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(54) OXINDOLE DERIVATIVES AS GROWTH HORMONE RELEASERS

## WACHSTUMSHORMON-FREISETZENDE OXINDOLDERivate

## DERIVES OXINDOLES EN TANT QU'AGENTS DE LIBERATION DE L'HORMONE DE CROISSANCE

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**Description**Technical Field

5 [0001] The present invention relates to an oxindole derivative useful for growth hormone releaser etc.

Background Art

10 [0002] Various factors are related to growth in individuals. However, growth hormone should apparently be the most important factor for growing, since surplus secretion of growth hormone may result in gigantism or acromegaly, and deficiency in growth hormone may result in dwarfism. Growth hormone is known to have basic effects on the metabolic processeses of the body: to increase rate of protein synthesis, to decrease rate of carbohydrate utilization, and to increase mobilization of free fatty acids and use of fatty acids for energy.

15 [0003] Various compounds such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia are known to cause a release of growth hormone. Activities such as sleep and exercise are also known to release growth hormone. These compounds and activities indirectly cause growth hormone to be released from the pituitary by acting on the hypothalamus in various ways such as to decrease somatostatin secretion and to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone.

20 [0004] Providing exogenous growth hormone is used as one way to increase levels of growth hormone. The sources of growth hormone used are either from extractions of pituitary glands of cadavers or recombinant growth hormone. However, the resulting growth hormone is very expensive and the extracted products from pituitary glands have risks that diseases associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Growth hormone should be given by injection or by a nasal spray, because its oral administration is difficult.

25 [0005] Another way to increase levels of growth hormone is to administer compounds which stimulate the release of endogenous growth hormone such as GRF or its derivatives (Schoen W.R. et al., "Growth hormone secretagogues" in Annual Reports in Medicinal Chemistry: Academic Press, Vol. 28, Chapter 19, 1993) and peptidyl compounds (US 4, 411, 890). These peptides are considerably smaller than growth hormones, but are still susceptible to various proteases. Therefore, their potential for oral bioavailability is low.

30 [0006] WO 94/01369 discloses non-peptide compounds useful as growth hormone releasers. Though these compounds are stable under various physiological environments and applicable parenterally, intranasally or orally, these compounds have not been approved as a drug.

[0007] J. Chem. Soc. Perkin Trans. I, 1975-1979(1991) describes that benzodiazocine derivatives were formed by heating oxindole derivatives in the presence of acid catalyst.

35 [0008] Chem. Pharm. Bull., 21, 960-971(1973) describes that oxindole derivatives without any substituents on its benzene ring have analgesic and anti-inflammatory effects.

[0009] GB-1,125,671 discusses oxindole derivatives but does not mention their usefulness as growth hormone releasers.

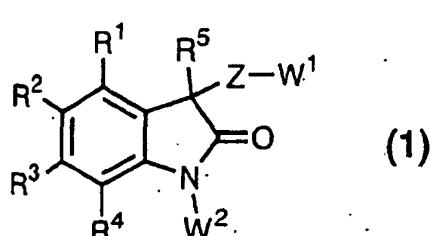
40 [0010] US 5,283,241 discusses a further group of oxindole derivatives.

DETAILED DESCRIPTION OF THE INVENTION

45 [0011] The inventors of the present invention have intensively carried out research on growth hormone releasers, and found that oxindole derivatives and pharmaceutically acceptable salts thereof are growth hormone releasers which are applicable as a medicine. Thus, the present invention has been accomplished.

[0012] That is, the present invention is as follows:

50 [1] An oxindole derivative of Formula 1 or a pharmaceutically acceptable salt thereof:



wherein

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup>

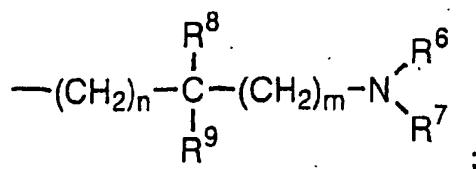
are the same or different and each is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, halogen, cyano, nitro, hydroxy, optionally substituted amino, alkoxy, alkanoyl, alkoxy carbonyl, optionally substituted sulfamoyl, optionally substituted carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino or alkanoylamino, provided that all of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are not simultaneously hydrogen; is optionally substituted aryl or optionally substituted heteroaryl; is -O- or -NH-; is hydrogen, alkyl or -Y-CON(R<sup>10</sup>)R<sup>11</sup>; is

R<sup>5</sup>

Z

one of W<sup>1</sup> and W<sup>2</sup>

the other of W<sup>1</sup> and W<sup>2</sup>



n

Y

R<sup>6</sup> and R<sup>7</sup>

is 1, 2 or 3; m is 0, 1, 2 or 3;

is single bond or C<sub>1</sub>-C<sub>3</sub> alkylene;

are the same or different and each is independently hydrogen, optionally substituted alkyl or optionally substituted cycloalkyl; or R<sup>6</sup> and R<sup>7</sup> are taken together with the adjacent nitrogen atom to form optionally substituted saturated heterocyclic ring;

R<sup>8</sup> and R<sup>9</sup>

are the same or different and each is independently hydrogen or optionally substituted alkyl; or R<sup>8</sup> and R<sup>9</sup> are taken together with the adjacent carbon atom to form optionally substituted cycloalkane or optionally substituted saturated heterocyclic ring;

R<sup>8</sup> and R<sup>6</sup>

may be taken together to form C<sub>1</sub>-C<sub>5</sub> alkylene in which case R<sup>7</sup> is hydrogen, optionally substituted alkyl or optionally substituted cycloalkyl, and R<sup>9</sup> is hydrogen or optionally substituted alkyl;

R<sup>10</sup> and R<sup>11</sup>

are the same or different and each is independently hydrogen or alkyl; or R<sup>10</sup> and R<sup>11</sup> are taken together with the adjacent nitrogen atom to form optionally substituted saturated heterocyclic ring; other than compounds of formula GB-1,125,671 as defined in claim 1.

[2] An oxindole derivative or a pharmaceutically acceptable salt thereof according to [1] wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently hydrogen, alkyl optionally substituted by halogen, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbamoyl, halogen, cyano, nitro, alkanoyl, alkoxy carbonyl, alkylsulfinyl or alkylsulfonyl, provided that all of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are not simultaneously hydrogen.

[3] An oxindole derivative or a pharmaceutically acceptable salt thereof according to [1] wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently hydrogen, trifluoromethyl, carbamoyl, halogen, 4-carbamoyl-1-butynyl, 4-alkylcarbamoyl-1-butynyl, 4-dialkylcarbamoyl-1-butynyl, 4-morpholinocarbonyl-1-butynyl, -C≡C-(CH<sub>2</sub>)<sub>k</sub>-Q, wherein k is 1 or 2; Q is hydroxy, alkylsulfonyl, alkanoylamino, alkylureido, 2-oxo-1-imidazolidinyl or 2-oxo-1,3-oxazolin-3-yl, provided that all of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are not simultaneously hydrogen.

[4] An oxindole derivative or a pharmaceutically acceptable salt thereof according to [3] wherein both of R<sup>2</sup> and R<sup>4</sup> are hydrogen.

[5] An oxindole derivative or a pharmaceutically acceptable salt thereof according to [1] wherein both of R<sup>2</sup> and R<sup>4</sup> are hydrogen; R<sup>1</sup> is trifluoromethyl, chlorine or bromine; and R<sup>3</sup> is carbamoyl, halogen, 4-carbamoyl-1-butynyl, 4-alkylcarbamoyl-1-butynyl, 4-dialkylcarbamoyl-1-butynyl, 4-morpholinocarbonyl-1-butynyl, -C≡C-(CH<sub>2</sub>)<sub>k</sub>-Q, wherein k and Q are as defined above.

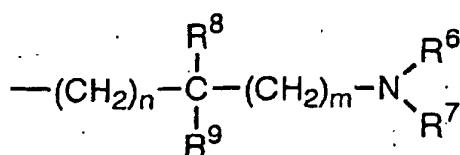
[6] An oxindole derivative or a pharmaceutically acceptable salt thereof according to [1] wherein both of R<sup>2</sup> and R<sup>4</sup> are hydrogen; R<sup>1</sup> is trifluoromethyl, chlorine or bromine; and R<sup>3</sup> is carbamoyl.

[7] An oxindole derivative or a pharmaceutically acceptable salt thereof according to any one of [1] to [6] wherein R<sup>5</sup> is optionally substituted phenyl or optionally substituted 2-naphthyl.

5 [8] An oxindole derivative or a pharmaceutically acceptable salt thereof according to any one of [1] to [6] wherein R<sup>5</sup> is phenyl optionally substituted by halogen(s) and/or trifluoromethyl(s) or 2-naphthyl optionally substituted by halogen(s) and/or trifluoromethyl(s).

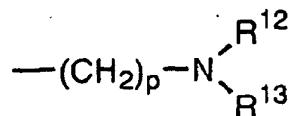
10 [9] An oxindole derivative or a pharmaceutically acceptable salt thereof according to any one of [1] to [8] wherein R<sup>6</sup> and R<sup>7</sup> are independently optionally substituted alkyl or optionally substituted cycloalkyl; or R<sup>6</sup> and R<sup>7</sup> are taken together with the adjacent nitrogen atom to form optionally substituted saturated heterocyclic ring.

15 [10] An oxindole derivative or a pharmaceutically acceptable salt thereof according to any one of [1] to [9] wherein one of W<sup>1</sup> and W<sup>2</sup> is hydrogen or -CONHR<sup>10</sup>; and the other of W<sup>1</sup> and W<sup>2</sup> is



wherein n, m, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> are as defined in [1].

25 [11] An oxindole derivative or a pharmaceutically acceptable salt thereof according to any one of [1] to [9] wherein one of W<sup>1</sup> and W<sup>2</sup> is hydrogen; and the other of W<sup>1</sup> and W<sup>2</sup> is

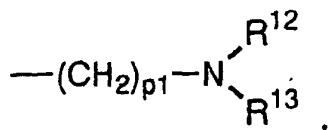


wherein p is an integer of 2 to 7; and R<sup>12</sup> and R<sup>13</sup> are independently optionally substituted alkyl.

35 [12] An oxindole derivative or a pharmaceutically acceptable salt thereof according to any one of [1] to [9], wherein

(1) W<sup>1</sup> is hydrogen; and W<sup>2</sup> is

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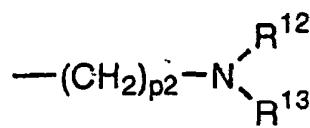


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or

(2) W<sup>2</sup> is hydrogen; and W<sup>1</sup> is

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55

wherein p1 is an integer of 2 to 7; p2 is an integer of 3 to 7; and R<sup>12</sup> and R<sup>13</sup> are independently optionally substituted alkyl.

[13] An oxindole derivative or a pharmaceutically acceptable salt thereof according to [11] or [12] wherein R<sup>12</sup> and R<sup>13</sup> are independently methyl or ethyl.

5 [14] An optical isomer of an oxindole derivative according to any one of [1] to [13], of which the configuration at the C-3 position is equivalent to that of (+)-1-diethylaminoethyl-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole, or a pharmaceutically acceptable salt thereof.

10 [15] A medicament containing an oxindole derivative or a pharmaceutically acceptable salt thereof according to any one of [1] to [14] and a pharmaceutically acceptable carrier or diluent.

15 [16] An oxindole derivative or a pharmaceutically acceptable salt thereof according to any one of [1] to [14] for use in therapy.

15 [17] Use of an oxindole derivative or a pharmaceutically acceptable salt thereof as defined in claim 17 for the manufacture of a medicament which is a growth hormone releaser.

20 [0013] "Alkyl" is straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl. Typical examples are methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, pentyl, 1-methylbutyl, 2-methylbutyl, 1-ethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, and 1-ethylbutyl. The alkyls in "alkylthio", "alkylsulfinyl", "alkylsulfonyl" and "alkylsulfonylamino" have the same meaning:

"Alkenyl" is straight or branched C<sub>2</sub>-C<sub>6</sub> alkenyl. Typical examples are vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-but enyl, and 3-pentenyl.

25 "Alkynyl" is straight or branched C<sub>2</sub>-C<sub>6</sub> alkynyl. Typical examples are ethynyl, 1-propynyl, 2-propynyl, 3-butynyl and 2-pentynyl.

"Alkoxy" is straight or branched C<sub>1</sub>-C<sub>6</sub> alkoxy. Typical examples are methoxy, ethoxy, propoxy, 1-methylethoxy, buoxy, 1-methylpropoxy, 2-methylpropoxy, pentoxy, 1-methylbutoxy, 2-methylbutoxy, 1-ethylpropoxy, hexoxy, 1-methylpentoxy, 2-methylpentoxy and 1-ethylbutoxy. The alkoxy in "alkoxycarbonyl" has the same, meaning.

30 "Alkanoyl" is straight or branched C<sub>1</sub>-C<sub>6</sub> alkanoyl. Typical examples are formyl, acetyl, propanoyl and butanoyl. The alkanoyl in "alkanoylamino" has the same meaning.

"C<sub>1</sub>-C<sub>5</sub> alkylene" includes straight or branched C<sub>1</sub>-C<sub>5</sub> alkylene. Typical examples are methylene, ethylene, propylene, trimethylene, tetramethylene, 1-methyltrimethylene, 2-methyltrimethylene, pentamethylene, 1-methyltetramethylene and 2-methyltetramethylene. "C<sub>1</sub>-C<sub>3</sub> alkylene" in Y includes straight or branched C<sub>1</sub>-C<sub>3</sub> alkylene. Typical examples are methylene, ethylene and trimethylene, preferably methylene and ethylene.

35 [0014] The substituents of "substituted alkyl" are halogen, optionally substituted amino, alkoxy, alkoxycarbonyl, aryl, hydroxy, carboxy, optionally substituted carbamoyl, alkanoyl, arylcarbonyl, heteroarylcarbonyl, saturated heterocyclic group-carbonyl, alkanoylamino, alkylsulfonylamino, optionally substituted ureido, alkoxycarbonylamino, optionally substituted saturated heterocyclic group and optionally substituted sulfamoyl.

40 [0015] Preferred examples of substituted alkyl in R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are alkyls substituted by halogen(s) such as trifluoromethyl, pentafluoroethyl and 2-chloroethyl.

45 [0016] The substituents of "substituted alkenyl" and "substituted alkynyl" are halogen, optionally substituted amino, alkoxy, alkoxycarbonyl, aryl, hydroxy, carboxy, optionally substituted carbamoyl, alkanoyl, arylcarbonyl, heteroarylcarbonyl, saturated heterocyclic group-carbonyl, alkanoylamino, alkylsulfonylamino, optionally substituted ureido, alkoxycarbonylamino, optionally substituted saturated heterocyclic group and optionally substituted sulfamoyl.

50 [0017] Preferred examples of substituted alkynyl in R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are C<sub>3</sub>-C<sub>6</sub> 1-alkynyl substituted by polar substituent(s) such as hydroxy, alkylsulfonylamino, alkanoylamino, alkylureido, oxo-saturated heterocyclic group (e.g. 2-oxo-1-imidazolodinyl, 2-oxo-1,3-oxazolin-3-yl) and optionally substituted carbamoyl. The examples include 4-carbamoyl-1-butynyl, 4-alkylcarbamoyl-1-butynyl, 4-dialkylcarbamoyl-1-butynyl, 4-morpholinocarbonyl-1-butynyl, -C≡C-(CH<sub>2</sub>)<sub>k</sub>-Q, wherein k and Q are as defined above

55 [0018] "Aryl" is C<sub>6</sub>-C<sub>10</sub> aryl. Typical examples are phenyl, 1-naphthyl and 2-naphthyl. The aryl in "arylcarbonyl" has the same meaning.

[0019] "Heteroaryl" is 5- to 7-membered mono- or bi-cyclic heteroaryl containing 1 to 3 atoms of nitrogen, sulfur and/or oxygen atoms. Typical examples include 5- to 7-membered mono-cyclic heteroaryl containing 1 to 3 atoms of nitrogen, sulfur and/or oxygen atoms such as pyridyl, pyridazinyl, isothiazolyl, pyrrolyl, furyl, thieryl, thiazolyl, imidazolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyrazinyl, isothiazolyl, triazinyl, triazolyl, imidazolidinyl, oxadiazolyl, triazolyl, triazinyl and tetrazolyl; 5- to 7-membered bi-cyclic heteroaryl containing 1 to 3 atoms of nitrogen, sulfur and/or oxygen atoms such as indolyl, chromenyl, quinolyl, isoquinolyl, benzofuranyl, benzothienyl, benzoxazolyl, ben-

zothiazolyl, benzisoxazolyl, benzisothiazolyl, benzotriazolyl and benzimidazolyl . The heteroaryl in "heteroarylcarbonyl" has the same meaning.

**[0020]** "Cycloalkyl" is C<sub>3</sub>-C<sub>8</sub> cycloalkyl. Typical examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

**[0021]** "Cycloalkane" is C<sub>3</sub>-C<sub>8</sub> cycloalkane. Typical examples are cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane and cyclooctane.

**[0022]** "Saturated heterocyclic ring" is 5- to 7-membered mono-cyclic saturated heterocyclic ring containing 1 to 3 atoms of nitrogen, sulfur and/or oxygen atoms. Typical examples include 5-membered mono-cyclic saturated heterocyclic rings containing 1 to 3 atoms of nitrogen, sulfur and/or oxygen atoms such as tetrahydrofuran, pyrrolidine, pyrazoline, thiazolidine and oxazolidine; 6-membered mono-cyclic saturated heterocyclic rings containing 1 to 3 atoms of nitrogen, sulfur and/or oxygen atoms such as piperidine, morpholine, thiamorpholine and piperazine ; 7-membered mono-cyclic saturated heterocyclic rings containing 1 to 3 atoms of nitrogen, sulfur and/or oxygen atoms such as perhydroazepine.

**[0023]** "Saturated heterocyclic group" is a radical formed by removing hydrogen from saturated heterocyclic ring. The saturated heterocyclic group in "saturated heterocyclic group-carbonyl" has the same meaning.

**[0024]** The substituents of "substituted aryl", "substituted phenyl", "substituted 2-naphthyl", "substituted heteroaryl", "substituted cycloalkyl", "substituted cycloalkane", "substituted saturated heterocyclic ring" and "substituted saturated heterocyclic group" are selected from halogen, aryl, heteroaryl, optionally substituted alkyl, alkenyl, alkynyl, optionally substituted amino, cyano, nitro, hydroxy, mercapto, alkoxy, alkanoyl, alkoxy carbonyl, carboxy, optionally substituted sulfamoyl, optionally substituted carbamoyl, alkylsulfamoylamino, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino and alkanoylamino . The substituents of "substituted saturated heterocyclic ring" and "substituted saturated heterocyclic group" also include oxo. Examples of the "oxo-saturated heterocyclic ring" and "oxo-saturated heterocyclic group" include oxo-5-membered saturated heterocyclic rings or groups such as. pyrrolidinone(yl), thiazolidinone(yl), 2-oxo-1,3-oxazoline(yl), and 2-oxo-imidazolidine(yl) ; oxo-6-membered saturated heterocyclic rings or groups such as piperidinone(yl).

**[0025]** Preferred examples of substituents of "substituted aryl" and "substituted heteroaryl" in R<sup>5</sup> are halogen, alkoxy, and alkyl substituted by halogen(s), especially chlorine, fluorine, methoxy, and trifluoromethyl.

**[0026]** "Halogen" is fluorine, chlorine, bromine and iodine.

**[0027]** The substituents of "substituted amino" are selected from alkyl optionally substituted by hydroxy or alkoxy. Amino may be substituted by two substituents.

**[0028]** The substituents of "substituted sulfamoyl", "substituted carbamoyl" and "substituted ureido" are selected from alkyl optionally substituted by hydroxy or alkoxy. Sulfamoyl, carbamoyl and ureido may be substituted by two substituents. When sulfamoyl, carbamoyl or ureido is substituted by two substituents, the two substituents may be taken together with adjacent nitrogen atom to form saturated heterocyclic ring such as morpholine.

**[0029]** The oxindole derivative may be in the form of pure optical isomer, partially purified optical isomer, racemate, mixture of diastereomers or the like. Preferred optical isomers of the oxindole derivatives are the optical isomers, of which the configurations at the 3rd position are equivalent to that of (+)-1-diethylaminoethyl-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole. The optical isomers are usually distinguishable from their retention times in HPLC on a Chiralpak OD™ with isopropanol/hexane as the eluent. The referred optical isomer is usually eluted later than its enantiomer.

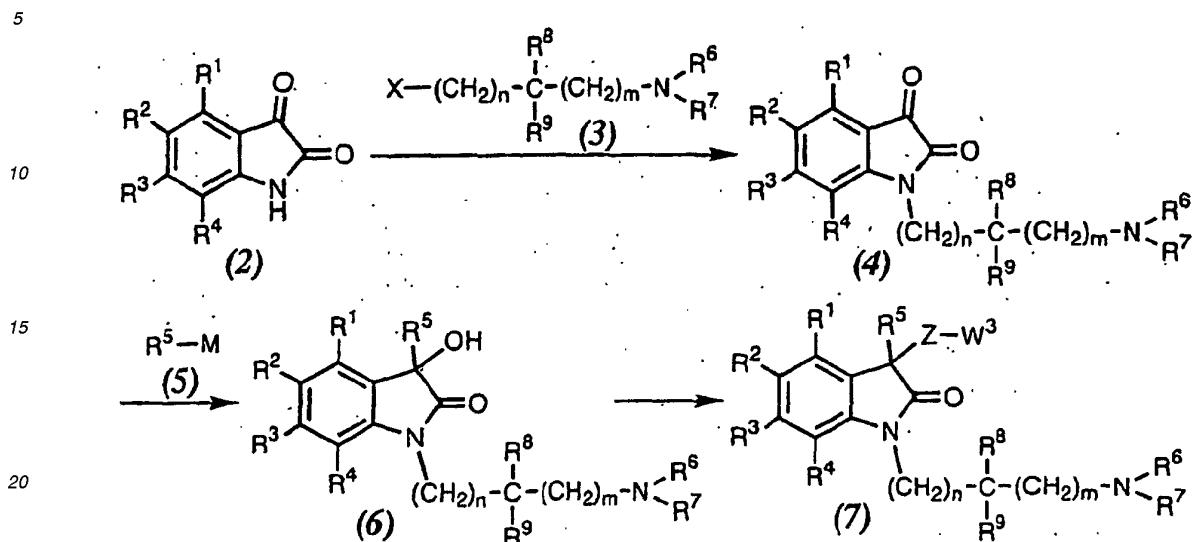
**[0030]** Pharmaceutically acceptable salts of the oxindole derivatives include salts with inorganic acids and salts with organic acids. Typical examples of the salts with inorganic acids are the hydrochloride, hydrobromide, nitrate, sulfate and phosphate salts . Typical examples of the salts with organic acids are the formate, acetate, trifluoroacetate, propionate, lactate, tartrate, oxalate, fumarate, maleate, citrate, malonate, methanesulfonate and benzenesulfonate salts.

**[0031]** In case that the oxindole derivatives have acidic group(s) such as carboxyl, salts thereof with bases may be formed. The salts include salts with organic bases such as the arginine, lysine and triethylammonium salts; salts with inorganic bases such as the alkaline metal (sodium, potassium, etc.), alkaline earth metal (calcium, barium, etc.) and ammonium salts . The oxindole derivative or pharmaceutically acceptable salt thereof may be in the form of a solvate such as a hydrate.

**[0032]** The oxindole derivative of Formula I can be produced for example by the following methods.

Method A

[0032]



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, X, n and m are as defined above. X is chlorine, bromine; iodine, methanesulfoxy or toluenesulfonyl; M is lithium, magnesium bromide, magnesium iodide or magnesium chloride; W<sup>3</sup> is hydrogen, alkyl or -Y-CON(R<sup>10</sup>)R<sup>11</sup> wherein R<sup>10</sup> and R<sup>11</sup> are as defined above.

[0033] Compound (4) is produced by reacting isatin derivative (2) with compound (3) in the presence of a base. The reaction can be carried out according to conventional conditions of N-alkylation reaction. The base includes an alkaline hydride such as sodium hydride, potassium hydride and the like; alkaline amide such as sodium amide, lithium amide and the like; alkaline alkoxide such as potassium t-butoxide, sodium methoxide and the like; and the like. The amount of the base is usually 1 to 10 equivalents, preferably 1.5 to 5 equivalents, per equivalent of the isatin derivative (2). When a salt of compound (3) such as the hydrochloride and the like is used, the corresponding equivalents of the base may be added in surplus. The amount of compound (3) is usually 1 to 3 equivalents, preferably 1.2 to 2 equivalents, per equivalent of the isatin derivative (2). The reaction solvent includes an inert organic solvent such as tetrahydrofuran (THF), N,N-dimethylformamide (DMF) and the like. The reaction temperature may be in the range of 0 °C to the boiling point of the solvent, preferably in the range of room temperature to 80 °C.

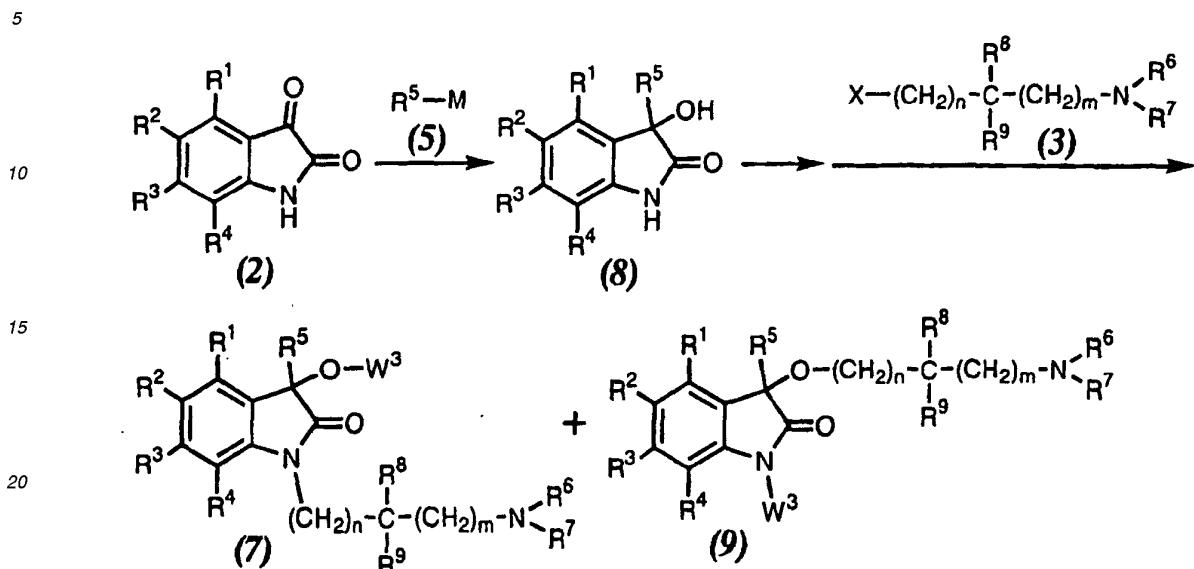
[0034] Compound (6) is produced by reacting compound (4) with compound (5). The reaction of compound (4) with compound (5) can be carried out by conventional methods. The amount of compound (5) is usually 1 to 2 equivalents per equivalent of compound (4). The reaction solvent includes ethers such as diethyl ether, THF and the like. The reaction temperature may be in the range of -78 °C to room temperature.

[0035] The hydroxy group of compound (6) may be converted to an amino group, if needed. Chlorination of compound (6) with thionyl chloride, followed by azidation and reduction affords the corresponding amine. The chlorination is usually carried out without solvents at the temperature between room temperature and 50 °C. The azidation is for example performed using alkaline azide such as sodium azide in the presence of a base such as triethylamine in an inert solvent such as THF and DMF at the temperature between room temperature and 80 °C. The reducing agent includes tin chloride. The reaction solvent includes alcohols such as methanol and ethanol. The reaction temperature may be in the range of room temperature to the boiling point of the solvent.

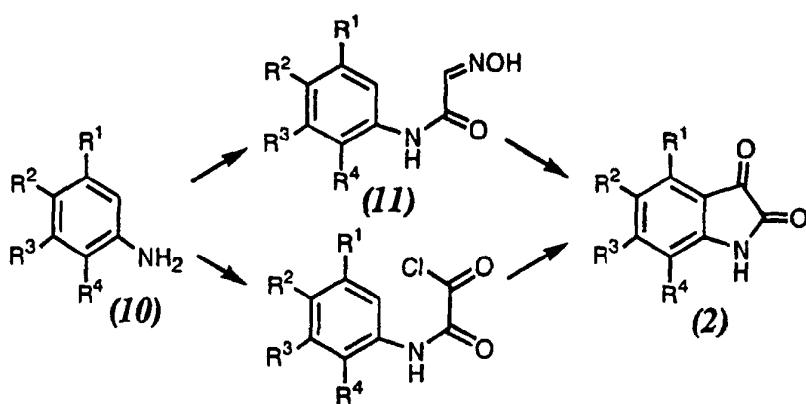
[0036] Oxindole derivative (7) can be produced by introducing alkyl or -Y-CON(R<sup>10</sup>)R<sup>11</sup> wherein R<sup>10</sup> and R<sup>11</sup> are as defined above to compound (6) or the corresponding amine, if needed. Introduction of alkyl or -Y-CON(R<sup>10</sup>)R<sup>11</sup> can be carried out by conventional methods, for example, reaction with alkyl halide, X<sup>1</sup>-Y-CON(R<sup>10</sup>)R<sup>11</sup> wherein R<sup>10</sup> and R<sup>11</sup> are as defined above; X<sup>1</sup> is chlorine, bromine, iodine, methanesulfonyl or toluenesulfonyl, or R<sup>10</sup>-NCO wherein R<sup>10</sup> is as defined above, in the presence or absence of a base. The base includes an alkaline hydride such as sodium hydride, potassium hydride and the like; an alkaline amide such as sodium amide, lithium amide and the like; organic base such as triethylamine, ethyldiisopropylamine and the like. The amount of the base is usually 1 to 10 equivalents per equivalent of compound (6) or the corresponding amine. The amount of the alkyl halide, X<sup>1</sup>-Y-CON(R<sup>10</sup>)R<sup>11</sup> or R<sup>10</sup>-NCO is usually 1 to 10 equivalents per equivalent of compound (6) or the corresponding amine. The reaction solvent includes inert solvents such as THF, DMF and the like. The reaction temperature may be in the range of 0 °C to the boiling point of the solvent, preferably in the range of room temperature to 80 °C.

Method B

[0037]

Method for preparing isatin derivatives (Method C)

[0040]



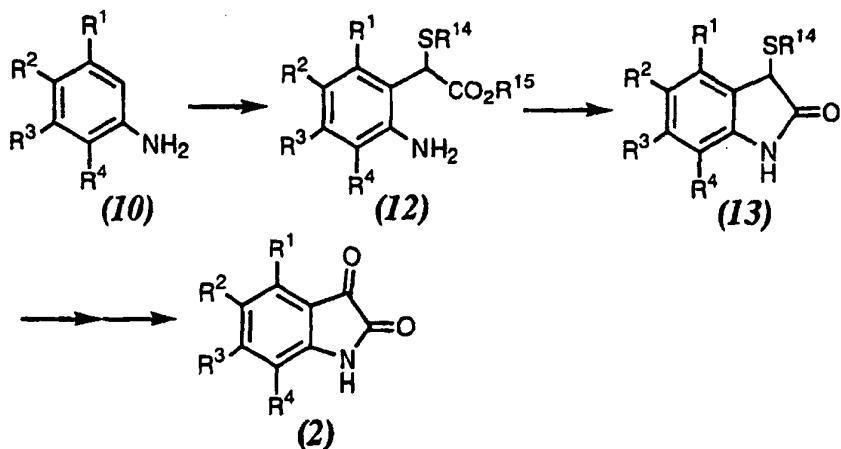
**[0041]** Isatin derivative (2) can be prepared according to Sandmeyer's method (Org. Synth., Coll. Vol. I, 321(1941)). Isatin derivative (2) is prepared by reacting aniline derivative (10) with chloral hydrate and hydroxylamine in water under reflux to give compound (11), followed by treating the compound with acid and then with water. The acid includes conc. sulfuric acid, polyphosphoric acid and the like. The acid may be used as a solvent preferably. The temperature in the treatment with acid may be in the range of 50 to 100 °C. The treatment with water is performed by adding the

reaction mixture into water. The temperature of the treatment with water is preferably in the range of 0 °C to room temperature. Ice may be used in place of the water, because the treatment makes a lot of heat.

**[0042]** Isatin derivative (2) is prepared by reacting Aniline derivative (10) with oxalyl chloride, followed by intramolecular Friedel-Crafts reaction. These two reactions may also be done all at once in the same vessel. The reaction solvent includes halogenated solvents such as methylene chloride, 1,2-dichloroethane and the like. The reaction may be carried out without solvents. In the Friedel-Craft's reaction, Lewis acid may be added. The Lewis acid includes aluminum chloride and the like.

Method for preparing isatin derivative (Method D)

**[0043]**



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as defined above; R<sup>14</sup> and R<sup>15</sup> are independently alkyl.

**[0044]** Isatin derivative (2) can be prepared according to Gassman's method (J. Am. Chem. Soc., 96, 5508(1974)). Compound (12) is prepared by chlorination of aniline derivative (10) followed by adding compound: R<sup>14</sup>SCH<sub>2</sub>CO<sub>2</sub>R<sup>15</sup> and then a base. The reaction solvent includes halogenated solvents such as methylene chloride, 1,2-dichloroethane and the like. The chlorination agent includes sulfonyl chloride, t-butoxy chloride and the like. The temperature of the chlorination and the addition of compound: R<sup>14</sup>SCH<sub>2</sub>CO<sub>2</sub>R<sup>15</sup> may be in the range of -20 to -78 °C. The base includes organic bases such as triethylamine and the like. The addition of a base may be carried out by warming the reaction mixture to room temperature and keeping the mixture at the temperature.

**[0045]** Compound (13) is produced by treating compound (12) with an acid. The acid includes hydrochloric acid, sulfuric acid, methanesulfonic acid and the like. The reaction temperature may be room temperature. This reaction may be carried out in the same vessel of the previous reaction successively.

**[0046]** Compound (2) is produced by oxidation of compound (13). The oxidizing agent includes copper(II) oxide and the like. The reaction temperature may be in the range of room temperature to the boiling temperature of the solvent. The reaction solvent includes an inert organic solvent such as acetone, acetonitrile and the like.

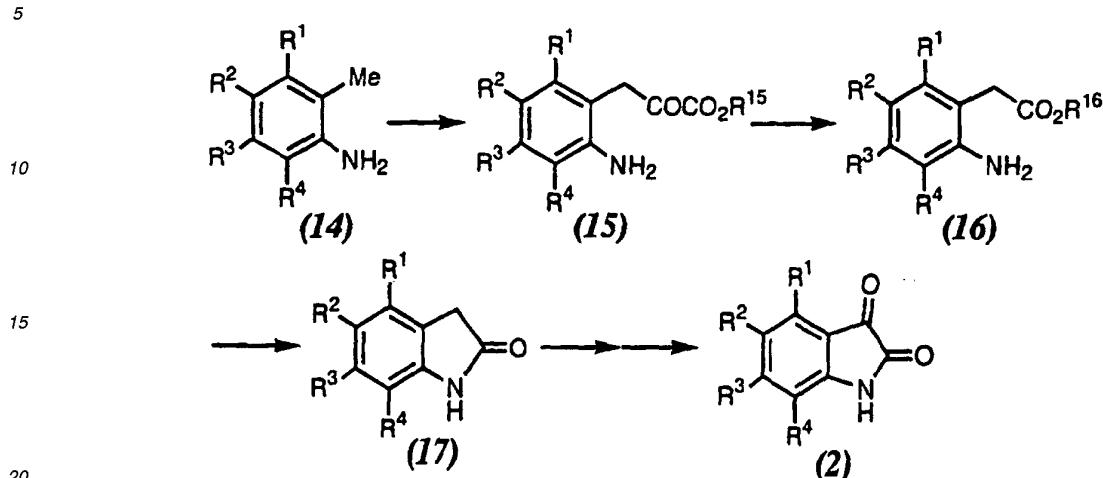
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### Method for preparing isatin derivative (Method E)

[0047]



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as defined above; R<sup>15</sup> and R<sup>16</sup> are independently alkyl.

