OXINDOLE DERIVATIVES, PREPARATION THEREOF AND THERAPEUTIC USE THEREOF

The present invention relates to oxindole derivatives, and to the preparation and 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.

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 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 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 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 are described below:

<u>Metabolic diseases including obesity and type 2 diabetes</u>

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.

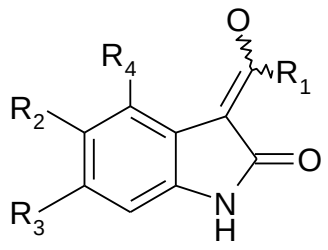
Numerous data accumulated over the past few years support the rationale which presents AMPK (AMP-activated protein kinase) as a therapeutic target of interest for the treatment of metabolic diseases including obesity and type 2 diabetes (Fang et al. Current topics in Medicinal Chemistry, 2010, 10, 397-340). 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; Merril, 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).

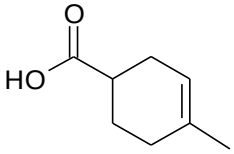
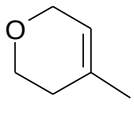
The present invention relates to compounds corresponding to formula (I):



(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 and $R_{f'}$, 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  group

- a (C_1-C_3)alkyl group unsubstituted or substituted with one or more substituents chosen from a halogen atom, a hydroxyl group and a (C_1-C_4)alkenyl group,
- a (C_3-C_6)cycloalkyl group, unsubstituted or substituted with a hydroxy(C_1-C_3)alkyl group, a hydroxyl group or an (C_1-C_4)alkoxy group,
- a –OR_b group, in which R_b represents
  - a hydrogen atom,
  - a –CF_3 group,
  - a (C_3-C_6)cycloalkyl group, unsubstituted or substituted with a hydroxyl group
  - a (C_3-C_6)heterocycloalkyl group, said (C_3-C_6)heterocycloalkyl being unsubstituted or substituted with a (C_1-C_3)alkyl group,
  - or an (C_1-C_3)alkyl group, said (C_1-C_3)alkyl group being unsubstituted or substituted with one or more :
    - hydroxyl group,
    - (C_1-C_4)alkoxy group,
    - (C_2-C_{10})heteroaryl group,
    - acetamido group,
    - di(C_1-C_3)alkyl-amino group,
    - (C_3-C_6)cycloalkyl group, said (C_3-C_6)cycloalkyl group being unsubstituted or substituted with one or more hydroxyl group, or
    - (C_3-C_6)heterocycloalkyl group, said (C_3-C_6)heterocycloalkyl group being unsubstituted or substituted with a (C_1-C_3)alkyl group;
- a (C_3-C_6)heterocycloalkyl group unsubstituted or substituted with one or more halogen atom, (C_1-C_3)alkyl group, hydroxyl group, hydroxy(C_1-C_3)alkyl group, (C_1-C_4)alkoxy group or (C_1-C_4)fluoroalkyl group,
- an (C_6-C_{10})aryl group, unsbstituted 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 (C_2-C_{10})heteroaryl group, unsubstituted or substituted with one or more -NH_2 group,

- a $-NR_dR_{d'}$ group, in which R_d and $R_{d'}$, independently, identical or different, represent a hydrogen atom, a $(C_1\text{-}C_3)$alkyl group, a hydroxy$(C_1\text{-}C_4)$alkyl or a $(C_3\text{-}C_6)$cycloalkyl group,

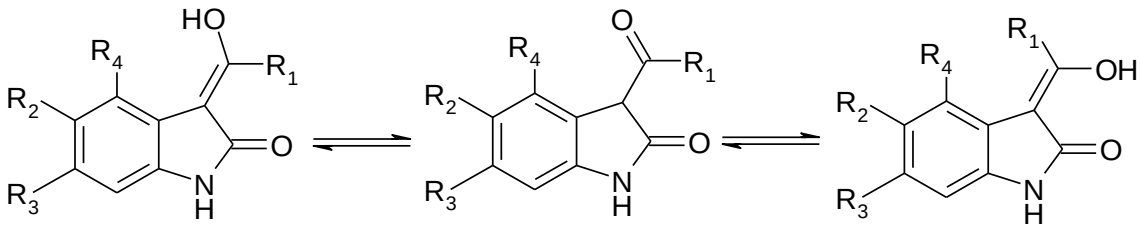
- a $(C_2\text{-}C_{10})$heteroaryl group, unsubstituted or substituted with one or more substituents chosen from:
  - a $(C_1\text{-}C_3)$alkyl group
  - a $(C_3\text{-}C_6)$cycloalkyl group, unsubstituted or substituted with a hydroxy$(C_1\text{-}C_3)$alkyl group,
  - a $-NR_gR_{g'}$ group, in which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

- R_3 represents :
  - a halogen atom,
  - a $(C_1\text{-}C_3)$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.

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 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;
- 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 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 hydroxyoalkyl group: an alkyl group in which one or more hydrogen atoms 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 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 naphtalene group;
- 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;

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

- 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 and $R_{d'}$, 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(C_1-C_3)alkyl group,

➢ R_3 represents :

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

➢ R_4 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:

➢ R_1 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 (C_1-C_3)alkyl group in particular a methyl group,
  - a (C_1-C_3)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

chosen from a halogen atom in particular a bromine atom, a (C_1-C_4)alkyl group, in particular a methyl group or a tert-butyl group, a cycloalkyl group, in particular a cyclopropyl group, an (C_1-C_3)alkoxy group in particular a methoxy group,

- R_2 represents :
  - an aryl group, in particular a phenyl or naphtalene group, optionally substituted by one or more substituents chosen from :
    - a halogen atom, in particular a fluorine or a chlorine atom,
    - a cyano group,
    - a (C_1-C_3)alkyl group, in particular an ethyl group,
    - a cycloalkyl group, in particular a cyclopropyl or a cyclobutyl group, optionally substituted by a hydroxy(C_1-C_3)alkyl group, in particular a hydroxymethyl group,
    - a $–OR_b$ group, in which R_b represents a hydrogen atom, a $–CF_3$ group or an alkyl group in particular a (C_1-C_3)alkyl group, optionally substituted by one heterocycloalkyl group, in particular a piperazinyl group, the said heterocycloalkyl group being optionally substituted by a (C_1-C_3)alkyl group, in particular a methyl group;
    - a heterocycloalkyl group, in particular a morpholinyl, a dihydropyranyl, a tetrahydropyranyl, a pyrrolidinyl, a tetrahydrofuranyl, a piperidinyl or a piperazinyl group, optionally substituted by one or more a (C_1-C_3)alkyl group, in particular a methyl group,
    - 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 (C_1-C_3)alkyl group, in particular a methyl group,
    - a heteroaryl group, in particular a pyridinyl, a thiazolyl or a furanyl group, optionally substituted by one or more $-NH_2$ group,
    - a $–NR_dR_{d'}$ group, in which R_d and $R_{d'}$, independently, identical or different, represent a hydrogen atom, a (C_1-C_3)alkyl group, in particular a methyl group,
  - 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(C_1-C_3)alkyl group in particular a hydroxymethyl group,

- R_3 represents :
  - a halogen atom, in particular a chlorine or a fluorine atom,
  - a (C_1-C_3)alkyl group, in particular a methyl group,
- R_4 represents :
  - a halogen atom, in particular a fluorine atom
  - a hydrogen atom,

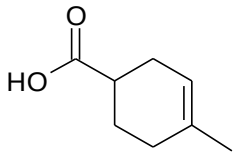
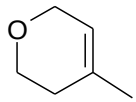
in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

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

- R_1 represents :
  - 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 CF_3 group,
    - a di or trifluoro-methyl group,
    - a carboxyl group,
    - a cyano group,
    - a morpholine group, a methylpiperazine group
  - 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 gtoup, an indolynonyl group, unsubstituted or substituted with one or more 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 group, an ethyl group, an isopropyl group, a methoxyethyl group, a morpholinoethyl group
- a dimethylamino group,

➢ R_2 represents :

- a phenyl or a naphtalene 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, unsubsituted or substituted with one or two hydroxyl groups,
  - an propyl group, unsubsituted 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 pyrrolidinyle, 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 azetidinyl 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 hydroxyxyxlohexyl 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 gtoup,
  - an acetamidoethyl group
  - an oxetanylmethyl group
  - an hydroxycyxlobutylmethyl group,
- a pyridinyl, a thiazolyl, a furanyl group, unsubstituted or substituted with one -NH_2 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,

➢ R_3 represents :
- a chlorine or a fluorine atom,
- a methyl group,

➢ R_4 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:

- R_1 represents a (C_2-C_{10})heteroaryl group, optionally substituted by one or more substituents chosen from a halogen atom, a (C_1-C_3)alkyl group, a (C_3-C_5)cycloalkyl group, a (C_1-C_4)alkoxy 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 fifth subgroup of compounds of formula (I) in which:

- R_1 represents an isoxazolyl group, optionally substituted by one substituent chosen from a (C_1-C_4)alkyl group in particular a methyl group, a (C_3-C_5)cycloalkyl group, in particular a cyclopropyl group or a cyclohexyl group or an alkoxy group, in particular a methoxy 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 sixth subgroup of compounds of formula (I) in which:

- R_1 represents a phenyl group, substituted with one substituent chosen from halogen atom and an a $–OR_a$ group, in which R_a represents a (C_1-C_3)alkyl group,

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

- R_2 represents :
  - an aryl group, in particular a phenyl group, optionally substituted by one or more substituents chosen from :
    - a (C_1-C_3)alkyl group,
    - a (C_3-C_6)cycloalkyl group, optionally substituted by a hydroxy(C_1-C_3)alkyl group,
    - a (C_3-C_6)heterocycloalkyl group, in particular a morpholinyl, a dihydropyranyl, a tetrahydropyranyl, a pyrrolidinyl, a tetrahydrofuranyl, a piperidinyl or a piperazinyl group, optionally

substituted by one or more (C_1-C_3)alkyl group, in particular a methyl group or an hydroxyl group,

- an (C_6-C_{10})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 (C_1-C_3)alkyl group,
- a (C_2-C_{10})heteroaryl group, in particular a pyridinyl, a thiazolyl or a furanyl group, optionally substituted by one or more -NH_2 group,
- a –$NR_dR_{d'}$ group, in which R_d and $R_{d'}$, independently, identical or different, represent a hydrogen atom, a (C_1-C_3)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:

- R_2 represents :
  - a phenyl group, optionally substituted by one substituent chosen from :
    - a halogen atom,
    - a (C_3-C_6)cycloalkyl group, in particular a cyclopropyl group, optionally substituted by a hydroxy(C_1-C_3)alkyl group in particular a hydroxymethyl group,
    - a (C_3-C_6)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 (C_1-C_3)alkyl group in particular a methyl group,
    - a pyridinyl group,
    - a –$NR_dR_{d'}$ group, in which R_d and $R_{d'}$, identical, represent a (C_1-C_3)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

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.

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.

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:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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.

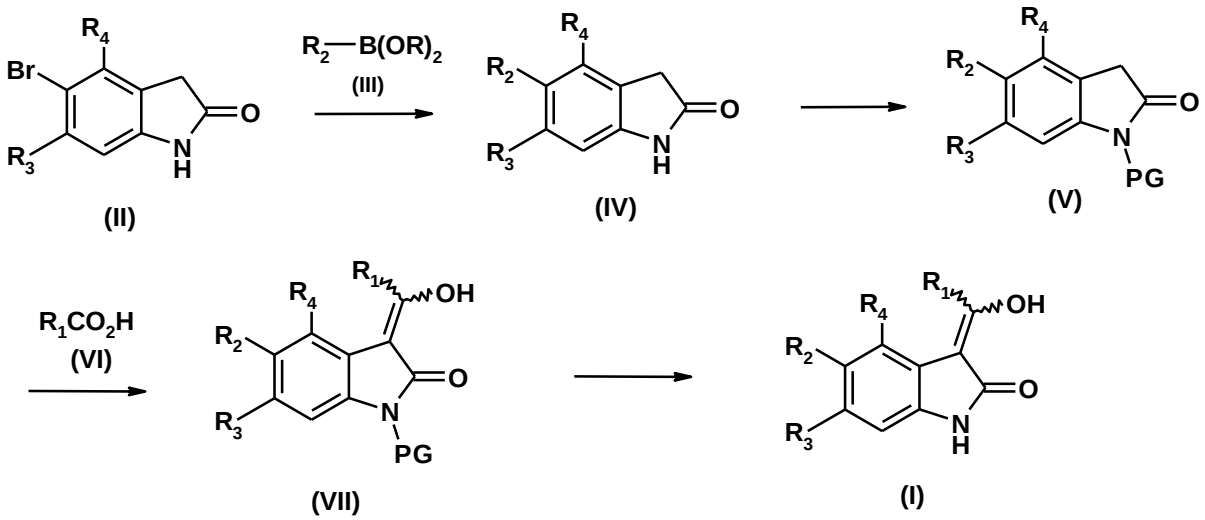
In what follows, we understand by protective group (PG), a group which allows, on one hand to protect a reactive function such as a hydroxy or an amine during a synthesis and, on the other hand to regenerate the intact reactive function at the end of the synthesis. Examples of protective groups as well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

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.

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).

