2 6.2	$(M+H)^+$ = 527	0.61 (B)
1.051	Me			VI.9 60.8	$(M+H)^+$ = 470	0.4 (A)
1.052	Me			VI.11 29.0	$(M-H)^-$ = 440	0.05 (A)
1.053	Me			VI.10 29.0	$(M+H)^+$ = 442	0.24 (A)

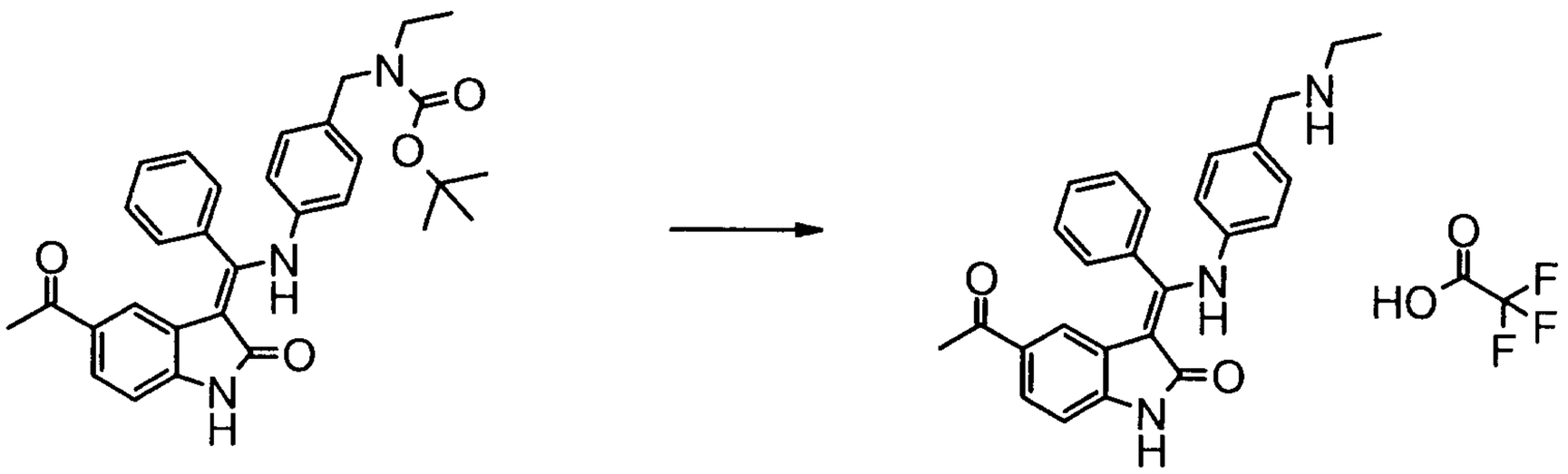
1.054	Me			VI.14 46.3	$(M+H)^+$ = 480/482/ 484 (Cl2)	0.33 (A)
1.055	Me			VI.15 58.7	$(M+H)^+$ = 472	0.15 (A)
1.056	Me			VI.9 75.2	$(M+H)^+$ = 471	0.42 (A)
1.057	Me			VI.9 46.8	$(M+H)^+$ = 438	0.44 (A)
1.058	Me			VI.9 25.2	$(M+H)^+$ = 438	0.38 (A)
1.059	Me			VI.9 74.7	$(M+H)^+$ = 498	0.27(A)
1.060	Me			VI.9 39.9	$(M+H)^+$ = 542	0.47 (A)
1.061	Me			VI.7 69.9	$(M+H)^+$ = 446	0.34 (A)
1.062	Me			VI.7 58.2	$(M+H)^+$ = 446	0.23 (A)
1.063	Me			VI.7 47.0	$(M+H)^+$ = 460	0.38 (A)

1.064	Me			VI.7 70.2	$(M-H)^-$ = 450	0.52 (A)
1.065	Me			VI.22 48.1	$(M+H)^+$ = 526	0.37 (A)
1.066	Me			VI.22 65.9	$(M+H)^+$ = 512	0.22 (A)
1.067	Me	Ph		III 82.3	$(M+H)^+$ = 426	0.6 (A)
1.068	Me			VI.22 56.5	$(M+H)^+$ = 498	0.36 (A)
1.069	Et			VI.12 32.3	$(M+H)^+$ = 470	0.13 (A)
1.070	Me	Me		IV.2 83.9	$(M+H)^+$ = 440	0.80 (A)
1.071	Me	Me		IV.2 73.0	$(M+H)^+$ = 350	0.33 (A)
1.072	Me	Et		III.3 49.0	$(M+H)^+$ = 364	0.33 (E)
1.073	Me	n-Pr		III.4 21.0	$(M+H)^+$ = 378	0.52 (C)

1.074	Me	Ph		III 56.0	$(M+H)^+$ = 510	0.51 (C)
1.075	Me	Ph		III 21.0	$(M+H)^+$ = 524	0.49 (C)
1.076	Me			VI.8 64.0	$(M+H)^+$ = 480	0.32 (A)
1.077	Me	n-Bu		III.5 38.0	$(M+H)^+$ = 390	0.45 (E)
1.078	Me			VI.26 62.6	$(M+H)^+$ = 432	0.30 (A)

Example 2

5-acetyl-3-[(4-ethylaminomethyl-phenylamino)-phenyl-methylidene]-2-indolinone-triflate



250 mg (0.49 mmol) 5-acetyl-3-[(4-((tert-butoxycarbonyl-ethyl-amino)-methyl)-phenyl-amino-phenyl-methylidene]-2-indolinone (Example 1.038) are dissolved in 10 ml methylene chloride and combined batchwise with 5 ml trifluoroacetic acid. Then the solution is stirred for 3 h at ambient temperature. It is then concentrated to dryness by rotary evaporation and the residue is washed with methanol.

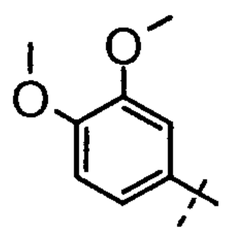
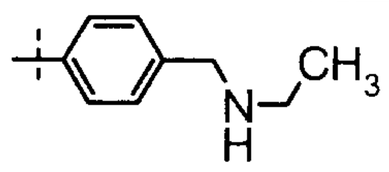
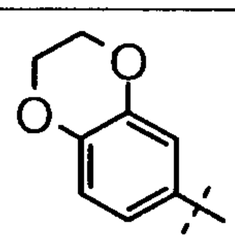
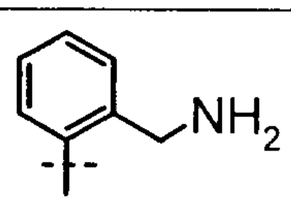
Yield: 300 mg (97 % of theory)

R_f = 0.37 (silica gel, methylene chloride/methanol 4:1)

$C_{26}H_{25}N_3O_2$ (MW = 411.51)

