

OXINDOLE DERIVATIVES, PREPARATION THEREOF AND THERAPEUTIC USE IN THE TREATMENT OF AMPK-RELATED DISEASES

The present invention relates to oxindole derivatives, and to the preparation and
5 therapeutic use thereof.

The compounds according to the invention modulate the activity of AMP-
activated protein kinase (AMPK) and are of use for the prevention or treatment of
pathological conditions in which such a modulation is beneficial, as in case of metabolic
disorders including obesity and type 2 diabetes, as well as in case of kidney diseases.

10

AMPK is a sensor of the energy level in mammalian cells and also of the overall
energy level in the organism. AMPK is activated by an increase in the intracellular
AMP/ATP ratio, induced for example by a metabolic stress, hormones or the nutrient
signalling pathways (Viollet et al., Critical Reviews in Biochemistry and Molecular
15 Biology, 2010; 45(4); 276). When it is activated, AMPK blocks the metabolic pathways
which consume ATP (such as fatty acid synthesis in adipocytes, cholesterol synthesis
in the liver and insulin secretion in β -cells) and activates the metabolic pathways which
produce ATP (such as fatty acid absorption and beta-oxidation in various tissues,
glycolysis in the heart and the biogenesis of mitochondria in skeletal muscle). AMPK
20 also modulates the transcription of genes which participate in energy metabolism,
exerting a metabolic control over the longer term (Viollet et al., 2006). Moreover, the
activity of AMPK also participates in the regulation of non-metabolic processes such as
cell growth, progression of the cell cycle and organization of the cytoskeleton (Williams,
T., and Brenman, J.E. (2008). Trends in Cell Biology 18(4):193-8). Although the
25 activation of AMPK is an adaptive response to an energy stress in many biological
systems, AMPK plays an important role in maintaining physiological functions and in
adaptation to pathophysiological conditions.

The main pathological conditions in which the activation of AMPK intervenes
30 are described below:

Metabolic diseases including obesity and type 2 diabetes

Diabetes is characterized by a high level of plasma glucose (hyperglycaemia) in
the fasted state or after the administration of glucose during an oral glucose tolerance
test. Patients with type 2 (or non-insulin-dependent) diabetes exhibit, in addition to an

increase in plasma glucose level, resistance to insulin. It is characterized by a lack of response to a stimulation induced by an increase in blood glucose at the level of the main target tissues of insulin, such as muscle, liver and adipose tissue. These patients compensate for the reduction in insulin effectiveness by increasing its production and are hyperinsulinemic (high level of plasma insulin) (Polonsky, *Int. J. Obes. relat. Metab. Disord.* 24 Suppl 2:S29-31, 2000). This increase in insulin secretion contributes, for a limited period of time, to maintaining a normal plasma glucose level. Over time, the pancreatic β -cells become exhausted, insulin production decreases and plasma glucose level increases leading to type 2 diabetes. Persistent or uncontrolled hyperglycaemia is associated with an increase in morbidity and premature mortality. It is directly or indirectly associated with obesity, hypertension and an impairment of lipid, lipoprotein and apolipoprotein metabolism. Patients with type 2 diabetes have a significant increase in the risks of macrovascular and microvascular complications, including atherosclerosis, coronary artery disease, strokes, peripheral vascular diseases, nephropathy, neuropathy and retinopathy. A considerable therapeutic need exists since virtually half the patients treated do not manage to correctly control their plasma glucose levels. Moreover, effective therapeutic control of glucose homeostasis prevents the occurrence of diabetes-related complications and significantly decreases mortality and morbidity. Insulin-resistant patients often have numerous symptoms which combined together are known as metabolic syndrome. This syndrome is associated with an increase in the risk of developing atherosclerosis and also coronary heart disease.

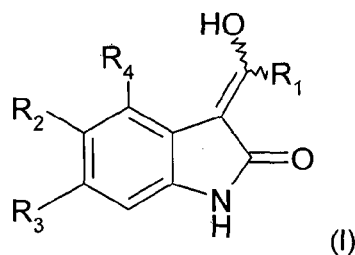
Numerous data accumulated over the past few years support the rationale which presents AMPK (AMP-activated protein kinase) as a therapeutic target of interest for the treatment of metabolic diseases including obesity and type 2 diabetes (Fang et al. *Current topics in Medicinal Chemistry*, 2010, 10, 397-340). The activation of AMPK via a modification of the AMP/ATP ratio or following phosphorylation by an upstream kinase like LKB1 or CaMKK can result in an increase in glucose uptake in the muscles and in a decrease in neoglucogenesis in the liver, both leading to a decrease in plasma glucose level. In terms of lipid metabolism, AMPK activation leads to an increase in fatty acid oxidation in the liver and the adipose tissue and also an increase in mitochondrial biogenesis (Hardie, D. *Annu. Rev. Pharmacol. Toxicol.*, 2007, 47, 185-210). Moreover, it has been reported that the overexpression of an active form of AMPK in mouse liver produces a slight hypoglycaemia and decreases hyperglycaemia in a diabetic mouse model (Foretz et al. *Diabetes*, 2005, 54, 1331-1339). Furthermore, two classes of drugs widely used to treat type 2 diabetes, biguanides (Metformin, etc.)

and thiazolidinediones (rosiglitazone, etc.), although indirectly, activate AMPK and this activation may at least partially explain their widely described antidiabetic effects (Lebrasseur, N. K. et al. Am. J. Physiol. Endocrinol. Metab., 2006, 291, E175-181; Musi, N. et al. Diabetes, 2002, 51, 2074-2081). Direct activators of AMPK have, moreover, shown positive effects in *in vitro* and *in vivo* preclinical models: AICAR (5-aminoimidazole-4-carboxamide riboside; Sullivan, J. E. et al. FEBS Lett., 1994, 353, 33-36; Merrill, G. F. et al.; Am. J. Physiol., 1997, 273, E1107-1112), A769662 (Cool, B. et al., Cell Metabolism, 2006, 3, 403-416), and PT1 (Pang, T. et al. J. Biol. Chem., 2008, 283, 16051-16060). These data supports the rationale that direct activation of AMPK has the potential to improve the metabolic profile of type 2 diabetic patients with or without associated obesity. Moreover, the activation of AMPK using pharmacological agents could play a key role in the prevention of the occurrence of diabetic complications (nephropathy, neuropathy, retinopathy, atherosclerosis, microangiopathy).

AMPK activation and kidney diseases

AMPK has been highlighted as a promising target for pharmacological modulation that yield benefits in the treatment of several kidney diseases (K.R. Hallows et al. AM. J. Renal. Physiol. 2010, 298, F1067-F1077). AMPK has been recently identified as regulator of several ion channels, transporters, and pumps in the kidney and treatment with AMPK activators may be beneficial in preventing deleterious effects in the kidney in the setting of various diseases (N. M. Pastor-Soler et al. Curr. Opin. Nephrol. Hypertens. 2012, 21(5): 523-33). Moreover, AMPK activation has been shown to induce autophagy, a lysosomal protein degradation pathway in cells, which has been shown to be renoprotective in several animal models (Y. Tanaka Exp. Diabetes Res. 2012, ID628978).

The present invention relates to compounds corresponding to formula (I):



in which

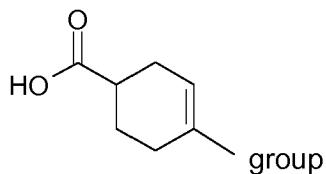
➤ R_1 represents :

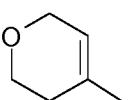
- an (C_6 - C_{10})aryl group, unsubstituted or substituted with one or more substituents chosen from
 - a halogen atom,
 - a $-OR_a$ group, in which R_a represents a hydrogen atom, a (C_1 - C_3)alkyl group or a $-CF_3$ group
 - a (C_1 - C_3)alkyl group, unsubstituted or substituted with one or more halogen atoms,
 - a carboxyl group,
 - a cyano group,
 - a (C_3 - C_6)heterocycloalkyl group, unsubstituted or substituted with one or more (C_1 - C_3)alkyl group,
- a (C_2 - C_{10})heteroaryl group, unsubstituted or substituted with one or more substituents chosen from
 - a halogen atom,
 - a (C_1 - C_4)alkyl group,
 - a (C_3 - C_6)cycloalkyl group,
 - a $-OR_e$ group, in which R_e represents an hydrogen atom or a (C_1 - C_4)alkyl group, said (C_1 - C_4)alkyl group being unsubstituted or substituted with one or more (C_1 - C_4)alkoxy or heterocycloalkyl group
 - a $-NR_fR_f$ group, in which R_f et R_f , independently, identical or different, represent a (C_1 - C_3)alkyl group

➤ R_2 represents :

- an (C_6 - C_{10})aryl group, unsubstituted or substituted with one or more substituents chosen from :

- a halogen atom,
- a cyano group,



- a  group

- a (C₁-C₃)alkyl group unsubstituted or substituted with one or more substituents chosen from a halogen atom, a hydroxyl group and a (C₁-C₄)alkenyl group,
- 5 ▪ a (C₃-C₆)cycloalkyl group, unsubstituted or substituted with a hydroxy(C₁-C₃)alkyl group, a hydroxyl group or an (C₁-C₄)alkoxy group,
- 10 ▪ a -OR_b group, in which R_b represents
 - a hydrogen atom,
 - a -CF₃ group,
 - 10 • a (C₃-C₆)cycloalkyl group, unsubstituted or substituted with a hydroxyl group
 - a (C₃-C₆)heterocycloalkyl group, said (C₃-C₆)heterocycloalkyl being unsubstituted or substituted with a (C₁-C₃)alkyl group,
 - 15 • or an (C₁-C₃)alkyl group, said (C₁-C₃)alkyl group being unsubstituted or substituted with one or more :
 - hydroxyl group,
 - (C₁-C₄)alkoxy group,
 - (C₂-C₁₀)heteroaryl group,
 - 20 ○ acetamido group,
 - di(C₁-C₃)alkyl-amino group,
 - (C₃-C₆)cycloalkyl group, said (C₃-C₆)cycloalkyl group being unsubstituted or substituted with one or more hydroxyl group, or
 - 25 ○ (C₃-C₆)heterocycloalkyl group, said (C₃-C₆)heterocycloalkyl group being unsubstituted or substituted with a (C₁-C₃)alkyl group;
- 30 ▪ a (C₃-C₆)heterocycloalkyl group unsubstituted or substituted with one or more halogen atom, (C₁-C₃)alkyl group, hydroxyl group, hydroxy(C₁-C₃)alkyl group, (C₁-C₄)alkoxy group or (C₁-C₄)fluoroalkyl group,
- 35 ▪ an (C₆-C₁₀)aryl group, unsubstituted or substituted with one or more -OR_c group, in which R_c represents a hydrogen atom or a (C₁-C₃)alkyl group,
- a (C₂-C₁₀)heteroaryl group, unsubstituted or substituted with one or more -NH₂ group,

- a $-NR_dR_{d'}$ group, in which R_d et $R_{d'}$, independently, identical or different, represent a hydrogen atom, a (C_1-C_3) alkyl group, a hydroxy (C_1-C_4) alkyl or a (C_3-C_6) cycloalkyl group,
- a (C_2-C_{10}) heteroaryl group, unsubstituted or substituted with one or more substituents chosen from:
 - a (C_1-C_3) alkyl group
 - a (C_3-C_6) cycloalkyl group, unsubstituted or substituted with a hydroxy (C_1-C_3) alkyl group,
 - a $-NR_gR_{g'}$ group, in which R_g et $R_{g'}$, independently, identical or different, represent a (C_1-C_3) alkyl group,

➤ R_3 represents :

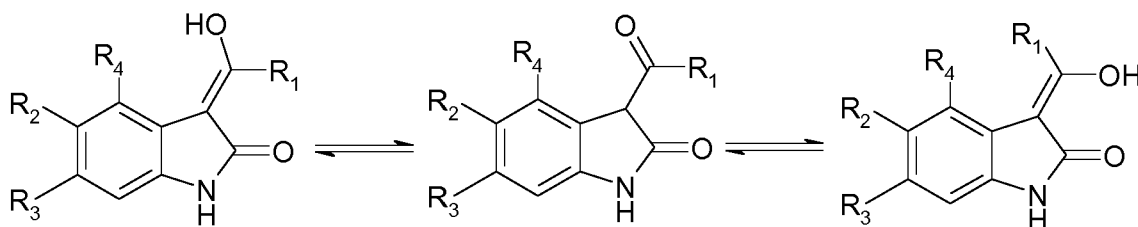
- a halogen atom,
- a (C_1-C_3) alkyl group,

➤ R_4 represents :

- a halogen atom,
- a hydrogen atom,

in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

The compounds of formula (I) may exist under the form of cis/trans isomers and/or under the form of isomers called tautomers. Such tautomers can be represented as follow:



All isomer forms which are not restricted to those described above and the mixtures of them are considered as part of the present invention.

The compounds of formula (I) may contain one or more asymmetric carbon atoms.

They may therefore exist in the form of enantiomers or diastereoisomers. These enantiomers and diastereoisomers, and also mixtures thereof, including the racemic mixtures, form part of the invention.

- 5 The compounds of formula (I) may exist in the form of bases or acids which can be salified with acids or bases, especially pharmaceutically acceptable acids or bases. Such addition salts are part of the invention.

These salts are prepared with pharmaceutically acceptable acids or bases, but salts of other acids and bases that are of use, for example, for purifying or isolating the
10 compounds of formula (I) also form part of the invention. In particular, use will be made in the context of the invention of the sodium salt and hydrochloride salt.

In the context of the present invention, and unless otherwise mentioned in the text:

- a halogen atom: a fluorine atom, a chlorine atom, a bromine atom or an iodine atom;
- 15 - an alkyl group: unless otherwise mentioned in the text, a linear or branched saturated aliphatic group containing from 1 to 4. Examples that may be mentioned include methyl, ethyl, propyl, isopropyl, butyl, isobutyl or tert-butyl groups, in particular methyl, ethyl or tert-butyl groups;
- an alkenyl group: a linear or branched mono- or polyunsaturated aliphatic group
20 containing, for example, one or two ethylenic unsaturations;optionally substituted: not substituted or substituted;
- a halogenoalkyl group: an alkyl group in which one or more hydrogen atoms have been substituted by a halogen atom;
- a hydroxyalkyl group: an alkyl group in which one or more hydrogen atoms
25 have been substituted by a OH group;
- an alkoxy group: a radical -O-alkyl in which the alkyl group is as defined previously, in particular the -O-alkyl group is a methoxy or an ethoxy group;
- a cycloalkyl group: a saturated mono or bi-cyclic aliphatic group comprising
30 between 3 and 6 carbon atoms. Examples that may be mentioned include cyclopropyl, cyclobutyl or cyclohexyl group;
- a heterocycloalkyl group: a mono or bi-cyclic alkyl group comprising between 3 and 6 carbon atoms and comprising 1 or 2 heteroatoms, such as nitrogen or oxygen. Examples that may be mentioned include piperazinyl, morpholinyl, tetrahydropyranyl, piperidinyl or pyrrolidinyl groups;

- an aryl group (Ar): a mono or bi-cyclic aromatic group comprising between 6 and 10 carbon atoms. An example of an aryl group that may be mentioned is the phenyl or naphthalene group;

5 - a heteroaryl group: a mono or bi cyclic aromatic group comprising between 2 and 10 carbon atoms and comprising between 1 and 3 heteroatoms, such as nitrogen, oxygen or sulfur. Examples that may be mentioned include pyridinyl, pyrazolyl, furanyl, isoxazolyl, thiazolyl, isothiazolyl, thiophenyl, indolyl, furopyridinyl, benzofuranyl, thienopyridinyl, pyrimidinyl and 1,3,4-oxadiazolyl groups;

10 Among the compounds of the present invention, mention may be made of a first subgroup of compounds of formula (I) in which

➤ R₁ represents :

- An aryl group, unsubstituted or substituted with one or more substituents chosen from

- 15 ▪ a halogen atom,
- a –OR_a group, in which R_a represents a hydrogen atom or a (C₁-C₃)alkyl group,
- a (C₁-C₃)alkyl group, unsubstituted or substituted with one or more halogen atoms,
- 20 ▪ a carboxyl group,
- a cyano group,

- a heteroaryl group, unsubstituted or substituted with one or more substituents chosen from a halogen atom, a (C₁-C₄)alkyl group, a (C₃-C₆)cycloalkyl group, a (C₁-C₄)alkoxy group,

25 ➤ R₂ represents :

- an aryl group, unsubstituted or substituted with one or more substituents chosen from :

- 30 ▪ a halogen atom,
- a cyano group,
- a (C₁-C₃)alkyl group,
- a (C₃-C₆)cycloalkyl group, unsubstituted or substituted with a hydroxy(C₁-C₃)alkyl group,
- 35 ▪ a –OR_b group, in which R_b represents a hydrogen atom, a –CF₃ group or an alkyl group, unsubstituted or substituted with one heterocycloalkyl group, the said heterocycloalkyl group being unsubstituted or substituted with a (C₁-C₃)alkyl group;

- a heterocycloalkyl group, unsubstituted or substituted with one or more (C₁-C₃)alkyl group,
 - an aryl group, unsubstituted or substituted with one or more –OR_c group, in which R_c represents a hydrogen atom or a (C₁-C₃)alkyl group,
 - a heteroaryl group, unsubstituted or substituted with one or more –NH₂ group,
 - a –NR_dR_{d'} group, in which R_d et R_{d'}, independently, identical or different, represent a hydrogen atom, a (C₁-C₃)alkyl group,
- 10 • a heteroaryl group, unsubstituted or substituted with one or more cycloalkyl group, unsubstituted or substituted with a hydroxy(C₁-C₃)alkyl group,
- R₃ represents :
- a halogen atom,
 - a (C₁-C₃)alkyl group,
- 15 ➤ R₄ represents an hydrogen atom

in the form of the base or of an addition salt with an acid or with a base.

Among the compounds of the present invention, mention may be made of a second subgroup of compounds of formula (I) in which:

- 20 ➤ R₁ represents :
- An aryl group, in particular a phenyl group, optionally substituted with one or more substituents chosen from
 - a halogen atom, in particular a fluorine or a chlorine atom,
 - a –OR_a group, in which R_a represents a hydrogen atom or a (C₁-C₃)alkyl group in particular a methyl group,
 - a (C₁-C₃)alkyl group, in particular a methyl group, optionally substituted by one or more halogen atoms, in particular a di or trifluoro-methyl group,
 - a carboxyl group,
 - a cyano group,
 - a heteroaryl group, in particular a pyridinyl group, a pyrazolyl group, an isoxazolyl group, a thiazolyl group, an isothiazolyl group or a 1,3,4-oxadiazolyl group, optionally substituted by one or more substituents
- 25
- 30

chosen from a halogen atom in particular a bromine atom, a (C₁-C₄)alkyl group, in particular a methyl group or a tert-butyl group, a cycloalkyl group, in particular a cyclopropyl group, an (C₁-C₃)alkoxy group in particular a methoxy group,

5

➤ R₂ represents :

- an aryl group, in particular a phenyl or naphtalene group, optionally substituted by one or more substituents chosen from :

10

- a halogen atom, in particular a fluorine or a chlorine atom,
- a cyano group,
- a (C₁-C₃)alkyl group, in particular an ethyl group,
- a cycloalkyl group, in particular a cyclopropyl or a cyclobutyl group, optionally substituted by a hydroxy(C₁-C₃)alkyl group, in particular a hydroxymethyl group,

15

- a -OR_b group, in which R_b represents a hydrogen atom, a -CF₃ group or an alkyl group in particular a (C₁-C₃)alkyl group, optionally substituted by one heterocycloalkyl group, in particular a piperazinyl group, the said heterocycloalkyl group being optionally substituted by a (C₁-C₃)alkyl group, in particular a methyl group;

20

- a heterocycloalkyl group, in particular a morpholiny, a dihydropyranyl, a tetrahydropyranyl, a pyrrolidiny, a tetrahydrofuranyl, a piperidiny or a piperazinyl group, optionally substituted by one or more a (C₁-C₃)alkyl group, in particular a methyl group,

25

- an aryl group, in particular a phenyl group, optionally substituted by one or more -OR_c group, in which R_c represents a hydrogen atom or a (C₁-C₃)alkyl group, in particular a methyl group,

30

- a heteroaryl group, in particular a pyridiny, a thiazoly or a furanyl group, optionally substituted by one or more -NH₂ group,
- a -NR_dR_{d'} group, in which R_d et R_{d'}, independently, identical or different, represent a hydrogen atom, a (C₁-C₃)alkyl group, in particular a methyl group,

35

- a heteroaryl group, in particular a thiophene group, optionally substituted by one or more cycloalkyl group in particular a cyclopropyl group,

optionally substituted by a hydroxy(C₁-C₃)alkyl group in particular a hydroxymethyl group,

➤ R₃ represents :

- 5
- a halogen atom, in particular a chlorine or a fluorine atom,
 - a (C₁-C₃)alkyl group, in particular a methyl group,

➤ R₄ represents :

- a halogen atom, in particular a fluorine atom
- a hydrogen atom,

10 in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

Among the compounds of the present invention, mention may be made of a third subgroup of compounds of formula (I) in which:

15 ➤ R₁ represents :

- a phenyl group, unsubstituted or substituted with one or more substituents chosen from:

- 20
- a fluorine atom or a chlorine atom,
 - a -OR_a group, in which R_a represents a methyl group, a CF₃ group,
 - a di or trifluoro-methyl group,
 - a carboxyl group,
 - a cyano group,
 - a morpholine group, a methylpiperazine group

- 25
- a pyridinyl group, a pyrazolyl group, a pyrimidinyl group, an isoxazolyl group, a thiazolyl group, an isothiazolyl group, a 1,3,4-oxadiazolyle group, a thiazol-2onyl group, a thienyl group, a furyl group, a furopyridinyl group, a benzofuran-2-yl group, a thienopyridinyl group, an indolynonyl group, unsubstituted or substituted with one or more

30 substituents chosen from:

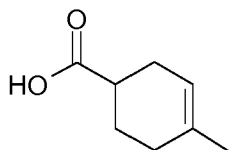
- a bromine atom, a chlorine atom, a fluorine atom
- a methyl or tert-butyl group,
- a hydroxyl group
- a cyclopropyl group or a cyclohexyl group

- a $-OR_e$ group, in which R_e represents a methyl group, an ethyl group, an isopropyl group, a methoxyethyl group, a morpholinoethyl group
- a dimethylamino group,

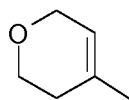
5 ➤ R_2 represents :

- a phenyl or a naphthalene group, unsubstituted or substituted with one or more substituents chosen from :

- a fluorine atom or a chlorine atom,



- a group



- a group

- a cyano group,

- an ethyl group, unsubstituted or substituted with one or two hydroxyl groups,

- an propyl group, unsubstituted or substituted with two or more groups chosen from a chlorine atom, an hydroxyl group and a propenyl group,

- a cyclopropyl or a cyclobutyl group, unsubstituted or substituted with a hydroxyl group, a hydroxymethyl group or a methoxy group

- a $-OR_b$ group, in which R_b represents a hydrogen atom, a $-CF_3$ group or an (C_1-C_3) alkyl group, unsubstituted or substituted with one piperazinyl group, the said piperazinyl group being unsubstituted or substituted with a methyl group;

- a morpholinyl, a dihydropyranyl, a tetrahydropyranyl, a pyrrolidinyl, a tetrahydrofuranyl, a piperazinyl, a piperidinyl group, a dioxane group, an oxaazaspiro[3.3]heptanyl, unsubstituted or substituted with one or more methyl group, hydroxyl group, methoxy group, hydroxymethyl group or fluorine atom,

- an azetidiny group unsubstituted or substituted with one or two fluorine atoms, methyl groups, or hydroxymethyl group,

- a pyrrolidinyl group substituted with a trifluoroethyl group,
 - a phenyl group, unsubstituted or substituted with one or more –
OR_c group, in which R_c represents :
 - a hydrogen atom
 - a methyl group,
 - an hydroxypropyl group
 - an hydroxyxylhexyl group,
 - a methoxypropyl group,
 - a dimethylaminopropyl group
 - a morpholinoethyl group, a morpholinopropyl group
 - a hydroxypropyl group, a methoxyethyl group,
 - a tetrahydropyranyl,
 - a pyridylmethyl group,
 - a pyrimidinyl group,
 - a methylpiperidyl group,
 - a thiazolylmethyl group,
 - an acetamidoethyl group
 - an oxetanylmethyl group
 - an hydroxycyclobutylmethyl group,
 - a pyridinyl, a thiazolyl, a furanyl group, unsubstituted or substituted with one -NH₂ group,
 - a –NR_dR_{d'} group, in which R_d et R_{d'}, independently, identical or different, represent a methyl group, an hydroxypropyl group or a cyclopropyl group,
 - a thiophene group, unsubstituted or substituted with a cyclopropyl group, unsubstituted or substituted with a hydroxymethyl group,
 - a pyrimidinyl or a pyridinyl group substituted with a dimethylamino group
 - an indolyl group, substituted with a methyl group,
- R₃ represents :
- a chlorine or a fluorine atom,
 - a methyl group,
- R₄ represents a fluorine or an hydrogen atom.

in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

Among the compounds of the present invention, mention may be made of a fourth subgroup of compounds of formula (I) in which:

- R₁ represents a (C₂-C₁₀)heteroaryl group, optionally substituted by one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a (C₃-C₅)cycloalkyl group, a (C₁-C₄)alkoxy group,
- 5 in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

Among the compounds of the present invention, mention may be made of a fifth subgroup of compounds of formula (I) in which:

10

- R₁ represents an isoxazolyl group, optionally substituted by one substituent chosen from a (C₁-C₄)alkyl group in particular a methyl group, a (C₃-C₅)cycloalkyl group, in particular a cyclopropyl group or a cyclohexyl group or an alkoxy group, in particular a methoxy group,
- 15 in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

Among the compounds of the present invention, mention may be made of a sixth subgroup of compounds of formula (I) in which:

- R₁ represents a phenyl group, substituted with one substituent chosen from halogen atom and an -OR_a group, in which R_a represents a (C₁-C₃)alkyl group,
- 20

Among the compounds of the present invention, mention may be made of an seventh subgroup of compounds of formula (I) in which:

25

- R₂ represents :
- an aryl group, in particular a phenyl group, optionally substituted by one or more substituents chosen from :
 - a (C₁-C₃)alkyl group,
 - a (C₃-C₆)cycloalkyl group, optionally substituted by a hydroxy(C₁-C₃)alkyl group,
 - a (C₃-C₆)heterocycloalkyl group, in particular a morpholinyl, a dihydropyranyl, a tetrahydropyranyl, a pyrrolidinyl, a tetrahydrofuranyl, a piperidinyl or a piperazinyl group, optionally
- 30

substituted by one or more (C₁-C₃)alkyl group, in particular a methyl group or an hydroxyl group,

- an (C₆-C₁₀)aryl group, in particular a phenyl group, optionally substituted by one or more -OR_c group, in which R_c represents a hydrogen atom or a (C₁-C₃)alkyl group,
- a (C₂-C₁₀)heteroaryl group, in particular a pyridinyl, a thiazolyl or a furanyl group, optionally substituted by one or more -NH₂ group,
- a -NR_dR_{d'} group, in which R_d et R_{d'}, independently, identical or different, represent a hydrogen atom, a (C₁-C₃)alkyl group, in particular a methyl group,

in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

Among the compounds of the present invention, mention may be made of an eighth subgroup of compounds of formula (I) in which:

➤ R₂ represents :

- a phenyl group, optionally substituted by one substituent chosen from :
 - a halogen atom,
 - a (C₃-C₆)cycloalkyl group, in particular a cyclopropyl group, optionally substituted by a hydroxy(C₁-C₃)alkyl group in particular a hydroxymethyl group,
 - a (C₃-C₆)heterocycloalkyl group, in particular a dihydropyranyl group,
 - a phenyl group, optionally substituted by several -OR_c group, in which R_c represents a hydrogen atom or a (C₁-C₃)alkyl group in particular a methyl group,
 - a pyridinyl group,
 - a -NR_dR_{d'} group, in which R_d et R_{d'}, identical, represent a (C₁-C₃)alkyl group, in particular a methyl group,

in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

Among the compounds of the present invention, mention may be made of a ninth subgroup of compounds of formula (I) in which R_3 represents a halogen atom, in particular a chlorine or a fluorine atom in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base

5

Among the compounds of the present invention, mention may be made of a tenth subgroup of compounds of formula (I) in which: R_4 represents a fluorine atom, in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

10

Among the compounds of the present invention, mention may be made of a eleventh subgroup of compounds of formula (I) in which: when R_4 represents a fluorine then R_3 also represents a fluorine atom, in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

15

The subgroups defined above, taken separately or in combination, also form part of the invention.