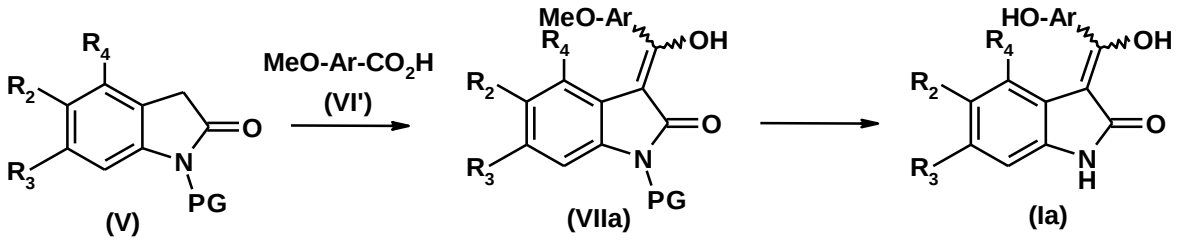
Schemes 1 through 6 outline the general procedures useful for the preparation of compounds of the present invention.

In accordance with the invention, oxindole derivatives of general formula (I), wherein R_1, R_2, R_3 and R_4 are as defined above, can be synthesized as shown in Scheme 1.



Scheme1

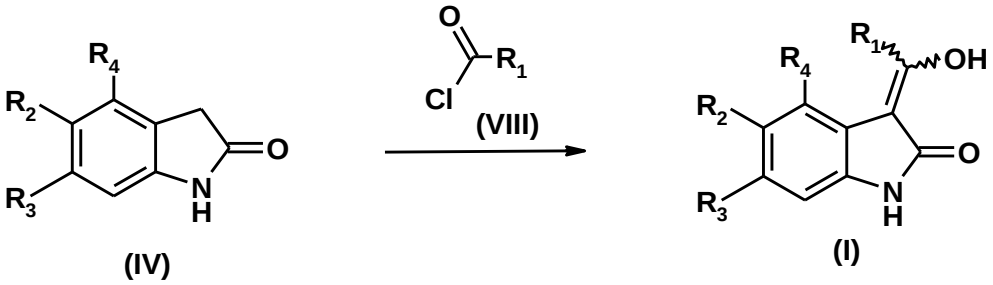
5-bromo oxindoles of general formula (II), wherein R_3 and R_4 are as defined in general formula (I), and boron derivatives of general formula (III), wherein R_2 is as defined in general formula (I) and $B(OR)_2$ is a boronic acid or a boronate, can be coupled using palladium catalysts such as $PddppfCl_2$ or tetrakistriphenylphosphine 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 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

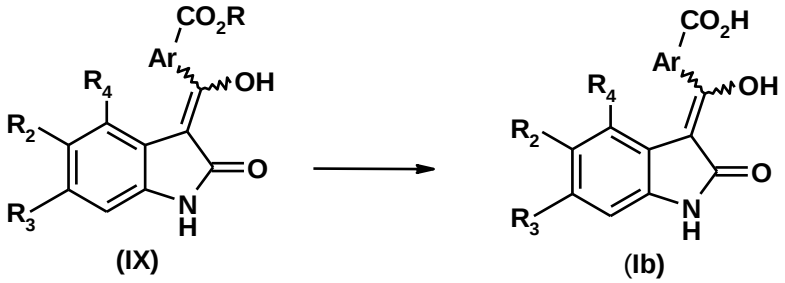
Oxindoles of general formula (Ia) corresponding to the compounds of general formula (I), wherein R_2, R_3 and R_4 are as defined in the general formula (I) and R_1 represents

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.



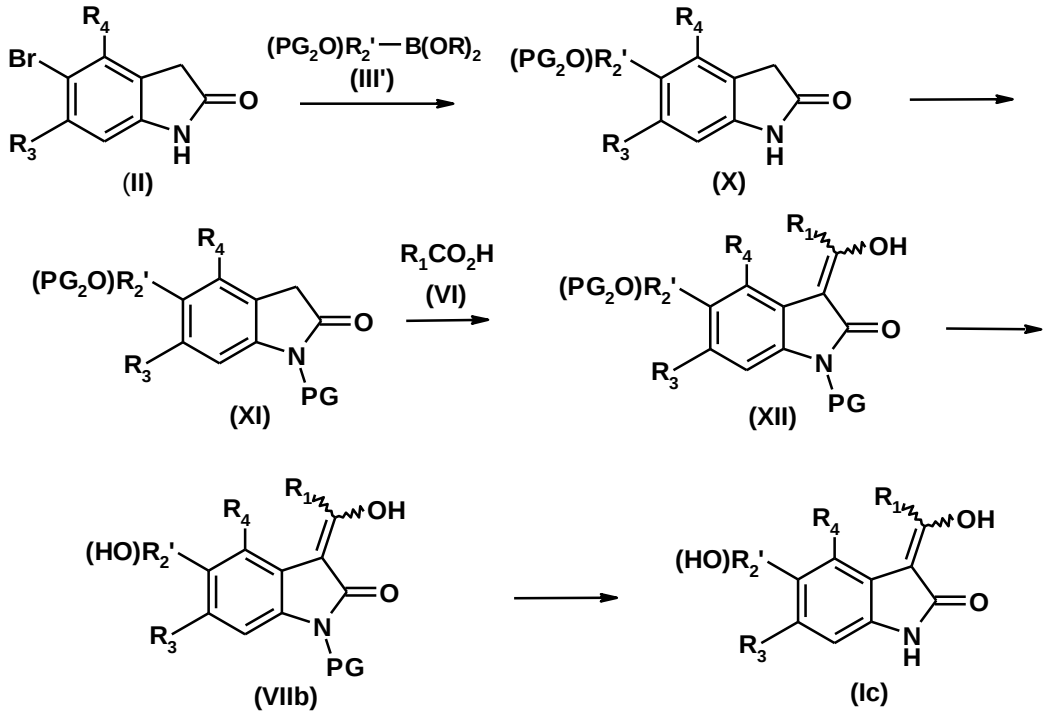
Scheme 3

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 hydroxyde in an alcohol solvent like methanol or ethanol. Compounds of general formula (IX) can be prepared as described in Schemes 1 or 3.

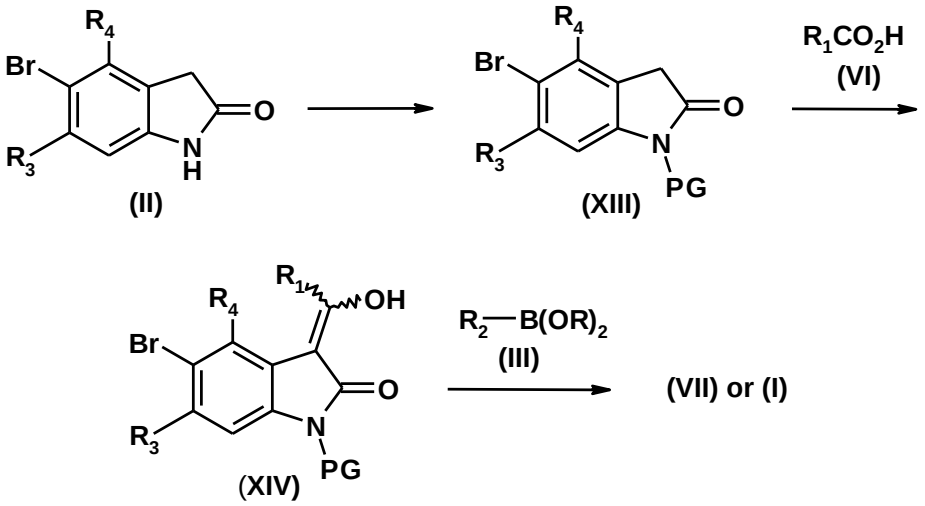


Scheme 5

Oxindoles of general formula (Ic) corresponding to compounds of general formula (I), 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 $PddppfCl_2$ or tetrakistriphenylphosphine 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 (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.

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 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 PG_2 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 $PddppfCl_2$ or tetrakistriphenylphosphine 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 Scheme1.

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
DTT : dithiothreitol
DMF : dimethylformamide
DMSO : dimethylsulfoxide
HCOOH : formic acid
TFA : trifluoroacetic acid
Eq : equivalent
ESI : electrospray Ionization
g : gram
NMR : nuclear magnetic resonance
h : hour
min : minute
HPLC : high performance liquid chromatography
Hz : Hertz
M : mass
MHz : megahertz
mL : millilitre
mmol : millimole
$PddppfCl_2$: [1,1′Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
N : normal
M : molar
nM : nanomolar
ppm : parts per millions
THF : tetrahydrofuran
t_R : retention time
UPLC : ultra-pressure liquid chromatography

UV : ultra-violet

% : percentage

RT : room temperature

DMAP : 4-dimethylaminopyridine

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

Boc_2O : di-tert-butyl dicarbonate

AcOEt : ethyl acetate

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400MHz in DMSO-d_6, using DMSO-d5 signal as reference. Chemical deplacement δ were expressed in ppm. The observed signals were expressed as following: s = singlet ; d = doublet ; t = triplet ; m = massif or broad singlet.

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.

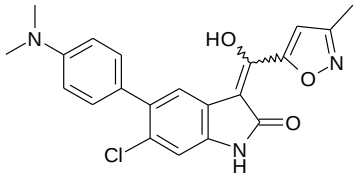
Column Acquity BEH C18 (50 x 2.1 mm; 1.7 µm) or equivalent (Acquity Cortex C18+, 50x2.1mm; 1.6µM)

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

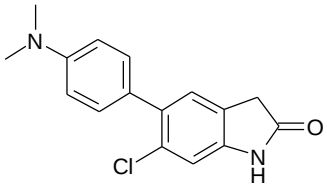
Gradient from 2% to 100% ACN with 0.1% HCOOH in water with 0.1% HCOOH in 2.6 min.

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).

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



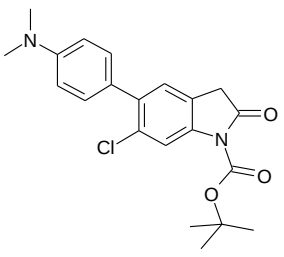
<u>Step 1.1</u> : 6-Chloro-5-(4-dimethylamino-phenyl)-2-oxo-2,3-dihydro-indole



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 Na_2CO_3 2N (3.25 ml, 6.49 mmol) was added in one portion and the reaction mixture was degassed with nitrogen during 10 minutes. $PdCl_2$(dppf). CH_2Cl_2 (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 remaining crude product was purified by flash chromatography using a gradient CH_2Cl_2/MeOH/NH_3 [100/0/0 to 98/2/0.2]. The resulting orange powder was triturated with ACN, filtered, rinsed with Et_2O and dried under vacuum (P_2O_5) 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.

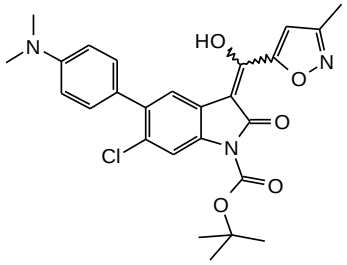
<u>Step 1.2</u> : 6-Chloro-5-(4-dimethylamino-phenyl)-2-oxo-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester



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 CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and H_2O, dried over $MgSO_4$ 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 $MgSO_4$, 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.

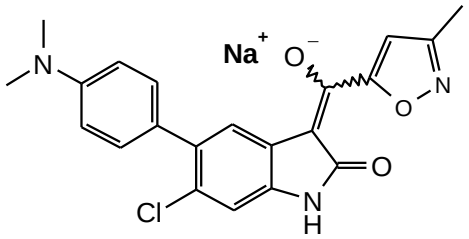
Step 1.4: 6-Chloro-5-(4-dimethylamino-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-2-oxo-2,3-dihydro-indole (example 1)

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 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 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 (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 yellow solid.

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

1H NMR (400 MHz, 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).

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

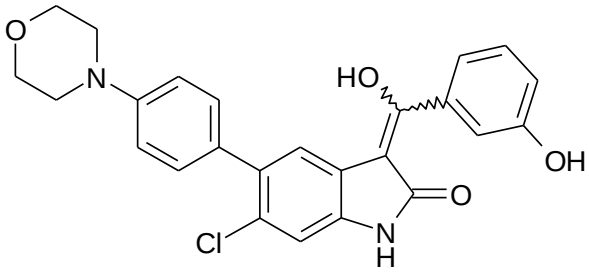


6-Chloro-5-(4-dimethylamino-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-2-oxo-2,3-dihydro-indole (0.5 g, 1.26 mmol) was suspended in methanol (15 mL). 1M NaOH (1.26 mL, 1.26 mmol) are added rapidly and stirring is continued for 1 h. Concentration under vacuum without heating and drying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

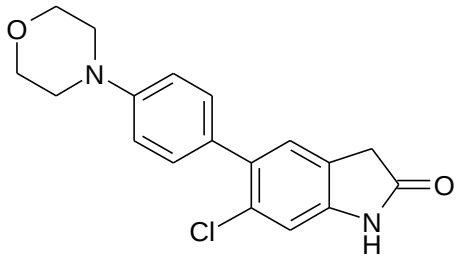
provided 6-chloro-5-(4-dimethylamino-phenyl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-2-oxo-2,3-dihydro-indole, Na salt (0.51 g) as an ochre-coloured solid.

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

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



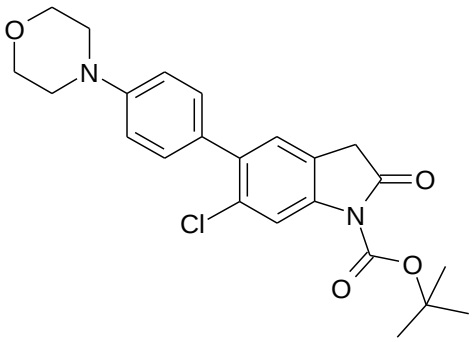
Step 3.1 : 6-chloro-5-(4-morpholinophenyl)indolin-2-one



[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 Na_2CO_3 2N (3.25 mL, 6.5 mmol) in ethanol (3 mL) and toluene (6 mL). This process is repeated ten times. The 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 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.

