Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
The present invention relates to a new use of indolinones of general formula I, substituted in the 6 position, the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof, particularly the physiologically acceptable salts thereof.

BACKGROUND

Compounds of the above general formula I, the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof, particularly the physiologically acceptable salts thereof, have been described in WO 04/009547 as having valuable pharmacological properties, in particular an inhibiting effect on various kinases, especially receptor tyrosine kinases such as VEGFR1, VEGFR2, VEGFR3, PDGFRα, PDGFRβ, FGFR1, FGFR3, EGFR, HER2, c-Kit, IGF1R and HGF, Flt-3, and on the proliferation of cultivated human cells, in particular endothelial cells, e.g. in angiogenesis, but also on the proliferation of other cells, in particular tumour cells.

However, none of these compounds have been described for their use in the treatment or prevention of the fibrotic diseases referred to in the present invention.

Remodeling is a normal response to tissue injury and inflammation that is observed in many tissues throughout the body. After resolution of the inflammation and repair of tissue damage, the tissue is generally returned to its original condition. Excessive uncontrolled tissue repair or the failure to stop remodeling when it is no longer required leads to a condition known as fibrosis. Fibrosis is characterized by excessive deposition of extracellular matrix components and overgrowth of fibroblasts. Fibrosis can occur in all tissues but is especially prevalent in organs with frequent exposure to chemical and biological insults including the lung, skin, digestive tract, kidney, and liver (Eddy, 1996, J Am Soc Nephrol, 7(12):2495-503; Dacic et al., 2003, Am J Respir Cell Mol Biol, 29:S5-9; Wynn, 2004, Nat Rev Immunol, 4(8):583-94). Fibrosis often severely compromises the normal function(s) of the organ and many fibrotic diseases are, in fact, life-threatening or severely disfiguring, such as idiopathic pulmonary fibrosis (IPF), liver cirrhosis, scleroderma, or renal fibrosis. Treatment options for these diseases are often limited to organ transplantation, a risky and expensive procedure.


Inhibition of PDGF attenuates both liver fibrosis and lung fibrosis in experimental models, suggesting fibrosis in different organs may have a common origin (Borkham-Kamphorst et al., 2004, Biochem Biophys Res Commun; Rice et al., 1999, Amer J Pathol, 155(1):213-221). An EGF receptor kinase inhibitor was also active in this lung fibrosis model. Three-fold overexpression of an EGF family member, HB-EGF, in mouse pancreas islets was sufficient to cause devel-
opment of fibrosis in both the exocrine and endocrine compartments (Means et al., 2003, Gastroenterology, 124 (4): 1020-36).

[0008] Similarly, FGF1/FGF2-deficient mice show dramatically decreased liver fibrosis after chronic carbon tetrachloride (CCl4) exposure (Yu et al., 2003, Am J Pathol, 163(4):1653-62). FGF expression is increased in human renal interstitial fibrosis where it strongly correlates with interstitial scarring (Strutz et al., 2000, Kidney Intl, 57:1521-38) as well as in a model of experimental lung fibrosis (Barrios et al., 1997, Am J Physiol, 273 (2 Pt 1):L451-8), again lending credence to the idea that fibrosis in various tissues has a common basis.


[0011] As summarized above, several growth factors are upregulated in fibrosis and the inhibition of a single factor seems to reduce the severity of fibrosis in the fibrosis models.

SUMMARY OF THE INVENTION

[0012] Surprisingly, we found that the compounds of above general formula I are effective in the treatment or prevention of specific fibrotic diseases.

[0013] The present invention thus relates to the use of the compounds of above general formula I for the preparation of a medicament for the treatment or prevention of specific fibrotic diseases.

[0014] The present invention also relates to a method for the treatment or prevention of specific fibrotic diseases, by administration to a patient in need thereof of a pharmaceutical composition comprising a compound of above general formula I, together with a pharmaceutically suitable carrier. The expression "patient" is meant to comprise the mammalian animal body, preferably the human body.

[0015] The present invention further relates to a pharmaceutical composition for the treatment or prevention of specific fibrotic diseases which comprises a compound of above general formula I alone or in combination with one or more further therapeutic agents.

DETAILED DESCRIPTION OF THE INVENTION

[0016] In accordance with the present invention, the compounds of general formula I are the compounds

$$\text{(I)}$$

in which

1. In the above formula I,
   X is an oxygen atom,
   R1 is a hydrogen atom,
   R2 is a fluorine, chlorine or bromine atom or a cyano group,
R³ is a phenyl group or a phenyl group which is monosubstituted by a fluorne, chlorine, bromine or iodine atom or 
by a C₁₋₃-alkoxy group, where the abovementioned unsubstituted and the monosubstituted phenyl groups may 
additionally be substituted in the 3- or 4-position 
by a fluorne, chlorine or bromine atom, 
by a cyano group, 
by a C₁₋₃-alkoxy or C₁₋₂-alkyl-carbonyl-amino group, 
by a cyano-C₁₋₃-alkyl, carboxy-C₁₋₃-alkyl, carboxy-C₁₋₄-alkoxy, carboxy-C₁₋₃-alkylamino, carboxy-C₁₋₃-alkyl-
N-(C₁₋₃-alkyl)-amino, C₁₋₄-alkoxy-carbonyl-C₁₋₃-alkyl, C₁₋₄-alkoxy-carbonyl-C₁₋₃-alkoxy, C₁₋₄-alkoxy-carbonyl-
C₁₋₄-alkoxyaminocarbonyl-C₁₋₃-alkylamino, C₁₋₄-alkoxyaminocarbonyl-C₁₋₃-alkyl-N-(C₁₋₃-alkyl)-amino, amino-C₁₋₃-alkyl, aminocarbonyl-C₁₋₃-alkyl, 
(C₁₋₂-alkylaminocarbonyl)-carbonyl-C₁₋₃-alkyl, di-(C₁₋₂-alkyl)-amino-carbonyl-C₁₋₃-alkyl, (C₁₋₂-alkyl-carbonyl) -amino-
C₁₋₃-alkyl, (C₁₋₄-alkoxy-carbonyl)-amino-C₁₋₃-alkyl, (C₂₋₆-alkyl-carbonyl)-amino-C₁₋₃-alkyl, (phenyl-carbonyl) amin
-C₁₋₃-alkyl, (C₂₋₆-cycloalkylcarbonyl)-amino-C₁₋₃-alkyl, (C₂₋₆-cycloalkyl-C₁₋₃-alkyl-carbonyl)-amino-C₁₋₃-alkyl, -amino-C₁₋₃-alkyl, (tiophen-2-yl-carbonyl)-amino-C₁₋₃-alkyl, (furan-2-yl-carbonyl) - amino-C₁₋₃-alkyl, (phenyl-C₁₋₃-alkyl-carbonyl) - 
amino-C₁₋₃-alkyl, (C₁₋₄-alkoxy)-benzoyl-carbonyl-amino-C₁₋₃-alkyl, (pyridin-2-yl-carbonyl) -amino-C₁₋₃-alkyl, (pyridin-3-yl-carbonyl) -amino-C₁₋₃-alkyl, (pyridin-4-yl-carbonyl) -amino-C₁₋₃-alkyl- or C₁₋₃-alkyl-piperazin-1-yl-carbonyl-C₁₋₃-alkyl group, 
by a carboxy-C₂₋₃-alkenyl, aminocarbonyl-C₂₋₃-alkenyl, (C₁₋₃-alkylaminocarbonyl) -aminocarbonyl-C₂₋₃-alkenyl, di-
(C₁₋₃-alkyl) -aminocarbonyl-C₂₋₃-alkenyl or C₁₋₄-alkoxy-carbonyl-C₂₋₃-alkenyl group, 
where the substituents may be identical or different, 
R⁴ is a phenyl group or a phenyl group which is monosubstituted 
by a C₁₋₃-alkyl group which is terminally substituted by an amino, guanidino, mono- or di-(C₁₋₂-alkyl)-amino-, N-
[ω-di-(C₁₋₂-alkyl)-amino]-C₂₋₃-alkyl-N-(C₁₋₃-alkyl)-amino, N-[ω-di-(C₁₋₂-alkyl)-amino]-C₂₋₃-alkyl-N-(C₁₋₃-alkyl)-N-benzylamin, 
N- (C₁₋₄-alkoxyaminocarbonyl)-amino, N- (C₁₋₄-alkoxyaminocarbonyl)-C₁₋₄-alkylamino, 4-(C₁₋₃-alkyl)-piperazin-1-yl, imidazol-
1-yl, pyrroloidin-1-yl, azetidin-1-yl, morpholin-4-yl, piperezin-1-yl, thiomorpholin-4-yl group, 
by a di-(C₁₋₃-alkyl) -amino-(C₁₋₃-alkyl)-sulphonyl, 2- [di-(C₁₋₃-alkyl) -amino]-ethoxy, 4- (C₁₋₃-alkyl)-piperezin-1-yl-
carbonyl, ω- [di-(C₁₋₃-alkyl) -amino]- (C₂₋₃-alkyl)]-N- (C₁₋₃-alkyl)-amino-carbonyl, 1- (C₁₋₃-alkyl) imidazol-2-yl, 
(C₁₋₃-alkyl)-sulphonyl group, or 
by a group of the formula 
\[
\begin{align*}
R^8 & \quad N \\
\quad & \quad R^7
\end{align*}
\]
in which 
R⁷ is a C₂₋₃-alkyl, C₁₋₂-alkyl-carbonyl, di-(C₁₋₂-alkyl) -aminocarbonyl-C₁₋₃-alkyl or C₁₋₃-alkylsulphonyl group and 
R⁸ is C₁₋₃-alkyl, ω-[di-(C₁₋₂-alkyl)-amino]-C₂₋₃-alkyl, ω-[mono- (C₁₋₂-alkyl) -amino]-C₂₋₃-alkyl group, or 
a (C₁₋₃-alkyl)-carbonyl, (C₂₋₆-alkyl)-carbonyl or carbonyl- (C₁₋₃-alkyl) group which is terminally substituted by a 
di-(C₁₋₂-alkyl)-amino, piperezin-1-yl or 4- (C₁₋₃-alkyl) - piperezin-1-yl group, 
where all dialkylamino groups present in the radical R⁸ may also be present in quaternized form, for example as an 
N-methyl-(N,N-dialkyl)-ammonium group, where the counterion is preferably selected from the group consisting of 
iodide, chloride, bromide, methylsulphonate, para-toluennesulphonate and trifluoroacetate, 
R⁵ is a hydrogen atom and 
R⁶ is a hydrogen atom, 
where the abovementioned alkyl groups include linear and branched alkyl groups in which additionally one to 3 
hydrogen atoms may be replaced by fluorine atoms, where additionally a carboxyl, amino or imino group present 
may be substituted by an in vivo cleavable radical or may be present in the form of a prodrug radical, for example 
in the form of a group which can be converted in vivo into a carboxyl group or in the form of a group which can be 
converted in vivo into an imino or amino group, 
their tautomers, enantiomers, diastereomers, their mixtures and their salts. 
Il. Particularly preferred compounds of the above formula I are those compounds in which X, R¹, R⁵ and R⁶ are as 
defined under I. and: 
Il.i. R² and R⁴ are as defined under I. and 
R³ is a phenyl group or a phenyl group which is monosubstituted by a fluorne, chlorine, bromine or iodine atom 
or by a C₁₋₃-alkoxy group, where the abovementioned unsubstituted and the monosubstituted phenyl groups
may additionally be substituted in the 3- or 4-position
by a fluorine, chlorine or bromine atom,
by a cyano group,
by a -C1-3-alkoxy or C1-2-alkyl-carbonyl-amino group,
by a cyano-C1-3-alkyl, carboxy-C1-3-alkyl, carboxy-C1-4-alkoxy, carboxy-C1-3-alkylamino, carboxy-C1-3-alkyl-
N(C1-2-alkyl)-amino, C1-4-alkoxycarbonyl-C1-3-alkyl, C1-4-alkoxycarbonyl-C1-2-alkoxy, C1-4-alkoxy-carbonyl-
C1-3-alkylamino, C1-4-alkoxycarbonyl-C1-3-alkyl-N-(C1-3-alkyl)-amino, amino-C1-3-alkyl, N-amino-C1-3-alkyl,
aminocarbonyl-C1-3-alkyl, (C1-2-alkylamino)-carbonyl-C1-3-alkyl, di-(C1-2-alkyl)-amino-carbonyl-C1-3-alkyl, (C1-2-alkyl-carbon-
yl)-amino-C1-3-alkyl, (C1-4-alkoxycarbonyl)-amino-C1-3-alkyl, (C3-4-alkyl-carbonyl)-amino-C1-3-alkyl, (phenyl-
carbonyl)-amino-C1-3-alkyl, (C3-6-cycloalkylcarbonyl)-amino-C1-3-alkyl, (C5-6-cycloalkyl-C1-3-alkyl-carbonyl-
amino-C1-3-alkyl, (thiophen-2-yl-carbonyl)-amino-C1-3-alkyl, (furan-2-yl-carbonyl)-amino-C1-3-alkyl, (phenyl-
carbonyl)-amino-C1-3-alkyl, (2-(C1-4-alkoxy)-benzoyl-carbonyl)-amino-C1-3-alkyl, (pyridin-2-yl-carbonyl)-amino-C1-3-alkyl, (pyridin-3-yl-carbonyl)-amino-C1-3-alkyl, (pyridin-4-yl-carbonyl)-amino-C1-3-alkyl or
C1-3-alkyl-piperazin-1-yl-carbonyl-C1-3-alkyl group,
by a carboxy-C2-3-alkenyl, aminocarbonyl-C2-3-alkenyl-, (C1-3-alkylamino)-carbonyl-C2-3-alkenyl-, di-(C1-3-alkyl)-amino-carbonyl-C2-3-alkenyl or C1-4-alkoxy-carbonyl-C2-3-alkenyl group,
by the substituents may be identical or different;

II.ii. R2 and R4 are as defined under I. and
R3 is a phenyl group which is substituted
by a C1-2-alkyl-carbonyl-amino group,
by a carboxy-C1-3-alkyl, carboxy-C1-4-alkoxy, C1-4-alkoxy-carbonyl-C1-3-alkyl, C1-4-alkoxycarbonyl-
C1-3-alkylamino, aminocarbonyl-C1-3-alkyl, (C1-2-alkylamino)carbonyl-C1-3-alkyl, di-(C1-2-alkyl)-amino-carbonyl-
C1-3-alkyl, (C1-2-alkyl-carbonyl)-amino-C1-3-alkyl, (C1-4-alkoxy-carbonyl)-amino-C1-3-alkyl, (phenyl-carbonyl-
amino-C1-3-alkyl, (C3-6-cycloalkylcarbonyl)-amino-C1-3-alkyl, (thiophen-2-yl-carbonyl)-amino-C1-3-alkyl, (furan-2-yl-carbonyl)-amino-C1-3-alkyl, (phenyl-carbonyl)-amino-C1-3-alkyl, (2-(C1-4-alkoxy)-benzoyl-carbonyl)-amino-C1-3-alkyl, (pyridin-2-yl-carbonyl)-amino-C1-3-alkyl, (pyridin-3-yl-carbonyl)-amino-C1-3-alkyl, (pyridin-4-yl-carbonyl)-amino-C1-3-alkyl or
C1-3-alkyl-piperazin-1-yl-carbonyl-C1-3-alkyl group,
by an aminocarbonyl-C2-3-alkenyl, (C1-3-alkylamino)-carbonyl-C2-3-alkenyl-di-(C1-3-alkyl)-amino-carbonyl-
C2-3-alkenyl or C1-4-alkoxy-carbonyl-C2-3-alkenyl group;

II.iii. R2 and R4 are as defined under I. and
R3 is a phenyl group substituted by a carboxy-C1-3-alkyl or C1-4-alkoxy-carbonyl-C1-3-alkyl group;

II.iv. R3 and R4 are as defined under I. and
R2 is a fluorine or chlorine atom;

II.v. R2 and R3 are as defined under I. and
R4 is a phenyl group or a phenyl group which is monosubstituted
by a C1-2-alkyl group which is terminally substituted by an amino, guanidino, mono- or di-(C1-2-alkyl)-amino-,N- [ω-di-(C1-3-alkyl)-amino-C2-3-alkyl]N- [C1-3-alkyl]-amino, N-methyl-(C3-4-alkyl)-amino, N-(C1-3-alkyl)-N-
benzylamino, N- (C1-4-alkoxy carbonyl)-amino, N- (C1-4-alkoxycarbonyl)-amino, N- (C1-4-alkoxy carbonyl)-amino, N- (C1-4-alkoxycarbonyl)-amino, 4-(C1-3-alkyl)-piperazin-1-yl, imidazol-1-yl, imidazol-1-yl, imidazol-1-yl, azetidin-1-yl, morpholin-4-yl, piperazin-1-yl, thiomorpholin-4-yl group,
by di-(C1-3-alkyl)-amino-C1-3-alkyl-sulphonyl, 2-di(C1-3-alkyl)-amino]-ethoxy, 4- (C1-3-alkyl)-piperazin-
1-yl-carbonyl, [ω-di-(C1-3-alkyl)-amino]- (C2-3-alkyl) -N- (C1-3-alkyl)-amino-carbonyl-1-(C1-3-alkyl) imidazol-
2-yl, (C1-3-alkyl)-sulphonyl group, or
by a group of the formula

\[
\begin{align*}
\text{R}^7 & \text{ a C1-2-alkyl, C1-2-alkyl-carbonyl, di-(C1-2-alkyl)-amino-carbonyl-C1-3-alkyl or C1-3-alkylsulphonyl group and} \\
\end{align*}
\]
R^8 is C_{1-3}-alkyl, ω-[di-(C_{1-2}-alkyl)-amino]-C_{2-3}-alkyl, ω-[mono-(C_{1-2}-alkyl)-amino]-C_{2-3}-alkyl group, or a (C_{1-3}-alkyl)-carbonyl, (C_{4-6}-alkyl)-carbonyl or carbonyl-(C_{1-3}-alkyl) group which is terminally substituted by a di-(C_{2-3}-alkyl)-amino, piperazin-1-yl or 4-(C_{1-3}-alkyl)-piperazin-1-yl group, where all dialkylamino groups present in the radical R^4 may also be present in quaternized form, for example as an N-methyl-(N,N-dialkyl)-ammonium group, where the counterion is preferably selected from the group consisting of iodide, chloride, bromide, methylsulphonate, para-toluenesulphonate and trifluoroacetate.