Among the compounds of formula (I) that are subjects of the invention, mention may be made especially of the following compounds:

20

Compound 1. 6-Chloro-5-(4-dimethylamino-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 2. 6-Chloro-5-(4-dimethylamino-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one, sodium salt

25

Compound 3. 6-Chloro-3-[1-hydroxy-1-(3-hydroxy-phenyl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

Compound 4. 3-[[6-Chloro-5-(4-morpholin-4-yl-phenyl)-2-oxo-1,2-dihydro-indolylidene]-hydroxy-methyl]-benzoic acid

Compound 5. 6-Chloro-5-(2'-hydroxy-3'-methoxy-biphenyl-4-yl)-3-[1-hydroxy-1-(3-methoxy-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

30

Compound 6. 6-Chloro-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 7. 5-Biphenyl-4-yl-6-chloro-3-[1-hydroxy-1-phenyl-methylidene]-1,3-dihydro-indol-2-one

Compound 8. 3-[[6-Chloro-5-(4-dimethylamino-phenyl)-2-oxo-1,2-dihydro-indolylidene]-hydroxy-methyl]-benzoic acid

Compound 9. 4-[[6-Chloro-5-(4-dimethylamino-phenyl)-2-oxo-1,2-dihydro-indolylidene]-hydroxy-methyl]-benzoic acid

5 Compound 10. 6-Chloro-5-(4-dimethylamino-phenyl)-3-[1-hydroxy-1-(2-methyl-thiazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 11. 6-Chloro-3-[1-(3-fluoro-phenyl)-1-hydroxy-methylidene]-5-naphthalen-2-yl-1,3-dihydro-indol-2-one

10 Compound 12. 6-Chloro-5-(2'-hydroxy-3'-methoxy-biphenyl-4-yl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 13. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isothiazol-5-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

Compound 14. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

15 Compound 15. 6-Chloro-3-[1-(2,4-dimethyl-thiazol-5-yl)-1-hydroxy-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

Compound 16. 6-Chloro-3-[1-hydroxy-1-(5-methyl-[1,3,4]oxadiazol-2-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

20 Compound 17. 6-Chloro-3-[1-hydroxy-1-(3-methoxy-isoxazol-5-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

Compound 18. 3-[[6-Chloro-5-(4-morpholin-4-yl-phenyl)-2-oxo-1,2-dihydro-indolylidene]-hydroxy-methyl]-benzonitrile

Compound 19. 6-Chloro-3-[1-(3-fluoro-phenyl)-1-hydroxy-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

25 Compound 20. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-(4-methoxy-phenyl)-1,3-dihydro-indol-2-one

Compound 21. 6-Chloro-5-[4-(3,6-dihydro-2H-pyran-4-yl)-phenyl]-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

30 Compound 22. 6-Chloro-5-(4-cyclopropyl-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 23. 6-Chloro-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-3-[1-hydroxy-1-(3-methyl-isothiazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 24. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-(4-pyrrolidin-1-yl-phenyl)-1,3-dihydro-indol-2-one

35 Compound 25. 6-Chloro-3-[1-hydroxy-1-pyridin-3-yl-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

Compound 26. 6-Chloro-5-(4-cyclopropyl-phenyl)-3-[1-(3-fluoro-phenyl)-1-hydroxy-methylidene]-1,3-dihydro-indol-2-one

Compound 27. 6-Chloro-3-[1-(3-fluoro-phenyl)-1-hydroxy-methylidene]-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-1,3-dihydro-indol-2-one

5 Compound 28. 6-Chloro-3-[1-hydroxy-1-(5-methyl-isoxazol-3-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

Compound 29. 6-Fluoro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

10 Compound 30. 6-Chloro-5-(4-fluoro-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 31. 3-[1-Hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-6-methyl-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

Compound 32. 6-Chloro-3-[1-(2-fluoro-phenyl)-1-hydroxy-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

15 Compound 33. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one

Compound 34. 6-Chloro-3-[1-(3-chloro-phenyl)-1-hydroxy-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

20 Compound 35. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-(4-pyridin-4-yl-phenyl)-1,3-dihydro-indol-2-one, hydrochloride

Compound 36. 6-Chloro-3-[1-(4-fluoro-phenyl)-1-hydroxy-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

Compound 37. 5-[4-(2-Amino-thiazol-4-yl)-phenyl]-6-chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

25 Compound 38. 4-{6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-2-oxo-2,3-dihydro-1H-indol-5-yl}-benzonitrile

Compound 39. 6-Chloro-3-[1-(3-difluoromethyl-phenyl)-1-hydroxy-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

30 Compound 40. 6-Chloro-3-[1-hydroxy-1-(3-trifluoromethyl-phenyl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

Compound 41. 3-[1-(3-Bromo-isoxazol-5-yl)-1-hydroxy-methylidene]-6-chloro-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

Compound 42. 6-Chloro-5-(2'-hydroxy-3'-methoxy-biphenyl-4-yl)-3-[1-hydroxy-1-(3-methyl-isothiazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

35 Compound 43. 6-Chloro-3-[1-hydroxy-1-phenyl-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

Compound 44. 6-Chloro-5-(3-fluoro-4-hydroxy-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 45. 6-Chloro-5-[5-(1-hydroxymethyl-cyclopropyl)-thiophen-2-yl]-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

5 Compound 46. 6-Chloro-3-[1-(2-fluoro-phenyl)-1-hydroxy-methylidene]-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-1,3-dihydro-indol-2-one

Compound 47. 6-Chloro-3-[1-(2-fluoro-phenyl)-1-hydroxy-methylidene]-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-1,3-dihydro-indol-2-one, sodium salt

10 Compound 48. 6-Chloro-5-[4-(3,6-dihydro-2H-pyran-4-yl)-phenyl]-3-[1-hydroxy-1-(3-methyl-isothiazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 49. 6-Chloro-5-[4-(1-hydroxymethyl-cyclobutyl)-phenyl]-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 50. 6-Chloro-3-[1-hydroxy-1-(3-methoxy-phenyl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

15 Compound 51. 6-Chloro-5-(2'-hydroxy-3'-methoxy-biphenyl-4-yl)-3-[1-hydroxy-1-(2-methyl-thiazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 52. 6-Chloro-5-[4-(3,6-dihydro-2H-pyran-4-yl)-phenyl]-3-[1-(3-fluoro-phenyl)-1-hydroxy-methylidene]-1,3-dihydro-indol-2-one

20 Compound 53. 6-Chloro-3-[1-hydroxy-1-(1-methyl-1H-pyrazol-3-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

Compound 54. 6-Chloro-3-[1-hydroxy-1-(3-methoxy-isoxazol-5-yl)-methylidene]-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-1,3-dihydro-indol-2-one

Compound 55. 6-Chloro-5-(3-fluoro-4-methoxy-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

25 Compound 56. 6-Chloro-5-(4-fluoro-2-hydroxy-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 57. 6-Chloro-3-[1-hydroxy-1-(2-methyl-thiazol-4-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

30 Compound 58. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-(4-trifluoromethoxy-phenyl)-1,3-dihydro-indol-2-one

Compound 59. 6-Chloro-3-[1-hydroxy-1-isoxazol-5-yl-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

Compound 60. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-4-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

35 Compound 61. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-[4-(tetrahydro-pyran-4-yl)-phenyl]-1,3-dihydro-indol-2-one

Compound 62. 6-Chloro-3-[1-(5-cyclopropyl-isoxazol-3-yl)-1-hydroxy-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

Compound 63. 6-Chloro-5-(4-chloro-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

5 Compound 64. 6-Chloro-5-(4-ethyl-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 65. 6-Chloro-5-(4-furan-2-yl-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

10 Compound 66. 6-Chloro-5-(4-ethoxy-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 67. 6-Chloro-5-[4-(3,6-dihydro-2H-pyran-4-yl)-phenyl]-3-[1-hydroxy-1-(3-methoxy-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 68. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-[4-(tetrahydro-furan-2-yl)-phenyl]-1,3-dihydro-indol-2-one.

15 Compound 69. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-[4-(3-piperazin-1-yl-propoxy)-phenyl]-1,3-dihydro-indol-2-one, hydrochloride

Compound 70. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-{4-[3-(4-methyl-piperazin-1-yl)-propoxy]-phenyl}-1,3-dihydro-indol-2-one, hydrochloride

20 Compound 71. 6-Fluoro-5-(2'-hydroxy-3'-methoxy-biphenyl-4-yl)-3-[1-hydroxy-1-(3-methoxy-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 72. 6-Fluoro-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 73. 3-[1-(3-Bromo-isoxazol-5-yl)-1-hydroxy-methylidene]-6-chloro-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-1,3-dihydro-indol-2-one

25 Compound 74. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1,3-dihydro-indol-2-one, hydrochloride

Compound 75. 6-Chloro-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-3-[1-hydroxy-1-(2-methyl-thiazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

30 Compound 76. 3-[1-(3-tert-Butyl-isoxazol-5-yl)-1-hydroxy-methylidene]-6-chloro-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-1,3-dihydro-indol-2-one

Compound 77. 6-Chloro-3-[1-(3-fluoro-4-methoxy-phenyl)-1-hydroxy-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

Compound 78. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-[4-(1-methyl-piperidin-4-yl)-phenyl]-1,3-dihydro-indol-2-one, hydrochloride

35 Compound 79. 6-chloro-3-[hydroxy-[3-(2-methoxyethoxy)isoxazol-5-yl]methylene]-5-[4-(2-hydroxy-3-methoxy-phenyl)phenyl]indolin-2-one

Compound 80. 6-chloro-5-[4-[1-(chloromethyl)-1,2-dihydroxy-ethyl]phenyl]-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]indolin-2-one

Compound 81. 6-chloro-5-(4-hydroxy-3-methoxy-phenyl)-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]indolin-2-one

5 Compound 82. 6-chloro-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]-5-[4-(2-morpholinoethoxy)phenyl]indolin-2-one hydrochloride

Compound 83. 4,6-difluoro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

10 Compound 84. 6-chloro-3-[(3-fluoro-4-methoxy-phenyl)-hydroxy-methylene]-5-[4-(2-hydroxy-3-methoxy-phenyl)phenyl]indolin-2-one

Compound 85. 6-chloro-5-[2-fluoro-4-[1-(hydroxymethyl)cyclopropyl]phenyl]-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]indolin-2-one

Compound 86. 6-chloro-3-[(3-cyclohexylisoxazol-5-yl)-hydroxy-methylene]-5-(4-morpholinophenyl)indolin-2-one

15 Compound 87. 6-chloro-3-[(3-cyclopropylisoxazol-5-yl)-hydroxy-methylene]-5-(4-morpholinophenyl)indolin-2-one

Compound 88. 6-chloro-3-[(3-fluoro-4-methoxy-phenyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

20 Compound 89. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(4-hydroxytetrahydropyran-4-yl)phenyl]indolin-2-one

Compound 90. 6-chloro-5-[4-(2-hydroxy-3-methoxy-phenyl)phenyl]-3-[hydroxy-[3-(2-morpholinoethoxy)isoxazol-5-yl]methylene]indolin-2-one

Compound 91. 6-chloro-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]-5-[4-(3-hydroxypropoxy)phenyl]indolin-2-one

25 Compound 92. 4,6-difluoro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(2-hydroxy-3-methoxy-phenyl)phenyl]indolin-2-one

Compound 93. 6-chloro-3-[hydroxy-[3-(4-methylpiperazin-1-yl)phenyl]methylene]-5-(4-morpholinophenyl)indolin-2-one hydrochloride

30 Compound 94. 6-chloro-3-[hydroxy-(3-morpholinophenyl)methylene]-5-(4-morpholinophenyl)indolin-2-one

Compound 95. 6-chloro-3-[[3-fluoro-4-(trifluoromethoxy)phenyl]-hydroxy-methylene]-5-(4-morpholinophenyl)indolin-2-one

Compound 96. 6-chloro-5-[3-fluoro-4-[1-(hydroxymethyl)cyclopropyl]phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

35 Compound 97. 6-chloro-3-[(3-chloro-5-fluoro-4-methoxy-phenyl)-hydroxy-methylene]-5-(4-morpholinophenyl)indolin-2-one

Compound 98. 6-chloro-3-[(2,3-difluoro-4-methoxy-phenyl)-hydroxy-methylene]-5-(4-morpholinophenyl)indolin-2-one

Compound 99. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(3-morpholinopropoxy)phenyl]indolin-2-one

5 Compound 100. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(3-pyridylmethoxy)phenyl]indolin-2-one

Compound 101. 6-chloro-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]-5-[4-(pyrimidin-2-ylmethoxy)phenyl]indolin-2-one

10 Compound 102. 6-chloro-3-[hydroxy-(3-hydroxyisoxazol-5-yl)methylene]-5-(4-morpholinophenyl)indolin-2-one

Compound 103. 6-chloro-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]-5-[4-(2-methoxyethoxy)phenyl]indolin-2-one

Compound 104. N-[2-[4-[6-chloro-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]-2-oxo-indolin-5-yl]phenoxy]ethyl]acetamide

15 Compound 105. 6-chloro-3-[(3-ethoxyisoxazol-5-yl)-hydroxy-methylene]-5-[4-(2-hydroxy-3-methoxy-phenyl)phenyl]indolin-2-one

Compound 106. 6-chloro-3-[(3-cyclopropylisoxazol-5-yl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

20 Compound 107. 5-[-[6-chloro-5-(4-morpholinophenyl)-2-oxo-indolin-3-ylidene]-hydroxy-methyl]-4-methyl-3H-thiazol-2-one

Compound 108. 6-chloro-3-[(2,5-difluoro-4-methoxy-phenyl)-hydroxy-methylene]-5-(4-morpholinophenyl)indolin-2-one

Compound 109. 6-chloro-3-[hydroxy-(3-isopropoxyisoxazol-5-yl)methylene]-5-[4-(2-hydroxy-3-methoxy-phenyl)phenyl]indolin-2-one

25 Compound 110. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(1-methoxycyclobutyl)phenyl]indolin-2-one

Compound 111. 6-chloro-5-[2-fluoro-4-[1-(hydroxymethyl)cyclopropyl]phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

30 Compound 112. 3-[(3-tert-butylisoxazol-5-yl)-hydroxy-methylene]6-chloro-5-(4-morpholinophenyl)indolin-2-one

Compound 113. 6-chloro-3-[(3-cyclopropylisoxazol-5-yl)-hydroxy-methylene]-5-[2-fluoro-4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

Compound 114. 6-chloro-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]-3-[hydroxy(2-thienyl)methylene]indolin-2-one

35 Compound 115. 6-chloro-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]-5-[4-(oxetan-2-ylmethoxy)phenyl]indolin-2-one

Compound 116. 6-chloro-3-[hydroxy-(6-methoxy-3-pyridyl)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one hydrochloride

Compound 117. 6-chloro-3-[(3-cyclopropylisoxazol-5-yl)-hydroxy-methylene]-5-[4-(2-hydroxy-3-methoxy-phenyl)phenyl]indolin-2-one

5 Compound 118. 6-fluoro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

Compound 119. 3-[(3-cyclopropylisoxazol-5-yl)-hydroxy-methylene]6-fluoro-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

10 Compound 120. 3-[(3-cyclopropylisoxazol-5-yl)-hydroxy-methylene]-4,6-difluoro-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

Compound 121. 6-chloro-5-[4-[2-hydroxy-1-(hydroxymethyl)ethyl]phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

Compound 122. 6-chloro-5-[4-(1,2-dihydroxyethyl)phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

15 Compound 123. 6-chloro-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]-3-[hydroxy-(5-methyl-2-thienyl)methylene]indolin-2-one

Compound 124. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(1-methyl-4-piperidyl)oxy]phenyl]indolin-2-one hydrochloride

20 Compound 125. 6-fluoro-3-[(3-fluoro-4-methoxy-phenyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

Compound 126. 6-chloro-3-[2-furyl(hydroxy)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

Compound 127. 6-chloro-5-(4-dimethylaminophenyl)-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

25 Compound 128. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-(4-tetrahydropyran-4-yloxyphenyl)indolin-2-one

Compound 129. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(3-hydroxypropoxy)phenyl]indolin-2-one

30 Compound 130. 6-chloro-3-[(5-chloro-2-thienyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

Compound 131. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(3-methoxypropoxy)phenyl]indolin-2-one

Compound 132. 6-chloro-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]-5-[4-(oxetan-3-ylmethoxy)phenyl]indolin-2-one

35 Compound 133. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(1-methylpyrrolidin-3-yl)phenyl]indolin-2-one hydrochloride

Compound 134. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-(4-pyrrolidin-3-ylphenyl)indolin-2-one hydrochloride

Compound 135. 6-chloro-5-[4-(3-hydroxycyclobutyl)phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

5 Compound 136. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(thiazol-5-ylmethoxy)phenyl]indolin-2-one

Compound 137. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-(4-pyrrolidin-1-ylphenyl)indolin-2-one

10 Compound 138. 6-chloro-3-[(2,3-difluorophenyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

Compound 139. 6-chloro-5-[4-[(3-hydroxycyclobutyl)methoxy]phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

Compound 140. 6-chloro-3-[hydroxy-(5-methoxy-2-pyridyl)methylene]-5-(4-morpholinophenyl)indolin-2-one

15 Compound 141. 6-chloro-3-[(2,4-difluorophenyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

Compound 142. 6-chloro-3-[(5-fluoro-3-pyridyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

20 Compound 143. 6-chloro-3-[(3,4-difluorophenyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

Compound 144. 6-chloro-3-[(3,5-difluorophenyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

Compound 145. 6-chloro-5-[2-(dimethylamino)pyrimidin-5-yl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

25 Compound 146. 6-chloro-5-[6-(dimethylamino)-3-pyridyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

Compound 147. 6-chloro-5-[4-(dimethylamino)-3-fluoro-phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

30 Compound 148. 6-chloro-5-[4-(dimethylamino)-2-fluoro-phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

Compound 149. 6-chloro-5-(3-fluoro-4-morpholino-phenyl)-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

Compound 150. 6-chloro-3-[(3,5-difluorophenyl)-hydroxy-methylene]-5-[4-(1-methylpyrrolidin-3-yl)phenyl]indolin-2-one hydrochloride

35 Compound 151. 6-chloro-3-[hydroxy-(6-methoxy-3-pyridyl)methylene]-5-(4-morpholinophenyl)indolin-2-one

Compound 152. 6-chloro-5-[4-(4-hydroxycyclohexoxy)phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

Compound 153. 6-chloro-5-[4-[cyclopropyl(methyl)amino]phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

5 Compound 154. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-(1-methylindol-5-yl)indolin-2-one

Compound 155. 6-chloro-3-[(2,4-difluorophenyl)-hydroxy-methylene]-5-[4-(3-hydroxycyclobutyl)phenyl]indolin-2-one

10 Compound 156. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(3-hydroxypyrrolidin-1-yl)phenyl]indolin-2-one

Compound 157. 6-chloro-3-[furo[2,3-b]pyridin-2-yl(hydroxy)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

Compound 158. 6-chloro-3-[hydroxy-(2-methoxy-4-pyridyl)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

15 Compound 159. 6-chloro-3-[(2,5-difluoro-4-methoxy-phenyl)-hydroxy-methylene]-5-[4-(3-hydroxycyclobutyl)phenyl]indolin-2-one

Compound 160. 6-chloro-3-[(3-fluoro-4-pyridyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

20 Compound 161. 6-chloro-3-[(3,5-difluorophenyl)-hydroxy-methylene]-5-[4-(3-hydroxycyclobutyl)phenyl]indolin-2-one

Compound 162. 5-[4-(azetidin-1-yl)phenyl]6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

Compound 163. 6-chloro-3-[(2,4-dimethoxyphenyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

25 Compound 164. 3-[(3-tert-butylisoxazol-5-yl)-hydroxy-methylene]6-chloro-5-[4-(3-hydroxycyclobutyl)phenyl]indolin-2-one

Compound 165. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(3-methoxycyclobutyl)phenyl]indolin-2-one

30 Compound 166. 6-chloro-5-[4-(3-hydroxycyclobutyl)phenyl]-3-[hydroxy-(3-isopropoxyisoxazol-5-yl)methylene]indolin-2-one

Compound 167. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl]phenyl]indolin-2-one hydrochloride

Compound 168. 3-[benzofuran-2-yl(hydroxy)methylene]6-chloro-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

35 Compound 169. 6-chloro-3-[furo[3,2-b]pyridin-2-yl(hydroxy)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

Compound 170. 6-chloro-3-[(5-chlorobenzofuran-2-yl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

Compound 171. 6-chloro-3-[(2-fluorophenyl)-hydroxy-methylene]-5-[4-(3-hydroxycyclobutyl)phenyl]indolin-2-one

5 Compound 173. 6-chloro-5-[4-[3-(dimethylamino)propoxy]phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

Compound 174. 6-chloro-3-[(3-cyclopropylisoxazol-5-yl)-hydroxy-methylene]-5-[4-(3-hydroxycyclobutyl)phenyl]indolin-2-one

10 Compound 175. 6-chloro-3-[hydroxy-(3-methoxy-4-pyridyl)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

Compound 176. 6-chloro-5-[4-(2,2-dimethyl-1,3-dioxan-5-yl)phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

Compound 177. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(6-oxa-2-azaspiro[3.3]heptan-2-yl)phenyl]indolin-2-one

15 Compound 178. 6-chloro-3-[hydroxy-(2-methoxy-3-pyridyl)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

Compound 179. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[3-hydroxypropyl(methyl)amino]phenyl]indolin-2-one

20 Compound 180. 6-chloro-5-[4-(3-fluoroazetidin-1-yl)phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

Compound 181. 6-chloro-5-[4-(3,3-difluoroazetidin-1-yl)phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

Compound 182. 6-chloro-3-[furo[3,2-b]pyridin-2-yl(hydroxy)methylene]-5-[4-(3-hydroxypyrrolidin-1-yl)phenyl]indolin-2-one

25 Compound 183. 6-chloro-3-[hydroxy-(6-methoxy-2-pyridyl)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

Compound 184. 6-chloro-3-[hydroxy-(3-methoxy-2-pyridyl)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

30 Compound 185. 6-chloro-3-[(3-ethoxyisoxazol-5-yl)-hydroxy-methylene]-5-[4-(3-hydroxycyclobutyl)phenyl]indolin-2-one

Compound 186. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(1-methylazetidin-3-yl)phenyl]indolin-2-one

Compound 187. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(3R)-3-hydroxypyrrolidin-1-yl]phenyl]indolin-2-one

35 Compound 188. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(3S)-3-hydroxypyrrolidin-1-yl]phenyl]indolin-2-one

Compound 189. 6-chloro-3-[(2-fluorophenyl)-hydroxy-methylene]-5-[4-(3-hydroxypyrrolidin-1-yl)phenyl]indolin-2-one

Compound 190. 6-chloro-3-[[2-(dimethylamino)pyrimidin-5-yl]-hydroxy-methylene]-5-[4-(3-hydroxypyrrolidin-1-yl)phenyl]indolin-2-one

5 Compound 191. 6-chloro-5-[4-(3,3-dimethylazetidin-1-yl)phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

Compound 192. 6-chloro-3-[(3-cyclopropylisoxazol-5-yl)-hydroxy-methylene]-5-[4-(3-hydroxypyrrolidin-1-yl)phenyl]indolin-2-one

10 Compound 193. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[3-(hydroxymethyl)azetidin-1-yl]phenyl]indolin-2-one

Compound 194. 6-chloro-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]-3-[hydroxy(thieno[2,3-b]pyridin-2-yl)methylene]indolin-2-one hydrochloride

Compound 195. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(3S,4S)-3-hydroxy-4-methoxy-pyrrolidin-1-yl]phenyl]indolin-2-one

15 Compound 196. 6-chloro-5-[4-[1-(2-chloroethyl)-2-methyl-prop-1-enyl]phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

Compound 197. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(4-hydroxy-1-piperidyl)phenyl]indolin-2-one

20 Compound 198. 6-chloro-5-[4-[(3R)-3-fluoropyrrolidin-1-yl]phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

Compound 199. 6-chloro-3-[hydroxy-(1-methylindol-5-yl)methylene]-5-[4-(3-hydroxypyrrolidin-1-yl)phenyl]indolin-2-one

Compound 200. 6-chloro-5-(2,6-difluoro-4-morpholino-phenyl)-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one

25 Compound 201. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[2-(hydroxymethyl)azetidin-1-yl]phenyl]indolin-2-one

Compound 202. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]phenyl]indolin-2-one

30 Compound 203. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]phenyl]indolin-2-one

Compound 204. 4-[4-[6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-2-oxo-indolin-5-yl]phenyl]cyclohex-3-ene-1-carboxylic acid

Compound 205. trans-6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(3S,4R)-4-hydroxytetrahydrofuran-3-yl]phenyl]indolin-2-one

35 Compound 206. cis-6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(2S,4S)-4-hydroxytetrahydrofuran-2-yl]phenyl]indolin-2-one

Compound 207. trans-6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(2R,4S)-4-hydroxytetrahydrofuran-2-yl]phenyl]indolin-2-one

Compound 208. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(4-hydroxy-4-methyl-1-piperidyl)phenyl]indolin-2-one

5 Compound 209. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[2-(hydroxymethyl)morpholin-4-yl]phenyl]indolin-2-one

Compound 210. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[3-(hydroxymethyl)morpholin-4-yl]phenyl]indolin-2-one

10 in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

It should be noted that the above compounds were named according to the IUPAC nomenclature by means of the Autonom software.

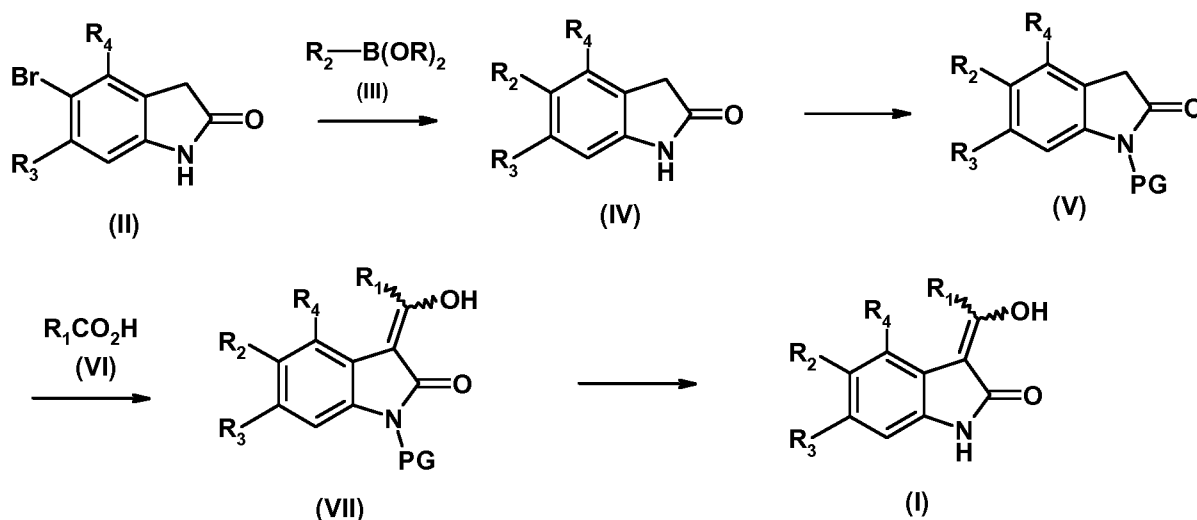
15 In what follows, we understand by protective group (PG), a group which allows, on one hand to protect a reactive function such as a hydroxy or an amine during a synthesis and, on the other hand to regenerate the intact reactive function at the end of the synthesis. Examples of protective groups as well as methods of protection and of deprotection are given in " Protective Groups in Organic Synthesis ", Green and al., 4rd Edition (Publishing) (John Wiley and Sons, Inc., New York).