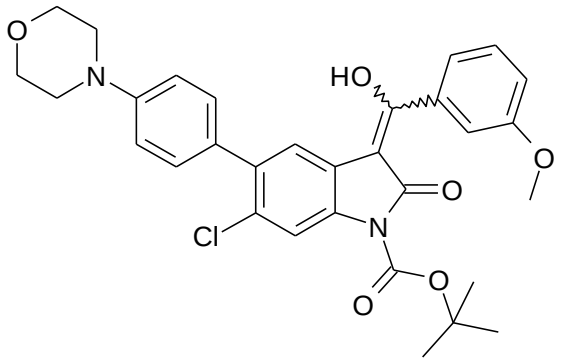
Step 3.2 : tert-Butyl 6-chloro-5-(4-morpholinophenyl)-2-oxoindoline-1-carboxylate



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 Boc_2O (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 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



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 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).

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

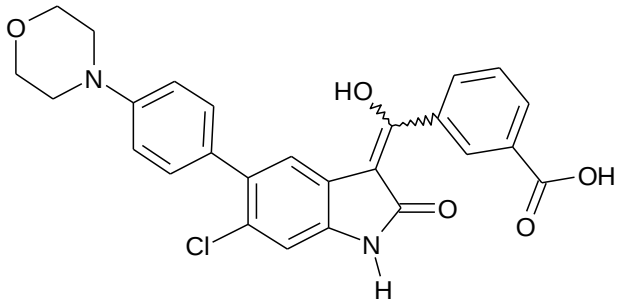
Step 3.4: 6-chloro-3-(hydroxy(3-hydroxyphenyl)methylene)-5-(4-morpholinophenyl) indolin-2-one (example 3)

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 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 cristallized in dichloromethane to yield 6-chloro-3-(hydroxy(3-hydroxyphenyl)methylene)-5-(4-morpholinophenyl)indolin-2-one (0.011 g, 28% yield).

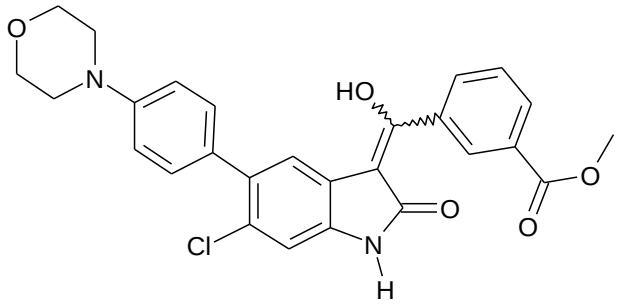
LCMS (method A) $(M+H)^+$= 449, t_R 1.33 min.

1H NMR (400 MHz, DMSO-d_6) 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)

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



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.

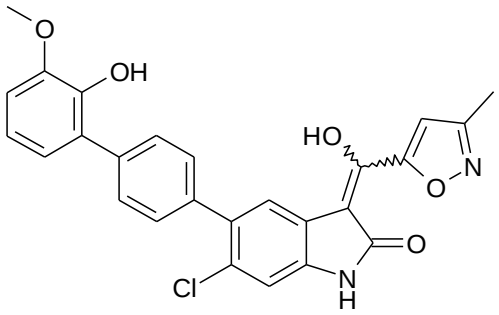
Step 4.2: -{[6-Chloro-5-(4-morpholin-4-yl-phenyl)-2-oxo-1,2-dihydro-indolylidene]-hydroxy-methyl}-benzoic acid (example 4).

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). Tetrahydrofurane (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.

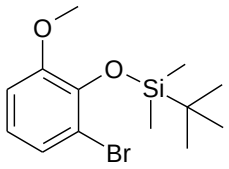
LCMS (method A) $(M+H)^+ = 477$, $t_R = 1.05$ min.

1H NMR (400 MHz, DMSO-d_6) d 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



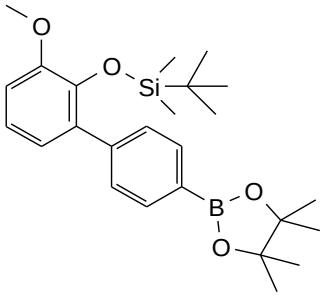
Step 5.1 : 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene



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 CH_2Cl_2 (30 mL). To the white suspension were added CH_2Cl_2 (50mL) and the mixture was washed with HCl 1N (2 x 30 ml) and H_2O (30 mL). The aqueous phase was extracted with CH_2Cl_2 (30 mL), the combined organic layers were dried over $MgSO_4$, 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.

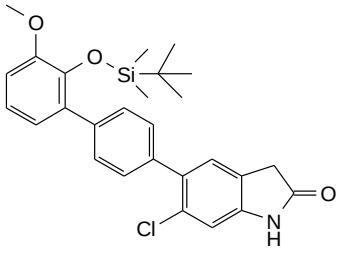
LCMS (method B) observed $(M+H)^+$ = 296, t_R = 2.44 min.

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 flasked equipped with a reflux condenser, thermometer and a nitrogen inlet were subsequently introduced to a solvent mixture of dioxane (135 mL) and of H_2O (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, 0.93mmol) and K_2CO_3 (9.64 g). This white suspension was degassed during 10 min with nitrogen, $Pd_2(dba)_3$ (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 $MgSO_4$ 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 CH_2Cl_2 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

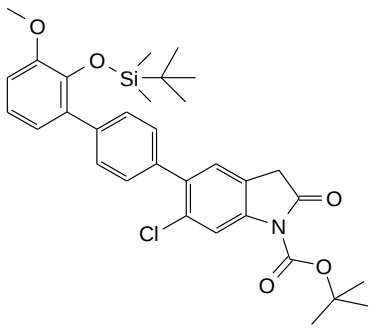


In a 25 mL microwave vial were introduced tert-butyl-((3-methoxy-4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-2-yl)oxy)dimethylsilane (2.14 g, 4.87 mmol), 5-bromo-6-chloroindolin-2-one (0.8 g, 3.25 mmol) in toluene (6 mL) and ethanol (3mL) (brownish suspension). 2N aqueous Na_2CO_3 (3.25 ml, 6.49 mmol) was

added in one portion and the reaction mixture was degassed with nitrogen during 10 minutes. $PdCl_2(dppf).CH_2Cl_2$ (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 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 CH_2Cl_2/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.

LCMS (method B) $(M+H+ACN)^+$ = 521, $(M+H)^+$ = 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

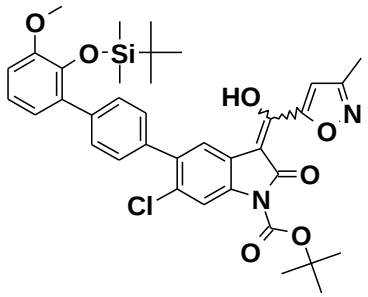


In a 250 mL round bottomed flask under inert atmosphere were suspended 5-(2'-((tert-butyldimethylsilyl)oxy)-3'-methoxy-1',2'-dihydro-[1,1'-biphenyl]-4-yl)-6-chloroindolin-2-one (1.2 g, 2.49 mmol) in anhydrous THF (50 mL). Na_2CO_3 (1.88 g, 22.40 mmol) and Boc_2O (0.717 g, 2.74 mmol) were added in one 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) $(M+ACN+Na)^+$ = 579+23+41= 643 observed , t_R = 2.72 min.

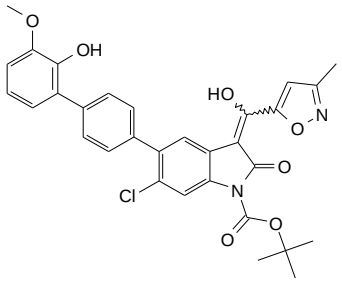
Step 5.5 : 5-[2'-(tert-Butyl-dimethyl-silanyloxy)-3'-methoxy-biphenyl-4-yl]-6-chloro-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-2-oxo-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester



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-butyldimethylsilyl)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 $NaHCO_3$ solution and water, dried over $MgSO_4$ and cencentrated under vacuum. The crude mixture was purified on silica gel (gradient CH_2Cl_2/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-methyl-isoxazol-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.

<u>Step 5.6</u> : 6-Chloro-5-(2'-hydroxy-3'-methoxy-biphenyl-4-yl)-3-[1-hydroxy-1-(3-methyl-isoxazol-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-butyldimethylsilyl)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 $MgSO_4$ 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.

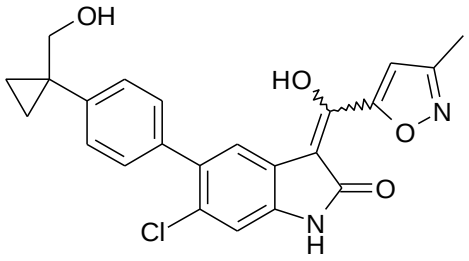
Step 5.7: 6-Chloro-5-(2'-hydroxy-3'-methoxy-biphenyl-4-yl)-3-[1-hydroxy-1-(3-methyl-isoxazol-5-yl)-methylidene]-1,3-dihydro-indol-2-one (example 5).

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 appears. 15 mL of CH_2Cl_2 were added; the organic layer was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure to obtain a brownish oil which was crystallized by adding water. After filtration and drying under reduced pressure (P_2O_5) 0.114 g (63 % yield) of a green solid were isolated.

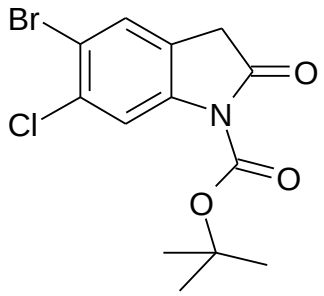
LCMS (method A) $(M+H)^+$= 475, t_R = 1.71 min.

1H NMR (400 MHz, DMSO-d_6) 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-(hydroxymethyl)cyclopropyl)phenyl)indolin-2-one



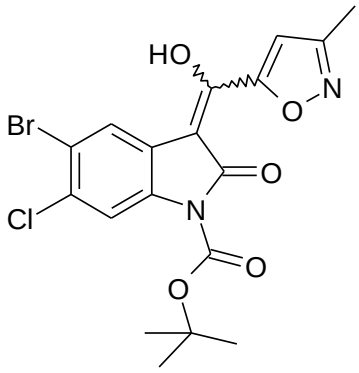
Step 6.1 : tert-butyl 5-bromo-6-chloro-2-oxoindoline-1-carboxylate



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).

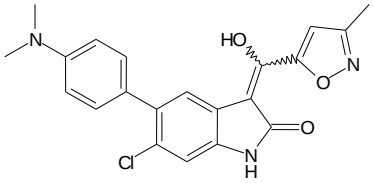
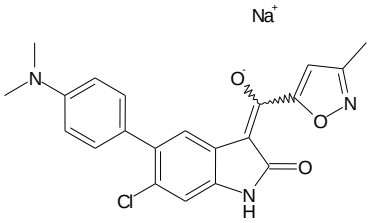
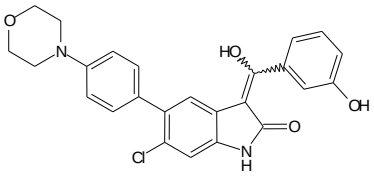
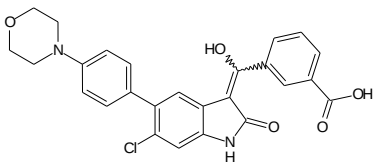
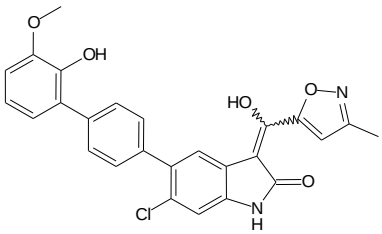
4-(1-(Hydroxymethyl)cyclopropyl)phenylboronic acid (0.26 g, 1.32 mmol), aqueous sodium carbonate 2M (1.10 mL, 2.19 mmol) and [1,1′bis(diphenylphosphino)ferrocene] dichloropalladium(II), complex with dichloromethane (0.045 g, 0.055 mmol) were added under nitrogen atmosphere to a solution of tert-butyl 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 C_{18} 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).

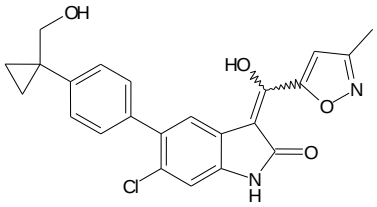
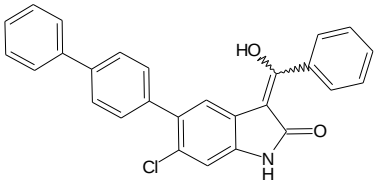
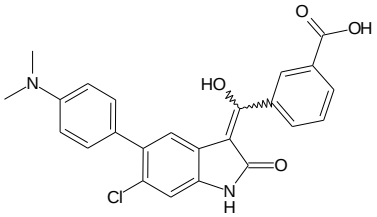
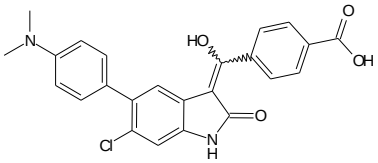
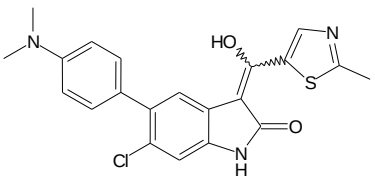
LCMS (method A) $(M+H)^+$= 423, t_R = 1.19 min.