III. Subgroups of particularly preferred compounds of the above formula I which are to be mentioned in particular are those in which:

III.i. X, R^1, R^2, R^5 and R^6 are as defined under I., R^3 is as defined under II.i. and R^4 is as defined under II.v.;

III. ii. X, R^1, R^2, R^5 and R^6 are as defined under I., R^3 is as defined under II.ii. and R^4 is as defined under II.v.;

III.iii. X, R^1, R^2, R^5 and R^6 are as defined under I., R^3 is as defined under II.iii. and R^4 is as defined under II.v.;

III.iv. X, R^1, R^2 and R^6 are as defined under I., R^2 is as defined under II.iv., R^3 is as defined under II.i., II.ii. or II.iii. and R^4 is as defined under II.v.

[0017] A further preferred group of compounds of the above formula I are those in which
X is an oxygen atom,
R^1 is a hydrogen atom,
R^2 is a fluorine, chlorine or bromine atom or a cyano group,
R^3 is a phenyl group or a phenyl group which is monosubstituted by a fluorine, chlorine, bromine or iodine atom or by a C_{1-3}-alkoxy group, where the abovementioned unsubstituted and the monosubstituted phenyl groups may additionally be substituted in the 3- or 4-position by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkoxy or C_{1-2}-alkyl-carbonyl-amino group, by a carboxy-C_{1-3}-alkyl, aminocarbonyl-C_{1-3}-alkyl, (C_{1-2}-alkylamino)-carbonyl-C_{1-3}-alkyl, di-(C_{1-2}-alkyl)-amino-carbonyl-C_{1-3}-alkyl, (C_{1-2}-alkyl-carbonyl)-amino-C_{1-3}-alkyl or (phenyl-carbonyl)-amino-C_{1-3}-alkyl group, where the substituents may be identical or different, R^4 is a phenyl group which is substituted by a C_{1-3}-alkyl group terminally substituted by a di-(C_{1-2}-alkyl)-amino group, or by a group of the formula

[0018] The following compounds of the formula I are particularly preferred:

(a) 3-Z-[1-(4-dimethylaminomethylamino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone
(b) 3-Z-[1-(4-dimethylaminomethylamino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone
(c) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(d) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(e) 3-Z-[1-(4-(dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(f) 3-Z-[1-(4-(N-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(g) 3-Z-[1-(4-(1-methylimidazo-2-yl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(h) 3-Z-[1-(4-(N-(dimethylaminomethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(i) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(j) 3-Z-[1-(4-(pyrrolidin-1-ylmethyl) anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(k) 3-Z-[1-(4-(diethylaminomethyl) anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(l) 3-Z-[1-(4-(2-dimethylaminoethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(m) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(n) 3-Z-[1-(4-(pyrrolidin-1-ylmethyl) anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(o) 3-Z-[1-(4-(pyrrolidin-1-ylmethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(p) 3-Z-[1-(4-(diethylaminomethylanilino)-1-(4-(2-carboxyethyl)methylene]-6-bromo-2-indolinone

(q) 3-Z-[1-(4-(dimethylaminomethylanilino)-1-(4-(2-carboxyethyl)methylene]-6-bromo-2-indolinone

where additionally a carboxyl, amino or imino group present may be substituted by an in vivo cleavable radical or may be present in the form of a prodrug radical, for example in the form of a group which can be converted in vivo into a carboxyl group or in the form of a group which can be converted in vivo into an imino or amino group, their tautomers, enantiomers, diastereomers, their mixtures and their salts.

[0019] A group which can be converted in vivo into a carboxyl group is to be understood as meaning, for example, a hydroxymethyl group, a carboxyl group which is esterified with an alcohol in which the alcoholic moiety is preferably a C1-6-alkanol, a phenyl-C1-3-alkanol, a C3-9-cycloalkanol, where a C5-8-cycloalkanol may additionally be substituted by one or two C1-3-alkyl groups, a C5-8-cycloalkanol in which one alkene group in the 3- or 4-position is replaced by an oxygen atom or by an imino group optionally substituted by a C1-3-alkyl, phenyl-C1-3-alkyl, phenyl-C1-3-alkoxy-carbonyl or C1-6-alkyl-carbonyl group and in which the cycloalkanol moiety may additionally be substituted by one or two C1-3-alkyl groups, a C4-8-cycloalkanol, a C3-5-alkenol, a phenyl-C3-5-alkenol, a C3-5-alkynol or a phenyl-C3-5-alkynol, with the proviso that no bond to the oxygen atom originates from a carbon atom which carries a double or triple bond, a C3-8-cycloalkynyl-C1-3-alkanol, a bicycloalkanol having a total of 8 to 10 carbon atoms which may additionally be substituted in the bicycloalkynyl moiety by one or two C1-3-alkyl groups, a 1,3-dihydro-3-oxo-1-isobenzofuranor an alcohol of the formula

$$R_A-CO-O-(R_BCR_C)-OH,$$

in which

$R_A$ is a C1-8-alkyl, C5-7-cycloalkyl, phenyl or phenyl-C1-3-alkyl group.

$R_B$ is a hydrogen atom, a C1-3-alkyl, C5-7-cycloalkyl or phenyl group, and

$R_C$ is a hydrogen atom or a C1-3-alkyl group,

and a radical cleavable in vivo from an imino or amino group is to be understood as meaning, for example, a hydroxyl group, an acyl group, such as the benzoyl or pyridinoyl group, or a C1-16-alkylcarbonyl group, such as the formyl, acetyl,
propionyl, butanoyl, pentanoyl or hexanoyl group, an allyloxycarbonyl group, a C_{1-16}-alkoxycarbonyl group, such as the methoxy carbonyl, ethoxy carbonyl, propoxy carbonyl, butoxy carbonyl, tert-butoxy carbonyl, pentoxy carbonyl, hexoxy carbonyl, octoxy carbonyl, nonoxy carbonyl, dodec oxy carbonyl, undec oxy carbonyl, hexadec oxy carbonyl or hexadec oxy carbonyl group, a phenyl-C_{1-6-alkoxycar bonyl} group, such as the benzoxycarbonyl, phe nylethoxycarbonyl or phenylprop oxy carbonyl group, a C_{1-3-alkylsulphonyl-C_{1-4-alkoxy-carbonyl}}, C_{1-3-alkoxy- C_{2-4-alkoxy-C_{2-4-alkoxy-C_{2-4-alkoxy-carbonyl}}}} or R_3CO-O-(R_3CR_2)-O-CO- group, in which

R_3 is a C_{1-12-alkyl}, C_{5-7-cycloalkyl}, phenyl or phenyl-C_{1-3-alkyl} group, R_3 is a hydrogen atom, a C_{1-3-alkyl}, C_{5-7-cycloalkyl} or phenyl group and R_3 is a hydrogen atom, a C_{1-3-alkyl} or R_3CO-O-(R_3CR_2)-O-group, in which R_3 to R_3 are as defined above, and additionally, for an amino group, the phthal imido group, where the ester radicals mentioned above can also be used as a group which can be converted in vivo into a carboxyl group.

Preferred prodrug radicals for a carboxyl group are a C_{1-6-alkoxy-carbonyl} group, such as the methoxy carbonyl, ethoxy carbonyl, n-propoxy carbonyl, isopropyloxy carbonyl, n-butoxy carbonyl, n-hexyloxy carbonyl or cyclohexyloxy carbonyl group, or a phenyl-C_{1-3-alkoxy-carbonyl} group, such as the benzoxycarbonyl group, and, for an imino or amino group, a C_{1-9-alkoxy-carbonyl} group, such as the methoxy carbonyl, ethoxy carbonyl, n-propoxy carbonyl, isopropyloxy carbonyl, n-butoxy carbonyl, n-hexyloxy carbonyl, cyclohexyloxy carbonyl, n-heptyloxy carbonyl, n-octyloxy carbonyl or n-nonxyloxy carbonyl group, a phenyl-C_{1-3-alkoxy-carbonyl} group, such as the benzoxycarbonyl group, a phenylcarbonyl group optionally substituted by a C_{1-3-alkyl} group, such as the benzoyl or 4-ethyl-benzoyl group, a pyridinoyl group, such as the nicotinoyl group, a C_{1-3-alkylsulphonyl-n-C_{2-3-alkoxy-carbonyl}} or C_{1-3-alkoxy-C_{2-3-alkoxy-C_{1-4-alkoxy-carbonyl}}} group, such as the 2-methy sulphonylethoxycarbonyl or 2-(2-ethoxy)-ethoxycarbonyl group.

The above exemplified compounds, their tautomers, their stereoisomers or the physiologically acceptable salts thereof, as well as their manufacturing process, have been described in WO 04/009547, the content of which is incorporated herein by reference.

The following list of specific compounds is illustrative of the present invention, without constituting any limitation of its scope:

1. \[3-Z-[1-(4-(N-methyl-N-methysulphonylamino)anilino)-1-(3-iodophenyl)methylene]-6-chloro-2-indolinone\]
2. \[3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(3-iodophenyl)methylene]-6-chloro-2-indolinone\]
3. \[3-Z-[1-(4-(N-(dimethylaminomethylcarbonyl)-N-methylamino)anilino)-1-(4-chlorophenyl)methylene]-6-chloro-2-indolinone\]
4. \[3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-acetylamino)anilino)-1-(4-chlorophenyl)methylene]-6-chloro-2-indolinone\]
5. \[3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-chlorophenyl)methylene]-6-chloro-2-indolinone\]
6. \[3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetylamino)anilino)-1-(4-chlorophenyl)methylene]-6-chloro-2-indolinone\]
7. \[3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(4-chlorophenyl)methylene]-6-chloro-2-indolinone\]
8. \[3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-acetylamino)anilino)-1-(3,4-dimethoxyphenyl)methylene]-6-chloro-2-indolinone\]
9. \[3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(3,4-dimethoxyphenyl)methylene]-6-chloro-2-indolinone\]
10. \[3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylcarbamoyl)anilino)-1-(3,4-dimethoxyphenyl)methylene]-6-chloro-2-indolinone\]
11. \[3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(3,4-dimethoxyphenyl)methylene]-6-chloro-2-indolinone\]
12. \[3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylcarbamoyl)anilino)-1-(3,4-dimethoxyphenyl)methylene]-6-chloro-2-indolinone\]
(13) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(4-cyanophenyl)methylene]-6-chloro-2-indolinone
(14) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(4-iodophenyl)methylene]-6-fluoro-2-indolinone
(15) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(3-fluorophenyl)methylene]-6-fluoro-2-indolinone
(16) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetylamino)anilino)-1-(3-fluorophenyl)methylene]-6-fluoro-2-indolinone
(17) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(3-fluorophenyl)methylene]-6-fluoro-2-indolinone
(18) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(4-(2-acetylaminoethyl)phenyl)methylene]-6-fluoro-2-indolinone
(19) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetylamino)anilino)-1-(4-(2-acetylaminoethyl)phenyl)methylene]-6-fluoro-2-indolinone
(20) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-acetylaminoethyl)phenyl)methylene]-6-fluoro-2-indolinone
(21) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(4-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone
(22) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(3-iodophenyl)methylene]-6-fluoro-2-indolinone
(23) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(3-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone
(24) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(3-(N-tert-butoxycarbonylamino)phenyl)methylene]-6-fluoro-2-indolinone
(25) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-(4-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone
(26) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone
(27) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-fluoro-2-indolinone
(28) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetylamino)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-fluoro-2-indolinone
(29) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-fluoro-2-indolinone
(30) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(3-(N-tert-butoxycarbonyl-2-aminoethyl)phenyl)methylene]-6-fluoro-2-indolinone
(31) 3-Z-[1-(4-(N-Acetyl-N-methylamino)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-fluoro-2-indolinone
(32) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-fluoro-2-indolinone
(33) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-(4-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone
(34) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetylamino)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-fluoro-2-indolinone
(35) 3-Z-[1-(4-(N-tert-butoxycarbonylmethylaminomethyl)anilino)-1-(4- (2-methoxycarboxylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(36) 3-Z-[1-(4-(4-methylpiperazin-1-yl-carbonyl)anilino)-1-(4- (2-methoxycarboxylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(37) 3-Z-[1-(4-(1-methylimidazol-2-yl)anilino)-1-(4- (2-methoxycarboxylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(38) 3-Z-[1-(4-(methylsulphonylanilino)-1-(4-(2-methoxycarboxylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(39) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylcarbonyl)-N-methy lamino)anilino)-1-(3-methoxycarbonyl methylphenyl)methylene]-6-fluoro-2-indolinone

(40) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-(3-methoxycarboxyl methylphenyl)methylene]-6-fluoro-2-indolinone

(41) 3-Z-[1-(4-(4-methylpiperazin-1-yl-carbonyl)anilino)-1-(3-methoxycarboxylethylphenyl)methylene]-6-fluoro-2-indolinone

(42) 3-Z-[1-(4-(N-(dimethylaminomethylcarbonyl)-N-methy lamino)anilino)-1-(3-methoxycarbonyl methylphenyl)methylene]-6-fluoro-2-indolinone

(43) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetylamino)anilino)-1-(3-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone

(44) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-acetylamino)anilino)-1-(3-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone

(45) 3-Z-[1-(4-(N-(3-dimethylaminopropylcarbonyl)-N-methy lamino)anilino)-1-(3-methoxycarbonyl methylphenyl)methylene]-6-fluoro-2-indolinone

(46) 3-Z-[1-Anilino-1-(4-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone

(47) 3-Z-[1-(4-(1-methylimidazol-2-yl) anilino)-1-(4-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone

(48) 3-Z-[1-(4-(4-methylpiperazin-1-ylcarbonyl)anilino)-1-(4-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone

(49) 3-Z-[1-(4-(N-(dimethylaminocarbonylmethyl)-N-methyl sulphynylamino)anilino)-1-(4-methoxycarbonyl methylphenyl)methylene]-6-fluoro-2-indolinone