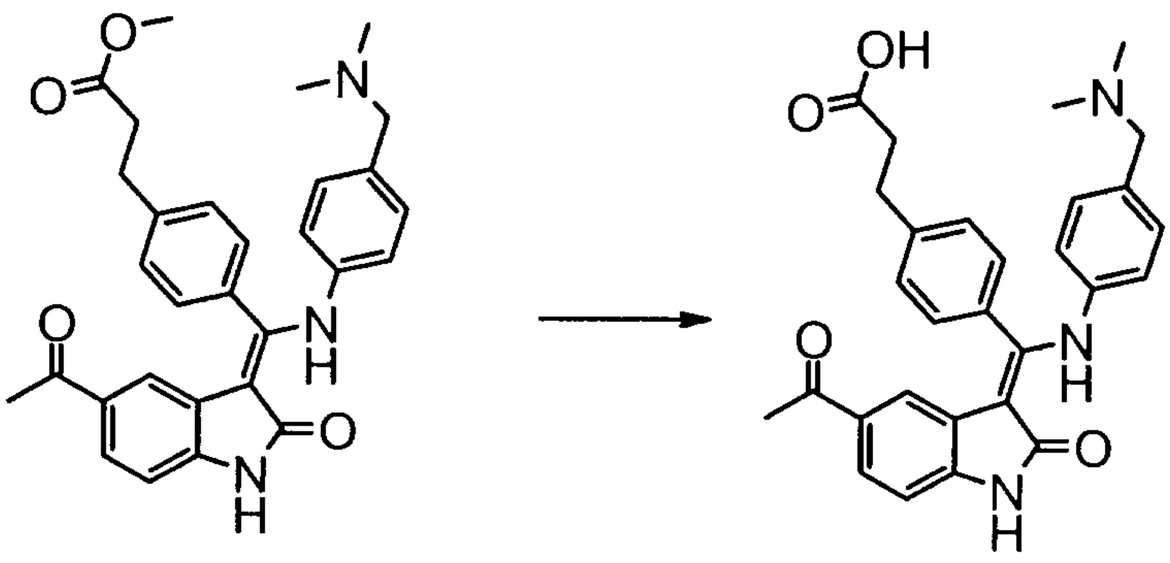
Mass spectrum: m/z = 412 $(M+H)^+$

The following compounds of formula I are prepared analogously to Example 2, in each case as the triflate:

Ex-ample	R^1	R^2	R^3	Educt Yield [%]	Mass spectrum (ES) m/z	R_f value (silica gel) (eluant)
2.001	Me			1.039 93.1	$(M+H)^+$ = 472	0.39 (B)
2.002	Me			1.060 97.5	$(M+H)^+$ = 442	0.21 (A)

Example 3

5-acetyl-3-{[4-(2-carboxy-ethyl)-phenyl]-[4-(dimethylaminomethyl)-phenylamino]-methylidene}-2-indolinone



100 mg (0.20 mmol) 5-acetyl-3-{[4-(2-methoxycarbonyl-ethyl)-phenyl]-[4-(dimethyl-aminomethyl)-phenylamino]-methylidene}-2-indolinone (Example 1.068) are

suspended in 0.4 ml 1 N sodium hydroxide solution and 4 ml of methanol and stirred overnight. Then the mixture is left to cool, 0.8 ml 1 N hydrochloric acid are added and the mixture is evaporated to dryness. The residue is taken up in 20 ml methylene chloride/methanol 30:1, dried over sodium sulphate and evaporated down.

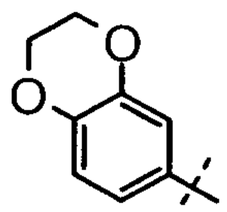
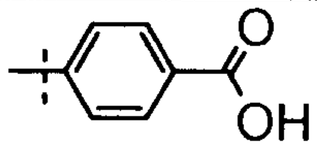
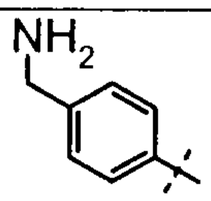
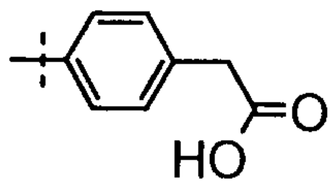
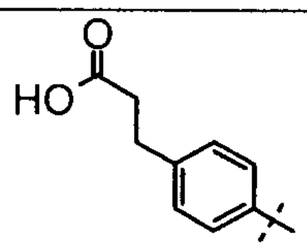
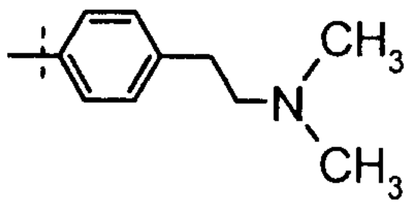
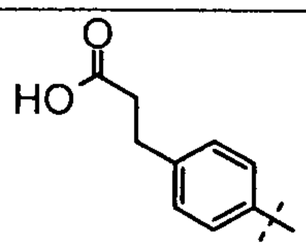
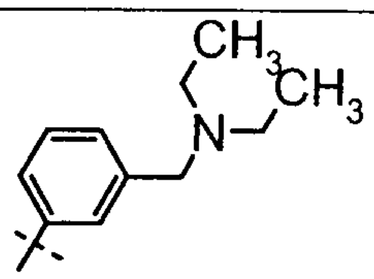
Yield: 96 mg (98 % of theory)

R_f = 0.50 (silica gel, methanol)

$C_{29}H_{29}N_3O_4$ (MW = 483.565)

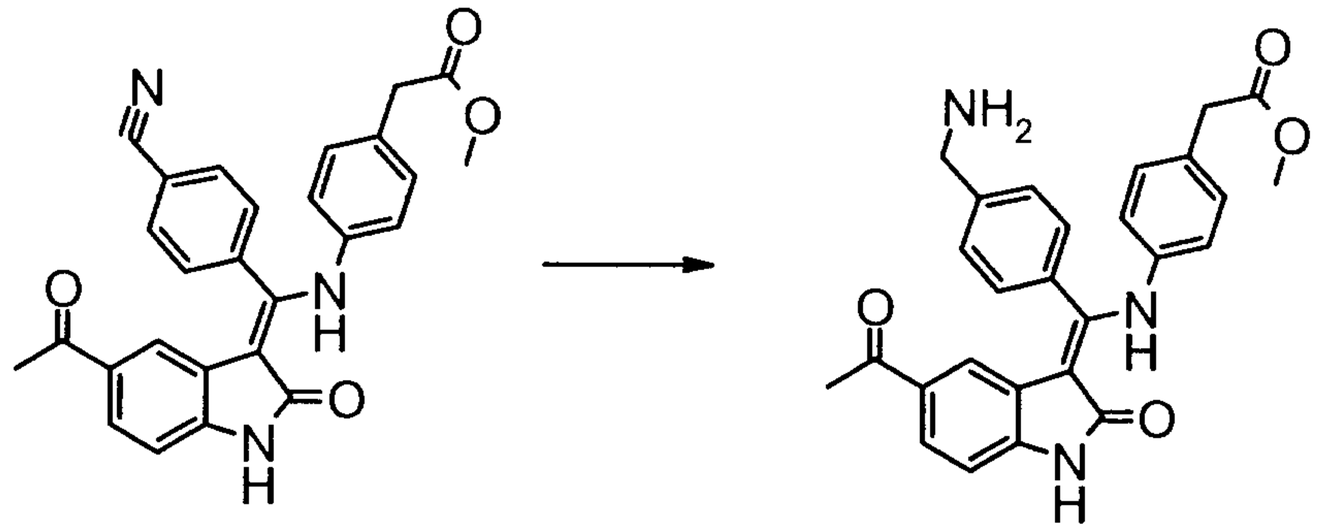
Mass spectrum: m/z = 484 $(M+H)^+$

The following compounds of formula I are prepared analogously to Example 3:

Example	R^1	R^2	R^3	Educt Yield [%]	Mass spectrum (ES) m/z	R_f value (silica gel) (eluant)
3.001	Me			1.055 92.8	$(M+H)^+$ = 457	0.27 (A)
3.002	Me			4.002 45.0	$(M-H)^-$ = 440	0.47 (MeOH)
3.003	Me			1.066 94.8	$(M+H)^+$ = 498	0.29 (MeOH)
3.004	Me			1.065 98	$(M+H)^+$ = 512	0.31 (MeOH)

Example 4

5-acetyl-3-[(4-aminomethyl-phenyl)-(4-(methoxycarbonylmethyl)-phenylamino)-methylidene]-2-indolinone



100 mg (0.22 mmol) 5-acetyl-3-[(4-cyano-phenyl)-(4-(methoxycarbonylmethyl)-phenylamino)-methylidene]-2-indolinone (Example 1.064) are dissolved in 12 ml of methanolic ammonia, combined with 80 mg Raney nickel and hydrogenated at ambient temperature for 7 h at a pressure of 50 psi. Then the catalyst is filtered off and the solution is evaporated down. The residue is chromatographed through a silica gel column with methylene chloride:methanol 30:1. The desired fraction is collected and evaporated down.