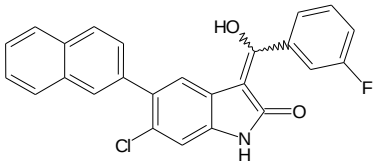
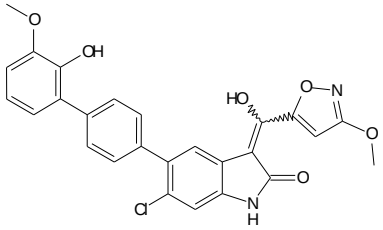
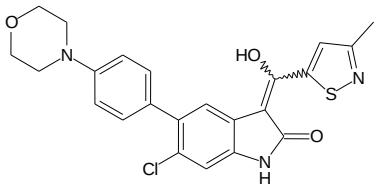
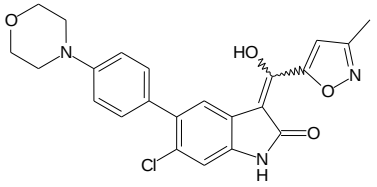
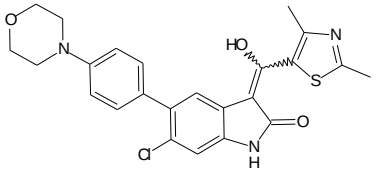
1H NMR (400 MHz, DMSO-d_6) d ppm: 0.76 - 0.91 (m, 4 H) 2.34 (s, 3 H) 3.56 - 3.61 (m, 2 H) 7.03 - 7.13 (m, 1 H) 7.21 - 7.28 (m, 1 H) 7.29 - 7.42 (m, 4 H) 7.90 - 8.00 (m, 1 H) 11.00 - 11.55 (m, 1 H)

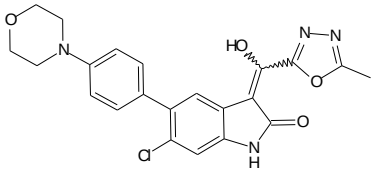
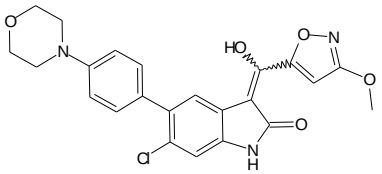
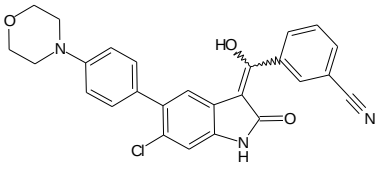
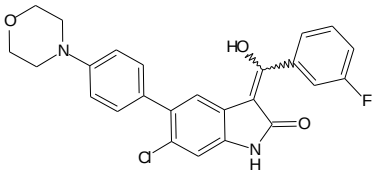
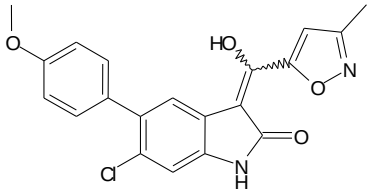
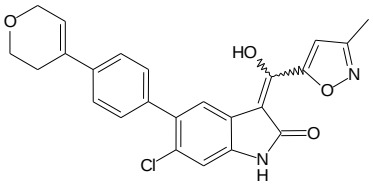
Compounds of table 1 are synthetized according to methods outlined in schemes 1 to 6 and illustrated in examples 1 to 6.

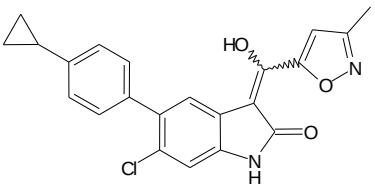
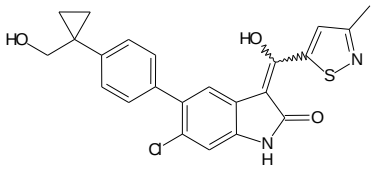
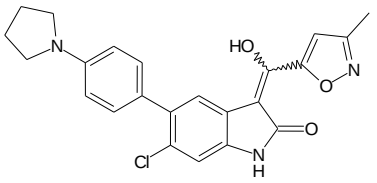
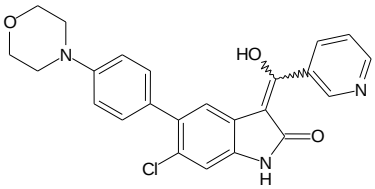
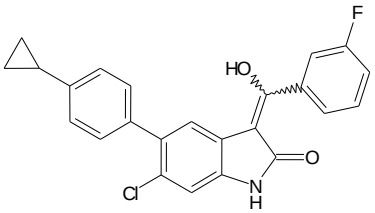
Table 1

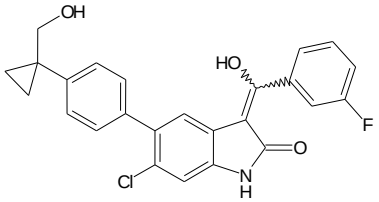
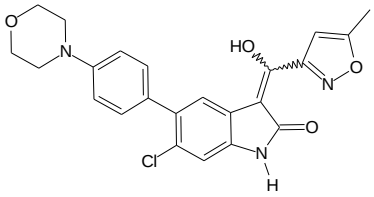
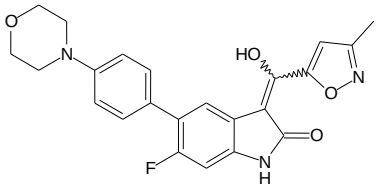
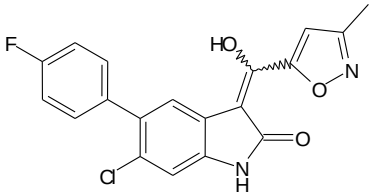
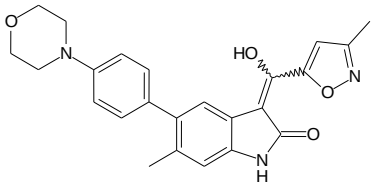
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
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2			**396 1.22**
3		**2**	**449 1.33**
4		**3 & 4**	**477 1.05**
5		**1**	**475 1.35**

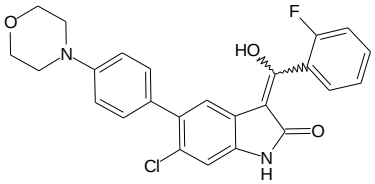
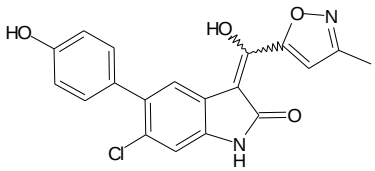
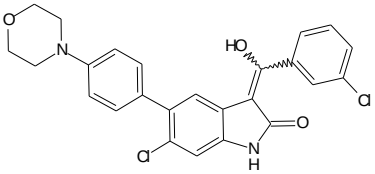
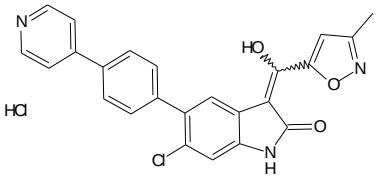
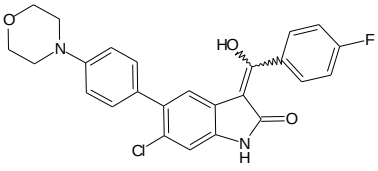
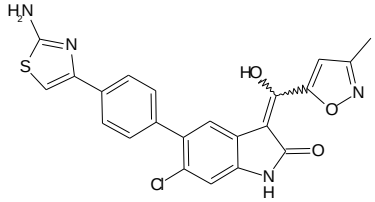
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
6		**6**	**423 1.19**
7		**3**	**424 1.55**
8		**3 & 4**	**433 1.08**
9		**1**	**433 1.04**
10		**1**	**412 1.12**

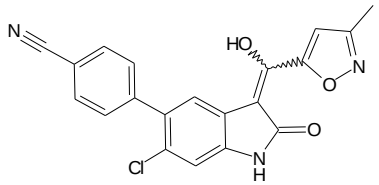
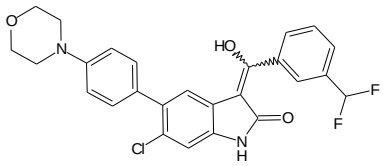
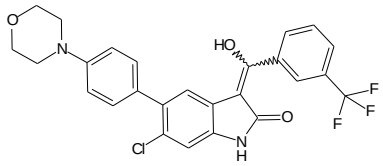
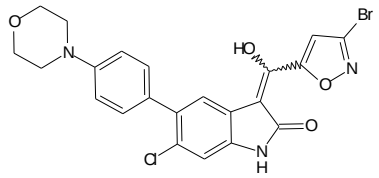
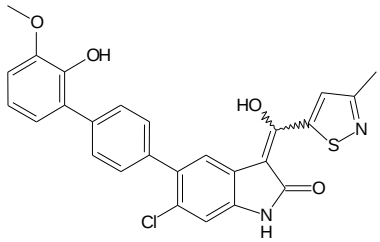
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
11		**1**	**416 1.54**
12		**5**	**491 1.64**
13		**1**	**454 1.26**
14		**1**	**438 1.24**
15		**1**	**468 1.24**

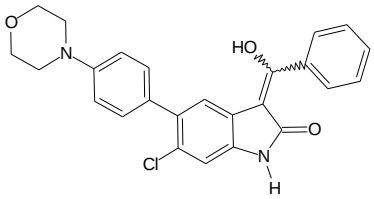
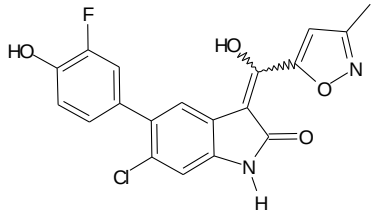
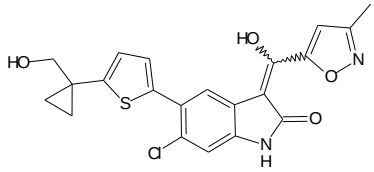
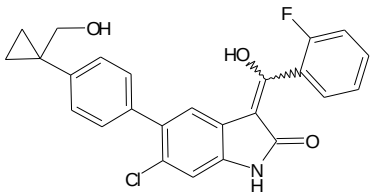
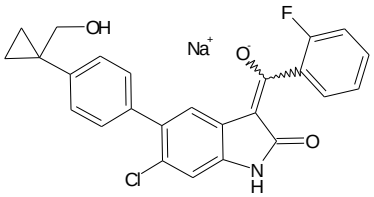
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
16		**1**	**439 1.09**
17		**1**	**454 1.26**
18		**1**	**458 1.22**
19		**1**	**451 1.31**
20		**1**	**383 1.30**
21		**1**	**435 1.62**

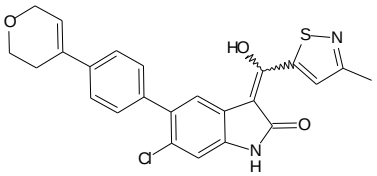
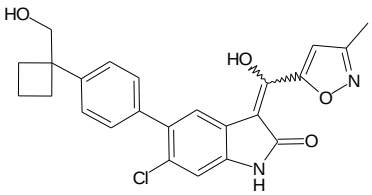
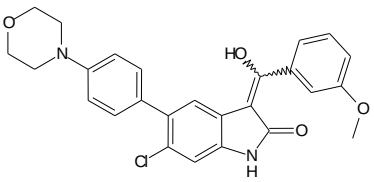
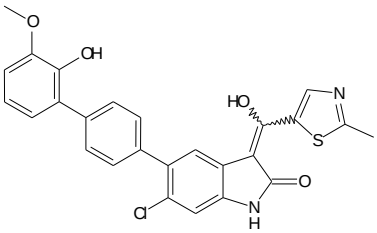
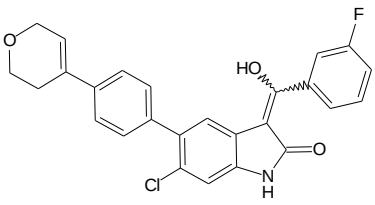
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
22		**1**	**393 1.93**
23		**1**	**439 1.41**
24		**1**	**422 1.75**
25		**1**	**432 1.12**
26		**1**	**406 1.80**

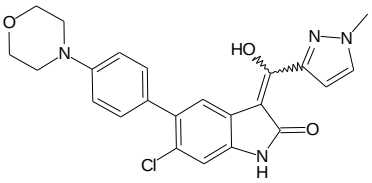
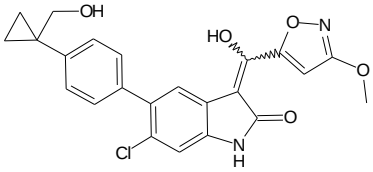
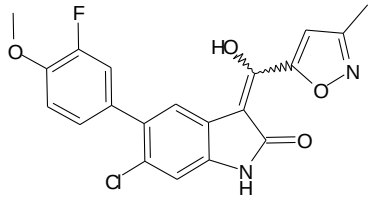
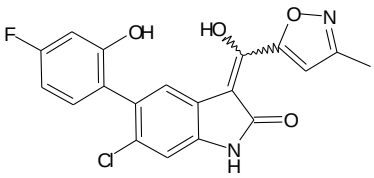
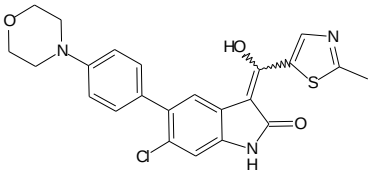
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
27		**1**	**436 1.48**
28		**1**	**438 1.50**
29		**1**	**422 1.43**
30		**1**	**369 1.58**
31		**1**	**418 1.43**