**[0048]** Isatin derivative (2) can be prepared by Reisert reaction. For example, Reisert reaction of nitrotoluene (14) with dialkyl oxalate in the presence of metal alkoxide in an alcoholic solvent provides ketoester (15) (J. Am. Chem. Soc., 78, 221 (1956)). Suitable combinations of the dialkyl oxalate, metal alkoxide and alcoholic solvent are dimethyl oxalate-sodium methoxide-methanol, dimethyl oxalate-potassium methoxide-methanol and diethyl oxalate-sodium ethoxide-ethanol. Treating ketoester (15) with aqueous hydrogen peroxide in the presence of acid such as perchloric acid (J. Org. Chem., 16, 1785 (1951)) followed by methylation using methanol-hydrogen chloride or thionyl chloride affords ester (16). Reduction of the nitro group with Fe-acetic acid, aqueous titanium trichloride or tin(II) chloride forms oxindole (17) (Synthesis, 1993, 51). Two steps conversion of oxindole (17) into isatin (2) are effected by treating pyridinium tribromide followed by hydrolysis using acid such as hydrogen bromide (Tetrahedron Lett., 39, 7679 (1998)).

**[0049]** In the above reactions, functional groups in each compound may be protected if needed. The protective groups include the well known protective groups (Protective Groups in Organic Synthesis, T. W. Greene, A Wiley-Interscience Publication (1981) etc.) and the like.

35 [0050] Oxindole derivative (1) produced according to the above methods may be mixture of isomers. In that case, each isomer can be isolated by a suitable method such as silica chromatography and the like at the final stage or an intermediate stage.

**[0051]** Optical isomers of oxindole derivative (1) may be obtained by conventional optical resolution methods such as recrystallization of salts thereof with an optical acid such as tartaric acid and the like.

[0052] Prodrug of the oxindole derivative (1) may be obtained by conventional methods (as described in Chemistry and Industry, 1980, 435; Advanced Drug Discovery Reviews 3, 39(1989)).

[0053] The pharmaceutically acceptable salt of the oxindole derivative (1) or a prodrug thereof can be formed by mixing the oxindole derivative (1) or a prodrug thereof with a pharmaceutically acceptable acid such as hydrogen chloride, citric acid, methanesulfonic acid and the like in a solvent such as water, methanol, ethanol, acetone and the like.

**[00541]** Specifically preferred examples of the oxindole derivatives are:

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chloro-3-pyridyl)oxindole,  
1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chloro-3-thienyl)oxindole,  
1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(5-indolyl)oxindole,  
1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-[3-(3-methyl-2-oxo-1-imidazolidinyl)-1-propynyl]-3-hydroxy-3-(2-chlorophenyl)oxindole,  
1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-[4-(3-methyl-2-oxo-1-imidazolidinyl)-1-butynyl]-3-hydroxy-3-(2-chlorophenyl)oxindole,  
1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-[4-dimethylcarbamoyl-1-butynyl]-3-hydroxy-3-(2-chlorophenyl)oxindole,  
1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-[5-dimethylcarbamoyl-1-pentynyl]-3-hydroxy-3-(2-chlorophenyl)oxindole.

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-dimethylcarbamoylethynyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoylethynyl-3-hydroxy-3-(2-chloro-4-bromophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(2-carbamoylethenyl)-3-hydroxy-3-(2-chloro-4-bromophenyl)oxindole,  
 5 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(2-carbamoylethyl)-3-hydroxy-3-(2-chloro-4-bromophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-amino-1-butynyl)-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-acetamino-1-butynyl)-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(5-carboxy-1-pentynyl)-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 10 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-sulfamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-methylsulfamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-dimethylsulfamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-sulfamoyl-1-butynyl)-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(1-naphthyl)oxindole,  
 15 1-(2-Diethylaminoethyl)-4-trifluoromethyl-7-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-methyl-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-methoxy-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-fluoro-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 20 1-(2-Diethylaminoethyl)-4-cyano-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-hydroxy-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-5-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-5-chloro-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-trifluoromethyl-5-chloro-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 25 1-(2-(2-Piperidinyl)ethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-(2-Pyrrolidinyl)ethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-(N-methyl-2-pyrrolidinyl)ethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Piperidinylmethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(3-Amino-3-methylbutyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 30 1-(3-Aminobutyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(4-Dimethylamino-3,3-dimethylbutyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2,3-dichlorophenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chloro-4-methoxyphenyl)oxindole,  
 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chloro-4-bromophenyl)oxindole, and  
 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2,3,4-trichlorophenyl)oxindole.  
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**[0055]** The oxindole derivatives of the present invention have effects and usage similar to those of growth hormone, because the oxindole derivatives can stimulate the release of growth hormone from the pituitary. Examples of the growth hormone's effects and usage are as follows:

40 stimulation of growth hormone release in the elderly; treating growth hormone deficient adults; prevention of catabolic side effects of glucocorticoids; prevention and treatment of osteoporosis; stimulation of the immune system; acceleration of wound healing accelerating bone fracture repair; treatment of growth retardation; treating acute or chronic renal failure or insufficiency; treatment of physiological short stature including growth hormone deficient children and short stature associated with chronic illness; treatment of obesity and growth retardation associated with obesity; treating growth retardation associated with the Prader-Willi syndrome and Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients or following major surgery such as gastrointestinal surgery; treatment of intrauterine growth retardation, skeletal dysplasia, hypercortisolism and Cushing's syndrome; induction of pulsatile growth hormone release; replacement of growth hormone in stressed patients; treatment of osteochondrodysplasias, Noonan's syndrome, schizophrenia, depressions, Alzheimer's disease, delayed wound healing and psychosocial deprivation; treatment of pulmonary dysfunction and ventilator dependency; attenuation of protein catabolic responses after major surgery; treating malabsorption syndromes; reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; accelerating weight gain and protein accretion in patients on TPN (total parenteral nutrition); treatment of hyperinsulinemia including nesidioblastosis; adjuvant treatment for ovulation induction and to prevent and treat gastric and duodenal ulcers; stimulation of thymic development; prevention of the age-related decline of thymic function; adjunctive therapy for patients on chronic hemodialysis; treatment of immunosuppressed patients; enhancing antibody response following vaccination; improvement in muscle strength and mobility in the frail elderly; maintenance of skin thickness, metabolic homeostasis, renal homeostasis in the frail elderly; stimulation of osteoblasts, bone remodelling and cartilage growth in the frail elderly;  
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treatment of neurological diseases such as peripheral and drug induced neuropathy, Guillain-Barre Syndrome, amyotrophic lateral sclerosis, multiple sclerosis, cerebrovascular accidents and demyelinating diseases; stimulation of the immune system in companion animals; treatment of disorders of aging in companion animals; growth promotion in livestock; stimulation of wool growth in sheep; and the like.

- 5 [0056] In particular, the oxindole derivatives are useful for treating medical disorders resulting from a deficiency in growth hormone.
- 10 [0057] The oxindole derivatives of the present invention may be applicable to not only humans but also various non-human mammals such as mice, rats, dogs, cows, horses, goats, sheep, rabbits, pigs and the like.
- [0058] The oxindole derivative of the present invention may be administered orally or parenterally (intramuscularly, intravenously, subcutaneously, percutaneously, intranasally, by suppository, by eye drops, by injection into brain). Pharmaceutical forms include generally acceptable forms, for example, powders, granules, fine granules, tablets, capsules, pills, syrups, suspensions, injections such as solutions, emulsions, suppository for administration through the rectum, dermal preparations (ointments, creams, lotions etc.) and the like.
- 15 [0059] These compositions can be prepared by the conventional methods using conventional carriers or diluents. The solid compositions such as tablets can be prepared by mixing the active compound with pharmaceutically acceptable conventional carriers or excipients such as lactose, sucrose, corn starch or the like; binders such as hydroxypropylcellulose, polyvinylpyrrolidone, hydroxypropylmethylcellulose or the like; disintegrating agents such as sodium carboxymethylcellulose, sodium starch glycolate or the like; lubricants such as stearic acid, magnesium stearate or the like; or preservatives or the like. For parenteral administration such as solutions and suspensions, the active compound can be dissolved or suspended in a physiologically acceptable carrier or diluent such as water, saline, oil, dextrose solution or the like, which may contain auxiliary agents such as pH adjusters, buffers, stabilizers, solubilizers, emulsifiers, salts for influencing osmotic pressure and the like, if desired.
- 20 [0060] The dose and the frequency for administration of the oxindole derivative or a prodrug thereof, or a pharmaceutically acceptable salt thereof generally varies depending on the species to be cured, the administration route, the severity of the symptoms, the body weight and the like. The oxindole derivative, a prodrug thereof and a pharmaceutically acceptable salt thereof are usually administered to an adult (body weight: 60 kg) in a dose of about 1 mg to about 1 g, preferably about 1 mg to about 200 mg, more preferably about 5 mg to about 50 mg per day in one portion or several portions. They may be also administered once in 2 days to 1 week. No toxic effects were observed at therapeutic doses.

#### Examples

- 35 [0061] The present invention will be described in detail below, referring to reference examples and examples, which are not limitative of the present invention.

#### Reference example 1

##### 4,6-Dichloroisatin

- 40 [0062] To a solution of trichloroacetaldehyde monohydrate (13.25 g, 1.3 eq) in H<sub>2</sub>O (150 mL) was successively added sodium sulfate (17.55 g, 4.0 eq), a hot solution (ca. 80°C) of 3,5-dichloroaniline (10.0 g, 61.5 mmol) in H<sub>2</sub>O (50 mL) and 37% HCl (6.1 mL), and a solution of hydroxylamine hydrochloride (16.3 g, 3.8 eq) in H<sub>2</sub>O (75 mL) with rapid stirring. Once the addition was completed the reaction mixture was heated at reflux for 2 minutes and then allowed to cool to room temperature. The resulting light brown precipitate was filtered, washed with H<sub>2</sub>O (200 mL) and then dried to yield the crude isonitrosoacetanilide (20.13 g).

- 45 [0063] The above product (20.13 g) was added portion wise to rapidly stirred conc. sulfuric acid (72 mL) at such a rate so as to keep the reaction temperature from 50°C to 70°C. The resulting solution was stirred at 80°C for 10 minutes after which the mixture was allowed to cool to room temperature. The cooled mixture was poured carefully onto ice (ca. 300 g). The ice mixture was allowed to stand for 1 hour. The orange precipitate formed was filtered, washed with H<sub>2</sub>O (300 mL) and then dried to yield 4,6-dichloroisatin.

1<sup>H</sup> NMR (DMSO-d<sub>6</sub>, 270 MHz) δ 11.34 (brs, 1H), 7.25 (d, J=1.6 Hz, 1H), 6.89 (d, J=1.6 Hz, 1H).

#### Reference example 2

##### Mixture of 4-bromoisatin and 6-bromoisatin

- 55 [0064] This mixture (2.5:1) was prepared by the same method as that described in reference example 1, using 3-bro-

moaniline in place of 3,5-dicloroaniline.

4-Bromoisatin:

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 11.17 (brs, 1H), 7.46 (dd, J=8.0, 8.0 Hz, 1H), 7.22 (dd, J=0.7, 8.0 Hz, 1H), 6.89 (dd, J=0.7, 8.0 Hz, 1H).

5 6-Bromoisatin:

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 11.10 (brs, 1H), 7.47 (d, J=7.9 Hz, 1H), 7.26 (dd, J=1.7 and 7.9 Hz, 1H), 7.08 (d, J=1.7 Hz, 1H).

Reference example 3

10 7-Bromoisatin

[0065] This compound was prepared by the same method as that described in reference example 1, using 2-bromoaniline in place of 3,5-dicloroaniline.

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.94 (brs, 1H), 7.71 (d, J=7.9 Hz, 1H), 7.59 (d, J=7.9 Hz, 1H), 7.06 (dd, J=7.9 and 7.9 Hz, 1H).

Reference example 4

20 4,6-Dimethylisatin

[0066] This compound was prepared by the same method as that described in reference example 1, using 3,5-dimethylaniline in place of 3,5-dicloroaniline.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.72 (brs, 1H), 6.69 (s, 1H), 6.51 (s, 1H), 2.53 (s, 3H), 2.36 (s, 3H).

25 Reference example 5

Mixture of 4-ido-6-chloroisatin and 4-chloro-6-iodoisatin

30 [0067] This mixture (2.4:1) was prepared by the same method as that described in reference example 1, using 3-chloro-5-idoaniline (J. Med. Chem., 1991, 34, 1243) in place of 3,5-dicloroaniline.

4-Iodo-6-chloroisatin:

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 270 MHz) δ 11.17 (brs, 1H), 7.57 (brm, 1H), 6.94 (brm, 1H).

4-Chloro-6-iodoisatin:

35 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 270 MHz) δ 11.25 (brs, 1H), 7.53 (brm, 1H), 7.20 (brm, 1H).

Reference example 6

40 4-Trifluoromethylisatin

[0068] To a solution of 3-trifluoroaniline (3.29 g, 10 mmol) in dichloromethane (100 mL) was added sulfuryl chloride (1.2eq) at -78°C. The reaction solution was stirred for 30 minutes. To the mixture was then added ethyl methylthioacetate (1.2eq) and stirring was continued for a further 2 hours, at -78°C. Triethylamine (7 mL) was added next. Then the mixture was allowed to warm to room temperature. To the mixture was added an excess amount of 1N HCl and the mixture stirred overnight. The organic phase was separated, dried over MgSO<sub>4</sub> and concentrated. Purification was carried out by silica gel chromatography (3 : 1 hexane/ethyl acetate) to give 3-methylthio-4-trifluoromethyloxindole.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 8.35 (brs, 1H), 7.50 (d, 1H), 7.38 (d, 1H), 7.14 (s, 1H), 4.32 (1H, s), 2.07 (s, 3H).

[0069] To a solution of 3-methylthio-4-trifluoromethyloxindole (1 mmol) in acetone (6 mL) was added copper (II) chloride (1.5 eq) and copper (II) oxide (1.5 eq). The mixture was stirred at room temperature for 3 hours. To the resulting mixture was added 1N HCl, followed by ethyl acetate. The ethyl acetate phase was separated, washed further with 1N hydrochloric acid and brine, and then dried over anhydrous MgSO<sub>4</sub>. After filtration, the solvent was evaporated to give 4-trifluoromethylisatin quantitatively.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 270 MHz) δ 8.61 (brs, 1H), 7.72 (m, 1H), 7.41 (m, 1H), 7.17 (d, 1H).

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## Reference example 7

Mixture of 5-bromo-4-chloroisatin and 5-bromo-6-chloroisatin

5 [0070] The mixture of 4-chloroisatin and 6-chloroisatin (1:1) was prepared by the same method as that described in reference example 1, using 3-chloroaniline in place of 3,5-dichloroaniline.

## 4-Chloroisatin:

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 11.2 (1H, s), 7.55 (1H, J=8 Hz, t), 7.06 (1H, J=0.5, 8.0 Hz, dd), 6.85 (1H, J=0.5, 8.0 Hz, dd).

## 6-Chloroisatin:

10 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 11.2 (1H, s), 7.53 (1H, J=8.0 Hz, d), 7.11 (1H, J=2.0, 8.0 Hz, dd), 6.94 (1H, J=2.0 Hz, d).

[0071] The mixture of 4-chloroisatin and 6-chloroisatin (1:1, 1.03 g, 5.67 mmol) and N-bromosuccinimide (1.23 g, 6.91 mmol) were dissolved in DMF (10 mL) and the mixture was stirred at 60°C for 3 hours and then cooled to room temperature. Saturated aqueous NaHCO<sub>3</sub> was added to the reaction mixture and the mixture was extracted with a mixture of toluene and ethyl acetate (1:1). The organic phase was washed with brine and dried over anhydrous MgSO<sub>4</sub> to give the title mixture (1:1).

## 5-Bromo-4-chloroisatin:

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 270 MHz) δ 11.3 (1H, s), 7.90 (1H, J=8.5 Hz, d), 6.82 (1H, J=8.5 Hz, d).

## 5-Bromo-6-chloroisatin:

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 270 MHz) δ 11.3 (1H, s), 7.88 (1H, s), 7.13 (1H, s).

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## Reference example 8

1-(2-Diethylaminoethyl)-4,6-dichloroisatin

25 [0072] To the compound of reference example 1 (1.00 g, 4.63 mmol) in DMF (10 mL) was added 60% NaH (1.67 g, 10.2 mmol) with stirring, followed by 2-diethylaminoethyl chloride hydrochloride (876.4 mg, 5.09 mmol). The mixture was stirred at 60°C for 9 hours after which the reaction mixture was cooled to room temperature. Water was then added and the mixture extracted with a mixture of toluene and ethyl acetate (1:1). The organic phase was washed with brine and then dried over MgSO<sub>4</sub>. After concentration, purification was carried out by silica gel chromatography (ethyl acetate) to give the title compound.

30 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.05 (d, J=1.5 Hz, 1H), 6.91 (d, J=1.5 Hz, 1H), 3.77 (t, J=6 Hz, 2H), 2.68 (t, J=6 Hz, 2H), 2.54 (q, J=7 Hz, 4H), 0.97 (t, J=7 Hz, 6H).

## Reference example 9

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1-(2-Diisopropylaminoethyl)-4,6-dichloroisatin

[0073] This compound was prepared by the same method as that described in reference example 8, using 2-diisopropylaminoethyl chloride hydrochloride in place of 2-diethylaminoethyl chloride hydrochloride.

40 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.04 (d, J=1.3 Hz, 1H), 6.87 (s, 1H), 3.69 (t, J=6.6 Hz, 2H), 3.03 (hep, J=6.6 Hz, 2H), 2.70 (t, J=6.3 Hz, 2H), 0.96 (d, J=6.3 Hz, 12H).

## Reference example 10

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1-(2-Diethylaminoethyl)-4-bromoisatin and 1-(2-diethylaminoethyl)-6-bromoisatin

[0074] These compounds were prepared by the same method as that described in reference example 8, using the mixture of reference example 2 (2.5:1) in place of the compound of reference example 1. Separation of 1-(2-diethylaminoethyl)-4-bromoisatin and 1-(2-diethylaminoethyl)-6-bromoisatin was carried out by silica gel chromatography (hexane:ethyl acetate, 1:1 to 0:1 gradient).

## 1-(2-Diethylaminoethyl)-4-bromoisatin:

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.44 (d, J=7.7 Hz, 1H), 7.25 (dd, J=1.5, 7.7 Hz, 1H), 7.17 (d, J=1.5 Hz, 1H), 3.77 (t, J=6.6 Hz, 2H), 2.69 (t, J=6.6 Hz, 2H), 2.55 (q, J=7.1 Hz, 4H), 0.97 (t, J=7.1 Hz, 6H).

## 1-(2-Diethylaminoethyl)-6-bromoisatin:

55 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.39 (dd, J=7.8, 7.8 Hz, 1H), 7.23 (d, J=7.8 Hz, 1H), 6.90 (d, J=7.8 Hz, 1H), 3.80 (t, J=6.8 Hz, 2H), 2.68 (t, J=6.8 Hz, 2H), 2.56 (q, J=7.1 Hz, 4H), 0.97 (t, J=7.1 Hz, 6H).

## Reference example 11

1-(3-Dimethylaminoethyl)-4-bromoisatin

- 5 [0075] This compound was prepared by the same method as that described in reference example 8, using 3-dimethylaminoethyl chloride hydrochloride in place of 2-diethylaminoethyl chloride hydrochloride and using the mixture of reference example 2 (2.5:1) in place of the compound of reference example 1. Purification was carried out by silica gel chromatography (hexane:ethyl acetate, 1:1 to 0.1:1 gradient).
- 10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz) 7.40 (dd,  $J=7.9, 7.9$  Hz, 1H), 7.24 (d,  $J=7.9$  Hz, 1H), 6.89 (d,  $J=7.9$  Hz, 1H), 3.83 (t,  $J=6.8$  Hz, 2H), 2.57 (t, 2H,  $J=6.8$  Hz, 2H), 2.29 (s, 6H).

## Reference example 12

1-(3-Dimethylaminopropyl)-4-bromoisatin

- 15 [0076] This compound was prepared by the same method as that described in reference example 8, using 3-dimethylaminopropyl chloride hydrochloride in place of 2-diethylaminoethyl chloride hydrochloride and using the mixture of reference example 2 (2.5:1) in place of the compound of reference example 1. Purification was carried out by silica gel chromatography (hexane:ethyl acetate, 1:1 to 0.1:1 gradient).
- 20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  7.39 (dd,  $J=7.8, 7.8$  Hz, 1H), 7.23 (d,  $J=7.8$  Hz, 1H), 6.97 (d,  $J=7.8$  Hz, 1H), 3.81 (t,  $J=6.8$  Hz, 2H), 2.33 (t,  $J=6.8$  Hz, 2H), 2.18 (s, 6H), 1.84 (dt,  $J=6.8, 6.8$  Hz, 2H).

## Reference example 13

1-(2-Diethylaminoethyl)-7-bromoisatin

- 25 [0077] This compound was prepared by the same method as that described in reference example 8, using the compound of reference example 3 in place of the compound of reference example 1.
- 30  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  7.70 (dd,  $J=1.3, 8.2$  Hz, 1H), 7.58 (dd,  $J=1.3, 7.3$  Hz, 1H), 6.98 (dd,  $J=7.3, 8.2$  Hz, 1H), 4.27 (t,  $J=6.8$  Hz, 2H), 2.69 (t,  $J=6.8$  Hz, 2H), 2.51 (q,  $J=7.1$  Hz, 4H), 0.89 (t,  $J=7.1$  Hz, 6H).

## Reference example 14

1-(2-Diethylaminoethyl)-5-bromoisatin

- 35 [0078] This compound was prepared by the same method as that described in reference example 8, using 5-bromoisatin in place of the compound of reference example 1.
- 40  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  7.69 (d,  $J=2$  Hz, 1H), 7.69 (dd,  $J=9, 2$  Hz, 1H), 6.88 (d,  $J=9$  Hz, 1H), 3.78 (t,  $J=6.5$  Hz, 2H), 2.68 (t,  $J=6.5$  Hz, 2H), 2.55 (q,  $J=7$  Hz, 4H), 0.96 (t,  $J=7$  Hz, 6H).

## Reference example 15

1-(2-Diethylaminoethyl)-5-chloroisatin

- 45 [0079] This compound was prepared by the same method as that described in reference example 8, using 5-chloroisatin in place of the compound of reference example 1.
- 50  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  7.55 (d,  $J=2$  Hz, 1H), 7.54 (dd,  $J=9, 2$  Hz, 1H), 6.92 (d,  $J=9$  Hz, 1H), 3.79 (t,  $J=7$  Hz, 2H), 2.69 (t,  $J=7$  Hz, 2H), 2.55 (q,  $J=7$  Hz, 4H), 0.97 (t,  $J=7$  Hz, 6H).

## Reference example 16

1-(3-Diethylaminopropyl)-5-chloroisatin

- 55 [0080] This compound was prepared by the same method as that described in reference example 8, using 3-diethylaminopropyl chloride hydrochloride in place of 2-diethylaminoethyl chloride hydrochloride, and using 5-chloroisatin in place of the compound of reference example 1.

## Reference example 17

1-(2-Diethylaminoethyl)-4,6-dimethylisatin

- 5 [0081] This compound was prepared by the same method as that described in reference example 8, using the compound of reference example 4 in place of the compound of reference example 1.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 6.67 (s, 1H), 6.54 (s, 1H), 3.76 (t, J=7.0 Hz, 2H), 2.68 (t, J=7.0 Hz, 2H), 2.58 (q, J=7.1 Hz, 4H), 2.52 (s, 3H), 2.37 (s, 3H), 1.00 (t, J=7.1 Hz, 6H).

## 10 Reference example 18

Mixture of 1-(2-diethylaminoethyl)-4-iodo-6-chloroisatin and 1-(2-diethylaminoethyl)-6-iodo-4-chloroisatin

- 15 [0082] This mixture (3:1) was prepared by the same method as that described in reference example 8, using the mixture of reference example 5 in place of the compound of reference example 1.  
1-(2-Diethylaminoethyl)-4-iodo-6-chloroisatin:  
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 270 MHz) δ 7.53 (d, J=1.5 Hz, 1H), 6.99 (d, J=1.5 Hz, 1H), 3.77 (t, J=6.4 Hz, 2H), 2.67 (t, J=6.4 Hz, 2H), 2.55 (q, J=7.1 Hz, 4H), 0.97 (t, J=7.1 Hz, 6H).  
1-(2-Diethylaminoethyl)-6-iodo-4-chloroisatin:  
20 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 270 MHz) δ 7.46 (s, 1H), 7.30 (s, 1H), 3.77 (t, J=6.4 Hz, 2H), 2.67 (t, J=6.4 Hz, 2H), 2.55 (q, J=7.1 Hz, 4H), 0.97 (t, J=7.1 Hz, 6H).

## Reference example 19

25 1-(2-Diethylaminoethyl)-4-trifluoromethylisatin

- [0083] This compound was prepared by the same method as that described in reference example 8, using the compound of reference example 6 in place of the compound of reference example 1.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.73 (t, J=9 Hz, 1H), 7.40 (d, J=8.1 Hz, 1H), 7.31 (m, 1H), 3.87 (t, J=6.0 Hz, 2H), 2.85 (t, J=6.0 Hz, 2H), 2.60 (q, J=6.3 Hz, 4H), 1.03 (t, J=6.3 Hz, 6H).

## Reference example 20

Mixture of 1-(2-diethylaminoethyl)-5-bromo-4-chloroisatin and 1-(2-diethylaminoethyl)-5-bromo-4-chloroisatin

- 35 [0084] This mixture (1.8:1) was prepared by the same method as that described in reference example 8, using the mixture of reference example 7 in place of the compound of reference example 1.  
1-(2-Diethylaminoethyl)-5-bromo-4-chloroisatin:  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.79 (d, J=8.5 Hz, 1H), 6.81 (d, J=8.5 Hz, 1H), 3.79 (t, J=6.5 Hz, 2H), 2.68 (t, J=6.5 Hz, 2H), 2.56 (q, J=7 Hz, 4H), 0.96 (t, J=7 Hz, 6H).  
1-(2-Diethylaminoethyl)-5-bromo-4-chloroisatin:  
40 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.79 (1H, s), 7.15 (1H, s), 3.77 (t, J=6.5 Hz, 2H), 2.69 (t, J=6.5 Hz, 2H), 2.55 (q, J=7 Hz, 4H), 0.96 (t, J=7 Hz, 6H).

## 45 Reference example 21

Mixture of 1-(2-diethylaminoethyl)-4-chloro-6-(3-t-butyldimethylsilyloxy-1-propynyl)isatin and 1-(2-diethylaminoethyl)-6-chloro-4-(3-t-butyldimethylsilyloxy-1-propynyl)isatin

- 50 [0085] To the mixture of reference example 18 (3:1, 392.0 mg, 0.96 mmol) and bis(triphenylphosphine)palladium (II) chloride (33.7 mg, 20 mol%) in triethylamine (4.0 mL) was added t-butyldimethylsilyl(2-propynyl) silane (244.8 mg, 1.5 eq) and copper (I) iodide (8.3 mg, 22 mol%). The mixture was stirred at 60°C for 1.5 hours. After cooling, water was added and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous MgSO<sub>4</sub> and concentrated.  
55 Purification was carried out by silica gel chromatography (hexane:ethyl acetate, 1:1 to 1:1.5 gradient) to give the desired mixture (2:1). 1-(2-Diethylaminoethyl)-4-chloro-6-(3-t-butyldimethylsilyloxy-1-propynyl)isatin:  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.08 (d, J=1.7 Hz, 1H), 6.93 (d, J=1.7 Hz, 1H), 4.63 (s, 2H), 3.76 (t, J=6.4 Hz, 2H), 2.67 (t, J=6.4 Hz, 2H), 2.55 (q, J=7.1 Hz, 4H), 0.97 (t, J=7.1 Hz, 6H), 0.93 (s, 9H), 0.18 (s, 6H). 1-(2-Diethylaminoethyl)-

6-chloro-4-(3-t-butylidemethylsilyloxy-1-propynyl)isatin:

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.06 (s, 1H), 6.87 (s, 1H), 4.56 (s, 2H), 3.78 (t, J=6.4 Hz, 2H), 2.67 (t, J=6.4 Hz, 2H), 2.55 (q, J=7.1 Hz, 4H), 0.97 (t, J=7.1 Hz, 6H), 0.95 (s, 9H), 0.17 (s, 6H).

5 Reference example 22

Mixture of 1-(2-diethylaminoethyl)-4-chloro-6-(4-t-butylidemethylsilyloxy-1-butynyl)isatin and 1-(2-diethylaminoethyl)-6-chloro-4-(4-t-butylidemethylsilyloxy-1-butynyl)isatin

10 [0086] This mixture (3.7:1) was prepared by the same method as that described in reference example 21, using t-butylidemethylsilyl(3-butynylsilyloxy)silane in place of t-butylidemethylsilyl(2-propynylsilyloxy)silane. 1-(2-Diethylaminoethyl)-4-chloro-6-(4-t-butylidemethylsilyloxy-1-butynyl)isatin:

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.03 (d, J=1.7 Hz, 1H), 6.88 (d, J=1.7 Hz, 1H), 3.88 (t, J=7.0 Hz, 2H), 3.75 (t, J=6.6 Hz, 2H), 2.74 (t, J=7.0 Hz, 2H), 2.67 (t, J=6.6 Hz, 2H), 2.54 (q, J=7.1 Hz, 4H), 0.97 (t, J=7.1 Hz, 6H), 0.91 (s, 9H), 0.09 (s, 6H). 1-(2-Diethylaminoethyl)-6-chloro-4-(4-t-butylidemethylsilyloxy-1-butynyl)isatin:

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.03 (s, 1H), 6.82 (s, 1H), 3.88 (t, J=7.0 Hz, 2H), 3.83 (t, J=6.6 Hz, 2H), 2.74 (t, J=7.0 Hz, 2H), 2.67 (t, J=6.6 Hz, 2H), 2.54 (q, J=7.1 Hz, 4H), 0.97 (t, J=7.1 Hz, 6H), 0.92 (s, 9H), 0.10 (s, 6H).

Reference example 23

20 4,6-Dichloro-3-hydroxy-3-(2-naphthyl)oxindole

25 [0087] To a solution of 2-bromonaphthalene (2.952g) in anhydrous THF (25 mL) was added portion wise a solution of n-butyl lithium inn-hexane (1.55 N, 10.12 mL) at -78°C. The reaction solution was stirred for 30 minutes. To the mixture was then added portion wise a solution of 4,6-dichloroisatin (1.54g) in anhydrous THF (25ml) for 50 minutes. The reaction mixture was stirred for 2 hours. Then the mixture was allowed to warm to room temperature. To the mixture was added 1N HCl and extracted by ethyl acetate. The organic phase was separated, washed with 1N HCl and brine and dried over MgSO<sub>4</sub> and concentrated. Purification was carried out by silica gel chromatography (hexane:ethyl acetate, 2:1 to 1:1 gradient) to give the title compound (0.652 g, yield: 27%).

30 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 6.93 (1H, s), 6.96 (1H, d, J=1.7Hz), 7.12 (1H, d, J=1.7Hz), 7.23 (1H, m), 7.49 (2H, m), 7.80-7.94 (4H, m), 10.80 (1H, brs).

Reference example 24

35 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-iodoisatin

40 [0088] This compound was prepared by the same method as that described in reference example 8, using a mixture of 4-trifluoromethyl-6-iodoisatin and 6-trifluoromethyl-4-iodoisatin in place of the compound of reference example 18. Purification was carried out by silica gel chromatography.

45 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (s, 1H), 7.68 (s, 1H), 3.80 (t, 2H, J=6.1 Hz), 2.69 (t, 2H, J=6.1 Hz), 2.55 (q, 4H, J=7.1 Hz), 0.97 (t, 6H, J=7.1 Hz).

Example 1

50 4,6-Dichloro-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole

55 [0089] To a solution of the compound of reference example 8 (102.6 mg, 0.317 mmol) in anhydrous THF (0.6 mL) was added portionwise at room temperature the Grignard reagent which was prepared from 2-bromonaphthalene (98.5 mg, 1.5 eq) and magnesium (11.4 mg, 1.5 eq). The reaction mixture was stirred overnight. Methanol was added to stop the reaction and concentrated. Saturated aqueous NaHCO<sub>3</sub> was then added and the mixture extracted with ethyl acetate. The organic phase was dried over anhydrous MgSO<sub>4</sub> and concentrated. Purification by silica gel chromatography (1% methanol in chloroform) gave the title compound 33.3 mg.

60 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.98 (d, J=2 Hz, 1H), 7.78-7.83 (m, 2H), 7.77 (d, J=8.5 Hz, 1H), 7.44-7.50 (m, 2H), 7.36 (dd, J=8, 2 Hz, 1H), 7.04 (d, J=1.5 Hz, 1H), 6.95 (d, J=1.5 Hz, 1H), 3.87 (dt, J=13, 6.5 Hz, 1H), 3.69 (dt, J=13, 6.5 Hz, 1H), 2.70 (t, J=6.5 Hz, 2H), 2.56 (q, J=7 Hz, 4H), 0.96 (t, J=7 Hz, 6H).

## Example 2

4,6-Dichloro-1-(2-diethylaminoethyl)-3-hydroxy-3-(3-fluorophenyl)oxindole

- 5 [0090] This compound was prepared by the same procedure as described in example 1, using 1-bromo-3-fluorobenzene in place of 2-bromonaphthalene.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.24-7.32 (m, 1H), 7.13-7.21 (m, 2H), 7.03 (d, J=1.5 Hz, 1H), 6.96-7.03 (m, 1H), 6.92 (d, J=1.5 Hz, 1H), 3.88 (dt, J=14, 7 Hz, 1H), 3.65 (dt, J=14, 7 Hz, 1H), 2.69 (t, J=7 Hz, 1H), 2.68 (t, J=7 Hz, 1H), 2.55 (q, J=7 Hz, 4H), 0.95 (t, J=7 Hz, 6H).

## 10 Example 3

4,6-Dichloro-1-(2-diethylaminoethyl)-3-hydroxy-3-(4-fluorophenyl)oxindole

- 15 [0091] This compound was prepared by the same procedure as described in example 1, using 1-bromo-4-fluorobenzene in place of 2-bromonaphthalene.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.35-7.42 (m, 2H), 7.03 (d, J=1.5 Hz, 1H), 6.97-7.07 (m, 2H), 6.91 (d, J=1.5 Hz, 1H), 3.66-3.88 (m, 2H), 2.70 (t, J=7 Hz, 2H), 2.57 (q, J=7 Hz, 4H), 0.96 (t, J=7 Hz, 6H).

## 20 Example 4

4,6-Dichloro-1-(2-diethylaminoethyl)-3-hydroxy-3-(4-methoxyphenyl)oxindole

- 25 [0092] This compound was prepared by the same procedure as described in example 1, using 1-bromo-4-methoxyanisole in place of 2-bromonaphthalene.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.21 (d, J=9 Hz, 2H), 7.03 (d, J=1.5 Hz, 1H), 6.90 (d, J=1.5 Hz, 1H), 6.85 (d, J=9 Hz, 2H), 3.79 (s, 3H), 3.82 (dt, J=14, 6.5 Hz, 1H), 3.67 (dt, J=14, 6.5 Hz, 1H), 2.68 (t, J=6.5 Hz, 2H), 2.55 (q, J=7 Hz, 4H), 0.96 (t, J=7 Hz, 6H).

## 30 Example 5

4,6-Dichloro-1-(2-diethylaminoethyl)-3-hydroxy-3-(3,4-difluorophenyl)oxindole

- 35 [0093] This compound was prepared by the same procedure as described in example 1, using 1-bromo-3,4-difluorobenzene in place of 2-bromonaphthalene.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.29-7.37 (m, 1H), 7.04-7.14 (m, 2H), 7.03 (d, J=1.5 Hz, 1H), 6.91 (d, J=1.5 Hz, 1H), 3.89 (dt, J=14, 7 Hz, 1H), 3.65 (dt, J=14, 7 Hz, 1H), 2.65-2.72 (m, 2H), 2.55 (q, J=7 Hz, 4H), 0.94 (t, J=7 Hz, 6H).