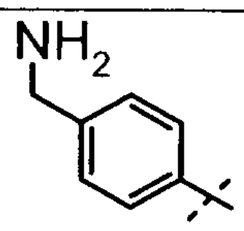
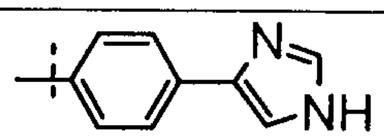
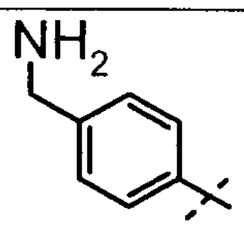
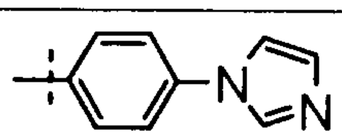
Yield: 10 mg (9 % of theory)

R_f = 0.54 (silica gel, methylene chloride/methanol/conc. ammonia 9:1:0.1)

$C_{27}H_{25}N_3O_4$ (MW = 455.512)

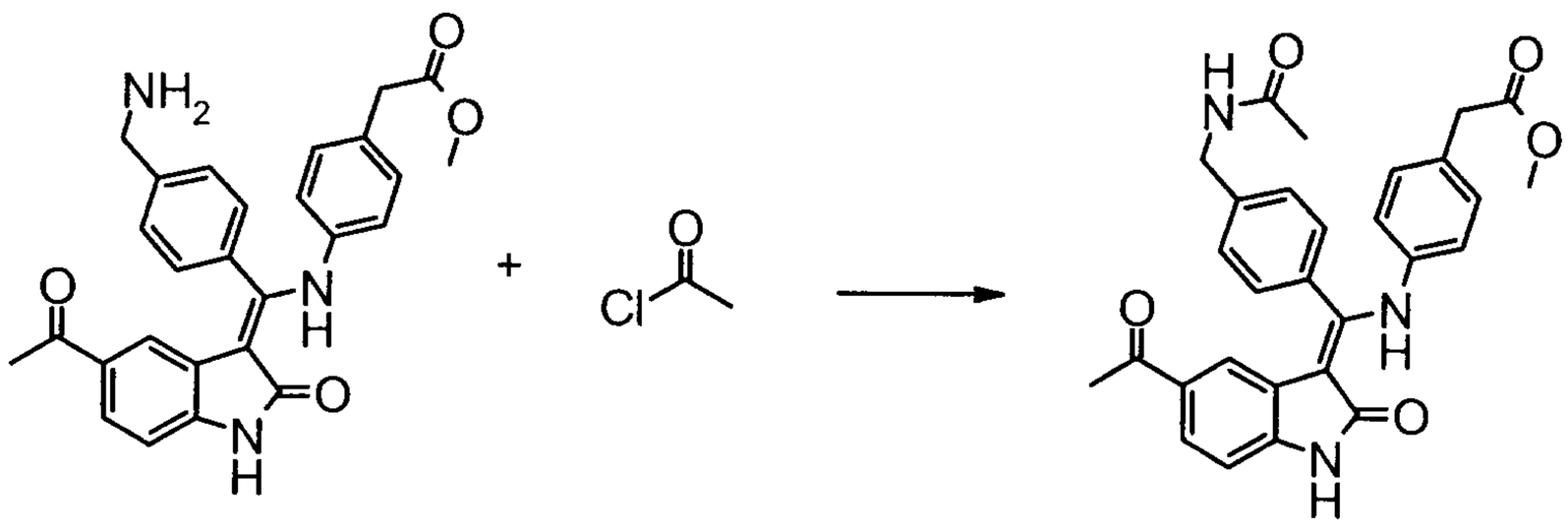
Mass spectrum: m/z = 456 $(M+H)^+$

The following compounds of formula I are prepared analogously to Example 4:

Ex-ample	R^1	R^2	R^3	Educt Yield [%]	Mass spectrum (ES) m/z	R_f value (silica gel) (eluant)
4.001	Me			1.061 35.7	$(M+H)^+$ = 450	0.28 (C)
4.002	Me			1.062 11.6	$(M+H)^+$ = 450	0.31 (C)

Example 5

5-acetyl-3-[(4-acetylamino-methyl-phenyl)-(4-(methoxycarbonylmethyl)-phenyl-amino)-methylidene]-2-indolinone



80 mg (0.17 mmol) 5-acetyl-3-[(4-aminomethyl-phenyl)-(4-(methoxycarbonylmethyl)-phenylamino)-methylidene]-2-indolinone (Example 4) are placed in 4 ml methylene chloride and combined with 75 µl triethylamine. 40 µl acetyl chloride are added dropwise to this solution while cooling with ice and the mixture is then stirred for 10 min. It is then left to warm up to ambient temperature and stirred for 5 h. The solution is then washed with water, the organic phase is washed over sodium sulphate, suction filtered and concentrated by rotary evaporation.

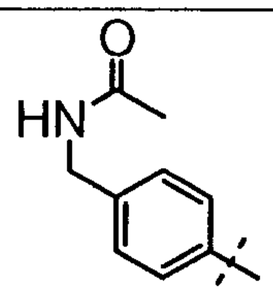
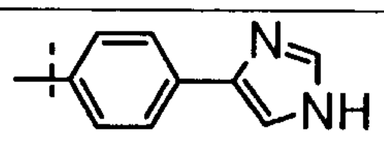
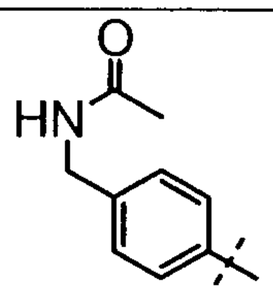
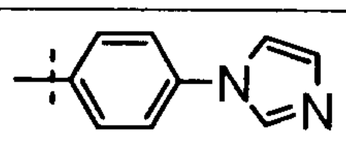
Yield: 46 mg (52 % of theory)

R_f = 0.53 (silica gel, methylene chloride/methanol 9:1)

$C_{29}H_{27}N_3O_5$ (MW = 497.548)

Mass spectrum: m/z = 496 $(M-H)^-$

The following compound of formula I is prepared analogously to Example 5:

Example	R^1	R^2	R^3	Educt Yield [%]	Mass spectrum (ES) m/z	R_f value (silica gel) (eluant)
5.001	Me			4.001 53.5	$(M+H)^+$ = 492	0.20 (C)
5.002	Me			4.002 64.7	$(M+H)^+$ = 492	0.41 (C)

Example 6

Coated tablets containing 75 mg of active substance

1 tablet core contains:

active substance	75.0 mg
calcium phosphate	93.0 mg
corn starch	35.5 mg
polyvinylpyrrolidone	10.0 mg
hydroxypropylmethylcellulose	15.0 mg
magnesium stearate	1.5 mg
	230.0 mg

Preparation:

The active substance is mixed with calcium phosphate, corn starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Blanks 13 mm in diameter are produced in a tablet-making machine and these are then rubbed through a screen with a mesh size of 1.5 mm using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form tablets of the desired shape.