(50) 3-Z-[1-(4-(N-(dimethylaminomethylcarbonyl)-N-methyl amino)anilino)-1-(4-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone

(51) 3-Z-[1-(4-(N-methyl-N-acetylamino)anilino)-1-(4-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone

(52) 3-Z-[1-(4-(N-(2-dimethylaminocarboxylic acid)-N-methyl amino)anilino)-1-(4-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone

(53) 3-Z-[1-(4-methoxycarbonylmethylphenyl)-1-(4-meth oxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone

(54) 3-Z-[1-(4-(N-(3-dimethylaminopropylcarbonyl)-N-methyl amino)anilino)-1-(4-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone

(55) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetylamino)anilino)-1-(4-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone
ene]-6-fluoro-2-indolinone

(56) 3-Z-[1-Anilino-1-(3-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone

(57) 3-Z-[1-(4-methylsulphonylanilino)-1-(3-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone

(58) 3-Z-[1-(4-(1-methylimidazol-2-yl)anilino)-1-(3-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone

(59) 3-Z-[1-(4-(N-(dimethylaminocarbonylmethyl)-N-methylsulphonylamino)anilino)-1-(3-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone

(60) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)carbonyl)-N-methylamino)anilino)-1-(3-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone

(61) 3-Z-[1-(4-(N-(2-dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(3-methoxycarbonylmethylphenyl)methylene]-6-fluoro-2-indolinone

(62) 3-Z-[1-(4-(N(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(3-methoxycarbonylethylphenyl)methylene]-6-fluoro-2-indolinone

(63) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-(3-methoxycarbonylethylphenyl)methylene]-6-fluoro-2-indolinone

(64) 3-Z-[1-(4-(N-(3-dimethylaminomethylcarbonyl)-N-methylamino)anilino)-1-(3-methoxycarbonylethylphenyl)methylene]-6-fluoro-2-indolinone

(65) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetylamino)anilino)-1-(3-methoxycarbonylethylphenyl)methylene]-6-fluoro-2-indolinone

(66) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(3-methoxycarbonylethylphenyl)methylene]-6-fluoro-2-indolinone

(67) 3-Z-[1-(4-(N-(N-methyl-N-acetylamino)anilino)-1-(3-acetylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(68) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetylamino)anilino)-1-(3-acetylaminomethylphenyl)methylene]-6-chloro-2-indolinone

(69) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-(3-acetylaminomethylphenyl)methylene]-6-chloro-2-indolinone

(70) 3-Z-[1-(4-(N-(dimethylaminomethylcarbonyl)-N-methylamino)anilino)-1-(3-acetylaminomethylphenyl)methylene]-6-chloro-2-indolinone

(71) 3-Z-[1-(4-(2-dimethylaminoethyl)anilino)-1-(4-(2-methoxycarbonylethylphenyl)methylene]-6-fluoro-2-indolinone

(72) 3-Z-[1-(4-(N-(2-dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-methoxycarbonylethylphenyl)methylene]-6-fluoro-2-indolinone

(73) 3-Z-[1-(4-(N-(dimethylaminomethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-methoxycarbonylethylphenyl)methylene]-6-fluoro-2-indolinone

(74) 3-Z-[1-(4-(2-dimethylaminoethyl)anilino)-1-(3-(2-ethoxycarbonylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(75) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-acetylamino)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-fluoro-2-indolinone
(76) 3-Z-[1-(4-(N-(3-dimethylaminopropylcarbonyl)-N-methylamino)anilino)-1-(3-(2-ethoxycarbonylethyl)phenyl)methylene]-6-flouro-2-indolinone

(77) 3-Z-[1-(4-(N-(4-dimethylaminobutylcarbonyl)-N-methylamino)anilino)-1-(3-(2-ethoxycarbonylethyl)phenyl)methylene]-6-flouro-2-indolinone

(78) 3-Z-[1-(4-(1-methylimidazol-2-yl)anilino)-1-(3-(2-ethoxycarbonylethyl)phenyl)methylene]-6-flouro-2-indolinone

(79) 3-Z-[1-(4-(N-(4-dimethylaminobutylcarbonyl)-N-methylamino)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-flouro-2-indolinone

(80) 3-Z-[lanilino-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-flouro-2-indolinone

(81) 3-Z-[1-(4-(pyrrolidin-1-ylmethyl)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-flouro-2-indolinone

(82) 3-Z-[1-(4-(diethylaminomethyl)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-flouro-2-indolinone

(83) 3-Z-[1-(4-(N-tert-butoxycarbonylaminomethyl)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-flouro-2-indolinone

(84) 3-Z-[1-(4-(2-dimethylaminoethyl)anilino)-1-(3-methoxycarbonylphenyl)methylene]-6-flouro-2-indolinone

(85) 3-Z-[1-(4-(2-dimethylaminoethyl)anilino)-1-(4-(methoxycarbonylphenyl)methylene)-6-flouro-2-indolinone

(86) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(3-(2-ethoxycarbonylethyl)phenyl)methylene]-6-flouro-2-indolinone

(87) 3-Z-[1-(4-(2-dimethylaminoethyl)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-chloro-2-indolinone

(88) 3-Z-[1-(4-(1-methylimidazol-2-yl)anilino)-1-(4-(2-ethoxycarbonylethyl)phenyl)methylene]-6-chloro-2-indolinone

(89) 3-Z-[1-(4-dimethylaminomethyl)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-chloro-2-indolinone

(90) 3-Z-[1-(4-dimethylaminomethyl)anilino)-1-(4-(2-ethoxycarbonylethyl)phenyl)methylene]-6-flouro-2-indolinone

(91) 3-Z-[1-(4-(4-methyl/piperazin-1-yl)methyl)anilino)-1-(3-(2-methoxycarbonylethyl)phenyl)methylene]-6-flouro-2-indolinone

(92) 3-Z-[1-(4-(imidazol-1-yl)methyl)anilino)-1-(3-(2-methoxycarbonylethyl)phenyl)methylene]-6-flouro-2-indolinone

(93) 3-Z-[1-(4-(4-methyl/piperazin-1-yl)methyl)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-flouro-2-indolinone

(94) 3-Z-[1-(4-(imidazol-1-yl)methyl)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-flouro-2-indolinone

(95) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylaminomethyl)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-flouro-2-indolinone

(96) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylaminomethyl)anilino)-1-(3-(2-ethoxycarbonylethyl)phenyl)methylene]-6-flouro-2-indolinone
(97) 3-Z-[1-(4-(pyrrolidin-1-ylmethyl)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-chloro-2-indolinone

(98) 3-Z-[lanilino-1-(3-(2-ethoxycarboxylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(99) 3-Z-[1-(4-(N-tert-butoxycarbonylamino)-1-(4-(2-methoxycarboxylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(100) 3-Z-[1-(4-(N-tert-butoxycarbonylaminomethyl)anilino)-1-(3-(2-ethoxycarbonylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(101) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(3-(2-ethoxycarbonylphenyl)methylene)-6-fluoro-2-indolinone

(102) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(4-methoxycarbonylmethoxy-phenyl)methylene]-6-fluoro-2-indolinone

(103) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-ethoxycarbonyl-ethoxy)phenyl)methylene]-6-fluoro-2-indolinone

(104) 3-Z-[1-(4-(pyrrolidin-1-ylmethyl)anilino)-1-(4-(2-methoxycarboxylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(105) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(4-(2-methoxycarbonylvinyl)phenyl)methylene]-6-bromo-2-indolinone

(106) 3-Z-[1-(4-(diethylaminomethyl)anilino)-1-(4-(2-methoxycarbonylvinyl)phenyl)methylene]-6-bromo-2-indolinone

(107) 3-Z-[1-(3-dimethylaminomethylanilino)-1-(4-(2-methoxycarbonylvinyl)phenyl)methylene]-6-fluoro-2-indolinone

(108) 3-Z-[1-(3-dimethylaminomethylanilino)-1-(3-(2-methoxycarbonylvinyl)phenyl)methylene]-6-fluoro-2-indolinone

(109) 3-Z-[1-(3-dimethylaminomethylanilino)-1-(4-(2-methoxycarbonylvinyl)phenyl)methylene]-6-chloro-2-indolinone

(110) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(3,4-dimethoxyphenyl)methylene]-6-cyano-2-indolinone

(111) 3-Z-[1-(4-(N-methyl-N-methylsulphonylamino)anilino)-1-(3-(2-methoxycarbonylvinyl)phenyl)methylene]-6-chloro-2-indolinone

(112) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(4-(2-methoxycarbonyl-vinyl)phenyl)methylene]-6-chloro-2-indolinone

(113) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(4-(2-carbamoyl-vinyl)phenyl)methylene]-6-fluoro-2-indolinone

(114) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(4-(2-methoxycarbonyl-vinyl)phenyl)methylene]-6-fluoro-2-indolinone

(115) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(3-(2-methoxycarbonylvinyl)phenyl)methylene]-6-fluoro-2-indolinone

(116) 3-Z-[1-(4-(dimethylaminomethylanilino)-1-(3-(2-methoxycarbonylethyl)phenyl)methylene]-6-chloro-2-indolinone

(117) 3-Z-[1-(4-(N-methyl-N-methylsulphonylamino)anilino)-1-(3-(2-methoxycarbonylethyl)phenyl)methylene]-6-chloro-2-indolinone
(118) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(4-(2-carbamoyl-ethyl)phenyl)methylene]-6-fluoro-2-indolinone

(119) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(120) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-methoxycarbonylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(121) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(4-aminomethylphenyl)methylene]-6-chloro-2-indolinone

(122) 3-Z-[1-(4-(N-((4-methylpiperazin-1-yl) methylcarbonyl)-N-methylamino) anilino)-1-(4-aminomethylphenyl)methylene]-6-chloro-2-indolinone

(123) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(3-aminomethylphenyl)methylene]-6-fluoro-2-indolinone

(124) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(3-(2-aminoethyl)phenyl)methylene]-6-fluoro-2-indolinone

(125) 3-Z-[1-(4-(dimethylaminomethyl)anilino)-1-(4-aminomethylphenyl)methylene]-6-fluoro-2-indolinone

(126) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-aminomethylphenyl)methylene]-6-fluoro-2-indolinone

(127) 3-Z-[1-(4-(N-methylaminomethyl) anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(128) 3-Z-[1-(4-(N-methylaminomethyl)anilino)-1-(4-(2-methylcarbamoyl-ethyl)phenyl)methylene]-6-fluoro-2-indolinone

(129) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(3-aminomethylphenyl)methylene]-6-fluoro-2-indolinone

(130) 3-Z-[1-(4-(aminomethyl)anilino)-1-(4-(2-methoxycarbonylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(131) 3-Z-[1-(4-(aminomethyl)anilino)-1-(3-(2-ethoxycarbonylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(132) 3-Z-[1-(4-(N-methylaminomethyl)anilino)-1-(3-(2-ethoxycarbonylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(133) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(134) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(135) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(136) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(137) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(4-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(138) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(139) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-(4-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(140) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(141) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(142) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone
ene]-6-fluoro-2-indolinone

(143) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetylamino) anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(144) 3-Z-[1-(4-(N-tert-butoxycarbonylmethylaminomethyl) anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(145) 3-Z-[1-(4-(4-methylpiperazin-1-ylcarbonyl) anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(146) 3-Z-[1-(4-(1-methylimidazol-2-yl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(147) 3-Z-[1-(4-methylsulphonylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(148) 3-Z-[1-(4-(4-methylpiperazin-1-ylcarbonyl) anilino)-1-(3-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(149) 3-Z-[1-(4-(N-(4-methylpiperazin-1-yl)-N-methylsulphonylamino) anilino)-1-(3-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(150) 3-Z-[1-(4-(N-(dimethylaminocarbonylmethyl)-N-methylsulphonylamino) anilino)-1-(3-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(151) 3-Z-[1-(4-(N-(dimethylaminocarbonylmethyl)-N-methylsulphonylamino) anilino)-1-(3-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(152) 3-Z-[1-(Anilino)-1-(3-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(153) 3-Z-[1-(4-methylsulphonylanilino)-1-(3-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(154) 3-Z-[1-(4-(1-methylimidazol-2-yl)anilino)-1-(3-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(155) 3-Z-[1-(4-(N-(dimethylaminocarbonylmethyl)-N-methylsulphonylamino) anilino)-1-(3-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(156) 3-Z-[lanilino]-6-fluoro-2-indolinone

(157) 3-Z-[1-(4-(1-methylimidazol-2-yl)anilino)-1-(4-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(158) 6-fluoro-2-indolinone

(159) 3-Z-[1-(4-(N-(3-dimethylaminopropylcarbonyl)-N-methylamino) aniline)-1-(4-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(160) 3-Z-[1-(4-(N-(dimethylaminocarbonylmethyl)-N-methylsulphonylamino) anilino)-1-(4-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(161) 3-Z-[1-(4-(4-methylpiperazin-1-ylcarbonyl) anilino)-1-(4-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(162) 3-Z-[1-(4-methylsulphonylanilino)-1-(4-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(163) 3-Z-[1-(4-(N-methyl-N-acetylamino)anilino)-1-(4-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(164) 3-Z-[1-(4-(dimethylaminocarbonylmethyl)-N-methylsulphonylamino)anilino)-1-(4-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone
(165) 3-Z-[1-(4-(N-(2-dimethylaminoethyldcarbonyl)-N-methylamino)anilino)-1-(4-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(166) 3-Z-[1-(4-(N-(3-dimethylaminopropylcarbonyl)-N-methylamino)anilino)-1-(4-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(167) 3-Z-[1-(4-(N-(4-methylpiperezin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(168) 3-Z-[1-(4-(N-(2-dimethylaminomethylcarbonyl)-N-methylsulphonylamino)anilino)-1-(3-carboxymethylphenyl)methylene]-6-fluoro-2-indolinone

(169) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(170) 3-Z-[1-(4-(N-(dimethylaminomethylcarbonyl)-N-acetamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(171) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(172) 3-Z-[1-(4-(N-(dimethylaminomethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(173) 3-Z-[1-(4-(2-dimethylaminoethyldanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(174) 3-Z-[1-(4-(N-(2-dimethylaminoethyldcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(175) 3-Z-[1-(4-(N-(2-dimethylaminoethyldanilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(176) 3-Z-[1-(4-(N-(2-dimethylaminoethyldcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(177) 3-Z-[1-(4-(N-(3-dimethylaminopropylcarbonyl)-N-methylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(178) 3-Z-[1-(4-(N-(4-dimethylamino-butylcarbonyl)-N-methylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(179) 3-Z-[1-(4-(1-methylimidazol-2-yl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(180) 3-Z-[1-(4-(N-(4-dimethylaminobutylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(181) 3-Z-[1-(4-(2-dimethylaminoethyl)anilino)-1-(4-(3-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(182) 3-Z-[1-(4-(pyrrolidin-1-ylmethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(183) 3-Z-[1-(4-(diethylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(184) 3-Z-[1-(4-(aminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(185) 3-Z-[1-(4-(2-dimethylaminoethyldanilino)-1-(3-carboxyethyl)methylene]-6-fluoro-2-indolinone

(186) 3-Z-[1-(4-(2-dimethylaminoethyldanilino)-1-(4-carboxyethyl)methylene]-6-fluoro-2-indolinone

(187) 3-Z-[1-(4-(2-dimethylaminoethyldanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone
(188) 3-Z-[1-(4-(1-methylimidazol-2-yl)anilino)-1-(4-(2-carboxyethyl)phenyl)ethylene]-6-chloro-2-indolinone

(189) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(4-(2-carboxyethyl)phenyl)ethylene]-6-chloro-2-indolinone

(190) 3-Z-[1-(4-((4-methylpiperazin-1-yl) methyl) anilino) -1-(3-(2-carboxyethyl) phenyl) methylene]-6-fluoro-2-indolinone

(191) 3-Z-[1-(4-(imidazol-1-yl)methylanilino)-1-(3-(2-carboxyethyl)phenyl)ethylene]-6-fluoro-2-indolinone

(192) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)ethylene]-6-fluoro-2-indolinone

(193) 3-Z-[1-(4-((4-methylpiperazin-1-yl) methyl) anilino)-1-(4-(2-carboxyethyl)phenyl) methylene]-6-fluoro-2-indolinone