## 40 Example 6

4,6-Dichloro-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-fluorophenyl)oxindole

- 45 [0094] This compound was prepared by the same procedure as described in example 1, using 1-bromo-2-fluorobenzene in place of 2-bromonaphthalene.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.97 (ddd, J=1.9, 7.8, 7.8 Hz, 1H), 7.21-7.36 (m, 3H), 6.96 (d, J=1.7 Hz, 1H), 6.91 (d, J=1.7 Hz, 1H), 6.89-6.97 (m, 1H), 3.75-3.90 (m, 3H), 2.51-2.82 (m, 6H), 1.03 (t, J=7.3 Hz, 6H).

## Example 7

50 4,6-Dichloro-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-chlorophenyl)oxindole

- 55 [0095] This compound was prepared by the same procedure as described in example 1, using 1-bromo-2-chlorobenzene in place of 2-bromonaphthalene.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 8.16 (dd, J=1.5, 7.5 Hz, 1H), 7.40 (ddd, J=1.5, 7.5, 7.5 Hz, 1H), 7.23-7.33 (m, 2H), 6.95 (d, J=1.7 Hz, 1H), 6.88 (d, J=1.7 Hz, 1H), 3.90-4.01 (m, 1H), 3.65-3.75 (m, 1H), 2.52-2.85 (m, 6H), 1.03 (t, J=7.3 Hz, 6H).

## Example 8

4,6-Dichloro-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-trifluoromethylphenyl)oxindole

**[0096]** This compound was prepared by the same procedure as described in example 1, using 1-bromo-2-trifluorobenzene in place of 2-bromonaphthalene.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  8.42 (br, 1H), 7.66-7.69 (m, 2H), 7.48 (dd,  $J=7.6, 7.6$  Hz, 1H), 6.95 (d,  $J=1.5$  Hz, 1H), 6.88 (d,  $J=1.5$  Hz, 1H), 3.91-4.02 (m, 1H), 3.59-3.69 (m, 1H), 2.75-2.86 (m, 2H), 2.49-2.71 (m, 4H), 1.01 (t,  $J=7.1$  Hz, 6H).

## Example 9

4,6-Dichloro-1-(2-diethylaminoethyl)-3-hydroxy-3-(3,4-dichlorophenyl)oxindole

**[0097]** This compound was prepared by the same procedure as described in example 1, using 1-bromo-3,4-dichlorobenzene in place of 2-bromonaphthalene.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  7.53 (d,  $J=2.1$  Hz, 1H), 7.40 (d,  $J=8.4$  Hz, 1H), 7.27 (dd,  $J=2.1, 8.4$  Hz, 1H), 7.04 (d,  $J=1.7$  Hz, 1H), 6.90 (d,  $J=1.7$  Hz, 1H), 3.81-3.91 (m, 1H), 3.65-3.75 (m, 1H), 2.70 (t,  $J=5.6$  Hz, 2H), 2.56 (q,  $J=7.1$  Hz, 4H), 0.94 (t,  $J=7.1$  Hz, 6H).

## Example 10

4,6-Dichloro-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-dimethylaminosulfonylphenyl)oxindole

**[0098]** To a solution of the compound of reference example 8 (45.4 mg, 0.14 mmol) in anhydrous THF (0.6 mL) was added portionwise at 0°C the organolithium reagent which was prepared from a solution of N,N-dimethylbenzenesulfonamide (40.0 mg, 0.22 mmol) in anhydrous THF (1.0 mL) and n-butyllithium (0.135 mL, 1.6M in hexanes) at 0°C. The mixture was stirred overnight. Methanol was added to stop the reaction and concentrated. Saturated aqueous  $\text{NaHCO}_3$  was then added and the mixture extracted with ethyl acetate. The organic phase was dried over anhydrous  $\text{MgSO}_4$  and concentrated. Purification by silica gel chromatography (1% methanol in chloroform) gave the title compound.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  8.61 (d,  $J=7.6$  Hz, 1H), 7.74-7.66 (m, 2H), 7.51 (dd,  $J=7.6, 7.6$  Hz, 1H), 6.91 (s, 1H), 6.84 (s, 1H), 3.52-3.57 (m, 2H), 2.83-2.90 (m, 2H), 2.60 (s, 6H), 2.53-2.72 (m, 4H), 1.01 (t,  $J=7.1$  Hz, 6H).

## Example 11

4,6-Dichloro-1-(2-diisopropylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole

**[0099]** This compound was prepared by the same procedure as described in example 1, using the compound of reference example 9 in place of the compound of reference example 8.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  7.93 (d,  $J=2.0$  Hz, 1H), 7.78-7.83 (m, 3H), 7.45-7.51 (m, 2H), 7.35 (dd,  $J=2.0, 8.6$  Hz, 1H), 7.05 (d,  $J=1.7$  Hz, 1H), 6.95 (d,  $J=1.7$  Hz, 1H), 3.56-3.77 (m, 2H), 2.99-3.08 (m, 2H), 2.70 (t,  $J=6.8$  Hz, 2H), 0.98 (d,  $J=6.6$  Hz, 6H), 0.97 (d,  $J=6.6$  Hz, 6H).

## Example 12

4,6-Dichloro-1-(2-diisopropylaminoethyl)-3-hydroxy-3-(2-chlorophenyl)oxindole

**[0100]** This compound was prepared by the same procedure as described in example 1, using the compound of reference example 9 in place of the compound of reference example 8 and using 1-bromo-2-chlorobenzene in place of 2-bromonaphthalene.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  8.12 (dd,  $J=1.3, 7.9$  Hz, 1H), 7.24-7.43 (m, 3H), 6.94 (d,  $J=1.7$  Hz, 1H), 6.86 (d,  $J=1.7$  Hz, 1H), 3.57-3.81 (m, 2H), 3.02-3.11 (m, 2H), 2.63-2.82 (m, 2H), 1.05 (d,  $J=6.6$  Hz, 6H), 1.04 (d,  $J=6.6$  Hz, 6H).

## Example 13

4,6-Dichloro-1-(2-diisopropylaminoethyl)-3-hydroxy-3-(2-trifluoromethylphenyl)oxindole

- <sup>5</sup> [0101] This compound was prepared by the same procedure as described in example 1, using the compound of reference example 9 in place of the compound of reference example 8 and using 1-bromo-2-trifluoromethylbenzene in place of 2-bromonaphthalene.  
<sup>10</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  8.31 (br, 1H), 7.68-7.71 (m, 2H), 7.45-7.51 (m, 2H), 7.49 (dd,  $J=7.6, 7.6$  Hz, 1H), 6.95 (d,  $J=1.7$  Hz, 1H), 6.87 (d,  $J=1.7$  Hz, 1H), 3.54-3.76 (m, 2H), 3.01-3.13 (m, 2H), 2.69 (t,  $J=7.4$  Hz, 2H), 1.04 (d,  $J=6.6$  Hz, 6H), 1.03 (d,  $J=6.6$  Hz, 6H).

## Example 14

4,6-Dichloro-1-(2-diisopropylaminoethyl)-3-hydroxy-3-(2-dimethylaminosulfonylphenyl)oxindole

- <sup>15</sup> [0102] This compound was prepared by the same procedure as described in example 10, using the compound of reference example 9 in place of the compound of reference example 8.  
<sup>20</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  8.54 (d,  $J=8.3$  Hz, 1H), 7.66-7.74 (m, 2H), 7.49-7.55 (m, 1H), 6.90 (s, 1H), 6.85 (s, 1H), 3.81-3.83 (m, 1H), 3.53-3.55 (m, 1H), 3.05 (m, 2H), 2.67-2.75 (m, 2H), 2.61 (s, 6H), 1.02-1.06 (m, 12H).

## Example 15

4,6-Dichloro-1-(2-diisopropylaminoethyl)-3-hydroxy-3-(3,4-dichlorophenyl)oxindole

- <sup>25</sup> [0103] This compound was prepared by the same procedure as described in example 1, using the compound of reference example 9 in place of the compound of reference example 8 and using 1-bromo-3,4-dichlorobenzene in place of 2-bromonaphthalene.  
<sup>30</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  7.47 (d,  $J=2.1$  Hz, 1H), 7.40 (d,  $J=8.5$  Hz, 1H), 7.19 (dd,  $J=2.1, 8.5$  Hz, 1H), 7.05 (d,  $J=1.7$  Hz, 1H), 6.92 (d,  $J=1.7$  Hz, 1H), 3.53-3.76 (m, 2H), 2.99-3.08 (m, 2H), 2.68 (t,  $J=6.6$  Hz, 2H), 0.97 (d,  $J=6.6$  Hz, 6H), 0.96 (d,  $J=6.6$  Hz, 6H).

## Example 16

5-Chloro-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole

- <sup>35</sup> [0104] This compound was prepared by the same procedure as described in example 1, using the compound of reference example 16 in place of the compound of reference example 8.  
<sup>40</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  7.96 (s, 1H), 7.74 (m, 3H), 7.41-7.48 (m, 3H), 7.29 (dd,  $J=8, 2$  Hz, 1H), 6.89 (d,  $J=8$  Hz, 1H), 3.96 (dt,  $J=14, 7$  Hz, 1H), 3.74 (dt,  $J=14, 7$  Hz, 1H), 2.75 (t,  $J=7$  Hz, 2H), 2.61 (q,  $J=7$  Hz, 2H), 2.60 (q,  $J=7$  Hz, 2H), 0.99 (t,  $J=7$  Hz, 6H).

## Example 17

5-Chloro-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-methoxyphenyl)oxindole

- <sup>45</sup> [0105] This compound was prepared by the same procedure as described in example 1, using the compound of reference example 15 in place of the compound of reference example 8 and using 1-bromo-2-methoxybenzene in place of 2-bromonaphthalene.  
<sup>50</sup>  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  7.69 (dd,  $J=7.5, 2$  Hz, 1H), 7.31 (td,  $J=8, 2$  Hz, 1H), 7.26 (dd,  $J=8, 2$  Hz, 1H), 7.08 (d,  $J=2$  Hz, 1H), 7.04 (ddd,  $J=8, 7.5, 2$  Hz, 1H), 6.85 (d,  $J=8$  Hz, 1H), 6.84 (dd,  $J=8, 2$  Hz, 1H), 3.83 (t,  $J=7$  Hz, 2H), 3.62 (s, 3H), 2.75 (t,  $J=7$  Hz, 2H), 2.64 (q,  $J=7$  Hz, 4H), 1.06 (t,  $J=7$  Hz, 6H).

## Example 18

5-Chloro-1-(3-diethylaminopropyl)-3-hydroxy-3-(2-fluorophenyl)oxindole

- [0106] This compound was prepared by the same procedure as described in example 1, using the compound of reference example 16 in place of the compound of reference example 8 and using 1-bromo-2-fluorobenzene in place

of 2-bromonaphthalene.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.91 (td, J=7.5, 2 Hz, 1H), 7.18-7.36 (m, 3H), 7.08 (d, J=2 Hz, 1H), 6.93 (td, J=8, 2 Hz, 1H), 6.90 (d, J=8.5 Hz, 1H), 3.68-3.95 (m, 2H), 2.53-2.70 (m, 6H), 1.92-2.05 (m, 2H), 1.08 (t, J=7 Hz, 6H).

5 Example 19

5-Chloro-1-(3-diethylaminopropyl)-3-hydroxy-3-(2-methoxyphenyl)oxindole

10 [0107] This compound was prepared by the same procedure as described in example 1, using the compound of reference example 16 in place of the compound of reference example 8 and using 1-bromo-2-methoxybenzene in place of 2-bromonaphthalene.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.72 (dd, J=8, 2 Hz, 1H), 7.31 (td, J=8, 2 Hz, 1H), 7.25 (dd, J=8, 2 Hz, 1H), 7.05 (td, J=8, 2 Hz, 1H), 7.05 (d, J=2 Hz, 1H), 6.85 (d, J=8 Hz, 1H), 6.82 (d, J=8 Hz, 1H), 3.77 (t, J=7 Hz, 2H), 3.59 (s, 3H), 2.54-2.62 (m, 6H), 1.85-1.96 (m, 2H), 1.04 (t, J=7 Hz, 6H).

15

Example 20

5-Chloro-1-(3-diethylaminopropyl)-3-hydroxy-3-(2-naphthyl)oxindole

20 [0108] This compound was prepared by the same procedure as described in example 1, using the compound of reference example 16 in place of the compound of reference example 8.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.90 (d, J=2 Hz, 1H), 7.76-7.82 (m, 1H), 7.77 (d, J=9 Hz, 1H), 7.45-7.50 (m, 2H), 7.33 (dd, J=8, 2 Hz, 1H), 7.30 (d, J=2 Hz, 1H), 7.26 (dd, J=8, 2 Hz, 1H), 6.92 (d, J=8 Hz, 1H), 3.72-3.79 (m, 2H), 2.47-2.58 (m, 6H), 1.83-1.94 (m, 2H), 0.99 (t, J=7 Hz, 6H).

25

Example 21

4-Bromo-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-fluorophenyl)oxindole

30 [0109] This compound was prepared by the same procedure as described in example 1, using 1-(2-diethylaminoethyl)-4-bromoisoatin (reference example 10) in place of the compound of reference example 8 and using 1-bromo-2-fluorobenzene in place of 2-bromonaphthalene. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 8.00 (ddd, J=2.1, 7.8, 7.8 Hz, 1H), 7.05-7.47 (m, 4H), 6.88-6.95 (m, 2H), 3.83 (t, J=7.3 Hz, 2H), 2.53-2.82 (m, 6H), 1.03 (t, J=7.1 Hz, 6H).

35 Example 22

4-Bromo-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-methoxyphenyl)oxindole

40 [0110] This compound was prepared by the same procedure as described in example 1, using 1-(2-diethylaminoethyl)-4-bromoisoatin (reference example 10) in place of the compound of reference example 8 and using 1-bromo-2-methoxybenzene in place of 2-bromonaphthalene.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.72 (brd, 1H), 7.31 (ddd, J=1.8, 7.7, 7.7 Hz, 1H), 7.01-7.20 (m, 3H), 6.86 (dd, J=1.3, 7.7 Hz, 1H), 6.83 (d, J=8.3 Hz, 1H), 3.79-3.86 (m, 2H), 3.58 (s, 3H), 2.70-2.76 (m, 2H), 2.63 (q, J=6.9 Hz, 4H), 1.06 (t, J=6.9 Hz, 6H).

45

Example 23

4-Bromo-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole

50 [0111] This compound was prepared by the same procedure as described in example 1, using 1-(2-diethylaminoethyl)-4-bromoisoatin (reference example 10) in place of the compound of reference example 8.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 8.00 (d, J=1.6 Hz, 1H), 7.75-7.85 (m, 3H), 7.44-7.50 (m, 2H), 7.34 (dd, J=2.0, 8.6 Hz, 1H), 7.19-7.30 (m, 2H), 6.97 (dd, J=1.0, 7.6 Hz, 1H), 3.61-3.93 (m, 2H), 2.72 (t, J=6.9 Hz, 2H), 2.57 (q, J=7.1 Hz, 4H), 0.97 (t, J=7.1 Hz, 6H).

55

## Example 24

4-Bromo-1-(2-diethylaminoethyl)-3-hydroxy-3-(4-biphenyl)oxindole

- 5 [0112] This compound was prepared by the same procedure as described in example 1, using 1-(2-diethylaminoethyl)-4-bromoisoatin (reference example 10) in place of the compound of reference example 8 and using 4-bromo-biphenyl in place of 2-bromonaphthalene.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.54-7.58 (m, 4H), 7.20-7.47 (m, 8H), 6.97 (d, J=5.6 Hz, 1H), 3.86 (m, 2H), 2.64-2.85 (m, 6H), 1.03 (t, J=7.1 Hz, 6H).

## 10 Example 25

6-Bromo-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-fluorophenyl)oxindole

- 15 [0113] This compound was prepared by the same procedure as described in example 1, using 1-(2-diethylaminoethyl)-6-bromoisoatin (reference example 10) in place of the compound of reference example 8 and using 1-bromo-2-fluorobenzene in place of 2-bromonaphthalene.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.86 (ddd, J=1.9, 7.8, 7.8 Hz, 1H), 6.90-7.48 (m, 6H), 3.83 (t, J=6.9 Hz, 2H), 2.55-2.82 (m, 6H), 1.05 (t, J=7.1 Hz, 6H).

## 20 Example 26

7-Bromo-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-fluorophenyl)oxindole

- 25 [0114] This compound was prepared by the same procedure as described in example 1, using the compound of reference example 13 in place of the compound of reference example 8 and using 1-bromo-2-fluorobenzene in place of 2-bromonaphthalene.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.91 (ddd, J=1.9, 7.6, 7.6 Hz, 1H), 6.78-7.57 (m, 6H), 4.20-4.48 (m, 2H), 2.37-2.75 (m, 6H), 0.97 (t, J=7.3 Hz, 6H).

## 30 Example 27

7-Bromo-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole

- 35 [0115] This compound was prepared by the same procedure as described in example 1, using the compound of reference example 13 in place of the compound of reference example 8.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.97 (s, 1H), 7.75-7.83 (m, 3H), 7.41-7.49 (m, 4H), 7.20 (dd, J=1.3, 7.3 Hz, 1H), 6.91 (dd, J=7.8, 7.8 Hz, 1H), 4.31 (t, J=6.8 Hz, 2H), 2.69-2.84 (m, 2H), 2.53-2.66 (m, 4H), 0.96 (t, J=7.3 Hz, 6H).

## 40 Example 28

7-Bromo-1-(2-diethylaminoethyl)-3-hydroxy-3-(4-biphenyl)oxindole

- 45 [0116] This compound was prepared by the same procedure as described in example 1, using the compound of reference example 13 in place of the compound of reference example 8 and using 4-bromo-biphenyl in place of 2-bromonaphthalene.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.33-7.56 (m, 10H), 7.24 (dd, J=7.5, 1 Hz, 1H), 6.94 (dd, J=8, 7.5 Hz, 1H), 4.29 (t, J=7 Hz, 2H), 2.70-2.87 (m, 2H), 2.56-2.75 (m, 4H), 0.96 (t, J=7 Hz, 6H).

## 50 Example 29

5-Bromo-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-fluorophenyl)oxindole

- 55 [0117] This compound was prepared by the same procedure as described in example 1, using the compound of reference example 14 in place of the compound of reference example 8 and using 1-bromo-2-fluorobenzene in place of 2-bromonaphthalene.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.86 (td, J=8, 2 Hz, 1H), 7.43-7.49 (m, 1H), 7.43 (dd, J=8, 2 Hz, 1H), 7.23 (d, J=2 Hz, 1H), 6.94 (ddd, J=12, 8, 1 Hz, 1H), 6.84 (dd, J=8, 3 Hz, 1H), 3.73-3.93 (m, 2H), 2.68-2.76 (m, 2H), 2.62 (q, J=7 Hz,

2H), 2.61 (q, J=7 Hz, 2H), 1.03 (t, J=7 Hz, 6H).

Example 30

5 5-Bromo-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole

**[0118]** This compound was prepared by the same procedure as described in example 1, using the compound of reference example 14 in place of the compound of reference example 8.

10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  7.95 (d, J=2 Hz, 1H), 7.75-7.80 (m, 1H), 7.75 (d, J=8.5 Hz, 1H), 7.44-7.49 (m, 3H), 7.41 (d, J=2 Hz, 1H), 7.37 (d, J=2 Hz, 1H), 6.84 (d, J=8.5 Hz, 1H), 3.94 (dt, J=14, 7 Hz, 1H), 3.71 (dt, J=14, 7 Hz, 1H), 2.73 (t, J=7 Hz, 1H), 2.71 (t, J=7 Hz, 1H), 2.59 (q, J=7 Hz, 2H), 2.58 (q, J=7 Hz, 2H), 0.98 (t, J=7 Hz, 6H).

Example 31

15 5-Bromo-4-chloro-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole

**[0119]** This compound was prepared by the same procedure as described in example 1, using the mixture of reference example 20 in place of the compound of reference example 8 and separated by silica gel chromatography (0.5% methanol in chloroform).

20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  8.00 (d, J=1.5 Hz, 1H), 7.78-7.84 (m, 2H), 7.77 (d, J=8.5 Hz, 1H), 7.65 (d, J=8 Hz, 1H), 7.44-7.50 (m, 2H), 7.34 (dd, J=8.5, 2 Hz, 1H), 6.84 (d, J=8.5 Hz, 1H), 3.88 (dt, J=14, 6.5 Hz, 1H), 3.73 (dt, J=14, 6.5 Hz, 1H), 2.72 (t, J=6.5 Hz, 2H), 2.57 (q, J=7 Hz, 4H), 0.96 (t, J=7 Hz, 6H).

Example 32

25 5-Bromo-6-chloro-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole

**[0120]** This compound was prepared by the same procedure as described in example 1, using the mixture of reference example 20 in place of the compound of reference example 8 and separated by silica gel chromatography (0.5% methanol in chloroform).

30  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  7.93 (d, J=1.5 Hz, 1H), 7.76-7.81 (m, 2H), 7.76 (d, J=8 Hz, 1H), 7.45-7.50 (m, 2H), 7.46 (s, 1H), 7.41 (dd, J=8.5, 2 Hz, 1H), 7.10 (s, 1H), 3.93 (dt, J=14, 6.5 Hz, 1H), 3.70 (dt, J=14, 6.5 Hz, 1H), 2.73 (t, J=6.5 Hz, 2H), 2.60 (q, J=7 Hz, 4H), 0.98 (t, J=7 Hz, 6H).

35 Example 33

4-Bromo-1-(2-dimethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole

**[0121]** This compound was prepared by the same procedure as described in example 1, using the compound of reference example 11 in place of the compound of reference example 8.

40  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  8.01 (d, J=1.7 Hz, 1H), 7.74-7.84 (m, 3H), 7.43-7.49 (m, 2H), 7.33 (dd, J=2.0, 8.6 Hz, 1H), 7.18-7.28 (m, 2H), 6.96 (dd, J=1.3, 7.3 Hz, 1H), 3.84 (t, J=6.7 Hz, 2H), 2.70 (dt, J=12.5, 6.7 Hz, 1H), 2.52 (dt, J=12.5, 6.7 Hz, 1H), 2.26 (s, 6H).

45 Example 34

4-Bromo-1-(2-dimethylaminoethyl)-3-hydroxy-3-(3,4-difluorophenyl)oxindole

**[0122]** This compound was prepared by the same procedure as described in example 1, using the compound of reference example 11 in place of the compound of reference example 8 and using 1-bromo-3,4-difluorobenzene in place of 2-bromonaphthalene.

50  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 270 MHz)  $\delta$  7.18-7.35 (m, 3H), 7.07-7.15 (m, 2H), 6.90 (dd, J=1.5, 7.1 Hz, 1H), 3.73-3.90 (m, 2H), 2.69 (dt, J=12.7, 6.4 Hz, 1H), 2.51 (dt, J=12.7, 6.4 Hz, 1H), 2.24 (s, 6H).

## Example 35

4-Bromo-1-(3-dimethylaminopropyl)-3-hydroxy-3-(2-naphthyl)oxindole

5 [0123] This compound was prepared by the same procedure as described in example 1, using the compound of reference example 12 in place of the compound of reference example 8.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 8.00 (d, J=2.0 Hz, 1H), 7.75-7.85 (m, 3H), 7.43-7.49 (m, 2H), 7.18-7.29 (m, 3H), 6.99 (dd, J=1.3, 7.3 Hz, 1H), 3.76 (t, J=6.9 Hz, 2H), 2.25-2.49 (m, 2H), 2.19 (s, 6H), 1.82-1.93 (m, 2H).

## 10 Example 36

4-Bromo-1-(3-dimethylaminopropyl)-3-hydroxy-3-(3,4-difluorophenyl)oxindole

15 [0124] This compound was prepared by the same procedure as described in example 1, using the compound of reference example 12 in place of the compound of reference example 8 and using 1-bromo-3,4-difluorobenzene in place of 2-bromonaphthalene.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.19-7.30 (m, 3H), 6.95-7.15 (m, 3H), 3.66-3.78 (m, 2H), 2.22-2.44 (m, 2H), 2.14 (s, 6H), 1.79-1.87 (m, 2H).

## 20 Example 37

4-Bromo-1-(2-diethylaminoethyl)-3-hydroxy-3-(3-fluorophenyl)oxindole

25 [0125] This compound was prepared by the same procedure as described in example 1, using 1-(2-diethylaminoethyl)-4-bromoisoatin (reference example 10) in place of the compound of reference example 8 and using 1-bromo-3-fluorobenzene in place of 2-bromonaphthalene.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.14-7.33 (m, 5H), 7.00 (dddd, J=1.5, 1.5, 8.4, 8.4 Hz, 1H), 6.93 (dd, J=1.3, 7.3 Hz, 1H), 3.87 (dt, J=13.7, 6.8 Hz, 1H), 3.71 (dt, J=13.7, 6.8 Hz, 1H), 2.70 (t, J=6.8 Hz, 2H), 2.55 (q, J=7.2 Hz, 4H), 0.95 (t, J=7.2 Hz, 6H).

## 30 Example 38

4-Bromo-1-(2-diethylaminoethyl)-3-hydroxy-3-(4-fluorophenyl)oxindole

35 [0126] This compound was prepared by the same procedure as described in example 1, using 1-(2-diethylaminoethyl)-4-bromoisoatin (reference example 10) in place of the compound of reference example 8 and using 1-bromo-4-fluorobenzene in place of 2-bromonaphthalene.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.34-7.42 (m, 2H), 7.18-7.26 (m, 2H), 6.90-7.07 (m, 3H), 3.83 (m, 2H), 2.57-2.73 (m, 6H), 0.88-1.09 (m, 6H).

## 40 Example 39

4-Bromo-1-(2-diethylaminoethyl)-3-hydroxy-3-(4-methoxyphenyl)oxindole

45 [0127] This compound was prepared by the same procedure as described in example 1, using 1-(2-diethylaminoethyl)-4-bromoisoatin (reference example 10) in place of the compound of reference example 8 and using 1-bromo-4-methoxybenzene in place of 2-bromonaphthalene.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.18-7.33 (m, 4H), 6.84-6.93 (m, 3H), 3.79 (s, 3H), 3.66-3.85 (m, 2H), 2.68 (t, J=7.1 Hz, 2H), 2.56 (q, J=7.2 Hz, 4H), 0.97 (t, J=7.2 Hz, 6H).

## 50 Example 40

4-Bromo-1-(2-diethylaminoethyl)-3-hydroxy-3-(3,4-difluorophenyl)oxindole

55 [0128] This compound was prepared by the same procedure as described in example 1, using 1-(2-diethylaminoethyl)-4-bromoisoatin (reference example 10) in place of the compound of reference example 8 and using 1-bromo-3,4-difluorobenzene in place of 2-bromonaphthalene.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) δ 7.18-7.33 (m, 4H), 6.84-6.93 (m, 3H), 3.79 (s, 3H), 3.66-3.85 (m, 2H), 2.68 (t, J=7.1 Hz,

2H), 2.56 (q, J=7.2 Hz, 4H), 0.97 (t, J=7.2 Hz, 6H).

Example 41

5 4,6-Dichloro-1-(2-diethylaminoethyl)-3-hydroxy-3-(1-naphthyl)oxindole

[0129] This compound was prepared by the same procedure as described in example 1, using 1-bromonaphthalene in place of 2-bromonaphthalene.

10 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 270 MHz: hydrochloride) δ 10.53 (brs, 1H), 8.2 (br, 1H), 7.93-7.96 (m, 2H), 7.18-7.68 (m, 6H), 4.25 (m, 2H), 3.26-3.52 (m, 6H), 1.20-1.24 (m, 6H).

Example 42

15 4,6-Dimethyl-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole

[0130] This compound was prepared by the same procedure as described in example 1, using the compound of reference example 17 in place of the compound of reference example 8.

10 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 270 MHz: hydrochloride) δ 10.61 (brs, 1H), 7.78-7.92 (m, 4H), 7.48-7.51 (m, 2H), 7.18 (d, J=8.6 Hz, 1H), 7.06 (s, 1H), 6.70 (m, 2H), 4.10 (m, 2H), 3.20-3.31 (m, 6H), 2.36 (s, 3H), 1.90 (s, 3H), 1.21 (t, J=6.6 Hz, 6H).

20 Example 43

25 4-Trifluoromethyl-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole

[0131] This compound was prepared by the same procedure as described in example 1, using the compound of reference example 19 in place of the compound of reference example 8.

10 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 270 MHz: hydrochloride) δ 10.38 (brs, 1H), 7.72-7.91 (m, 6H), 7.42-7.56 (m, 3H), 7.16 (d, J=6.9 Hz, 1H), 6.99 (s, 1H), 4.18 (t, J=6.6 Hz, 2H), 3.16-3.37 (m, 6H), 1.21 (t, J=6.9 Hz, 6H).

30 Example 44

35 4-Chloro-6-(4-hydroxy-1-butynyl)-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole

[0132] 4-Chloro-6-(4-t-butyldimethylsilyloxy-1-butynyl)-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole was prepared as a mixture of regioisomers by the same procedure as described in example 1, using the mixture of reference example 22 in place of the compound of reference example 8. To a solution of this mixture (36 mg) in anhydrous acetonitrile (0.8 mL) was added aqueous 46% HF (0.1 mL) and the mixture stirred at room temperature for 3 hours. Saturated aqueous NaHCO<sub>3</sub> was then added and the mixture extracted with ethyl acetate. The organic phase was dried over anhydrous MgSO<sub>4</sub>, and concentrated.

40 Purification was carried out by silica gel chromatography (methanol:chloroform, 1:40 to 1:30 gradient) to give the title compound (4.9 mg).

10 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 270 MHz: hydrochloride) δ 7.97 (s, 1H), 7.75-7.83 (m, 3H), 7.44-7.50 (m, 2H), 7.36 (dd, J=1.8, 8.7 Hz, 1H), 7.10 (d, J=1.2 Hz, 1H), 6.95 (d, J=1.2 Hz, 1H), 3.72-3.91 (m, 4H), 2.70-2.76 (m, 4H), 2.60 (q, J=7.1 Hz, 4H), 0.98 (t, J=7.1 Hz, 6H).

45 Example 45

4-Chloro-6-(3-hydroxy-1-propynyl)-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole

50 [0133] 4-Chloro-6-(3-t-butyldimethylsilyloxy-1-propynyl)-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole was prepared as a mixture of regio-isomers by the same procedure as described in example 1, using the mixture of reference example 21 in place of the compound of reference example 8. The silyl group was removed by the same procedure as example 44, and separated by silica gel chromatography to give the title compound.

10 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 270 MHz: hydrochloride) δ 7.99 (d, J=1.7 Hz, 1H), 7.75-7.84 (m, 3H), 7.44-7.50 (m, 2H), 7.36 (dd, J=1.8, 8.7 Hz, 1H), 7.11 (d, J=1.2 Hz, 1H), 6.96 (d, J=1.2 Hz, 1H), 4.50 (s, 2H), 3.83 (t, J=6.3 Hz, 2H), 2.71-2.85 (m, 2H), 2.65 (q, J=7.2 Hz, 4H), 0.99 (t, J=7.2 Hz, 6H).

## Example 46

4,6-Dichloro-1-(2-diethylaminoethyl)-3-(diethylcarbamoylmethoxy)-3-(2-fluorophenyl)oxindole

**[0134]** To a solution of the compound of example 6 (40.0 mg, 0.0973 mmol) in anhydrous THF (1.0 mL) was added potassium t-butoxide (18.7 mg, 0.167 mmol) and N,N-diethylchloroacetamide (27 $\mu$ L, 0.197 mmol). The mixture was stirred at room temperature for 6 hours. H<sub>2</sub>O and saturated aqueous NaHCO<sub>3</sub> was then added and the mixture extracted with ethyl acetate. The organic phase was dried over anhydrous MgSO<sub>4</sub> and concentrated. Purification by silica gel chromatography (methanol:chloroform, 1:40) to give the free compound (41.6 mg). Under nitrogen stream, to the free compound was added 4N HCl/dioxane solution (0.3 ml). After the solvent was evaporated, ether was added and the white solid formed was filtered to give the title compound (20.6 mg, 38%).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 270 MHz: hydrochloride)  $\delta$  10.41 (brs, 1H), 7.97 (ddd, J=1.8, 7.9, 7.9 Hz, 1H), 7.64 (d, J=1.5 Hz, 1H), 7.33-7.48 (m, 2H), 7.26 (d, J=1.5 Hz, 1H), 7.08-7.18 (m, 1H), 4.17-4.26 (m, 2H), 4.12 (s, 2H), 3.20-3.40 (m, 10H), 1.26 (t, J=7.1 Hz, 6H), 1.07 (t, J=6.8 Hz, 3H), 0.99 (t, J=7.1 Hz, 3H).

## Example 47

4,6-Dichloro-3-(3-diethylaminopropoxy)-3-(2-naphthyl)oxindole

**[0135]** To a solution of the compound of reference example 23 (41.0 mg) in diethylene glycol dimethyl ether (1 mL) was added 60% NaH (14.3 mg) and the mixture stirred at room temperature for one hour. To the mixture was added diethylaminopropyl chloride hydrochloride (22.2 mg) and the mixture stirred at 90°C for 7 hours. After cooling, 1N HCl (1 mL) was added into it. The organic phase was dried over anhydrous MgSO<sub>4</sub> and concentrated. Purification was carried out by HPLC to give the title compound (28.8 mg).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz: trifluoroacetate)  $\delta$  1.21 (t, J=7.1 Hz, 6H), 1.99 (m, 2H), 3.10-3.45 (m, 8H), 7.06 (d, J=1.8 Hz, 1H), 7.28 (d, J=1.7 Hz, 1H), 7.31 (dd, J=8.6, 1.8Hz, 1H), 7.52 (m, 2H), 7.82-7.94 (m, 4H), 9.15 (brs, 1H), 11.24 (s, 1H).

## Example 48

4-Trifluoromethyl-6-iodo-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole

**[0136]** This compound was prepared by the same procedure as described in example 1, using the compound of reference example 24 in place of the compound of reference example 8.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz)  $\delta$  7.87 (d, J=1.8 Hz, 1H), 7.73-7.82 (m, 3H), 7.68 (s, 1H), 7.61 (s, 1H), 7.43-7.48 (m, 2H), 7.20 (dd, J=1.8, 8.7 Hz, 1H), 3.68-3.91 (m, 2H), 2.70 (t, J=5.8 Hz, 2H), 2.56 (q, J=7.0 Hz, 4H), 0.96 (t, J=7.0 Hz, 6H).

## Example 49

4-Trifluoromethyl-6-(3-hydroxy-1-propynyl)-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole

**[0137]** 4-Trifluoromethyl-6-(3-t-butyldimethylsilyloxy-1-propynyl)-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl) oxindole was prepared by the same procedure as described in reference example 21, using the compound of example 48. The silyl group was removed by the same procedure as example 44, and separated by silica gel chromatography to give the title compound.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 270 MHz: hydrochloride)  $\delta$  10.21 (brs, 1H), 7.77-7.92 (m, 5H), 7.48-7.52 (m, 2H), 7.42 (s, 1H), 7.18-7.25 (m, 1H), 7.04 (s, 1H), 5.46 (brs, 1H), 4.39 (s, 2H), 4.17 (m, 2H), 3.20-3.37 (m, 6H), 1.20 (t, J = 6.9 Hz, 6H).

## Example 50

4-Chloro-6-(4-hydroxybutyl)-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole

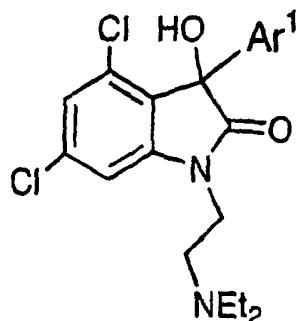
**[0138]** Under nitrogen stream, to a solution of 4-chloro-6-(4-hydroxy-1-butynyl)-1-(2-diethylaminoethyl)-3-hydroxy-3-(2-naphthyl)oxindole (8.6 mg, 0.0180 mmol) in methanol (1.5 mL) was added 10% palladium/carbon (4.0 mg). The mixture was stirred under hydrogen atmosphere at room temperature for one hour. After filtration with Celite, the solvent was removed to give the title compound (8.7 mg).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>: hydrochloride)  $\delta$  10.50 (brs, 1H), 7.80-7.93 (m, 4H), 7.48-7.52 (m, 2H), 7.18-7.28 (m, 2H), 6.94 (s, 1H), 6.86 (s, 1H), 4.13-4.18 (m, 2H), 3.45 (t, J=6.4 Hz, 2H), 3.21-3.40 (m, 6H), 2.67 (t, J=7.8 Hz, 2H), 1.64-1.72

(m, 2H), 1.46-1.54 (m, 2H), 1.22 (t, J=7.1 Hz, 6H).