Weight of core: 230 mg

die: 9 mm, convex

The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose. The finished film-coated tablets are polished with beeswax.

Weight of coated tablet: 245 mg.

Example 7

Tablets containing 100 mg of active substance

Composition:

1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	2.0 mg
	220.0 mg

Method of Preparation:

The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has

been screened (2.0 mm mesh size) and dried in a rack-type drier at 50°C it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets.

Weight of tablet: 220 mg

Diameter: 10 mm, biplanar, facetted on both sides and notched on one side.

Example 8

Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

active substance	150.0 mg
powdered lactose	89.0 mg
corn starch	40.0 mg
colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	1.0 mg
	300.0 mg

Preparation:

The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45°C, are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture.

Weight of tablet: 300 mg

die: 10 mm, flat

Example 9

Hard gelatine capsules containing 150 mg of active substance

1 capsule contains:

active substance		150.0 mg
corn starch (dried	approx.	180.0 mg
lactose (powdered)	approx.	87.0 mg
magnesium stearate		3.0 mg
	approx.	420.0 mg

Preparation:

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules.

Capsule filling: approx. 320 mg

Capsule shell: size 1 hard gelatine capsule.

Example 10

Suppositories containing 150 mg of active substance

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	840.0 mg
	2,000.0 mg

Preparation:

After the suppository mass has been melted the active substance is homogeneously distributed therein and the melt is poured into chilled moulds.

Example 11

Suspension containing 50 mg of active substance

100 ml of suspension contain:

active substance		1.00 g
carboxymethylcellulose-Na-salt		0.10 g
methyl p-hydroxybenzoate		0.05 g
propyl p-hydroxybenzoate		0.01 g
glucose		10.00 g
glycerol		5.00 g
70% sorbitol solution		20.00 g
flavouring		0.30 g
dist. water	ad	100 ml

Preparation:

The distilled water is heated to 70°C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, the sorbitol solution and the flavouring have been added and dissolved, the suspension is evacuated with stirring to eliminate air.

5 ml of suspension contain 50 mg of active substance.

Example 12

Ampoules containing 10 mg active substance

Composition:

active substance		10.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	2.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 2 ml ampoules.

Example 13

Ampoules containing 50 mg of active substance

Composition:

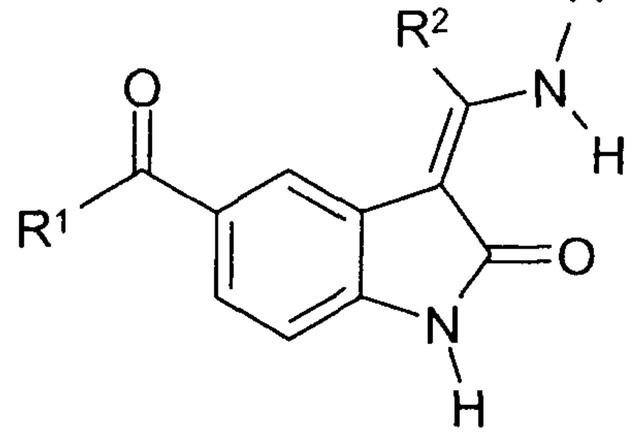
active substance		50.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	10.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 10 ml ampoules.

Patent Claims

1. Compounds of general formula



(I),

wherein

R^1 denotes a straight-chain or branched C_{1-5}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or

an aryl group optionally substituted by a fluorine, chlorine or bromine atom,

while by an aryl group is meant a phenyl or naphthyl group,

R^2 denotes a C_{1-7}-alkyl or C_{3-7}-cycloalkyl group,

a 5- or 6-membered heteroaryl group with one to three heteroatoms selected from the group N, S and O, optionally substituted by one or two fluorine, chlorine, bromine or iodine atoms or one or two nitro, cyano, amino, C_{1-3}-alkyl or C_{1-3}-alkoxy groups, while both the heteratoms and the substituents may be identical or different,

a phenyl group wherein two adjacent carbon atoms are linked together through a methylenedioxy, ethylenedioxy or difluoromethylenedioxy group,

a phenyl group, to which another phenyl ring or a 5- or 6-membered heteroaromatic ring with one to three heteroatoms selected from the group N, S and O, while the

heteratoms may be identical or different, is anellated, and while the bicyclic group may be substituted by one or two fluorine, chlorine, bromine or iodine atoms or one or two nitro, cyano, amino, C_{1-3}-alkyl or C_{1-3}-alkoxy groups and the substituents may be identical or different,

or

a phenyl group which may be substituted by one to three fluorine, chlorine, bromine or iodine atoms or by one to three C_{1-3}-alkyl, nitro, cyano, amino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkyl-carbonylamino, phenylcarbonylamino, C_{1-3}-alkylsulphonylamino, arylsulphonylamino, trifluoromethyl, C_{1-3} alkylsulphonyl, carboxy, C_{1-3}-alkoxy, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyloxy, C_{1-3}-alkoxy-carbonyl, C_{1-3}-alkylaminocarbonyl, hydroxy-carbonyl-C_{1-3}-alkyl-aminocarbonyl, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-amino-carbonyl-C_{1-3}-alkoxy, C_{1-3}-alkyl-amino-carbonyl-C_{1-3}-alkoxy, carboxy-C_{1-3}-alkoxy, C_{1-3}-alkyloxy-carbonyl-C_{1-3}-alkoxy, carboxy-C_{1-3}-alkyl, C_{1-3}-alkoxy-carbonyl-C_{1-3}-alkyl, C_{1-3}-alkoxy-carbonyl-amino-C_{1-3}-alkyl, amino-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl, C_{1-3}-alkyl-carbonyl-amino-C_{1-3}-alkyl, phthalimido, pyrrolyl or mono- or di-(C_{1-3}-alkyl)-pyrrolyl groups, while the substituents are identical or different, and

R^3 denotes a phenyl, naphthyl or heteroaryl group as hereinbefore defined which may be mono-, di- or trisubstituted

by a fluorine, chlorine, bromine or iodine atom,

by a cyano, hydroxy, carboxy, C_{1-3}-alkoxy, C_{1-3}-alkoxycarbonyl or di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkoxy group,

by a C_{1-3}-alkyl group which may be substituted by a hydroxycarbonyl, C_{1-3}-alkoxy-carbonyl or heteroaryl) group,

by a C_{1-3}-alkyl group which is substituted by a 3- to 7-membered cyclcoalkyleneimino group, while a benzene ring may be fused to the cyclo-alkyleneimino group via two adjacent carbon atoms,

by an amino-C_{1-3}-alkyl group which may be substituted at the nitrogen atom by one or two C_{1-3}-alkyl, phenyl-C_{1-3}-alkyl or C_{1-4}-alkoxy-carbonyl groups, while the substituents are identical or different,

by a C_{1-3}-alkyl-carbonyl-amino group which may be substituted at the nitrogen atom by a C_{1-3}-alkyl group or a C_{2-3}-alkyl group terminally substituted by a di-(C_{1-3}-alkyl)-amino group and in the alkyl moiety by a di-(C_{1-3}-alkyl)-amino, piperazinyl or 4-(C_{1-3}-alkyl)-piperazin-1-yl group,

by a C_{2-3}-alkyl-aminocarbonyl group terminally substituted in the alkyl moiety by a di-(C_{1-3}-alkyl)-amino group which may additionally be substituted at the nitrogen atom by a C_{1-3}-alkyl group,

or by a heteroaryl group,

while the substituents may be identical or different,

while the above-mentioned alkyl groups may be straight-chain or branched,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