20 In schemes 1 to 6, the starting materials and reagents, when method for preparing them is not described, are commercially available or are readily prepared using methods well-known to those skilled in the art or described in the literature.

25 According to another of its aspects, a subject of the invention is also the compounds of formulae (VII), (IX), (XI), (XII) and (XIV). These compounds are useful as intermediates in the synthesis of the compounds of formula (I).

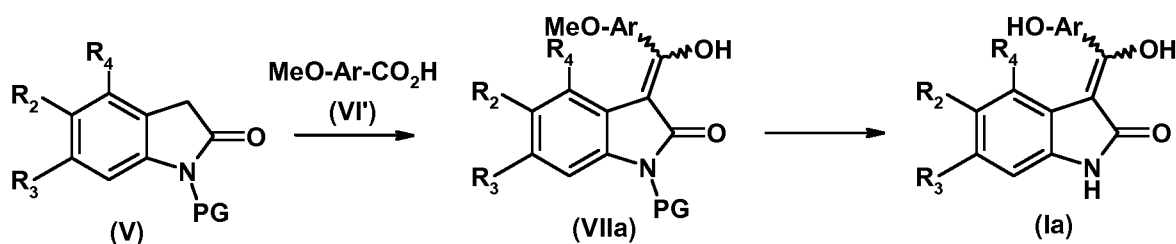
Schemes 1 through 6 outline the general procedures useful for the preparation of compounds of the present invention.

30 In accordance with the invention, oxindole derivatives of general formula (I), wherein R₁, R₂, R₃ and R₄ are as defined above, can be synthesized as shown in Scheme 1.



Scheme1

5-bromo oxindoles of general formula (II), wherein R_3 and R_4 are as defined in general formula (I), and boron derivatives of general formula (III), wherein R_2 is as defined in general formula (I) and $B(OR)_2$ is a boronic acid or a boronate, can be coupled using
 5 palladium catalysts such as $PdppfCl_2$ or tetrakis(triphenylphosphine) palladium at temperatures ranging from 25°C to 130°C with conventional heat or microwave heat for 30 minutes to 24 hours to provide compounds of general formula (IV). Compounds of general formula (IV) can be treated with protecting reagents such as acetyl chloride, Boc_2O or the like to provide oxindoles of general formula (V). Oxindoles of general formula (V) can be acylated with a variety of carboxylic acid derivatives of formula (VI) (wherein R_1 is as defined in the general formula (I)). The reaction can be carried out in solvents like dimethylformamide in the presence of an activating agent such as TBTU to provide compounds of general formula (VII). Removal of the protective group can be
 10 performed with a variety of acidic or basic reagents such as hydrogen chloride in dioxane or other solvents, trifluoroacetic acid, sodium hydroxide in an alcohol like ethanol or methanol, to provide compounds of general formula (I).

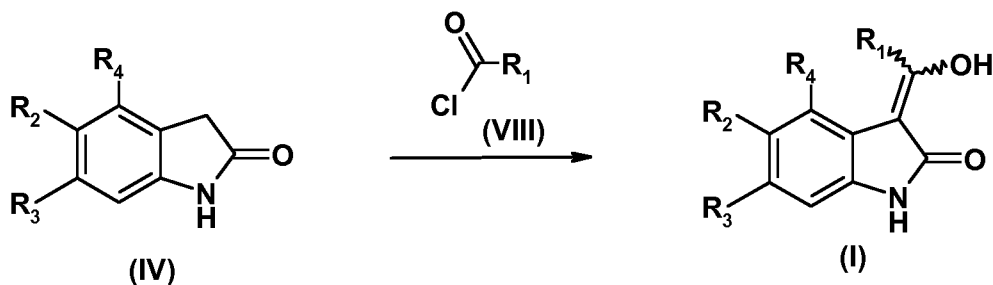


Scheme 2

20

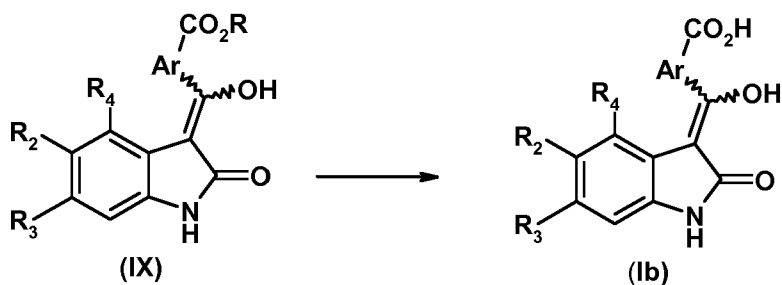
Oxindoles of general formula (Ia) corresponding to the compounds of general formula (I), wherein R_2 , R_3 and R_4 are as defined in the general formula (I) and R_1 represents

an aryl group substituted with a hydroxy group (HO-Ar), can be prepared as shown in Scheme 2 by both deprotection and demethylation of a compound of general formula (VIIa), wherein R_2 , R_3 and R_4 are as defined in the general formula (I) and R_1 represents an aryl group substituted with a methoxy group (MeO-Ar), with an acidic reagent such as BBr_3 . Compounds of formula (VIIa) can be prepared according to Scheme 1.



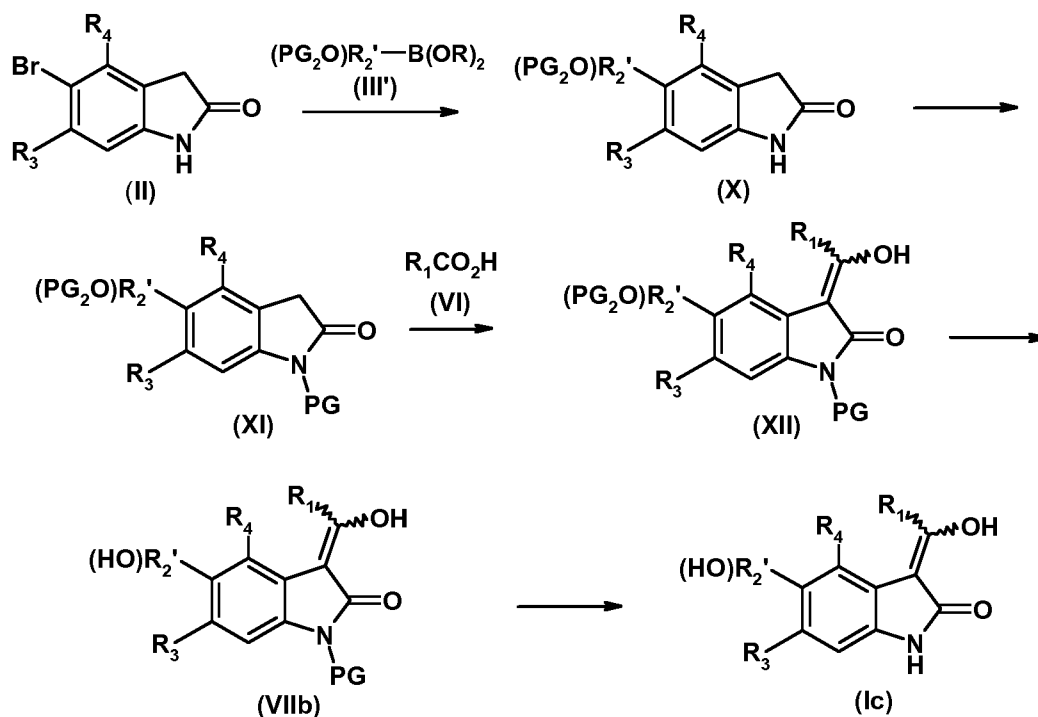
Scheme 3

Oxindoles of general formula (I), wherein R_1 , R_2 , R_3 and R_4 are as defined above can also be synthesized according to Scheme 3 by reaction of a compound (IV) with an acyl halide such as an acyl chloride of general formula (VIII), wherein R_1 is as defined in general formula (I), by heating in solvents like dioxane in the presence of a basic reagent like calcium hydroxide.



Scheme 4

Oxindoles of general formula (Ib) corresponding to compounds of general formula (I), wherein R_1 represents an aryl group substituted with a carboxylic group ($Ar-CO_2H$), R_2 , R_3 and R_4 are as defined in general formula (I) can be prepared according to Scheme 4 by treatment of a compound of general formula (IX), wherein R_2 , R_3 and R_4 are as defined in the general formula (I) and R is an alkyl group such as a methyl or an ethyl group, with a basic reagent such as sodium hydroxide or lithium hydroxide in an alcohol solvent like methanol or ethanol. Compounds of general formula (IX) can be prepared as described in Schemes 1 or 3.

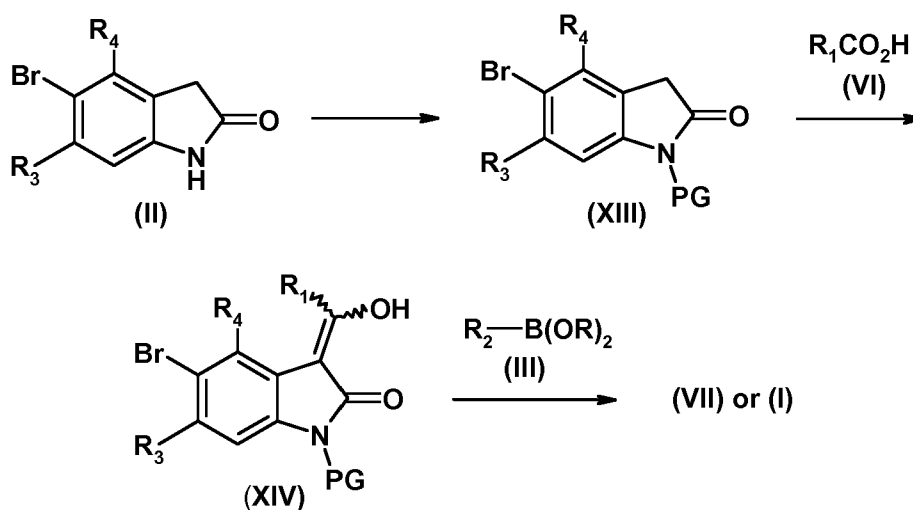


Scheme 5

Oxindoles of general formula (Ic) corresponding to compounds of general formula (I),
 5 wherein R_2 represents a group R_2' substituted with at least a hydroxy group [i.e. $(OH)R_2'$], wherein R_2' is an aryl group substituted with an aryl group, R_1 , R_3 and R_4 are as defined in general formula (I) can be prepared as described in Scheme 5. 5-bromo-oxindoles of general formula (II), wherein R_3 and R_4 are as defined in general formula (I), and boron derivatives of general formula (III') can be coupled using palladium catalysts, such as $Pd(dppf)Cl_2$ or tetrakis(triphenylphosphine) palladium at temperatures
 10 ranging from 25°C to 130°C with conventional heat or microwave heat for 30 minutes to 24 hours to provide compounds of general formula (X). In compounds of formula (III'), R_2' represents an aryl group substituted with an aryl group substituted with at least an hydroxy group, the said hydroxy group being protected with a PG_2 group, such as a silyl ether and $B(OR)_2$ being a boronic acid or boronate ester.
 15

Compounds of general formula (X) can be treated with protecting reagents such as acetyl chloride, Boc_2O or the like to provide oxindoles of general formula (XI). Oxindoles of general formula (XI) can be acylated with a variety of carboxylic acid derivatives (VI), wherein R_1 is as defined in the general formula (I). The reaction can be
 20 carried out in solvents like DMF in the presence of an activating agent such as TBTU to

provide compounds of general formula (XII). Removal of the protective group PG₂ can be performed with different reagents, for example if the protective group is a silyl moiety, acidic reagents or a fluoride reagent can be used to provide compounds of general formula (VIIb). Subsequent deprotection of the oxindole protecting group can be performed with a variety of acidic or basic reagents such as hydrogen chloride in dioxane or other solvents, trifluoroacetic acid, sodium hydroxyde in an alcohol solvent like ethanol or methanol to provide compounds of general formula (Ic).



Scheme 6

Intermediates (VII), wherein R_1 , R_2 , R_3 and R_4 are as defined above can also be synthesized according to Scheme 6. Compounds of general formula (II) can be treated with protecting reagents such as acetyl chloride, Boc_2O or the like to provide oxindoles of general formula (XIII). Intermediates (XIII) can be acylated with a variety of carboxylic acids derivatives (VI) (wherein R_1 is as defined in the general formula I). The reaction can be carried out in solvents like dimethylformamide in the presence of coupling reagents like TBTU to provide compounds of general formula (XIV). Intermediates (XIV) and boron derivatives of general formula (III), wherein R_2 is as defined in general formula I and $B(OR)_2$ is a boronic acid or a boronate, can be coupled using palladium catalysts such as $Pd(dppf)Cl_2$ or tetrakis(triphenylphosphine) palladium, at temperatures ranging from 25°C to 130°C with conventional heat or microwave heat for 30 minutes to 24 hours to provide compounds of general formula (VII) or directly compounds of general formula (I) depending on coupling conditions. Deprotection of intermediate (VII) is described in Scheme 1.

The following examples describe the preparation of some compounds corresponding to the invention. These examples are not restrictive and are not only illustrating the present invention. The numbers of the exemplified compounds send back to those given in the tables which illustrate the chemical structures and the physical properties of some compounds according to the invention.

Abbreviations and units used in the examples that follow are :

ACN : acetonitrile

°C : Celsius degree

10 DTT : dithiothreitol

DMF : dimethylformamide

DMSO : dimethylsulfoxide

HCOOH : formic acid

TFA : trifluoroacetic acid

15 Eq : equivalent

ESI : electrospray ionization

g : gram

NMR : nuclear magnetic resonance

h : hour

20 min : minute

HPLC : high performance liquid chromatography

Hz : Hertz

M : mass

MHz : megahertz

25 mL : millilitre

mmol : millimole

PddppfCl₂ : [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane

N : normal

30 M : molar

nM : nanomolar

ppm : parts per millions

THF : tetrahydrofuran

t_R : retention time

35 UPLC : ultra-pressure liquid chromatography

UV : ultra-violet

% : percentage

RT : room temperature

DMAP : 4-dimethylaminopyridine

5 TBTU : O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate

Boc₂O : di-tert-butyl dicarbonate

AcOEt : ethyl acetate

10 Proton nuclear magnetic resonance spectra (¹H NMR) were recorded at 400MHz in DMSO-d₆, using DMSO-d₅ signal as reference. Chemical displacement δ were expressed in ppm. The observed signals were expressed as following: s = singlet ; d = doublet ; t = triplet ; m = massif or broad singlet.

15 In the table of examples the peak (M+H)⁺ identified by mass spectrometry as well as the retention time (t_R) are indicated.

Compounds are analyzed by UPLC from Waters equipped with UV detector (220nm) coupled with a mass spectrometer SQD2 from Waters using electrospray ionization (Method A). The analytical method is detailed below.

20 Column Acquity BEH C18 (50 x 2.1 mm; 1.7 μm) or equivalent (Acquity Cortex C18+, 50x2.1mm; 1.6μM)

Flow : 1,0mL/min – T° = 45°C – injection 1 μL.

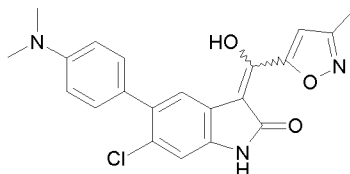
Gradient from 2% to 100% ACN with 0.1% HCOOH in water with 0.1% HCOOH in 2.6 min.

25

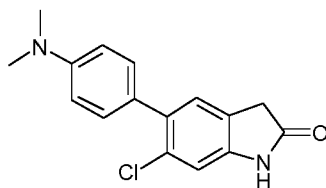
The intermediates are preferentially analysed using UPLC / SQD2 (ESI) apparatus from Waters equipped with a UV detector (220 nm) and a column Acquity UPLC BEH C18 (50 x 2.1 mm; 1.7μm) eluted with a gradient of 5% to 99% ACN with 0.1% TFA in water with 0.1% TFA in 2.5 min (method B).

30

Example 1 : 6-Chloro-5-(4-dimethylamino-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl) methylidene]-1,3-dihydro-indol-2-one



Step 1.1 : 6-Chloro-5-(4-dimethylamino-phenyl)-2-oxo-2,3-dihydro-indole



5

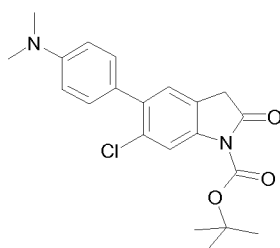
To a suspension of N,N-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.1 g, 4.45 mmol) and 5-bromo-6-chloroindolin-2-one (0.8 g, 3.25 mmol) in toluene (6 mL) and ethanol (3 mL), aqueous Na₂CO₃ 2N (3.25 ml, 6.49 mmol) was added in one portion and the reaction mixture was degassed with nitrogen during 10 minutes.

10 PdCl₂(dppf). CH₂Cl₂ (0.13 g, 0.16 mmol) was added and the resulting mixture was heated for 1h at 130°C in a microwave oven. The reaction mixture was diluted with AcOEt (65 mL) and water (65 mL) and the precipitate was filtered and rinsed with AcOEt (35 mL) and THF (5 mL). Organic layer was separated and washed with water (2 x 20 mL) and concentrated under reduced pressure to give a brown paste. The

15 remaining crude product was purified by flash chromatography using a gradient CH₂Cl₂/MeOH/NH₃ [100/0/0 to 98/2/0.2]. The resulting orange powder was triturated with ACN, filtered, rinsed with Et₂O and dried under vacuum (P₂O₅) to obtain 6-chloro-5-(4-dimethylamino-phenyl)-2-oxo-2,3-dihydro-indole (0.263 g, 28% yield).

LCMS (method B) (M+H)⁺ = 287, t_R = 1.13 min.

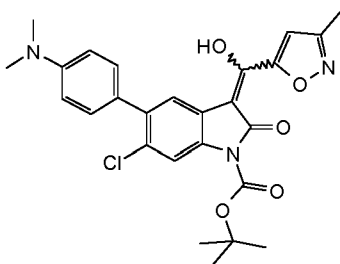
20 **Step 1.2 : 6-Chloro-5-(4-dimethylamino-phenyl)-2-oxo-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester**



To a suspension of 6-chloro-5-(4-(dimethylamino)phenyl)indolin-2-one (1.58 g, 5.51 mmol), triethylamine (0.77 mL, 5.51 mmol) in THF (75 mL) was added di-tert-butyl dicarbonate (1.50 g, 6.61 mmol) in one portion under nitrogen atmosphere and stirring was continued for 30 min at room temperature. DMAP (0.033 g, 0.28 mmol), THF (20 mL) and DMF (2 mL) were added. Stirring was continued for 3h at RT. The reaction mixture was diluted with CH₂Cl₂, washed with saturated aqueous NaHCO₃ and H₂O, dried over MgSO₄ and concentrated under vacuum. The residue was purified by flash chromatography using a gradient of ethyl acetate in heptane to provide 6-chloro-5-(4-dimethylamino-phenyl)-2-oxo-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester (1.1 g, 51 % yield).

LCMS (method B) (M+H)⁺ = 386, t_R = 2.01 min.

Step 1.3: 6-Chloro-5-(4-dimethylamino-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-2-oxo-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester



3-methylisoxazole-5-carboxylic acid (0.42 g, 3.13 mmol), tert-butyl 6-chloro-5-(4-(dimethylamino)phenyl)-2-oxoindoline-1-carboxylate (1.1 g, 2.84 mmol), TBTU, (1.02 g, 3.13 mmol) and triethylamine (1.98 mL, 14.22 mmol) were subsequently introduced into DMF (15 mL) and stirred at room temperature overnight. The reaction mixture was diluted with AcOEt (30 mL), washed with brine, dried over MgSO₄, concentrated under reduced pressure and further purified by flash chromatography using a gradient of methanol in dichloromethane to obtain a brownish foam which was precipitated in methanol (5 mL) to provide 6-chloro-5-(4-dimethylamino-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-2-oxo-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester (0.80 g, 56% yield) as a yellow solid.

LCMS (method B) (M+H)⁺ = 496, t_R = 2.20 min.

Step 1.4: 6-Chloro-5-(4-dimethylamino-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-2-oxo-2,3-dihydro-indole (example 1)

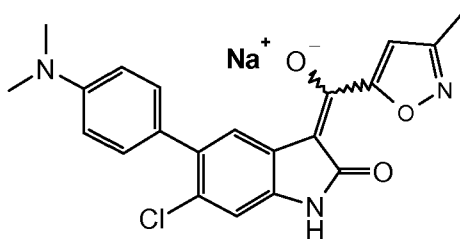
A solution of tert-butyl 6-chloro-5-(4-(dimethylamino)phenyl)-3-(hydroxy(3-methylisoxazol-5-yl)methylene)-2-oxoindoline-1-carboxylate (0.95 g, 1.91 mmol) in CH_2Cl_2 (10 mL) was cooled to 0°C and trifluoroacetic acid (1 mL) was added drop wise. The solution was stirred for 3h at room temperature and kept at 4°C overnight to
5 complete deprotection. The mixture was concentrated under vacuum without heating, diluted with AcOEt (100 mL) and poured into icecold saturated aqueous NaHCO_3 . The separated organic layer is washed with saturated aqueous NaHCO_3 and brine, dried over MgSO_4 , filtrated and concentrated under reduced pressure to obtain 0.3 g of a brown solid. The MgSO_4 -filtercake is solubilized in water, exposed for 3 min in an
10 ultrasonic bath at room temperature and filtrated to obtain further 0.4 g of a yellow solid. These two batches are suspended in water (100 mL) and acidified with an aqueous SO_2 solution ($\text{pH} = 2$), stirred for 20 min, filtered and rinsed thoroughly with water to provide after drying 6-chloro-5-(4-dimethylamino-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-2-oxo-2,3-dihydro-indole (0.7 g, 92% yield) as a
15 yellow solid.

LCMS (method A) $(\text{M}+\text{H})^+ = 396$, $t_R = 1.22$ min.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.34 (s, 3 H) 2.95 (s, 6 H) 6.80 (d, $J=8.78$ Hz, 2 H) 7.01 - 7.10 (m, 1 H) 7.24 (d, $J=8.53$ Hz, 3 H) 7.81 - 8.07 (m, 1 H) 11.03 - 11.60 (m, 1 H).

20

Example 2 : 6-Chloro-5-(4-dimethylamino-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-2-oxo-2,3-dihydro-indole, Na salt

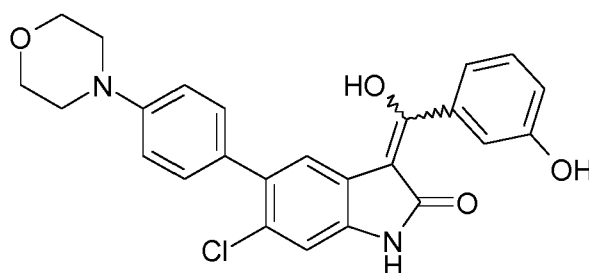


6-Chloro-5-(4-dimethylamino-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-
25 methylidene]-2-oxo-2,3-dihydro-indole (0.5 g, 1.26 mmol) was suspended in methanol (15 mL). 1M NaOH (1.26 mL, 1.26 mmol) are added rapidly and stirring is continued for 1 h. Concentration under vacuum without heating and drying under reduced pressure

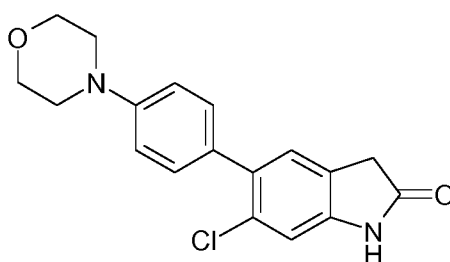
provided 6-chloro-5-(4-dimethylamino-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-2-oxo-2,3-dihydro-indole, Na salt (0.51 g) as an ochre-coloured solid.

LCMS (method A) (M+H)⁺ = 396 , t_R = 1.22 min.

5 **Example 3 : 6-Chloro-3-(hydroxy(3-hydroxyphenyl)methylene)-5-(4-morpholinophenyl)indolin-2-one**

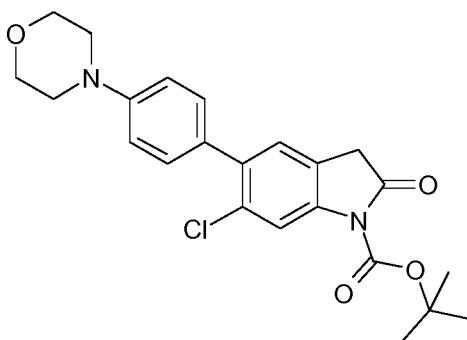


Step 3.1 : 6-chloro-5-(4-morpholinophenyl)indolin-2-one



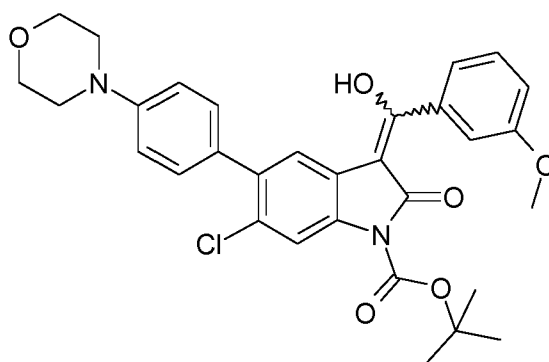
10 [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with
dichloromethane (0.13 g, 0.16 mmol) was added under nitrogen atmosphere to a
suspension of 5-bromo-6-chloroindolin-2-one (0.8 g, 3.25 mmol), 4-
morpholinophenylboronic acid (1.03 g, 4.87 mmol), aqueous Na₂CO₃ 2N (3.25 mL, 6.5
mmol) in ethanol (3 mL) and toluene (6 mL). This process is repeated ten times. The
15 resulting mixture was heated under microwave irradiation at 130°C for 1 hour. The
collected crude material was washed with water (200 mL) and ethyl acetate (100 mL).
The brown solid was filtrated off and washed with water and ethyl acetate. The
resulting solid was heated in acetonitrile (50 mL) under reflux, filtrated off and washed
with acetonitrile (10 mL). The brown solid was purified by flash chromatography using a
20 gradient of methanol in dichloromethane to yield 6-chloro-5-(4-
morpholinophenyl)indolin-2-one (4.64 g, 44% yield).

LCMS (method B) (M+H)⁺ = 329, t_R = 1.28 min.