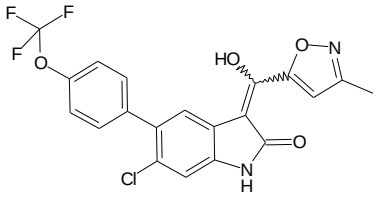
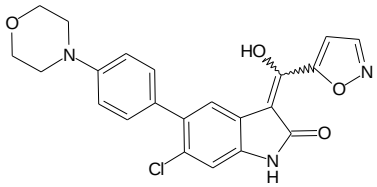
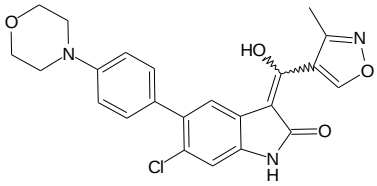
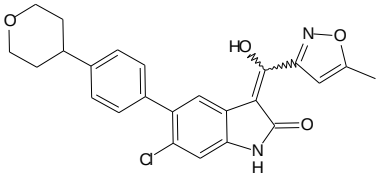
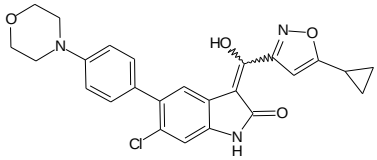
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
32		**1**	**451 1.50**
33		**6**	**369 1.26**
34		**1**	**467 1.67**
35		**6**	**430 1.12**
36		**1**	**451 1.57**
37		**6**	**451 0.74**

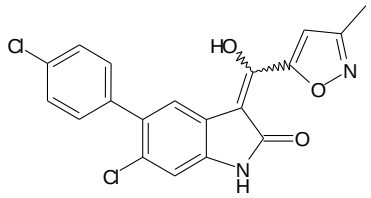
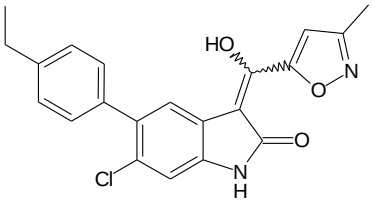
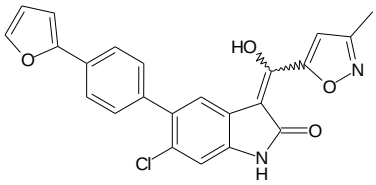
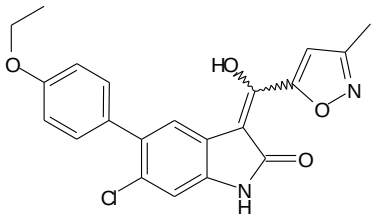
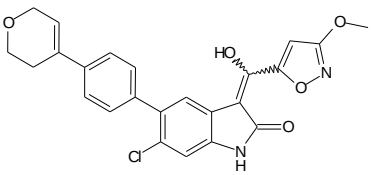
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
38		**1**	**378 1.46**
39		**1**	**483 1.55**
40		**1**	**501 1.68**
41		**1**	**502 1.59**
42		**5**	**491 1.64**

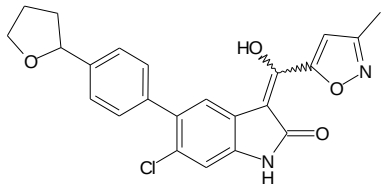
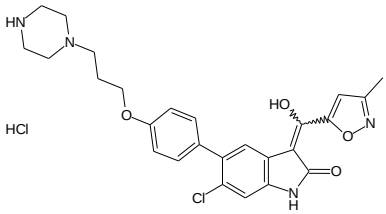
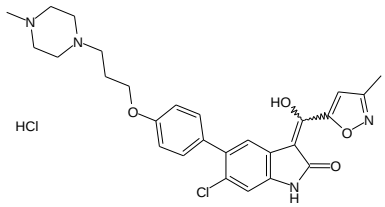
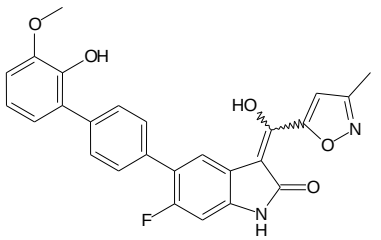
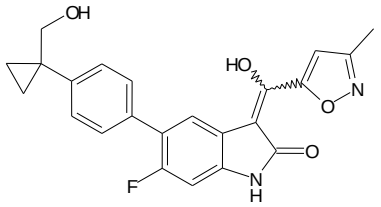
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
43		**1**	**433 1.54**
44		**1**	**385 1.31**
45		**1**	**429 1.4**
46		**1**	**436 1.41**
47			**435 1.42**

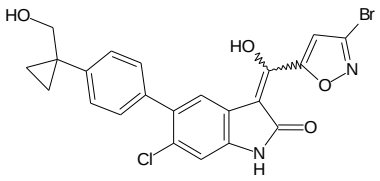
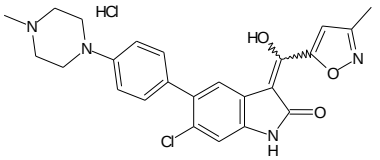
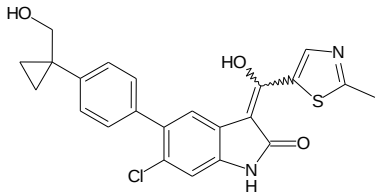
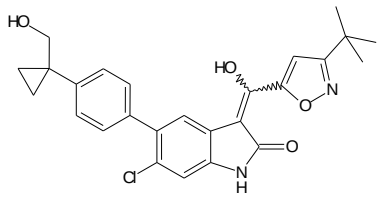
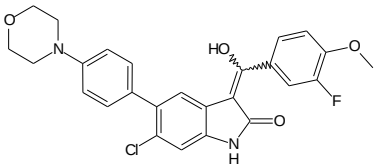
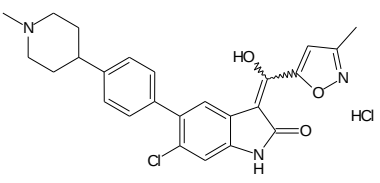
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
48		**1**	**451 1.65**
49		**1**	**437 1.51**
50		**1**	**463 1.56**
51		**5**	**491 1.53**
52		**1**	**448 1.71**

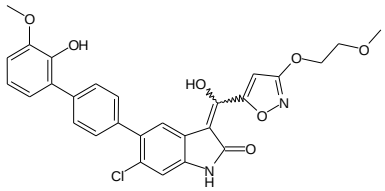
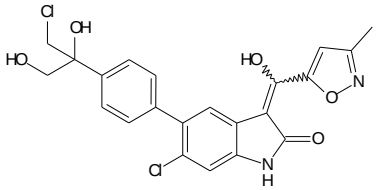
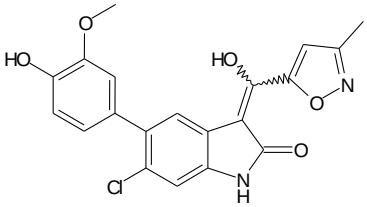
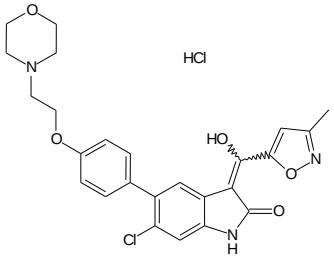
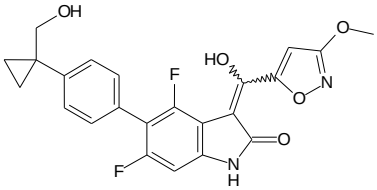
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
53		**1**	**437 1.29**
54		**1**	**436 1.43**
55		**1**	**401 1.54**
56		**6**	**387 1.32**
57		**1**	**454 1.42**

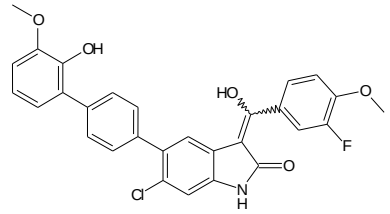
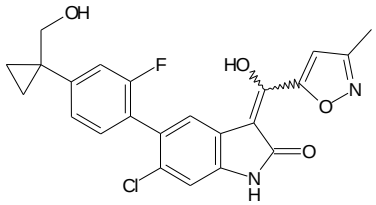
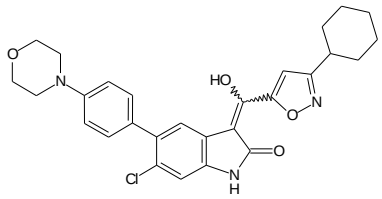
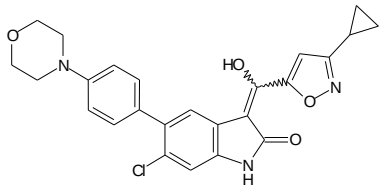
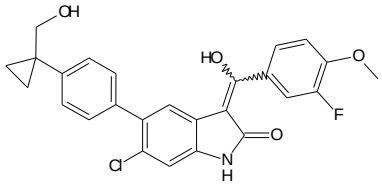
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
58		**1**	**437 1.71**
59		**1**	**424 1.38**
60		**1**	**438 1.31**
61		**1**	**437 1.61**
62		**1**	**464 1.61**

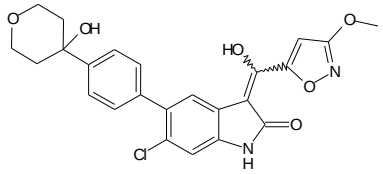
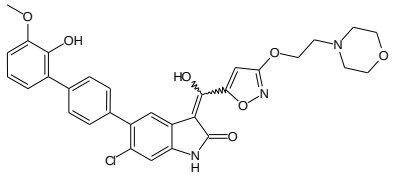
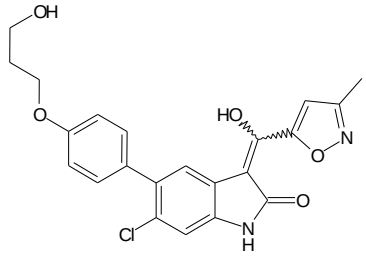
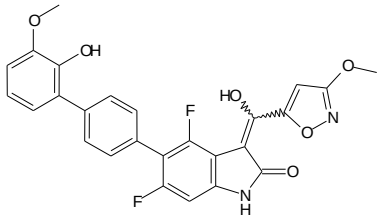
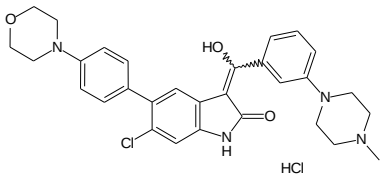
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
63		**6**	**387 1.68**
64		**6**	**381 1.72**
65		**6**	**419 1.70**
66		**6**	**397 1.62**
67		**1**	**451 1.64**

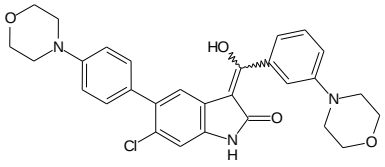
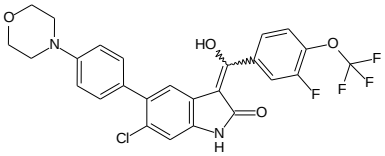
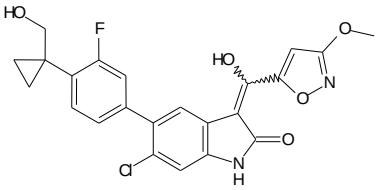
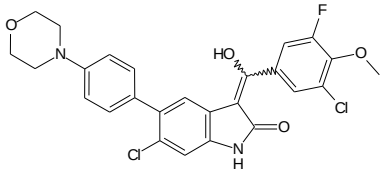
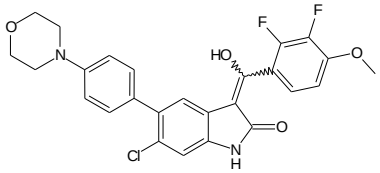
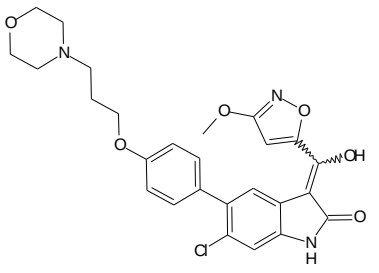
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
68		**1**	**423 1.58**
69		**6**	**495 0.78**
70		**6**	**509 0.85**
71		**5**	**475 1.68**
72		**1**	**407 1.42**

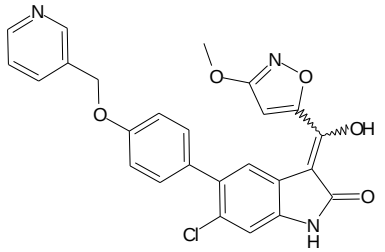
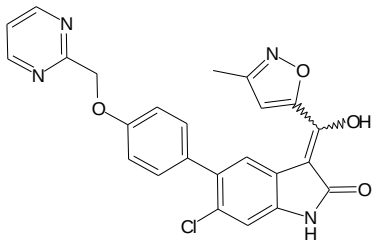
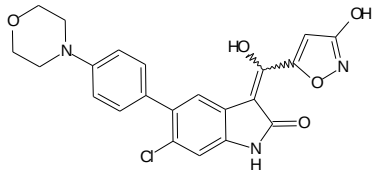
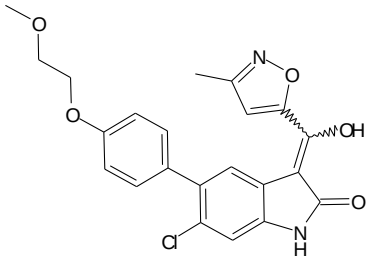
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
73		**1**	**487 1.57**
74		**6**	**451 0.89**
75		**1**	**439 3.71 (10 min gradient)**
76		**1**	**463 1.64**
77		**1**	**481 1.65**
78		**6**	**450 0.93**