(194) 3-Z-[1-(4-(imidazol-1-yl)methylanilino)-1-(4-(2-carboxyethyl)phenyl)ethylene]-6-fluoro-2-indolinone

(195) 3-Z-[1-(4-(pyrrolidin-1-yl)methylanilino)-1-(4-(2-carboxyethyl)phenyl)ethylene]-6-chloro-2-indolinone

(196) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)ethylene]-6-fluoro-2-indolinone

(197) 3-Z-[lanilino-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(198) 3-Z-[1-(4-aminomethylanilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(199) 3-Z-[1-(4-methylaminomethylanilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(200) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-carboxymethoxy-phenyl)-methylene]-6-fluoro-2-indolinone

(201) 3-Z-[1-(4- dimethylaminomethylanilino)-1-(4- carboxymethoxy-phenyl) phenyl) methylene]-6- fluoro-2- indolinone

(202) 3-Z-[1-(4-(pyrrolidin-1-yl)methylanilino)-1-(4-(2-carboxyethyl)phenyl)ethylene]-6-bromo-2-indolinone

(203) 3-Z-[1-(4-(dimethylaminomethyl) anilino)-1-(4-(2-carboxyethyl)phenyl)ethylene]-6-bromo-2-indolinone

(204) 3-Z-[1-(4-(diethylaminomethyl)anilino)-1-(4-(2-carboxyethyl)-methylene]-6-bromo-2-indolinone

(205) 3-Z-[1-(3-dimethylaminomethylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(206) 3-Z-[1-(3-dimethylaminomethylanilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(207) 3-Z-[1-(3-dimethylaminomethylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(208) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-carbamoyl-ethyl)phenyl)methylene]-6-chloro-2-indolinone

(209) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-methylcarbamoyl-ethyl) phenyl) methylene]-6- chloro-2- indolinone

(210) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(4-(2-methylcarbamoyl-ethyl) phenyl) methylene]-6-fluoro-2-indolinone

(211) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(dimethylcarbamoylmethyl)phenyl) methylene]-6-fluoro-2-indolinone

(212) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-carbamoyl-ethyl)phenyl)methylene]-6-fluoro-2-indolinone
(213) 3- Z-[1-(4- dimethylaminomethylanilino)- 1-[(3- (2- methylcarbamoyl- ethyl) phenyl) methylene]- 6- fluoro- 2- indolinone

(214) 3- Z-[1-(4-dimethylaminomethylanilino)-1-[(3-(2-methylcarbamoyl-ethyl)phenyl)methylene]-6-fluoro-2-indolinone

(215) 3- Z-[1-(4-dimethylaminomethylanilino)-1-[(3-carbamoylmethylphenyl)-methylene]-6-fluoro-2-indolinone

(216) 3- Z-[1-(4-dimethylaminomethylanilino)-1-[(3-methylcarbamoylmethylphenyl)methylene]-6-fluoro-2-indolinone

(217) 3- Z-[1-(4-dimethylaminomethylanilino)-1-[(4-carbamoylmethylphenyl)-methylene]-6-fluoro-2-indolinone

(218) 3- Z-[1-(4-dimethylaminomethylanilino)-1-[(4-(2-methylcarbamoyl-ethyl) phenyl) methylene]-6-fluoro-2-indolinone

(219) 3- Z-[1-(4-dimethylaminomethylanilino)-1-[(4-((2-methylpiperazin-1-yl-carbonyl)ethyl)phenyl)methylene]-6-fluoro-2-indolinone

(220) 3- Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-[(4-carbamoylmethylphenyl) methylene]-6-fluoro-2-indolinone

(221) 3- Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-[(4-carbamoylmethylphenyl)methylene]-6-fluoro-2-indolinone

(222) 3- Z-[1-(4- dimethylaminomethylanilino)- 1-[(4- dimethylcarbamoylmethylphenyl) methylene]- 6- fluoro- 2- indolinone

(223) 3- Z-[1-(4-dimethylaminomethylanilino)-1-[(4-methylcarbamoylmethylphenyl)methylene]-6-fluoro-2-indolinone

(224) 3- Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-[(4-methylcarbamoylmethylphenyl) methylene]-6-fluoro-2-indolinone

(225) 3- Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-[(4-dimethylcarbamoylmethylphenyl)methylene]-6-fluoro-2-indolinone

(226) 3- Z-[1-(4-(N-(2-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-[(4-methylcarbamoylmethylphenyl)methylene]-6-fluoro-2-indolinone

(227) 3- Z-[1-(4-(N-methyl-N-acetylamino)anilino)-1-[(4-(2-methylcarbamoyl-ethyl)phenyl)methylene]-6-fluoro-2-indolinone

(228) 3- Z-[1-(4-(N-(2-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-[(4-(2-methylcarbamoyl-ethyl)phenyl)methylene]-6-fluoro-2-indolinone

(229) 3- Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-[(4-(2-methylcarbamoylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(230) 3- Z-[1-(4-(N-tert-butoxycarbonylmethylaminomethyl)anilino)-1-[(4-(2-methylcarbamoylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(231) 3- Z-[1-(4-(1-methylimidazol-2-yl)anilino)-1-[(4-(2-methylcarbamoyl-ethyl)phenyl)methylene]-6-fluoro-2-indolinone

(232) 3- Z-[1-(4-methylsulphonylanilino)-1-[(4-(2-methylcarbamoyl-ethyl)phenyl)methylene]-6-fluoro-2-indolinone

(233) 3- Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-[(4-methylcarbamoylmethylphenyl)methylene]-6-fluoro-2-indolinone
(234) 3-Z-[1-(4-(4-methylpiperazin-1-ylcarbonyl)anilino)-1-(3-methylcarbamoylmethylphenyl)methylene]-6-fluoro-2-indolinone

(235) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(3-methylcarbamoylmethylphenyl)methylene]-6-fluoro-2-indolinone

(236) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(4-acetyliminomethylphenyl)methylene]-6-chloro-2-indolinone

(237) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-acetyliminomethylphenyl)methylene]-6-chloro-2-indolinone

(238) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(4-benzylylaminophenyl)methylene]-6-chloro-2-indolinone

(239) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-benzoyliminomethylphenyl)methylene]-6-chloro-2-indolinone

(240) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-acetyliminomethylphenyl)methylene]-6-fluoro-2-indolinone

(241) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-propionylinomethylphenyl)methylene]-6-fluoro-2-indolinone

(242) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-benzylylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(243) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-phenylacetilaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(244) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-acetyliminoethylethyl)phenyl)methylene]-6-fluoro-2-indolinone

(245) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-benzylylaminophenyl)methylene]-6-fluoro-2-indolinone

(246) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-propionylinomethylphenyl)methylene]-6-fluoro-2-indolinone

(247) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-phenylacetilaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(248) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-acetyliminomethylphenyl)methylene]-6-fluoro-2-indolinone

(249) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-propionylinomethylphenyl)methylene]-6-fluoro-2-indolinone

(250) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(4-phenylacetilaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(251) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-acetyliminomethylphenyl)methylene]-6-fluoro-2-indolinone

(252) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-propionylinomethylphenyl)methylene]-6-fluoro-2-indolinone

(253) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(9-phenylacetilaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(254) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(3-cyclopropylcarbonylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(255) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(3-cyclobutylcarbonylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(256) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(3-pyridin-2-yl-carbonylaminomethylphenyl)methylene]-6-fluoro-2-indolinone
(257) 3-Z-[1-(4-N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino]-1-(3-cyclohexylcarbonylaminomethylphenyl)-methylene]-6-fluoro-2-indolinone

(258) 3-Z-[1-(4-N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino]-1-(3-pyridin-3-yl-carbonylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(259) 3-Z-[1-(4-N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino]-1-(3-isobutrylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(260) 3-Z-[1-(4-N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino]-1-(3-(3-methylbutrylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(261) 3-Z-[1-(4-N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)aniline]-1-(3-cyclohexylmethylcarbonylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(262) 3-Z-[1-(4-N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino]-1-(3-methoxyacetylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(263) 3-Z-[1-(4-N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino]-1-(3-(2-methoxybenzoylaminomethyl)phenyl)methylene]-6-fluoro-2-indolinone

(264) 3-Z-[1-(4-N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino]-1-(3-(tert-butylacetylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(265) 3-Z-[1-(4-N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino]-1-(3-(2-thiophen-carbonylaminomethyl)phenyl)methylene]-6-fluoro-2-indolinone

(266) 3-Z-[1-(4-N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino]-1-(3-pivaloylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(267) 3-Z-[1-(4-N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino]-1-(3-(2-furoylaminomethyl)phenyl)methylene]-6-fluoro-2-indolinone

(268) 3-Z-[1-(4-N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino]-1-(3-acetylaminoethylphenyl)methylene]-6-fluoro-2-indolinone

(269) 3-Z-[1-(4-N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino]-1-(3-propionylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(270) 3-Z-[1-(4-N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino]-1-(3-benzoylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(271) 3-Z-[1-(4-N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino]-1-(3-phenylacetylaminoethylphenyl)methylene]-6-fluoro-2-indolinone

(272) 3-Z-[1-(4-dimethylaminomethylamino)-1-(3-cyclopropylcarbonylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(273) 3-Z-[1-(4-dimethylaminomethylamino)-1-(3-cyclobutylcarbonylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(274) 3-Z-[1-(4-dimethylaminomethylamino)-1-(3-pyridin-2-yl-carbonylaminomethyl)phenyl)methylene]-6-fluoro-2-indolinone

(275) 3-Z-[1-(4-dimethylaminomethylamino)-1-(3-cyclohexylcarbonylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(276) 3-Z-[1-(4-dimethylaminomethylamino)-1-(3-pyridin-3-yl-carbonylaminomethyl)phenyl)methylene]-6-fluoro-
2-indolinone

(277) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-isobutrylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(278) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(3-methylbutyryl-aminomethylphenyl)methylene]-6-fluoro-2-indolinone

(279) 3-Z-[1-(4- dimethylaminomethylanilino)-1-(3-cyclohexylmethylocarbonylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(280) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-methoxyacetylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(281) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-methoxybenzoyl-aminomethyl)phenyl)methylene]-6-fluoro-2-indolinone

(282) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-tert-butylacetylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(283) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-thiophenecarbonylaminomethyl)phenyl)methylene]-6-fluoro-2-indolinone

(284) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-pivaloylaminomethylphenyl)methylene]-6-fluoro-2-indolinone

(285) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-furoylaminomethyl)phenyl)methylene]-6-fluoro-2-indolinone

(286) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(pyridin-4-yl-carbonylaminomethyl)phenyl)methylene]-6-fluoro-2-indolinone

(287) 3-Z-[1-(4-trimethylammoniummethylphenyl)methylene]-6-fluoro-2-indolinone iodide

(288) 3-Z-[1-(4-trimethylammoniummethylphenyl)methylene]-6-fluoro-2-indolinone iodide

(289) 3-Z-[1-(4-guanidinomethylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(290) 3-Z-[1-(4-guanidinomethylanilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(291) 3-Z-[1-(4-((N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(292) 3-Z-[1-(4-((N-dimethylaminomethylcarbonyl)-N-methylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(293) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-acetylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(294) 3-Z-[1-(4-(N-(2-methylaminoethyl)-N-acetylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(295) 3-Z-[1-(4-((N-(3-dimethylaminopropyl)-N-acetylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(296) 3-Z-[1-(4-((N-(3-methyaminopropyl)-N-acetylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(297) 3-Z-[1-(4-(3-dimethylaminopropyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone
(298) 3-Z-[1-(4-ethylaminomethylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(299) 3-Z-[1-(4-methylaminomethylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(300) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl) methylene]-6-chloro-2-indolinone

(301) 3-Z-[1-(4-(4-methylpiperazin-1-ylcarbonyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(302) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-methylsulphonylaminio)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(303) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-propylsulphonylaminio)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(304) 3-Z-[1-(4-aminomethylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(305) 3-Z-[1-(3-(methylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(306) 3-Z-[1-(3-(2-dimethylaminooethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(307) 3-Z-[1-(3-(3-dimethylaminopropyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(308) 3-Z-[1-(4-(N-(dimethylamino-carbonylmethyl)-N-methylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(309) 3-Z-[1-(4-(N-methyl-N-methylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(310) 3-Z-[1-(4-(N-methyl-N-acetylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(311) 3-Z-[1-(4-(N-(N-(2-dimethylaminoethyl)-N-methylaminomethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(312) 3-Z-[1-(4-(2-diethylaminooethylsulphonyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(313) 3-Z-[1-(4-(N-(2-dimethylaminooethyl-carbonyl)-N-methylamino)aniline)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(314) 3-Z-[1-(4-(N-(2-dimethylaminooethyl)-N-methylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(315) 3-Z-[1-(4-(2-dimethylaminooxy)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(316) 3-Z-[1-(4-(N-(4-dimethylaminobutylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(317) 3-Z-[1-(4-(N-(3-dimethylaminopropylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(318) 3-Z-[1-(4-(methyllethylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(319) 3-Z-[1-(4-(methylpropaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(320) 3-Z-[1-(4-(methylbenzylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone
(321) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methyaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(322) 3-Z-[1-(4-(azetidin-1-ylmethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(323) 3-Z-[1-(4-((4-methylpiperazin-1-yl)methyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(324) 3-Z-[1-(4-(piperazin-1-ylmethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(325) 3-Z-[1-(4-((thiomorpholin-4-yl)methyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(326) 3-Z-[1-(4-((imidazol-1-yl)methyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(327) 3-Z-[1-(4-((imidazol-1-yl)methyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(328) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(329) 3-Z-[1-(4-((N-(2-dimethylaminoethyl)-N-acetylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(330) 3-Z-[1-(4-((N-(2-dimethylaminoethyl)-N-methylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(331) 3-Z-[1-(4-(N-(2-methylaminopropyl)-N-acetylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(332) 3-Z-[1-(4-(N-(2-methylaminopropyl)-N-acetylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(333) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-methylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(334) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(335) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(336) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(337) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethyl)carbonyl)-N-methyaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(338) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethyl)carbonyl)-N-methyaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(339) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethyl)carbonyl)-N-methyaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(340) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethyl)carbonyl)-N-methyaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(341) 3-Z-[1-(3-(dimethylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(342) 3-Z-[1-(3-(dimethylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(343) 3-Z-[1-(3-(dimethylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone
(344) 3-Z-[1-(3-(2-dimethylaminoethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(345) 3-Z-[1-(3-(3-dimethylaminopropyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(346) 3-Z-[1-(4-(2-dimethylaminoethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(347) 3-Z-[1-(4-(N-(dimethylaminocarbonylmethyl)-N-methylsulphonylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(348) 3-Z-[1-(4-(N-methyl-N-methylsulphonylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(349) 3-Z-[1-(4-(N-methyl-N-acetylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(350) 3-Z-[1-(4-(1-methylimidazol-2-yl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(351) 3-Z-[1-(4-(N-(N-(2-dimethylaminoethyl)-N-methylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(352) 3-Z-[1-(4-(2-diethylaminosulphonyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(353) 3-Z-[1-(4-(N-(2-dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(354) 3-Z-[1-(4-(N-(N-(2-dimethylaminoethyl)-N-methylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(355) 3-Z-[1-(4-(2-dimethylaminooxy)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(356) 3-Z-[1-(4-(N-(4-dimethylaminobutylcarbonyl)-N-methylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(357) 3-Z-[1-(4-(N-(3-dimethylaminopropylcarbonyl)-N-methylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(358) 3-Z-[1-(4-(methylethylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(359) 3-Z-[1-(4-(N-methylpropylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(360) 3-Z-[1-(4-(methylbenzylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(361) 3-Z-[1-(4-(3-diethylaminomethoxy)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(362) 3-Z-[1-(4-(N-(3-dimethylaminopropylcarbonyl)-N-methylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(363) 3-Z-[1-(4-(pyrrolidin-1-yl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(364) 3-Z-[1-(4-(azetidin-1-yl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(365) 3-Z-[1-(4-(4-methylpiperazin-1-yl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(366) 3-Z-[1-(4-(piperazin-1-yl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(367) 3-Z-[1-(4-(morpholin-4-yl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone
(368) 3-Z-[1-(4-(thiomorpholin-4-ylmethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(369) 3-Z-[1-(4-(imidazol-1-ylmethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone

(370) 3-Z-[1-(4-(N-(2-methylaminoethyl)-N-acetylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(371) 3-Z-[1-(4-(N-(3-methylaminopropyl)-N-acetylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(372) 3-Z-[1-(4-(3-dimethylaminopropyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(373) 3-Z-[1-(4-ethylaminomethylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(374) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-methylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(375) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-propylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(376) 3-Z-[1-(3-(methylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(377) 3-Z-[1-(3-(2-dimethylaminomethyl)amino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(378) 3-Z-[1-(3-(3-dimethylaminopropyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(379) 3-Z-[1-(4-(N-(dimethylaminocarbonylmethyl)-N-methylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(380) 3-Z-[1-(4-(N-methyl-N-methylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(381) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylaminomethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(382) 3-Z-[1-(4-(2-diethylaminoethylsulphonyl)aniline)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(383) 3-Z-[1-(4-(2-dimethylaminoethoxy)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(384) 3-Z-[1-(4-(N-(3-dimethylaminopropylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(385) 3-Z-[1-(4-(methylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(386) 3-Z-[1-(4-(methylpropionaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(387) 3-Z-[1-(4-(methylbenzylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(388) 3-Z-[1-(4-(azetidin-1-ylmethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(389) 3-Z-[1-(4-(piperazin-1-ylmethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(390) 3-Z-[1-(4-(morpholin-4-ylmethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(391) 3-Z-[1-(4-(thiomorpholin-4-ylmethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(392) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-acetylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-
fluoro-2-indolinone

(393) 3-Z-[1-(4-(N-(2-methylaminoethyl)-N-acetylamino) anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(394) 3-Z-[1-(4-(N-(3-methylenopropyl)-N-acetylamino) anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(395) 3-Z-[1-(4-(3-dimethylaminopropyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(396) 3-Z-[1-(4-ethylenaminomethylanilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(397) 3-Z-[1-(4-(4-methylpiperazin-1-yl)carbonyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(398) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-methylsulphonylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(399) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-methylsulphonylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(400) 3-Z-[1-(3-(methylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(401) 3-Z-[1-(3-(2-dimethylaminopropyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(402) 3-Z-[1-(3-(3-dimethylaminopropyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(403) 3-Z-[1-(4-(N-(dimethylaminocarbonylmethyl)-N-methylsulphonylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(404) 3-Z-[1-(4-(N-methyl-N-methylsulphonylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(405) 3-Z-[1-(4-(N-methyl-N-acetylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(406) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(407) 3-Z-[1-(4-(2-diethylaminomethylsulphonyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(408) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)carbonyl)-N-methylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(409) 3-Z-[1-(4-(2-methylaminomethyl)N-methylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(410) 3-Z-[1-(4-(2-dimethylaminoethoxy)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(411) 3-Z-[1-(4-(methylethylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(412) 3-Z-[1-(4-(methylpropaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(413) 3-Z-[1-(4-(methylbenzylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(414) 3-Z-[1-(4-(diethylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(415) 3-Z-[1-(4-(pyrrolidin-1-yl)carbonyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone
(416) 3-Z-[1-(4-(azetidin-1-ylmethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(417) 3-Z-[1-(4-(piperazin-1-ylmethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(418) 3-Z-[1-(4-(morpholin-4-ylmethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(419) 3-Z-[1-(4-(thiomorpholin-4-ylmethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone

(420) 3-Z-[1-(4-(N-(dimethylaminomethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(421) 3-Z-[1-(4-(N-(dimethylaminomethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(422) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-acetylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(423) 3-Z-[1-(4-(N-(2-methylaminoethyl)-N-acetylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(424) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(425) 3-Z-[1-(4-(N-(3-methylaminopropyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(426) 3-Z-[1-(4-(3-dimethylaminopropyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(427) 3-Z-[1-(4-ethylaminomethylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(428) 3-Z-[1-(4-methylaminomethylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(429) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(430) 3-Z-[1-(4-aminomethylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(431) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-methylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(432) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(433) 3-Z-[1-(4-aminomethylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(434) 3-Z-[1-(3-(dimethylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(435) 3-Z-[1-(3-(methylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(436) 3-Z-[1-(3-(2-dimethylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(437) 3-Z-[1-(3-(3-dimethylaminopropyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(438) 3-Z-[1-(4-(2-dimethylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(439) 3-Z-[1-(4-(N-(dimethylaminocarbonyl)methyl)-N-methylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone
(440) 3-Z-[1-(4-(N-methyl-N-methylsulphonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(441) 3-Z-[1-(4-(N-methyl-N-acetylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(442) 3-Z-[1-(4-(1-methylimidazol-2-yl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(443) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(444) 3-Z-[1-(4-(2-diethylaminoethylsulphonyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(445) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(446) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(447) 3-Z-[1-(4-(2-dimethylaminoethoxy)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(448) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(449) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(450) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(451) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(452) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(453) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(454) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(455) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(456) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(457) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(458) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(459) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(460) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(461) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(462) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(463) 3-Z-[1-(4-(N-(2-dimethylaminoethyl))-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone
(464) 3-Z-[1-(4-(N-(dimethylaminomethyl)carbonyl)-N-methylamino)anilino]-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(465) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-acetylamino)anilino]-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(466) 3-Z-[1-(4-(N-(2-methylaminomethyl)-N-acetylamino)anilino]-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(467) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetylamino)anilino]-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(468) 3-Z-[1-(4-(N-(3-methylanilino)-N-acetylamino)anilino]-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(469) 3-Z-[1-(4-(3-dimethylaminopropyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(470) 3-Z-[1-(4-ethylaminomethyl)anilino]-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(471) 3-Z-[1-(4-methylaminomethyl)anilino]-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(472) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylcarbonyl)N-methylamino)anilino]-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(473) 3-Z-[1-(4-(4-methylpiperazin-1-ylcarbonyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(474) 3-Z-[1-(4-(N-(3-dimethylaminomethyl)acetamino)N-methylsulphonylamino)anilino]-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(475) 3-Z-[1-(4-(N-(3-methylaminomethyl)acetylamino)N-methylsulphonylamino)anilino]-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(476) 3-Z-[1-(4-aminomethyl)anilino]-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(477) 3-Z-[1-(3-(dimethylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(478) 3-Z-[1-(3-(methylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(479) 3-Z-[1-(3-(2-dimethylaminoethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(480) 3-Z-[1-(3-(3-dimethylaminopropyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(481) 3-Z-[1-(4-(2-dimethylaminoethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(482) 3-Z-[1-(4-(N-(dimethylaminocarbonylmethyl)-N-methylsulphonylamino)anilino]-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(483) 3-Z-[1-(4-(N-methyl-N-methylsulphonylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(484) 3-Z-[1-(4-(N-methyl-N-acetamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(485) 3-Z-[1-(4-(1-methylimidazol-2-yl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(486) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylaminomethyl)carbonyl)-N-methylamino)anilino]-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone
(487) 3-Z-[1-(4-(2-diethylaminoethylsulphonyl)aniline)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(488) 3-Z-[1-(4-(N-(2-dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(489) 3-Z-[1-(4-(N-(2-dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(490) 3-Z-[1-(4-(2-dimethylaminoethoxy)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(491) 3-Z-[1-(4-(N-(4-dimethylaminobutylcarbonyl)-N-methylamino)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(492) 3-Z-[1-(4-(N-(3-dimethylaminopropylcarbonyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(493) 3-Z-[1-(4-(methylpropilaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(494) 3-Z-[1-(4-(N-(methylbenzylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(495) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(496) 3-Z-[1-(4-(diethylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(497) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(498) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methylaminomethyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(499) 3-Z-[1-(4-(N-(3-dimethylaminopropylcarbonyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(500) 3-Z-[1-(4-(N-(4-methylpiperazin-1-yl)methyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(501) 3-Z-[1-(4-(N-(4-methylpiperazin-1-yl)methyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(502) 3-Z-[1-(4-(N-(4-methylpiperazin-1-yl)methyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(503) 3-Z-[1-(4-(N-(4-methylpiperazin-1-yl)methyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(504) 3-Z-[1-(4-(N-(4-methylpiperazin-1-yl)methyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(505) 3-Z-[1-(4-(N-(4-methylpiperazin-1-yl)methyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(506) 3-Z-[1-(4-(N-(4-methylpiperazin-1-yl)methyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(507) 3-Z-[1-(4-(N-(4-methylpiperazin-1-yl)methyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(508) 3-Z-[1-(4-(N-(4-methylpiperazin-1-yl)methyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(509) 3-Z-[1-(4-(N-(4-methylpiperazin-1-yl)methyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(510) 3-Z-[1-(4-(N-(4-methylpiperazin-1-yl)methyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone

(511) 3-Z-[1-(4-(N-(4-methylpiperazin-1-yl)methyl)anilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone
(512) 3-Z-[1-(4-dimethylaminomethylamino)-1-(3-carboxymethylaminophenyl)-methylene]-6-chloro-2-indolinone

(513) 3-Z-[1-(4-dimethylaminomethylamino)-1-(4-(N-methyl-carboxymethylamino)phenyl)methylene]-6-chloro-2-indolinone

(514) 3-Z-[1-(4-dimethylaminomethylamino)-1-(3-(N-methyl-carboxymethylamino)phenyl)methylene]-6-chloro-2-indolinone

(515) 3-Z-[1-(4-dimethylaminomethylamino)-1-(4-carboxymethoxyphenyl)-methylene]-6-bromo-2-indolinone

(516) 3-Z-[1-(4-dimethylaminomethylamino)-1-(3 carboxymethoxyphenyl)-methylene]-6-bromo-2-indolinone

(517) 3-Z-[1-(4-dimethylaminomethylamino)-1-(4-carboxymethylaminophenyl)-methylene]-6-bromo-2-indolinone

(518) 3-Z-[1-(4-dimethylaminomethylamino)-1-(3-carboxymethylaminophenyl)-methylene]-6-bromo-2-indolinone

(519) 3-Z-[1-(4-dimethylaminomethylamino)-1-(4-(N-methyl-carboxymethylamino)phenyl)methylene]-6-bromo-2-indolinone

(520) 3-Z-[1-(4-dimethylaminomethylamino)-1-(3-(N-methyl-carboxymethylamino)phenyl)methylene]-6-bromo-2-indolinone,

as well as their tautomers, their stereoisomers or the physiologically acceptable salts thereof.

[0023] The compounds of general formula I, their tautomers, their stereoisomers or the physiologically acceptable salts thereof are thus suitable for the prevention or treatment of a specific fibrotic disease selected from the group consisting of:

[0024] Fibrosis and remodeling of lung tissue in chronic obstructive pulmonary disease (COPD), chronic bronchitis, and emphysema;

[0025] Lung fibrosis and pulmonary diseases with a fibrotic component including but not limited to idiopathic pulmonary fibrosis (IPF), giant cell interstitial pneumonia (GIP), sarcoidosis, cystic fibrosis, respiratory distress syndrome (ARDS), granulomatosis, silicosis, drug-induced lung fibrosis (for example, induced by drugs such as bleomycin, bis-chloronitrosourea, cyclophosphamide, amiodarone, procainamide, penicillamine, gold or nitrofurantoin), silicosis, asbestosis, systemic sclerosis;

[0026] Fibrosis and remodeling in asthma;

[0027] In a preferred embodiment in accordance with the present invention, the compounds of general formula I, their tautomers, their stereoisomers or the physiologically acceptable salts thereof are especially suitable for the prevention or treatment of idiopathic pulmonary fibrosis.

BIOLOGICAL ACTIVITY

[0028] The following experimental results illustrate the present invention without representing a limitation of its scope.

Abreviations

[0029]

DEPC (diethylpyrocarbonate)
dNTP (deoxyribonucleotide triphosphates)
CT (Cycle at which amplification reaches a set Threshold)
DNA (deoxyribonucleic acid)
cDNA (complementary DNA)
RNA (ribonucleic acid)
mRNA (messenger RNA)
PCR (polymerase chain reaction)

Example B1:

[0030] In the following experiments of Example B1, Example A denotes the compound 3-Z-[1-(4-dimethylaminometh-
ylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone, which is compound (134) of the list of compounds and compound (b) of the list of preferred compounds.

(A) Effect of a representative compound on lung morphology following bleomycin-induced pulmonary fibrosis.

Materials and Methods

[0031] Bleomycin sulfate (Bleomycin HEXAL™) was purchased from a local pharmacy.

[0032] Bleomycin administration and treatment protocols All experiments were performed in accordance with German guidelines for animal welfare, performed by persons certified to work with animals and approved by the responsible authorities. Male Wistar rats were intratracheally injected with Bleomycin sulfate (10U/kg body weight in 300μl saline) or saline alone (saline control) using a catheter (0.5mm internal diameter, 1.0mm external diameter) through the nasal passage, following exposure to the anaesthetic Isofluorane for 5 minutes. The following day, the rats were orally treated with Example A (compound (134)) or saline suspended in 1ml 0.1% Natrosol. Control rats were administered 1ml 0.1% Natrosol (vehicle control).

[0033] A total of 30 rats were investigated and were grouped and treated as shown in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Intratracheal instillation</th>
<th>No. of animals</th>
<th>Compound</th>
<th>Treatment Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin 10U /kg</td>
<td>10</td>
<td>Example A (Compound (134))</td>
<td>Days 1-21</td>
</tr>
<tr>
<td>Bleomycin 10U /kg</td>
<td>10</td>
<td>Vehicle only</td>
<td>Days 1-21</td>
</tr>
<tr>
<td>Saline (300μl)</td>
<td>10</td>
<td>Vehicle only</td>
<td>Days 1-21</td>
</tr>
</tbody>
</table>

[0034] 21 days following bleomycin instillation, the rats were killed with a lethal intraperitoneal injection of Narcoren™ (Pentobarbital Sodium, Rhone Merieux). The lungs were then removed, blotted dry and half was snap frozen in liquid nitrogen and stored at -80°C. The other half was fixed in 4% formalin for subsequent paraffin embedding and histology.

Histology

[0035] The lung tissues fixed in 4% formalin were embedded into paraffin and 5μm sections were cut using a microtome (Leica SM200R) and placed on poly-L-lysine coated slides. The sections were then dried onto the slides (60°C 2 hours) and then left to cool at room temperature. Collagen deposition was assessed using Masson's Trichrome staining.

Results

[0036] Figure 1A shows the result obtained with the control group, which received saline and the vehicle instead of bleomycin intratracheally.

[0037] Rats treated intratracheally with bleomycin and the vehicle developed severe lung fibrosis, as seen in Figure 1B. The alveoli have been largely replaced by fibroblasts and extracellular matrix and the normal lung structure is nearly obliterated.

[0038] Daily treatment of bleomycin-treated rats with 50 mg/kg of Example A (compound (134)) showed a consistent, nearly complete reversal of lung fibrosis in this model. A typical example is shown in Figure 1C. Alveoli are intact and little or no fibroblast infiltration or extracellular matrix deposition has occurred. Normal lung structure has been maintained, which is evidenced by a comparison of Figure 1C with Figure 1A.

(B) Effect of a representative compound on expression of fibrotic marker genes following bleomycin-induced pulmonary fibrosis.

mRNA extractions and synthesis of cDNA

[0039] One part of the frozen lung tissue dedicated to investigation of gene expression was cut into small pieces using a sterile scalpel blade. Approximately 100mg of tissue was then placed into a 2ml Eppendorf tube and 1.5ml of Trizol (Invitrogen) was added. A sterile tungsten carbide bead (Qiagen) was then added to the tube and the tube was placed in a Retsch MM300 Tissue disruptor (Qiagen) at a frequency of 30.0Hz for 8 minutes. After this time, the bead was
removed and the sample centrifuged at 12000 rpm for 10 minutes to remove tissue debris. The RNA was extracted using a modified version of the manufacturer's protocol supplied with Trizol. Briefly, 0.3ml chloroform was added to the tube and the tube shaken vigorously and then left to incubate at room temperature for 5 minutes, after which the tube was centrifuged for 15 minutes at 12000 rpm at 4°C. The upper colorless aqueous phase was then collected and added to 750μl isopropanol. This was then shaken vigorously and stored at -80°C overnight. The samples were then incubated at room temperature for 15 minutes, after which they were centrifuged for 40 minutes at 12000 rpm at 4°C. The supernatant was then removed and 500μl of 70% ethanol was added to wash the pellet then the sample was centrifuged for 10 minutes at 12000 rpm an 4°C, this wash step was repeated twice, after which the pellet was left to dry for 10 - 15 minutes. Finally the pellet was resuspended in 20μl RNase free water and stored at -80°C. The concentration of each sample was then measured using a spectrophotometer.