[0139] The structures of the compounds obtained in Examples 1 to 50 are shown below.

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- Example 1 : Ar<sup>1</sup>= 2-naphthyl  
 Example 2 : Ar<sup>1</sup>= 3-fluorophenyl  
 Example 3 : Ar<sup>1</sup>= 4-fluorophenyl  
 Example 4 : Ar<sup>1</sup>= 4-methoxyphenyl  
 Example 5 : Ar<sup>1</sup>= 3,4-difluorophenyl  
 Example 6 : Ar<sup>1</sup>= 2-fluorophenyl  
 Example 7 : Ar<sup>1</sup>= 2-chlorophenyl  
 Example 8 : Ar<sup>1</sup>= 2-trifluoromethylphenyl  
 Example 9 : Ar<sup>1</sup>= 3,4-dichlorophenyl  
 Example 10: Ar<sup>1</sup>= 2-dimethylaminosulfonylphenyl

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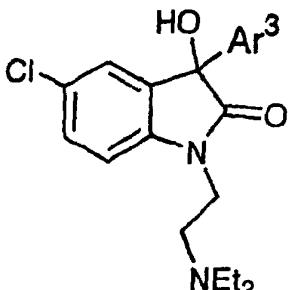
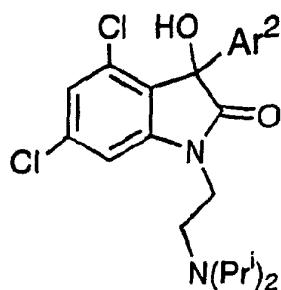
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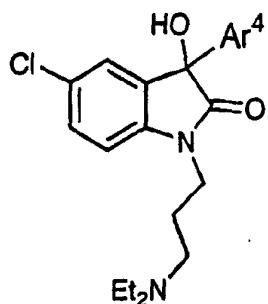
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- Example 11: Ar<sup>2</sup>= 2-naphthyl      Example 16: Ar<sup>3</sup>= 2-naphthyl  
 Example 12: Ar<sup>2</sup>= 2-chlorophenyl      Example 17: Ar<sup>3</sup>= 2-methoxyphenyl  
 Example 13: Ar<sup>2</sup>= 2-trifluoromethylphenyl  
 Example 14: Ar<sup>2</sup>= 2-dimethylaminosulfonylphenyl  
 Example 15: Ar<sup>2</sup>= 3,4-dichlorophenyl

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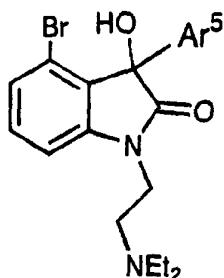
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Example 18:  $\text{Ar}^4 = 2\text{-fluorophenyl}$   
 Example 19:  $\text{Ar}^4 = 2\text{-methoxyphenyl}$   
 Example 20:  $\text{Ar}^4 = 2\text{-naphthyl}$

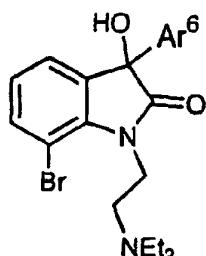
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Example 21:  $\text{Ar}^5 = 2\text{-fluorophenyl}$   
 Example 22:  $\text{Ar}^5 = 2\text{-methoxyphenyl}$   
 Example 23:  $\text{Ar}^5 = 2\text{-naphthyl}$   
 Example 24:  $\text{Ar}^5 = 4\text{-biphenyl}$   
 Example 37:  $\text{Ar}^5 = 3\text{-fluorophenyl}$   
 Example 38:  $\text{Ar}^5 = 4\text{-fluorophenyl}$   
 Example 39:  $\text{Ar}^5 = 4\text{-methoxyphenyl}$   
 Example 40:  $\text{Ar}^5 = 3, 4\text{-difluorophenyl}$

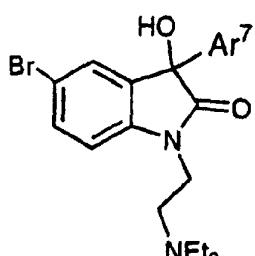
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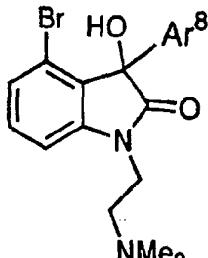
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Example 26:  $\text{Ar}^6 = 2\text{-fluorophenyl}$   
 Example 27:  $\text{Ar}^6 = 2\text{-naphthyl}$   
 Example 28:  $\text{Ar}^6 = 4\text{-biphenyl}$   
 Example 29:  $\text{Ar}^7 = 2\text{-fluorophenyl}$   
 Example 30:  $\text{Ar}^7 = 2\text{-naphthyl}$

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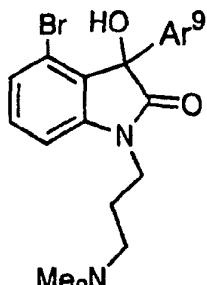
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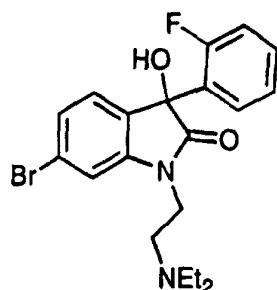
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Example 33:  $\text{Ar}^8 = 2\text{-naphthyl}$   
 Example 34:  $\text{Ar}^8 = 3, 4\text{-difluorophenyl}$   
 Example 35:  $\text{Ar}^9 = 2\text{-naphthyl}$   
 Example 36:  $\text{Ar}^9 = 3, 4\text{-difluorophenyl}$

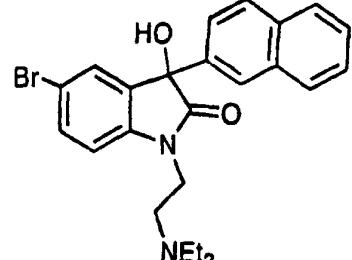
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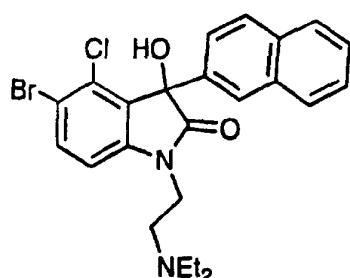
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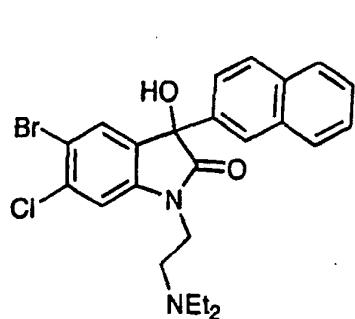


Example 30

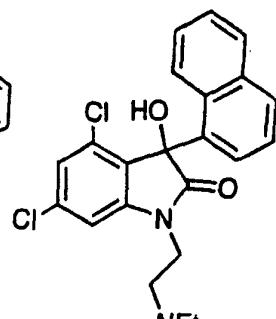


Example 31

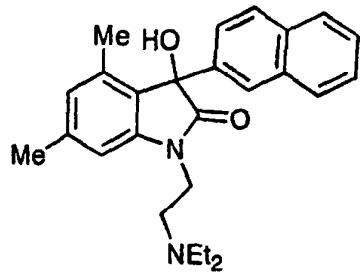
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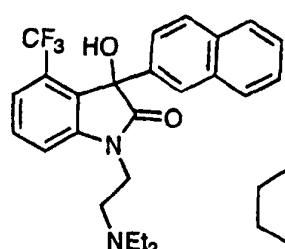


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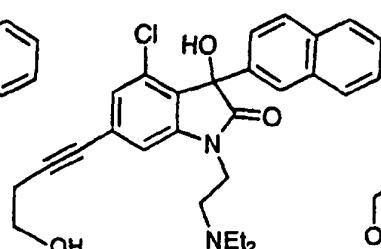


Example 42

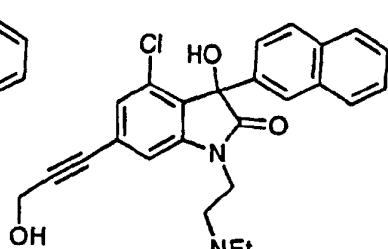
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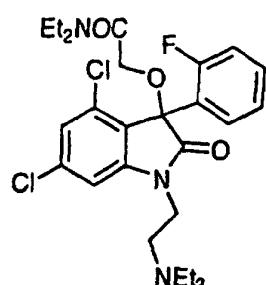


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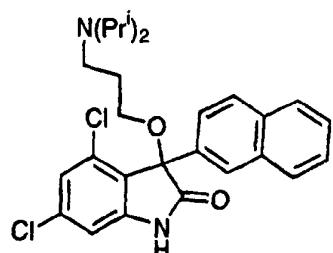


Example 45

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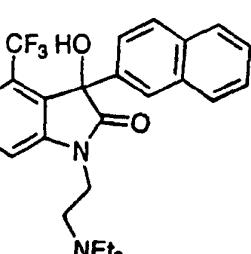


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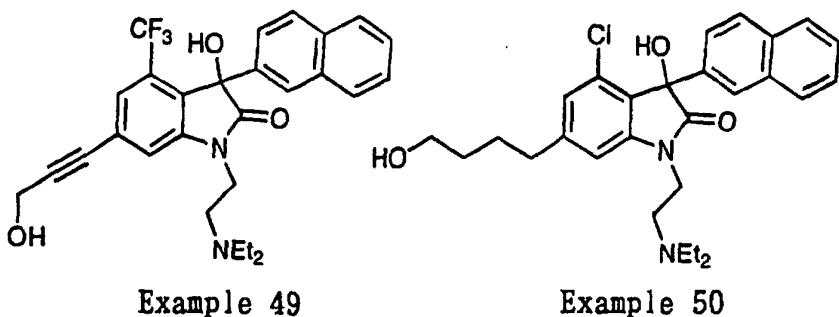
Example 46

Example 47



Example 48

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## Example 51

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-morpholinocarbonyl-1-butynyl)-3-hydroxy-3-(2-naphthyl)oxindole

## (1) Morpholinocarbonyl-1-butyne

20 [0140] A mixture of 4-pentynoic acid (210 mg, 2.14 mmol), morpholine hydrochloride (265 mg, 2.14 mmol), 1-hydroxybenzotriazol (338 mg, 2.50 mmol), WSC HCl (484 mg, 2.52 mmol), and triethylamine (0.37 ml, 2.65 mmol) in DMF (7 mL) was stirred for 1 h at room temperature. Water was added. The mixture was extracted with ethyl acetate-toluene, and the extracts were washed with water, dried over  $\text{MgSO}_4$ , and concentrated. The residue was purified by silica gel column chromatography with 1 : 1 to 1 : 5 hexane/ethyl acetate to give the title compound (325 mg, 91%).

25  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  3.64-3.70 (m, 6H), 3.48-3.50 (m, 2H), 2.56 (s, 2H), 2.56 (s, 2H), 1.97 (s, 1H).

## (2) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-morpholinocarbonyl-1-butynyl)-3-hydroxy-3-(2-naphthyl)oxindole

30 [0141] The title compound (26.1 mg) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-naphthyl)oxindole of Example 48 (35 mg, 0.0616 mmol) and 4-morpholinocarbonyl-1-butyne by the procedure similar to that described in Reference Example 21. The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.

35  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ : hydrochloride)  $\delta$  10.31 (brs, 1H), 7.79-7.91 (m, 4H), 7.73 (s, 1H), 7.48-7.51 (m, 2H), 7.36 (s, 1H), 7.17-7.25 (m, 1H), 7.03 (s, 1H), 4.17 (m, 2H), 3.08-3.57 (m, 14H), 2.71 (s, 4H), 1.20 (t, 6H,  $J=7.1$  Hz).

## Example 52

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(3-dimethylamino-1-propynyl)-3-hydroxy-3-(2-naphthyl)oxindole

40 [0142] The title compound (18.0 mg) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-naphthyl)oxindole of Example 48 (40.1 mg, 0.0706 mmol) and 3-dimethylamino-1-propyne by the procedure similar to that described in Reference Example 21. The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.

45  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ , 270 MHz: hydrochloride)  $\delta$  11.05 (brs, 1H), 10.76 (brs, 1H), 8.02 (s, 1H), 7.79-7.92 (m, 4H), 7.61 (s, 1H), 7.48-7.52 (m, 2H), 7.20 (d, 1H,  $J=10.2$  Hz), 7.10 (s, 1H), 4.40 (s, 2H), 4.21-4.23 (m, 2H), 3.18-3.38 (m, 6H), 2.91 (s, 6H), 1.21 (t, 6H,  $J=7.3$  Hz).

## Example 53

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-diethylcarbamoyl-1-butynyl)-3-hydroxy-3-(2-naphthyl)oxindole

## (1) 4-Diethylcarbamoyl-1-butyne

50 [0143] The title compound (370 mg, 95%) was prepared from 4-pentynoic acid (250 mg, 2.55 mmol) and diethylamine hydrochloride (310 mg, 2.83 mmol) by the procedure similar to that described in Example 51(1).

55  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  3.39 (q, 2H,  $J=6.8$  Hz), 3.31 (q, 2H,  $J=6.8$  Hz), 2.56 (s, 2H), 2.55 (s, 2H), 1.96 (s, 1H), 1.19 (t, 3H,  $J=6.8$  Hz), 1.12 (t, 3H,  $J=6.8$  Hz).

## (2) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-diethylcarbamoyl-1-butynyl)-3-hydroxy-3-(2-naphthyl)oxindole

**[0144]** The title compound (28.9 mg) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-naphthyl)oxindole of Example 48 (40.5 mg, 0.0713 mmol) and 4-diethylcarbamoyl-1-butyne by the procedure similar to that described in Reference Example 21. The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.

<sup>5</sup> <sup>10</sup> <sup>15</sup> <sup>20</sup> <sup>25</sup> <sup>30</sup> <sup>35</sup> <sup>40</sup> <sup>45</sup> <sup>50</sup> <sup>55</sup> <sup>60</sup> <sup>65</sup> <sup>70</sup> <sup>75</sup> <sup>80</sup> <sup>85</sup> <sup>90</sup> <sup>95</sup> <sup>100</sup> <sup>105</sup> <sup>110</sup> <sup>115</sup> <sup>120</sup> <sup>125</sup> <sup>130</sup> <sup>135</sup> <sup>140</sup> <sup>145</sup> <sup>150</sup> <sup>155</sup> <sup>160</sup> <sup>165</sup> <sup>170</sup> <sup>175</sup> <sup>180</sup> <sup>185</sup> <sup>190</sup> <sup>195</sup> <sup>200</sup> <sup>205</sup> <sup>210</sup> <sup>215</sup> <sup>220</sup> <sup>225</sup> <sup>230</sup> <sup>235</sup> <sup>240</sup> <sup>245</sup> <sup>250</sup> <sup>255</sup> <sup>260</sup> <sup>265</sup> <sup>270</sup> <sup>275</sup> <sup>280</sup> <sup>285</sup> <sup>290</sup> <sup>295</sup> <sup>300</sup> <sup>305</sup> <sup>310</sup> <sup>315</sup> <sup>320</sup> <sup>325</sup> <sup>330</sup> <sup>335</sup> <sup>340</sup> <sup>345</sup> <sup>350</sup> <sup>355</sup> <sup>360</sup> <sup>365</sup> <sup>370</sup> <sup>375</sup> <sup>380</sup> <sup>385</sup> <sup>390</sup> <sup>395</sup> <sup>400</sup> <sup>405</sup> <sup>410</sup> <sup>415</sup> <sup>420</sup> <sup>425</sup> <sup>430</sup> <sup>435</sup> <sup>440</sup> <sup>445</sup> <sup>450</sup> <sup>455</sup> <sup>460</sup> <sup>465</sup> <sup>470</sup> <sup>475</sup> <sup>480</sup> <sup>485</sup> <sup>490</sup> <sup>495</sup> <sup>500</sup> <sup>505</sup> <sup>510</sup> <sup>515</sup> <sup>520</sup> <sup>525</sup> <sup>530</sup> <sup>535</sup> <sup>540</sup> <sup>545</sup> <sup>550</sup> <sup>555</sup> <sup>560</sup> <sup>565</sup> <sup>570</sup> <sup>575</sup> <sup>580</sup> <sup>585</sup> <sup>590</sup> <sup>595</sup> <sup>600</sup> <sup>605</sup> <sup>610</sup> <sup>615</sup> <sup>620</sup> <sup>625</sup> <sup>630</sup> <sup>635</sup> <sup>640</sup> <sup>645</sup> <sup>650</sup> <sup>655</sup> <sup>660</sup> <sup>665</sup> <sup>670</sup> <sup>675</sup> <sup>680</sup> <sup>685</sup> <sup>690</sup> <sup>695</sup> <sup>700</sup> <sup>705</sup> <sup>710</sup> <sup>715</sup> <sup>720</sup> <sup>725</sup> <sup>730</sup> <sup>735</sup> <sup>740</sup> <sup>745</sup> <sup>750</sup> <sup>755</sup> <sup>760</sup> <sup>765</sup> <sup>770</sup> <sup>775</sup> <sup>780</sup> <sup>785</sup> <sup>790</sup> <sup>795</sup> <sup>800</sup> <sup>805</sup> <sup>810</sup> <sup>815</sup> <sup>820</sup> <sup>825</sup> <sup>830</sup> <sup>835</sup> <sup>840</sup> <sup>845</sup> <sup>850</sup> <sup>855</sup> <sup>860</sup> <sup>865</sup> <sup>870</sup> <sup>875</sup> <sup>880</sup> <sup>885</sup> <sup>890</sup> <sup>895</sup> <sup>900</sup> <sup>905</sup> <sup>910</sup> <sup>915</sup> <sup>920</sup> <sup>925</sup> <sup>930</sup> <sup>935</sup> <sup>940</sup> <sup>945</sup> <sup>950</sup> <sup>955</sup> <sup>960</sup> <sup>965</sup> <sup>970</sup> <sup>975</sup> <sup>980</sup> <sup>985</sup> <sup>990</sup> <sup>995</sup> <sup>1000</sup> <sup>1005</sup> <sup>1010</sup> <sup>1015</sup> <sup>1020</sup> <sup>1025</sup> <sup>1030</sup> <sup>1035</sup> <sup>1040</sup> <sup>1045</sup> <sup>1050</sup> <sup>1055</sup> <sup>1060</sup> <sup>1065</sup> <sup>1070</sup> <sup>1075</sup> <sup>1080</sup> <sup>1085</sup> <sup>1090</sup> <sup>1095</sup> <sup>1100</sup> <sup>1105</sup> <sup>1110</sup> <sup>1115</sup> <sup>1120</sup> <sup>1125</sup> <sup>1130</sup> <sup>1135</sup> <sup>1140</sup> <sup>1145</sup> <sup>1150</sup> <sup>1155</sup> <sup>1160</sup> <sup>1165</sup> <sup>1170</sup> <sup>1175</sup> <sup>1180</sup> <sup>1185</sup> <sup>1190</sup> <sup>1195</sup> <sup>1200</sup> <sup>1205</sup> <sup>1210</sup> <sup>1215</sup> <sup>1220</sup> <sup>1225</sup> <sup>1230</sup> <sup>1235</sup> <sup>1240</sup> <sup>1245</sup> <sup>1250</sup> <sup>1255</sup> <sup>1260</sup> <sup>1265</sup> <sup>1270</sup> <sup>1275</sup> <sup>1280</sup> <sup>1285</sup> <sup>1290</sup> <sup>1295</sup> <sup>1300</sup> <sup>1305</sup> <sup>1310</sup> <sup>1315</sup> <sup>1320</sup> <sup>1325</sup> <sup>1330</sup> <sup>1335</sup> <sup>1340</sup> <sup>1345</sup> <sup>1350</sup> <sup>1355</sup> <sup>1360</sup> <sup>1365</sup> <sup>1370</sup> <sup>1375</sup> <sup>1380</sup> <sup>1385</sup> <sup>1390</sup> <sup>1395</sup> <sup>1400</sup> <sup>1405</sup> <sup>1410</sup> <sup>1415</sup> <sup>1420</sup> <sup>1425</sup> <sup>1430</sup> <sup>1435</sup> <sup>1440</sup> <sup>1445</sup> <sup>1450</sup> <sup>1455</sup> <sup>1460</sup> <sup>1465</sup> <sup>1470</sup> <sup>1475</sup> <sup>1480</sup> <sup>1485</sup> <sup>1490</sup> <sup>1495</sup> <sup>1500</sup> <sup>1505</sup> <sup>1510</sup> <sup>1515</sup> <sup>1520</sup> <sup>1525</sup> <sup>1530</sup> <sup>1535</sup> <sup>1540</sup> <sup>1545</sup> <sup>1550</sup> <sup>1555</sup> <sup>1560</sup> <sup>1565</sup> <sup>1570</sup> <sup>1575</sup> <sup>1580</sup> <sup>1585</sup> <sup>1590</sup> <sup>1595</sup> <sup>1600</sup> <sup>1605</sup> <sup>1610</sup> <sup>1615</sup> <sup>1620</sup> <sup>1625</sup> <sup>1630</sup> <sup>1635</sup> <sup>1640</sup> <sup>1645</sup> <sup>1650</sup> <sup>1655</sup> <sup>1660</sup> <sup>1665</sup> <sup>1670</sup> <sup>1675</sup> <sup>1680</sup> <sup>1685</sup> <sup>1690</sup> <sup>1695</sup> <sup>1700</sup> <sup>1705</sup> <sup>1710</sup> <sup>1715</sup> <sup>1720</sup> <sup>1725</sup> <sup>1730</sup> <sup>1735</sup> <sup>1740</sup> <sup>1745</sup> <sup>1750</sup> <sup>1755</sup> <sup>1760</sup> <sup>1765</sup> <sup>1770</sup> <sup>1775</sup> <sup>1780</sup> <sup>1785</sup> <sup>1790</sup> <sup>1795</sup> <sup>1800</sup> <sup>1805</sup> <sup>1810</sup> <sup>1815</sup> <sup>1820</sup> <sup>1825</sup> <sup>1830</sup> <sup>1835</sup> <sup>1840</sup> <sup>1845</sup> <sup>1850</sup> <sup>1855</sup> <sup>1860</sup> <sup>1865</sup> <sup>1870</sup> <sup>1875</sup> <sup>1880</sup> <sup>1885</sup> <sup>1890</sup> <sup>1895</sup> <sup>1900</sup> <sup>1905</sup> <sup>1910</sup> <sup>1915</sup> <sup>1920</sup> <sup>1925</sup> <sup>1930</sup> <sup>1935</sup> <sup>1940</sup> <sup>1945</sup> <sup>1950</sup> <sup>1955</sup> <sup>1960</sup> <sup>1965</sup> <sup>1970</sup> <sup>1975</sup> <sup>1980</sup> <sup>1985</sup> <sup>1990</sup> <sup>1995</sup> <sup>2000</sup> <sup>2005</sup> <sup>2010</sup> <sup>2015</sup> <sup>2020</sup> <sup>2025</sup> <sup>2030</sup> <sup>2035</sup> <sup>2040</sup> <sup>2045</sup> <sup>2050</sup> <sup>2055</sup> <sup>2060</sup> <sup>2065</sup> <sup>2070</sup> <sup>2075</sup> <sup>2080</sup> <sup>2085</sup> <sup>2090</sup> <sup>2095</sup> <sup>2100</sup> <sup>2105</sup> <sup>2110</sup> <sup>2115</sup> <sup>2120</sup> <sup>2125</sup> <sup>2130</sup> <sup>2135</sup> <sup>2140</sup> <sup>2145</sup> <sup>2150</sup> <sup>2155</sup> <sup>2160</sup> <sup>2165</sup> <sup>2170</sup> <sup>2175</sup> <sup>2180</sup> <sup>2185</sup> <sup>2190</sup> <sup>2195</sup> <sup>2200</sup> <sup>2205</sup> <sup>2210</sup> <sup>2215</sup> <sup>2220</sup> <sup>2225</sup> <sup>2230</sup> <sup>2235</sup> <sup>2240</sup> <sup>2245</sup> <sup>2250</sup> <sup>2255</sup> <sup>2260</sup> <sup>2265</sup> <sup>2270</sup> <sup>2275</sup> <sup>2280</sup> <sup>2285</sup> <sup>2290</sup> <sup>2295</sup> <sup>2300</sup> <sup>2305</sup> <sup>2310</sup> <sup>2315</sup> <sup>2320</sup> <sup>2325</sup> <sup>2330</sup> <sup>2335</sup> <sup>2340</sup> <sup>2345</sup> <sup>2350</sup> <sup>2355</sup> <sup>2360</sup> <sup>2365</sup> <sup>2370</sup> <sup>2375</sup> <sup>2380</sup> <sup>2385</sup> <sup>2390</sup> <sup>2395</sup> <sup>2400</sup> <sup>2405</sup> <sup>2410</sup> <sup>2415</sup> <sup>2420</sup> <sup>2425</sup> <sup>2430</sup> <sup>2435</sup> <sup>2440</sup> <sup>2445</sup> <sup>2450</sup> <sup>2455</sup> <sup>2460</sup> <sup>2465</sup> <sup>2470</sup> <sup>2475</sup> <sup>2480</sup> <sup>2485</sup> <sup>2490</sup> <sup>2495</sup> <sup>2500</sup> <sup>2505</sup> <sup>2510</sup> <sup>2515</sup> <sup>2520</sup> <sup>2525</sup> <sup>2530</sup> <sup>2535</sup> <sup>2540</sup> <sup>2545</sup> <sup>2550</sup> <sup>2555</sup> <sup>2560</sup> <sup>2565</sup> <sup>2570</sup> <sup>2575</sup> <sup>2580</sup> <sup>2585</sup> <sup>2590</sup> <sup>2595</sup> <sup>2600</sup> <sup>2605</sup> <sup>2610</sup> <sup>2615</sup> <sup>2620</sup> <sup>2625</sup> <sup>2630</sup> <sup>2635</sup> <sup>2640</sup> <sup>2645</sup> <sup>2650</sup> <sup>2655</sup> <sup>2660</sup> <sup>2665</sup> <sup>2670</sup> <sup>2675</sup> <sup>2680</sup> <sup>2685</sup> <sup>2690</sup> <sup>2695</sup> <sup>2700</sup> <sup>2705</sup> <sup>2710</sup> <sup>2715</sup> <sup>2720</sup> <sup>2725</sup> <sup>2730</sup> <sup>2735</sup> <sup>2740</sup> <sup>2745</sup> <sup>2750</sup> <sup>2755</sup> <sup>2760</sup> <sup>2765</sup> <sup>2770</sup> <sup>2775</sup> <sup>2780</sup> <sup>2785</sup> <sup>2790</sup> <sup>2795</sup> <sup>2800</sup> <sup>2805</sup> <sup>2810</sup> <sup>2815</sup> <sup>2820</sup> <sup>2825</sup> <sup>2830</sup> <sup>2835</sup> <sup>2840</sup> <sup>2845</sup> <sup>2850</sup> <sup>2855</sup> <sup>2860</sup> <sup>2865</sup> <sup>2870</sup> <sup>2875</sup> <sup>2880</sup> <sup>2885</sup> <sup>2890</sup> <sup>2895</sup> <sup>2900</sup> <sup>2905</sup> <sup>2910</sup> <sup>2915</sup> <sup>2920</sup> <sup>2925</sup> <sup>2930</sup> <sup>2935</sup> <sup>2940</sup> <sup>2945</sup> <sup>2950</sup> <sup>2955</sup> <sup>2960</sup> <sup>2965</sup> <sup>2970</sup> <sup>2975</sup> <sup>2980</sup> <sup>2985</sup> <sup>2990</sup> <sup>2995</sup> <sup>3000</sup> <sup>3005</sup> <sup>3010</sup> <sup>3015</sup> <sup>3020</sup> <sup>3025</sup> <sup>3030</sup> <sup>3035</sup> <sup>3040</sup> <sup>3045</sup> <sup>3050</sup> <sup>3055</sup> <sup>3060</sup> <sup>3065</sup> <sup>3070</sup> <sup>3075</sup> <sup>3080</sup> <sup>3085</sup> <sup>3090</sup> <sup>3095</sup> <sup>3100</sup> <sup>3105</sup> <sup>3110</sup> <sup>3115</sup> <sup>3120</sup> <sup>3125</sup> <sup>3130</sup> <sup>3135</sup> <sup>3140</sup> <sup>3145</sup> <sup>3150</sup> <sup>3155</sup> <sup>3160</sup> <sup>3165</sup> <sup>3170</sup> <sup>3175</sup> <sup>3180</sup> <sup>3185</sup> <sup>3190</sup> <sup>3195</sup> <sup>3200</sup> <sup>3205</sup> <sup>3210</sup> <sup>3215</sup> <sup>3220</sup> <sup>3225</sup> <sup>3230</sup> <sup>3235</sup> <sup>3240</sup> <sup>3245</sup> <sup>3250</sup> <sup>3255</sup> <sup>3260</sup> <sup>3265</sup> <sup>3270</sup> <sup>3275</sup> <sup>3280</sup> <sup>3285</sup> <sup>3290</sup> <sup>3295</sup> <sup>3300</sup> <sup>3305</sup> <sup>3310</sup> <sup>3315</sup> <sup>3320</sup> <sup>3325</sup> <sup>3330</sup> <sup>3335</sup> <sup>3340</sup> <sup>3345</sup> <sup>3350</sup> <sup>3355</sup> <sup>3360</sup> <sup>3365</sup> <sup>3370</sup> <sup>3375</sup> <sup>3380</sup> <sup>3385</sup> <sup>3390</sup> <sup>3395</sup> <sup>3400</sup> <sup>3405</sup> <sup>3410</sup> <sup>3415</sup> <sup>3420</sup> <sup>3425</sup> <sup>3430</sup> <sup>3435</sup> <sup>3440</sup> <sup>3445</sup> <sup>3450</sup> <sup>3455</sup> <sup>3460</sup> <sup>3465</sup> <sup>3470</sup> <sup>3475</sup> <sup>3480</sup> <sup>3485</sup> <sup>3490</sup> <sup>3495</sup> <sup>3500</sup> <sup>3505</sup> <sup>3510</sup> <sup>3515</sup> <sup>3520</sup> <sup>3525</sup> <sup>3530</sup> <sup>3535</sup> <sup>3540</sup> <sup>3545</sup> <sup>3550</sup> <sup>3555</sup> <sup>3560</sup> <sup>3565</sup> <sup>3570</sup> <sup>3575</sup> <sup>3580</sup> <sup>3585</sup> <sup>3590</sup> <sup>3595</sup> <sup>3600</sup> <sup>3605</sup> <sup>3610</sup> <sup>3615</sup> <sup>3620</sup> <sup>3625</sup> <sup>3630</sup> <sup>3635</sup> <sup>3640</sup> <sup>3645</sup> <sup>3650</sup> <sup>3655</sup> <sup>3660</sup> <sup>3665</sup> <sup>3670</sup> <sup>3675</sup> <sup>3680</sup> <sup>3685</sup> <sup>3690</sup> <sup>3695</sup> <sup>3700</sup> <sup>3705</sup> <sup>3710</sup> <sup>3715</sup> <sup>3720</sup> <sup>3725</sup> <sup>3730</sup> <sup>3735</sup> <sup>3740</sup> <sup>3745</sup> <sup>3750</sup> <sup>3755</sup> <sup>3760</sup> <sup>3765</sup> <sup>3770</sup> <sup>3775</sup> <sup>3780</sup> <sup>3785</sup> <sup>3790</sup> <sup>3795</sup> <sup>3800</sup> <sup>3805</sup> <sup>3810</sup> <sup>3815</sup> <sup>3820</sup> <sup>3825</sup> <sup>3830</sup> <sup>3835</sup> <sup>3840</sup> <sup>3845</sup> <sup>3850</sup> <sup>3855</sup> <sup>3860</sup> <sup>3865</sup> <sup>3870</sup> <sup>3875</sup> <sup>3880</sup> <sup>3885</sup> <sup>3890</sup> <sup>3895</sup> <sup>3900</sup> <sup>3905</sup> <sup>3910</sup> <sup>3915</sup> <sup>3920</sup> <sup>3925</sup> <sup>3930</sup> <sup>3935</sup> <sup>3940</sup> <sup>3945</sup> <sup>3950</sup> <sup>3955</sup> <sup>3960</sup> <sup>3965</sup> <sup>3970</sup> <sup>3975</sup> <sup>3980</sup> <sup>3985</sup> <sup>3990</sup> <sup>3995</sup> <sup>4000</sup> <sup>4005</sup> <sup>4010</sup> <sup>4015</sup> <sup>4020</sup> <sup>4025</sup> <sup>4030</sup> <sup>4035</sup> <sup>4040</sup> <sup>4045</sup> <sup>4050</sup> <sup>4055</sup> <sup>4060</sup> <sup>4065</sup> <sup>4070</sup> <sup>4075</sup> <sup>4080</sup> <sup>4085</sup> <sup>4090</sup> <sup>4095</sup> <sup>4100</sup> <sup>4105</sup> <sup>4110</sup> <sup>4115</sup> <sup>4120</sup> <sup>4125</sup> <sup>4130</sup> <sup>4135</sup> <sup>4140</sup> <sup>4145</sup> <sup>4150</sup> <sup>4155</sup> <sup>4160</sup> <sup>4165</sup> <sup>4170</sup> <sup>4175</sup> <sup>4180</sup> <sup>4185</sup> <sup>4190</sup> <sup>4195</sup> <sup>4200</sup> <sup>4205</sup> <sup>4210</sup> <sup>4215</sup> <sup>4220</sup> <sup>4225</sup> <sup>4230</sup> <sup>4235</sup> <sup>4240</sup> <sup>4245</sup> <sup>4250</sup> <sup>4255</sup> <sup>4260</sup> <sup>4265</sup> <sup>4270</sup> <sup>4275</sup> <sup>4280</sup> <sup>4285</sup> <sup>4290</sup> <sup>4295</sup> <sup>4300</sup> <sup>4305</sup> <sup>4310</sup> <sup>4315</sup> <sup>4320</sup> <sup>4325</sup> <sup>4330</sup> <sup>4335</sup> <sup>4340</sup> <sup>4345</sup> <sup>4350</sup> <sup>4355</sup> <sup>4360</sup> <sup>4365</sup> <sup>4370</sup> <sup>4375</sup> <sup>4380</sup> <sup>4385</sup> <sup>4390</sup> <sup>4395</sup> <sup>4400</sup> <sup>4405</sup> <sup>4410</sup> <sup>4415</sup> <sup>4420</sup> <sup>4425</sup> <sup>4430</sup> <sup>4435</sup> <sup>4440</sup> <sup>4445</sup> <sup>4450</sup> <sup>4455</sup> <sup>4460</sup> <sup>4465</sup> <sup>4470</sup> <sup>4475</sup> <sup>4480</sup> <sup>4485</sup> <sup>4490</sup> <sup>4495</sup> <sup>4500</sup> <sup>4505</sup> <sup>4510</sup> <sup>4515</sup> <sup>4520</sup> <sup>4525</sup> <sup>4530</sup> <sup>4535</sup> <sup>4540</sup> <sup>4545</sup> <sup>4550</sup> <sup>4555</sup> <sup>4560</sup> <sup>4565</sup> <sup>4570</sup> <sup>4575</sup> <sup>4580</sup> <sup>4585</sup> <sup>4590</sup> <sup>4595</sup> <sup>4600</sup> <sup>4605</sup> <sup>4610</sup> <sup>4615</sup> <sup>4620</sup> <sup>4625</sup> <sup>4630</sup> <sup>4635</sup> <sup>4640</sup> <sup>4645</sup> <sup>4650</sup> <sup>4655</sup> <sup>4660</sup> <sup>4665</sup> <sup>4670</sup> <sup>4675</sup> <sup>4680</sup> <sup>4685</sup> <sup>4690</sup> <sup>4695</sup> <sup>4700</sup> <sup>4705</sup> <sup>4710</sup> <sup>4715</sup> <sup>4720</sup> <sup>4725</sup> <sup>4730</sup> <sup>4735</sup> <sup>4740</sup> <sup>4745</sup> <sup>4750</sup> <sup>4755</sup> <sup>4760</sup> <sup>4765</sup> <sup>4770</sup> <sup>4775</sup> <sup>4780</sup> <sup>4785</sup> <sup>4790</sup> <sup>4795</sup> <sup>4800</sup> <sup>4805</sup> <sup>4810</sup> <sup>4815</sup> <sup>4820</sup> <sup>4825</sup> <sup>4830</sup> <sup>4835</sup> <sup>4840</sup> <sup>4845</sup> <sup>4850</sup> <sup>4855</sup> <sup>4860</sup> <sup>4865</sup> <sup>4870</sup> <sup>4875</sup> <sup>4880</sup> <sup>4885</sup> <sup>4890</sup> <sup>4895</sup> <sup>4900</sup> <sup>4905</sup> <sup>4910</sup> <sup>4915</sup> <sup>4920</sup> <sup>4925</sup> <sup>4930</sup> <sup>4935</sup> <sup>4940</sup> <sup>4945</sup> <sup>4950</sup> <sup>4955</sup> <sup>4960</sup> <sup>4965</sup> <sup>4970</sup> <sup>4975</sup> <sup>4980</sup> <sup>4985</sup> <sup>4990</sup> <sup>4995</sup> <sup>5000</sup> <sup>5005</sup> <sup>5010</sup> <sup>5015</sup> <sup>5020</sup> <sup>5025</sup> <sup>5030</sup> <sup>5035</sup> <sup>5040</sup> <sup>5045</sup> <sup>5050</sup> <sup>5055</sup> <sup>5060</sup> <sup>5065</sup> <sup>5070</sup> <sup>5075</sup> <sup>5080</sup> <sup>5085</sup> <sup>5090</sup> <sup>5095</sup> <sup>5100</sup> <sup>5105</sup> <sup>5110</sup> <sup>5115</sup> <sup>5120</sup> <sup>5125</sup> <sup>5130</sup> <sup>5135</sup> <sup>5140</sup> <sup>5145</sup> <sup>5150</sup> <sup>5155</sup> <sup>5160</sup> <sup>5165</sup> <sup>5170</sup> <sup>5175</sup> <sup>5180</sup> <sup>5185</sup> <sup>5190</sup> <sup>5195</sup> <sup>5200</sup> <sup>5205</sup> <sup>5210</sup> <sup>5215</sup> <sup>5220</sup> <sup>5225</sup> <sup>5230</sup> <sup>5235</sup> <sup>5240</sup> <sup>5245</sup> <sup>5250</sup> <sup>5255</sup> <sup>5260</sup> <sup>5265</sup> <sup>5270</sup> <sup>5275</sup> <sup>5280</sup> <sup>5285</sup> <sup>5290</sup> <sup>5295</sup> <sup>5300</sup> <sup>5305</sup> <sup>5310</sup> <sup>5315</sup> <sup>5320</sup> <sup>5325</sup> <sup>5330</sup> <sup>5335</sup> <sup>5340</sup> <sup>5345</sup> <sup>5350</sup> <sup>5355</sup> <sup>5360</sup> <sup>5365</sup> <sup>5370</sup> <sup>5375</sup> <sup>5380</sup> <sup>5385</sup> <sup>5390</sup> <sup>5395</sup> <sup>5400</sup> <sup>5405</sup> <sup>5410</sup> <sup>5415</sup> <sup>5420</sup> <sup>5425</sup> <sup>5430</sup> <sup>5435</sup> <sup>5440</sup> <sup>5445</sup> <sup>5450</sup> <sup>5455</sup> <sup>5460</sup> <sup>5465</sup> <sup>5470</sup> <sup>5475</sup> <sup>5480</sup> <sup>5485</sup> <sup>5490</sup> <sup>5495</sup> <sup>5500</sup> <sup>5505</sup> <sup>5510</sup> <sup>5515</sup> <sup>5520</sup> <sup>5525</sup> <sup>5530</sup> <sup>5535</sup> <sup>5540</sup>