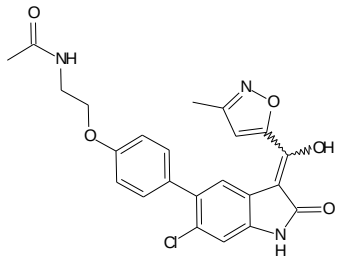
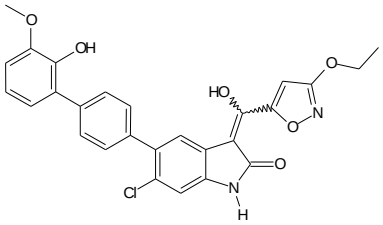
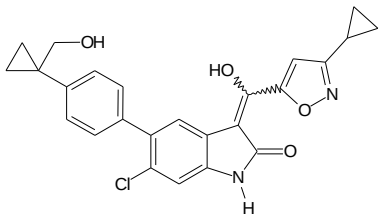
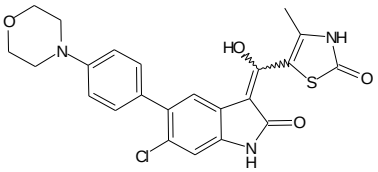
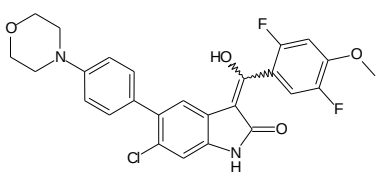
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
79		**5**	**535 1.61**
80		**6**	**459 1.24**
81		**6**	**399 1.32**
82		**6**	**482 0.87**
83		**1**	**441 1.14**

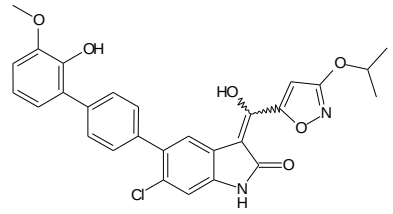
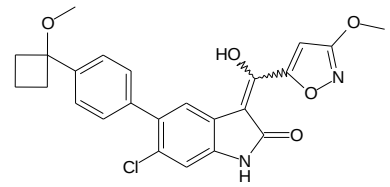
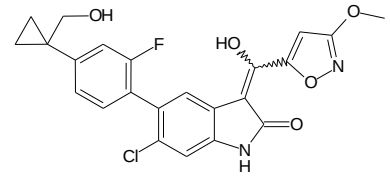
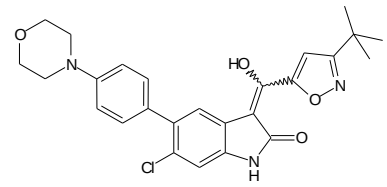
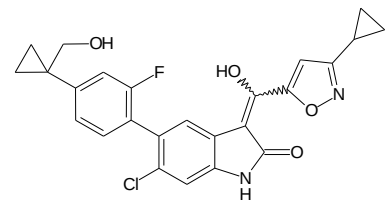
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
84		**6**	**518 1.66**
85		**6**	**441 1.39**
86		**1**	**506 1.83**
87		**1**	**464 1.55**
88		**1**	**466 1.48**

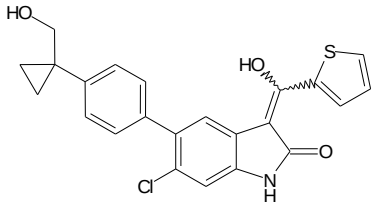
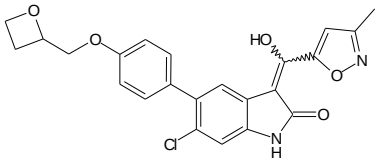
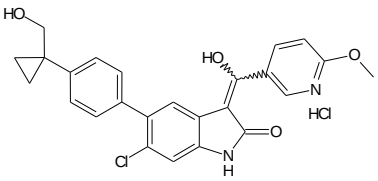
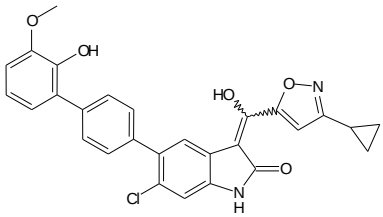
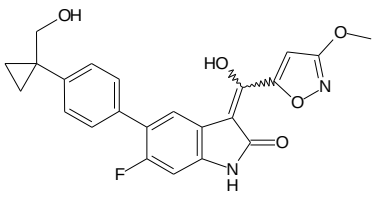
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
89		**1**	**469 2.90 (7 min gradient)**
90		**5**	**590 1.04**
91		**6**	**427 2.89 (7 min gradient)**
92		**5**	**493 1.38**
93		**1**	**529 0.96**

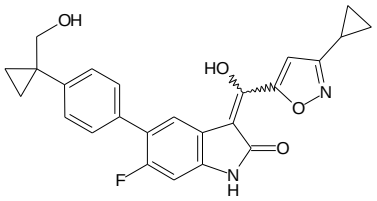
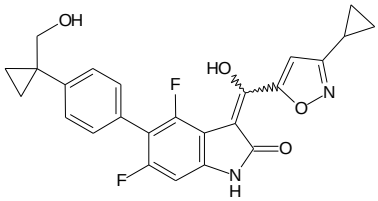
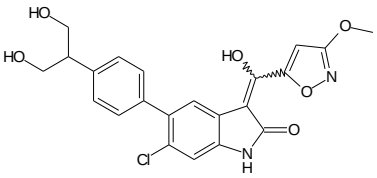
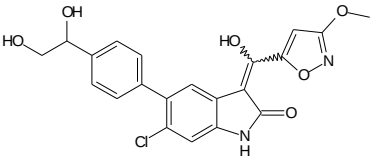
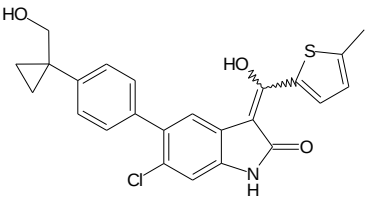
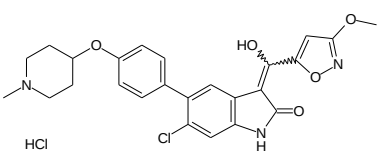
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
94		**1**	**518 1.4**
95		**1**	**535 1.56**
96		**1**	**457 1.37**
97		**1**	**515 1.52**
98		**1**	**499 1.62**
99		**1**	**512 0.98**

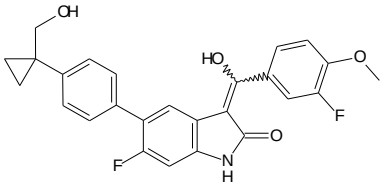
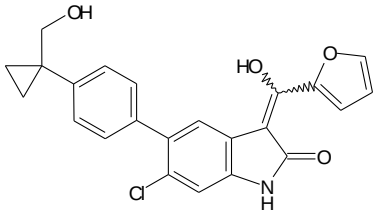
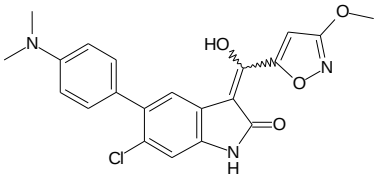
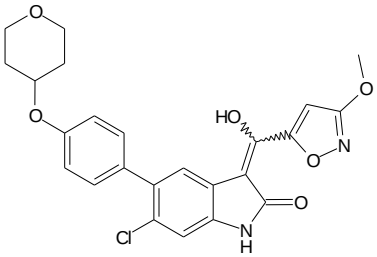
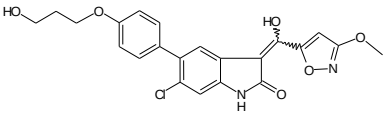
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
100		**1**	**476 1.22**
101		**1**	**461 1.36**
102		**1**	**440 1.19**
103		**1**	**427 1.38**

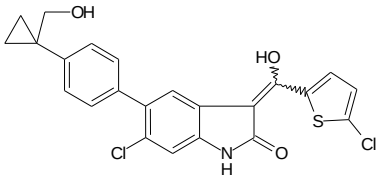
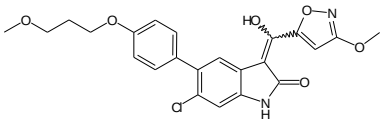
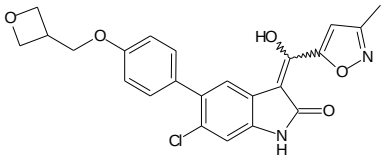
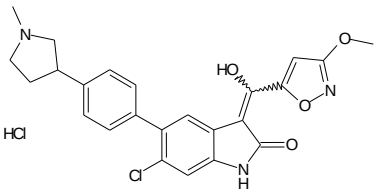
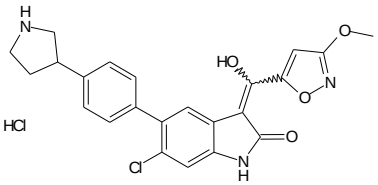
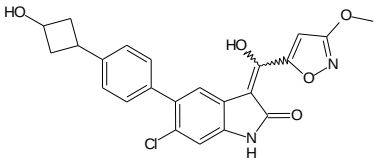
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
104		**1**	**454 1.22**
105		**5**	**505 1.58**
106		**1**	**449 1.41**
107		**1**	**470 1.17**
108		**1**	**499 1.50**

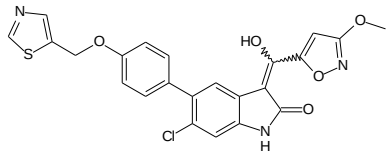
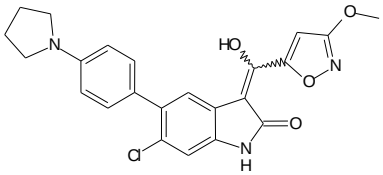
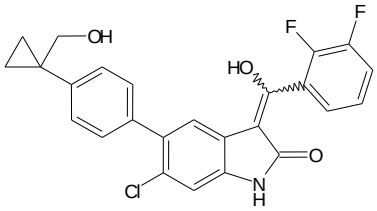
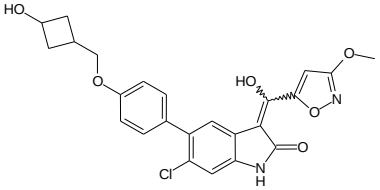
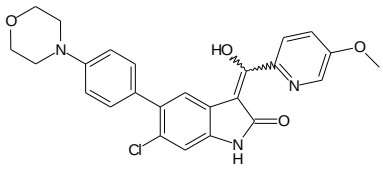
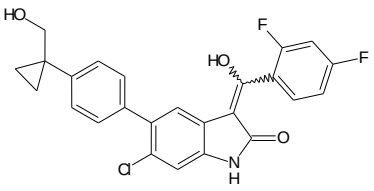
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
109		**5**	**519 1.71**
110		**1**	**453 1.64**
111		**1**	**457 1.42**
112		**1**	**480 1.54**
113		**1**	**467 1.40**

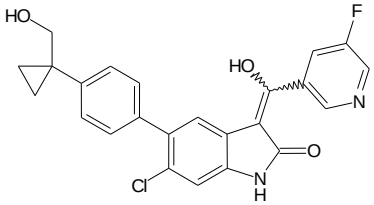
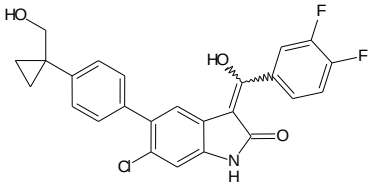
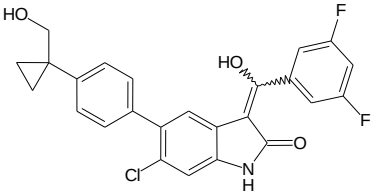
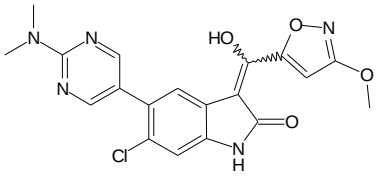
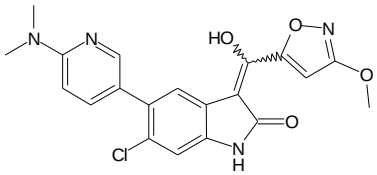
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
114		**1**	**424 1.32**
115		**6**	**439 1.36**
116		**1**	**449 1.41**
117		**6**	**501 1.70**
118		**6**	**423 1.32**

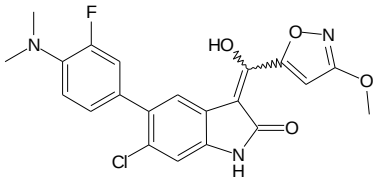
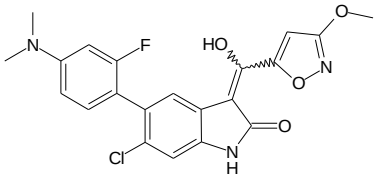
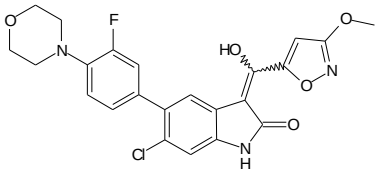
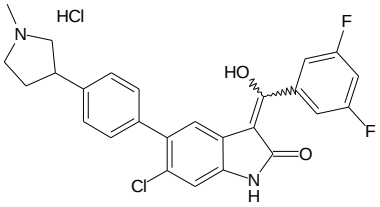
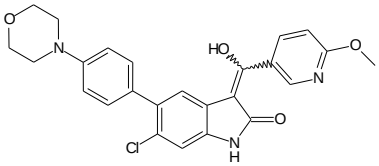
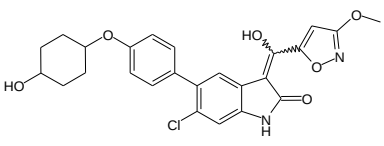
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
119		**6**	**433 1.38**
120		**6**	**451 1.31**
121		**6**	**443 1.22**
122		**6**	**429 1.21**
123		**6**	**438 1.47**
124		**6**	**482 0.99**