2. Compounds of general formula I according to claim 1, wherein

R^2 and R^3 are defined as in claim 1 and

R^1 denotes a methyl, ethyl, n-propyl, isopropyl, n-pentyl, trifluoromethyl or phenyl group,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

3. Compounds of general formula I according to claim 2, wherein

R^1 denotes a methyl, ethyl, n-propyl, isopropyl, n-pentyl or phenyl group,

R^2 denotes a C_{1-7}-alkyl group,

a phenyl group wherein two adjacent carbon atoms are linked together through a methylenedioxy, ethylenedioxy or difluoromethylenedioxy group, or

a phenyl group which may be substituted by one or two fluorine, chlorine, bromine or iodine atoms or by one or two C_{1-3}-alkyl, nitro, cyano, amino, C_{1-3}-alkylcarbonylamino, phenylcarbonylamino, C_{1-3}-alkylsulphonylamino, trifluoromethyl, carboxy, C_{1-3}-alkoxy, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyloxy, C_{1-3}-alkoxy-carbonyl, C_{1-3}-alkylaminocarbonyl, hydroxycarbonyl-C_{1-3}-alkyl-aminocarbonyl, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkylaminocarbonyl, carboxy-C_{1-3}-alkyl, C_{1-3}-alkoxy-carbonyl-C_{1-3}-alkyl, amino-C_{1-3}-alkyl or C_{1-3}-alkyl-carbonylamino-C_{1-3}-alkyl groups, while the substituents are identical or different, and

R^3 denotes a phenyl group which may be mono- or disubstituted

by a fluorine, chlorine or bromine atom,

by a cyano, hydroxy, carboxy, C_{1-3}-alkoxy, C_{1-3}-alkoxycarbonyl or di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkoxy group,

by a C_{1-3}-alkyl group which may be substituted by a hydroxycarbonyl, C_{1-3}-alkoxy-carbonyl or imidazolyl group,

by a C_{1-3}-alkyl group which is substituted by a 3- to 7-membered cyclcoalkyleneimino group, while a benzene ring may be fused to the cycloalkyleneimino group via two adjacent carbon atoms,

by an amino-C_{1-3}-alkyl group which may be substituted at the nitrogen atom by one or two C_{1-3}-alkyl, benzyl or C_{1-4}-alkoxy-carbonyl groups, while the substituents are identical or different,

by a C_{1-3}-alkyl-carbonyl-amino group which may be substituted at the nitrogen atom by a C_{1-3}-alkyl group or a C_{2-3}-alkyl group terminally substituted by a di-(C_{1-3}-alkyl)-amino group and in the alkyl moiety by a di-(C_{1-3}-alkyl)-amino, piperazinyl or 4-(C_{1-3}-alkyl)-piperazin-1-yl group,

by a C_{2-3}-alkyl-aminocarbonyl group terminally substituted in the alkyl moiety by a di-(C_{1-3}-alkyl)-amino group which may additionally be substituted at the nitrogen atom by a C_{1-3}-alkyl group,

or by an imidazolyl group

while the substituents may be identical or different,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

4. Compounds of general formula I according to claim 3, wherein

R^1 denotes a methyl group,

R^2 denotes an ethyl, propyl, butyl or pentyl group,

a phenyl group wherein two adjacent carbon atoms are linked together through a methylenedioxy, ethylenedioxy or difluoromethylenedioxy group, or

a phenyl group which may be substituted by one or two fluorine, chlorine, bromine atoms or by one or two C_{1-3}-alkyl, cyano, C_{1-3}-alkoxy, carboxy-C_{1-3}-alkyl, C_{1-3}-alkoxy-carbonyl-C_{1-3}-alkyl, amino-C_{1-3}-alkyl or C_{1-3}-alkyl-carbonylamino-C_{1-3}-alkyl groups, while the substituents are identical or different, and

R^3 denotes a phenyl group which may be monosubstituted

by a fluorine, chlorine or bromine atom,

by a cyano, carboxy, C_{1-3}-alkoxy or C_{1-3}-alkoxycarbonyl group,

by a C_{1-3}-alkyl group which may be substituted by a hydroxycarbonyl or C_{1-3}-alkoxy-carbonyl group,

by a C_{1-3}-alkyl group which is substituted by a 3- to 7-membered cyclcoalkyleneimino group,

by an amino-C_{1-3}-alkyl group which may be substituted at the nitrogen atom by one or two C_{1-3}-alkyl or C_{1-4}-alkoxy-carbonyl groups, while the substituents are identical or different,

by a C_{1-3}-alkyl-carbonyl-amino group which may be substituted at the nitrogen atom by a C_{1-3}-alkyl group or a C_{2-3}-alkyl group terminally substituted by a di-(C_{1-3}-alkyl)-amino group and in the alkyl moiety by a di-(C_{1-3}-alkyl)-amino or 4-(methyl)-piperazin-1-yl group,

or by a C_{2-3}-alkyl-aminocarbonyl group terminally substituted in the alkyl moiety by a di-(C_{1-3}-alkyl)-amino group which may additionally be substituted at the nitrogen atom by a C_{1-3}-alkyl group,

or may be disubstituted by a hydroxy and a di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl group, while the substituents may be identical or different,

while the above-mentioned alkyl groups may be straight-chain or branched,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

5. Compounds of general formula I according to claim 4, wherein

R^1 denotes a methyl group,

R^2 denotes a phenyl group wherein two adjacent carbon atoms are linked together through a methylenedioxy or ethylenedioxy group, or

a phenyl group which may be substituted by one or two methoxy groups, and

R^3 denotes a phenyl group which is substituted

by a cyano group or

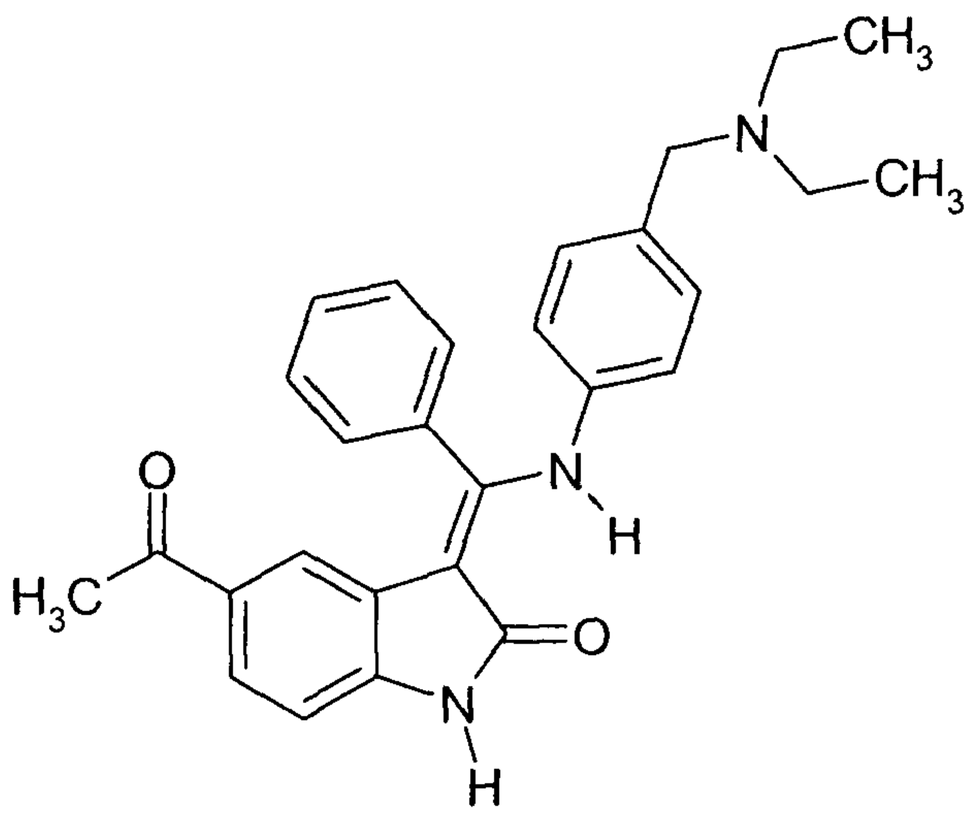
by an amino-C_{1-3}-alkyl group which may be substituted at the nitrogen atom by one or two C_{1-3}-alkyl groups, while the substituents may be identical or different,