[0040] Using the Superscript™ III (Invitrogen, Paisley, UK) RT-first strand synthesis kit, 2μg of each mRNA sample was reversed transcribed using a modified version of the manufacturer's protocol. Briefly, a mixture of 2μg RNA, 1μl random hexamer primers (50ng/μl), 1μl dNTP mix (10mM) was made up to 10μl with DEPC-treated water and incubated at 65°C for 5 minutes, after which it was placed on ice for 5 minutes. Following this, to each reaction, 2μl RT buffer (10X), 4μl MgCl₂ (25mM), 2μl DTT (0.1M), 1μl RNaseOUT™ (40U/μl) and 1μl SuperScript™ III enzyme (200U/μl) was added and the mixture placed in a thermal cycler (Applied Biosystems) under the following conditions: 25°C for 10 minutes, 50°C for 50 minutes and 85°C for 5 minutes, after which 1μl of RNase H was added and incubated at 37°C for 20 minutes. The synthesized cDNA was diluted to 5ng/μl using the assumption that the RT reaction fully transcribed all of the mRNA to cDNA and was a concentration of 100ng/μl.

Investigation of gene expression using real time PCR

[0041] Gene expression was investigated in each of the samples using the Applied Biosystems 7700 sequence detection system. Primers for the 18S endogenous control were purchased as pre-developed assay reagent kits, whereas primers and probes (see Table 2 below) for pro-collagen I and fibronectin were designed using PrimerExpress™ (Applied Biosystems), ensuring that at least one of the primers or probes in each set overlapped an intron / exon junction, thus eliminating the possibility of amplifying any contaminating genomic DNA in the cDNA sample. The purchased PDARs also amplified only cDNA.

<table>
<thead>
<tr>
<th>Target</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibronectin</td>
<td><strong>5'-GAT GCC GAT CAG AAG TTT GGA-3'</strong></td>
</tr>
<tr>
<td></td>
<td><strong>5'-TCG TTG GTC GTG CAG ATC TC-3'</strong></td>
</tr>
<tr>
<td></td>
<td><strong>5'-FAM-CTG CCC AAT GGC TGC CCA TGA-TAMRA-3'</strong></td>
</tr>
<tr>
<td>Pro-Collagen I</td>
<td><strong>5'-CAG ACT GGC AAC CTG AAG AAG TCC 3'</strong></td>
</tr>
<tr>
<td></td>
<td><strong>5'-TCG CCC CTG AGC TCG AT-3'</strong></td>
</tr>
<tr>
<td></td>
<td><strong>5'-FAM-CTG CTC CTC CAG GGC TCC AAC GA-TAMRA3'</strong></td>
</tr>
</tbody>
</table>

[0042] Real Time PCR was carried out in 25μl reactions, using 25ng (5μl) of cDNA per reaction. A quantitative PCR core kit was purchased (Eurogentec) and a master-mix was made up as follows for 100 reactions: 500μl 10X reaction buffer, 500μl MgCl₂ (50mM) , 200μl dNTP mix solution (5mM) , 25μl Hot Goldstar enzyme, 75μl 18S PDAR, 22.5μl forward primer, 22.5μl reverse primer, 15μl probe and 640μl DEPC treated water. 20μl of this master-mix was then added to 25ng (5μl) target cDNA. Each analysis was carried out in triplicate.

[0043] In order to quantify the gene expression, a standard curve was constructed for each primer set and was included on each plate. The standards were made up of a mix of all the cDNA's under investigation; this mix of cDNA's was
serially diluted 10, 20, 50, 100, 100 times. A standard curve was constructed of the obtained Ct (Cycle at which amplification reaches a set Threshold) against the LOG of the dilution factor. Curves were drawn for the target gene and the 18S rRNA endogenous control. The Ct value for both targets for each of the samples was then converted to a fold dilution using the standard curve and the target gene value was normalized to the 18S gene value.

Statistics

[0044] All statistical analyses were carried out using GraphPad Prism V 4.02 software. Comparisons were made using a non-parametric T-test (Mann-Whitney U test) and a significant value was considered to be p = 0.05.

Results

[0045] The results are shown in Figures 2 (procollagen I) and 3 (fibronectin). Each data point represents RNA isolated from the lung of a single rat.

[0046] Intratracheal administration of bleomycin and subsequent treatment with vehicle only showed large increases in procollagen I and fibronectin gene expression in the lung, as seen in Figures 2 and 3, consistent with the histologically apparent lung fibrosis seen in Figure 1B.

[0047] Daily treatment of Bleomycin-treated rats with 50 mg/kg of Example A (compound (134)) showed a significant (p ≤ 0.0001) inhibition of expression of fibrotic marker genes in this model, as seen in Figures 2 and 3.

[0048] This experiment thus demonstrates that expression of fibrotic markers, and therefore deposition of extracellular matrix, may be dramatically reduced by treatment with Example A (compound (134)).

[0049] Thus, expression of fibrotic markers, and therefore deposition of extracellular matrix, may be dramatically reduced by treatment with the compounds in accordance with the present invention.

[0050] By reason of their biological properties the compounds according to the invention may be used in monotherapy or in conjunction with other pharmacologically active compounds. Such pharmacologically active compounds may be compounds which are, for example, also pharmacologically active in the treatment of fibrosis. Such pharmacologically active compounds may also be substances with a secretolytic, bronchodilatory and/or anti-inflammatory activity.

[0051] In a preferred embodiment in accordance with the present invention, such pharmacologically active compounds are preferably selected from the group consisting of anticholinergic agents, beta-2 mimetics, steroids, PDE-IV inhibitors, p38 MAP kinase inhibitors, NKT antagonists, LTD4 antagonists, EGFR inhibitors and endothelin-antagonists.

[0052] Anticholinergic agents may preferably be selected from the group consisting of the tiotropium salts, oxtipropium salts, flutiproprium salts, ipratropium salts, glycopyrronium salts and trospium salts.

[0053] Beta-2 mimetics may preferably be selected from the beta-2 mimetics disclosed, for example, in US 4,460,581, which is incorporated herein by reference.

[0054] PDE-IV inhibitors may preferably be selected from the group consisting of enprofyllin, theophyllin, rolflumilast, arifilo (cilomilast), CP-325,366, BY343, D-4396 (Sch-351591), AWD-12-281 (GW-842470), N-(3,5-dichloro-1-oxo-pyrindin-4-yl)-4-difluoromethoxy-3-cyclopropylimethoxybenzamide, NCS-613, pumafentine, (+)-[4R*,10S*]-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[5,6]naphthyridin-6-yl]-N,N-disopropylbenzamide, (R)-(+)-1-(4-bromobenzyl)-4-(3-cyclopropylcyclohexa-1-carboxylic acid, 2-carboxymethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, cis[4-cyano-4-(3-cyclopropylcyclohexa-1-carboxylic acids, 2-carboxymethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol], (R)-(+-) ethyl [4-(3-cyclopropylcyclohexa-1-carboxylic acid]pyrrolidin-2-ylidene)[acetate, (S)-(+-)ethyl[4-(3-cyclopropylcyclohexa-1-carboxylic acid]pyrrolidin-2-ylidene][acetate, CD840, Bay-198004, D-4418, PD-168787, T-2585, arofyllin, atizoram, V-11294A, C1-1018, CDC-801, CDC-3052, D-22888, YM-58997, Z-15370, 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9H-pyrazolo[3,9-c][1,2,4-triazolo[4,3-a]pyridine, 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(tert-butyl)-9H-pyrazolo[3,4-c][1,2,4-triazolo[4,3-a]pyridine. These compounds may be used, as available, in the form of their racemates, enantiomers or diastereoisomers, or in the form of pharmacologically acceptable acid addition salts thereof, or in the form of their solvates or hydrates.

[0055] Steroids may preferably be selected from the group consisting of prednisolone, prednisone, butoxycorticopronate, RPR-106541, flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, roflumilast, ST-126, dexamethasone, 6c,9α-difluoro-17α-[2-furanyl(carbonyl oxy)-11β-hydroxy-16c-methyl-3-oxo-androst-1-4-dien-17β-carbothionic acid (S)-fluoromethylester, and 6c,9α-difluoro-11β-hydroxy-16c-methyl-3-oxo-17α-propionoloxo-androsta-1,4-diene-17β-carbothionic acid (S)-[2-oxo-tetrahydro-furan-3S-y]ester. These compounds may be used, as available, in the form of their racemates, enantiomers or diastereoisomers, or in the form of pharmacologically acceptable acid addition salts thereof, or in the form of their solvates or hydrates.

wherein

\[ \text{R}_1 \text{ is 4-pyridyl, pyrimidinyl, 4-pyridazinyl, 1,2,4-triazin-5-yl, quinolyl, isoquinolinyl, or quinazolin-4-yl ring, which ring is substituted with Y-R}_4 \text{ and optionally with an additional independent substituent selected from C}_1\text{-C}_4 \text{ alkyl, halogen, hydroxyl, C}_1\text{-C}_4 \text{ alkoxy, C}_1\text{-C}_4 \text{ alkylthio, C}_1\text{-C}_4 \text{ alkylsulfinyl, CH}_2\text{OR}} \text{, amino, mono and di-C}_1\text{-C}_6 \text{ alkyl substituted amino, an N-heterocyclic ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR}_4\text{.}} \]

\[ \text{Y is oxygen or sulfur;} \]

\[ \text{R}_4 \text{ is phenyl, naphth-1-yl or naphthyl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4naphth-1-yl or 6naphth-2-yl substituent, is halogen, cyano, nitro, C(Z)NR}_7\text{R}_1\text{, C(Z)OR}_6\text{, COR}_7\text{, SR}_5\text{, OR}_5\text{, OR}_1\text{, halo-substituted-C}_1\text{-C}_4 \text{ alkyl, C}_1\text{-C}_4 \text{ alkoxy, C}_1\text{-C}_4 \text{ aminosulfinyl, CH}_2\text{OR}_2\text{, amino, mono and di-C}_1\text{-C}_6 \text{ alkyl substituted amino, an N-heterocylic ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR}_4\text{.}} \]

\[ \text{Z is oxygen or sulfur;} \]

\[ \text{n is an integer having a value of 1 to 10;} \]

\[ \text{m is 0, or integer 1 or 2;} \]

\[ \text{m'* is 0, or an integer having a value of 1 or 2;} \]

\[ \text{v is 0, or an integer having a value of 1 to 2;} \]

\[ \text{R}_2 \text{ is -C-H (A) (R}_2\text{);} \]

\[ \text{A is optionally substituted aryl, heterocyclyl, or heteroaryl ring, or A is substituted C}_1\text{-C}_10 \text{ alkyl;} \]

\[ \text{R}_2\text{ is an optionally substituted C}_1\text{-C}_10 \text{ alkyl;} \]

\[ \text{R}_4 \text{ is aryl, arylC}_1\text{-C}_4 \text{ alkyl, heterocyclic, heterocyclylC}_1\text{-C}_4 \text{ alkyl, heteroaryl, heteroarylC}_1\text{-C}_4 \text{alkyl, wherein each of these moieties may be optionally substituted;} \]
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R₁ is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, aryl C₁₋₄ alkyl, heteroaryl, heteroaryl C₁₋₄ alkyl, heterocyclyl, or heterocyclyl C₁₋₄ alkyl, wherein each of these moieties may be optionally substituted;

R₂ is heterocyclyl, heterocyclyl C₁₋₁₀ alkyl or R₃;

R₃ is hydrogen, C₁₋₄ alkyl, C₂₋₉ alkenyl, C₂₋₉ alkynyl or NR₇R₁₇, excluding the moieties SR₅ being SNR₇R₁₇ and SOR₅ being SOH;

R₄ is hydrogen, a pharmaceutically acceptable cation, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, aryl, aryl C₁₋₄ alkyl, heteroaryl C₁₋₄ alkyl, heterocyclyl, aryl, or C₁₋₁₀ alkanoyl; R₇ and R₁₇ is each independently selected from hydrogen or C₁₋₄ alkyl or R₇ and R₁₇ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅;

R₅ is C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, aryl C₁₋₁₀ alkyl, heteroaryl, heteroaryl C₁₋₁₀ alkyl, (CR₁₀R₂₀)ₙOR₁₁, (CR₁₀R₂₀)ₙS(O)ₘR₁₈, (CR₁₀R₂₀)ₙNHS(O)₂R₁₈, (CR₁₀R₂₀)ₙNR₁₃R₁₄; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

R₆ is hydrogen, C(Z) R₁₁ or optionally substituted C₁₋₁₀ alkyl, S(O)₂R₁₈, optionally substituted aryl or optionally substituted aryl C₁₋₄ alkyl;

R₁₀ and R₅₀ is each independently selected from hydrogen or C₁₋₄ alkyl;

R₁₁ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀ alkyl, aryl, aryl C₁₋₁₀ alkyl, heteroaryl or heteroaryl C₁₋₁₀ alkyl, wherein these moieties may be optionally substituted;

R₁₂ is hydrogen or R₁₆;

R₁₃ and R₁₄ is each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉;

R₁₅ is R₁₀ or C(Z)-C₁₋₄ alkyl;

R₁₆ is C₁₋₄ alkyl, halo-substituted C₁₋₄ alkyl, or C₃₋₇ cycloalkyl;

R₁₈ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, aryl, aryl C₁₋₁₀ alkyl, heterocyclyl, heterocyclyl- C₁₋₁₀alkyl, heteroaryl or heteroaryl C₁₋₁₀ alkyl;

or a pharmaceutically acceptable salt thereof.

[0057] NK₁ antagonists may preferably be selected from the group consisting of N-[2-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-2-{4-cyclopropylmethyl-piperazin-1-yl}-N-methyl-2-phenyl-acetamide (BIIF 1149), CP-122721, FK-888, NKP 608C, NKP 608A, CGP 60829, GR 48968 (Saredutant), SR 140333 (Nolpitantium besilate/chloride), LY 303 870 (Lane-pipitan), MEN-11420 (Nepadutant), SB 223412, MDL-105172A, MDL-103896, MEN-1149, MEN-11467, DNK 333A, SR-144190, YM-49244, YM-44778, ZM-274773, MEN-10930, S-19752, Neuronorm, YM-35375, DA-5018, Aprepitant (MK-869), L-754030, CJ-11974, L-758298, DNK-33A, 6b-l, CJ-11974, TAK-637, GR 205171 and the arylglycine amide derivates of general formula (VIII)

![Chemical Structure](VIII)

wherein

R¹ and R² together with the N-atom they are bound to form a ring of formula
or wherein \( r \) and \( s \) independently denote the number 2 or 3;
\( R^6 \) denotes \( \text{H, -C}_1\text{-C}_5\text{-alkyl, C}_3\text{-C}_5\text{-alkenyl, propinyl, hydroxy (C}_2\text{-C}_4\text{)alkyl, methoxy (C}_2\text{-C}_9\text{)alkyl, di (C}_1\text{-C}_3\text{) alkylamino (C}_2\text{-C}_4\text{) alkyl, amino (C}_2\text{-C}_4\text{) alkyl, amino, di (C}_1\text{-C}_3\text{)alkylamino, monofluoro- up to perfluoro(C}_1\text{-C}_2\text{)alkyl, N-methylpipera-}
\( \text{ridinyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl,}
\)
\( R^7 \) denotes any of the groups defined under (a) to (d):

(a) hydroxy
(b) 4-piperidinopiperidyl,
(c) 

wherein \( R^{16} \) and \( R^{17} \) independently denote \( \text{H, (C}_1\text{-C}_2\text{)alkyl, (C}_2\text{-C}_4\text{)cycloalkyl, hydroxy(C}_2\text{-C}_4\text{)alkyl, dihydroxy(C}_2\text{-C}_4\text{)alkyl, (C}_1\text{-C}_3\text{)alkoxycarrying alkoxy(C}_2\text{-C}_4\text{)alkyl, phenyl(C}_1\text{-C}_3\text{)alkyl or di(C}_1\text{-C}_3\text{)alkylamino(C}_2\text{-C}_4\text{)alkyl, and}
\( R^8 \) denotes \( \text{H,}
\)
optionally in the form of enantiomers, mixtures of enantiomers or the racemates.