Step 3.2 : tert-Butyl 6-chloro-5-(4-morpholinophenyl)-2-oxoindoline-1-carboxylate

To a solution of 6-chloro-5-(4-morpholinophenyl)indolin-2-one (3.3 g, 10.04 mmol) in tetrahydrofuran (100 ml) were added sodium bicarbonate (7.59 g, 90.33 mmol) and
5 Boc₂O (2.80 ml, 12.04 mmol). The resulting mixture was stirred under reflux for 4 hours. Ethyl acetate was added and the mixture was washed with water and a brine solution and then dried over magnesium sulfate. After concentration under vacuum, the resulting solid was washed with ethyl ether to yield tert-butyl 6-chloro-5-(4-morpholinophenyl)-2-oxoindoline-1-carboxylate (2.16 g, 50% yield) as an orange
10 powder.

LCMS (method B) (M+H)⁺ = 429, t_R = 1.92 min.

Step 3.3: tert-Butyl 6-chloro-3-(hydroxy(3-methoxyphenyl)methylene)-5-(4-morpholinophenyl)-2-oxoindoline-1-carboxylate

15 To a solution of 3-methoxybenzoic acid (0.11 g, 0.70 mmol), tert-butyl 6-chloro-5-(4-morpholinophenyl)-2-oxoindoline-1-carboxylate (0.30 g, 0.70 mmol) and triethylamine (0.49 mL, 3.50 mmol) in DMF (5 mL) was added TBTU (0.25 g, 0.77 mmol) at room temperature under nitrogen atmosphere. The resulting mixture is stirred for 4 hours. Ethyl acetate and water were added. The organic phase was dried over sodium sulfate
20 and concentrated under vacuum. The remaining crude product was purified by flash

chromatography using a gradient of methanol in dichloromethane. The resulting solid was washed with methanol to yield tert-butyl 6-chloro-3-(hydroxy(3-methoxyphenyl)methylene)-5-(4-morpholinophenyl)-2-oxoindoline-1-carboxylate (0.13 g, 33% yield).

5 LCMS (method B) (M+H)⁺ = 563, t_R = 2.39 min.

Step 3.4: 6-chloro-3-(hydroxy(3-hydroxyphenyl)methylene)-5-(4-morpholinophenyl)indolin-2-one (example 3)

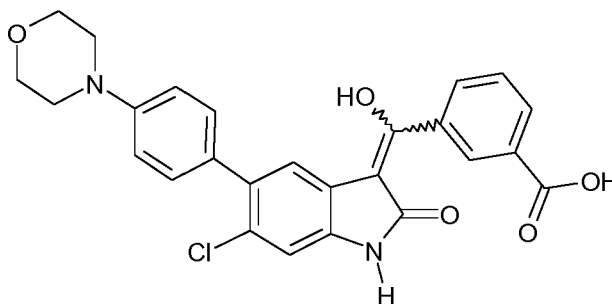
A mixture of tert-butyl 6-chloro-3-(hydroxy(3-methoxyphenyl)methylene)-5-(4-morpholinophenyl)-2-oxoindoline-1-carboxylate (0.049 mL, 0.087 mmol) in
 10 dichloromethane (2 mL) is cooled to 0°C. Boron tribromide (0.049 mL, 0.044 mmol) was added and the resulting mixture was stirred at room temperature for 2 hours. Additionnal boron tribromide (0.050 mL, 0.045 mmol) was added and the mixture was stirred for another hour. Ethyl acetate and water were added. The organic phase was dried over sodium sulfate and concentrated under vacuum. The resulting residue was
 15 cristallized in dichloromethane to yield 6-chloro-3-(hydroxy(3-hydroxyphenyl)methylene)-5-(4-morpholinophenyl)indolin-2-one (0.011 g, 28% yield).

LCMS (method A) (M+H)⁺ = 449, t_R 1.33 min.

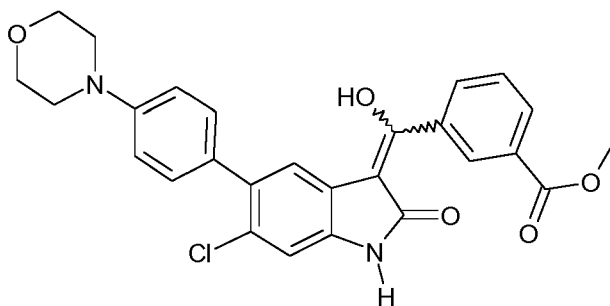
¹H NMR (400 MHz, DMSO-d₆) δ ppm 3.08 - 3.19 (m, 4 H) 3.70 - 3.81 (m, 4 H) 6.83 - 7.41 (m, 10 H) 9.79 - 9.91 (m, 1 H) 11.36 - 11.49 (m, 1 H)

20

Example 4 : {[6-Chloro-5-(4-morpholin-4-yl-phenyl)-2-oxo-1,2-dihydro-indolylidene]-hydroxy-methyl}-benzoic acid



Step 4.1: 3-[[6-Chloro-5-(4-morpholin-4-yl-phenyl)-2-oxo-1,2-dihydro-indolylidene]-hydroxy-methyl]-benzoic acid methyl ester
 25



Calcium hydroxyde (0.069 g, 0.6 mmol) was added to a solution of 6-chloro-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one (intermediate 3.1) (0.2 g, 0.6 mmol) in 1,4-dioxane. The resulting suspension was refluxed for 4 h, then cooled at room temperature before adding methyl 3-(chloroformyl)benzoate (0.124 g, 0.6 mmol). The mixture was heated under reflux for 4h, then methyl 3-(chloroformyl)benzoate (0.06 g, 0.3 mmol) was added. The mixture was additionally heated under reflux for 4h, and then concentrated under vacuum. Water and a solution of hydrochloric acid were added. The resulting solid was filtered off, and then washed with water, ethanol and pentane to yield 3-[[6-Chloro-5-(4-morpholin-4-yl-phenyl)-2-oxo-1,2-dihydro-indolylidene]-hydroxy-methyl]-benzoic acid methyl ester (0.1 g, 32% yield) which was used in the following reaction without further purification.

LCMS (method B) (M+H)⁺ = 491, t_R = 1.84 min.

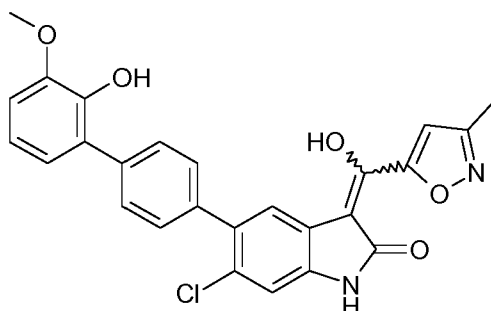
Step 4.2: -[[6-Chloro-5-(4-morpholin-4-yl-phenyl)-2-oxo-1,2-dihydro-indolylidene]-hydroxy-methyl]-benzoic acid (example 4).

Lithium hydroxide (0.01 g, 0.407 mmol) was added to a suspension of 3-[[6-chloro-5-(4-morpholin-4-yl-phenyl)-2-oxo-1,2-dihydro-indolylidene]-hydroxy-methyl]-benzoic acid methyl ester (0.1 g, 0.203 mmol) in water (2 mL) and methanol (2 mL). Tetrahydrofuran (3 mL) was added, and the resulting mixture was stirred for 20 h at room temperature. Lithium hydroxide (0.01 g, 0.407 mmol) was added, and the mixture was additionally stirred for 24 h, and then concentrated under vacuum. Water and a 6% aqueous solution of sulphur dioxide were added up to pH=1. The resulting solid was filtered off, and then washed with water to yield 3-[[6-chloro-5-(4-morpholin-4-yl-phenyl)-2-oxo-1,2-dihydro-indolylidene]-hydroxy-methyl]-benzoic acid (0.021 g, 22 % yield) as a yellow powder.

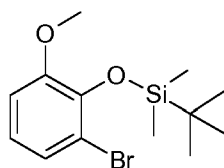
LCMS (method A) (M+H)⁺ = 477, t_R = 1.05 min.

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 2.98 - 3.23 (m, 4 H) 3.69 - 3.82 (m, 4 H) 6.80 - 7.39 (m, 6 H) 7.50 - 8.56 (m, 5 H) 11.27 - 11.67 (m, 1 H) 12.92 - 13.74 (m, 1 H)

Example 5 : 6-Chloro-5-(2'-hydroxy-3'-methoxy-biphenyl-4-yl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-meth--ylidene]-1,3-dihydro-indol-2-one



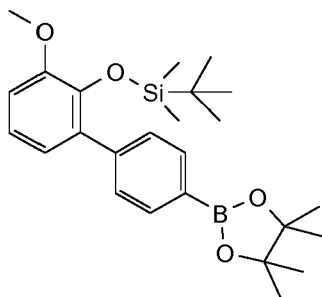
Step 5.1 : 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene



2-bromo-6-methoxyphenol (5 g, 24.6 mmol), tert-butyldimethylchlorosilane (4.08 g, 27.1 mmol) and imidazole (1.79 g, 26.4 mmol) were stirred under nitrogen at room temperature for 6 h in anhydrous CH₂Cl₂ (30 mL). To the white suspension were added CH₂Cl₂ (50mL) and the mixture was washed with HCl 1N (2 x 30 ml) and H₂O (30 mL). The aqueous phase was extracted with CH₂Cl₂ (30 mL), the combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure without heating to obtain 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (7.8 g, 99 % yield) as a colourless oil.

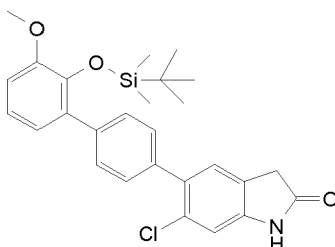
LCMS (method B) observed (M+H)⁺ = 296, t_R = 2.44 min.

Step 5.2 : 2-[2'-(tert-Butyl-dimethyl-silanyloxy)-3'-methoxy-biphenyl-4-yl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane



Into a 0.5 L three necked flask equipped with a reflux condenser, thermometer and a nitrogen inlet were subsequently introduced to a solvent mixture of dioxane (135 mL) and of H₂O (45 mL), 2-bromo-6-methoxy-phenoxy-tert-butyldimethylsilane (7.379 g, 23.3 mmol), 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (14.39 g, 41.9 mmol), 2,6-di-tert-butyl-4-methylphenol (5.12 g, 23.3 mmol), tricyclohexylphosphine (0.261 g, 0.93 mmol) and K₂CO₃ (9.64 g). This white suspension was degassed during 10 min with nitrogen, Pd₂(dba)₃ (0.43 g, 0.47 mmol) was added and the mixture was heated to reflux for 2 hours. Once cooled to room temperature the mixture was poured into water (200 mL), acidified to pH 1 with HCl 1N and of AcOEt (250 mL) were added. The organic layer was washed twice with water (200 mL), the aqueous layer extracted once with AcOEt (100 mL) and the combined organic layers were filtered, dried over MgSO₄ and concentrated under reduced pressure to give 11 g of a crude yellow oil which was further purified by flash chromatography using a gradient of CH₂Cl₂ in heptane to provide 2-[2'-(tert-Butyl-dimethyl-silanyloxy)-3'-methoxy-biphenyl-4-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.3 g, 62% yield) as a white solid. LCMS (method B) observed (M+H)⁺ = 454, t_R = 2.66 min.

Step 5.3 : 5-[2'-(tert-Butyl-dimethyl-silanyloxy)-3'-methoxy-biphenyl-4-yl]-6-chloro-1,3-dihydro-indol-2-one



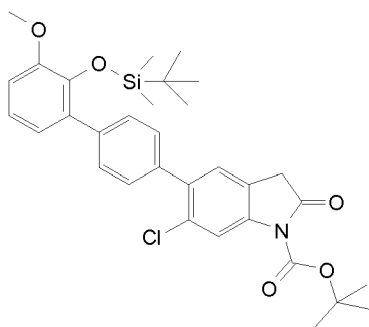
In a 25 mL microwave vial were introduced tert-butyl-((3-methoxy-4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-2-yl)oxy)dimethylsilane (2.14 g, 4.87 mmol), 5-bromo-6-chloroindolin-2-one (0.8 g, 3.25 mmol) in toluene (6 mL) and ethanol (3 mL) (brownish suspension). 2N aqueous Na₂CO₃ (3.25 mL, 6.49 mmol) was

added in one portion and the reaction mixture was degassed with nitrogen during 10 minutes. $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (0.133 g, 0.162 mmol) was added, the vial was closed and heated for 1h at 130°C in a microwave oven. The reaction mixture was diluted with 20mL AcOEt and 10mL of water. The precipitate was filtered. The filter cake was

- 5 washed with water, THF, acetonitrile, CH_2Cl_2 and methanol to obtain 0.66 g of a crude grey colored product. Final purification on silica gel column (gradient $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100/0 to 97.2/2.5 in 20 minutes) provided 5-[2'-(tert-Butyl-dimethyl-silanyloxy)-3'-methoxy-biphenyl-4-yl]-6-chloro-1,3-dihydro-indol-2-one (0.49 g, 32% yield) as a white solid.

10 LCMS (method B) $(\text{M}+\text{H}+\text{ACN})^+ = 521$, $(\text{M}+\text{H})^+ = 480$ (low intensity peak), $t_R = 2.34$ min.

Step 5.4 : 5-[2'-(tert-Butyl-dimethyl-silanyloxy)-3'-methoxy-biphenyl-4-yl]-6-chloro-2-oxo-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester

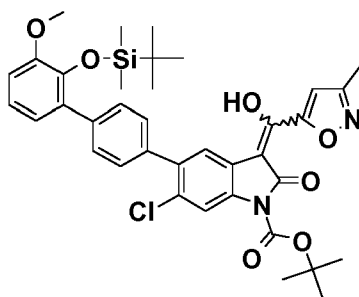


- 15 In a 250 mL round bottomed flask under inert atmosphere were suspended 5-(2'-((tert-butyl)dimethylsilyl)oxy)-3'-methoxy-1',2'-dihydro-[1,1'-biphenyl]-4-yl)-6-chloroindolin-2-one (1.2 g, 2.49 mmol) in anhydrous THF (50 mL). Na_2CO_3 (1.88 g, 22.40 mmol) and Boc_2O (0.717 g, 2.74 mmol) were added in one portion respectively.

- The mixture was refluxed for 3h. The reaction mixture was poured onto 30 mL AcOEt and 30 mL of water, the organic layer was separated, washed with brine and dried over MgSO_4 . Concentration under reduced pressure provided 5-[2'-(tert-Butyl-dimethyl-silanyloxy)-3'-methoxy-biphenyl-4-yl]-6-chloro-2-oxo-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester (1.35 g, 93% yield) as an orange solid.

LCMS (method B) $(\text{M}+\text{ACN}+\text{Na})^+ = 579+23+41 = 643$ observed, $t_R = 2.72$ min.

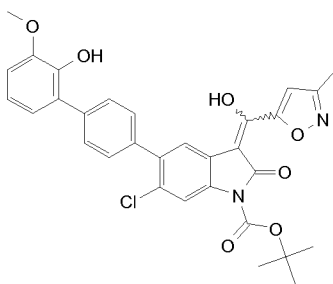
- 25 **Step 5.5** : 5-[2'-(tert-Butyl-dimethyl-silanyloxy)-3'-methoxy-biphenyl-4-yl]-6-chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-2-oxo-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester



Into a 25 mL round-bottomed flask under nitrogen were introduced DMF (3 mL), 3-methylisoxazole-5-carboxylic acid (0.1015 g, 0.758 mmol), tert-butyl 5-(2'-((tert-butyl-
 5 dimethylsilyl)oxy)-3'-methoxy-[1,1'-biphenyl]-4-yl)-6-chloro-2-oxoindoline-1-carboxylate (0.4 g, 0.689 mmol), triethylamine (0.48 mL, 3.45 mmol) to obtain a brownish suspension. TBTU (0.248 g, 0.758 mmol) was added in one portion and the mixture was stirred for 4h at room temperature. 10 mL AcOEt were added, the organic layer was washed with saturated aqueous NaHCO₃ solution and water, dried over MgSO₄ and concentrated under vacuum. The crude mixture was purified on silica gel
 10 (gradient CH₂Cl₂/MeOH 100/0 to 95/5 during 30 min) to provide 5-[2'-(tert-butyl-dimethyl-silanyloxy)-3'-methoxy-biphenyl-4-yl]-6-chloro-3-[1-hydroxy-1-(3-methylisoxazol-5-yl)-methylidene]-2-oxo-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester (0.39 g, 81 % yield) as a yellow solid.

LCMS (method B), no M⁺ detected, t_R = 2.91 min.

15 **Step 5.6** : 6-Chloro-5-(2'-hydroxy-3'-methoxy-biphenyl-4-yl)-3-[1-hydroxy-1-(3-methylisoxazol-5-yl)-methylidene]-2-oxo-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester



Into a 100 mL round-bottomed flask tert-butyl 5-(2'-((tert-butyl-
 20 dimethylsilyl)oxy)-3'-methoxy-[1,1'-biphenyl]-4-yl)-6-chloro-3-(hydroxy(3-methylisoxazol-5-yl)methylidene)-2-oxoindoline-1-carboxylate (0.31 g, 0.450 mmol) were solubilized in 5 mL THF (yellow solution). 0.9 mL (0.9 mmol) of an 1N solution of TBAF in THF were added slowly and the mixture was stirred at room temperature for 5 hours. The reaction mixture was poured into 15 mL AcOEt, washed with water, dried over MgSO₄ and concentrated

under reduced pressure. The crude gummy material was triturated in 5 mL of an ether/pentane 1/1 mixture, solvents were decanted and 0.26 g (quantitative yield) of a yellow-green foam were obtained under reduced pressure.

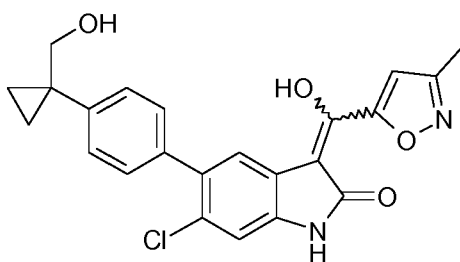
Step 5.7: 6-Chloro-5-(2'-hydroxy-3'-methoxy-biphenyl-4-yl)-3-[1-hydroxy-1-(3-methyl-
5 isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one (example 5).

In a 25 mL round-bottomed flask tert-butyl-6-chloro-3-(hydroxy(3-methylisoxazol-5-yl)methylene)-5-(2'-hydroxy-3'-methoxy-[1,1'-biphenyl]-4-yl)-2-oxoindoline-1-carboxylate (0.220 g, 0.383 mmol) were solubilized in 4 mL of 4N HCl in dioxane (brown solution) and stirred for two hours at room temperature, a slight precipitate
10 appears. 15 mL of CH₂Cl₂ were added; the organic layer was washed with water, dried over MgSO₄ and concentrated under reduced pressure to obtain a brownish oil which was crystallized by adding water. After filtration and drying under reduced pressure (P₂O₅) 0.114 g (63 % yield) of a green solid were isolated.

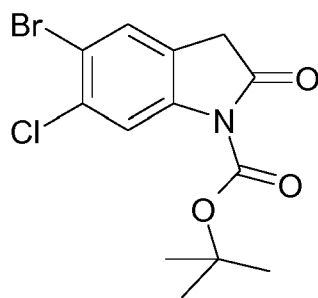
LCMS (method A) (M+H)⁺ = 475, t_R = 1.71 min.

15 ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 2.34 (s, 3 H) 3.86 (s, 3 H) 6.83 - 7.03 (m, 3 H) 7.06 - 7.17 (m, 1 H) 7.20 - 7.29 (m, 1 H) 7.44 (d, J=8.28 Hz, 2 H) 7.63 (d, J=8.28 Hz, 2 H) 7.95 - 8.08 (m, 1 H) 8.54 - 8.72 (m, 1 H) 11.09 - 11.47 (m, 1 H)

Example 6 : 6-Chloro-3-(hydroxy(3-methylisoxazol-5-yl)methylene)-5-(4-(1-(
20 (hydroxymethyl)cyclopropyl)phenyl)indolin-2-one



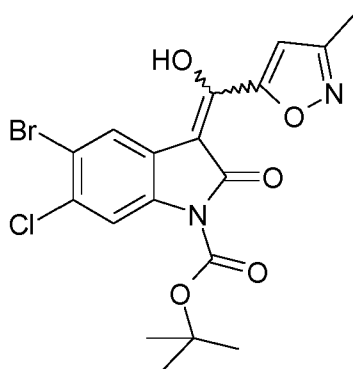
Step 6.1 : tert-butyl 5-bromo-6-chloro-2-oxoindoline-1-carboxylate



To a solution of 5-bromo-6-chloroindolin-2-one (7 g, 28.40 mmol) in tetrahydrofuran (200 mL) was added sodium bicarbonate (16.3 g, 192.09 mmol) and di-tert-butyl dicarbonate (6.89 g, 31.24 mmol). The resulting mixture was heated under reflux for 5 hours. After concentration under vacuum, ethyl acetate and water were added. The organic phase was dried over sodium sulfate and concentrated under vacuum to yield tert-butyl 5-bromo-6-chloro-2-oxoindoline-1-carboxylate (9.1 g, 94 % yield) which was used in the following reaction without further purification.

LCMS (method B) ($M + ACN + Na$)⁺ = 410, t_R = 1.92 min.

Step 6.2 : tert-Butyl 5-bromo-6-chloro-3-(hydroxy(3-methylisoxazol-5-yl)methylene)-2-oxoindoline-1-carboxylate



To a solution of tert-butyl 5-bromo-6-chloro-2-oxoindoline-1-carboxylate (2.99 g, 8.63 mmol), 3-methylisoxazole-5-carboxylic acid (1.27 g, 9.49 mmol) and TBTU (3.11 g, 9.49 mmol) in DMF (10 mL) was added triethylamine (6.01 mL, 43.13 mmol). The resulting mixture is stirred for 18 hours at room temperature. Dichloromethane and water were added. The organic phase was dried over magnesium sulfate and concentrated under vacuum. The remaining crude product was purified by flash chromatography using a gradient of ethyl acetate in dichloromethane to yield tert-butyl 5-bromo-6-chloro-3-(hydroxy(3-methylisoxazol-5-yl)methylene)-2-oxoindoline-1-carboxylate (3.02 g, 77 % yield) as a yellow powder.

LCMS (method A) (M+H)⁺ = 455, t_R = 1.48 min.

Step 6.3: 6-Chloro-3-(hydroxy(3-methylisoxazol-5-yl)methylene)-5-(4-(1-(hydroxymethyl)cyclopropyl)phenyl)indolin-2-one (example 6).

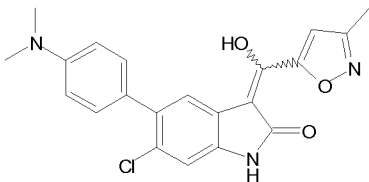
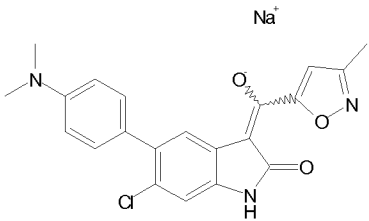
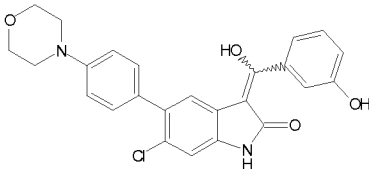
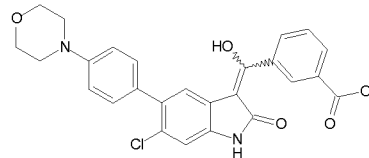
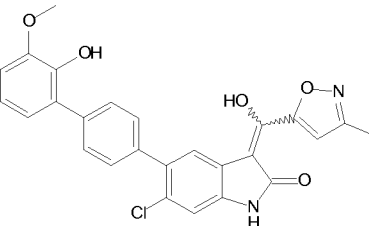
4-(1-(Hydroxymethyl)cyclopropyl)phenylboronic acid (0.26 g, 1.32 mmol), aqueous sodium carbonate 2M (1.10 mL, 2.19 mmol) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (0.045 g, 0.055 mmol) were added under nitrogen atmosphere to a solution of tert-butyl 5-bromo-6-chloro-3-(hydroxy(3-methylisoxazol-5-yl)methylene)-2-oxoindoline-1-carboxylate (0.5 g, 1.10 mmol) in a mixture of ethanol (1.1 mL) and toluene (2.2 mL). The resulting mixture was stirred at 120°C for 1 h in a microwave oven. After filtration and concentration under vacuum, ethyl acetate and water were added. The organic phase was dried over magnesium sulfate and concentrated under vacuum. The remaining crude product was purified by chromatography on a C₁₈ reverse phase using a gradient of acetonitrile in water. The resulting solid was washed with pentane to yield 6-chloro-3-(hydroxy(3-methylisoxazol-5-yl)methylene)-5-(4-(1-(hydroxymethyl)cyclopropyl)phenyl)indolin-2-one (0.14 g, 31 % yield).

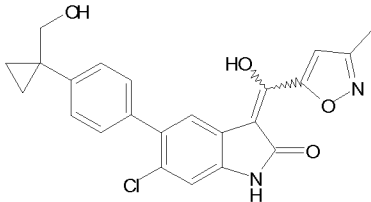
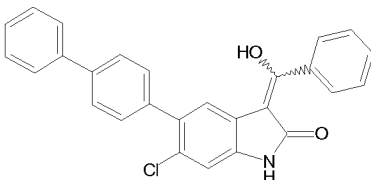
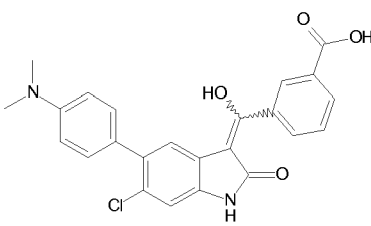
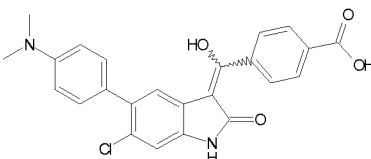
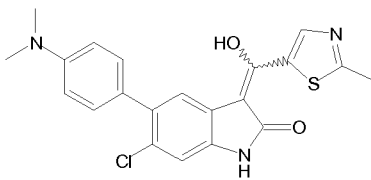
LCMS (method A) (M+H)⁺ = 423, t_R = 1.19 min.

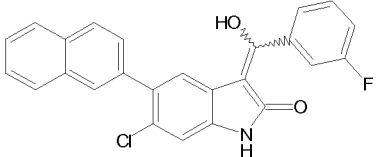
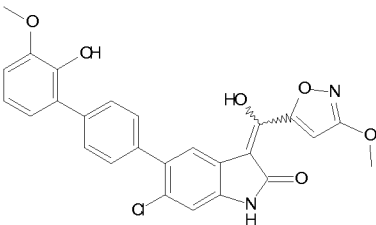
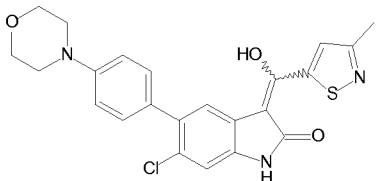
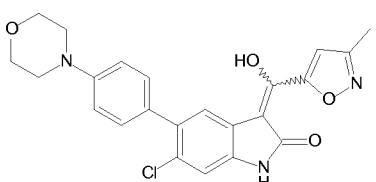
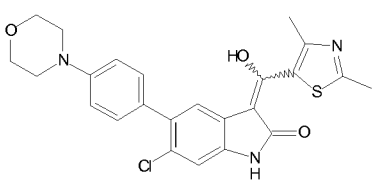
¹H NMR (400 MHz, DMSO-d₆) δ ppm: 0.76 - 0.91 (m, 4 H) 2.34 (s, 3 H) 3.56 - 3.61 (m, 2 H) 7.03 - 7.13 (m, 1 H) 7.21 - 7.28 (m, 1 H) 7.29 - 7.42 (m, 4 H) 7.90 - 8.00 (m, 1 H) 11.00 - 11.55 (m, 1 H)

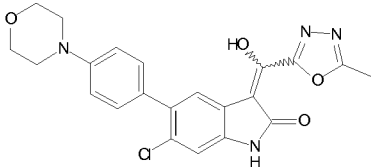
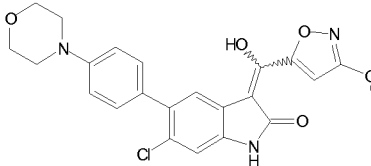
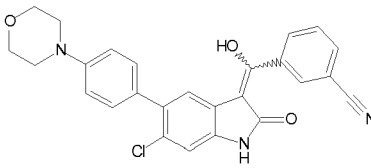
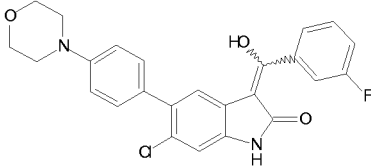
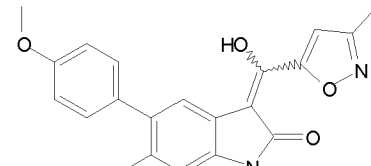
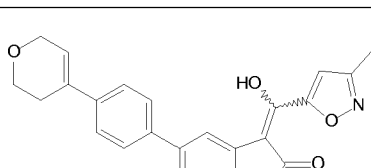
Compounds of table 1 are synthesized according to methods outlined in schemes 1 to 6 and illustrated in examples 1 to 6.