## Example 57

3-Diethylaminopropoxy-4-trifluoromethyl-6-(3-hydroxy-1-propynyl)-3-(2-naphthyl)oxindole

## 5 (1) 5-Iodo-2-methyl-3-nitrobenzotrifluoride

[0149] To  $H_2SO_4$  (110 mL, 96%) stirring under a nitrogen atmosphere at 0–5°C was added N-iodosuccinimide (41.13 g, 1.5 eq). The resulting black/dark red mixture was stirred at 0–5°C for 40 minutes. To this was added dropwise commercially available 2-methyl-3-nitrobenzotrifluoride (25.0 g, 121.9 mmol) in  $H_2SO_4$  (75 mL). Once the addition was completed, ca. 1 hour, the mixture was stirred at 5–10°C for 5 hours. The resulting mixture was poured into ice (600 mL) and extracted with EtOAc (400 mL, 3 x 200 mL). The extracts were combined, washed with saturated aqueous  $Na_2SO_3$  (500 mL) and  $H_2O$  (400 mL). The organic phase was then dried (anhydrous  $MgSO_4$ ). After filtration the solvent was removed in vacuo to give a dark oil. Purification was carried out by column chromatography (silica gel, eluting hexane) to give the title compound as a light yellow/green oil which solidified on standing (34.81 g, 86%).

15  $^1H$ -NMR ( $CDCl_3$ , 270 MHz) δ 2.494 (3H, dd,  $J=1.65$  and 1.65 Hz), 8.145 (1H, dd,  $J=1.3$  and 0.7 Hz), 8.195 (1H, s).

## (2) Methyl 3-[2-nitro-4-iodo-6-(trifluoromethyl)phenyl]-2-oxo-propanoate

[0150] Dimethyl oxalate (127.79 g, 5.0 eq) was added to sodium methylate (216.4mL, 28%, 5.0 eq). The resulting mixture was stirred at room temperature for 1.5 hours. To the mixture was then added 5-iodo-2-methyl-3-nitrobenzotrifluoride (71.64 g, 216.4 mmol), dissolved in MeOH (216 mL). The dark red mixture was then stirred at room temperature for 6 hours and left over night. The solvent was removed in vacuo to give a red solid which was subsequently added to aqueous 2.5N HCl (800 mL). The mixture was extracted with EtOAc (500 mL and 2 x 300 mL). The extracts were combined and dried (anhydrous  $MgSO_4$ ). After filtration, the solvent was removed in vacuo to give a yellow solid of the crude product (161.41 g). A fraction of this was purified by column chromatography (silicagel, eluting 15:1 to 10:1 hexane:EtOAc) to give the title compound as a yellow solid.

20  $^1H$ -NMR ( $CDCl_3$ , 270 MHz) δ 3.957 (3H, s), 4.624 (2H, s), 8.291 (1H, d,  $J=1.3$  Hz), 8.544 (1H, d,  $J=2.0$  Hz).

## (3) [2-Nitro-4-iodo-6-(trifluoromethyl)phenyl]acetic acid

[0151] To crude methyl 3-[2-nitro-4-iodo-6-(trifluoromethyl)phenyl]-2-oxo-propanoate prepared above (40. 98g) in AcOH (750 mL) was added aqueous 30%  $H_2O_2$  solution (266 mL) followed by 70%  $HClO_4$  (41 mL). The resulting mixture was stirred at 50°C (bath temperature) for 4.5 hours. The solution was cooled and solid  $Na_2SO_3$  (100 g) was added. The solvent was then removed in vacuo. The resulting orange solid was suspended in EtOAc (500 mL) and washed with  $H_2O$  (300 mL). The organic phase was then extracted with aqueous saturated  $NaHCO_3$ :aqueous 2N NaOH (6:1, 600 mL) followed by aqueous saturated  $NaHCO_3$  (200 mL). The aqueous extracts were combined and cooled in an ice-water bath. The solution was then acidified with aqueous 35% HCl. The resulting solid was isolated by filtration and dried to give the title compound as a yellow solid (7.086 g). The organic phase was then re-extracted with aqueous saturated  $NaHCO_3$  (6 x 50 mL). The extracts were combined and cooled in an ice-water bath, and then acidified with aqueous 35% HCl. The resulting solid was isolated by filtration and dried to give the title compound as a yellow solid (6.896 g).

25  $^1H$ -NMR ( $CDCl_3$ , 270 MHz) δ 4.162 (2H, s), 8.266 (1H, d,  $J=1.3$  Hz), 8.509 (1H, d,  $J=1.65$  Hz).

## (4) Methyl [2-nitro-4-iodo-6-(trifluoromethyl)phenyl]acetate

[0152] [2-Nitro-4-iodo-6-(trifluoromethyl)phenyl]acetic acid (34.7 g, 96.2 mmol) was dissolved in HCl/MeOH (300 mL) and the solution was heated at reflux for 4.5 hours. The solvent was removed in vacuo and the resulting oil was dissolved in EtOAc (400 mL). The solution was washed with saturated aqueous  $NaHCO_3$  (60 mL, 100 mL and 80 mL) and then dried (anhydrous  $MgSO_4$ ). After filtration, the solvent was removed in vacuo to yield the title compound (33.11 g, 92%).

30  $^1H$ -NMR ( $CDCl_3$ , 270 MHz) δ 3.726 (3H, s), 4.109 (2H, s), 8.258 (1H, s), 8.486 (1H, d,  $J=1.65$  Hz).

## (5) 4-Trifluoromethyl-6-iodooxindole

[0153] To methyl [2-nitro-4-iodo-6-(trifluoromethyl)phenyl]acetate (33.11 g, 85.1 mmol) in MeOH (1000 mL) at 0°C was added aqueous 20%  $TiCl_3$  (815 g, 12.4 eq). The cooling bath was removed and the resulting mixture stirred at room temperature for 3 hours and then left overnight. To the mixture was then added aqueous 6N HCl (900 mL) and the mixture extracted with EtOAc:toluene (1:1, 3 x 1000 mL) and EtOAc:toluene (2:1, 3 x 900 mL and 3 x 500 mL).

The extracts were combined and dried (anhydrous MgSO<sub>4</sub>). After filtration, the solvent was removed in vacuo to give a light brown solid. Purification was carried out by crystallization from EtOH (300 mL) to give the title compound as a light brown crystalline solid (21.588g, 78%).

<sup>5</sup> <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 270 MHz) δ 3.970 (2H, s), 7.387 (1H, s), 7.597 (1H, s), 7.930 (1H, brs).

(6) 3,3-Dibromo-4-trifluoromethyl-6-iodooxindole

**[0154]** To 4-trifluoromethyl-6-iodooxindole (21.00 g, 64.2 mmol) suspended in t-BuOH (610 mL) was added pyridinium bromide perbromide (91.32 g, 90%, 4.0 eq). The resulting mixture was stirred rapidly at room temperature for 4 hours. Water (1200 mL) was added and the mixture was stirred until all the solid material had dissolved. The red solution was then extracted with EtOAc (4 x 250 mL). The extracts were combined, washed with water (3 x 400 mL) and then dried (anhydrous MgSO<sub>4</sub>). After filtration, the solvent was removed in vacuo to give the desired crude product as a light purple/grey solid (35.11 g).

<sup>15</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 270 MHz) δ 7.563 (1H, s), 7.780 (1H, s), 11.735 (1H, brs).

(7) 4-Trifluoromethyl-6-iodoisatin

**[0155]** The crude 3,3-dibromo-4-trifluoromethyl-6-iodooxindole (35.11 g) prepared above was dissolved in MeOH (1200 mL) and H<sub>2</sub>O (300 mL) was added. The resulting mixture was heated at reflux for 3 hours and then aqueous 48% HBr (10 mL) was added. The solution was then heated at reflux for 27 hours. The MeOH solvent was removed in vacuo to give a brown/yellow solid. The solid was isolated by filtration, washing the collected solid with copious amounts of H<sub>2</sub>O. The solid was then dried overnight in a vacuum desiccator (NaOH as desiccant) to give the desired isatin as a light brown solid (20.8214 g, 95% (two steps)).

<sup>25</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 270 MHz) δ 7.552 (1H, s), 7.680 (1H, s), 11.310 (1H, brs, NH).

(8) 4-Trifluoromethyl-6-ido-3-hydroxy-3-(2-naphthyl)oxindole

**[0156]** The title compound (35.8 mg, 6.5%) was prepared from 4-trifluoromethyl-6-iodoisatin (400 mg, 1.17 mmol) and 2-naphthyl magnesium bromide by the procedure similar to that described in Example 1.

<sup>30</sup> <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.77-7.87 (m, 4H), 7.71 (s, 1H), 7.56 (s, 1H), 7.47-7.50 (m, 2H), 7.21-7.26 (m, 1H).

(9) 3-Diethylaminopropoxy-4-trifluoromethyl-6-ido-3-(2-naphthyl)oxindole

**[0157]** The title compound (13.9 mg, 33%) was prepared from 4-trifluoromethyl-6-ido-3-hydroxy-(2-naphthyl)oxindole (34.5 mg, 0.0735 mmol) and 3-chloropropyl-N,N-diethylamine hydrochloride by the procedure similar to that described in Reference Example 8.

<sup>35</sup> <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.71-7.77 (m, 4H), 7.67 (s, 1H), 7.63 (s, 1H), 7.42-7.46 (m, 2H), 7.24 (d, 1H, J=10.2 Hz), 3.28-3.46 (m, 2H), 2.48-2.82 (m, 6H), 1.97-2.01 (m, 2H), 1.11 (t, 6H, J=6.8 Hz).

(10) 3-Diethylaminopropoxy-4-trifluoromethyl-6-(3-hydroxy-1-propynyl)-3-(2-naphthyl)oxindole

**[0158]** The title compound (3.7 mg, 34%) was prepared from 3-diethylaminopropoxy-4-trifluoromethyl-6-ido-3-(2-naphthyl)oxindole (12.4 mg, 0.0213 mmol) and 1-propyn-3-ol by the procedure similar to that described in Reference Example 21.

<sup>40</sup> <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.70-7.79 (m, 4H), 7.53 (s, 1H), 7.42-7.47 (m, 2H), 7.39 (s, 1H), 7.19 (d, 1H, J=8.3 Hz), 4.52 (s, 2H), 3.11-3.39 (m, 8H), 2.22-2.25 (m, 2H), 1.37 (t, 6H, J=7.4 Hz).

Example 58

<sup>50</sup> 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-morpholinocarbonyl-3-hydroxy-3-(2-naphthyl)oxindole

**[0159]** A mixture of 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-hydroxy-3-(2-naphthyl)oxindole (30 mg, 0.0642 mmol), conc. HCl (2 mL), and acetic acid (2 mL) was heated at reflux for 5 h. Excess solvents were azeotropically removed in vacuo by using toluene to give crude carboxylic acid. The residue was dissolved in DMF (0.5 mL) and morpholine hydrochloride (5.6 mg, 0.0453 mmol), 1-hydroxybenzotriazole (7.5 mg, 0.0555 mmol), WSC HCl (8.5 mg, 0.0443 mmol), and triethylamine (0.04 mL, 0.287 mmol) were added. The mixture was stirred for 16 h at room temperature and diluted with sat. aqueous NaHCO<sub>3</sub>. The mixture was extracted with ethyl acetate-toluene and the extracts were washed with sat. aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel

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column chromatography with 30 : 1 to 25 : 1 chloroform/methanol to give the title compound (4.8 mg, 18%).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.90 (s, 1H), 7.74-7.83 (m, 3H), 7.46-7.49 (m, 2H), 7.34 (s, 1H), 7.30 (s, 1H), 7.22 (dd, 1H, J=2.0, 8.6 Hz), 3.55-3.90 (m, 10H), 2.69-2.87 (m, 2H), 2.62 (q, 4H, J=7.1 Hz), 0.97 (t, 6H, J=7.1 Hz).

5 Example 59

### 1-(2-Diethylaminoethyl)-4-trifluoromethyl-7-(4-morpholinocarbonyl-1-butynyl)-3-hydroxy-3-(2-naphthyl)oxindole

10 (1) 7-Iodo-4-trifluoromethylisatin

[0160] A mixture of 4-trifluoromethylisatin (450 mg, 2.09 mmol) and N-iodosuccinimide (800 mg, 3.72 mmol) in conc. H<sub>2</sub>SO<sub>4</sub> (5 mL) was stirred for 6 h at 40 °C and poured into crushed ice. The mixture was extracted with ethyl acetate and the extracts were washed with aqueous Na<sub>2</sub>SO<sub>3</sub>, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography with 3 : 1 hexane/ethyl acetate to give the title compound (296 mg, 42%).

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ 11.24 (brs, 1H), 8.15 (d, 1H, J=8.4 Hz), 7.14 (d, 1H, J=8.4 Hz).

(2) 1-(2-Diethylaminoethyl)-7-iodo-4-trifluoromethylisatin

[0161] The title compound (245 mg, 76%) was prepared from 7-iodo-4-trifluoromethylisatin (250 mg, 0.733 mmol) and 2-chloroethyl-N,N-diethylamine hydrochloride by the procedure similar to that described in Reference Example 8.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 8.15 (d, 1H, J=8.4 Hz), 7.09 (d, 1H, J=8.4 Hz), 4.40 (t, 2H, J=6.5 Hz), 2.60 (t, 2H, J=6.5 Hz), 2.45 (q, 4H, J=7.3 Hz), 0.82 (t, 6H, J=7.3 Hz).

(3) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-7-iodo-3-hydroxy-3-(2-naphthyl)oxindole

[0162] The title compound (103 mg, 53%) was prepared from 1-(2-diethylaminoethyl)-7-iodo-4-trifluoromethylisatin (152 mg, 0.345 mmol) and 2-naphthylmagnesium bromide by the procedure similar to that described in Example 1.  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 8.01 (d, 1H, J=8.2 Hz), 7.88 (s, 1H), 7.73-7.84 (m, 3H), 7.44-7.48 (m, 2H), 7.19 (dd, 1H, J=2.0, 8.6 Hz), 7.08 (d, 1H, J=8.2 Hz), 4.24-4.45 (m, 2H), 2.39-2.83 (m, 6H), 0.88 (t, 6H, J=7.1 Hz).

(4) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-7-(4-morpholinocarbonyl-1-butynyl)-3-hydroxy-3-(2-naphthyl)oxindole

[0163] The title compound (28.2 mg) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-7-iodo-3-hydroxy-3-(2-naphthyl)oxindole (43.4 mg, 0.0764 mmol) and 4-morpholinocarbonyl-1-butyne by the procedure similar to that described in Reference Example 21. The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>; hydrochloride) δ 10.19 (brs, 1H), 7.79-7.92 (m, 4H), 7.65 (d, 1H, J=8.2 Hz), 7.48-7.51 (m, 2H), 7.40 (d, 1H, J=8.2 Hz), 7.11-7.28 (m, 1H), 7.04 (s, 1H), 4.41-4.60 (m, 2H), 3.14-3.60 (m, 14H), 2.76-2.80 (m, 4H), 1.17-1.23 (m, 6H).

40 Example 60

### (+)- and (-)-1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-morpholinocarbonyl-1-butynyl)-3-hydroxy-3-(2-naphthyl)oxindole

45 (Optical isomers of the compound of Example 51)

[0164] Racemic compound 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-(4-morpholinocarbonyl-1-butynyl)-3-hydroxy-3-(2-naphthyl)oxindole of Example 51 was separated to (+)- and (-)-enantiomers by using a preparative HPLC on a Chiralpak OD™ with 80 : 20 : 1 hexane/isopropanol/diethylamine as the eluent. The enantiomeric excess was determined by using HPLC on a Chiralpak AD™ (250 x 4.6 mm) with 100 : 100 : 1 hexane/isopropanol/diethylamine as the eluent at the flow rate of 0.5 ml/min. Under these conditions, two enantiomers were eluted at the retention time of 11.2 and 18.7 min, respectively.

55

## Example 61

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-morpholinocarbonyl-1-butynyl)-3-amino-3-(2-naphthyl)oxindole

5 (1) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-amino-3-(2-naphthyl)oxindole

[0165] A mixture of 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-naphthyl)oxindole of Example 48 (100 mg, 0.176 mmol) and thionyl chloride (2 mL) was stirred for 1.5 h at room temperature and the excess reagent was evaporated in vacuo to give the crude chloride. The residue was dissolved in DMF (1.5 mL) and triethylamine (0.06 mL, 0.43 mmol) and NaN<sub>3</sub> (27 mg, 0.415 mmol) were added. The mixture was stirred for 2.5 h at 70°C. Sat. aqueous NaHCO<sub>3</sub> was added. The mixture was extracted with ethyl acetate-toluene and the extracts were washed with sat. aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, and concentrated to give the crude azide (100 mg, 96%). The crude azide (89 mg, 0.15 mmol) was dissolved in MeOH (1.5 mL) and SnCl<sub>2</sub>·2 H<sub>2</sub>O (58.5 mg, 0.259 mmol). The mixture was stirred for 1.5 h at room temperature and concentrated. To the residue was added sat. aqueous NaHCO<sub>3</sub> and ethyl acetate and the organic layer was separated. The layer was dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography with 40 : 1 chloroform/methanol to give the title compound.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.77-7.85 (m, 3H), 7.72 (d, 1H, J=8.7 Hz), 7.67 (s, 1H), 7.60 (s, 1H), 7.45-7.50 (m, 2H), 7.12 (dd, 1H, J=1.8, 8.7 Hz), 3.85-3.95 (m, 1H), 3.64-3.74 (m, 1H), 2.68 (t, 2H, J=6.6 Hz), 2.54 (q, 4H, J=7.1 Hz), 2.47 (brs, 2H), 0.96 (t, 6H, J=7.1 Hz).

20 (2) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-morpholinocarbonyl-1-butynyl)-3-amino-3-(2-naphthyl)oxindole

[0166] The title compound (34.3 mg) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-amino-3-(2-naphthyl)oxindole (36.3 mg, 0.0640 mmol) and 4-morpholinocarbonyl-1-butyne by the procedure similar to that described in Reference Example 21. The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>: hydrochloride) δ 10.38 (brs, 1H), 7.89-7.95 (m, 5H), 7.57-7.60 (m, 2H), 7.49 (s, 1H), 7.15 (d, 1H, J=9.2 Hz), 4.15-4.39 (m, 2H), 3.19-3.57 (m, 14H), 2.72-2.75 (m, 4H), 1.22 (t, 6H, J=7.1 Hz).

## 30 Example 62

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-morpholinocarbonyl-1-butynyl)-3-hydroxy-3-(2-fluorophenyl)oxindole

(1) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-fluorophenyl)oxindole

[0167] To a solution of 1-bromo-2-fluorobenzene (0.09 mL, 0.823 mmol) in THF (4 mL) was added dropwise 1.53 N BuLi in hexane (0.54 mL, 0.826 mmol) over 10 min at -78 °C and the mixture was stirred for 10 min. The resulting solution was then transferred into the cooled solution of 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodoisatin (330 mg, 0.75 mmol) in THF (2 mL) at -78 °C via a cannula. The mixture was stirred for 30 min at the same temperature and the reaction was quenched with aqueous NaHCO<sub>3</sub>. The mixture was extracted with ethyl acetate and the extracts were dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silicagel column chromatography with 50 : 1 to 30 : 1 chloroform/methanol to give the title compound (35.9 mg, 9%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.88 (dd, 1H, J=7.1, 7.1 Hz), 7.60 (s, 1H), 7.56 (s, 1H), 7.21-7.35 (m, 2H), 6.89 (ddd, 1H, J=1.5, 8.1, 11.8 Hz), 3.75-3.95 (m, 2H), 2.54-2.83 (m, 6H), 1.03 (t, 6H, J=6.9 Hz).

45 (2) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-morpholinocarbonyl-1-butynyl)-3-hydroxy-3-(2-fluorophenyl)oxindole

[0168] The title compound (19.2 mg) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-fluorophenyl)oxindole (27.4 mg, 0.0511 mmol) and 4-morpholinocarbonyl-1-butyne by the procedure similar to that described in Reference Example 21. The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>: hydrochloride) δ 10.43 (brs, 1H), 7.91 (dd, 1H, J=7.3, 7.3 Hz), 7.68 (s, 1H), 7.14-7.38 (m, 4H), 7.01 (dd, 1H, J=8.3, 10.9 Hz), 4.10-4.30 (m, 2H), 3.24-3.63 (m, 14H), 2.69 (m, 4H), 1.24 (t, 6H, J=7.1 Hz).

## Example 63

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-morpholinocarbonyl-1-butynyl)-3-hydroxy-3-(2-trifluoromethylphenyl)oxindole

5 (1) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-trifluoromethylphenyl)oxindole

[0169] To a solution of 2-bromobenzotrifluoride (0.3 mL, 2.23 mmol) in THF (1.5 mL) was added dropwise 1.53 N BuLi in hexane (1.45 mL, 2.22 mmol) over 10 min at -78 °C and the mixture was stirred for 10 min. The resulting solution (1.2 mL, 0.82 mmol) was then added dropwise to the cooled solution of 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodoisatin (352 mg, 0.8 mmol) in THF (4 mL) at -78 °C via a syringe. The mixture was allowed to warm to room temperature and stirred for 30 min. The reaction was quenched with aqueous NaHCO<sub>3</sub>. The mixture was extracted with ethyl acetate, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography with 50 : 1 to 40 : 1 chloroform/methanol to give the title compound (96.3 mg, 21%).

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 8.44 (d, 1H, J=7.9 Hz), 7.60-7.74 (m, 3H), 7.45-7.53 (m, 2H), 4.01-4.08 (m, 1H), 3.60-3.70 (m, 1H), 2.50-2.87 (m, 6H), 1.01 (t, 6H, J=7.1 Hz).

(2) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-morpholinocarbonyl-1-butynyl)-3-hydroxy-3-(2-trifluoromethylphenyl)oxindole

20 [0170] The title compound (22.1 mg) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-trifluoromethylphenyl)oxindole (25.2 mg, 0.043 mmol) and 4-morpholinocarbonyl-1-butyne by the procedure similar to that described in Reference Example 21. The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.

25 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>: hydrochloride) δ 10.27 (brs, 1H), 8.42 (d, 1H, J=7.7 Hz), 7.82 (dd, 1H, J=7.7, 7.7 Hz), 7.66-7.70 (m, 2H), 7.59 (dd, 1H, J=7.7, 7.7 Hz), 7.49 (s, 1H), 7.28 (s, 1H), 4.06-4.26 (m, 2H), 3.26-3.57 (m, 14H), 2.69-2.75 (m, 4H), 1.24 (t, 6H, J=6.9 Hz).

## Example 64

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-hydroxy-3-(2-trifluoromethylphenyl)oxindole

[0171] The title compound (26.1 mg, 63%) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-trifluoromethylphenyl)oxindole (49.8 mg, 0.0849 mmol) by the procedure similar to that described in Example 55.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 8.47 (d, 1H, J=7.8 Hz), 7.73 (dd, 1H, J=7.8, 7.8 Hz), 7.65 (d, 1H, J=7.8 Hz), 7.57 (s, 1H), 7.51 (dd, 1H, J=7.8, 7.8 Hz), 7.42 (s, 1H), 4.11-4.22 (m, 1H), 3.60-3.70 (m, 1H), 2.82-2.93 (m, 1H), 2.51-2.74 (m, 5H), 1.00 (t, 6H, J=7.1 Hz).

## Example 65

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-carbamoyl-1-butynyl)-3-hydroxy-3-(2-naphthyl)oxindole

## (1) 4-Carbamoyl-1-butyne

45 [0172] A mixture of 4-pentyoic acid (189 mg, 1.93 mmol) and thionyl chloride (1.5 mL) was heated at reflux for 1 h and the excess reagent was evaporated off. The residue was dissolved in THF (5 mL) and added dropwise to the ice-cooled conc. aqueous ammonia (5 mL). The mixture was stirred for 2 h at room temperature, acidified by adding hydrochloric acid, and extracted with ethyl acetate. The organic layers were dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography with ethyl acetate to give the title compound (61.1 mg, 33%).

50 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 5.61 (brs, 2H), 2.43-2.58 (m, 4H), 2.03 (s, 1H).

## (2) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-carbamoyl-1-butynyl)-3-hydroxy-3-(2-naphthyl)oxindole

55 [0173] The title compound (28.9 mg) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-naphthyl)oxindole of Example 48 (50.1 mg, 0.0881 mmol) and 4-carbamoyl-1-butyne by the procedure similar to that described in Reference Example 21. The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.

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<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>: hydrochloride) δ 10.01 (brs, 1H), 7.79-7.94 (m, 4H), 7.71 (s, 1H), 7.47-7.53 (m, 2H), 7.44 (brs, 1H), 7.37 (s, 1H), 7.14-7.28 (m, 1H), 7.03 (brs, 1H), 6.94 (brs, 1H), 4.12-4.19 (m, 2H), 3.13-3.50 (m, 6H), 2.69 (t, 2H, J=7.3 Hz), 2.40 (t, 2H, J=7.3 Hz), 1.19 (t, 6H, J=7.3 Hz).

### 5 Example 66

#### 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(3-amino-1-propynyl)-3-hydroxy-3-(2-naphthyl)oxindole

(1) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(3-t-butoxycarbonylamino-1-propynyl)-3-hydroxy-3-(2-naphthyl)  
10 oxindole

**[0174]** The title compound (170 mg, 83%) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-naphthyl)oxindole of Example 48 (195 mg, 0.343 mmol) and 3-t-butoxycarbonylamino-1-propyne by the procedure similar to that described in Reference Example 21.

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.88 (s, 1H), 7.72-7.82 (m, 3H), 7.43-7.49 (m, 2H), 7.41 (s, 1H), 7.24 (s, 1H), 7.21 (dd, 1H, J=2.0, 8.9 Hz), 4.84 (brs, 1H), 4.20 (d, 2H, J=5.6 Hz), 3.76-3.91 (m, 2H), 2.66-2.79 (m, 2H), 2.50-2.64 (m, 4H), 1.49 (s, 9H), 0.95 (t, 6H, J=7.1 Hz).

(2) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(3-amino-1-propynyl)-3-hydroxy-3-(2-naphthyl)oxindole  
20

**[0175]** The hydrochloride of the title compound was obtained by treating 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-(3-t-butoxycarbonylamino-1-propynyl)-3-hydroxy-3-(2-naphthyl)oxindole with 4 N HCl in dioxane at 50 °C for 1.5 h followed by concentration to dryness.

25 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ 10.63 (brs, 1H), 8.53 (brs, 3H), 7.79-7.99 (m, 5H), 7.47-7.56 (m, 2H), 7.44 (s, 1H), 7.11-7.25 (m, 1H), 7.10 (s, 1H), 4.12-4.28 (m, 2H), 4.08 (m, 2H), 3.13-3.39 (m, 6H), 1.21 (t, 6H, J=7.1 Hz).

### Example 67

#### 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-[3-(N-ethylureido)-1-propynyl]-3-hydroxy-3-(2-naphthyl)oxindole

30 **[0176]** A mixture of 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-(3-amino-1-propynyl)-3-hydroxy-3-(2-naphthyl)oxindole (40 mg, 0.074 mmol), ethyl isocyanate (0.0065 mL, 0.0821 mmol), and triethylamine (0.025 mL, 0.0821 mmol) in THF (0.5 mL) was stirred for 4 h at room temperature and the reaction was quenched with sat. aqueous NaHCO<sub>3</sub>. The mixture was extracted with ethyl acetate and the extracts were dried over MgSO<sub>4</sub> and concentrated. The residue was purified by column chromatography with 40 : 1 to 20 : 1 chloroform/methanol to give the title compound (20.6 mg). The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.

35 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>: hydrochloride) δ 10.21 (brs, 1H), 7.79-7.96 (m, 4H), 7.74 (s, 1H), 7.47-7.56 (m, 2H), 7.39 (s, 1H), 7.14-7.28 (m, 1H), 7.05 (brs, 1H), 6.35 (brs, 1H), 6.08 (brs, 1H), 4.13-4.18 (m, 4H), 3.17-3.41 (m, 6H), 3.04 (q, 2H, J=7.1 Hz), 1.19 (t, 6H, J=6.9 Hz), 1.01 (t, 3H, J=7.1 Hz).

### Example 68

#### 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(3-methansulfonylamino-1-propynyl)-3-hydroxy-3-(2-naphthyl)oxindole

45 **[0177]** The title compound (26.3 mg) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-(3-amino-1-propynyl)-3-hydroxy-3-(2-naphthyl)oxindole (40 mg, 0.0704 mmol) and methanesulfonyl chloride by the procedure similar to that described in Example 67. The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.

50 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>: hydrochloride) δ 10.24 (brs, 1H), 7.79-7.92 (m, 5H), 7.74 (t, 1H, J=6.1Hz), 7.48-7.52 (m, 2H), 7.45 (s, 1H), 7.18-7.25 (m, 1H), 7.07 (s, 1H), 4.14-4.16 (m, 4H), 3.18-3.33 (m, 6H), 3.07 (s, 3H), 1.20 (t, 6H, J=7.1 Hz).

### Example 69

55 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-[4-(N-hydroxyethylcarbamoyl)-1-butynyl]-3-hydroxy-3-(2-naphthyl)oxindole

**[0178]** N-Hydroxyethyl-4-pentynamide (128 mg, 45%) was prepared from 4-pentyneoic acid (200 mg, 2.03 mmol) and

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2-ethanolamine by the procedure similar to that described in Example 65(1). The title compound (34.2 mg) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-naphthyl)oxindole of Example 48 (50.4 mg, 0.0887 mmol) and N-hydroxyethyl-4-pentynamide by the procedure similar to that described in Reference Example 21. The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.

<sup>5</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>: hydrochloride) δ 10.27 (brs, 1H), 8.03 (m, 1H), 7.78-7.92 (m, 4H), 7.72 (s, 1H), 7.48-7.51 (m, 2H), 7.37 (s, 1H), 7.14-7.28 (m, 1H), 7.04 (brs, 1H), 4.16 (m, 2H), 3.72 (m, 2H), 3.12-3.44 (m, 8H), 2.70 (t, 2H, J=7.3 Hz), 2.43 (t, 2H, J=7.3 Hz), 1.19 (t, 6H, J=6.8 Hz).

### 10 Example 70

#### 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-morpholinocarbonyl-1-butynyl)-3-hydroxy-3-(2-chlorophenyl)oxindole

##### (1) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-chlorophenyl)oxindole

<sup>15</sup> [0179] To a solution of 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodoisatin (4 g, 9.09 mmol) in a mixture of diethyl ether (60 mL) and toluene (20 mL) was added dropwise a freshly prepared 0.67 N 2-chlorophenylmagnesium iodide in ether (15 mL, 10.1 mmol) over 20 min at room temperature. The mixture was stirred for 20 min at the same temperature and the reaction was quenched with aqueous NaHCO<sub>3</sub>. The mixture was extracted with ethyl acetate and the extracts were washed with sat. aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography with 100 : 1 to 50 : 1 chloroform/methanol to give the title compound (2.81 g, 56%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 8.09 (d, 1H, J=6.8 Hz), 7.61 (s, 1H), 7.53 (s, 1H), 7.41 (dd, 1H, J=6.8, 6.8 Hz), 7.21-7.32 (m, 2H), 3.97-4.11 (m, 1H), 3.68-3.78 (m, 1H), 2.55-2.84 (m, 6H), 1.03 (t, 6H, J=7.1 Hz).

<sup>20</sup> (2) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-morpholinocarbonyl-1-butynyl)-3-hydroxy-3-(2-chlorophenyl)oxindole

<sup>25</sup> [0180] The title compound (26.5 mg) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-chlorophenyl)oxindole (35.2 mg, 0.0637 mmol) and 4-morpholinocarbonyl-1-butyne by the procedure similar to that described in Reference Example 21. The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.

<sup>30</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>: hydrochloride) δ 10.33 (brs, 1H), 8.06 (d, 1H, J=7.4 Hz), 7.64 (s, 1H), 7.46 (dd, 1H, J=7.4, 7.4 Hz), 7.12-7.39 (m, 4H), 4.11-4.34 (m, 2H), 3.20-3.65 (m, 14H), 2.68 (m, 4H), 1.24 (t, 6H, J=7.1 Hz).