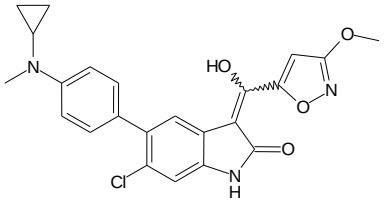
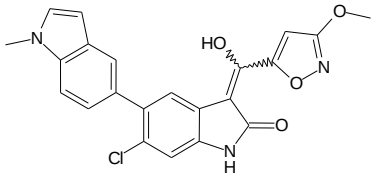
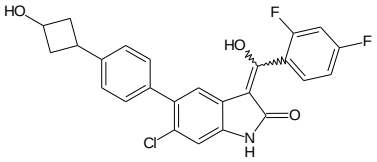
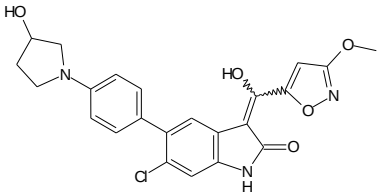
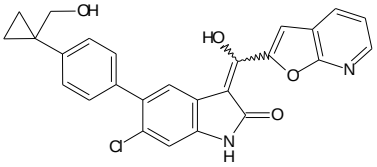
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
125		**6**	**450 3.77 (10 min gradient)**
126		**1**	**408 1.49**
127		**6**	**412 1.55**
128		**6**	**469 1.68**
129		**6**	**443 1.38**

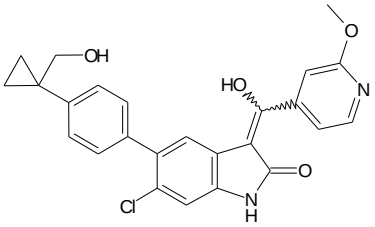
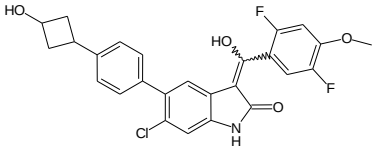
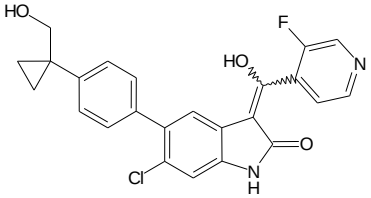
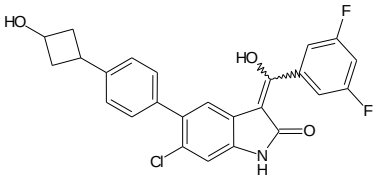
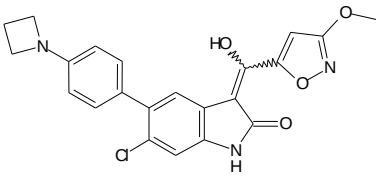
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
130		**1**	**458 1.57**
131		**6**	**457 1.50**
132		**6**	**439 1.47**
133		**6**	**452 0.88**
134		**6**	**438 0.87**
135		**6**	**439 1.35**

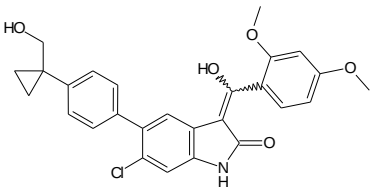
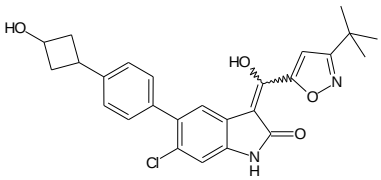
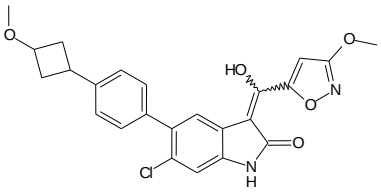
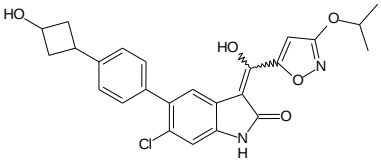
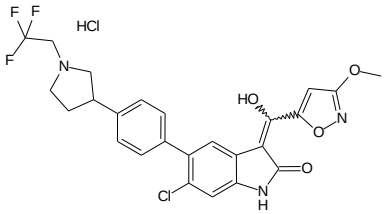
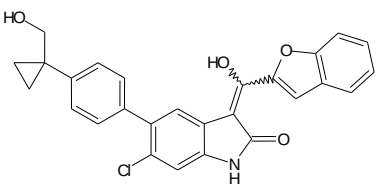
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
136		**6**	**482 1.53**
137		**6**	**438 1.79**
138		**6**	**454 1.53**
139		**6**	**469 1.43**
140		**1**	**464 1.25**
141		**6**	**454 1.43**

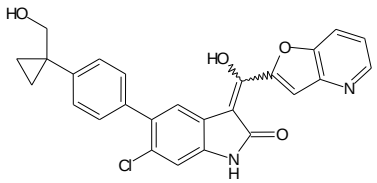
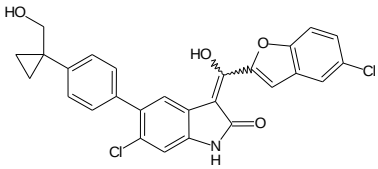
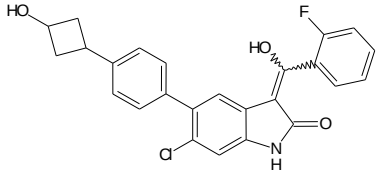
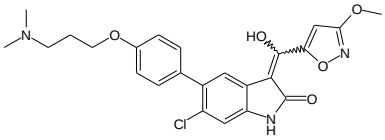
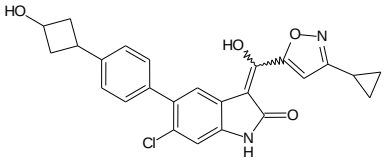
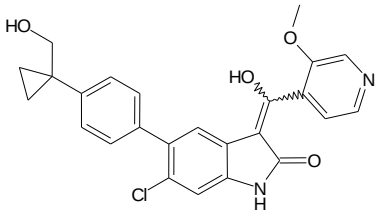
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
142		**1**	**437 1.28**
143		**1**	**454 1.49**
144		**1**	**454 1.50**
145		**1**	**414 1.42**
146		**6**	**413 0.79**

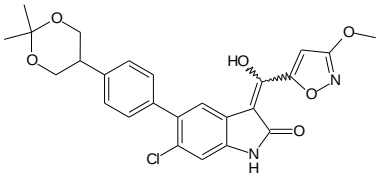
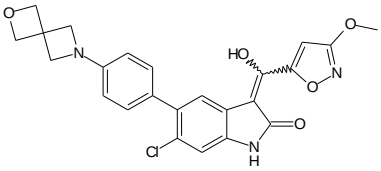
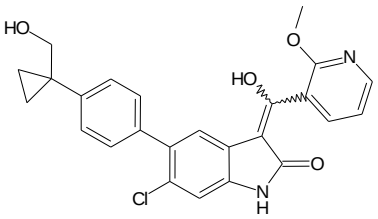
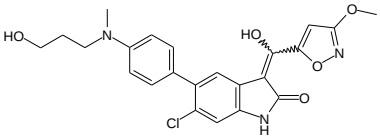
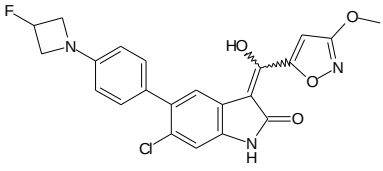
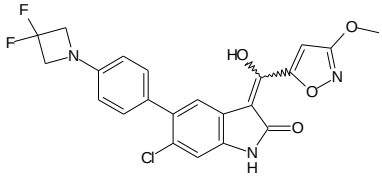
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
147		**6**	**430 4.41 (10 min gradient)**
148		**6**	**430 1.61**
149		**6**	**472 1.43-1.80 very broad peak**
150		**6**	**467 0.91**
151		**1**	**464 1.50**
152		**6**	**483 1.45**

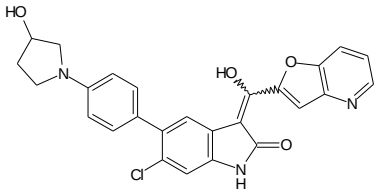
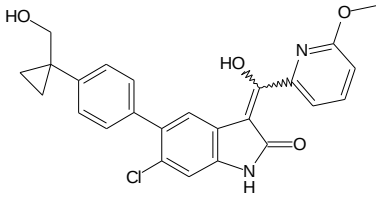
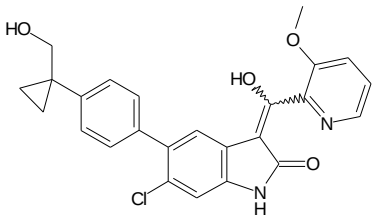
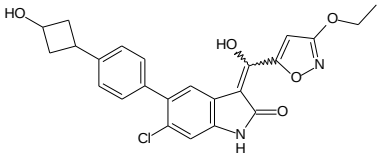
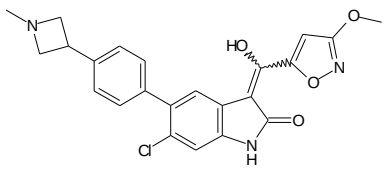
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
153		**6**	**438 1.77**
154		**6**	**422 1.60**
155		**6**	**454 1.42**
156		**6**	**454 1.40**
157		**6**	**457 1.45**

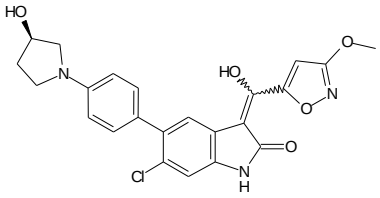
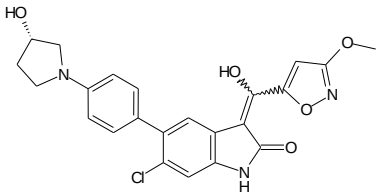
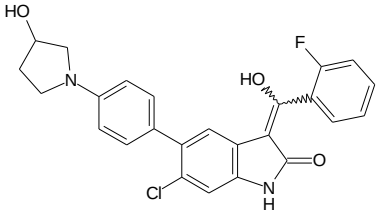
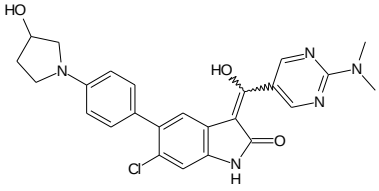
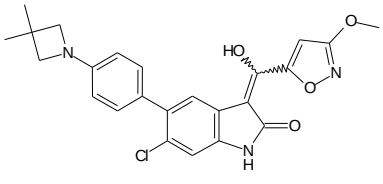
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
158		**6**	**449 1.43**
159		**6**	**484 1.42**
160		**6**	**437 1.17**
161		**6**	**454 1.47**
162		**6**	**424 1.61**

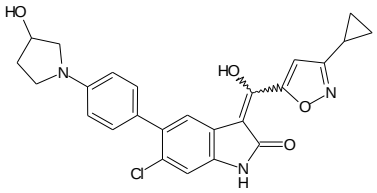
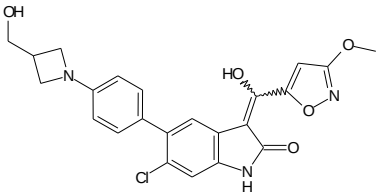
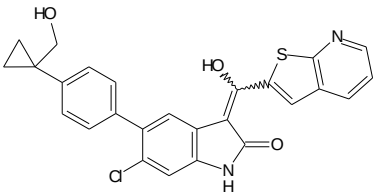
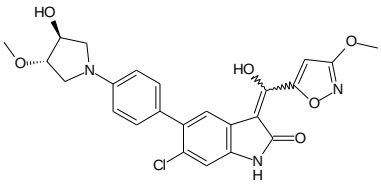
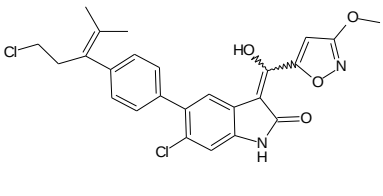
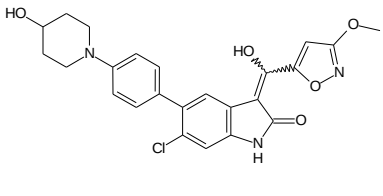
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
163		**6**	**478 1.39**
164		**6**	**465 1.61**
165		**6**	**453 1.47**
166		**6**	**467 1.54**
167		**6**	**520 1.52**
168		**6**	**458 1.62**

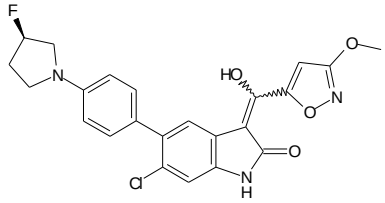
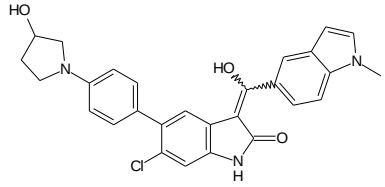
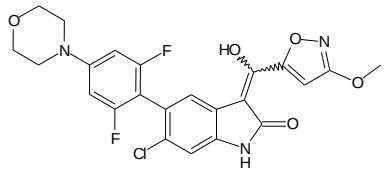
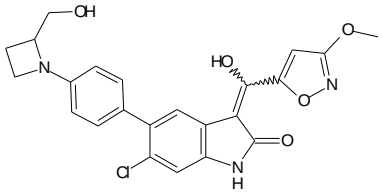
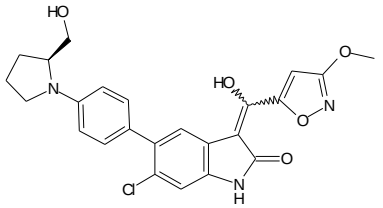
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
169		6	459 1.38
170		6	491 1.76
171		6	436 4.50 (14%)- 4.55 (96%) (10 min gradient)
173		6	470-468 1.05
174		6	449 4.82 (10 min gradient)
175		6	449 1.08