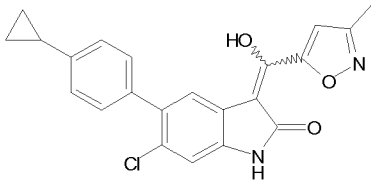
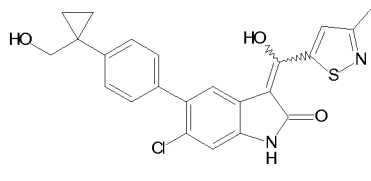
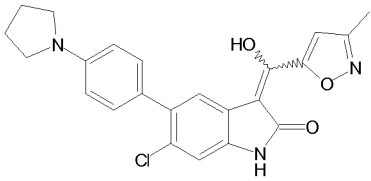
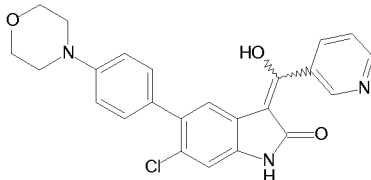
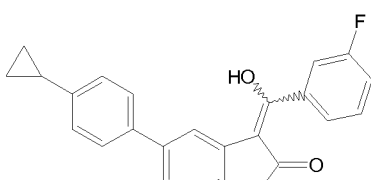
Table 1

Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
1		1	396 1.22
2			396 1.22
3		2	449 1.33
4		3 & 4	477 1.05
5		1	475 1.35

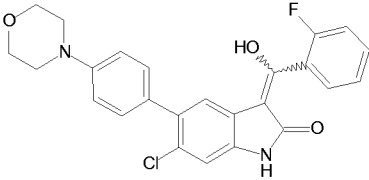
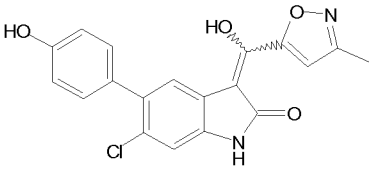
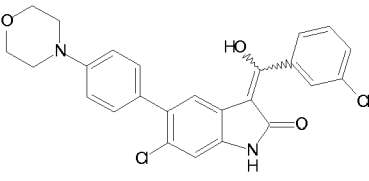
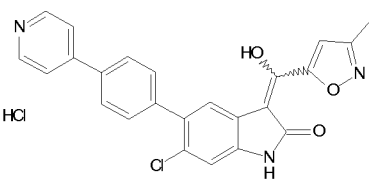
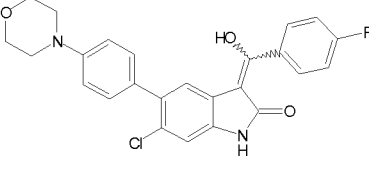
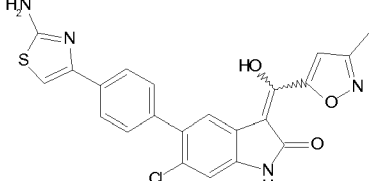
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
6		6	423 1.19
7		3	424 1.55
8		3 & 4	433 1.08
9		1	433 1.04
10		1	412 1.12

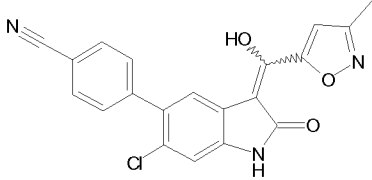
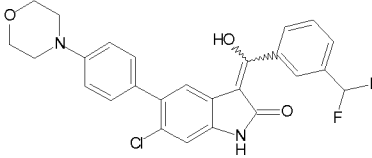
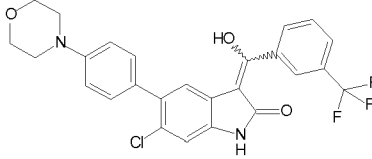
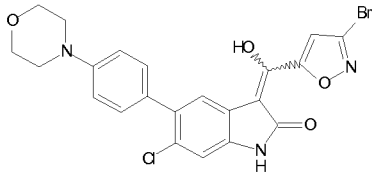
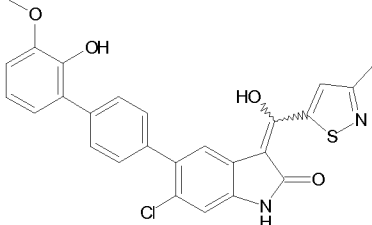
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
11		1	416 1.54
12		5	491 1.64
13		1	454 1.26
14		1	438 1.24
15		1	468 1.24

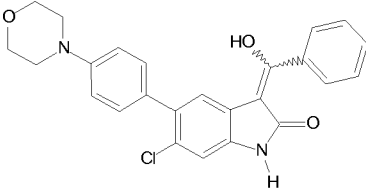
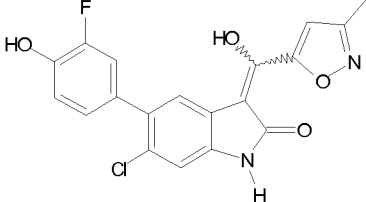
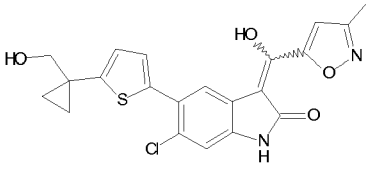
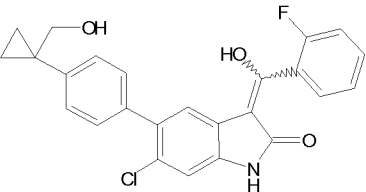
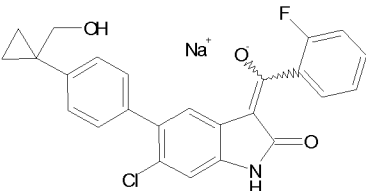
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
16		1	439 1.09
17		1	454 1.26
18		1	458 1.22
19		1	451 1.31
20		1	383 1.30
21		1	435 1.62

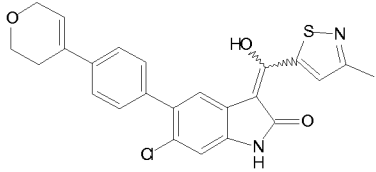
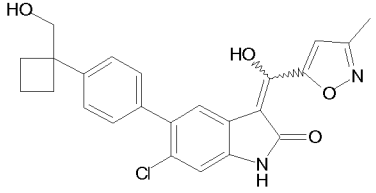
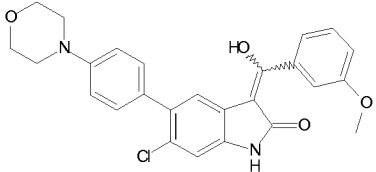
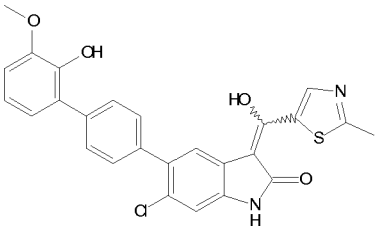
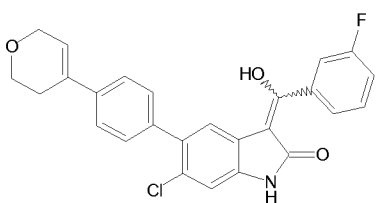
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
22		1	393 1.93
23		1	439 1.41
24		1	422 1.75
25		1	432 1.12
26		1	406 1.80

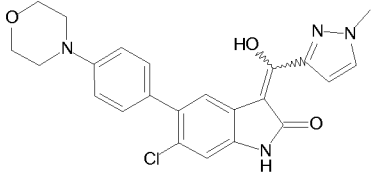
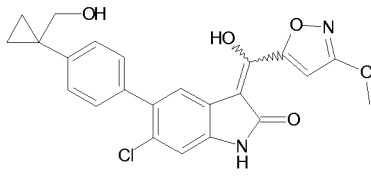
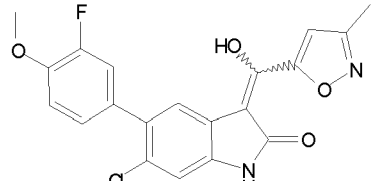
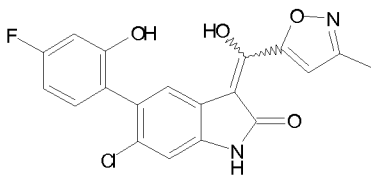
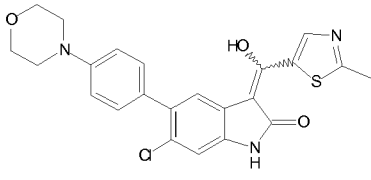
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
27		1	436 1.48
28		1	438 1.50
29		1	422 1.43
30		1	369 1.58
31		1	418 1.43

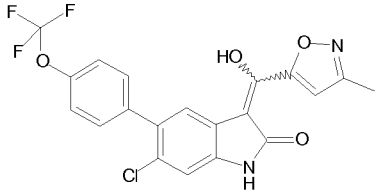
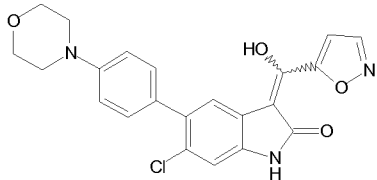
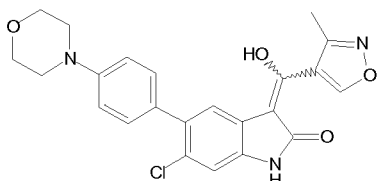
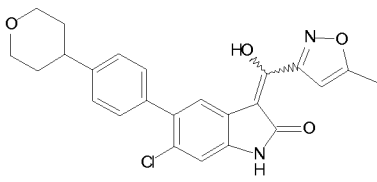
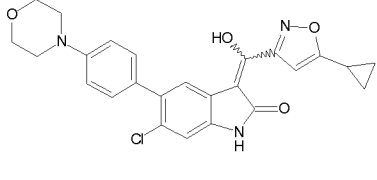
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
32		1	451 1.50
33		6	369 1.26
34		1	467 1.67
35		6	430 1.12
36		1	451 1.57
37		6	451 0.74

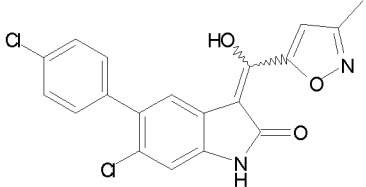
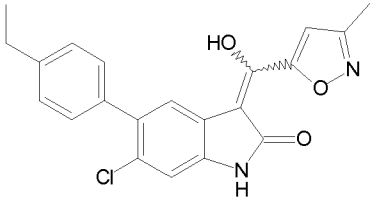
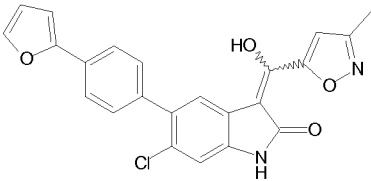
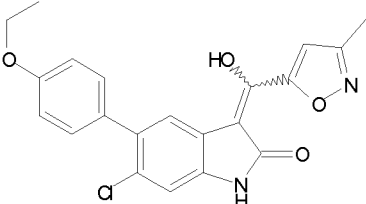
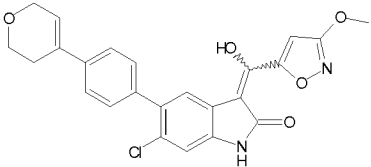
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
38		1	378 1.46
39		1	483 1.55
40		1	501 1.68
41		1	502 1.59
42		5	491 1.64

Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
43		1	433 1.54
44		1	385 1.31
45		1	429 1.4
46		1	436 1.41
47			435 1.42

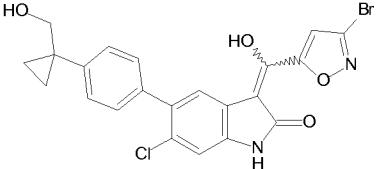
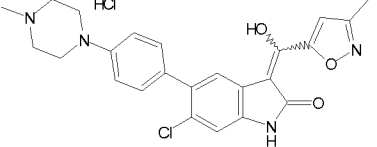
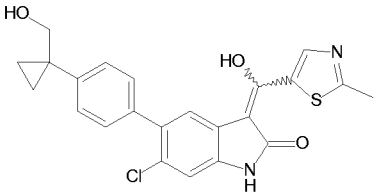
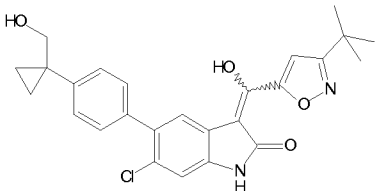
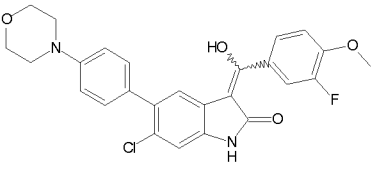
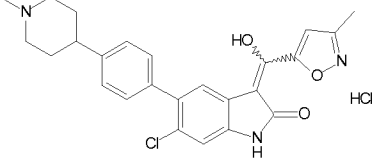
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
48		1	451 1.65
49		1	437 1.51
50		1	463 1.56
51		5	491 1.53
52		1	448 1.71

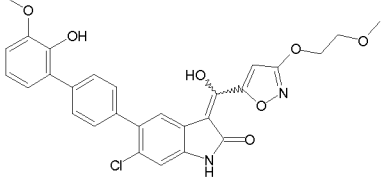
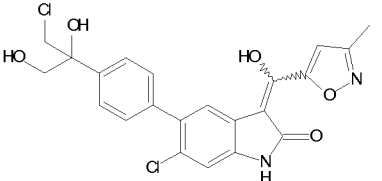
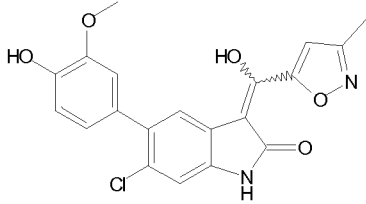
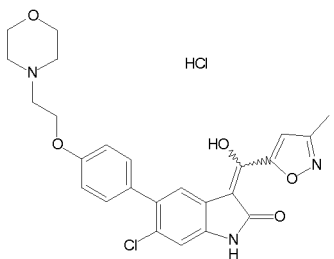
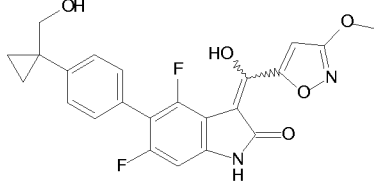
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
53		1	437 1.29
54		1	436 1.43
55		1	401 1.54
56		6	387 1.32
57		1	454 1.42

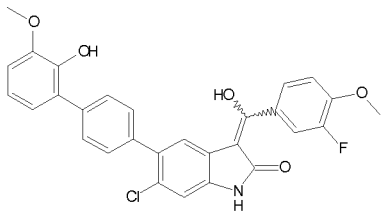
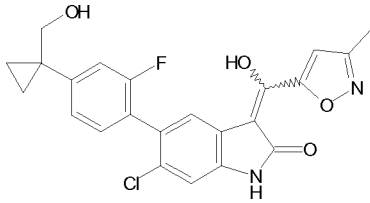
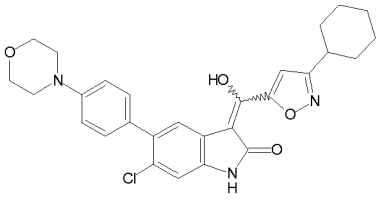
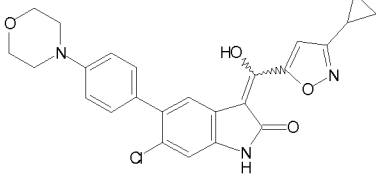
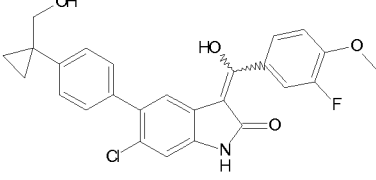
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
58		1	437 1.71
59		1	424 1.38
60		1	438 1.31
61		1	437 1.61
62		1	464 1.61

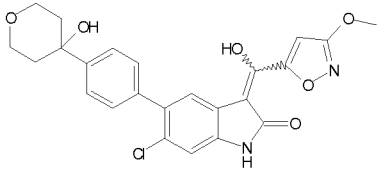
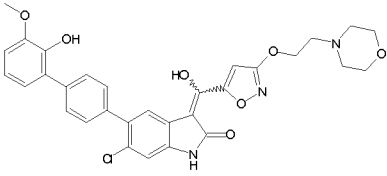
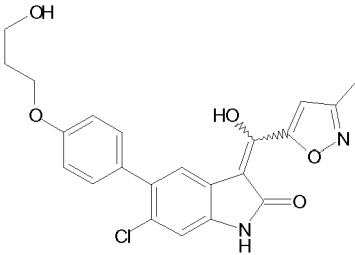
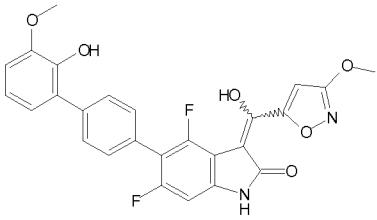
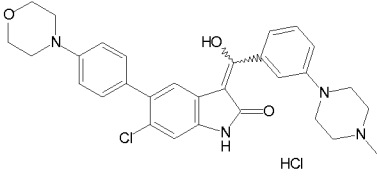
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
63		6	387 1.68
64		6	381 1.72
65		6	419 1.70
66		6	397 1.62
67		1	451 1.64

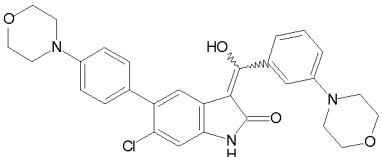
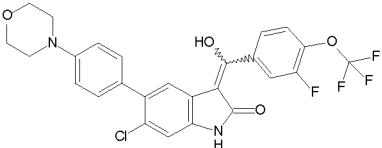
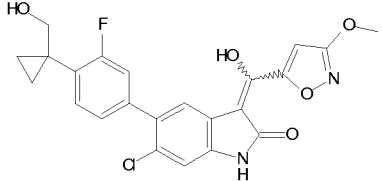
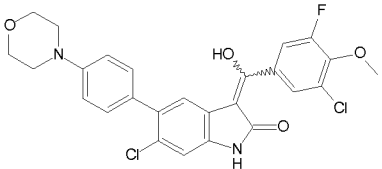
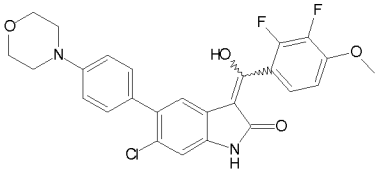
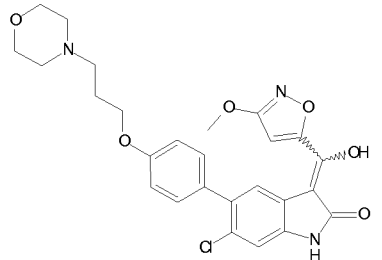
Compound	Structure	Scheme	LC/MS data [M+H]⁺ T_R [min]
68		1	423 1.58
69		6	495 0.78
70		6	509 0.85
71		5	475 1.68
72		1	407 1.42

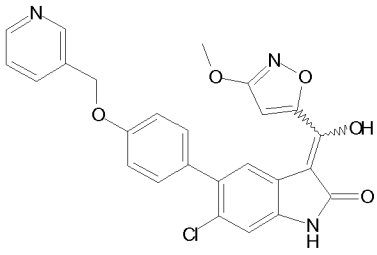
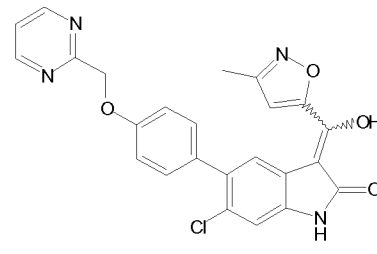
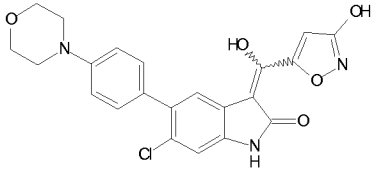
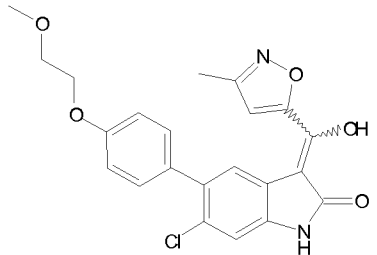
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
73		1	487 1.57
74		6	451 0.89
75		1	439 3.71 (10 min gradient)
76		1	463 1.64
77		1	481 1.65
78		6	450 0.93

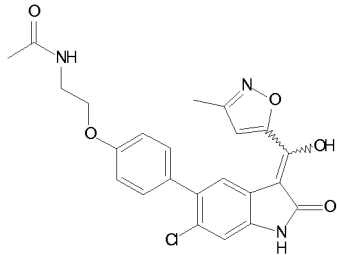
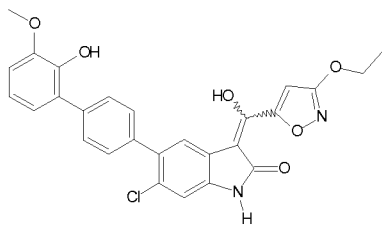
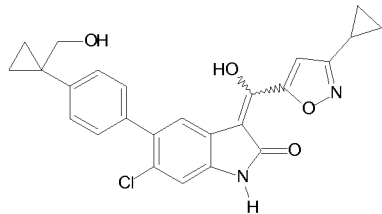
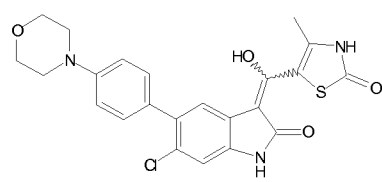
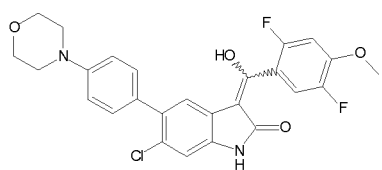
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
79		5	535 1.61
80		6	459 1.24
81		6	399 1.32
82		6	482 0.87
83		1	441 1.14

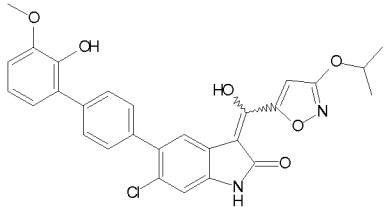
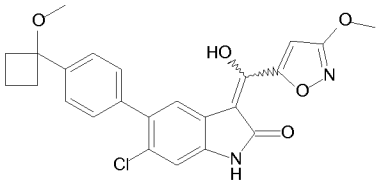
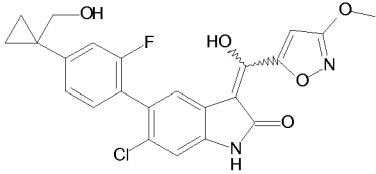
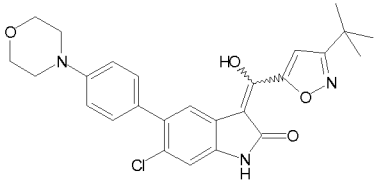
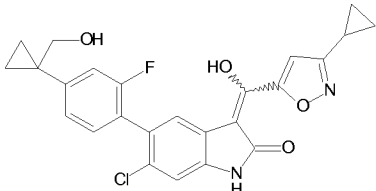
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
84		6	518 1.66
85		6	441 1.39
86		1	506 1.83
87		1	464 1.55
88		1	466 1.48

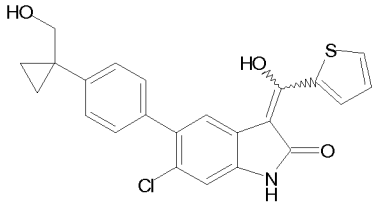
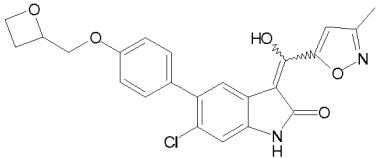
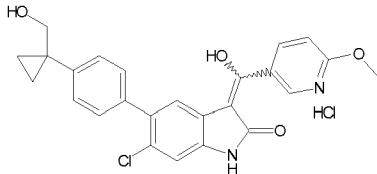
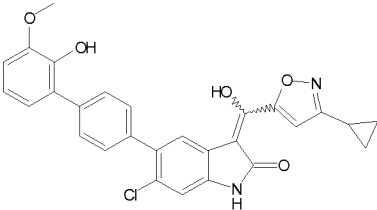
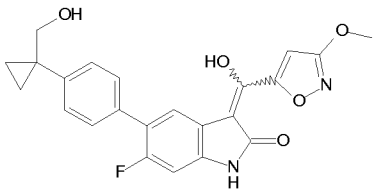
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
89		1	469 2.90 (7 min gradient)
90		5	590 1.04
91		6	427 2.89 (7 min gradient)
92		5	493 1.38
93		1	529 0.96

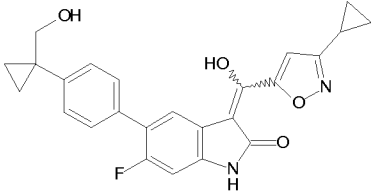
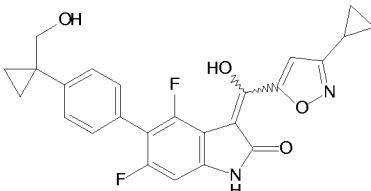
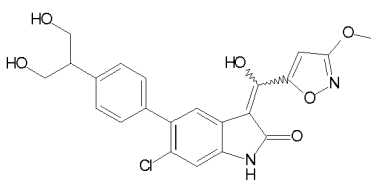
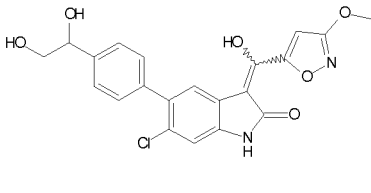
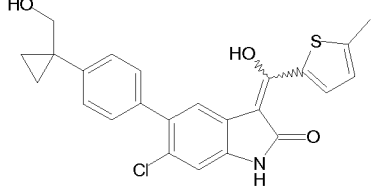
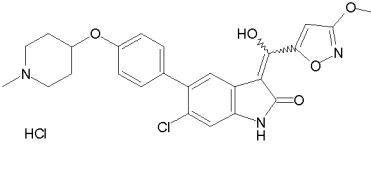
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
94		1	518 1.4
95		1	535 1.56
96		1	457 1.37
97		1	515 1.52
98		1	499 1.62
99		1	512 0.98