### 35 Example 71

#### 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(2-morpholinocarboxy-1-ethynyl)-3-hydroxy-3-(2-naphthyl)oxindole

##### (1) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(2-t-butoxycarbonyl-1-ethynyl)-3-hydroxy-3-(2-naphthyl)oxindole

<sup>40</sup> [0181] The title compound (75.7 mg, quant.) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-naphthyl)oxindole of Example 48 (75.1 mg, 0.132 mmol) and t-butyl propionate by the procedure similar to that described in Reference Example 21.

<sup>45</sup> <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.73-7.86 (m, 4H), 7.61 (s, 1H), 7.44-7.49 (m, 2H), 7.42 (s, 1H), 7.27 (dd, 1H, J=2.0, 8.6 Hz), 3.87-3.97 (m, 1H), 3.70-3.80 (m, 1H), 2.67 (t, 2H, J=6.3 Hz), 2.44-2.58 (m, 4H), 1.42 (s, 9H), 0.89 (t, 6H, J=7.1 Hz).

##### (2) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(2-carboxy-1-ethynyl)-3-hydroxy-3-(2-naphthyl)oxindole

<sup>50</sup> [0182] The hydrochloride of the title compound (72.8 mg, 100%) was obtained by treating 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-(2-t-butoxycarbonyl-1-ethynyl)-3-hydroxy-3-(2-naphthyl)oxindole (73 mg, 0.129 mmol) with 4 N HCl in dioxane at 50 °C for 2 h followed by concentration to dryness.

<sup>55</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ 7.83-7.97 (m, 5H), 7.54-7.56 (m, 3H), 7.14-7.31 (m, 1H), 4.22-4.26 (m, 2H), 3.17-3.54 (m, 6H), 1.13-1.23 (m, 6H).

(3) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(2-morpholinocarboxy-1-ethynyl)-3-hydroxy-3-(2-naphthyl)oxindole

[0183] A solution of 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-(2-carboxy-1-ethynyl)-3-hydroxy-3-(2-naphthyl)oxindole (35 mg, 0.064 mmol), morpholine hydrochloride (14.6 mg, 0.118 mmol), 1-hydroxybenzotriazole (11 mg, 0.0814

mmol), WSC HCl (14.7 mg, 0.0767 mmol), and triethylamine (0.04 mL, 0.287 mmol) in DMF (0.6 mL) was stirred for 21 h at room temperature and sat. aqueous NaHCO<sub>3</sub> was added. The mixture was extracted with ethyl acetate-toluene and the extracts were washed with sat. aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography with 50 : 1 to 30 : 1 chloroform/methanol to give the title compound (2.5 mg, 4.6 %).

<sup>5</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ 7.73-7.81 (m, 4H), 7.45-7.55 (m, 3H), 7.22-7.30 (m, 2H), 3.48-3.96 (m, 10 H), 2.51-2.71 (m, 6H), 0.89 (t, 6H, J=7.1 Hz).

<sup>10</sup> Example 72

(+)-1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-morpholinocarbonyl-1-butynyl)-3-hydroxy-3-(2-chlorophenyl)oxindole

<sup>15</sup> (Optical isomer of the compound of Example 70)

<sup>20</sup> (1) (+)- and (-)-1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-chlorophenyl)oxindole

**[0184]** Racemic compound 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-chlorophenyl)oxindole was separated to (+)- and (-)-enantiomers by using a preparative HPLC on a Chiralpak OD™ with 6% isopropanol/hexane as the eluent. The enantiomeric excess was determined by using HPLC on a Chiralpak OD™ (250 x 4.6 mm) with 7% isopropanol/hexane as the eluent at the flow rate of 0.5 ml/min. Under these conditions, (+)- and (-)-enantiomers were eluted at the retention time of 20.8 and 16.7 min, respectively.

(+) Enantiomer: [α]<sub>D</sub> +43.2° (c = 0.210, MeOH)

(-) Enantiomer: [α]<sub>D</sub> -49.0° (c = 0.220, MeOH)

<sup>25</sup> (2) (+)-1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-morpholinocarbonyl-1-butynyl)-3-hydroxy-3-(2-chlorophenyl)oxindole

<sup>30</sup> **[0185]** The title compound (246 mg) was prepared from (+)-1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-chlorophenyl)oxindole (300 mg, 0.543 mmol) and 4-morpholinocarbonyl-1-butyne by the procedure similar to that described in Reference Example 21. The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness. The NMR spectra of the title compound exhibited the same as in Example 70. [α]<sub>D</sub> +58.3° (c = 0.252, MeOH)

<sup>35</sup> Example 73

(+)-1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-[3-(N-ethylureido)-1-propynyl]-3-hydroxy-3-(2-chlorophenyl)oxindole

<sup>40</sup> (Optical isomer of the compound of Example 93)

(1) N-Ethyl-N'-propargylurea

**[0186]** To a solution of propargylamine (2 mL, 31.2 mmol) in THF (100 mL) was added dropwise ethyl isothiononate (2.47 mL, 31.2 mmol) at 0 °C and the mixture was stirred for 30 min at room temperature. The solvent was evaporated and the residual solid was washed with ether to give the title compound (3.43 g, 87%).

<sup>45</sup> <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 4.75 (br, 2H), 4.02 (d, 1H, J=12.0 Hz), 3.96 (d, 1H, J=12.0 Hz), 3.23 (q, 2H, J=7.3 Hz), 2.22 (m, 1H), 1.14 (t, 3H, J=7.3 Hz).

<sup>50</sup> (2) (+)-1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-[3-(N-ethylureido)-1-propynyl]-3-hydroxy-3-(2-chlorophenyl)oxindole

**[0187]** The title compound (232 mg) was prepared from (+)-1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-chlorophenyl)oxindole of Example 72(1) (347 mg, 0.628 mmol) and N-ethyl-N'-propargylurea by the procedure similar to that described in Reference Example 21. The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.

<sup>55</sup> <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ 10.36 (brs, 1H), 8.06 (d, 1H, J=6.9 Hz), 7.65 (s, 1H), 7.47 (dd, 1H, J=7.6, 7.6 Hz), 7.14-7.39 (m, 4H), 6.33 (brs, 1H), 6.06 (brs, 1H), 4.11-4.33 (m, 4H), 3.20-3.45 (m, 6H), 3.03 (q, 2H, J=7.1 Hz), 1.25 (t, 6H, J=7.1 Hz), 1.00 (t, 3H, J=7.1 Hz).

$[\alpha]_D +63.9^\circ$  (c = 0.504, MeOH)

Example 74

5    (+)-1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole

(Optical isomer of the compound of Example 78)

10    (1) (+)-1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-hydroxy-3-(2-chlorophenyl)oxindole

[0188] The title compound (335 mg, 63%) was prepared from (+)-1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-chlorophenyl)oxindole of Example 72(1) (645 mg, 1.17 mmol) by the procedure similar to that described in Example 55.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.07 (d, 1H,  $J=7.6$  Hz), 7.57 (s, 1H), 7.40-7.47 (m, 2H), 7.33 (ddd, 1H,  $J=1.5, 7.6, 7.6$  Hz), 7.24 (dd, 1H,  $J=1.5, 7.9$  Hz), 4.03-4.13 (m, 1H), 3.73-3.83 (m, 1H), 2.59-2.78 (m, 6H), 1.01 (t, 6H,  $J=7.1$  Hz).

$[\alpha]_D +72.8^\circ$  (c = 0.338, MeOH)

15    (2) (+)-1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole

20    [0189] The title compound (248 mg, 66%) was prepared from (+)-1-(2-diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-hydroxy-3-(2-chlorophenyl)oxindole (289 mg, 0.64 mmol) by the procedure similar to that described in Example 56.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ : hydrochloride)  $\delta$  10.41 (brs, 1H), 8.33 (brs, 1H), 8.15 (s, 1H), 8.08 (d, 1H,  $J=7.3$  Hz), 7.84 (s, 1H), 7.77 (brs, 1H), 7.48 (ddd, 1H,  $J=1.7, 7.6, 7.6$  Hz), 7.11-7.40 (m, 4H), 4.16-4.36 (m, 2H), 3.25-3.51 (m, 6H), 1.26 (t, 6H,  $J=7.3$  Hz).

25     $[\alpha]_D +75.7^\circ$  (c = 0.412, MeOH)

Example 75

30    (+)-1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(3-methanesulfonylamino-1-propynyl)-3-hydroxy-3-(2-chlorophenyl)oxindole

[0190] The title compound (270 mg) was prepared from (+)-1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-chlorophenyl)oxindole of Example 72(1) (347 mg, 0.628 mmol) and 1-methanesulfonylamino-2-propyne by the procedure similar to that described in Reference Example 21. The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ : hydrochloride)  $\delta$  10.40 (brs, 1H), 8.06 (d, 1H,  $J=7.6$  Hz), 7.67-7.72 (m, 2H), 7.47 (dd, 1H,  $J=7.6, 7.6$  Hz), 7.14-7.40 (m, 5H), 4.11-4.37 (m, 4H), 3.20-3.40 (m, 6H), 3.05 (s, 3H), 1.25 (t, 6H,  $J=7.3$  Hz).

$[\alpha]_D +68.1^\circ$  (c = 0.228, MeOH)

40    Example 76

(-)-1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-naphthyl)oxindole

(Optical isomer of the compound of Example 56)

45    (1) (+)- and (-)-1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-naphthyl)oxindole

[0191] Racemic compound 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-naphthyl)oxindole of Example 48 was separated to (+)- and (-)-enantiomers by using a preparative HPLC on a Chi ralpak OD™ with 10% isopropanol/hexane as the eluent. The enantiomeric excess was determined by using HPLC on a Chiralpak OD™ (250 x 4.6 mm) with 12% isopropanol/hexane as the eluent at the flow rate of 0.5 ml/min. Under these conditions, (+)- and (-)-enantiomers were eluted at the retention time of 16.0 and 18.7 min, respectively.

(+) Enantiomer:  $[\alpha]_D +4.25^\circ$  (c = 0.574, MeOH)

(-) Enantiomer:  $[\alpha]_D -1.82^\circ$  (c = 0.440, MeOH)

55    (2) Optically active 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-hydroxy-3-(2-naphthyl)oxindole

[0192] The title compound (298 mg, 59%) was prepared from (-)-1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-

3-hydroxy-3-(2-naphthyl)oxindole (619 mg, 1.09 mmol) by the procedure similar to that described in Example 55. The NMR spectra of the title compound exhibited the same as in Example 55.

(3) (-)-1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-naphthyl)oxindole

**[0193]** The title compound (196 mg, 95%) was prepared from above optically active 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-hydroxy-3-(2-naphthyl)oxindole (185 mg, 0.396 mmol) by the procedure similar to that described in Example 56.  
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>; hydrochloride) δ 10.26 (brs, 1H), 8.38 (brs, 1H), 8.21 (brs, 1H), 7.79-7.92 (m, 6H), 7.48-7.53 (m, 2H), 7.20 (d, 1H, J=9.9 Hz), 7.08 (s, 1H), 4.21 (m, 2H), 3.20-3.44 (m, 6H), 1.21 (t, 6H, J=7.1 Hz).  
[α]<sub>D</sub> -12.2° (c = 0.118, MeOH)

Example 77

(+)-1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-[4-(N-hydroxyethylcarbamoyl)-1-butynyl]-3-hydroxy-3-(2-chlorophenyl)oxindole

**[0194]** The title compound (740 mg) was prepared from (+)-1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-chlorophenyl)oxindole of Example 72(1) (102 mg, 0.185 mmol) and N-hydroxyethyl-4-pentynamide by the procedure similar to that described in Reference Example 21. The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.  
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>; hydrochloride) δ 10.30 (brs, 1H), 8.01-8.09 (m, 2H), 7.64 (s, 1H), 7.46 (ddd, 1H, J=1.5, 7.4, 7.4 Hz), 7.14-7.40 (m, 4H), 4.70 (brs, 1H), 4.13-4.31 (m, 2H), 3.10-3.48 (m, 10H), 2.68 (t, 2H, J=7.3 Hz), 2.40 (t, 2H, J=7.3 Hz), 1.24 (t, 6H, J=7.1 Hz).  
[α]<sub>D</sub> +66.2° (c = 0.172, MeOH)

Example 78

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole

(1) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-hydroxy-3-(2-chlorophenyl)oxindole

**[0195]** The title compound (316 mg, 64%) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-chlorophenyl)oxindole (600 mg, 1.09 mmol) by the procedure similar to that described in Example 74(1).  
The NMR spectra of the title compound exhibited the same as in Example 74(1).

(2) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole

**[0196]** The title compound (297 mg, quant.) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-hydroxy-3-(2-chlorophenyl)oxindole (261 mg, 0.578 mmol) by the procedure similar to that described in Example 56. The NMR spectra of the title compound exhibited the same as in Example 74(2).

Example 79

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-ethoxycarbonyl-3-hydroxy-3-(2-naphthyl)oxindole

**[0197]** A mixture of 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-naphthyl)oxindole of Example 48 (300 mg, 0.527 mmol), triethylamine (0.15 mL, 1.08 mmol), and (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub> (40 mg, 0.087 mmol) in a mixed solvent of ethanol (1.5 mL) and toluene (1.5 mL) was stirred for 7 h at 60 °C under CO atmosphere. Sat. aqueous NaHCO<sub>3</sub> was added and the mixture was extracted with ethyl acetate. The extracts were dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography with 50 : 1 chloroform/methanol to give the title compound (273 mg, quant.).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 8.06 (s, 1H), 7.90 (s, 1H), 7.87 (d, 1H, J=2.0 Hz), 7.72-7.81 (m, 3H), 7.44-7.49 (m, 2H), 7.21 (dd, 1H, J=2.0, 8.7 Hz), 4.47 (q, 2H, J=7.1 Hz), 3.78-3.99 (m, 2H), 2.74 (t, 2H, J=6.3 Hz), 2.57 (q, 4H, J=6.9 Hz), 1.45 (t, 3H, J=7.1 Hz), 0.95 (t, 6H, J=6.9 Hz).

## Example 80

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-N,N-dimethylcarbamoyl-3-hydroxy-3-(2-naphthyl)oxindole

**[0198]** To a solution of 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-ethoxycarbonyl-3-hydroxy-3-(2-naphthyl)oxindole (43.4 mg, 0.0843 mmol) in a mixed solvent of methanol (0.2 mL) and THF (0.2 mL) was added 4 N aqueous NaOH (0.13 mL, 0.52 mL) and the mixture was stirred for 2 h at room temperature. The solvent was removed in vacuo and 4 N HCl in dioxane was added. The solvent was evaporated in vacuo again. The residue was dissolved in DMF (1 mL) and dimethylamine hydrochloride (125 mg, 0.153 mmol), 1-hydroxybenzotriazole (220 mg, 0.163 mmol), WSC HCl (309 mg, 0.161 mmol), and triethylamine (0.1 mL, 0.717 mmol). The mixture was stirred for 64 h at room temperature and sat. aqueous NaHCO<sub>3</sub> was added. The mixture was extracted with ethyl acetate-toluene and the extracts were washed with sat. aqueous NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography with 50 : 1 to 20 : 1 chloroform/methanol to give the title compound (206 mg). The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>: hydrochloride) δ 10.37 (brs, 1H), 7.83-7.94 (m, 4H), 7.79 (s, 1H), 7.49-7.52 (m, 2H), 7.41 (s, 1H), 7.20 (dd, 1H, J=2.0, 8.6 Hz), 7.06 (s, 1H), 4.20 (m, 2H), 3.00-3.48 (m, 6H), 3.05 (s, 3H), 3.03 (s, 3H), 1.20 (t, 6H, J=7.1 Hz).

## Example 81

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-N-hydroxyethylcarbamoyl-3-hydroxy-3-(2-naphthyl)oxindole

**[0199]** The title compound (18.7 mg, 26%) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-ethoxycarbonyl-3-hydroxy-3-(2-naphthyl)oxindole (65.9 mg, 0.128 mmol) and 2-ethanolamine by the procedure similar to that described in Example 80.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>: hydrochloride) δ 10.14 (brs, 1H), 8.95 (t, 1H, J=5.3 Hz), 8.21 (s, 1H), 7.79-7.92 (m, 6H), 7.48-7.52 (m, 2H), 7.20 (dd, 1H, J=1.5, 8.4 Hz), 7.10 (s, 1H), 4.18-4.23 (m, 2H), 3.17-3.72 (m, 10H), 1.21 (t, 6H, J=7.3 Hz).

## Example 82

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-hydroxyethyl-3-hydroxy-3-(2-naphthyl)oxindole

**[0200]** To a solution of 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-ethoxycarbonyl-3-hydroxy-3-(2-naphthyl)oxindole (605 mg, 0.118 mmol) in toluene (1 mL) was added dropwise 1.01 N diisobutylaluminium hydride in toluene (0.36 mL, 0.364 mmol). The mixture was allowed to warm to room temperature over 4 h. Sat. aqueous NaHCO<sub>3</sub> and ethyl acetate were added. Insoluble materials were removed by filtration and the organic layer was separated, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography with 30 : 1 to 15 : 1 chloroform/methanol to give the title compound (5 mg, 9%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.89 (s, 1H), 7.72-7.82 (m, 3H), 7.44-7.49 (m, 2H), 7.31 (s, 2H), 7.22 (dd, 1H, J=2.0, 8.6 Hz), 4.82 (s, 2H), 3.79-3.92 (m, 2H), 2.62-2.84 (m, 2H), 2.60 (q, 4H, J=7.1 Hz), 0.97 (t, 6H, J=7.1 Hz).

## Example 83

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-N-methylcarbamoyl-3-hydroxy-3-(2-naphthyl)oxindole

**[0201]** The title compound (10.4 mg, 20%) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-ethoxycarbonyl-3-hydroxy-3-(2-naphthyl)oxindole (50.3 mg, 0.0978 mmol) and methylamine hydrochloride by the procedure similar to that described in Example 80.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>: hydrochloride) δ 10.16 (brs, 1H), 8.94 (br, 1H), 8.19 (s, 1H), 7.79-7.92 (m, 5H), 7.48-7.52 (m, 2H), 7.17-7.25 (m, 1H), 7.10 (s, 1H), 4.18-4.22 (m, 2H), 3.20-3.44 (m, 6H), 2.87 (d, 3H, J=4.3 Hz), 1.21 (t, 6H, J=7.3 Hz).

## Example 84

1-(2-Diethylaminoethyl)-3-hydroxy-3(2-chlorophenyl)-4-bromo-6-carbamoyloxindole

(1) 1-(2-Diethylaminoethyl)-3-hydroxy-3-(2-chlorophenyl)-4-bromo-6-cyanooxindole

**[0202]** To Pd<sub>2</sub>(dba)<sub>3</sub>CHCl<sub>3</sub> (60.1 mg, 5 mol%) and PPh<sub>3</sub> (60.9 mg, 20 mol%) under a nitrogen atmosphere was

added anhydrous DMF (0.5 mL). The resulting precipitate was stirred at room temperature for 30 minutes during which time the colour changed from red to yellow/orange. To this was added 1-(2-diethylaminoethyl)-3-hydroxy-3-(2-chlorophenyl)-4-bromo-6-iodooxindole (626.4 mg, 1.16 mmol) dissolved in anhydrous DMF (1.0 mL). To the resulting red solution was then added Zn(CN)<sub>2</sub>. The resulting precipitate was then heated to 60°C (bath temperature) and stirring was continued at that temperature for 4 hours. The mixture was allowed to cool to room temperature and diluted with EtOAc:toluene (1:1, 10 mL). The mixture was washed with H<sub>2</sub>O (6 mL). The aqueous phase was then extracted with EtOAc:toluene (1:1, 5 mL x 5). The organic phases were combined and dried (anhydrous MgSO<sub>4</sub>). After filtration the solvent was removed in vacuo. The orange solid obtained was then purified by flash chromatography (silica gel, eluting 1% to 2% to 3% MeOH in CHCl<sub>3</sub>) to give the title compound as a light brown/orange solid (462.6 mg, 91%).

<sup>5</sup> <sup>10</sup> <sup>15</sup>

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 270 MHz) δ 1.030 (6H, t, J=7.3 Hz), 2.666 (5H, m), 2.763 (1H, m), 3.679 (1H, ddd, J=11.6, 5.9 and 5.9 Hz), 4.109 (1H, ddd, J=14.8, 5.9 and 5.9 Hz), 7.140 (1H, d, J=1.3 Hz), 7.272-7.360 (2H, m), 7.410 (1H, d, J=1.0 Hz), 7.423 (1H, m), 8.197 (1H, dd, J=7.9 and 1.6 Hz).

(2) 1-(2-Diethylaminoethyl)-3-hydroxy-3(2-chlorophenyl)-4-bromo-6-carbamoyloxindole

<sup>20</sup> <sup>25</sup> <sup>30</sup>

**[0203]** To 1-(2-diethylaminoethyl)-3-hydroxy-3-(2-chlorophenyl)-4-bromo-6-cyanooxindole (462.6 mg, 1.06 mmol) dissolved in anhydrous t-BuOH (30 mL) at 50 °C was added powdered KOH (1.2 g, 20 eq). The resulting solution was stirred for 1 hour and then cooled to room temperature. Ice was added and the mixture extracted with EtOAc (3 x 20 mL). The extracts were combined and dried (anhydrous MgSO<sub>4</sub>). After filtration, the solvent was removed in vacuo to give a light brown solid. Purification was carried out by column chromatography (silica gel, eluting EtOAc:EtOH:Et<sub>3</sub>N, 80:20:2) to yield the title compound as a white solid (346.5 mg, 69%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 270 MHz) δ 1.025 (6H, t, J=7.3 Hz), 2.619 (2H, q, J=6.9 Hz), 2.638 (2H, q, J=7.3 Hz), 2.725 (1H, m), 2.816 (1H, m), 3.836 (1H, m), 3.958 (1H, m), 5.828 (1H, brs), 6.486 (1H, brs), 7.201-7.344 (2H, m), 7.412 (1H, ddd, J=7.6, 1.3 and 1.3 Hz), 7.508 (2H, m), 8.236 (1H, dd, J=7.9 and 1.3 Hz).

Example 85

1-(2-Diethylaminoethyl)-3-hydroxy-3-(2-chlorophenyl)-4-bromo-6-[3-(N-ethylureido)-1-propynyl]oxindole

<sup>35</sup> <sup>40</sup> <sup>45</sup>

**[0204]** To 1-(2-diethylaminoethyl)-3-hydroxy-3-(2-chlorophenyl)-4-bromo-6-iodooxindole (21.0 mg, 3.89 x 10<sup>-5</sup>mol), N-ethyl-N'-propargylurea (7.36 mg, 1.5 eq.), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (4.10 mg, 15 mol%) and Cul (1.10 mg, 15 mol%) under a nitrogen atmosphere was added anhydrous Et<sub>3</sub>N (0.5 mL), anhydrous toluene (0.5 mL) and anhydrous THF (0.5 mL). The resulting yellow mixture was heated to 50°C (bath temperature) and stirred at that temperature for 2 hours. The solvent was then removed in vacuo to give a yellow solid. Purification was carried out by column chromatography (silica gel, 10% MeOH in CHCl<sub>3</sub>) to yield the title compound (18.8 mg, 86%) as a light brown solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.958 (6H, t, J=7.25 Hz), 0.993 (3H, t, J=7.3 Hz), 2.486-2.637 (3H, m), 3.014 (3H, m), 3.757 (1H, brt, J=6.6 Hz), 3.877 (0.67H, brd, J=5.6 Hz), 4.062 (1.33H, brd, J=5.9 Hz), 5.991 (1H, brt, J=5.6 Hz), 6.247 (1H, brt, J=5.6 Hz), 7.096 (1H, d, J=1.3 Hz), 7.128 (1H, d, J=1.3 Hz), 7.310 (1H, td, J=7.9 and 1.65 Hz), 7.359 (1H, td, J=7.9 and 1.65 Hz), 7.449 (1H, td, J=7.3 and 1.65 Hz), 8.126 (1H, dd, J=7.9 and 1.65 Hz).

Example 86

1-(2-Diethylaminoethyl)-4-bromo-6-[3-(2-oxo-1-imidazolidinyl)-1-propynyl]-3-hydroxy-3-(2-chlorophenyl)oxindole

<sup>50</sup> <sup>55</sup>

**[0205]** To 1-(2-diethylaminoethyl)-3-hydroxy-3-(2-chlorophenyl)-4-bromo-6-iodooxindole (25.0 mg, 4.64 x 10<sup>-5</sup>mol), 3-(2-oxo-1-imidazolidinyl)-1-propyne (8.6 mg, 1.5 eq.), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (4.88 mg, 15 mol%) and Cul (1.32 mg, 15 mol%) under a nitrogen atmosphere was added anhydrous Et<sub>3</sub>N (0.5 mL), anhydrous toluene (0.5 mL) and anhydrous THF (0.5 mL). The resulting yellow mixture was heated to 50°C (bath temperature) and stirred at that temperature for 1 hour 20 minutes. The solvent was then removed in vacuo to give a yellow solid. Purification was carried out by column chromatography (silica gel, 6% MeOH in CHCl<sub>3</sub>) to yield the title compound (23.9 mg, 92%) as a light brown solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 270 MHz) δ 1.183 (6H, t, J=7.3 Hz), 2.920 (5H, m), 3.122 (1H, m), 3.481 (3H, m), 3.602 (2H, m), 4.043 (1H, m), 4.194 (2H, s), 4.703 (1H, brs), 7.111-7.432 (5H, m), 8.226 (1H, dd, J=7.43 and 1.65 Hz).

Example 87

1-(2-Diethylaminoethyl)-4-bromo-6-[3-(2-oxo-1,3-oxazolin-3-yl)-1-propynyl]-3-hydroxy-3-(2-chlorophenyl)oxindole

**[0206]** To 1-(2-diethylaminoethyl)-3-hydroxy-3-(2-chlorophenyl)-4-bromo-6-iodooxindole (31.5 mg, 5.84 x 10<sup>-5</sup>mol),

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3-(2-Oxo-1,3-oxazolin-3-yl)-1-propyne (10.95 mg, 1.5 eq.), Pd( $\text{PPh}_3$ )<sub>2</sub>Cl<sub>2</sub> (6.15 mg, 15 mol%) and Cul (1.7 mg, 15 mol%) under a nitrogen atmosphere was added anhydrous Et<sub>3</sub>N (0.5 mL), anhydrous toluene (0.5 mL) and anhydrous THF (0.5 mL). The resulting yellow mixture was heated to 50°C (bath temperature) and stirred at that temperature for 1 hour and 20 minutes. The solvent was then removed in vacuo to give a yellow solid. Purification was carried out by column chromatography (silica gel, 3% MeOH in CHCl<sub>3</sub>) to yield the title compound (24.9 mg, 76%) as a white solid. The hydrochloride of the title compound was obtained by treating with 4 N HCl in dioxane followed by concentration to dryness.