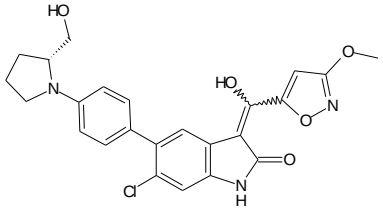
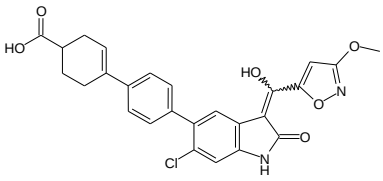
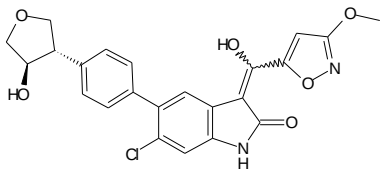
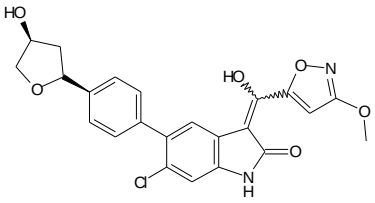
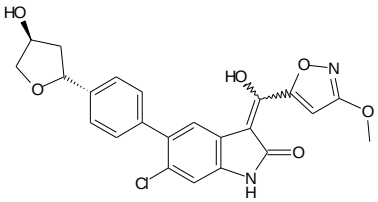
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
176		**6**	**483 1.58**
177		**6**	**466 1.49**
178		**6**	**449 1.31**
179		**6 (deprot globale)**	**456 1.17**
180		**6**	**442 1.58**
181		**6**	**460 1.65**

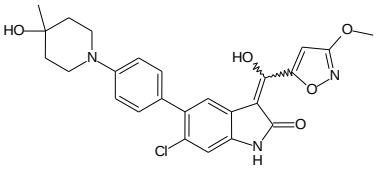
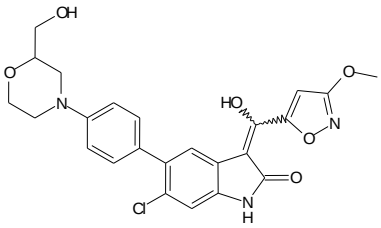
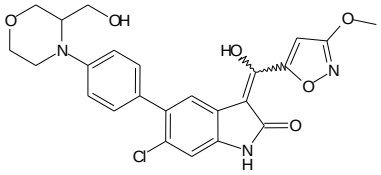
Compound	Structure	Scheme	LC/MS data $[M+H]^+$ $T_{R\ [min]}$
182		**6**	**474 1.39**
183		**6**	**449 1.37**
184		**6**	**449 1.10**
185		**6**	**453 1.49**
186		**6**	**438 0.83**

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).

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 hsAMPKα_2-2-552-His, hsAMPKβ_1-2-270 and hsAMPKγ_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 µL of test compounds in 0.5% DMSO were dispensed followed by 10 µL 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 10µL of a solution containing 200 µM of ATP as donor substrate, 2µM or 0.08µM 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 µl detection mixture containing Eu^{3+} cryptate-conjugated anti-pS^{133}-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	α2β1γ2 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	α2β1γ2 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	α2β1γ2 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	α2β1γ2 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	α2β1γ2 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)
142	6 (239)
143	3 (230)
144	0.9 (210)

Compound	α2β1γ2 AMPK EC_{50} (nM) (Emax %)
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) 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.

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 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, 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.

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 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:

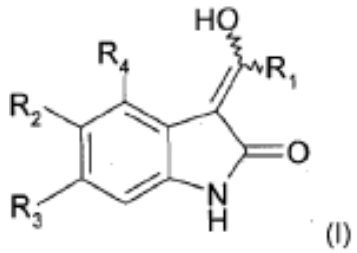
Compound according to the invention	50.0 mg
Mannitol	223.75 mg
Croscaramellose sodium	6.0 mg
Corn starch	15.0 mg
Hydroxypropylmethylcellulose	2.25 mg
Magnesium stearate	3.0 mg

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.

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

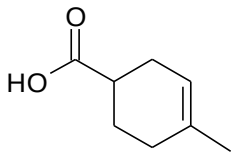
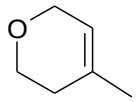
1. A compound corresponding to formula (I):



(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 group or heterocycloalkyl group
    - a $–NR_fR_{f'}$ group, in which R_f and $R_{f'}$, 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  group
    - a (C_1-C_3)alkyl group unsubstituted or substituted with one or more substituents chosen from a halogen atom, a hydroxyl group and a (C_1-C_4)alkenyl group,
    - a (C_3-C_6)cycloalkyl group, unsubstituted or substituted with a hydroxy(C_1-C_3)alkyl group, a hydroxyl group or an (C_1-C_4)alkoxy group,
    - a –OR_b group, in which R_b represents
      - a hydrogen atom,
      - a –CF_3 group,
      - a (C_3-C_6)cycloalkyl group, unsubstituted or substituted with a hydroxyl group
      - a (C_3-C_6)heterocycloalkyl group, said (C_3-C_6)heterocycloalkyl being unsubstituted or substituted with a (C_1-C_3)alkyl group,
      - or an (C_1-C_3)alkyl group, said (C_1-C_3)alkyl group being unsubstituted or substituted with one or more :
        - hydroxyl group,
        - (C_1-C_4)alkoxy group,
        - (C_2-C_{10})heteroaryl group,
        - acetamido group,
        - di(C_1-C_3)alkyl-amino group,

- $(C_3$-$C_6)$cycloalkyl group, said $(C_3$-$C_6)$cycloalkyl group being unsubstituted or substituted with one or more hydroxyl group, or
- $(C_3$-$C_6)$heterocycloalkyl group, said $(C_3$-$C_6)$heterocycloalkyl group being unsubstituted or substituted with a $(C_1$-$C_3)$alkyl group;

- a $(C_3$-$C_6)$heterocycloalkyl group unsubstituted or substituted with one or more halogen atom, $(C_1$-$C_3)$alkyl group, hydroxyl group, hydroxy$(C_1$-$C_3)$alkyl group, $(C_1$-$C_4)$alkoxy group or $(C_1$-$C_4)$fluoroalkyl group,
- an $(C_6$-$C_{10})$aryl group, unsbstituted 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 $(C_2$-$C_{10})$heteroaryl group, unsubstituted or substituted with one or more $-NH_2$ group,
- a $–NR_dR_{d'}$ group, in which R_d and $R_{d'}$, 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 and $R_{g'}$, 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.

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

- 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 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 (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 (C_1-C_4)alkoxy 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 (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 and $R_{d'}$, independently, identical or different, represent a hydrogen atom, a (C_1-C_3)alkyl group,

- a (C_2-C_{10})heteroaryl group, unsubstituted or substituted with one or more cycloalkyl group, unsubstituted or substituted with a hydroxy(C_1-C_3)alkyl group,

- R_3 represents :
  - a halogen atom,
  - a (C_1-C_3)alkyl group,

- R_4 represents an hydrogen atom

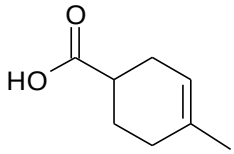
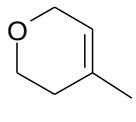
in the form of the base or of an addition salt with an acid or with a base.

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

- R_1 represents :
  - 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 CF_3 group,
    - a di or trifluoro-methyl group,
    - a carboxyl group,
    - a cyano group,
    - a morpholine group, a methylpiperazine group
  - 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 gtoup, an indolynonyl group, unsubstituted or substituted with one or more 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 group, an ethyl group, an isopropyl group, a methoxyethyl group, a morpholinoethyl group
- a dimethylamino group,

- R_2 represents :
  - a phenyl or a naphtalene 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, unsubsituted or substituted with one or two hydroxyl groups,
    - an propyl group, unsubsituted 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 $(C_1\text{-}C_3)$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 pyrrolidinyle, 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 azetidinyl 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 hydroxyxyxlohexyl 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 hydroxycyxlobutylmethyl group,
- a pyridinyl, a thiazolyl, a furanyl group, unsubstituted or substituted with one -NH_2 group,
- a –$NR_dR_{d'}$ group, in which R_d and $R_{d'}$, 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,

➢ R_3 represents :

- a chlorine or a fluorine atom,
- a methyl group,

➢ R_4 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.

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

➢ R_1 represents a (C_2-C_{10})heteroaryl group, unsubstituted or substituted with one or more substituents chosen from a halogen atom, a (C_1-C_3)alkyl group, a (C_3-C_5)cycloalkyl group, a (C_1-C_4)alkoxy group,

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:

➢ R_1 represents an isoxazolyl group, unsubstituted or substituted with one substituent chosen from a (C_1-C_4)alkyl group, a (C_3-C_6)cycloalkyl group or a (C_1-C_3)alkoxy group,

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

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

- R_1 represents a phenyl group, substituted with one substituent chosen from halogen atom and an a $–OR_a$ group, in which R_a represents a $(C_1\text{-}C_3)$alkyl group,

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

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

- R_2 represents :
  - an $(C_6\text{-}C_{10})$aryl group, unsubstituted or substituted with one or more substituents chosen from :
    - a $(C_1\text{-}C_3)$alkyl group,
    - a $(C_3\text{-}C_6)$cycloalkyl group, unsubstituted or substituted with a hydroxy$(C_1\text{-}C_3)$alkyl group,
    - a $(C_3\text{-}C_6)$heterocycloalkyl group, unsubstituted or substituted with one or more $(C_1\text{-}C_3)$alkyl group or hydroxyl group
    - an $(C_6\text{-}C_{10})$aryl group, unsubstituted or substituted with one or more $–OR_c$ group, in which R_c represents a hydrogen atom or a $(C_1\text{-}C_3)$alkyl group,
    - a $(C_2\text{-}C_{10})$heteroaryl group, unsubstituted or substituted with one or more $-NH_2$ group,
    - a $–NR_dR_{d'}$ group, in which R_d and $R_{d'}$, independently, identical or different, represent a hydrogen atom, a $(C_1\text{-}C_3)$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:

- R_2 represents :
  - a phenyl group, unsubstituted or substituted with one substituent chosen from :
    - a halogen atom

- a (C_3-C_6)ycloalkyl group, unsubstituted or substituted with one or more substituents chosen from hydroxy(C_1-C_3)alkyl group,
- a (C_3-C_6)heterocycloalkyl group, unsubstituted or substituted with one or more (C_1-C_3)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 (C_1-C_3)alkyl group,
- a pyridinyl group,
- a –$NR_dR_{d'}$ group, in which R_d and $R_{d'}$, identical, represent a (C_1-C_3)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 R_3 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.

10. The compounds of formula (I) as claimed in one of the preceding claims 1 to 9 characterized in that 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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.

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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

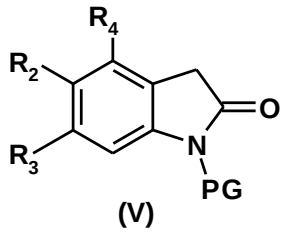
Compound 208. 6-chloro-3-[hydroxy-(3-methoxyisoxazol-5-yl)methylene]-5-[4-(4-hydroxy-4-methyl-1-piperidyl)phenyl]indolin-2-one

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

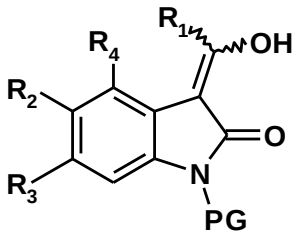
in the form of the base, enantiomers, diastereoisomers or of an addition salt with an acid or with a base.

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)



(V)

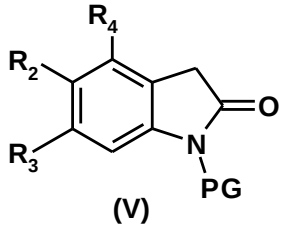
in which R_2, R_3, and R_4 are as defined in claim 1, PG is a protective group, with a carboxylic acid derivative (VI) of formula R_1CO_2H, wherein R_1 is as defined in claim 1, in the presence of an activating agent to obtain a compound of formula (VII)



(VII)

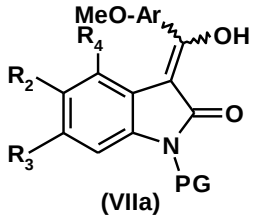
and the removal of the protective group with a an acidic or basic reagent.

13. A process for preparing a compound of formula (I) as claimed in one of claims 1 to 11, with R_2, R_3, and R_4 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)



(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)

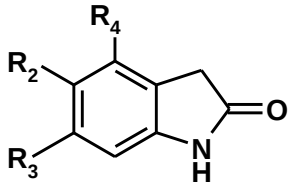


(VIIa)

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.

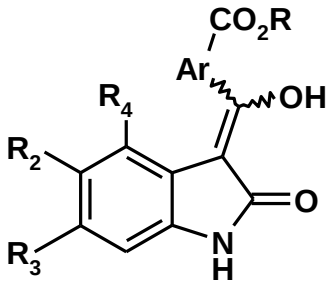
14. A process for preparing a compound of formula (I) as claimed in any one of claims 1 to 11, comprising the reaction of compound (IV)



(IV)

in which R_2, R_3, and R_4 are as defined in claim 1, with an acyl halide compound (VIII) of formula R_1COCl, 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, R_3, and R_4 being as defined in claim 1, comprising the reaction of compound (IX)



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

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

18. A pharmaceutical composition, characterized in that it comprises a compound 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.

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

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