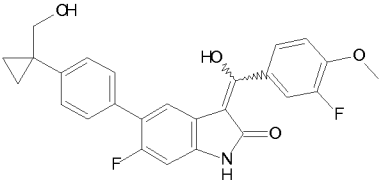
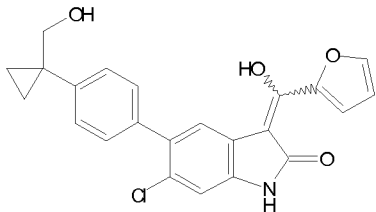
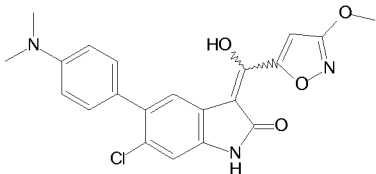
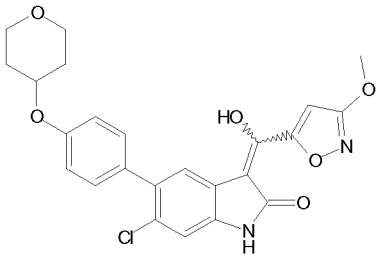
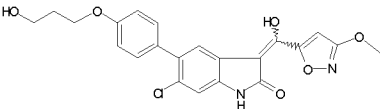
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
100		1	476 1.22
101		1	461 1.36
102		1	440 1.19
103		1	427 1.38

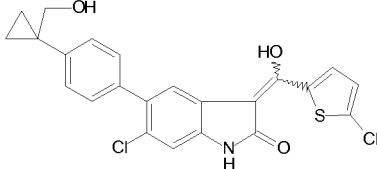
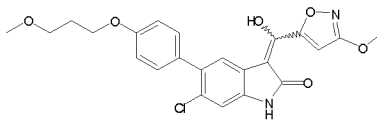
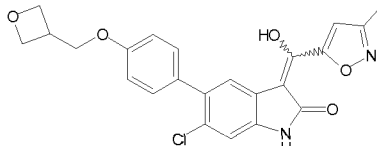
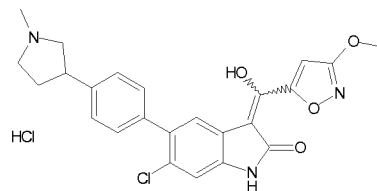
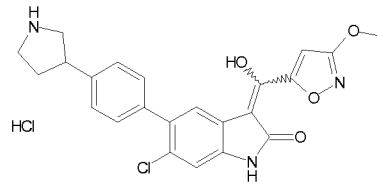
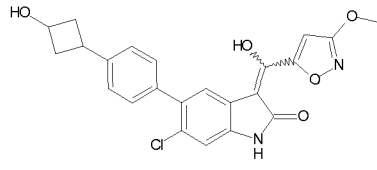
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
104		1	454 1.22
105		5	505 1.58
106		1	449 1.41
107		1	470 1.17
108		1	499 1.50

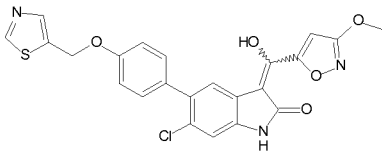
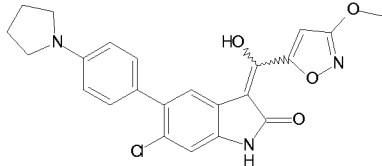
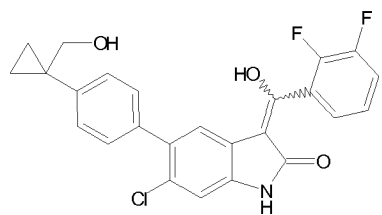
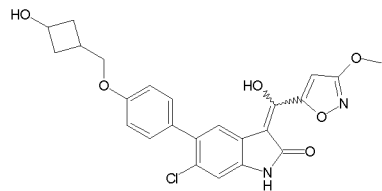
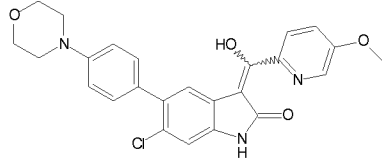
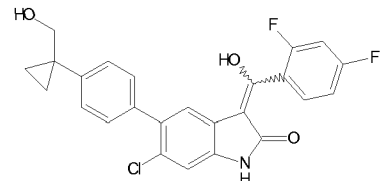
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
109		5	519 1.71
110		1	453 1.64
111		1	457 1.42
112		1	480 1.54
113		1	467 1.40

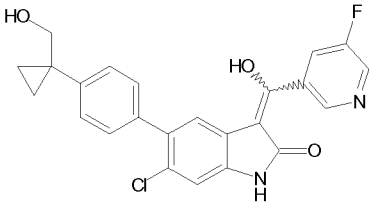
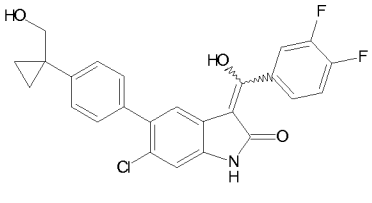
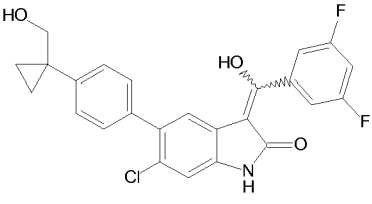
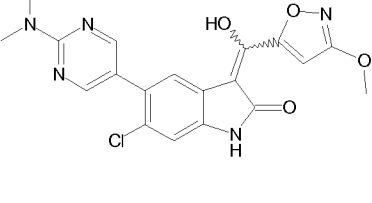
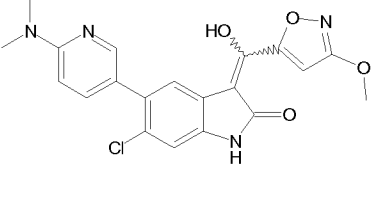
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
114		1	424 1.32
115		6	439 1.36
116		1	449 1.41
117		6	501 1.70
118		6	423 1.32

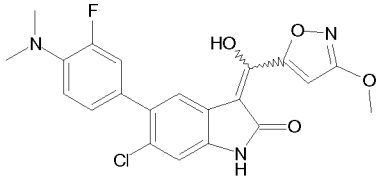
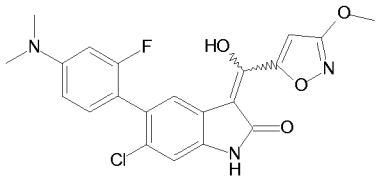
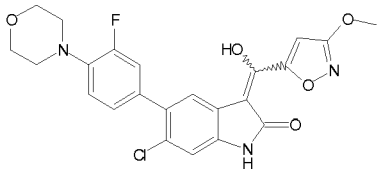
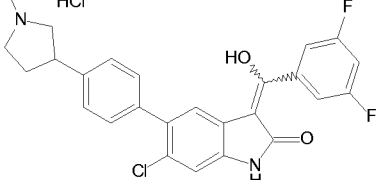
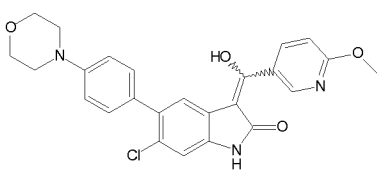
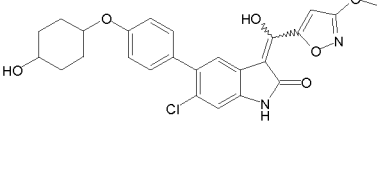
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
119		6	433 1.38
120		6	451 1.31
121		6	443 1.22
122		6	429 1.21
123		6	438 1.47
124		6	482 0.99

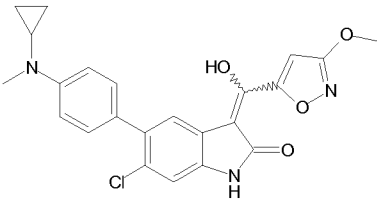
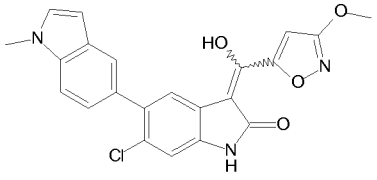
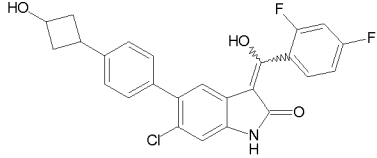
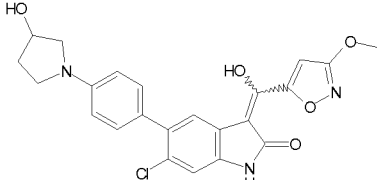
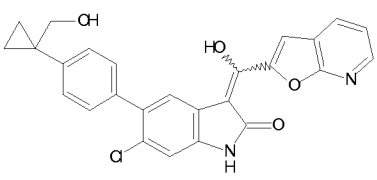
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
125		6	450 3.77 (10 min gradient)
126		1	408 1.49
127		6	412 1.55
128		6	469 1.68
129		6	443 1.38

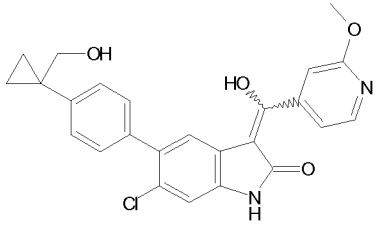
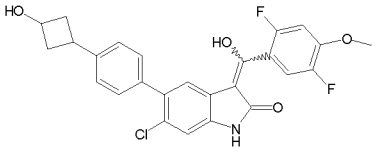
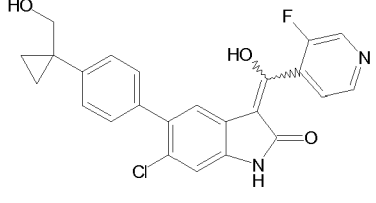
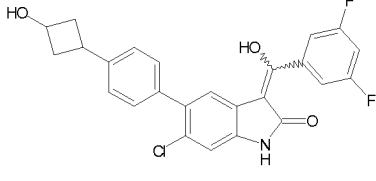
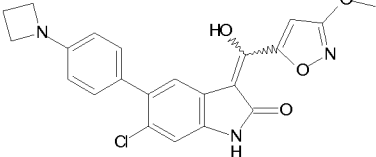
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
130		1	458 1.57
131		6	457 1.50
132		6	439 1.47
133		6	452 0.88
134		6	438 0.87
135		6	439 1.35

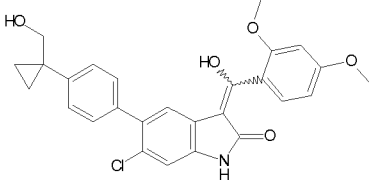
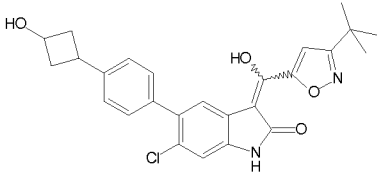
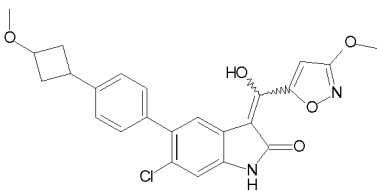
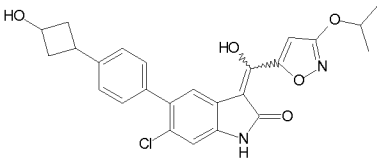
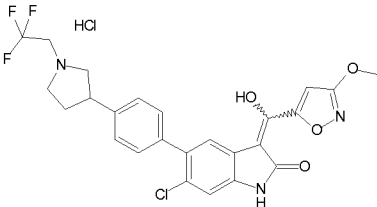
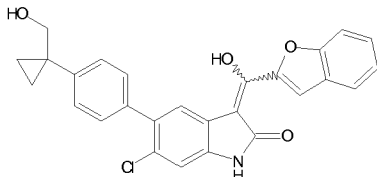
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
136		6	482 1.53
137		6	438 1.79
138		6	454 1.53
139		6	469 1.43
140		1	464 1.25
141		6	454 1.43

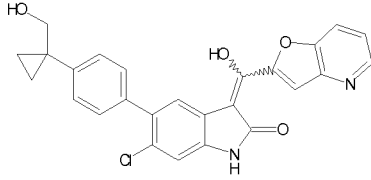
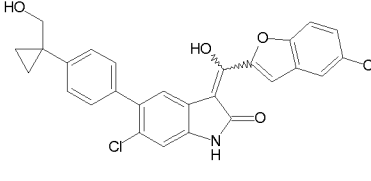
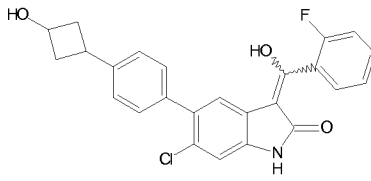
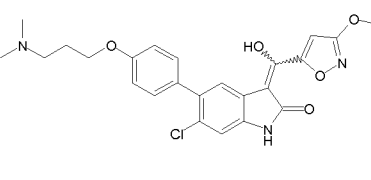
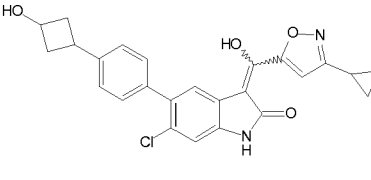
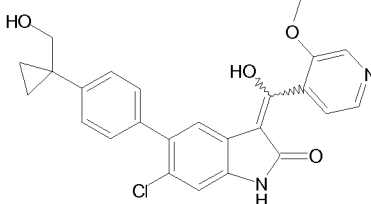
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
142		1	437 1.28
143		1	454 1.49
144		1	454 1.50
145		1	414 1.42
146		6	413 0.79

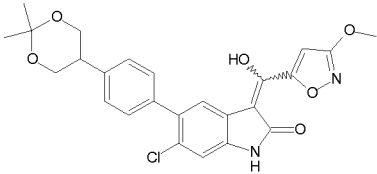
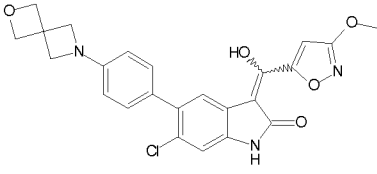
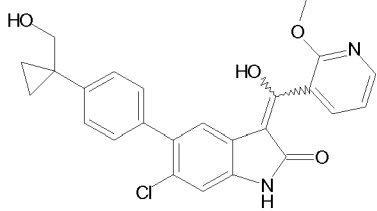
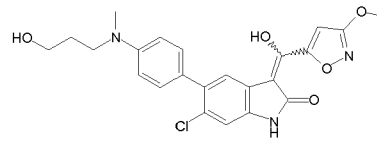
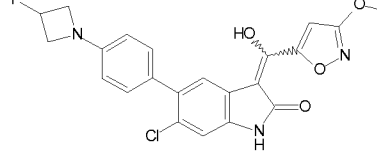
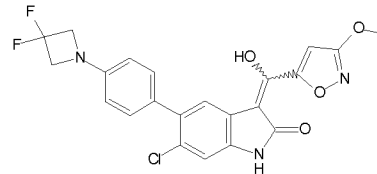
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
147		6	430 4.41 (10 min gradient)
148		6	430 1.61
149		6	472 1.43-1.80 very broad peak
150		6	467 0.91
151		1	464 1.50
152		6	483 1.45

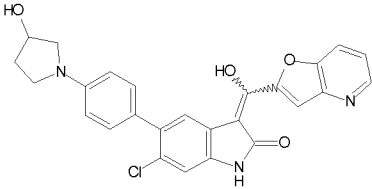
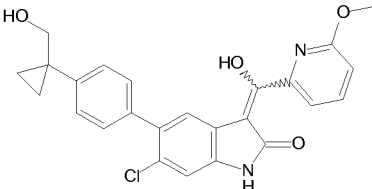
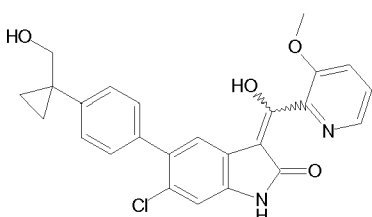
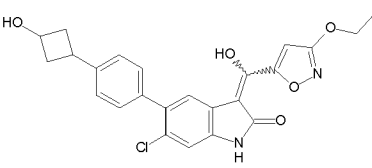
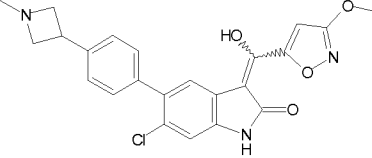
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
153		6	438 1.77
154		6	422 1.60
155		6	454 1.42
156		6	454 1.40
157		6	457 1.45

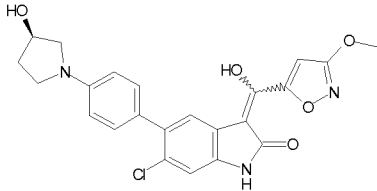
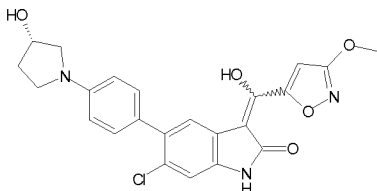
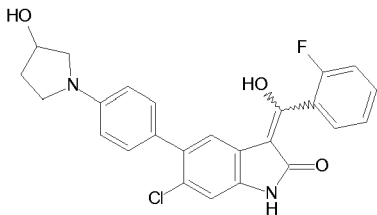
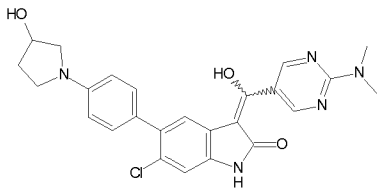
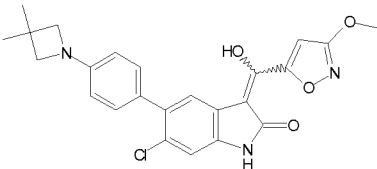
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
158		6	449 1.43
159		6	484 1.42
160		6	437 1.17
161		6	454 1.47
162		6	424 1.61

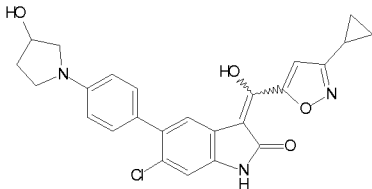
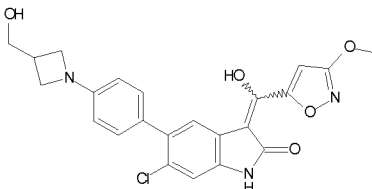
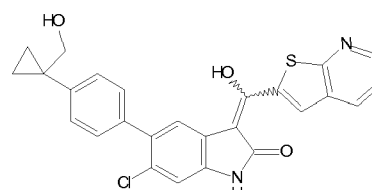
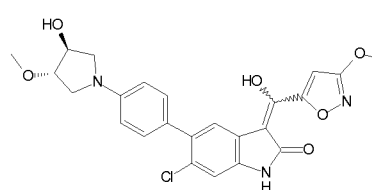
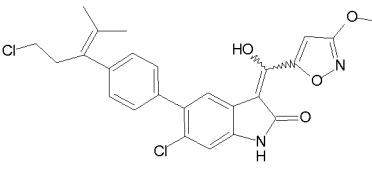
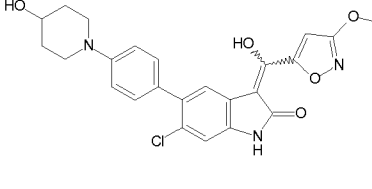
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
163		6	478 1.39
164		6	465 1.61
165		6	453 1.47
166		6	467 1.54
167		6	520 1.52
168		6	458 1.62

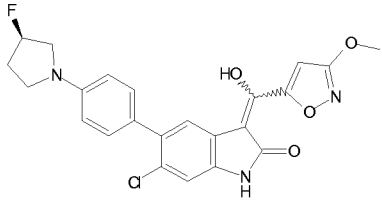
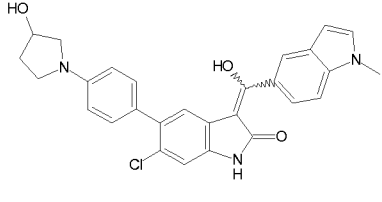
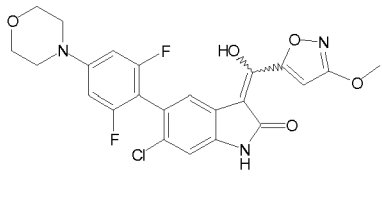
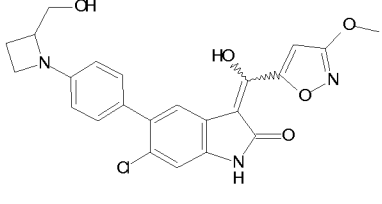
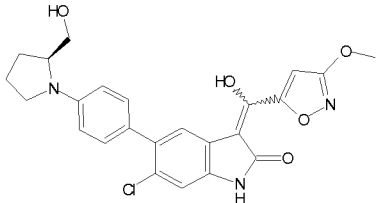
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
169		6	459 1.38
170		6	491 1.76
171		6	436 4.50 (14%)- 4.55 (96%) (10 min gradient)
173		6	470-468 1.05
174		6	449 4.82 (10 min gradient)
175		6	449 1.08

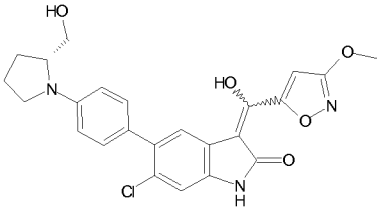
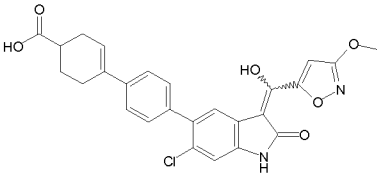
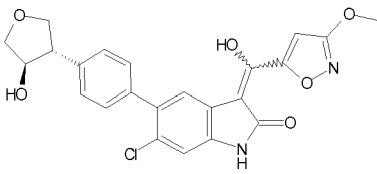
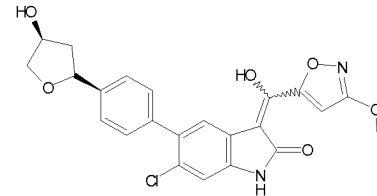
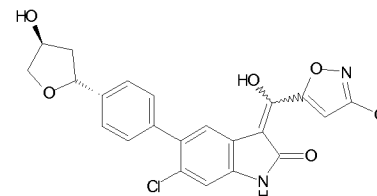
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
176		6	483 1.58
177		6	466 1.49
178		6	449 1.31
179		6 (deprot globale)	456 1.17
180		6	442 1.58
181		6	460 1.65

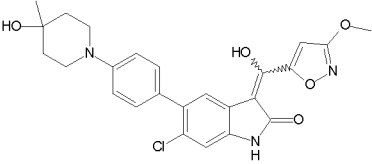
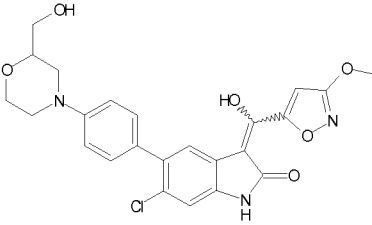
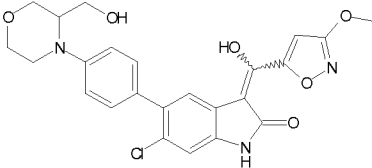
Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
182		6	474 1.39
183		6	449 1.37
184		6	449 1.10
185		6	453 1.49
186		6	438 0.83

Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
187		6	454 1.38
188		6	454 4.42 (10 min gradient)
189		6	451 1.39
190		6	478 1.36
191		6	452 1.83

Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
192		6	464 1.48
193		6	454 1.33
194		6	475 1.38
195		6	484 1.38
196		6	485 1.91
197		6	468 1.05

Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
198		6	456 1.63
199		6	486 1.48
200		6	490 1.50
201		6	454 1.37
202		6	468 1.46

Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
203		6	468 1.46
204		6	493 1.54
205		6	455 1.27
206		6	455 1.27
207		6	455 1.28

Compound	Structure	Scheme	LC/MS data [M+H] ⁺ T _R [min]
208		6	482 1.06
209		6	484 1.29
210		6	484 1.28

The compounds according to the invention underwent pharmacological trials to determine their activation effect of AMP-activated protein kinase (AMPK).

5 AMPK in vitro activation assay

The recombinant human AMPK complex, containing $\alpha_2\beta_1\gamma_2$ was obtained from baculovirus expression system and generated by cotransfection in *Spodoptera frugiperda* 21 (Sf21). 13.6 l of Sf21 cells were produced in serum free medium (SF900 II, Invitrogen) for 82 hours after a triple infection at a multiplicity of infection (M.O.I.) of 0.05, 0.06 and 0.045 for hsAMPK α_2 -2-552-His, hsAMPK β_1 -2-270 and hsAMPK γ_2 -2-569 respectively. Cells were harvested by centrifugation at 1,000xg for 10 minutes at 4°C and stored at -80°C. The insect cell pellet from 8 liters of culture was resuspended and homogenized in 580 ml of lysis buffer (20 mM Hepes pH 7.5, 150 mM NaCl, 10 mM imidazole, 50 mM NaF, 10% Glycerol and supplemented with EDTA free proteases

inhibitor cocktail Roche). The AMPK complex was partially purified using an affinity chromatography under a Ni-NTA Agarose column equilibrated in the lysis buffer and eluted with a gradient (0 to 400 mM) of Imidazol.

A homogeneous time-resolved fluorescence (HTRF) assay was used (Li et al, Anal. Biochem. (2003) 321, 151-156) to identify compounds with stimulating activity for the recombinant human AMPK. Enzyme reaction was performed into a 96-well microtiter plate. First, 20 μ L of test compounds in 0.5% DMSO were dispensed followed by 10 μ L of protein in 50 mM HEPES buffer at pH 7.0, 100 mM NaCl, 5 mM $MgCl_2$, 0.01% BSA, 0.8 mM DTT. After, 30 min incubation at room temperature, the reaction was initiated by the addition of 10 μ L of a solution containing 200 μ M of ATP as donor substrate, 2 μ M or 0.08 μ M of biotinylated ACC-CREBp peptide (PolyPeptide) as acceptor. Plates were then incubated 45 min at 37°C. The reaction was terminated by the addition of 40 μ L detection mixture containing Eu^{3+} cryptate-conjugated anti-pS¹³³-CREB antibody and streptavidine-XL665 (CisBio). Plates were further incubated for 2h30 at room temperature. The fluorescence signal was measured using an Envision multireader (Perkin Elmer). The non-specific signal was obtained without substrates. Potentiation of AMPK activity was expressed as a percent over the basal signal (without compound) from which an EC_{50} value was determined.

The EC_{50} of a graded dose response curve represents the concentration of a compound where 50% of its maximal effect is observed.

The EC_{50} values are between 1 nM and 5000 nM and in particular between 3 nM and 60 nM and even more particularly less than 5000nM.