while the above-mentioned alkyl groups may be straight-chain or branched,

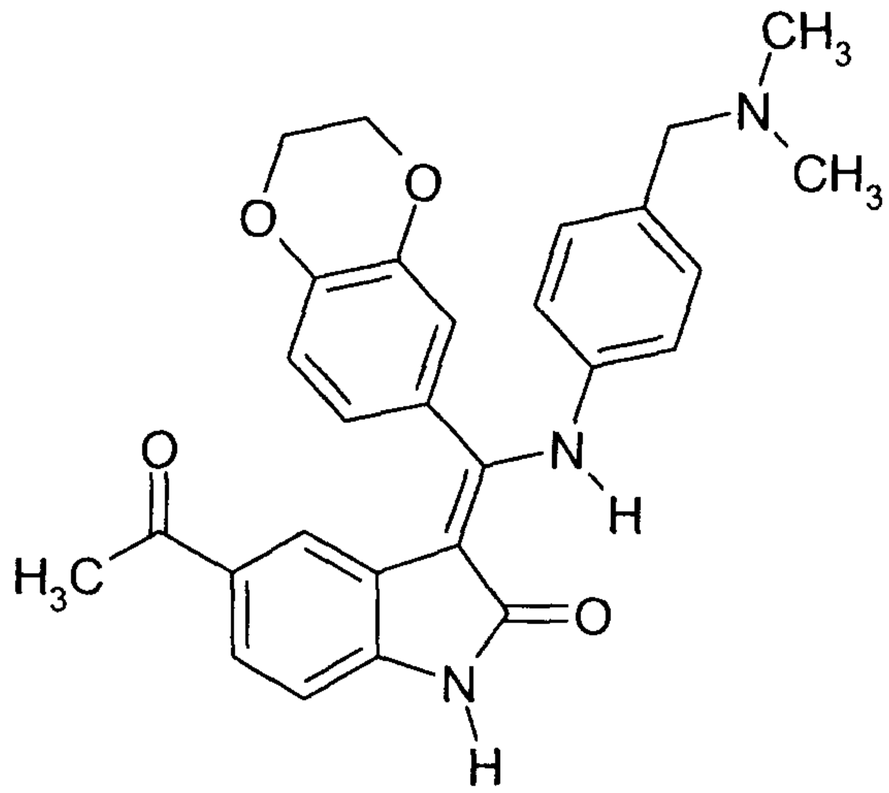
the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

6. The following compounds of general formula I according to claim 1:

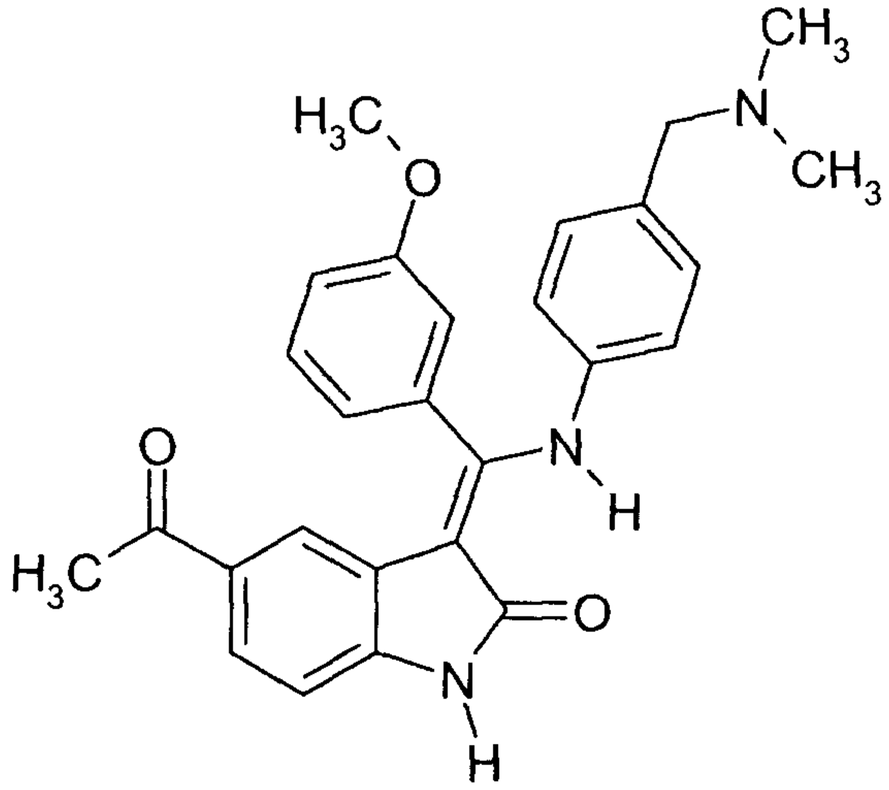
(a) 5-acetyl-3-{[4-(diethylaminomethyl)-phenylamino]-phenyl-methylidene}-2-indolinone



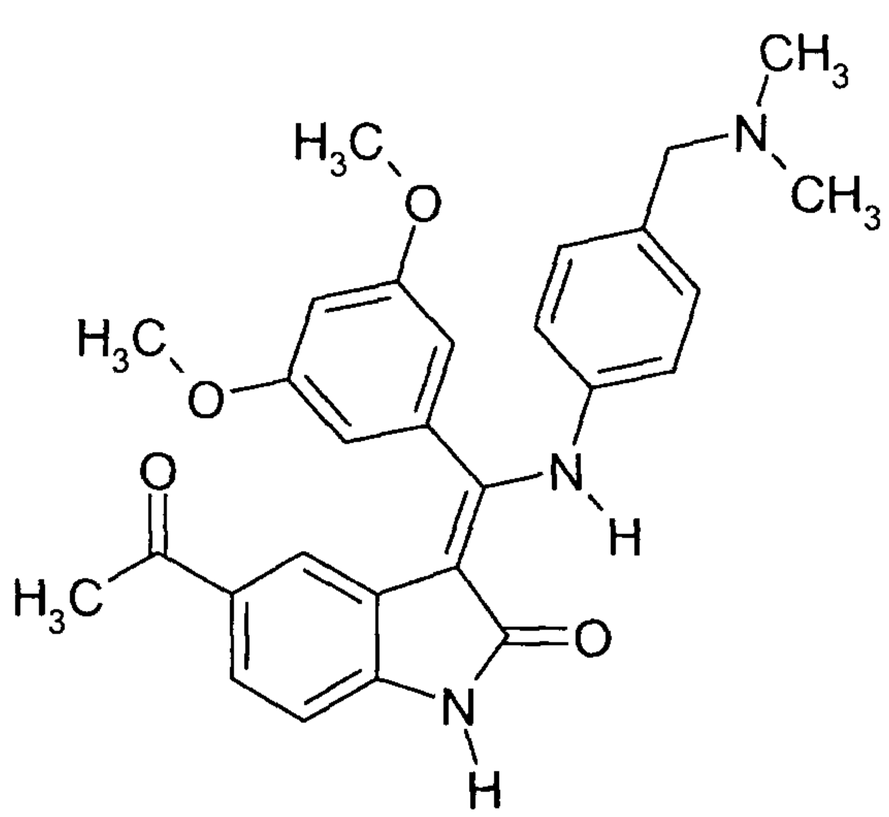
(b) 5-acetyl-3-{[4-(dimethylamino-methyl)-phenylamino]-(2,3-dihydro-benzo[1,4]-dioxin-6-yl)-methylidene}-2-indolinone