<sup>5</sup> <sup>10</sup> <sup>15</sup> <sup>20</sup> <sup>25</sup> <sup>30</sup> <sup>35</sup> <sup>40</sup> <sup>45</sup> <sup>50</sup> <sup>55</sup> <sup>60</sup> <sup>65</sup> <sup>70</sup> <sup>75</sup> <sup>80</sup> <sup>85</sup> <sup>90</sup> <sup>95</sup> <sup>100</sup> <sup>105</sup> <sup>110</sup> <sup>115</sup> <sup>120</sup> <sup>125</sup> <sup>130</sup> <sup>135</sup> <sup>140</sup> <sup>145</sup> <sup>150</sup> <sup>155</sup> <sup>160</sup> <sup>165</sup> <sup>170</sup> <sup>175</sup> <sup>180</sup> <sup>185</sup> <sup>190</sup> <sup>195</sup> <sup>200</sup> <sup>205</sup> <sup>210</sup> <sup>215</sup> <sup>220</sup> <sup>225</sup> <sup>230</sup> <sup>235</sup> <sup>240</sup> <sup>245</sup> <sup>250</sup> <sup>255</sup> <sup>260</sup> <sup>265</sup> <sup>270</sup> <sup>275</sup> <sup>280</sup> <sup>285</sup> <sup>290</sup> <sup>295</sup> <sup>300</sup> <sup>305</sup> <sup>310</sup> <sup>315</sup> <sup>320</sup> <sup>325</sup> <sup>330</sup> <sup>335</sup> <sup>340</sup> <sup>345</sup> <sup>350</sup> <sup>355</sup> <sup>360</sup> <sup>365</sup> <sup>370</sup> <sup>375</sup> <sup>380</sup> <sup>385</sup> <sup>390</sup> <sup>395</sup> <sup>400</sup> <sup>405</sup> <sup>410</sup> <sup>415</sup> <sup>420</sup> <sup>425</sup> <sup>430</sup> <sup>435</sup> <sup>440</sup> <sup>445</sup> <sup>450</sup> <sup>455</sup> <sup>460</sup> <sup>465</sup> <sup>470</sup> <sup>475</sup> <sup>480</sup> <sup>485</sup> <sup>490</sup> <sup>495</sup> <sup>500</sup> <sup>505</sup> <sup>510</sup> <sup>515</sup> <sup>520</sup> <sup>525</sup> <sup>530</sup> <sup>535</sup> <sup>540</sup> <sup>545</sup> <sup>550</sup> <sup>555</sup> <sup>560</sup> <sup>565</sup> <sup>570</sup> <sup>575</sup> <sup>580</sup> <sup>585</sup> <sup>590</sup> <sup>595</sup> <sup>600</sup> <sup>605</sup> <sup>610</sup> <sup>615</sup> <sup>620</sup> <sup>625</sup> <sup>630</sup> <sup>635</sup> <sup>640</sup> <sup>645</sup> <sup>650</sup> <sup>655</sup> <sup>660</sup> <sup>665</sup> <sup>670</sup> <sup>675</sup> <sup>680</sup> <sup>685</sup> <sup>690</sup> <sup>695</sup> <sup>700</sup> <sup>705</sup> <sup>710</sup> <sup>715</sup> <sup>720</sup> <sup>725</sup> <sup>730</sup> <sup>735</sup> <sup>740</sup> <sup>745</sup> <sup>750</sup> <sup>755</sup> <sup>760</sup> <sup>765</sup> <sup>770</sup> <sup>775</sup> <sup>780</sup> <sup>785</sup> <sup>790</sup> <sup>795</sup> <sup>800</sup> <sup>805</sup> <sup>810</sup> <sup>815</sup> <sup>820</sup> <sup>825</sup> <sup>830</sup> <sup>835</sup> <sup>840</sup> <sup>845</sup> <sup>850</sup> <sup>855</sup> <sup>860</sup> <sup>865</sup> <sup>870</sup> <sup>875</sup> <sup>880</sup> <sup>885</sup> <sup>890</sup> <sup>895</sup> <sup>900</sup> <sup>905</sup> <sup>910</sup> <sup>915</sup> <sup>920</sup> <sup>925</sup> <sup>930</sup> <sup>935</sup> <sup>940</sup> <sup>945</sup> <sup>950</sup> <sup>955</sup> <sup>960</sup> <sup>965</sup> <sup>970</sup> <sup>975</sup> <sup>980</sup> <sup>985</sup> <sup>990</sup> <sup>995</sup> <sup>1000</sup> <sup>1005</sup> <sup>1010</sup> <sup>1015</sup> <sup>1020</sup> <sup>1025</sup> <sup>1030</sup> <sup>1035</sup> <sup>1040</sup> <sup>1045</sup> <sup>1050</sup> <sup>1055</sup> <sup>1060</sup> <sup>1065</sup> <sup>1070</sup> <sup>1075</sup> <sup>1080</sup> <sup>1085</sup> <sup>1090</sup> <sup>1095</sup> <sup>1100</sup> <sup>1105</sup> <sup>1110</sup> <sup>1115</sup> <sup>1120</sup> <sup>1125</sup> <sup>1130</sup> <sup>1135</sup> <sup>1140</sup> <sup>1145</sup> <sup>1150</sup> <sup>1155</sup> <sup>1160</sup> <sup>1165</sup> <sup>1170</sup> <sup>1175</sup> <sup>1180</sup> <sup>1185</sup> <sup>1190</sup> <sup>1195</sup> <sup>1200</sup> <sup>1205</sup> <sup>1210</sup> <sup>1215</sup> <sup>1220</sup> <sup>1225</sup> <sup>1230</sup> <sup>1235</sup> <sup>1240</sup> <sup>1245</sup> <sup>1250</sup> <sup>1255</sup> <sup>1260</sup> <sup>1265</sup> <sup>1270</sup> <sup>1275</sup> <sup>1280</sup> <sup>1285</sup> <sup>1290</sup> <sup>1295</sup> <sup>1300</sup> <sup>1305</sup> <sup>1310</sup> <sup>1315</sup> <sup>1320</sup> <sup>1325</sup> <sup>1330</sup> <sup>1335</sup> <sup>1340</sup> <sup>1345</sup> <sup>1350</sup> <sup>1355</sup> <sup>1360</sup> <sup>1365</sup> <sup>1370</sup> <sup>1375</sup> <sup>1380</sup> <sup>1385</sup> <sup>1390</sup> <sup>1395</sup> <sup>1400</sup> <sup>1405</sup> <sup>1410</sup> <sup>1415</sup> <sup>1420</sup> <sup>1425</sup> <sup>1430</sup> <sup>1435</sup> <sup>1440</sup> <sup>1445</sup> <sup>1450</sup> <sup>1455</sup> <sup>1460</sup> <sup>1465</sup> <sup>1470</sup> <sup>1475</sup> <sup>1480</sup> <sup>1485</sup> <sup>1490</sup> <sup>1495</sup> <sup>1500</sup> <sup>1505</sup> <sup>1510</sup> <sup>1515</sup> <sup>1520</sup> <sup>1525</sup> <sup>1530</sup> <sup>1535</sup> <sup>1540</sup> <sup>1545</sup> <sup>1550</sup> <sup>1555</sup> <sup>1560</sup> <sup>1565</sup> <sup>1570</sup> <sup>1575</sup> <sup>1580</sup> <sup>1585</sup> <sup>1590</sup> <sup>1595</sup> <sup>1600</sup> <sup>1605</sup> <sup>1610</sup> <sup>1615</sup> <sup>1620</sup> <sup>1625</sup> <sup>1630</sup> <sup>1635</sup> <sup>1640</sup> <sup>1645</sup> <sup>1650</sup> <sup>1655</sup> <sup>1660</sup> <sup>1665</sup> <sup>1670</sup> <sup>1675</sup> <sup>1680</sup> <sup>1685</sup> <sup>1690</sup> <sup>1695</sup> <sup>1700</sup> <sup>1705</sup> <sup>1710</sup> <sup>1715</sup> <sup>1720</sup> <sup>1725</sup> <sup>1730</sup> <sup>1735</sup> <sup>1740</sup> <sup>1745</sup> <sup>1750</sup> <sup>1755</sup> <sup>1760</sup> <sup>1765</sup> <sup>1770</sup> <sup>1775</sup> <sup>1780</sup> <sup>1785</sup> <sup>1790</sup> <sup>1795</sup> <sup>1800</sup> <sup>1805</sup> <sup>1810</sup> <sup>1815</sup> <sup>1820</sup> <sup>1825</sup> <sup>1830</sup> <sup>1835</sup> <sup>1840</sup> <sup>1845</sup> <sup>1850</sup> <sup>1855</sup> <sup>1860</sup> <sup>1865</sup> <sup>1870</sup> <sup>1875</sup> <sup>1880</sup> <sup>1885</sup> <sup>1890</sup> <sup>1895</sup> <sup>1900</sup> <sup>1905</sup> <sup>1910</sup> <sup>1915</sup> <sup>1920</sup> <sup>1925</sup> <sup>1930</sup> <sup>1935</sup> <sup>1940</sup> <sup>1945</sup> <sup>1950</sup> <sup>1955</sup> <sup>1960</sup> <sup>1965</sup> <sup>1970</sup> <sup>1975</sup> <sup>1980</sup> <sup>1985</sup> <sup>1990</sup> <sup>1995</sup> <sup>2000</sup> <sup>2005</sup> <sup>2010</sup> <sup>2015</sup> <sup>2020</sup> <sup>2025</sup> <sup>2030</sup> <sup>2035</sup> <sup>2040</sup> <sup>2045</sup> <sup>2050</sup> <sup>2055</sup> <sup>2060</sup> <sup>2065</sup> <sup>2070</sup> <sup>2075</sup> <sup>2080</sup> <sup>2085</sup> <sup>2090</sup> <sup>2095</sup> <sup>2100</sup> <sup>2105</sup> <sup>2110</sup> <sup>2115</sup> <sup>2120</sup> <sup>2125</sup> <sup>2130</sup> <sup>2135</sup> <sup>2140</sup> <sup>2145</sup> <sup>2150</sup> <sup>2155</sup> <sup>2160</sup> <sup>2165</sup> <sup>2170</sup> <sup>2175</sup> <sup>2180</sup> <sup>2185</sup> <sup>2190</sup> <sup>2195</sup> <sup>2200</sup> <sup>2205</sup> <sup>2210</sup> <sup>2215</sup> <sup>2220</sup> <sup>2225</sup> <sup>2230</sup> <sup>2235</sup> <sup>2240</sup> <sup>2245</sup> <sup>2250</sup> <sup>2255</sup> <sup>2260</sup> <sup>2265</sup> <sup>2270</sup> <sup>2275</sup> <sup>2280</sup> <sup>2285</sup> <sup>2290</sup> <sup>2295</sup> <sup>2300</sup> <sup>2305</sup> <sup>2310</sup> <sup>2315</sup> <sup>2320</sup> <sup>2325</sup> <sup>2330</sup> <sup>2335</sup> <sup>2340</sup> <sup>2345</sup> <sup>2350</sup> <sup>2355</sup> <sup>2360</sup> <sup>2365</sup> <sup>2370</sup> <sup>2375</sup> <sup>2380</sup> <sup>2385</sup> <sup>2390</sup> <sup>2395</sup> <sup>2400</sup> <sup>2405</sup> <sup>2410</sup> <sup>2415</sup> <sup>2420</sup> <sup>2425</sup> <sup>2430</sup> <sup>2435</sup> <sup>2440</sup> <sup>2445</sup> <sup>2450</sup> <sup>2455</sup> <sup>2460</sup> <sup>2465</sup> <sup>2470</sup> <sup>2475</sup> <sup>2480</sup> <sup>2485</sup> <sup>2490</sup> <sup>2495</sup> <sup>2500</sup> <sup>2505</sup> <sup>2510</sup> <sup>2515</sup> <sup>2520</sup> <sup>2525</sup> <sup>2530</sup> <sup>2535</sup> <sup>2540</sup> <sup>2545</sup> <sup>2550</sup> <sup>2555</sup> <sup>2560</sup> <sup>2565</sup> <sup>2570</sup> <sup>2575</sup> <sup>2580</sup> <sup>2585</sup> <sup>2590</sup> <sup>2595</sup> <sup>2600</sup> <sup>2605</sup> <sup>2610</sup> <sup>2615</sup> <sup>2620</sup> <sup>2625</sup> <sup>2630</sup> <sup>2635</sup> <sup>2640</sup> <sup>2645</sup> <sup>2650</sup> <sup>2655</sup> <sup>2660</sup> <sup>2665</sup> <sup>2670</sup> <sup>2675</sup> <sup>2680</sup> <sup>2685</sup> <sup>2690</sup> <sup>2695</sup> <sup>2700</sup> <sup>2705</sup> <sup>2710</sup> <sup>2715</sup> <sup>2720</sup> <sup>2725</sup> <sup>2730</sup> <sup>2735</sup> <sup>2740</sup> <sup>2745</sup> <sup>2750</sup> <sup>2755</sup> <sup>2760</sup> <sup>2765</sup> <sup>2770</sup> <sup>2775</sup> <sup>2780</sup> <sup>2785</sup> <sup>2790</sup> <sup>2795</sup> <sup>2800</sup> <sup>2805</sup> <sup>2810</sup> <sup>2815</sup> <sup>2820</sup> <sup>2825</sup> <sup>2830</sup> <sup>2835</sup> <sup>2840</sup> <sup>2845</sup> <sup>2850</sup> <sup>2855</sup> <sup>2860</sup> <sup>2865</sup> <sup>2870</sup> <sup>2875</sup> <sup>2880</sup> <sup>2885</sup> <sup>2890</sup> <sup>2895</sup> <sup>2900</sup> <sup>2905</sup> <sup>2910</sup> <sup>2915</sup> <sup>2920</sup> <sup>2925</sup> <sup>2930</sup> <sup>2935</sup> <sup>2940</sup> <sup>2945</sup> <sup>2950</sup> <sup>2955</sup> <sup>2960</sup> <sup>2965</sup> <sup>2970</sup> <sup>2975</sup> <sup>2980</sup> <sup>2985</sup> <sup>2990</sup> <sup>2995</sup> <sup>3000</sup> <sup>3005</sup> <sup>3010</sup> <sup>3015</sup> <sup>3020</sup> <sup>3025</sup> <sup>3030</sup> <sup>3035</sup> <sup>3040</sup> <sup>3045</sup> <sup>3050</sup> <sup>3055</sup> <sup>3060</sup> <sup>3065</sup> <sup>3070</sup> <sup>3075</sup> <sup>3080</sup> <sup>3085</sup> <sup>3090</sup> <sup>3095</sup> <sup>3100</sup> <sup>3105</sup> <sup>3110</sup> <sup>3115</sup> <sup>3120</sup> <sup>3125</sup> <sup>3130</sup> <sup>3135</sup> <sup>3140</sup> <sup>3145</sup> <sup>3150</sup> <sup>3155</sup> <sup>3160</sup> <sup>3165</sup> <sup>3170</sup> 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<sup>3795</sup> <sup>3800</sup> <sup>3805</sup> <sup>3810</sup> <sup>3815</sup> <sup>3820</sup> <sup>3825</sup> <sup>3830</sup> <sup>3835</sup> <sup>3840</sup> <sup>3845</sup> <sup>3850</sup> <sup>3855</sup> <sup>3860</sup> <sup>3865</sup> <sup>3870</sup> <sup>3875</sup> <sup>3880</sup> <sup>3885</sup> <sup>3890</sup> <sup>3895</sup> <sup>3900</sup> <sup>3905</sup> <sup>3910</sup> <sup>3915</sup> <sup>3920</sup> <sup>3925</sup> <sup>3930</sup> <sup>3935</sup> <sup>3940</sup> <sup>3945</sup> <sup>3950</sup> <sup>3955</sup> <sup>3960</sup> <sup>3965</sup> <sup>3970</sup> <sup>3975</sup> <sup>3980</sup> <sup>3985</sup> <sup>3990</sup> <sup>3995</sup> <sup>4000</sup> <sup>4005</sup> <sup>4010</sup> <sup>4015</sup> <sup>4020</sup> <sup>4025</sup> <sup>4030</sup> <sup>4035</sup> <sup>4040</sup> <sup>4045</sup> <sup>4050</sup> <sup>4055</sup> <sup>4060</sup> <sup>4065</sup> <sup>4070</sup> <sup>4075</sup> <sup>4080</sup> <sup>4085</sup> <sup>4090</sup> <sup>4095</sup> <sup>4100</sup> 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<sup>4415</sup> <sup>4420</sup> <sup>4425</sup> <sup>4430</sup> <sup>4435</sup> <sup>4440</sup> <sup>4445</sup> <sup>4450</sup> <sup>4455</sup> <sup>4460</sup> <sup>4465</sup> <sup>4470</sup> <sup>4475</sup> <sup>4480</sup> <sup>4485</sup> <sup>4490</sup> <sup>4495</sup> <sup>4500</sup> <sup>4505</sup> <sup>4510</sup> <sup>4515</sup> <sup>4520</sup> <sup>4525</sup> <sup>4530</sup> <sup>4535</sup> <sup>4540</sup> <sup>4545</sup> <sup>4550</sup> <sup>4555</sup> <sup>4560</sup> <sup>4565</sup> <sup>4570</sup> <sup>4575</sup> <sup>4580</sup> <sup>4585</sup> <sup>4590</sup> <sup>4595</sup> <sup>4600</sup> <sup>4605</sup> <sup>4610</sup> <sup>4615</sup> <sup>4620</sup> <sup>4625</sup> <sup>4630</sup> <sup>4635</sup> <sup>4640</sup> <sup>4645</sup> <sup>4650</sup> <sup>4655</sup> <sup>4660</sup> <sup>4665</sup> <sup>4670</sup> <sup>4675</sup> <sup>4680</sup> <sup>4685</sup> <sup>4690</sup> <sup>4695</sup> <sup>4700</sup> <sup>4705</sup> <sup>4710</sup> <sup>4715</sup> <sup>4720</sup> 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<sup>5035</sup> <sup>5040</sup> <sup>5045</sup> <sup>5050</sup> <sup>5055</sup> <sup>5060</sup> <sup>5065</sup> <sup>5070</sup> <sup>5075</sup> <sup>5080</sup> <sup>5085</sup> <sup>5090</sup> <sup>5095</sup> <sup>5100</sup> <sup>5105</sup> <sup>5110</sup> <sup>5115</sup> <sup>5120</sup> <sup>5125</sup> <sup>5130</sup> <sup>5135</sup> <sup>5140</sup> <sup>5145</sup> <sup>5150</sup> <sup>5155</sup> <sup>5160</sup> <sup>5165</sup> <sup>5170</sup> <sup>5175</sup> <sup>5180</sup> <sup>5185</sup> <sup>5190</sup> <sup>5195</sup> <sup>5200</sup> <sup>5205</sup> <sup>5210</sup> <sup>5215</sup> <sup>5220</sup> <sup>5225</sup> <sup>5230</sup> <sup>5235</sup> <sup>5240</sup> <sup>5245</sup> <sup>5250</sup> <sup>5255</sup> <sup>5260</sup> <sup>5265</sup> <sup>5270</sup> <sup>5275</sup> <sup>5280</sup> <sup>5285</sup> <sup>5290</sup> <sup>5295</sup> <sup>5300</sup> <sup>5305</sup> <sup>5310</sup> <sup>5315</sup> <sup>5320</sup> <sup>5325</sup> <sup>5330</sup> <sup>5335</sup> <sup>5340</sup> <sup>5345</sup> <sup>5350</sup> <sup>5355</sup> <sup>5360</sup> <sup>5365</sup> <sup>5370</sup> <sup>5375</sup> <sup>5380</sup> <sup>5385</sup> <sup>5390</sup> <sup>5395</sup> <sup>5400</sup> <sup>5405</sup> <sup>5410</sup> <sup>5415</sup> <sup>5420</sup> <sup>5425</sup> <sup>5430</sup> <sup>5435</sup> <sup>5440</sup> <sup>5445</sup> <sup>5450</sup> <sup>5455</sup> <sup>5460</sup> <sup>5465</sup> <sup>5470</sup> <sup>5475</sup> <sup>5480</sup> <sup>5485</sup> <sup>5490</sup> <sup>5495</sup> <sup>5500</sup> <sup>5505</sup> <sup>5510</sup> <sup>5515</sup> <sup>552</sup>

mmol), and  $(PPh_3)_2PdCl_2$  (22.6 mg, 0.0322 mmol) in a mixed solvent of THF (0..5 mL) and toluene (0.5 mL) was stirred for 3 h at 50 °C. Water and sat. aqueous  $NaHCO_3$  were added and the mixture was extracted with ethyl acetate. The extracts were dried over  $MgSO_4$  and concentrated. The residue was purified by silica gel column chromatography with 30 : 1 to 20 : 1 chloroform/methanol to give the title compound (625 mg). The compound was dissolved in dioxane (4 mL) and 4 N HCl in dioxane (1.5 mL) was added. The solvent was evaporated azeotropically with toluene. The residual solid was washed with ether and dried in vacuo to give the hydrochloride (583 mg, 77%).

$^1H$ -NMR (DMSO-d<sub>6</sub>: hydrochloride) δ 10.30 (brs, 1H), 8.06 (d, 1H, J=7.3 Hz), 7.71 (s, 1H), 7.16-7.49 (m, 5H), 6.63 (s, 1H), 4.12-4.33 (m, 4H), 3.26-3.50 (m, 10H), 1.24 (t, 6H, J=7.1 Hz).

10 Example 90

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-[3-(2-oxo-1,3-oxazolin-3-yl)-1-propynyl]-3-hydroxy-3-(2-chlorophenyl)oxindole

15 (1) 3-(2-Oxo-1,3-oxazolin-3-yl)-1-propyne

[0211] To a suspension of 2-oxazoline (1.0 g, 11.5 mmol) in THF (40 mL) was added 60% NaH (460 mg, 11.5 mmol) and 3-bromopropyne (1..0 mL, 11.2 mmol). The mixture was stirred for 1 h at 50 °C then for 3 h at 60 °C, poured into aqueous 5%  $KHSO_4$ , and extracted with ethyl acetate. The Organic layers were dried over  $MgSO_4$  and concentrated.

20 The residue was purified by silica gel column chromatography with 1 : 1 hexane/ethyl acetate to give the title compound (1.02 g, 71%).

$^1H$ -NMR (CDCl<sub>3</sub>) δ 4.37 (dd, 2H, J=7.1, 8.7 Hz), 4.10 (d, 2H, J=2.4 Hz), 3.67 (dd, 2H, J=7.1, 8.7 Hz), 2.31 (t, 1H, J=2.4 Hz).

25 (2) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-[3-(2-oxo-1,3-oxazolin-3-yl)-1-propynyl]-3-hydroxy-3-(2-chlorophenyl)oxindole

[0212] A mixture of 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-chlorophenyl)oxindole (796 mg, 0.144 mmol), 3-(2-oxo-1,3-oxazolin-3-yl)-1-propyne (464 mg, 0.371 mmol), Cul (10.8 mg, 0.0567 mmol), and  $(PPh_3)_2PdCl_2$  (18.6 mg, 0.0265 mmol) in triethylamine (1 mL) was stirred for 4.5 h at 50 °C. Water and sat. aqueous  $NaHCO_3$  were added and the mixture was extracted with ethyl acetate. The extracts were dried over  $MgSO_4$  and concentrated. The residue was purified by silica gel column chromatography with 80 : 1 to 50 : 1 chloroform/methanol to give the title compound (738 mg). The compound was dissolved in dioxane (2 mL) and 4 N HCl in dioxane (1 mL) was added. The solvent was evaporated azeotropically with toluene. The residual solid was washed with ether and dried in vacuo to give the hydrochloride (528 mg, 63%).

$^1H$ -NMR (DMSO-d<sub>3</sub>: hydrochloride) δ 10.48 (brs, 1H), 8.06 (d, 1H, J=7.9 Hz), 7.78 (s, 1H), 7.28-7.49 (m, 5H), 4.07-4.38 (m, 6H), 3.71 (dd, 2H, J=8.1, 8.1 Hz), 3.26-3.44 (m, 6H), 1.25 (t, 6H, J=7.1 Hz).

Example 91

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2,4-dichlorophenyl)oxindole

(1) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2,4-dichlorophenyl)oxindole

[0213] To a solution of 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodoisatin (150 mg, 0.341 mmol) in a mixed solvent of diethyl ether (2 mL) and toluene (1 mL) was added dropwise a freshly prepared 0.794 N 2,4-dichlorophenyl magnesium iodide in ether (0.45 mL, 0.387 mmol) at room temperature. The mixture was stirred for 1 h at the same temperature and the reaction was quenched with aqueous  $NaHCO_3$ . The mixture was extracted with ethyl acetate and the extracts were dried over  $MgSO_4$  and concentrated. The residue was purified by silica gel column chromatography with 80 : 1 to 50 : 1 chloroform/methanol to give the title compound (111 mg, 55%).

$^1H$ -NMR (CDCl<sub>3</sub>) δ 8.03 (d, 1H, J=8.4 Hz), 7.61 (s, 1H), 7.54 (s, 1H), 7.39 (dd, 1H, J=2.0, 8.4 Hz), 7.26 (d, 1H, J=2.0 Hz), 3.98-4.08 (m, 1H), 3.68-3.80 (m, 1H), 2.51-2.79 (m, 6H), 1.02 (t, 6H, J=7.3 Hz).

(2) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-hydroxy-3-(2,4-dichlorophenyl)oxindole

[0214] The title compound (412 mg, 64%) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-ido-3-hydroxy-3-(2,4-dichlorophenyl)oxindole (782 mg, 0.138 mmol) by the procedure similar to that described in Example 55.  $^1H$ -NMR (CDCl<sub>3</sub>) δ 8.04 (d, 1H, J=8.6 Hz), 7.58 (d, 1H, J=0.7 Hz), 7.42 (d, 1H, J=0.7 Hz), 7.41 (dd, 1H, J=1.8, 8.6 Hz),

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7.26 (d, 1H, J=1.8 Hz), 4.06-4.17 (m, 1H), 3.68-3.78 (m, 1H), 2.53-2.86 (m, 6H), 1.00 (t, 6H, J=7.1 Hz).

(3) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2,4-dichlorophenyl)oxindole

5 [0215] To a solution of 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-hydroxy-3-(2,4-dichlorophenyl)oxindole (315 mg, 0.648 mmol) in t-butanol (5 mL) was added powdered KOH (ca. 300 mg) at 50 °C. The mixture was stirred for 30 min at the same temperature and passed through a celite pad. The celite was washed with THF and the filtrate was concentrated. The residue was dispersed between water and ethyl acetate and the organic layer was separated. The organic layer was dried over MgSO<sub>4</sub> and concentrated to give the title compound (248 mg, 66%). The compound was dissolved in dioxane (2.5 mL) and 4 N HCl in dioxane (0.5 mL) was added. The solvent was evaporated azeotropically with toluene to dryness to give the hydrochloride (331 mg, 94%).  
1H-NMR (DMSO-d<sub>6</sub>: hydrochloride) δ 10.37 (brs, 1H), 8.35 (brs, 1H), 8.15 (s, 1H), 8.08 (d, 1H, J=8.9 Hz), 7.85 (s, 1H), 7.80 (brs, 1H), 7.50-7.61 (m, 3H), 4.13-4.39 (m, 2H), 3.16-3.47 (m, 6H), 1.26 (t, 6H, J=7.3 Hz).

15 Example 92

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2,4-difluorophenyl)oxindole

(1) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2,4-difluorophenyl)oxindole

20 [0216] To a solution of 1-bromo-2,4-difluorobenzene (0.13 mL, 1.15 mmol) in THF (7.5 mL) was added dropwise 1.47 N BuLi in hexane (0.77 mL, 1.13 mmol) at -78 °C and the mixture was stirred for 15 min. To the resulting solution was added dropwise a solution of 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodoisatin (500 mg, 1.14 mmol) in THF (6 mL) over 15 min at -78 °C. The mixture was stirred for 40 min at the same temperature and the reaction was quenched with aqueous NaHCO<sub>3</sub>. The mixture was extracted with ethyl acetate and the extracts were dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography with 80 : 1 to 50 : 1 chloroform/methanol to give the title compound (576 mg, 91%).  
1H-NMR (CDCl<sub>3</sub>) δ 7.63 (s, 1H), 7.58 (s, 1H), 7.46-7.54 (m, 1H), 7.25-7.33 (m, 1H), 6.83-6.90 (m, 2H), 3.78-3.88 (m, 2H), 2.71 (t, 2H, J=6.4 Hz), 2.59 (q, 4H, J=7.1 Hz), 1.02 (dt, 6H, J=2.1, 7.1 Hz).

30 (2) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-hydroxy-3-(2,4-difluorophenyl)oxindole

[0217] The title compound (278 mg, 85%) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2,4-difluorophenyl)oxindole (400 mg, 0.722 mmol) by the procedure similar to that described in Example 91(2).  
1H-NMR (CDCl<sub>3</sub>) δ 7.51-7.60 (m, 2H), 7.49 (s, 1H), 7.26-7.36 (m, 1H), 6.82-6.93 (m, 2H), 3.77-3.94 (m, 2H), 2.72 (dt, 2H, J=2.4, 6.3 Hz), 2.58 (q, 4H, J=7.1 Hz), 0.99 (dt, 6H, J=2.2, 7.1 Hz).

(3) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2,4-difluorophenyl)oxindole

40 [0218] The title compound (234 mg, 88%) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-hydroxy-3-(2,4-difluorophenyl)oxindole (238 mg, 0.525 mmol) by the procedure similar to that described in Example 91.

1H-NMR (DMSO-d<sub>6</sub>: hydrochloride) δ 10.36 (brs, 1H), 8.34 (s, 1H), 8.15 (s, 1H), 7.73-7.87 (m, 2H), 6.99-7.47 (m, 4H), 4.19-4.35 (m, 2H), 3.21-3.40 (m, 6H), 1.25 (t, 6H, J=7.1 Hz).

45 Example 93

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-[3-(N-ethylureido)-1-propynyl]-3-hydroxy-3-(2-chlorophenyl)oxindole

50 [0219] The title compound (206 mg, 48%) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-chlorophenyl)oxindole (408 mg, 0.738 mmol) by the procedure similar to that described in Example 73. The NMR spectra of the title compound exhibited the same as in Example 73.

## Example 94

1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2,5-dichlorophenyl)oxindole

- 5 (1) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2,5-dichlorophenyl)oxindole

**[0220]** The title compound (137 mg, 51%) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodoisatin (200 mg, 0.454mmol) and 2,5-dichlorobromobenzene by the procedure similar to that described in Example 92(1).  
 10  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.08 (brs, 1H), 7.61 (s, 1H), 7.55 (s, 1H), 7.27 (dd, 1H,  $J=2.4, 8.6$  Hz), 7.15 (d, 1H,  $J=8.6$  Hz), 3.93-4.03 (m, 1H), 3.70-3.80 (m, 1H), 2.53-2.82 (m, 6H), 1.02 (t, 6H,  $J=7.1$  Hz).

(2) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-hydroxy-3-(2,5-dichlorophenyl)oxindole

**[0221]** The title compound (585 mg, 81%) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-idoisatin (870 mg, 1.48 mmol) by the procedure similar to that described in Example 91(2).  
 15  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  8.08 (brs, 1H), 7.58 (s, 1H), 7.46 (s, 1H), 7.30 (dd, 1H,  $J=2.5, 8.3$  Hz), 7.17 (d, 1H,  $J=8.3$  Hz), 4.01-4.11 (m, 1H), 3.72-3.82 (m, 1H), 2.49-2.86 (m, 6H), 0.99 (t, 6H,  $J=7.1$  Hz).

(3) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2,5-dichlorophenyl)oxindole

**[0222]** The title compound (34.8 mg, 75%) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-hydroxy-3-(2,5-dichlorophenyl)oxindole (41.7 mg, 0.0857 mmol) by the procedure similar to that described in Example 91.  
 20  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ : hydrochloride)  $\delta$  10.36 (brs, 1H), 8.35 (brs, 1H), 8.16 (s, 1H), 8.04 (d, 1H,  $J=2.6$  Hz), 7.85 (s, 1H), 7.80 (brs, 1H), 7.63 (s, 1H), 7.48 (dd, 1H,  $J=2.6, 8.6$  Hz), 7.37 (d, 1H,  $J=8.6$  Hz), 4.16-4.39 (m, 2H), 3.24-3.45 (m, 6H), 1.26 (t, 6H,  $J=7.1$  Hz).

## Example 95

Optically active 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-amino-3-(2-naphthyl)oxindole

**[0223]** The title compound (206 mg, 48%) was prepared from (+)-1-(2-diethylaminoethyl)-4-trifluoromethyl-6-ido-3-hydroxy-3-(2-naphthyl)oxindole of Example 76(1) (239 mg, 0.42 mmol) by the procedure similar to that described in Example 61(1). The NMR spectra of the title compound exhibited the same as in Example 61(1).  
 35

## Example 96

Optically active 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-amino-3-(2-naphthyl)oxindole

- 40 (1) Optically active 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-amino-3-(2-naphthyl)oxindole

**[0224]** The title compound (172mg, 43%) was prepared from optically active 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-amino-3-(2-naphthyl)oxindole of Example 95 (485 mg, 0.0855 mmol) by the procedure similar to that described in Example 91(2).

45  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.71-7.83 (m, 4H), 7.63 (s, 1H), 7.46-7.53 (m, 3H), 7.10 (dd, 1H,  $J=2.0, 8.6$  Hz), 3.91-3.99 (m, 1H), 3.66-3.76 (m, 1H), 2.67-2.72 (m, 2H), 2.53 (q, 4H,  $J=7.2$  Hz), 2.52 (brs, 2H), 0.93 (t, 6H,  $J=7.2$  Hz).

(2) Optically active 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-amino-3-(2-naphthyl)oxindole

50 **[0225]** The title compound (151 mg, 79%) was prepared from optically active 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-amino-3-(2-naphthyl)oxindole (160 mg, 0.0343 mmol) by the procedure similar to that described in Example 91.

55  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ : hydrochloride)  $\delta$  10.31 (brs, 1H), 8.48 (brs, 1H), 8.36 (s, 1H), 8.00 (s, 1H), 7.82-7.94 (m, 5H), 7.50-7.61 (m, 2H), 7.16 (d, 1H,  $J=8.6$ Hz), 4.18-4.41 (m, 2H), 3.13-3.81 (m, 6H), 1.23 (t, 6H,  $J=7.1$  Hz).

## Example 97

1-(2-Diethylaminoethyl)-3-hydroxy-3-(3-pyridyl)-4-bromooxindole

**[0226]** To a solution of n-BuLi (0.16 mL, 1.0 eq, 1.53 M in hexanes) at -78 °C, in anhydrous Et<sub>2</sub>O (1.0 mL), and under a nitrogen atmosphere was added a solution of 3-bromopyridine (40.8 mg, 0.0249 mL, 1.05 eq) in anhydrous Et<sub>2</sub>O (0.5 mL). The resulting light yellow coloured precipitate was stirred at -78 °C for 30 minutes and then a solution of isatin 1-(2-diethylaminoethyl)-4-bromoisatin (80.0 mg, 2.46 x 10<sup>-4</sup>mol), in anhydrous Et<sub>2</sub>O (1.5 mL) was added drop-wise. The solution was stirred for a further 7.5 hours. Saturated aqueous NH<sub>4</sub>Cl (1.5 mL) was added to the resulting brown coloured reaction mixture and the reaction was allowed to warm to room temperature. The mixture was extracted with EtOAc and the combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). After filtration, the solvent was removed in vacuo. Purification was carried out by column chromatography (silica gel, 1% to 1.5% to 2% MeOH in CHCl<sub>3</sub>) to yield the title compound as a light yellow oil (35.5 mg, 36%).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.946 (6H, t, J=7.3 Hz), 2.561 (4H, q, J=7.3 Hz), 2.706 (4H, m), 3.784 (2H, t, J=6.6 Hz), 6.916 (1H, dd, J=7.3 and 1.0 Hz), 7.174-7.305 (3H, m), 7.928 (1H, td, J=8.25 and 2.0 Hz), 8.413 (1H, d, J=2.0 Hz), 8.475 (1H, dd, J=4.95 and 1.3 Hz).

## Example 98

1-(2-Diethylaminoethyl)-3-hydroxy-3-(3-quinolinyl)-4-bromooxindole

**[0227]** To 3-bromoquinoline (56.3 mg, 1.1 eq) in anhydrous Et<sub>2</sub>O (1.0 mL) at -50 °C (internal temperature) and under a nitrogen atmosphere was added n-BuLi (0.18 mL, 1.1 eq, 1.53 M in hexanes). Stirring was continued for 20 minutes and then to the resulting red/brown coloured precipitate was added 1-(2-diethylaminoethyl)-4-bromoisatin (80.0 mg, 2.46 x 10<sup>-4</sup>mol) in anhydrous Et<sub>2</sub>O (2.0 mL) and the resulting dark blue coloured mixture was stirred for a further 8.5 hours at -50°C. Saturated aqueous NH<sub>4</sub>Cl (1.5 mL) was added and the mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc and the combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). After filtration, the solvent was removed in vacuo. Purification was carried out by flash chromatography (silica gel, eluting 2% MeOH in CHCl<sub>3</sub>) to yield the title compound as a yellow oil (5.3 mg, 5%).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.964 (6H, t, J=7.3 Hz), 2.592 (2H, q, J=7.3 Hz), 2.604 (2H, q, J=7.3 Hz), 2.747 (2H, m), 3.830 (2H, m), 6.966 (1H, dd, J=7.1 and 1.0 Hz), 7.228-7.283 (2H, m), 7.549 (1H, t, J=8.25 Hz), 7.710 (1H, ddd, J=6.9, 1.3 and 1.3 Hz), 7.845 (1H, d, J=8.2 Hz), 8.443 (1H, d, J=2.3 Hz), 8.654 (1H, d, J=2.3 Hz).

## Example 99

1-(2-Diethylaminoethyl)-3-hydroxy-3-(2-benzo[b]thienyl)-4-bromooxindole

**[0228]** To benzo[b]thiophene (86.8 mg, 2.1 eq) in anhydrous THF (2 mL) at -40 °C (bath temperature) was added n-BuLi (0.423 mL, 1.53 M in hexanes, 2.1 eq). The resulting colourless solution was stirred for 30 minutes, after which 1-(2-diethylaminoethyl)-4-bromoisatin (100.0 mg, 3.08 x 10<sup>-4</sup>mol) in anhydrous THF (2 mL) was added. Stirring was continued at -40 °C for 9 hours. Saturated aqueous NH<sub>4</sub>Cl (1.5 mL) was added and the mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc and the combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). After filtration, the solvent was removed in vacuo. Purification was carried out by column chromatography (silica gel, eluting 1%-2% MeOH in CHCl<sub>3</sub>) to give the title compound as a yellow oil (43.0 mg, 30%).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.970 (6H, t, J=7.3 Hz), 2.564 (2H, q, J=6.9 Hz), 2.578 (2H, q, J=7.3 Hz), 2.727 (2H, m), 3.792 (2H, m), 6.948 (1H, dd, J=6.9 and 2.3 Hz), 7.186 (1H, s), 7.305 (4H, m), 7.678 (1H, ddd, J=4.6, 3.7 and 3.0 Hz), 7.778 (1H, m).

## Example 100

1-(2-Diethylaminoethyl)-3-hydroxy-3-(2-benzo[b]furanyl)-4-bromooxindole

**[0229]** To benzo[b]furan (76.4 mg, 2.1 eq) in anhydrous THF (2 mL) at -40 °C (bath temperature) was added n-BuLi (0.423 mL, 1.53 M in hexanes, 2.1 eq). The resulting light yellow coloured solution was stirred for 30 minutes, after which 1-(2-diethylaminoethyl)-4-bromoisatin (100.0 mg, 3.08 x 10<sup>-4</sup>mol) in anhydrous THF (2 mL) was added. Stirring was continued at -40 °C for 9 hours. Saturated aqueous NH<sub>4</sub>Cl (1.5 mL) was added and the mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc and the combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). After filtration, the solvent was removed in vacuo. Purification was carried out by column chromatography

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(silica gel, eluting 1%-2% MeOH in CHCl<sub>3</sub>) to give the title compound as a yellow oil (29.0 mg, 21%).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 270 MHz) δ 0.992 (6H, t, J=6.9 Hz), 1.256 (1H, brs), 2.581 (2H, q, J=7.3 Hz), 2.596 (2H, q, J=6.9 Hz), 2.736 (2H, m), 3.836 (2H, m), 6.919 (1H, s), 6.943 (1H, dd, J=7.3 and 10.3 Hz), 7.249 (4H, m), 7.374 (1H, d, J=7.9 Hz), 7.552 (1H, m).

5

### Example 101

#### 1-(2-Diethylaminoethyl)-3-hydroxy-3-(3-benzo[b]thienyl)-4-bromooxindole

[0230] To 3-bromobenzo[b]thiophene (146.5 mg, 2.2 eq) in anhydrous THF (2 mL) at -40 °C (bath temperature) was added t-BuLi (0.40 mL, 1.70 M in pentane, 2.1 eq). The resulting light yellow coloured solution was stirred for 30 minutes, after which 1-(2-diethylaminoethyl)-4-bromoisoat (100.0 mg, 3.08 x 10<sup>-4</sup>mol) in anhydrous THF (2 mL) was added. Stirring was continued at -40 °C for 9 hours. Saturated aqueous NH<sub>4</sub>Cl (1.5 mL) was added and the mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc and the combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). After filtration, the solvent was removed in vacuo. Purification was carried out by column chromatography (silica gel, eluting 1%-2% MeOH in CHCl<sub>3</sub>) to give the title compound as a yellow/brown powder (119.3 mg, 84%).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 270 MHz) δ 1.025 (6H, t, J=7.3 Hz), 2.616 (2H, q, J=7.3 Hz), 2.656 (2H, q, J=7.2 Hz), 2.705 (1H, m), 2.884 (1H, ddd, J=13.5, 7.9 and 7.9 Hz), 3.732 (1H, ddd, J=12.5, 7.6 and 4.9 Hz), 4.061 (1H, ddd, J=14.2, 7.6 and 7.6 Hz), 6.930 (1H, d, J=7.3 Hz), 7.248 (3H, m), 7.393 (2H, m), 7.689 (1H, ddd, J 4.3, 2.6 and 2.6 Hz), 7.845 (1H, ddd, J=4.3, 2.6 and 2.6 Hz).

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dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). After filtration, the solvent was removed in vacuo. Purification was carried out by column chromatography (silica gel, eluting 1%-2% MeOH in CHCl<sub>3</sub>) to give the title compound as a yellow/brown powder (119.3

mg, 84%).

[0230] To 3-bromobenzo[b]thiophene (146.5 mg, 2.2 eq) in anhydrous THF (2 mL) at -40 °C (bath temperature) was added t-BuLi (0.40 mL, 1.70 M in pentane, 2.1 eq). The resulting light yellow coloured solution was stirred for 30 minutes, after which 1-(2-diethylaminoethyl)-4-bromoisoat (100.0 mg, 3.08 x 10<sup>-4</sup>mol) in anhydrous THF (2 mL) was added. Stirring was continued at -40 °C for 9 hours. Saturated aqueous NH<sub>4</sub>Cl (1.5 mL) was added and the mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc and the combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). After filtration, the solvent was removed in vacuo. Purification was carried out by column chromatography (silica gel, eluting 1%-2% MeOH in CHCl<sub>3</sub>) to give the title compound as a yellow/brown powder (119.3 mg, 84%).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 270 MHz) δ 1.025 (6H, t, J=7.3 Hz), 2.616 (2H, q, J=7.3 Hz), 2.656 (2H, q, J=7.2 Hz), 2.705 (1H, m), 2.884 (1H, ddd, J=13.5, 7.9 and 7.9 Hz), 3.732 (1H, ddd, J=12.5, 7.6 and 4.9 Hz), 4.061 (1H, ddd, J=14.2, 7.6 and 7.6 Hz), 6.930 (1H, d, J=7.3 Hz), 7.248 (3H, m), 7.393 (2H, m), 7.689 (1H, ddd, J 4.3, 2.6 and 2.6 Hz), 7.845 (1H, ddd, J=4.3, 2.6 and 2.6 Hz).

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dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). After filtration, the solvent was removed in vacuo. Purification was carried out by column chromatography (silica gel, eluting 1%-2% MeOH in CHCl<sub>3</sub>) to give the title compound as a yellow/brown powder (119.3

mg, 84%).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 270 MHz) δ 1.025 (6H, t, J=7.3 Hz), 2.616 (2H, q, J=7.3 Hz), 2.656 (2H, q, J=7.2 Hz), 2.705 (1H, m), 2.884 (1H, ddd, J=13.5, 7.9 and 7.9 Hz), 3.732 (1H, ddd, J=12.5, 7.6 and 4.9 Hz), 4.061 (1H, ddd, J=14.2, 7.6 and 7.6 Hz), 6.930 (1H, d, J=7.3 Hz), 7.248 (3H, m), 7.393 (2H, m), 7.689 (1H, ddd, J 4.3, 2.6 and 2.6 Hz), 7.845 (1H, ddd, J=4.3, 2.6 and 2.6 Hz).