[0058] The compounds of formula (VIII) mentioned hereinbefore are described in WO 96/32386, WO 97/32865 and WO 02/32865. The disclosure of these international patent applications is incorporated herein by reference in its entirety.

[0059] LTD4 antagonists may preferably be selected from the group consisting of montelukast, 1-(((R)-(3-(2-(6,7-difluoro-2-quinolinyl)ethenyl)phenyl)-3-(2-hydroxy-2-propyl)phenyl)thio)methylcyclopropane-acetate, 1-(((1(R)-3(2-(2,3-dichlorothieno[3,2-b]pyridin-5-yl)-E-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropane-acetate, pranlukast, zafirlukast, [2-[[2-(4-tert-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl]phenyl]aceta- etate, MCC-847 (ZD-3523), MN-001, MEN-91507 (LM-1507), VUF-5078, VUF-K-8707 and L-733321. These compounds may be used, as available, in the form of their racemates, enantiomers or diastereoisomers, or in the form of pharmaco- logically acceptable acid addition salts thereof, or in the form of their solvates and/or hydrates.

[0060] EGFR inhibitors may preferably be selected from the group consisting of 4-[[3-chlor-4-fluorphenyl]amino]-6-[(4-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropoxy-chinazoline, 4-[[3-chlor-4-fluorphenyl]amino]-6-[(4-N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-chinazoline, 4-[[3-chlor-4-fluorphenyl]amino]-6-[(4-N,N-diethylamino)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-chinazoline, 4-[[3-chlor-4-fluorphenyl]amino]-6-[[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-chinazoline, 4-[[3-chlor-4-fluorphenyl]amino]-6-[[4-((R)-(4-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-chinazoline, 4-[[3-chlor-4-fluorphenyl]amino]-6-[[4-((R)-(6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-chinazoline, 4-[[3-chlor-4-fluorphenyl]amino]-6-[[4-((R)-(6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-chinazoline, 4-[[3-chlor-4-fluorphenyl]amino]-6-[[4-((S)-(tetrahydrofur-an-3-yl)oxy)-chinazoline, 4-[[3-chlor-4-fluorphenyl]amino]-6-[[4-((R)-(2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-chinazoline, 4-[[3-chlor-4-fluorphenyl]amino]-6-[[4-(S)-(6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-chinazoline, 4-[[3-chlor-4-fluorphenyl]amino]-6-[[4-[[3-N-(2-methoxy-ethyl)-N-methylamino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-chinazoline, 4-[[3-chlor-4-fluorphenyl]amino]-6-[[4-((N,N-dimethylami- no)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-chinazoline, 4-[[4-(R)-(1-phenyl-ethyl) amino]-6-[[4-((N,N-bis-(2-methoxy-
The following examples of formulations illustrate the present invention without representing a limitation of its scope.

Example F1: Coated tablet containing 75 mg of active substance

Composition

1 tablet core contains:

[0067]
Preparation (direct compression)

[0068] The active substance is mixed with all components, sieved and compressed in a tablet-making machine to form tablets of the desired shape.

- Weight of core: 230 mg
- Appearance of core: 9 mm, biconvex

[0069] The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose.

Example F2: Tablet containing 100 mg of active substance

Composition

1 tablet contains:

- active substance 75.0 mg
- calcium phosphate 131.0 mg
- polyvinylpyrrolidone 10.0 mg
- carboxymethylcellulose sodium 10.0 mg
- silicon dioxide 2.5 mg
- magnesium stearate 1.5 mg
- total weight: 230.0 mg

Preparation (wet granulation)

[0070] The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the hydroxypropylmethylcellulose. 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
- Appearance of tablet: 10 mm, flat faced

with bevelled edges and breaking notch on one side.
Example F3: Tablet containing 150 mg of active substance

Composition

1 tablet contains:

[0072]

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>active substance</td>
<td>150.0 mg</td>
</tr>
<tr>
<td>lactose</td>
<td>85.0 mg</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>40.0 mg</td>
</tr>
<tr>
<td>polyvinylpyrrolidone</td>
<td>10.0 mg</td>
</tr>
<tr>
<td>silicon dioxide</td>
<td>10.0 mg</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>5.0 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>300.0 mg</strong></td>
</tr>
</tbody>
</table>

Preparation (dry granulation)

[0073] The active substance mixed with lactose, polyvinylpyrrolidone, and parts of the microcrystalline cellulose, magnesium stearate is compacted e.g. on a roller compactor. The ribbons are broken up in fine granules through a screen with a mesh size of 0.8 mm. After subsequent sieving through a screen with a mesh size of 0.5 mm and blending with the remaining components, tablets are pressed from the mixture.

Example F4: Hard gelatine capsule containing 150 mg of active substance

Composition

1 capsule contains:

[0074]

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>active substance</td>
<td>150.0 mg</td>
</tr>
<tr>
<td>lactose</td>
<td>85.0 mg</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>40.0 mg</td>
</tr>
<tr>
<td>polyvinylpyrrolidone</td>
<td>10.0 mg</td>
</tr>
<tr>
<td>silicon dioxide</td>
<td>10.0 mg</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>5.0 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>300.0 mg</strong></td>
</tr>
</tbody>
</table>

Preparation

[0075] The active substance mixed with lactose, polyvinylpyrrolidone, and parts of the microcrystalline cellulose, magnesium stearate is compacted e.g. on a roller compactor. The ribbons are broken up in fine granules through a screen with a mesh size of 0.8 mm. After subsequent sieving through a screen with a mesh size of 0.5 mm and blending with the remaining components, the finished mixture is packed into size 1 hard gelatine capsules.

Capsule-filling: approx. 300 mg
Capsule shell: size 1 hard gelatine capsule.
Example F5: Suppository containing 150 mg of active substance

1 suppository contains:

- **active substance**: 150.0 mg
- **polyethylene glycol 1500**: 800.0 mg
- **polyethylene glycol 6000**: 850.0 mg
- **polyoxyl 40 hydrogenated castor oil**: 200.0 mg

Total: 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 F6: Suspension containing 50 mg of active substance 100 ml of suspension contains

- **active substance**: 1.00 g
- **carboxymethylcellulose sodium**: 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**: 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.

Thus, 5 ml of suspension contains 50 mg of active substance.

Example F7: Ampoule containing 10 mg active substance

Composition

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

Preparation

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with sodium chloride, filtered sterile and transferred into a 2 ml ampoule.
Example F8: Ampoule containing 50 mg of active substance

Composition

[0083]

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

Preparation

[0084] The active substance is dissolved in the necessary amount of 0.01 N HC1, made isotonic with sodium chloride, filtered sterile and transferred into a 10 ml ampoule.

[0085] Example F9: Capsule for powder inhalation containing 5 mg of active substance

1 capsule contains

[0086]

active substance 5.0 mg
lactose for inhalation 15.0 mg
20.0 mg

Preparation

[0087] The active substance is mixed with lactose for inhalation. The mixture is packed into capsules in a capsule-making machine (weight of the empty capsule approx. 50 mg).

weight of capsule: 70.0 mg
size of capsule = size 3

Example F10: Solution for inhalation for a hand-held nebuliser containing 2.5 mg active substance

1 spray contains

[0088]

active substance 2.500 mg
benzalkonium chloride 0.001 mg
1N hydrochloric acid q.s.
ethanol/water (50/50) ad 15.000 mg

Preparation

[0089] The active substance and benzalkonium chloride are dissolved in ethanol/water (50/50). The pH of the solution is adjusted with 1N hydrochloric acid. The resulting solution is filtered and transferred into suitable containers for use in hand-held nebulisers (cartridges).

Contents of the container: 4.5 g

Claims

1. Use of the indolinones of general formula
in which
X is an oxygen atom,
R¹ is a hydrogen atom,
R² is a fluorine, chlorine or bromine atom or a cyano group,
R³ is a phenyl group or a phenyl group which is monosubstituted by a fluorine, chlorine, bromine or iodine atom or by a C₁₋₃-alkoxy group, where the abovementioned unsubstituted and the monosubstituted phenyl groups may additionally be substituted in the 3- or 4-position by a fluorine, chlorine or bromine atom,
by a cyano group,
by a C₁₋₃-alkoxy or C₁₋₂-alkyl-carbonyl-amino group,
by a carboxy-C₂₋₃-alkenyl, aminocarbonyl-C₂₋₃-alkenyl, (C₁₋₃-alkylamino)-carbonyl-C₂₋₃-alkenyl, di-(C₁₋₃-alkyl)-aminocarbonyl-C₂₋₃-alkenyl or C₁₋₄-alkoxy-carbonyl-C₂₋₃-alkenyl group, where the substituents may be identical or different,
R⁴ is a phenyl group or a phenyl group which is monosubstituted by an amino, guanidino, mono- or di-(C₁₋₂-alkyl)-amino-N-[ω-di-(C₁₋₂-alkyl)-amino-C₂₋₃-alkyl]-N[(C₁₋₂-alkyl)-amino, N-methyl-(C₁₋₂-alkyl)-amino, N-(C₁₋₂-alkyl)-N-benzylamino, N-(C₁₋₂-alkoxy-carbonyl)-amino, N-(C₁₋₂-alkoxy-carbonyl-C₂₋₄-alkylamino, 4-(C₁₋₃-alkyl)-piperazin-1-yl, imidazol-1-yl, pyrrolidin-1-yl, azetidin-1-yl, morpholin-4-yl, piperazin-1-yl, thiomorpholin-4-yl group,
by a di-(C₁₋₃-alkyl)-amino-(C₁₋₃-alkyl)-sulphonyl, 2-[di-(C₁₋₃-alkyl)-amino]-ethoxy, 4-(C₁₋₃-alkyl)-piperazin-1-yl-carbonyl, (R)-[di-(C₁₋₃-alkyl)-amino]-(C₂₋₃-alkyl)-N-(C₁₋₃-alkyl)-aminocarbonyl, 1-(C₁₋₃-alkyl) imidazol-2-yl, (C₁₋₃-alkyl)-sulphonyl group, or
by a group of the formula

in which
R⁷ is a C₁₋₂-alkyl, C₁₋₂-alkyl-carbonyl, di-(C₁₋₂-alkyl)-aminocarbonyl-C₁₋₃-alkyl or C₁₋₃-alkylsulphonyl group and
R⁸ is C₁₋₃-alkyl, ω-di-(C₁₋₂-alkyl)-amino-C₂₋₃-alkyl, ω-[mono-(C₁₋₂-alkyl)-amino]-C₂₋₃-alkyl group, or
a (C₁₋₃-alkyl)-carbonyl, (C₄₋₆-alkyl)-carbonyl or carbonyl-(C₁₋₃-alkyl) group which is terminally substituted by a
di-(C<sub>1-2</sub>-alkyl)-amino, piperazin-1-yl or 4-(C<sub>1-3</sub>-alkyl)-piperazin-1-yl group,
where all dialkylamino groups present in the radical R<sup>4</sup> may also be present in quaternized form, for example as an
N-methyl-(N,N-dialkyl)-ammonium group, where the counterion is preferably selected from the group consisting of
iodide, chloride, bromide, methylsulphonate, para-toluenesulphonate and trifluoroacetate,
R<sup>5</sup> is a hydrogen atom and
R<sup>6</sup> is a hydrogen atom,
where the abovementioned alkyl groups include linear and branched alkyl groups in which additionally one to 3
hydrogen atoms may be replaced by fluorine atoms,
where additionally a carboxyl, amino or imino group present may be substituted by an in vivo cleavable radical or
may be present in the form of a prodrug radical, for example in the form of a group which can be converted in vivo
into a carboxyl group or in the form of a group which can be converted in vivo into an imino or amino group,
the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof,
for the preparation of a medicament for the prevention or treatment of a fibrotic disease selected from the group
consisting of fibrosis and remodeling of lung tissue in chronic obstructive pulmonary disease, fibrosis and remodeling
of lung tissue in chronic bronchitis, fibrosis and remodeling of lung tissue in emphysema, lung fibrosis and pulmonary
diseases with a fibrotic component, fibrosis and remodeling in asthma.

2. Use in accordance with claim 1 wherein the substituted indolinone of general formula I is selected from the group
consisting of:

(a) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-chloro-2-indolinone
(b) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone
(c) 3-Z-[1-(4-dimethylaminomethylanilino)-1-(3-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone
(d) 3-Z-[1-(4-(N-(4-methylpiperazin-1-ylmethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)
methylene]-6-fluoro-2-indolinone
(e) 3-Z-[1-(4-(N-(2-dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-
fluoro-2-indolinone
(f) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone
(g) 3-Z-[1-(4-(1-methylimidazol-2-yl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone
(h) 3-Z-[1-(4-(N-(dimethylaminomethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-
fluoro-2-indolinone
(i) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone
(j) 3-Z-[1-(4-(diethylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone
(k) 3-Z-[1-(4-(pyrrolidin-1-ylmethyl anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone
(l) 3-Z-[1-(4-(N-(diethylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone
(m) 3-Z-[1-(4-(dimethylaminomethylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone
(n) 3-Z-[1-(4-(diethylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-fluoro-2-indolinone
(o) 3-Z-[1-(4-(diethylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone
(p) 3-Z-[1-(4-(dimethylaminomethylanilino)-1-(4-(2-carboxyethyl)phenyl)methylene]-6-bromo-2-indolinone,
and
(q) 3-Z-[1-(4-(diethylaminomethyl)anilino)-1-(4-(2-carboxyethyl)methylene]-6-bromo-2-indolinone,
the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

3. Use in accordance with any one of claims 1 or 2 wherein the disease is selected from the group consisting of the
lung fibrosis and pulmonary diseases with a fibrotic component selected from idiopathic pulmonary fibrosis, giant
cell interstitial pneumonia, sarcodosis, cystic fibrosis, respiratory distress syndrome, drug-induced lung fibrosis,
granulomatosis, silicosis, asbestosis, systemic scleroderma.

4. Use in accordance with any one of claims 1 to 3 wherein the disease is idiopathic pulmonary fibrosis.

5. Use in accordance with any one of claims 1 to 4 wherein the treatment is a combined treatment with a further
pharmacologically active substance selected from the group consisting of anticholinergic agents, beta-2 mimetics,
steroids, PDE-IV inhibitors, p38 MAP kinase inhibitors, NK<sub>3</sub> antagonists, LTD4 antagonists, EGFR inhibitors and
endothelin-antagonists.
6. A pharmaceutical composition comprising a substituted indolinone of formula I as defined in any one of claims 1 or 2, optionally together with one or more pharmaceutically acceptable carriers or excipients, for the prevention or treatment of a fibrotic disease selected from the group consisting of fibrosis and remodeling of lung tissue in chronic obstructive pulmonary disease, fibrosis and remodeling of lung tissue in chronic bronchitis, fibrosis and remodeling of lung tissue in emphysema, lung fibrosis and pulmonary diseases with a fibrotic component, fibrosis and remodeling in asthma, radiation-induced fibrosis.

7. The pharmaceutical composition in accordance with claim 6, wherein the disease is selected from the group consisting of the lung fibrosis and pulmonary diseases with a fibrotic component selected from idiopathic pulmonary fibrosis, giant cell interstitial pneumonia, sarcodosis, cystic fibrosis, respiratory distress syndrome, drug-induced lung fibrosis, granulomatosis, silicosis, asbestosis, systemic scleroderma.