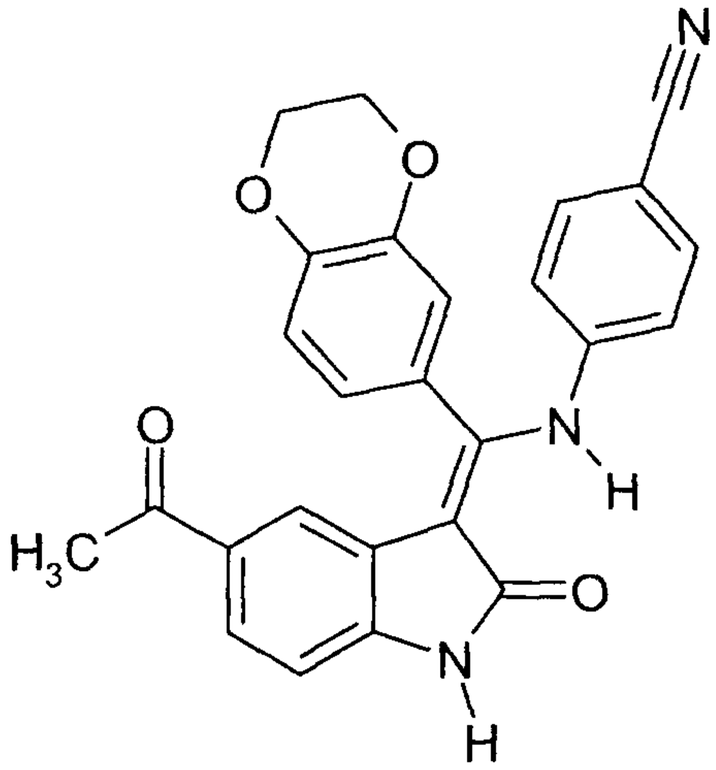
(c) 5-acetyl-3-{[4-(dimethylaminomethyl)-phenylamino]-(3-methoxy-phenyl)-methylidene}-2-indolinone



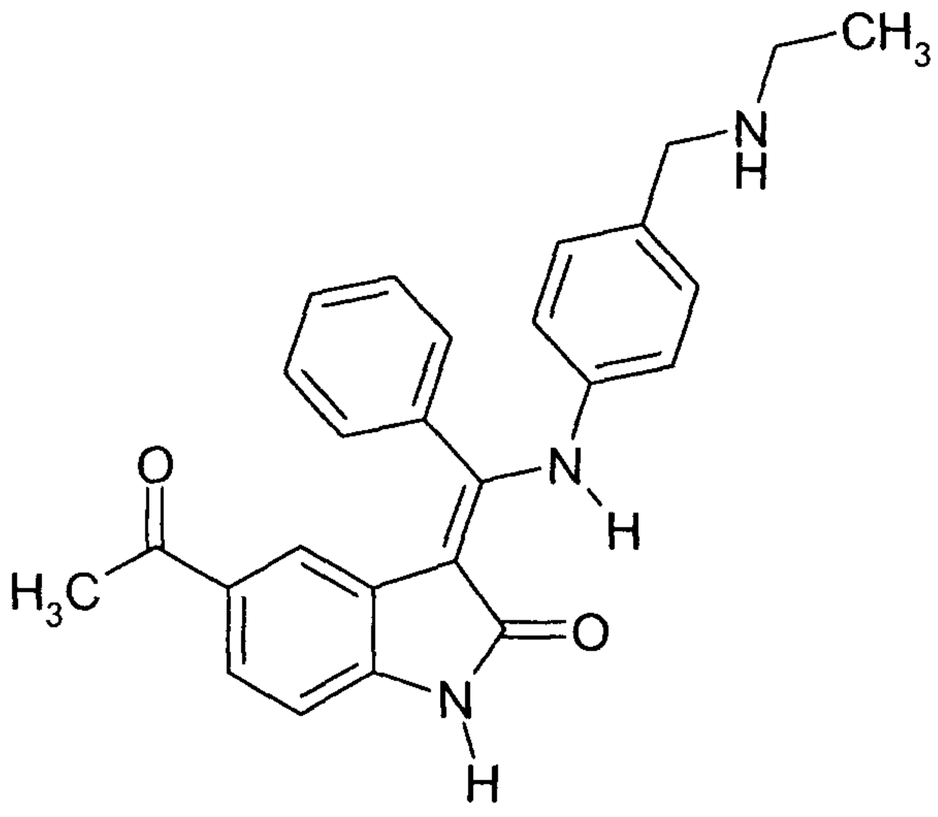
(d) 5-acetyl-3-{[4-(dimethylaminomethyl)-phenylamino]-(3,5-dimethoxy-phenyl)-methylidene}-2-indolinone



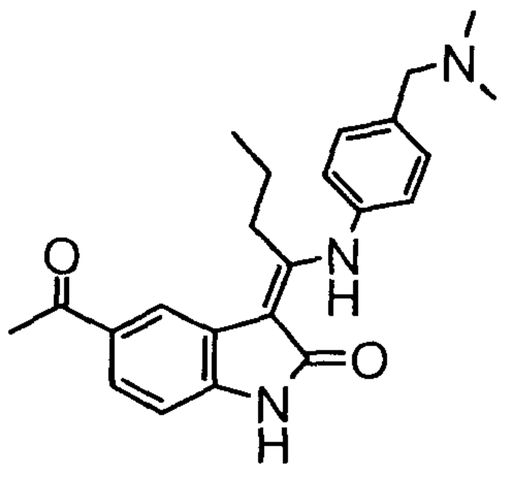
(e) 5-acetyl-3-[(4-cyano-phenylamino)-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-methylidene]-2-indolinone



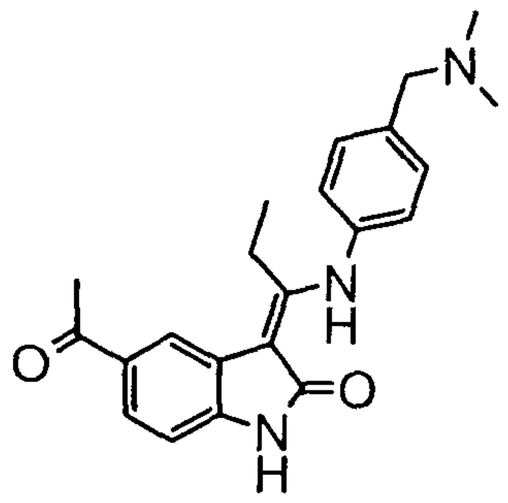
(f) 5-acetyl-3-{[4-(ethylaminomethyl)-phenylamino]-phenyl-methylidene}-2-indolinone



g) 5-acetyl-3-[1-(4-(dimethylaminomethyl)-phenylamino)-butylidene)-2-indolinone



(h) 5-acetyl-3-[1-(4-(dimethylaminomethyl)-phenylamino)-propylidene)-2-indolinone



as well as the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

7. Physiologically acceptable salts of the compounds according to at least one of claims 1 to 6 with inorganic or organic acids or bases.