The table of results for AMPK in vitro activation assay is given below:

Table 2

Compound	$\alpha 2\beta 1\gamma 2$ AMPK EC ₅₀ (nM) (Emax %)
1	21 +/- 26 (124 +/- 11) (n=3)
2	53 +/- 49 (183 +/- 51) (n=4)
3	190 (138)
4	15 +/- 2 (97 +/- 31) (n=3)
5	4 +/- 3 (193 +/- 46) (n=4)
6	7 +/- 3.3 (186 +/- 32) (n=4)
7	1400 (57)
8	33 +/- 19 (124 +/- 22) (n=6)
9	24 (120) 23 (115)
10	89 (127)
11	4000 (95)
12	1 +/- 0 (172 +/- 65) (n=3)
13	12 (158) 5 (361)
14	38 (283)
15	27 (257)
16	9 (268)
17	120 (289) 7 (337)
18	190 (135)

Compound	$\alpha 2\beta 1\gamma 2$ AMPK EC ₅₀ (nM) (Emax %)
19	38 (146) 230 (249)
20	410 (223)
21	5 (153) 1 (115)
22	250 (147)
23	3 (158)
24	110 (143)
25	320 (146)
26	440 (153)
27	2 (129)
28	130 (150)
29	58 (157)
30	240 (108)
31	540 (147)
32	140 (112)
33	390 (120)
34	630 (156)
35	23 (151)
36	380 (153)
37	37 (192)
38	700 (133)
39	620 (168)
40	720 (121)
41	3 (115)
42	27 (132)
43	220 (170)
44	470 (165)
45	230 (155)
46	6 (95)
47	25 (94)
48	95 (87)
49	12 (69) 120 (130)
50	40 (66) 40 (191)

Compound	$\alpha 2\beta 1\gamma 2$ AMPK EC ₅₀ (nM) (Emax %)
51	11 (129)
52	120 (147)
53	1710 (180)
54	5 (187)
55	430 (174)
56	150 (189)
57	3600 (139)
58	1400 (212)
59	29 (245)
60	770 (298)
61	49 (218)
62	98 (254)
63	4020 (134)
64	1630 (141)
65	120 (113)
66	3070 (192)
67	3 (192)
68	150 (208)
69	8 (134)
70	88 (142)
71	2 (158)
72	2 (159)
73	6 (148)
74	112 (213)
75	1 (142)
76	2 (124)
77	0.5 (128)
78	7 (141)
79	38 (133)
80	15 (99)
81	780 (136)
82	280 (130)
83	0.1 (160) 0.1 (196)

Compound	$\alpha 2\beta 1\gamma 2$ AMPK EC ₅₀ (nM) (Emax %)
84	0.6 (170) 1 (183)
85	1 (151)
86	61 (155)
87	0.5 (159) 0.6 (186)
88	0.6 (98) 0.4 (170)
89	7 (203)
90	0.1 (183) 0.2 (88)
91	4 (185)
92	0.3 (172)
93	58 (186)
94	14 (150)
95	396 (159)
96	0.3 (220) 0.2 (77)
97	41 (185)
98	2 (191)
99	5 (187)
100	36 (159)
101	63 (159)
102	2 (122)
103	16 (114)
104	15 (107)
105	0.3 (74)
106	0.1 (155)
107	36 (104)
108	6 (141)
109	0.6 (165)
110	6 (131)
111	1 (175)
112	13 (197)
113	0.6 (126)
114	4 (143)
115	30 (149)

Compound	$\alpha 2\beta 1\gamma 2$ AMPK EC ₅₀ (nM) (Emax %)
116	0.3 (136) 0.8 (295)
117	0.1 (129)
118	0.5 (133)
119	0.6 (133)
120	0.2 (169)
121	4 (172)
122	7 (172)
123	0.4 (272)
124	25 (231)
125	0.2 (230)
126	0.3 (295)
127	0.5 (296) 7 (293)
128	52 (288)
129	20 (478) 10 (158)
130	9 (373)
131	33 (377) 86 (273)
132	49 (364)
133	14 (397)
134	9 (394)
135	9 +/- 1 (319 +/- 87) (n = 4)
136	26 (309)
137	16 (271)
138	47 (310) 0.9 (269)
139	450 (320) 2 (218)
140	21 (227)
141	2 (229)

Compound	$\alpha 2\beta 1\gamma 2$ AMPK EC ₅₀ (nM) (Emax %)
142	6 (239)
143	3 (230)
144	0.9 (210)
145	95 (257)
146	88 (278)
147	15 (267)
148	1 (158)
149	6 (170)
150	14 (137)
151	6 (161)
152	9 (223)
153	7 (234)
154	0.7 (256)
155	60 (131)
156	2 (229)
157	0.6 (141)
158	0.5 (130)
159	10 (180)
160	0.1 (191)
161	15 (155)
162	0.7 (191)
163	3 (196)
164	11 (194)
165	18 (218)
166	13 (207)
167	117 (156)
168	0.3 (173)
169	0.1 (172)
170	6 (181)
171	6 (197)
173	1 (181)
174	1 (185)
175	2 (198)

The compounds according to the invention may be used for the preparation of drugs, in particular medicaments for activating AMP-activated protein kinase (AMPK).

Thus, according to another of its aspects, a subject of the invention is drugs that comprise a compound of formula (I), or an addition salt of the compound of formula (I)
5 with a pharmaceutically acceptable acid or base.

These drugs find their use in therapeutics, especially in the prevention or the treatment of metabolic disorders including obesity and type 2 diabetes.

These drugs also find their use in therapeutics in the treatment of kidney diseases.

10

According to another of its aspects, the present invention relates to pharmaceutical compositions comprising, as active ingredient, a compound according to the invention. These pharmaceutical compositions contain an effective dose of at least one compound according to the invention, or a pharmaceutically acceptable salt
15 of said compound, and also at least one pharmaceutically acceptable excipient.

Said excipients are chosen, according to the pharmaceutical form and the mode of administration desired, from the usual excipients which are known to those skilled in the art.

In the pharmaceutical compositions of the present invention for oral, sublingual,
20 subcutaneous, intramuscular, intravenous, topical, local, intratracheal, intranasal, transdermal or rectal administration, the active ingredient of formula (I) above, or its salt, can be administered in unit administration form, as a mixture with conventional pharmaceutical excipients, to animals or to human beings for the treatment of the above disorders or diseases.

25

The appropriate unit administration forms include oral-route forms such as tablets, soft or hard gel capsules, powders, granules and oral solutions or suspensions, sublingual, buccal, intratracheal, intraocular and intranasal administration forms, inhalation forms, topical, transdermal, subcutaneous, intramuscular or intravenous
30 administration forms, rectal administration forms and implants. For topical application, the compounds according to the invention can be used in creams, gels, ointments or lotions.

By way of example, a unit administration form of a compound according to the invention in tablet form may comprise the following components:

	Compound according to the invention	50.0 mg
5	Mannitol	223.75 mg
	Croscarmellose sodium	6.0 mg
	Corn starch	15.0 mg
	Hydroxypropylmethylcellulose	2.25 mg
	Magnesium stearate	3.0 mg

10

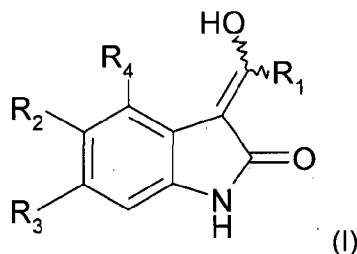
There may be particular cases where higher or lower dosages are appropriate; such dosages do not depart from the context of the invention. According to the usual practice, the dosage appropriate for each patient is determined by the physician according to the method of administration and the weight and response of said patient.

15

According to another of its aspects, the present invention also relates to a method for treating the pathological conditions indicated above, which comprises the administration, to a patient, of an effective dose of a compound according to the invention, or a pharmaceutically acceptable salt thereof.

CLAIMS

1. A compound corresponding to formula (I):



5 in which

➤ R_1 represents :

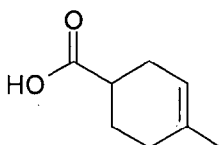
- an (C_6 - C_{10})aryl group, unsubstituted or substituted with one or more substituents chosen from
 - a halogen atom,
 - 10 ▪ a $-OR_a$ group, in which R_a represents a hydrogen atom, a (C_1 - C_3)alkyl group or a $-CF_3$ group
 - a (C_1 - C_3)alkyl group, unsubstituted or substituted with one or more halogen atoms,
 - a carboxyl group,
 - 15 ▪ a cyano group,
 - a (C_3 - C_6)heterocycloalkyl group, unsubstituted or substituted with one or more (C_1 - C_3)alkyl group,
- a (C_2 - C_{10})heteroaryl group, unsubstituted or substituted with one or more substituents chosen from
 - 20 ▪ a halogen atom,
 - a (C_1 - C_4)alkyl group,
 - a (C_3 - C_6)cycloalkyl group,
 - a $-OR_e$ group, in which R_e represents an hydrogen atom or a (C_1 - C_4)alkyl group, said (C_1 - C_4)alkyl group being unsubstituted or substituted with one or more (C_1 - C_4)alkoxy group or heterocycloalkyl group
 - 25 ▪ a $-NR_fR_f$ group, in which R_f et R_f , independently, identical or different, represent a (C_1 - C_3)alkyl group

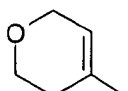
➤ R₂ represents :

- an (C₆-C₁₀)aryl group, unsubstituted or substituted with one or more substituents chosen from :

- a halogen atom,
- a cyano group,

5

- a  group

- a  group

- a (C₁-C₃)alkyl group unsubstituted or substituted with one or more substituents chosen from a halogen atom, a hydroxyl group and a (C₁-C₄)alkenyl group,

10

- a (C₃-C₆)cycloalkyl group, unsubstituted or substituted with a hydroxy(C₁-C₃)alkyl group, a hydroxyl group or an (C₁-C₄)alkoxy group,

- a -OR_b group, in which R_b represents

15

- a hydrogen atom,
- a -CF₃ group,
- a (C₃-C₆)cycloalkyl group, unsubstituted or substituted with a hydroxyl group
- a (C₃-C₆)heterocycloalkyl group, said (C₃-C₆)heterocycloalkyl being unsubstituted or substituted with a (C₁-C₃)alkyl group,
- or an (C₁-C₃)alkyl group, said (C₁-C₃)alkyl group being unsubstituted or substituted with one or more :

20

- hydroxyl group,
- (C₁-C₄)alkoxy group,
- (C₂-C₁₀)heteroaryl group,
- acetamido group,
- di(C₁-C₃)alkyl-amino group,
- (C₃-C₆)cycloalkyl group, said (C₃-C₆)cycloalkyl group being unsubstituted or substituted with one or more hydroxyl group, or

25

30

- (C₃-C₆)heterocycloalkyl group, said (C₃-C₆)heterocycloalkyl group being unsubstituted or substituted with a (C₁-C₃)alkyl group;
 - a (C₃-C₆)heterocycloalkyl group unsubstituted or substituted with one or more halogen atom, (C₁-C₃)alkyl group, hydroxyl group, hydroxy(C₁-C₃)alkyl group, (C₁-C₄)alkoxy group or (C₁-C₄)fluoroalkyl group;
 - an (C₆-C₁₀)aryl group, unsubstituted or substituted with one or more -OR_c group, in which R_c represents a hydrogen atom or a (C₁-C₃)alkyl group,
 - a (C₂-C₁₀)heteroaryl group, unsubstituted or substituted with one or more -NH₂ group,
 - a -NR_dR_{d'} group, in which R_d et R_{d'}, independently, identical or different, represent a hydrogen atom, a (C₁-C₃)alkyl group, a hydroxy(C₁-C₄)alkyl or a (C₃-C₆)cycloalkyl group,
 - a (C₂-C₁₀)heteroaryl group, unsubstituted or substituted with one or more substituents chosen from:
 - a (C₁-C₃)alkyl group
 - a (C₃-C₆)cycloalkyl group, unsubstituted or substituted with a hydroxy(C₁-C₃)alkyl group,
 - a -NR_gR_{g'} group, in which R_g et R_{g'}, independently, identical or different, represent a (C₁-C₃)alkyl group,
- R₃ represents :
- a halogen atom,
 - a (C₁-C₃)alkyl group,
- R₄ represents :
- a halogen atom,
 - a hydrogen atom,

in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

2. The compound of formula (I) as claimed in claim 1, characterized in that:

➤ R_1 represents :

- An aryl group, unsubstituted or substituted with one or more substituents chosen from

- a halogen atom,
- a $-OR_a$ group, in which R_a represents a hydrogen atom or a (C_1-C_3) alkyl group,
- a (C_1-C_3) alkyl group, unsubstituted or substituted with one or more halogen atoms,
- a carboxyl group,
- a cyano group,
- a heteroaryl group, unsubstituted or substituted with one or more substituents chosen from a halogen atom, a (C_1-C_4) alkyl group, a (C_3-C_6) cycloalkyl group, a (C_1-C_4) alkoxy group,

➤ R_2 represents :

- an aryl group, unsubstituted or substituted with one or more substituents chosen from :

- a halogen atom,
- a cyano group,
- a (C_1-C_3) alkyl group,
- a (C_3-C_6) cycloalkyl group, unsubstituted or substituted with a hydroxy (C_1-C_3) alkyl group,
- a $-OR_b$ group, in which R_b represents a hydrogen atom, a $-CF_3$ group or an alkyl group, unsubstituted or substituted with one heterocycloalkyl group, the said heterocycloalkyl group being unsubstituted or substituted with a (C_1-C_3) alkyl group;
- a heterocycloalkyl group, unsubstituted or substituted with one or more (C_1-C_3) alkyl group,
- an aryl group, unsubstituted or substituted with one or more $-OR_c$ group, in which R_c represents a hydrogen atom or a (C_1-C_3) alkyl group,
- a heteroaryl group, unsubstituted or substituted with one or more $-NH_2$ group,
- a $-NR_dR_{d'}$ group, in which R_d et $R_{d'}$, independently, identical or different, represent a hydrogen atom, a (C_1-C_3) alkyl group,

- a heteroaryl group, unsubstituted or substituted with one or more cycloalkyl group, unsubstituted or substituted with a hydroxy(C₁-C₃)alkyl group,

5 ➤ R₃ represents :

- a halogen atom,
- a (C₁-C₃)alkyl group,
-

➤ R₄ represents an hydrogen atom

10

in the form of the base or of an addition salt with an acid or with a base.

3. The compound of formula (I) as claimed in claim 1 or 2, characterized in that:

➤ R₁ represents :

15

- a phenyl group, unsubstituted or substituted with one or more substituents chosen from:

- a fluorine atom or a chlorine atom,
- a -OR_a group, in which R_a represents a methyl group, a CF₃ group,
- a di or trifluoro-methyl group,
- a carboxyl group,
- a cyano group,
- a morpholine group, a methylpiperazine group

20

- a pyridinyl group, a pyrazolyl group, a pyrimidinyl group, an isoxazolyl group, a thiazolyl group, an isothiazolyl group, a 1,3,4-oxadiazolyle group, a thiazol-2onyl group, a thienyl group, a furyl group, a furopyridinyl group, a benzofuran-2-yl group, a thienopyridinyl group, an indolynonyl group, unsubstituted or substituted with one or more substituents chosen from:

25

- a bromine atom, a chlorine atom, a fluorine atom
- a methyl or tert-butyl group,
- a hydroxyl group
- a cyclopropyl group or a cyclohexyl group

30

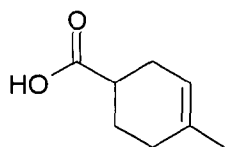
- a $-OR_e$ group, in which R_e represents a methyl group, an ethyl group, an isopropyl group, a methoxyethyl group, a morpholinoethyl group
- a dimethylamino group,

5

➤ R_2 represents :

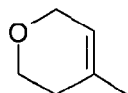
- a phenyl or a naphthalene group, unsubstituted or substituted with one or more substituents chosen from :

- a fluorine atom or a chlorine atom,



10

- a



- a

- a cyano group,

- an ethyl group, unsubstituted or substituted with one or two hydroxyl groups,

15

- an propyl group, unsubstituted or substituted with two or more groups chosen from a chlorine atom, an hydroxyl group and a propenyl group,

- a cyclopropyl or a cyclobutyl group, unsubstituted or substituted with a hydroxyl group, a hydroxymethyl group or a methoxy group

20

- a $-OR_b$ group, in which R_b represents a hydrogen atom, a $-CF_3$ group or an (C_1-C_3) alkyl group, unsubstituted or substituted with one piperazinyl group, the said piperazinyl group being unsubstituted or substituted with a methyl group;

25

- a morpholinyl, a dihydropyranyl, a tetrahydropyranyl, a pyrrolidinyl, a tetrahydrofuranyl, a piperazinyl, a piperidinyl group, a dioxane group, an oxazaspiro[3.3]heptanyl, unsubstituted or substituted with one or more methyl group, hydroxyl group, methoxy group, hydroxymethyl group or fluorine atom,

30

- 5
- an azetidiny group unsubstituted or substituted with one or two fluorine atoms, methyl groups, or hydroxymethyl group,
 - a pyrrolidiny group substituted with a trifluoroethyl group,
 - a phenyl group, unsubstituted or substituted with one or more –
- 10
- OR_c group, in which R_c represents :
- a hydrogen atom
 - a methyl group,
 - an hydroxypropyl group
 - an hydroxyxylhexyl group,
 - a methoxypropyl group,
 - a dimethylaminopropyl group
 - a morpholinoethyl group, a morpholinopropyl group
 - a hydroxypropyl group, a methoxyethyl group,
 - a tetrahydropyranyl,
 - a pyridylmethyl group,
 - a pyrimidinyl group,
 - a methylpiperidyl group,
 - a thiazolylmethyl group,
 - an acetamidoethyl group
 - an oxetanylmethyl group
 - an hydroxycyclobutylmethyl group,
- 15
- a pyridinyl, a thiazolyl, a furanyl group, unsubstituted or substituted with one -NH₂ group,
 - a –NR_dR_{d'} group, in which R_d et R_{d'}, independently, identical or
- 20
- different, represent a methyl group, an hydroxypropyl group or a cyclopropyl group,
- a thiophene group, unsubstituted or substituted with a cyclopropyl group, unsubstituted or substituted with a hydroxymethyl group,
 - a pyrimidinyl or a pyridinyl group substituted with a dimethylamino group
 - an indolyl group, substituted with a methyl group,
- 25
- 30
- 35
- R₃ represents :
- a chlorine or a fluorine atom,
 - a methyl group,

- R₄ represents a fluorine or an hydrogen atom.

in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

- 5 4. The compound of formula (I) as claimed in one of the preceding claims 1 to 3, characterized in that:

- R₁ represents a (C₂-C₁₀)heteroaryl group, unsubstituted or substituted with one or more substituents chosen from a halogen atom, a (C₁-C₃)alkyl group, a (C₃-C₅)cycloalkyl group, a (C₁-C₄)alkoxy group,

- 10 in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

5. The compounds of formula (I) as claimed in one of the preceding claims 1 to 4, characterized in that:

- 15 ➤ R₁ represents an isoxazolyl group, unsubstituted or substituted with one substituent chosen from a (C₁-C₄)alkyl group, a (C₃-C₆)cycloalkyl group or a (C₁-C₃)alkoxy group,

in the form of the base enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

20

6. The compounds of formula (I) as claimed in one of the preceding claims 1 to 4, characterized in that:

- R₁ represents a phenyl group, substituted with one substituent chosen from halogen atom and an a -OR_a group, in which R_a represents a (C₁-C₃)alkyl group,

25

in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

30

7. The compounds of formula (I) as claimed in one of the preceding claims 1 to 6, characterized in that:

- R₂ represents :

- an aryl group, unsubstituted or substituted with one or more substituents chosen from :
 - a (C₁-C₃)alkyl group,
 - a (C₃-C₆)cycloalkyl group, unsubstituted or substituted with a hydroxy(C₁-C₃)alkyl group,
 - a (C₃-C₆)heterocycloalkyl group, unsubstituted or substituted with one or more (C₁-C₃)alkyl group or hydroxyl group
 - an (C₆-C₁₀)aryl group, unsubstituted or substituted with one or more -OR_c group, in which R_c represents a hydrogen atom or a (C₁-C₃)alkyl group,
 - a (C₂-C₁₀)heteroaryl group, unsubstituted or substituted with one or more -NH₂ group,
 - a -NR_dR_{d'} group, in which R_d et R_{d'}, independently, identical or different, represent a hydrogen atom, a (C₁-C₃)alkyl group,
- in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

8. The compounds of formula (I) as claimed in one of the preceding claims 1 to 7 characterized in that:

- R₂ represents :
- a phenyl group, unsubstituted or substituted with one substituent chosen from :
 - a halogen atom
 - a (C₃-C₆)cycloalkyl group, unsubstituted or substituted with one or more substituents chosen from hydroxy(C₁-C₃)alkyl group,
 - a (C₃-C₆)heterocycloalkyl group, unsubstituted or substituted with one or more (C₁-C₃)alkyl group or hydroxyl group,
 - an phenyl group, unsubstituted or substituted with one or more -OR_c group, in which R_c represents a hydrogen atom or a (C₁-C₃)alkyl group,
 - a pyridinyl group,
 - a -NR_dR_{d'} group, in which R_d et R_{d'}, identical, represent a (C₁-C₃)alkyl group,
- in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

9. The compounds of formula (I) as claimed in one of the preceding claims 1 to 8 characterized in that R₃ represents a chlorine or a fluorine atom, in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

5

10. The compounds of formula (I) as claimed in one of the preceding claims 1 to 9 characterized in that R₄ represents a fluorine atom, in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

10 11. The compound as claimed in any one of the preceding claims 1 to 10, characterized in that it is chosen from:

Compound 1. 6-Chloro-5-(4-dimethylamino-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

15 Compound 2. 6-Chloro-3-[1-hydroxy-1-(3-hydroxy-phenyl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one, sodium salt

Compound 3. 6-Chloro-3-[1-hydroxy-1-(3-hydroxy-phenyl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

Compound 4. 3-[[6-Chloro-5-(4-morpholin-4-yl-phenyl)-2-oxo-1,2-dihydro-indolylidene]-hydroxy-methyl]-benzoic acid

20 Compound 5. 6-Chloro-5-(2'-hydroxy-3'-methoxy-biphenyl-4-yl)-3-[1-hydroxy-1-(3-methoxy-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 6. 6-Chloro-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

25 Compound 7. 5-Biphenyl-4-yl-6-chloro-3-[1-hydroxy-1-phenyl-methylidene]-1,3-dihydro-indol-2-one

Compound 8. 3-[[6-Chloro-5-(4-dimethylamino-phenyl)-2-oxo-1,2-dihydro-indolylidene]-hydroxy-methyl]-benzoic acid

Compound 9. 4-[[6-Chloro-5-(4-dimethylamino-phenyl)-2-oxo-1,2-dihydro-indolylidene]-hydroxy-methyl]-benzoic acid

30 Compound 10. 6-Chloro-5-(4-dimethylamino-phenyl)-3-[1-hydroxy-1-(2-methyl-thiazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

Compound 11. 6-Chloro-3-[1-(3-fluoro-phenyl)-1-hydroxy-methylidene]-5-naphthalen-2-yl-1,3-dihydro-indol-2-one

- Compound 12. 6-Chloro-5-(2'-hydroxy-3'-methoxy-biphenyl-4-yl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- Compound 13. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isothiazol-5-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- 5 Compound 14. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- Compound 15. 6-Chloro-3-[1-(2,4-dimethyl-thiazol-5-yl)-1-hydroxy-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- Compound 16. 6-Chloro-3-[1-hydroxy-1-(5-methyl-[1,3,4]oxadiazol-2-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- 10 Compound 17. 6-Chloro-3-[1-hydroxy-1-(3-methoxy-isoxazol-5-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- Compound 18. 3-[[6-Chloro-5-(4-morpholin-4-yl-phenyl)-2-oxo-1,2-dihydro-indolylidene]-hydroxy-methyl]-benzonitrile
- 15 Compound 19. 6-Chloro-3-[1-(3-fluoro-phenyl)-1-hydroxy-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- Compound 20. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-(4-methoxy-phenyl)-1,3-dihydro-indol-2-one
- Compound 21. 6-Chloro-5-[4-(3,6-dihydro-2H-pyran-4-yl)-phenyl]-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- 20 Compound 22. 6-Chloro-5-(4-cyclopropyl-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- Compound 23. 6-Chloro-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-3-[1-hydroxy-1-(3-methyl-isothiazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- 25 Compound 24. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-(4-pyrrolidin-1-yl-phenyl)-1,3-dihydro-indol-2-one
- Compound 25. 6-Chloro-3-[1-hydroxy-1-pyridin-3-yl-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- Compound 26. 6-Chloro-5-(4-cyclopropyl-phenyl)-3-[1-(3-fluoro-phenyl)-1-hydroxy-methylidene]-1,3-dihydro-indol-2-one
- 30 Compound 27. 6-Chloro-3-[1-(3-fluoro-phenyl)-1-hydroxy-methylidene]-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-1,3-dihydro-indol-2-one
- Compound 28. 6-Chloro-3-[1-hydroxy-1-(5-methyl-isoxazol-3-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- 35 Compound 29. 6-Fluoro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one

- Compound 30. 6-Chloro-5-(4-fluoro-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- Compound 31. 3-[1-Hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-6-methyl-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- 5 Compound 32. 6-Chloro-3-[1-(2-fluoro-phenyl)-1-hydroxy-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- Compound 33. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one
- Compound 34. 6-Chloro-3-[1-(3-chloro-phenyl)-1-hydroxy-methylidene]-5-(4-10 morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- Compound 35. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-(4-pyridin-4-yl-phenyl)-1,3-dihydro-indol-2-one, hydrochloride
- Compound 36. 6-Chloro-3-[1-(4-fluoro-phenyl)-1-hydroxy-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- 15 Compound 37. 5-[4-(2-Amino-thiazol-4-yl)-phenyl]-6-chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- Compound 38. 4-{6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-2-oxo-2,3-dihydro-1H-indol-5-yl}-benzonitrile
- Compound 39. 6-Chloro-3-[1-(3-difluoromethyl-phenyl)-1-hydroxy-methylidene]-20 5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- Compound 40. 6-Chloro-3-[1-hydroxy-1-(3-trifluoromethyl-phenyl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- Compound 41. 3-[1-(3-Bromo-isoxazol-5-yl)-1-hydroxy-methylidene]-6-chloro-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- 25 Compound 42. 6-Chloro-5-(2'-hydroxy-3'-methoxy-biphenyl-4-yl)-3-[1-hydroxy-1-(3-methyl-isothiazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- Compound 43. 6-Chloro-3-[1-hydroxy-1-phenyl-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- Compound 44. 6-Chloro-5-(3-fluoro-4-hydroxy-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- 30 Compound 45. 6-Chloro-5-[5-(1-hydroxymethyl-cyclopropyl)-thiophen-2-yl]-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- Compound 46. 6-Chloro-3-[1-(2-fluoro-phenyl)-1-hydroxy-methylidene]-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-1,3-dihydro-indol-2-one
- 35 Compound 47. 6-Chloro-3-[1-(2-fluoro-phenyl)-1-hydroxy-methylidene]-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-1,3-dihydro-indol-2-one, sodium salt

- Compound 48. 6-Chloro-5-[4-(3,6-dihydro-2H-pyran-4-yl)-phenyl]-3-[1-hydroxy-1-(3-methyl-isothiazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- Compound 49. 6-Chloro-5-[4-(1-hydroxymethyl-cyclobutyl)-phenyl]-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- 5 Compound 50. 6-Chloro-3-[1-hydroxy-1-(3-methoxy-phenyl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- Compound 51. 6-Chloro-5-(2'-hydroxy-3'-methoxy-biphenyl-4-yl)-3-[1-hydroxy-1-(2-methyl-thiazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- Compound 52. 6-Chloro-5-[4-(3,6-dihydro-2H-pyran-4-yl)-phenyl]-3-[1-(3-fluoro-phenyl)-1-hydroxy-methylidene]-1,3-dihydro-indol-2-one
- 10 Compound 53. 6-Chloro-3-[1-hydroxy-1-(1-methyl-1H-pyrazol-3-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- Compound 54. 6-Chloro-3-[1-hydroxy-1-(3-methoxy-isoxazol-5-yl)-methylidene]-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-1,3-dihydro-indol-2-one
- 15 Compound 55. 6-Chloro-5-(3-fluoro-4-methoxy-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- Compound 56. 6-Chloro-5-(4-fluoro-2-hydroxy-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- Compound 57. 6-Chloro-3-[1-hydroxy-1-(2-methyl-thiazol-4-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- 20 Compound 58. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-(4-trifluoromethoxy-phenyl)-1,3-dihydro-indol-2-one
- Compound 59. 6-Chloro-3-[1-hydroxy-1-isoxazol-5-yl-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- 25 Compound 60. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-4-yl)-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- Compound 61. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-[4-(tetrahydro-pyran-4-yl)-phenyl]-1,3-dihydro-indol-2-one
- Compound 62. 6-Chloro-3-[1-(5-cyclopropyl-isoxazol-3-yl)-1-hydroxy-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- 30 Compound 63. 6-Chloro-5-(4-chloro-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- Compound 64. 6-Chloro-5-(4-ethyl-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- 35 Compound 65. 6-Chloro-5-(4-furan-2-yl-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one