8. The pharmaceutical composition in accordance with claim 7 wherein the disease is idiopathic pulmonary fibrosis.

9. The pharmaceutical composition in accordance with any one of claims 6 to 8, wherein the treatment is a combined treatment with a further pharmacologically active substance selected from the group consisting of anticholinergic agents, beta-2 mimetics, steroids, PDE-IV inhibitors, p38 MAP kinase inhibitors, NK1 antagonists, LTD4 antagonists, EGFR inhibitors and endothelin-antagonists, said further pharmacologically active substance being administered either simultaneously or sequentially.

10. Pharmaceutical composition containing a substituted indolinone of formula I as defined in any one of claims 1 or 2 in combination with a further pharmacologically active substance selected from the group consisting of anticholinergic agents, beta-2 mimetics, PDE-IV inhibitors, p38 MAP kinase inhibitors, NK1 antagonists, LTD4 antagonists and endothelin-antagonists, optionally together with one or more pharmaceutically acceptable carriers or excipients.

**Patentansprüche**

1. Verwendung der Indolinone der allgemeinen Formel

![Formula Image]
EP 1 835 907 B1


\[
\begin{array}{c}
N \\
R^7 \\
R^8
\end{array}
\]

worin R⁷ eine C₁₋₂-Alkyl-, C₁₋₂-Alkylcarbonyl-, Di-(C₁₋₂-Alkyl)aminocarbonyl-C₁₋₃-alkyl- oder C₁₋₃-Alkylsulfonyl-Gruppe darstellt und R⁸ eine C₁₋₃-Alkyl-, ω-[Di-(C₁₋₂-Alkyl)amino]-C₂₋₃-alkyl-, ω-[Mono-(C₁₋₂-Alkyl)amino]-C₂₋₃-alkyl-Gruppe darstellt oder eine (C₁₋₃-Alkyl)carbonyl-, (C₄₋₆-Alkyl)carbonyl- oder Carbonyl-(C₁₋₃-alkyl)-Gruppe, die endständig substituiert ist mit einer Di-(C₂₋₂-alkyl)amino-, Piperazin-1-yl- oder 4-(C₁₋₃-Alkyl)piperazin-1-yl-Gruppe, worin sämtliche vorliegenden Dialkylaminogruppen im Rest R⁴ ebenfalls in quatemisierter Form vorliegen können, beispielsweise als eine N-Methyl-(N,N-dialkyl)ammoniumgruppe, wobei das Gegenion bevorzugt ausgewählt ist aus der Gruppe, bestehend aus Iodid, Chlorid, Bromid, Methylsulfonat, para-Toluolsulfonat und Trifluoracetat, R⁵ ein Wasserstoffatom ist und R⁶ ein Wasserstoffatom ist, wobei die zuvor erwähnten Alkylgruppen lineare und verzweigte Alkylgruppen umfassen, in denen zusätzlich 1 bis 3 Wasserstoffatome durch Fluoratome ersetzt sein können, wobei zusätzlich eine vorliegende Carboxyl-, Amino- oder Imingruppe mit einem in vivo spaltbaren Rest substituiert sein kann, oder in Form eines Propharmakonrests vorliegen kann, beispielsweise in Form einer Gruppe, die in vivo eine Carboxylgruppe umgewandelt werden kann, oder in Form einer Gruppe, die in vivo eine Imino- oder Aminogruppe umgewandelt werden kann, den Tautomeren, den Diastereomeren, den Enantiomeren, den Mischungen hiervon und den Salzen hiervon, zur Herstellung eines Medikaments zur Vorbeugung oder Behandlung einer fibrotischen Erkrankung, ausgewählt aus der Gruppe, bestehend aus Fibrose und Umbildung von Lungengewebe bei chronisch obstruktiver pulmonaler Erkrankung, Fibrose und Umbildung von Lungengewebe bei chronischer Bronchitis, Fibrose und Umbildung von Lungengewebe bei einem Emphysem, Lungenfibrose und pulmonale Erkrankungen mit einer fibrotischen Komponente, Fibrose und Umbildung bei Asthma.

2. Verwendung nach Anspruch 1, wobei das substituierte Indolinon der allgemeinen Formel I ausgewählt ist aus der Gruppe, bestehend aus:

(a) 3-Z-[1-(4-Dimethylaminoethylanilino)-1-(3-{2-carboxyethylphenyl}methyl)-6-chlor-2-indolinon,
(b) 3-Z-[1-(4-Dimethylaminoethylanilino)-1-(4-{2-carboxyethylphenyl}methyl)-6-fluor-2-indolinon,
(c) 3-Z-[1-(4-Dimethylaminoethylanilino)-1-(3-{2-carboxyethylphenyl}methyl)-6-fluor-2-indolinon,
(d) 3-Z-[1-{4-(N-{4-Methylpiperazin-1-yl-methyl}carbonyl)-N-methylamino-anilino)-1-(4-{2-carboxyethylphenyl}methyl)ethanaminocarbonyl-C₁₋₃-alkyl- oder C₁₋₃-Alkylpiperazin-1-yl-carbonyl-C₁₋₃-alkyl-Gruppe,
(n) 3-Z-[1-(4-(N-(3-dimethylaminopropyl)-N-acetylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(o) 3-Z-[1-(4-(N-(1-Methylimidazol-2-yl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(p) 3-Z-[1-(4-(N-(Dimethylaminomethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(q) 3-Z-[1-(4-(Pyrrolidin-1-ylmethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(r) 3-Z-[1-(4-(Dimethylaminomethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(s) 3-Z-[1-(4-(2-Dimethylaminoethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(t) 3-Z-[1-(4-(Pyrrolidin-1-ylmethyl)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(u) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(v) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(w) 3-Z-[1-(4-(N-(2-Dimethylamino)-N-methylsulfonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(x) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(y) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(z) 3-Z-[1-(4-(N-(2-Dimethylamino)-N-methylsulfonylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(aa) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(ab) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(ac) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(ad) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(ae) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(af) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(ag) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(ah) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(ai) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(aj) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(ak) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(al) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(am) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(an) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(ao) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(ap) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(aq) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(ar) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(as) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(at) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(au) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(ave) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(ave) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(ave) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(ave) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,

(ave) 3-Z-[1-(4-(N-(2-Dimethylaminoethylcarbonyl)-N-methylamino)anilino)-1-(4-(2-carboxyethyl)phenyl)methylen]-6-fluor-2-indolinon,
Ansprüche 1 oder 2 definiert, in Kombination mit einer weiteren pharmakologisch aktiven Substanz, ausgewählt aus der Gruppe, bestehend aus anticholinergen Mitteln, β-2-Mimetika, PDE-IV-Inhibitoren, p38-MAP-Kinase-Inhibitoren, NK1-Antagonisten, LTD4-Antagonisten und Endothelin-Antagonisten, gegebenenfalls zusammen mit einem oder mehreren pharmakologisch akzeptablen Trägem oder Hilfsstoffen.

Revendications

1. Utilisation des indolinones de formule générale
par un groupe de formule

dans lequel
R7 est un groupe alkyle en C1-C2, (alkyl en C1-C2)-carbonyle, di(alkyl en C1-C2)-aminocarbonyl-(alkyle en C1-C3) ou alkylsulfonyle en C1-C3, et
R8 est un groupe alkyle en C1-C3, ω-[di(alkyl en C1-C2)amino]-(alkyle en C2-C3), ou
un groupe (alkyl en C1-C3)-carbonyle, (alkyl en C4-C6)-carbonyle ou carbonyl-(alkyle en C1-C3) qui est substitué
en position terminale par un groupe di-(alkyl en C1-C2)-amino, pipérazin-1-yle ou 4-(alkyl en C1-C3)-pipérazin-1-yle;
tous les groupes dialkylamino présents dans le radical R4 pouvant aussi être présents sous forme quaternaire, par exemple sous forme d’un groupe N-méthyl-(N,N-dialkyl)ammonium, le contre-ion étant de préférence choisi dans le groupe constitué par les ions iodure, chlorure, bromure, méthylsulfonate, p-toluenesulfonate et trifluoroacétate,
R5 est un atome d’hydrogène et
R6 est un atome d’hydrogène,
ôù les groupes alkyle précités comprennent des groupes alkyle linéaires et ramifiés dans lesquels, de plus, 1 à 3 atomes d’hydrogène peuvent être remplacés par des atomes de fluor,
et où en outre un groupe carboxyle, amino ou imino présent peut être substitué par un radical dissociable in vivo
ou peut être présent sous la forme d’un radical de promédicament, par exemple sous forme d’un groupe qui peut être converti in vivo en un groupe carboxyle ou sous forme d’un groupe qui peut être converti in vivo en un groupe imino ou amino,
de leurs tautomères, diastréoisomères, énantiomères, leurs mélanges et leurs sels,
pour la préparation d’un médicament destiné à la prévention ou au traitement d’une maladie fibrogène choisie dans le groupe constitué par la fibrose et le remodelage du tissu pulmonaire dans la bronchopneumopathie chronique obstructive, la fibrose et le remodelage du tissu pulmonaire dans la bronchite chronique, la fibrose et le remodelage du tissu pulmonaire dans l’emphysème, la fibrose pulmonaire et les maladies pulmonaires ayant une composante fibrogène, la fibrose et le remodelage dans l’asthme.

2. Utilisation selon la revendication 1, dans laquelle l’indolinone substituée de formule générale 1 est choisie dans le groupe constitué par:

(a) la 3-Z-[1-(4-diméthylaminométhylanilino)-1-(3-(2-carboxyéthyl)phényl)méthylène]-6-chloro-2-indolinone
(b) la 3-Z-[1-(4-diméthylaminométhylanilino)-1-(4-(2-carboxyéthyl)phényl)méthylène]-6-fluoro-2-indolinone
(c) la 3-Z-[1-(4-diméthylaminométhylanilino)-1-(3-(2-carboxyéthyl)phényl)méthylène]-6-fluoro-2-indolinone
(d) la 3-Z-[1-(4-N-(4-méthylpipérazin-1-ylmétylecarbonyl)-N-méthylaminoanilino)-1-(4-(2-carboxyéthyl)phényl)méthylène]-6-fluoro-2-indolinone
(e) la 3-Z-[1-(4-(N-(2-diméthylaminoéthyl)sulfonylamino)anilino)-1-(4-(2-carboxyéthyl)phényl)méthylène]-6-fluoro-2-indolinone
(f) la 3-Z-[1-(4-(N-(3-diméthylaminopropyl)-N-acétylaminoanilino)-1-(4-(2-carboxyéthyl)phényl)méthylène]-6-fluoro-2-indolinone
(g) la 3-Z-[1-(4-(1-méthylimidazol-2-yl)anilino)-1-(4-(2-carboxyéthyl)phényl)méthylène]-6-fluoro-2-indolinone
(h) la 3-Z-[1-(4-(N-(4-diméthylaminométhylacrylate)-N-méthylaminoanilino)-1-(4-(2-carboxyéthyl)phényl)méthylène]-6-fluoro-2-indolinone
(i) la 3-Z-[1-(4-(N-(2-diméthylaminométhylacrylate)-N-méthylaminoanilino)-1-(4-(2-carboxyéthyl)phényl)méthylène]-6-fluoro-2-indolinone
(j) la 3-Z-[1-(4-pyrrolidin-1-ylméthyl)anilino)-1-(4-(2-carboxyéthyl)phényl)méthylène]-6-fluoro-2-indolinone
(k) la 3-Z-[1-(4-diéthylaminométhyl)anilino)-1-(4-(2-carboxyéthyl)phényl)méthylène]-6-fluoro-2-indolinone
(l) la 3-Z-[1-(4-(2-diméthylaminométhyl)anilino)-1-(4-(2-carboxyéthyl)phényl)méthylène]-6-fluoro-2-indolinone
(m) la 3-Z-[1-(4-(diméthylaminométhyl)anilino)-1-(4-(2-carboxyéthyl)phényl)méthylène]-6-fluoro-2-indolinone
(n) la 3-Z-[1-(4-pyrrolidin-1-ylméthyl)anilino)-1-(4-(2-carboxyéthyl)phényl)méthylène]-6-fluoro-2-indolinone
(o) la 3-Z-[1-(4-pyrrolidin-1-ylméthyl)anilino)-1-(4-(2-carboxyéthyl)phényl)méthylène]-6-bromo-2-indolinone
(p) la 3-Z-[1-(4-(diméthylaminométhyl)anilino)-1-(4-(2-carboxyéthyl)phényl)méthylène]-6-bromo-2-indolinone,
et
(q) la 3-Z-[1-(4-(diéthylaminométhyl)anilino)-1-(4-(2-carboxyéthyl)-méthylène]-6-bromo-2-indolinone,
leurs tautomères, diastéréoisomères, énantiomères, mélanges et sels.

3. Utilisation selon l'une quelconque des revendications 1 ou 2, dans laquelle la maladie est choisie dans le groupe constitué par la fibrose pulmonaire et les maladies pulmonaires ayant une composante fibrogène choisies parmi la fibrose pulmonaire idiopathique, la pneumonie interstitielle à cellules géantes, la sarcoïdose, la mucoviscidose, le syndrome de détresse respiratoire, la fibrose pulmonaire induite par des médicaments, la granulomatose, la silicose, l’amianteose, la sclérodermie généralisée.

4. Utilisation selon l'une quelconque des revendications 1 à 3, dans laquelle la maladie est la fibrose pulmonaire idiopathique.

5. Utilisation selon l’une quelconque des revendications 1 à 4, dans laquelle le traitement est un traitement combiné avec une autre substance pharmacologiquement active choisie dans le groupe constitué par les agents anticholinergiques, les β-2-mimétiques, les stéroïdes, les inhibiteurs de PDE-N, les inhibiteurs de la MAP-kinase p38, les antagonistes de NK1, les antagonistes de LTD4, les inhibiteurs d'EGFR et les antagonistes de l'endothéline.

6. Composition pharmaceutique comprenant une indolinone substituée de formule I telle que définie dans l’une quelconque des revendications 1 ou 2, éventuellement avec un ou plusieurs vecteurs ou excipients pharmaceutiquement acceptables, pour la prévention ou le traitement d’une maladie fibrogène choisie dans le groupe constitué par la fibrose et le remodelage du tissu pulmonaire dans la bronchopneumopathie chronique obstructive, la fibrose et le remodelage du tissu pulmonaire dans l’emphysème, la fibrose et les maladies pulmonaires ayant une composante fibrogène, la fibrose et le remodelage dans l’asthme, le fibrose induite par des rayonnements.

7. Composition pharmaceutique selon la revendication 6, dans laquelle la maladie est choisie dans le groupe constitué par la fibrose pulmonaire et les maladies pulmonaires ayant une composante fibrogène choisies parmi la fibrose pulmonaire idiopathique, la pneumonie interstitielle à cellules géantes, la sarcoïdose, la mucoviscidose, le syndrome de détresse respiratoire, la fibrose pulmonaire induite par des médicaments, la granulomatose, la silicose, l’amianteose, la sclérodermie généralisée.

8. Composition pharmaceutique selon la revendication 7, dans laquelle la maladie est la fibrose pulmonaire idiopathique.

9. Composition pharmaceutique selon l’une quelconque des revendications 6 à 8, dans laquelle le traitement est un traitement combiné avec une autre substance pharmacologiquement active choisie dans le groupe constitué par les agents anticholinergiques, les β-2-mimétiques, les stéroïdes, les inhibiteurs de PDE-IV, les inhibiteurs de la MAP-kinase p38, les antagonistes de NK1, les antagonistes de LTD4, les inhibiteurs d’EGFR et les antagonistes de l’endothéline, ladite autre substance pharmacologiquement active étant administrée simultanément ou successivement.

10. Composition pharmaceutique contenant une indolinone substituée de formule I telle que définie dans l’une quelconque des revendications 1 ou 2 en combinaison avec une autre substance pharmacologiquement active choisie dans le groupe constitué par les agents anticholinergiques, les β-2-mimétiques, les inhibiteurs de PDE-IV, les inhibiteurs de la MAP-kinase p38, les antagonistes de NK1, les antagonistes de LTD4 et les antagonistes de l’endothéline, éventuellement avec un ou plusieurs vecteurs ou excipients pharmaceutiquement acceptables.
FIGURE 2
FIGURE 3

Fold change gene expression relative to 18S RNA

Saline Only  Bleomycin  Bleo + Example A

$p=0.0089$  $p=0.0011$
REFERENCES CITED IN THE DESCRIPTION

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