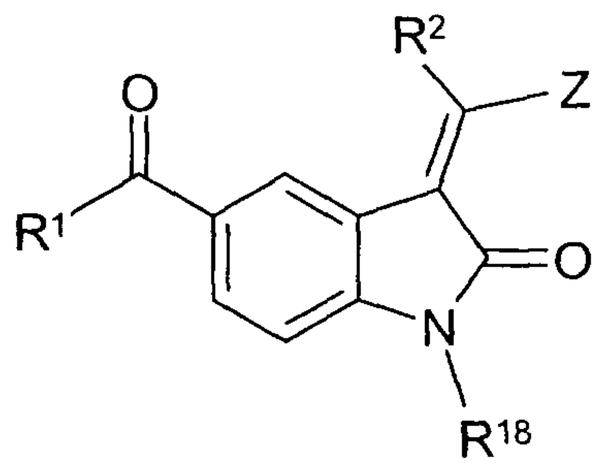
8. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 6 or a physiologically acceptable salt according to claim 7 optionally together with one or more inert carriers and/or diluents.

9. Use of a compound according to at least one of claims 1 to 7 for preparing a pharmaceutical composition which is suitable for the treatment of type I and type II diabetes mellitus, diabetes associated disorders such as diabetic neuropathy and degenerative neurological diseases such as Alzheimer's disease, stroke, neurotraumatic injuries and bipolar disorders.

10. Process for preparing a pharmaceutical composition according to claim 8, characterised in that a compound according to at least one of claims 1 to 7 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

11. Process for preparing the compounds of general formula I according to claims 1 to 7, characterised in that

a) a compound of general formula



(II),

wherein R^1 and R^2 are defined as in one of claims 1 to 6,
R^{18} denotes a hydrogen atom or a protective group for the nitrogen atom of the lactam group and
Z denotes a leaving group,

is reacted with an amine of general formula

R^3-NH_2 (III),

wherein R^3 is defined as in one of claims 1 to 6, while any hydroxy, amino or imino groups contained in the groups R^2 and/or R^3 may temporarily be protected by suitable protective groups,

b) in order to prepare a compound of formula I which contains an aminocarbonyl group, a compound which contains a carboxy group is reacted with the corresponding amine,

c) in order to prepare a compound of formula I which contains a carbonylamino group, a compound which contains an amino group is reacted with the corresponding acid chloride,

d) in order to prepare a compound of formula I which contains an aminomethyl group, a compound which contains a cyano group is hydrogenated to form the corresponding aminomethyl derivative,

e) in order to prepare a compound of formula I which contains an amino group, a compound which contains a nitro group is hydrogenated,

and/or

any protective groups which may be used during the reaction are then cleaved and/or

the compounds of general formula I thus obtained are resolved into their enantiomers and/or diastereomers and/or

the compounds of general formula I thus obtained are converted into their salts, particularly for pharmaceutical use into the physiologically acceptable salts thereof with inorganic or organic acids or bases.

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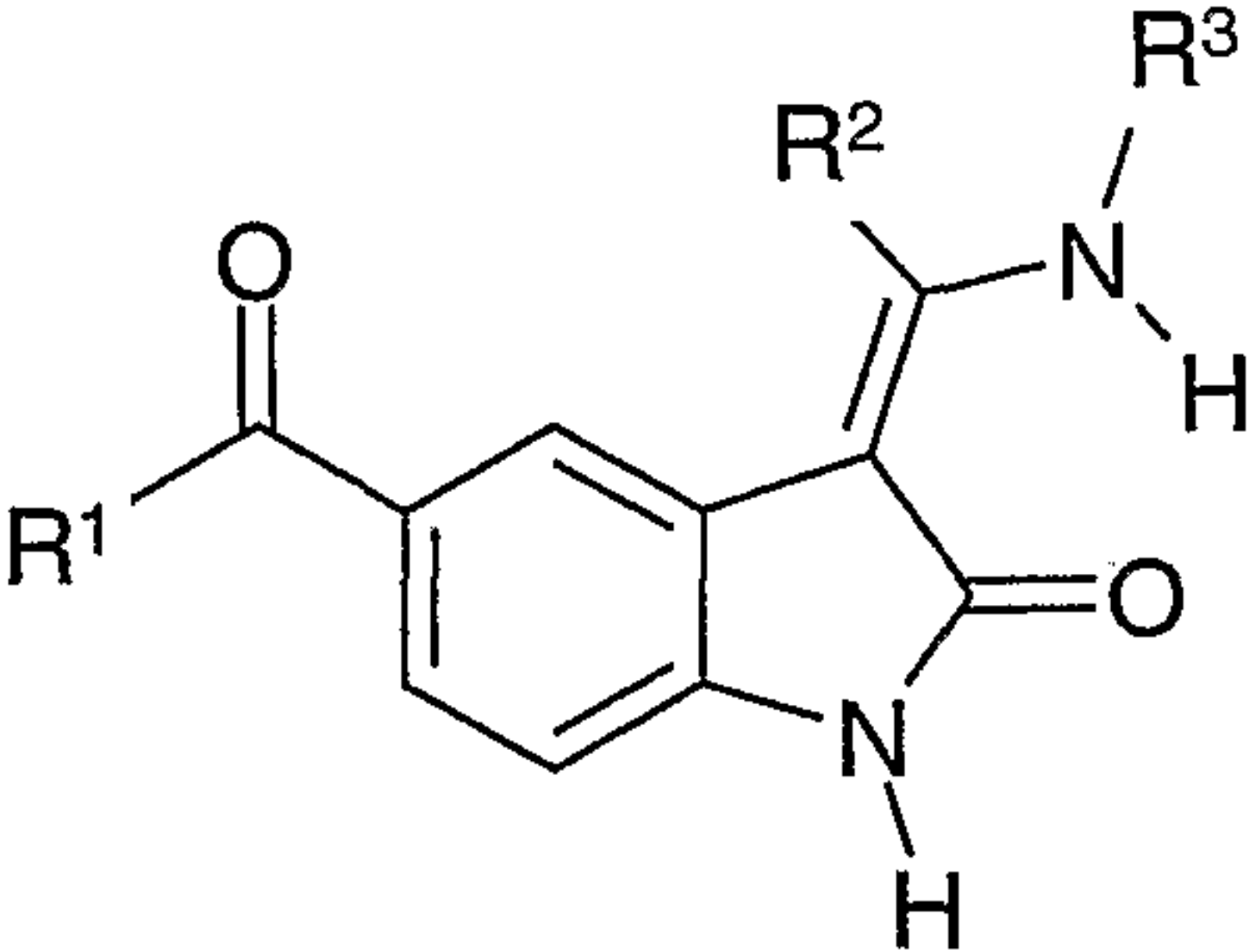

(I)