- Compound 66. 6-Chloro-5-(4-ethoxy-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- Compound 67. 6-Chloro-5-[4-(3,6-dihydro-2H-pyran-4-yl)-phenyl]-3-[1-hydroxy-1-(3-methoxy-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- 5 Compound 68. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-[4-(tetrahydro-furan-2-yl)-phenyl]-1,3-dihydro-indol-2-one.
- Compound 69. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-[4-(3-piperazin-1-yl-propoxy)-phenyl]-1,3-dihydro-indol-2-one, hydrochloride.
- Compound 70. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-
10 {4-[3-(4-methyl-piperazin-1-yl)-propoxy]-phenyl}-1,3-dihydro-indol-2-one, hydrochloride.
- Compound 71. 6-Fluoro-5-(2'-hydroxy-3'-methoxy-biphenyl-4-yl)-3-[1-hydroxy-1-(3-methoxy-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- Compound 72. 6-Fluoro-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- 15 Compound 73. 3-[1-(3-Bromo-isoxazol-5-yl)-1-hydroxy-methylidene]-6-chloro-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-1,3-dihydro-indol-2-one
- Compound 74. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-[4-(4-methyl-piperazin-1-yl)-phenyl]-1,3-dihydro-indol-2-one, hydrochloride.
- Compound 75. 6-Chloro-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-3-[1-
20 hydroxy-1-(2-methyl-thiazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one
- Compound 76. 3-[1-(3-tert-Butyl-isoxazol-5-yl)-1-hydroxy-methylidene]-6-chloro-5-[4-(1-hydroxymethyl-cyclopropyl)-phenyl]-1,3-dihydro-indol-2-one
- Compound 77. 6-Chloro-3-[1-(3-fluoro-4-methoxy-phenyl)-1-hydroxy-methylidene]-5-(4-morpholin-4-yl-phenyl)-1,3-dihydro-indol-2-one
- 25 Compound 78. 6-Chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-5-[4-(1-methyl-piperidin-4-yl)-phenyl]-1,3-dihydro-indol-2-one, hydrochloride
- Compound 79. 6-chloro-3-[hydroxy-[3-(2-methoxyethoxy)isoxazol-5-yl]methylene]-5-[4-(2-hydroxy-3-methoxy-phenyl)phenyl]indolin-2-one
- Compound 80. 6-chloro-5-[4-[1-(chloromethyl)-1,2-dihydroxy-ethyl]phenyl]-3-
30 [hydroxy-(3-methylisoxazol-5-yl)methylene]indolin-2-one
- Compound 81. 6-chloro-5-(4-hydroxy-3-methoxy-phenyl)-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]indolin-2-one
- Compound 82. 6-chloro-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]-5-[4-(2-morpholinoethoxy)phenyl]indolin-2-one hydrochloride
- 35 Compound 83. 4,6-difluoro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

- Compound 84. 6-chloro-3-[(3-fluoro-4-methoxy-phenyl)-hydroxy-methylene]-5-[4-(2-hydroxy-3-methoxy-phenyl)phenyl]indolin-2-one
- Compound 85. 6-chloro-5-[2-fluoro-4-[1-(hydroxymethyl)cyclopropyl]phenyl]-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]indolin-2-one
- 5 Compound 86. 6-chloro-3-[(3-cyclohexylisoxazol-5-yl)-hydroxy-methylene]-5-(4-morpholinophenyl)indolin-2-one
- Compound 87. 6-chloro-3-[(3-cyclopropylisoxazol-5-yl)-hydroxy-methylene]-5-(4-morpholinophenyl)indolin-2-one
- Compound 88. 6-chloro-3-[(3-fluoro-4-methoxy-phenyl)-hydroxy-methylene]-5-[4-10 [1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- Compound 89. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(4-hydroxytetrahydropyran-4-yl)phenyl]indolin-2-one
- Compound 90. 6-chloro-5-[4-(2-hydroxy-3-methoxy-phenyl)phenyl]-3-[hydroxy-[3-(2-morpholinoethoxy)isoxazol-5-yl]methylene]indolin-2-one
- 15 Compound 91. 6-chloro-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]-5-[4-(3-hydroxypropoxy)phenyl]indolin-2-one
- Compound 92. 4,6-difluoro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(2-hydroxy-3-methoxy-phenyl)phenyl]indolin-2-one
- Compound 93. 6-chloro-3-[hydroxy-[3-(4-methylpiperazin-1-20 yl)phenyl]methylene]-5-(4-morpholinophenyl)indolin-2-one hydrochloride
- Compound 94. 6-chloro-3-[hydroxy-(3-morpholinophenyl)methylene]-5-(4-morpholinophenyl)indolin-2-one
- Compound 95. 6-chloro-3-[[3-fluoro-4-(trifluoromethoxy)phenyl]-hydroxy-methylene]-5-(4-morpholinophenyl)indolin-2-one
- 25 Compound 96. 6-chloro-5-[3-fluoro-4-[1-(hydroxymethyl)cyclopropyl]phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- Compound 97. 6-chloro-3-[(3-chloro-5-fluoro-4-methoxy-phenyl)-hydroxy-methylene]-5-(4-morpholinophenyl)indolin-2-one
- Compound 98. 6-chloro-3-[(2,3-difluoro-4-methoxy-phenyl)-hydroxy-methylene]-30 5-(4-morpholinophenyl)indolin-2-one
- Compound 99. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(3-morpholinopropoxy)phenyl]indolin-2-one
- Compound 100. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(3-pyridylmethoxy)phenyl]indolin-2-one
- 35 Compound 101. 6-chloro-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]-5-[4-(pyrimidin-2-ylmethoxy)phenyl]indolin-2-one

- Compound 102. 6-chloro-3-[hydroxy-(3-hydroxyisoxazol-5-yl)methylene]-5-(4-morpholinophenyl)indolin-2-one
- Compound 103. 6-chloro-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]-5-[4-(2-methoxyethoxy)phenyl]indolin-2-one
- 5 Compound 104. N-[2-[4-[6-chloro-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]-2-oxo-indolin-5-yl]phenoxy]ethyl]acetamide
- Compound 105. 6-chloro-3-[(3-ethoxyisoxazol-5-yl)-hydroxy-methylene]-5-[4-(2-hydroxy-3-methoxy-phenyl)phenyl]indolin-2-one
- Compound 106. 6-chloro-3-[(3-cyclopropylisoxazol-5-yl)-hydroxy-methylene]-5-[4-10 [1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- Compound 107. 5-[-[6-chloro-5-(4-morpholinophenyl)-2-oxo-indolin-3-ylidene]-hydroxy-methyl]-4-methyl-3H-thiazol-2-one
- Compound 108. 6-chloro-3-[(2,5-difluoro-4-methoxy-phenyl)-hydroxy-methylene]-5-(4-morpholinophenyl)indolin-2-one
- 15 Compound 109. 6-chloro-3-[hydroxy-(3-isopropoxyisoxazol-5-yl)methylene]-5-[4-(2-hydroxy-3-methoxy-phenyl)phenyl]indolin-2-one
- Compound 110. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(1-methoxycyclobutyl)phenyl]indolin-2-one
- Compound 111. 6-chloro-5-[2-fluoro-4-[1-(hydroxymethyl)cyclopropyl]phenyl]-3-20 [hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- Compound 112. 3-[(3-tert-butylisoxazol-5-yl)-hydroxy-methylene]6-chloro-5-(4-morpholinophenyl)indolin-2-one
- Compound 113. 6-chloro-3-[(3-cyclopropylisoxazol-5-yl)-hydroxy-methylene]-5-[2-fluoro-4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- 25 Compound 114. 6-chloro-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]-3-[hydroxy(2-thienyl)methylene]indolin-2-one
- Compound 115. 6-chloro-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]-5-[4-(oxetan-2-ylmethoxy)phenyl]indolin-2-one
- Compound 116. 6-chloro-3-[hydroxy-(6-methoxy-3-pyridyl)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one hydrochloride
- 30 Compound 117. 6-chloro-3-[(3-cyclopropylisoxazol-5-yl)-hydroxy-methylene]-5-[4-(2-hydroxy-3-methoxy-phenyl)phenyl]indolin-2-one
- Compound 118. 6-fluoro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- 35 Compound 119. 3-[(3-cyclopropylisoxazol-5-yl)-hydroxy-methylene]6-fluoro-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one

- Compound 120. 3-[(3-cyclopropylisoxazol-5-yl)-hydroxy-methylene]-4,6-difluoro-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- Compound 121. 6-chloro-5-[4-[2-hydroxy-1-(hydroxymethyl)ethyl]phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- 5 Compound 122. 6-chloro-5-[4-(1,2-dihydroxyethyl)phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- Compound 123. 6-chloro-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]-3-[hydroxy-(5-methyl-2-thienyl)methylene]indolin-2-one
- Compound 124. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(1-methyl-4-piperidyl)oxy]phenyl]indolin-2-one hydrochloride
- 10 Compound 125. 6-fluoro-3-[(3-fluoro-4-methoxy-phenyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- Compound 126. 6-chloro-3-[2-furyl(hydroxy)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- 15 Compound 127. 6-chloro-5-(4-dimethylaminophenyl)-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- Compound 128. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-(4-tetrahydropyran-4-yloxyphenyl)indolin-2-one
- Compound 129. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(3-hydroxypropoxy)phenyl]indolin-2-one
- 20 Compound 130. 6-chloro-3-[(5-chloro-2-thienyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- Compound 131. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(3-methoxypropoxy)phenyl]indolin-2-one
- 25 Compound 132. 6-chloro-3-[hydroxy-(3-methylisoxazol-5-yl)methylene]-5-[4-(oxetan-3-ylmethoxy)phenyl]indolin-2-one
- Compound 133. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(1-methylpyrrolidin-3-yl)phenyl]indolin-2-one hydrochloride
- Compound 134. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-(4-pyrrolidin-3-ylphenyl)indolin-2-one hydrochloride
- 30 Compound 135. 6-chloro-5-[4-(3-hydroxycyclobutyl)phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- Compound 136. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(thiazol-5-ylmethoxy)phenyl]indolin-2-one
- 35 Compound 137. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-(4-pyrrolidin-1-ylphenyl)indolin-2-one

- Compound 138. 6-chloro-3-[(2,3-difluorophenyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- Compound 139. 6-chloro-5-[4-[(3-hydroxycyclobutyl)methoxy]phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- 5 Compound 140. 6-chloro-3-[hydroxy-(5-methoxy-2-pyridyl)methylene]-5-(4-morpholinophenyl)indolin-2-one
- Compound 141. 6-chloro-3-[(2,4-difluorophenyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- Compound 142. 6-chloro-3-[(5-fluoro-3-pyridyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- 10 Compound 143. 6-chloro-3-[(3,4-difluorophenyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- Compound 144. 6-chloro-3-[(3,5-difluorophenyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- 15 Compound 145. 6-chloro-5-[2-(dimethylamino)pyrimidin-5-yl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- Compound 146. 6-chloro-5-[6-(dimethylamino)-3-pyridyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- Compound 147. 6-chloro-5-[4-(dimethylamino)-3-fluoro-phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- 20 Compound 148. 6-chloro-5-[4-(dimethylamino)-2-fluoro-phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- Compound 149. 6-chloro-5-(3-fluoro-4-morpholino-phenyl)-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- 25 Compound 150. 6-chloro-3-[(3,5-difluorophenyl)-hydroxy-methylene]-5-[4-(1-methylpyrrolidin-3-yl)phenyl]indolin-2-one hydrochloride
- Compound 151. 6-chloro-3-[hydroxy-(6-methoxy-3-pyridyl)methylene]-5-(4-morpholinophenyl)indolin-2-one
- Compound 152. 6-chloro-5-[4-(4-hydroxycyclohexoxy)phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- 30 Compound 153. 6-chloro-5-[4-[cyclopropyl(methyl)amino]phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- Compound 154. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-(1-methylindol-5-yl)indolin-2-one
- 35 Compound 155. 6-chloro-3-[(2,4-difluorophenyl)-hydroxy-methylene]-5-[4-(3-hydroxycyclobutyl)phenyl]indolin-2-one

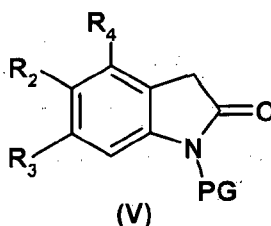
- Compound 156. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(3-hydroxypyrrolidin-1-yl)phenyl]indolin-2-one
- Compound 157. 6-chloro-3-[furo[2,3-b]pyridin-2-yl(hydroxy)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- 5 Compound 158. 6-chloro-3-[hydroxy-(2-methoxy-4-pyridyl)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- Compound 159. 6-chloro-3-[(2,5-difluoro-4-methoxy-phenyl)-hydroxy-methylene]-5-[4-(3-hydroxycyclobutyl)phenyl]indolin-2-one
- Compound 160. 6-chloro-3-[(3-fluoro-4-pyridyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- 10 Compound 161. 6-chloro-3-[(3,5-difluorophenyl)-hydroxy-methylene]-5-[4-(3-hydroxycyclobutyl)phenyl]indolin-2-one
- Compound 162. 5-[4-(azetidin-1-yl)phenyl]6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- 15 Compound 163. 6-chloro-3-[(2,4-dimethoxyphenyl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- Compound 164. 3-[(3-tert-butylisoxazol-5-yl)-hydroxy-methylene]6-chloro-5-[4-(3-hydroxycyclobutyl)phenyl]indolin-2-one
- Compound 165. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(3-methoxycyclobutyl)phenyl]indolin-2-one
- 20 Compound 166. 6-chloro-5-[4-(3-hydroxycyclobutyl)phenyl]-3-[hydroxy-(3-isopropoxyisoxazol-5-yl)methylene]indolin-2-one
- Compound 167. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl]phenyl]indolin-2-one hydrochloride
- 25 Compound 168. 3-[benzofuran-2-yl(hydroxy)methylene]6-chloro-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- Compound 169. 6-chloro-3-[furo[3,2-b]pyridin-2-yl(hydroxy)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- Compound 170. 6-chloro-3-[(5-chlorobenzofuran-2-yl)-hydroxy-methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- 30 Compound 171. 6-chloro-3-[(2-fluorophenyl)-hydroxy-methylene]-5-[4-(3-hydroxycyclobutyl)phenyl]indolin-2-one
- Compound 173. 6-chloro-5-[4-[3-(dimethylamino)propoxy]phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- 35 Compound 174. 6-chloro-3-[(3-cyclopropylisoxazol-5-yl)-hydroxy-methylene]-5-[4-(3-hydroxycyclobutyl)phenyl]indolin-2-one

- Compound 175. 6-chloro-3-[hydroxy-(3-methoxy-4-pyridyl)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- Compound 176. 6-chloro-5-[4-(2,2-dimethyl-1,3-dioxan-5-yl)phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- 5 Compound 177. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(6-oxa-2-azaspiro[3.3]heptan-2-yl)phenyl]indolin-2-one
- Compound 178. 6-chloro-3-[hydroxy-(2-methoxy-3-pyridyl)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- Compound 179. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[3-hydroxypropyl(methyl)amino]phenyl]indolin-2-one
- 10 Compound 180. 6-chloro-5-[4-(3-fluoroazetidin-1-yl)phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- Compound 181. 6-chloro-5-[4-(3,3-difluoroazetidin-1-yl)phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- 15 Compound 182. 6-chloro-3-[furo[3,2-b]pyridin-2-yl(hydroxy)methylene]-5-[4-(3-hydroxypyrrolidin-1-yl)phenyl]indolin-2-one
- Compound 183. 6-chloro-3-[hydroxy-(6-methoxy-2-pyridyl)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- Compound 184. 6-chloro-3-[hydroxy-(3-methoxy-2-pyridyl)methylene]-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]indolin-2-one
- 20 Compound 185. 6-chloro-3-[(3-ethoxyisoxazol-5-yl)-hydroxy-methylene]-5-[4-(3-hydroxycyclobutyl)phenyl]indolin-2-one
- Compound 186. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(1-methylazetidin-3-yl)phenyl]indolin-2-one
- 25 Compound 187. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(3R)-3-hydroxypyrrolidin-1-yl]phenyl]indolin-2-one
- Compound 188. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(3S)-3-hydroxypyrrolidin-1-yl]phenyl]indolin-2-one
- Compound 189. 6-chloro-3-[(2-fluorophenyl)-hydroxy-methylene]-5-[4-(3-hydroxypyrrolidin-1-yl)phenyl]indolin-2-one
- 30 Compound 190. 6-chloro-3-[[2-(dimethylamino)pyrimidin-5-yl]-hydroxy-methylene]-5-[4-(3-hydroxypyrrolidin-1-yl)phenyl]indolin-2-one
- Compound 191. 6-chloro-5-[4-(3,3-dimethylazetidin-1-yl)phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- 35 Compound 192. 6-chloro-3-[(3-cyclopropylisoxazol-5-yl)-hydroxy-methylene]-5-[4-(3-hydroxypyrrolidin-1-yl)phenyl]indolin-2-one

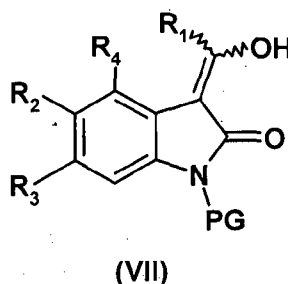
- Compound 193. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[3-(hydroxymethyl)azetidin-1-yl]phenyl]indolin-2-one
- Compound 194. 6-chloro-5-[4-[1-(hydroxymethyl)cyclopropyl]phenyl]-3-[hydroxy(thieno[2,3-b]pyridin-2-yl)methylene]indolin-2-one hydrochloride
- 5 Compound 195. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(3S,4S)-3-hydroxy-4-methoxy-pyrrolidin-1-yl]phenyl]indolin-2-one
- Compound 196. 6-chloro-5-[4-[1-(2-chloroethyl)-2-methyl-prop-1-enyl]phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- Compound 197. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(4-hydroxy-1-piperidyl)phenyl]indolin-2-one
- 10 Compound 198. 6-chloro-5-[4-[(3R)-3-fluoropyrrolidin-1-yl]phenyl]-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- Compound 199. 6-chloro-3-[hydroxy-(1-methylindol-5-yl)methylene]-5-[4-(3-hydroxypyrrolidin-1-yl)phenyl]indolin-2-one
- 15 Compound 200. 6-chloro-5-(2,6-difluoro-4-morpholino-phenyl)-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]indolin-2-one
- Compound 201. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[2-(hydroxymethyl)azetidin-1-yl]phenyl]indolin-2-one
- Compound 202. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]phenyl]indolin-2-one
- 20 Compound 203. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]phenyl]indolin-2-one
- Compound 204. 4-[4-[6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-2-oxo-indolin-5-yl]phenyl]cyclohex-3-ene-1-carboxylic acid
- 25 Compound 205. trans-6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(3S,4R)-4-hydroxytetrahydrofuran-3-yl]phenyl]indolin-2-one
- Compound 206. cis-6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(2S,4S)-4-hydroxytetrahydrofuran-2-yl]phenyl]indolin-2-one
- Compound 207. trans-6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[(2R,4S)-4-hydroxytetrahydrofuran-2-yl]phenyl]indolin-2-one
- 30 Compound 208. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(4-hydroxy-4-methyl-1-piperidyl)phenyl]indolin-2-one
- Compound 209. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[2-(hydroxymethyl)morpholin-4-yl]phenyl]indolin-2-one
- 35 Compound 210. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-[3-(hydroxymethyl)morpholin-4-yl]phenyl]indolin-2-one

in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

12. A process for preparing a compound of formula (I) as claimed in any one of claims 1 to 11, comprising the reaction of acylation compound of formula (V)

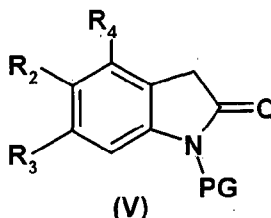


in which R_2 and R_3 are as defined in claim 1, PG is a protective group, with a carboxylic acid derivative (VI) of formula R_1CO_2H , wherein R_1 is as defined in claim 1, in the presence of an activating agent to obtain a compound of formula (VII)

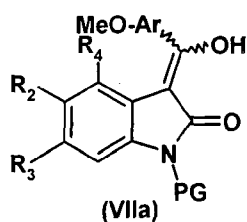


and the removal of the protective group with a an acidic or basic reagent.

13. A process for preparing a compound of formula (I) as claimed in one of claims 1 to 12, with R_2 and R_3 as defined in claim 1 and R_1 representing an aryl group substituted with a hydroxyl group, comprising the reaction of compound of formula (V)



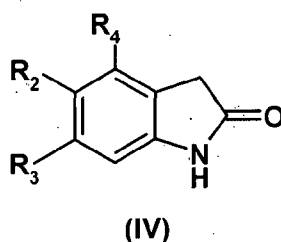
in which R_2 and R_3 are as defined in claim 1 and PG is a protecting group, with a compound (VI') of formula $MeO-Ar-CO_2H$ to obtain a compound of formula (VIIa)



in which R_2 and R_3 are as defined in the general formula (I) and R_1 represents an aryl group substituted with a methoxy group,

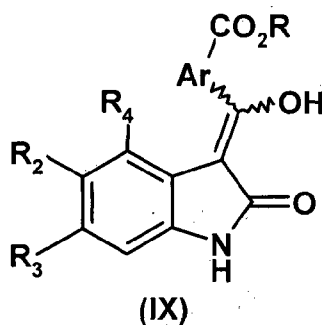
and a reaction of deprotection and demethylation of compound (VIIa) with an acidic reagent.

14. A process for preparing a compound of formula (I) as claimed in any one of claims 1 to 11, comprising the reaction of compound (IV)



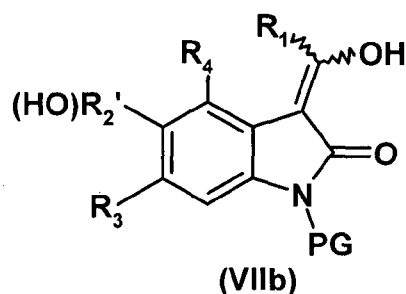
in which R_2 and R_3 are as defined in claim 1, with an acyl halide compound (VIII) of formula $R_1\text{COCl}$, in which R_1 is as defined in claim 1, in the presence of a basic reagent.

15. A process for preparing a compound of formula (I) as claimed in any one of claims 1 to 11, with R_1 representing an aryl substituted with a carboxylic group, R_2 and R_3 being as defined in claim 1, comprising the reaction of compound (IX)



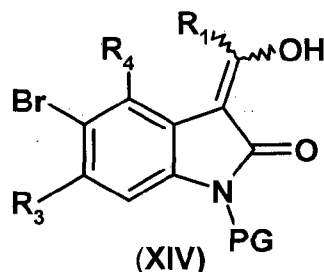
in which R_2 and R_3 are as defined in claim 1, and R is an alkyl group, with a basic reagent.

16. A process for preparing a compound of formula (I) as claimed in any one of claims 1 to 11, with R_2 represents a group R_2 substituted with at least a hydroxy group, wherein R_2 is an aryl group substituted with an aryl group, R_1 and R_3 are as defined in claim 1, comprising the reaction of compound (VIIb)



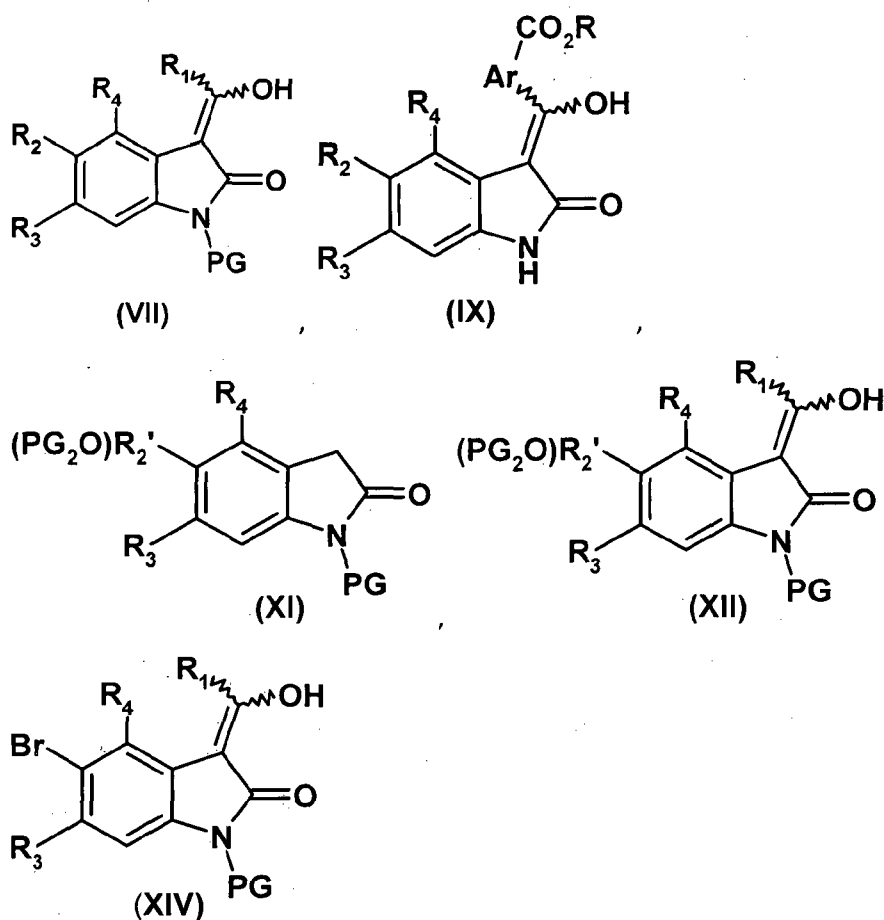
with an acidic or a basic reagent.

17. A process for preparing a compound of formula (I) as claimed in any one of claims 1 to 11, comprising the reaction of compound (XIV)



with a compound of general formula (III), $R_2-B(OR)_2$ wherein R_2 is as defined in general formula (I) and $B(OR)_2$ is a boronic acid or a boronate, in presence of palladium catalysts at temperatures ranging from 25°C to 130°C.

18. Compounds of formulae (VII), (IX), (XI), (XII) and (XIV):



in which R₁, R₂, R₃ are as defined in claim 1 and R represents an alkyl group, PG
 5 and PG₂ represent protective groups, R₂' represents an aryl group substituted with an
 aryl group.

19. A drug, characterized in that it comprises a compound as claimed in any one of
 10 claims 1 to 11, or an addition salt of this compound with a pharmaceutically acceptable
 acid or base.

20. The compound as claimed in any one of claims 1 to 11, as a medicament.

21. A pharmaceutical composition, characterized in that it comprises a compound
 15 as claimed in any one of claims 1 to 11, or a pharmaceutically acceptable salt of this
 compound, and also at least one pharmaceutically acceptable excipient.

22. The use of a compound as claimed in any of the claims 1 to 11, for the
 preparation of a medicament for the prevention or the treatment of diseases requiring
 20 the activation of AMPK.

23. The compound as claimed in any one of claims 1 to 11, for its use in the prevention or the treatment of metabolic diseases and kidney diseases.

- 5 24. The compound as claimed in any one of claims 1 to 11, for its use in the prevention or treatment of obesity and type 2 diabetes.