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### Example 102

#### 1-(2-Diethylaminoethyl)-3-hydroxy-3-(3-thienyl)-4-bromooxindole

[0231] To 3-bromothiophene (105.5 mg, 2.1 eq) in anhydrous THF (2 mL) under a nitrogen atmosphere and with stirring was added t-BuLi (0.38 mL, 2.1 eq, 1.7 M in pentane) at -40 °C (bath temperature). Stirring was continued for 30 minutes after which 1-(2-diethylaminoethyl)-4-bromoisoat (100.0 mg, 3.08 x 10<sup>-4</sup>mol) in anhydrous THF (2 mL) was added dropwise. The resulting red colored solution was stirred at -40 °C for 8 hours. Saturated aqueous NH<sub>4</sub>Cl (1.5 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc and the combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). After filtration the solvent was removed in vacuo. Purification was carried out by column chromatography (silica gel, eluting 1% to 2% MeOH in CHCl<sub>3</sub>) to give the title compound as a light brown foam (124.5 mg, 99%).

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added dropwise. The resulting red colored solution was stirred at -40 °C for 8 hours. Saturated aqueous NH<sub>4</sub>Cl (1.5 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc and the combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). After filtration the solvent was removed in vacuo. Purification was carried out by column chromatography (silica gel, eluting 1% to 2% MeOH in CHCl<sub>3</sub>) to give the title compound as a light brown foam (124.5 mg, 99%).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 270 MHz) δ 1.037 (6H, t, J=7.3 Hz), 2.660 (4H, m), 2.724 (1H, m), 2.872 (1H, m), 3.736 (1H, ddd, J=14.2, 7.9 and 5.3 Hz), 4.017 (1H, ddd, J=14.5, 7.6 and 7.6 Hz), 6.893 (1H, d, J=5.3 Hz), 6.902 (1H, dd, J=7.3 and 1.0 Hz), 7.157-7.269 (3H, m), 7.301 (1H, d, J=5.3 Hz).

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### Example 103

#### 1-(2-Diethylaminoethyl)-3-hydroxy-3-(3-furyl)-4-bromooxindole

[0232] To 3-bromofuran (95.1 mg, 2.1 eq) in anhydrous THF (2 mL) under a nitrogen atmosphere and with stirring was added t-BuLi (0.38 mL, 2.1 eq, 1.7 M in pentane) at -78 °C (bath temperature). Stirring was continued for 1 hour after which 1-(2-diethylaminoethyl)-4-bromoisoat (100.0 mg, 3.08 x 10<sup>-4</sup>mol) in anhydrous THF (2 mL) was added dropwise. The resulting red coloured solution was stirred at -40 °C for 8 hours. Saturated aqueous NH<sub>4</sub>Cl (1.5 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc and the combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). After filtration the solvent was removed in vacuo. Purification was carried out by column chromatography (silica gel, eluting 1% to 2% MeOH in CHCl<sub>3</sub>) to give the title compound as a yellow solid (103.3 mg, 85%).

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added dropwise. The resulting red coloured solution was stirred at -40 °C for 8 hours. Saturated aqueous NH<sub>4</sub>Cl (1.5 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc and the combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). After filtration the solvent was removed in vacuo. Purification was carried out by column chromatography (silica gel, eluting 1% to 2% MeOH in CHCl<sub>3</sub>) to give the title compound as a yellow solid (103.3 mg, 85%).  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 270 MHz) δ 1.207 (6H, t, J=7.3 Hz), 2.618 (4H, q, J=7.3 Hz), 2.746 (2H, m), 3.809 (2H, m), 6.431 (1H, d, J=2.0 Hz), 6.913 (1H, dd, J=7.3 and 1.6 Hz), 7.178-7.274 (3H, m), 7.398 (1H, d, J=2.0 Hz).

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### Example 104

#### 1-(2-Diethylaminoethyl)-3-hydroxy-3-(2-indolyl)-4-bromooxindole

[0233] To indole (39.7 mg, 1.1 eq) in anhydrous THF (2 mL) under a nitrogen atmosphere and with stirring was

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added n-BuLi (0.22 mL, 1.1 eq, 1.53 M in hexanes) at -78°C (bath temperature). Stirring was continued for 1 hour after which CO<sub>2</sub> (g) was bubbled through the solution for ca. 30 minutes. The reaction mixture was then allowed to warm to room temperature and stirred at room temperature for a further 30 minutes. The solvent was removed in vacuo to give a white/light yellow solid which was left under vacuum (10 mmHg) for 17 hours. To the thus dried solid under a nitrogen atmosphere was added anhydrous THF (2 mL). The resulting clear solution was cooled to -78 °C (bath temperature) and t-BuLi (0.20 mL, 1.1 eq, 1.7 M in pentane) added dropwise. The colourless solution was stirred for 1 hour and 1-(2-diethylaminoethyl)-4-bromoisoatin (100.0 mg, 3.08 x 10<sup>-4</sup>mol) in anhydrous THF (2 mL) was added dropwise. The resulting red coloured solution was stirred at -40 °C for 7.5 hours. To the solution was added H<sub>2</sub>O (1.5 mL) and the mixture allowed to warm to room temperature. Saturated aqueous NH<sub>4</sub>Cl (1.5 mL) was then added. The mixture was extracted with EtOAc and the combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). After filtration the solvent was removed in vacuo. Purification was carried out by column chromatography (silica gel, eluting 1% to 1.5% MeOH in CHCl<sub>3</sub>) to give the title compound as a red oil (39.4 mg, 29%).

<sup>5</sup> <sup>10</sup> <sup>15</sup> <sup>1H-NMR</sup> (CDCl<sub>3</sub>, 270 MHz) δ 0.936 (6H, m, J=6. 9 Hz), 2.564 (2H, q, J=7. 3 Hz), 2.622 (2H, q, J=7.3 Hz), 2.735 (2H, m), 3.662 (1H, ddd, J=11.9, 5.6 and 5.6 Hz), 3.966 (1H, ddd, J=14.2, 6.9 and 6.9 Hz), 6.406 (1H, d, J=2.0 Hz), 6.883 (1H, dd, J=5.9 and 3.0 Hz), 7.047 (1H, t, J=7.3 Hz), 7.145 (1H, dt, J=7.7 and 1.0 Hz), 7.203-7.534 (4H, m), 9.530 (1H, brs).

### Example 105

#### 1-(2-Diethylaminoethyl)-3-hydroxy-3-(2-benzothiazolyl)-4-bromooxindole

**[0234]** To benzothiazole (83.3 mg, 2.0 eq) in anhydrous THF (2 mL) under a nitrogen atmosphere and with stirring was added n-BuLi (0.40 mL, 2.0 eq, 1.53 M in hexanes) at -78°C (bath temperature). The resulting bright yellow coloured reaction mixture was stirred for 1 hour after which 1-(2-diethylaminoethyl)-4-bromoisoatin (100.0 mg, 3.08 x 10<sup>-4</sup>mol) in anhydrous THF (2 mL) was added dropwise. The resulting red coloured solution was stirred at -78 °C for 7.5 hours. Saturated aqueous NH<sub>4</sub>Cl (1.5 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc and the combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). After filtration the solvent was removed in vacuo. Purification was carried out by column chromatography (silica gel, eluting 1% to 3% MeOH in CHCl<sub>3</sub>) to give the title compound as a light yellow solid (20.7 mg, 15%).

<sup>20</sup> <sup>25</sup> <sup>30</sup> <sup>1H-NMR</sup> (CDCl<sub>3</sub>, 270 MHz) δ 1.014(6H, t, J=7.25 Hz), 1.256 (1H, brs), 2.622 (2H, q, J=6. 9 Hz), 2.632 (2H, q, J=7.3 Hz), 2.699 (1H, m), 2.807 (1H, m), 3.814 (1H, m), 3.881 (1H, m), 6.981 (1H, d, J=7.6 Hz), 7.244 (2H, m), 7.308-7.488 (2H, m), 7.869 (1H, dd, J=8.25 and 1.3 Hz), 7.982 (1H, ddd, J=7.9, 0.7 and 0.7 Hz).

### Example 106

#### 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-hydroxy-3-(2-fluorophenyl)oxindole

**[0235]** The title compound (10.9 mg, 74%) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(2-fluorophenyl)oxindole of Example 62(1) (18.1 mg) by the procedure similar to that described in Example 55.

<sup>35</sup> <sup>40</sup> <sup>1H-NMR</sup> (CDCl<sub>3</sub>, 300 MHz) δ 1.02 (6H, t, J=7.1 Hz), 2.88-2.57 (6H, m), 4.02-3.79 (2H, m), 6.93-6.86 (1H, m), 7.36-7.22 (2H, m), 7.47 (1H, s), 7.57 (1H, s), 7.91 (1H, t, J=7.1 Hz).

### Example 107

#### 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-fluorophenyl)oxindole

**[0236]** The title compound was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-cyano-3-hydroxy-3-(2-fluorophenyl)oxindole of Example 106 by the procedure similar to that described in Example 56.

<sup>45</sup> <sup>50</sup> <sup>1H-NMR</sup> (DMSO-d<sub>6</sub>, 300 MHz) δ 1.22 (6H, brs), 3.37-3.20 (6H, m), 4.30-4.10 (2H, m), 7.06-6.97 (1H, m), 7.42-7.20 (3H, m), 7.85-7.70 (2H, m), 7.92 (2H, t, J=6.9 Hz), 8.27 (1H, s), 9.48 (1H, brs).

### Example 108

#### 1-(2-Diethylaminoethyl)-4,6-dichloro-3-amino-3-(2-naphthyl)oxindole

**[0237]** The title compound was prepared from 1-(2-diethylaminoethyl)-4,6-dichloro-3-hydroxy-3-(2-naphthyl)oxindole by the procedure similar to that described in Example 61(1).

<sup>55</sup> <sup>1H-NMR</sup> (DMSO-d<sub>6</sub>, 300 MHz: hydrochloride) δ 1.18 (6H, t, J=7.2 Hz), 3.22 (4H, q, J=7.2 Hz), 3.30-3.45 (2H, m), 4.15

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(2H, d, J=7.2 Hz), 7.31 (1H, dd, J=8.6, 1.8 Hz), 7.43 (1H, d, J=1.5 Hz), 7.56-7.61 (2H, m), 7.64 (1H, d, J=1.7 Hz), 7.91-7.96 (4H, m).

Example 109

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1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-morpholinocarbonyl-1-butynyl)-3-hydroxy-3-(phenyl)oxindole

(1) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(phenyl)oxindole

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[0238] The title compound (53%) was prepared from 1-(2-diethylaminoethyl)-6-iodo-4-trifluoromethylisatin and phenylmagnesium bromide by the procedure similar to that described in Example 1. The compound obtained was further purified by reverse phase HPLC with water-acetonitrile-trifluoroacetic acid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz: trifluoroacetate) δ 0.95 (6H, t, J=7.2 Hz), 2.51-2.58 (4H, m), 2.63-2.68 (2H, m), 3.59-3.73 (1H, m), 3.80-3.89 (1H, m), 4.05 (1H, br), 7.23-7.33 (5H, m), 7.57 (1H, s), 7.65 (1H, s).

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(2) 1-(2-Diethylaminoethyl)-4-trifluoromethyl-6-(4-morpholinocarbonyl-1-butynyl)-3-hydroxy-3-(phenyl)oxindole

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[0239] The title compound (65.2 mg, 88%) was prepared from 1-(2-diethylaminoethyl)-4-trifluoromethyl-6-iodo-3-hydroxy-3-(phenyl)oxindole (57.2 mg) and 4-morpholinocarbonyl-1-butyne (31.1 mg) by the procedure similar to that described in Reference Example 21. The compound obtained was further purified by reverse phase HPLC with water-acetonitrile-trifluoroacetic acid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 300 MHz: trifluoroacetate) δ 1.14-1.19 (6H, m), 2.68 (4H, s), 3.18-3.21 (4H, m), 3.28-3.29 (2H, m), 3.50-3.59 (6H, m), 3.98-4.15 (2H, m), 6.86 (1H, br), 7.15-7.18 (2H, m), 7.25-7.29 (3H, m), 7.35 (1H, s), 7.61 (1H, s), 9.50 (1H, br).

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Example 110

1-Methyl-4,6-dichloro-3-(3-diethylaminopropoxy)-(2-naphthyl)oxindole

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(1) 1-Methyl-4,6-dichloroisatin

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[0240] A mixture of 60% NaH (20.5 mg), 4,6-dichloroisatin (947 mg), and iodomethane (0.328 mL) in THF (20 mL) were stirred overnight at room temperature, poured into 1 N hydrochloric acid, and extracted with ethyl acetate. The extracts were washed with sat. aqueous NaCl, dried over MgSO<sub>4</sub>, and concentrated. The residue was washed with hexane to give the title compound (849 mg, 84%).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 3.12-3.11 (3H, m), 7.33-7.30 (2H, m).

(2) 1-Methyl-4,6-dichloro-3-hydroxy-(2-naphthyl)oxindole

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[0241] The title compound (59.1 mg, 1.5%) was prepared from 1-methyl-4,6-dichloroisatin (250 mg) and 2-naphthyl magnesium bromide by the procedure similar to that described in Example 1.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz) δ 3.18 (3H, s), 3.96 (1H, brs), 6.85 (1H, d, J=1.8 Hz), 7.05 (1H, d, J=1.7 Hz), 7.28 (1H, dd, J=8.8, 2.0 Hz), 7.50-7.42 (2H, m), 7.81-7.73 (3H, m), 7.91 (1H, d, J=1.8 Hz).

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(3) 1-Methyl-4,6-dichloro-3-(3-diethylaminopropoxy)-(2-naphthyl)oxindole

[0242] The title compound (5.0 mg, 5%) was prepared from 1-methyl-4,6-dichloro-3-hydroxy-(2-naphthyl)oxindole (59.1 mg) by the procedure similar to that described in Example 47. The compound obtained was further purified by reverse phase HPLC with water-acetonitrile-trifluoroacetic acid.

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<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 300 MHz: trifluoroacetate) δ 1.19 (6H, t, J=7.0 Hz), 2.03-1.89 (2H, m), 3.22 (3H, s), 3.40-3.07 (8H, m), 7.35-7.29 (2H, m), 7.53-7.46 (3H, m), 7.91-7.84 (4H, m).

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## Example 111

1-(5-Aminopentyl)-4-bromo-6-carbamoyl-3-hydroxy-3-(2-naphthyl)oxindole

## 5 (1) 5-t-Butyldimethylsilyloxy-1-pentanol

[0243] Sixty % NaH in mineral oil (1 g, 25 mmol) was washed with hexane and suspended in THF (50 mL). To the suspension was added dropwise 1,5-pentanediol (2.62 mL, 25 mmol) at 0 °C and the mixture was stirred for 30 min. t-Butyldimethylsilyl chloride (3.77 g, 25 mmol) was added and the mixture was stirred for 1 h at room temperature. The mixture was dispersed between ether and 5% K<sub>2</sub>CO<sub>3</sub> and the organic layer was separated. The layer was dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography with 4 : 1 to 1 : 1 hexane/ethyl acetate to give the title compound (3/16 g, 58%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 3.60-3.67 (m, 4H), 1.37-1.65 (m, 6H), 0.89 (s, 9H), 0.05 (s, 6H).

## 15 (2) 5-t-Butyldimethylsilyloxy-1-iodopentane

[0244] To a mixture of imidazole (1.13 g, 16.6 mmol), triphenyl phosphine (2.16 g, 8.24 mmol), and iodine (1.92 g, 7.56 mmol) in a mixed solvent of toluene (40 mL) and acetonitrile (4 mL) was added 5-t-butyldimethylsilyloxy-1-pentanol (1.5 g, 6.87 mmol). The mixture was stirred for 1 h at room temperature and aqueous Na<sub>2</sub>SO<sub>3</sub> was added. The mixture was extracted with ethyl acetate and the extracts were dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography with 10 : 1 hexane/ethyl acetate to give the title compound (1.55 g, 69%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 3.61 (t, 2H, J=6.1 Hz), 3.20 (t, 2H, J=7.1 Hz), 1.85 (tt, 2H, J=7.1, 7.1 Hz), 1.41-1.57 (m, 4H), 0.90 (s, 9H), 0.05 (s, 6H).

## 25 (3) 1-(5-t-Butyldimethylsilyloxypentyl)-4-bromo-6-iodoisatin

[0245] To a mixture of 4-bromo-6-iodoisatin (450 mg, 1.32 mmol) and 60% NaH (60 mg, 1.5 mmol) was added 5-t-butyldimethylsilyloxy-1-iodopentane (600 mg, 1.83 mmol). The mixture was stirred for 4 h at 50 °C and water and 5% KHSO<sub>4</sub> was added. The mixture was extracted with toluene-ethyl acetate and the extracts were washed with 5% KHSO<sub>4</sub>, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography with 6 : 1 hexane/ethyl acetate to give the title compound (615 mg, 86%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.74 (s, 1H), 7.50 (s, 1H), 3.74 (t, 2H, J=7.4 Hz), 3.62 (t, 2H, J=6.1 Hz), 1.41-1.75 (m, 6H), 0.87 (s, 9H), 0.04 (s, 6H).

## 35 (4) 1-(5-t-Butyldimethylsilyloxypentyl)-4-bromo-6-ido-3-hydroxy-3-(2-naphthyl)oxindole

[0246] The title compound (463 mg, 75%) was prepared from 1-(5-t-butyldimethylsilyloxypentyl)-4-bromo-6-iodoisatin (500 mg, 0.923 mmol) and 2-naphthylmagnesium bromide by the procedure similar to that described in Example 1. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.73-7.86 (m, 4H), 7.70 (s, 1H), 7.46-7.49 (m, 3H), 7.13 (dd, 1H, J=2.0, 8.6 Hz), 3.74-3.84 (m, 1H), 3.61-3.69 (m, 1H), 3.55 (t, 2H, J=6.3 Hz), 1.69-1.74 (m, 2H), 1.35-1.57 (m, 4H), 0.86 (s, 9H), 0.01 (s, 6H).

## (5) 1-(5-Hydroxypentyl)-4-bromo-6-ido-3-hydroxy-3-(2-naphthyl)oxindole

[0247] To a solution of 1-(5-t-butyldimethylsilyloxypentyl)-4-bromo-6-ido-3-hydroxy-3-(2-naphthyl)oxindole (450 mg, 0.67 mmol) in THF (5 mL) was added 1 N n-tetrabutylammonium fluoride in THF (1 mL, 1 mmol) and the mixture was stirred for 4 h at room temperature. 5 % KHSO<sub>4</sub> was added and the mixture was extracted with ethyl acetate. The extracts were dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography with 1 : 1 to 0 : 1 hexane/ethyl acetate to give the title compound (349 mg, 94%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.73-7.86 (m, 4H), 7.70 (d, 1H, J=1.0 Hz), 7.44-7.51 (m, 3H), 7.14 (dd, 1H, J=1.8, 8.7 Hz), 3.61-3.83 (m, 3H), 3.57 (dt, 2H, J=1.4, 6.3 Hz), 1.38-1.77 (m, 6H).

## (6) 1-(5-Methanesulfonyloxypentyl)-4-bromo-6-ido-3-hydroxy-3-(2-naphthyl)oxindole

[0248] To a solution of 1-(5-hydroxypentyl)-4-bromo-6-ido-3-hydroxy-3-(2-naphthyl)oxindole (155 mg, 0.279 mmol) and triethylamine (0.06 mL, 0.43 mmol) in dichloromethane (5 mL) was added methanesulfonyl chloride (0.025 mL, 0.323 mmol) at 0 °C. The mixture was stirred for 5 min at the same temperature and water was added. The mixture was extracted with ethyl acetate and the extracts were dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography with 3 : 2 hexane/ethyl acetate to give the mixture (116 mg) of the title compound

and dimesylate.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.75-7.86 (m, 4H), 7.71 (d, 1H, J=0.7 Hz), 7.46-7.50 (m, 3H), 7.13 (dd, 1H, J=2.0, 8.6 Hz), 4.14 (t, 2H, J=6.3 Hz), 3.63-3.84 (m, 2H), 2.89 (s, 3H), 1.70-1.79 (m, 4H), 1.39-1.50 (m, 2H).

5 (7) 1-(5-Di-t-butoxycarbonylaminopentyl)-4-bromo-6-iodo-3-hydroxy-3-(2-naphthyl)oxindole

[0249] A mixture of crude 1-(5-methanesulfonyloxypentyl)-4-bromo-6-iodo-3-hydroxy-3-(2-naphthyl)oxindole (85.9 mg), di-t-butyl iminodicarboxylate (102 mg, 0.469 mmol), K<sub>2</sub>CO<sub>3</sub> (112 mg, 0.81 mmol), and a trace amount of KI in 2-butanone (2.5 mL) was heated at reflux for 3 h. Sat. aqueous NaCl was added and the mixture was extracted with ethyl acetate. The organic layers were dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography with 4 : 1 hexane/ethyl acetate to give the title compound (101 mg).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.70-7.87 (m, 5H), 7.45-7.52 (m, 3H), 7.12 (dd, 1H, J=2.0, 8.6 Hz), 3.60-3.82 (m, 2H), 3.53 (t, 2H, J=7.3 Hz), 1.32-1.85 (m, 6H), 1.48 (s, 18H).

15 (8) 1-(5-Di-t-butoxycarbonylaminopentyl)-4-bromo-6-cyano-3-hydroxy-3-(2-naphthyl)oxindole

[0250] The title compound (438 mg, 61% 2 steps) was prepared from 1-(5-di-t-butoxycarbonylaminopentyl)-4-bromo-6-iodo-3-hydroxy-3-(2-naphthyl)oxindole (81.5 mg, 0.108 mmol) by the procedure similar to that described in Example 55.

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.75-7.84 (m, 4H), 7.65 (s, 1H), 7.47-7.52 (m, 3H), 7.09 (dd, 1H, J=2.0, 8.6 Hz), 3.85 (s, 1H), 3.73-3.80 (m, 2H), 3.54 (t, 2H, J=7.3 Hz), 1.34-1.80 (m, 6H), 1.49 (s, 18H).

(9) 1-(5-t-Butoxycarbonylaminopentyl)-4-bromo-6-carbamoyl-3-hydroxy-3-(2-naphthyl)oxindole

25 [0251] To a solution of 1-(5-di-t-butoxycarbonylaminopentyl)-4-bromo-6-cyano-3-hydroxy-3-(2-naphthyl)oxindole (400 mg, 0.612 mmol) in t-butanol (1.5 mL) was added powdered KOH (ca. 1 g) at 50 °C. The mixture was stirred for 30 min at the same temperature and passed through a celite pad. The celite was washed with THF and the filtrate was concentrated. The residue was dispersed between water and ethyl acetate and the organic layer was separated. The organic layer was dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silicagel column chromatography with 2 : 3 to 1 : 4 hexane/ethyl acetate to give the title compound (321 mg, 92%).

30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.94 (s, 1H), 7.74-7.87 (m, 5H), 7.44-7.50 (m, 2H), 7.26 (brs, 1H), 7.15 (dd, 1H, J=2.0, 8.6 Hz), 5.81 (brs, 1H), 4.63 (br, 1H), 3.85 (brs, 1H), 3.68-3.81 (m, 2H), 3.13-3.19 (m, 2H), 1.72-1.86 (m, 2H), 1.38-1.54 (m, 4H), 1.42 (s, 9H).

35 (10) 1-(5-Aminopentyl)-4-bromo-6-carbamoyl-3-hydroxy-3-(2-naphthyl)oxindole

[0252] The hydrochloride of the title compound (220 mg, 85%) was obtained by treating 1-(5-t-butoxycarbonylaminopentyl)-4-bromo-6-carbamoyl-3-hydroxy-3-(2-naphthyl)oxindole (292 mg, 0.0511 mmol) with 4 N HCl in dioxane at room temperature for 2 h followed by concentration to dryness.

40 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>: hydrochloride) δ 8.40 (brs, 1H), 7.98 (s, 1H), 7.76-7.92 (m, 9H), 7.47-7.53 (m, 2H), 7.12 (d, 1H, J=8.6Hz), 7.07 (s, 1H), 3.69-3.86 (m, 2H), 2.67-2.78 (m, 2H), 1.51-1.74 (m, 4H), 1.32-1.40 (m, 2H).

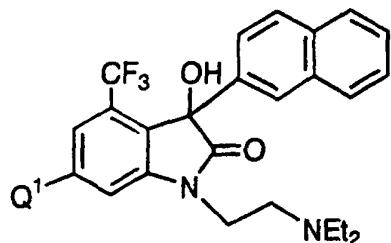
[0253] The structures of the compounds obtained in Examples 51 to 111 are shown below.

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**Example 51 :**  $Q^1 = 4\text{-morpholinocarbonyl-1-butynyl}$

**Example 52 :**  $Q^1 = 3\text{-dimethylamino-1-propynyl}$

**Example 53 :**  $Q^1 = 4\text{-diethylcarbamoyl-1-butynyl}$

**Example 54 :**  $Q^1 = 4\text{-carboxy-1-butynyl}$

**Example 55 :**  $Q^1 = \text{cyano}$

**Example 58 :**  $Q^1 = \text{morpholinocarbonyl}$

**Example 65 :**  $Q^1 = 4\text{-carbamoyl-1-butynyl}$

**Example 66 :**  $Q^1 = 3\text{-amino-1-butynyl}$

**Example 67 :**  $Q^1 = 3\text{-ethylureido-1-propynyl}$

**Example 68 :**  $Q^1 = 3\text{-methanesulfonylamino-1-propynyl}$

**Example 69 :**  $Q^1 = 4\text{-(2-hydroxyethylcarbamoyl)-1-butynyl}$

**Example 71 :**  $Q^1 = \text{morpholinocarbonyl-ethynyl}$

**Example 79 :**  $Q^1 = \text{ethoxycarbonyl}$

**Example 80 :**  $Q^1 = \text{dimethylcarbamoyl}$

**Example 81 :**  $Q^1 = (\text{2-hydroxyethyl})\text{carbamoyl}$

**Example 82 :**  $Q^1 = \text{hydroxymethyl}$

**Example 83 :**  $Q^1 = \text{methylcarbamoyl}$

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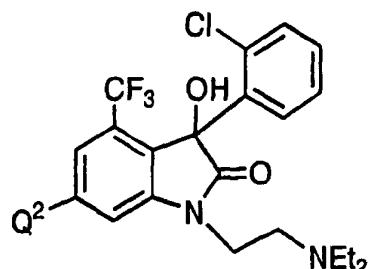
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**Example 70 :**  $Q^2 = 4\text{-morpholinocarbonyl-1-butynyl}$

**Example 75 :**  $Q^2 = 3\text{-methanesulfonylamino-1-propynyl}$

**Example 77 :**  $Q^2 = 4\text{-(2-hydroxyethylcarbamoyl)-1-butynyl}$

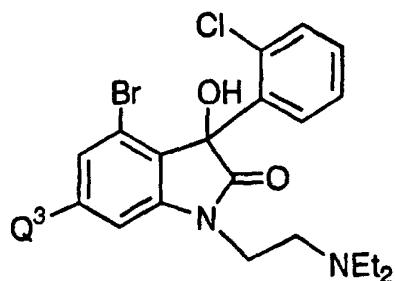
**Example 89 :**  $Q^2 = 3\text{-(2-oxo-1-imidazolidinyl)-1-propynyl}$

**Example 90 :**  $Q^2 = 3\text{-(2-oxo-1,3-oxazolin-3-yl)-1-propynyl}$

**Example 93 :**  $Q^2 = 3\text{-ethylureido-1-propynyl}$

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Example 84 : Q&lt;sup&gt;3&lt;/sup&gt;= carbamoyl

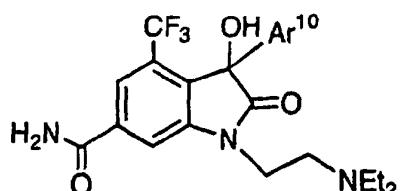
Example 85 : Q&lt;sup&gt;3&lt;/sup&gt;= 3-ethylureido-1-propynyl

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Example 86 : Q&lt;sup&gt;3&lt;/sup&gt;= 3-(2-oxo-1-imidazolidinyl)-1-propynyl

Example 87 : Q&lt;sup&gt;3&lt;/sup&gt;= 3-(2-oxo-1,3-oxazolin-3-yl)-1-propynyl

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Example 56 : Ar&lt;sup&gt;10&lt;/sup&gt;= 2-naphthyl

Example 78 : Ar&lt;sup&gt;10&lt;/sup&gt;= 2-chlorophenyl

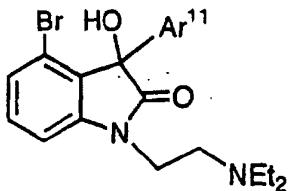
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Example 91 : Ar&lt;sup&gt;10&lt;/sup&gt;= 2, 4-dichlorophenyl

Example 92 : Ar&lt;sup&gt;10&lt;/sup&gt;= 2, 4-difluorophenyl

Example 94 : Ar&lt;sup&gt;10&lt;/sup&gt;= 2, 5-dichlorophenyl

Example 107: Ar&lt;sup&gt;10&lt;/sup&gt;= 2-fluorophenyl



Example 97 : Ar&lt;sup&gt;11&lt;/sup&gt;= 3-pyridyl

Example 98 : Ar&lt;sup&gt;11&lt;/sup&gt;= 3-quinolinyl

Example 99 : Ar&lt;sup&gt;11&lt;/sup&gt;= 2-benzo[b]thienyl

Example 100: Ar&lt;sup&gt;11&lt;/sup&gt;= 2-benzo[b]furyl

Example 101: Ar&lt;sup&gt;11&lt;/sup&gt;= 3-benzo[b]thienyl

Example 102: Ar&lt;sup&gt;11&lt;/sup&gt;= 3-thienyl

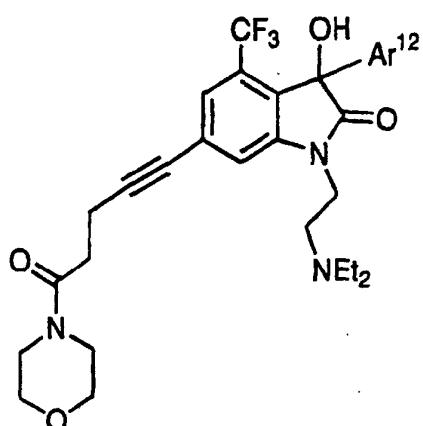
Example 103: Ar&lt;sup&gt;11&lt;/sup&gt;= 3-furyl

Example 104: Ar&lt;sup&gt;11&lt;/sup&gt;= 2-indolyl

Example 105: Ar&lt;sup&gt;11&lt;/sup&gt;= 2-benzothiazolyl

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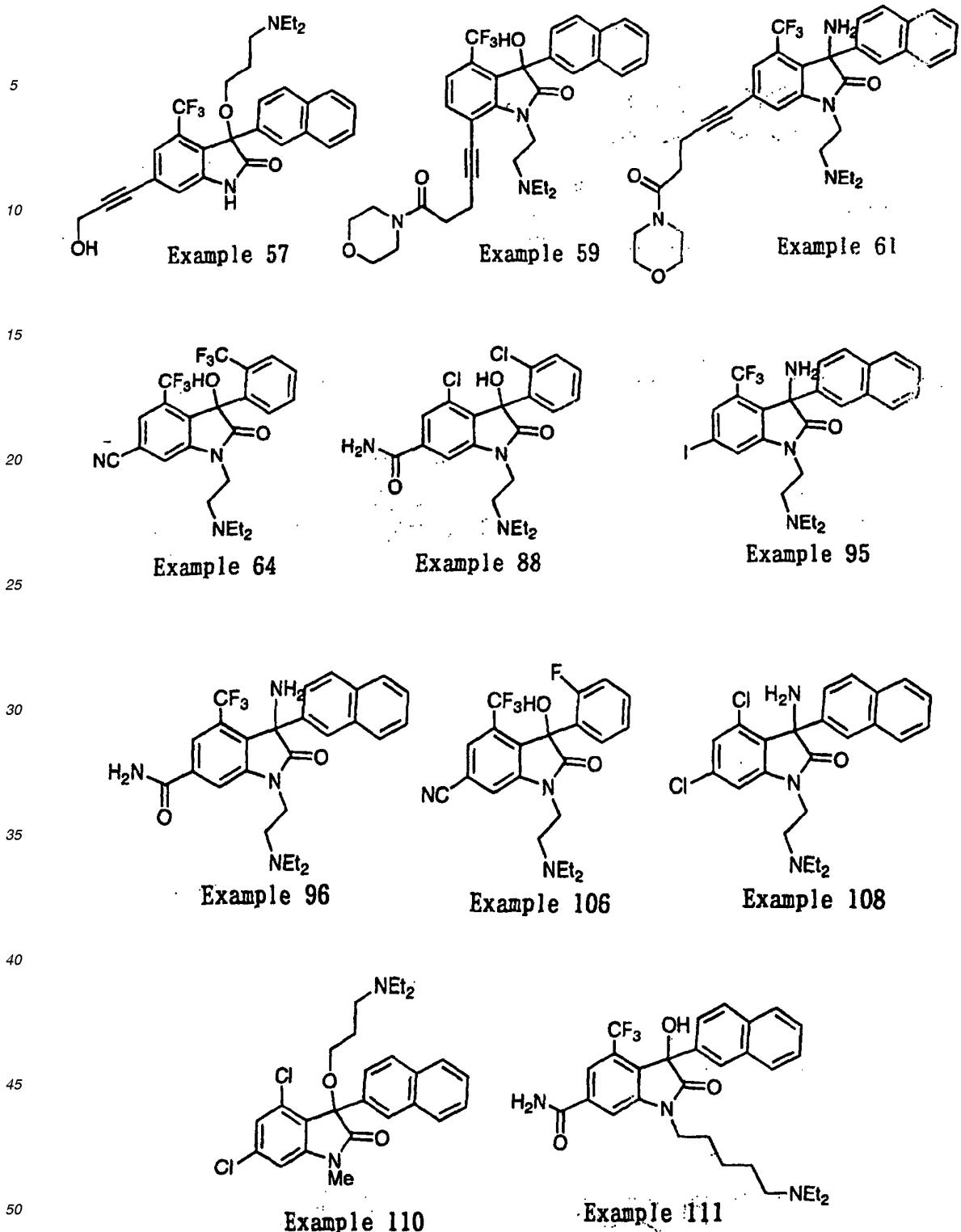
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Example 62 : Ar&lt;sup&gt;12&lt;/sup&gt;= 2-fluorophenyl

Example 63 : Ar&lt;sup&gt;12&lt;/sup&gt;= 2-trifluorophenyl

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Example 109: Ar&lt;sup&gt;12&lt;/sup&gt;= phenyl



## Experiment 1

## 55 Biological Activity

**[0254]** Compounds of the present invention were evaluated for their growth hormone releasing activity from rat pituitary cells in vitro in accordance with the method described in the literature (R. G. Smith et al., Science, 260, 1640

(1993)).

**[0255]** Pituitary glands removed from 7-week-old Wistar/ST male rats were washed with HBSS (Hank's balanced salt solution) three times and minced into small pieces (ca. 1 mm<sup>2</sup>) using a pair of scissors. The tissues were transferred to a 15 mL round-bottom centrifuge tube and washed with HBSS (10 mL x 3). An enzyme solution (0.1 mL per a pituitary gland) was added and the cell dispersion was carried out in a water bath at 37 °C for ca 20 - 30 min, during which time the digested mixture was mixed by successive up-take and down-take of the suspension using a pipette, every 5 minutes. The resulting cell suspension was centrifuged at 1200 rpm for 2 - 3 min at room temperature and the supernatant fluid was discarded. A cultured medium was added and the resulting cell suspension was again centrifuged at 1200 rpm for 2 - 3 min at room temperature and the supernatant fluid was discarded. This procedure was repeated another 2 times. An aliquot (0.1 mL) of the resulting cell suspension was placed in each well of a 96-well plate in the number of 2 x 10<sup>4</sup> cells per a well and incubation was carried out at 37 °C under 5% CO<sub>2</sub> atmosphere for 5 days.

**[0256]** The culture medium was discarded and an assay medium (0.1 mL) was added. The incubation was continued for 1.5 h and the cells were red with the assay medium. A test compound solution (0.1 mL) was added and the reaction was carried out at 37°C for 15 min in an incubator under 5% CO<sub>2</sub> atmosphere. The supernatant fluid was recovered and the GH content present was measured by RIA (radioimmunoassay). An aliquot of the solution was diluted to 0.05 mL with a RIA buffer which consisted of PBS (pH 7.3) containing 1% BSA, 0.1% NaN<sub>3</sub> and 25mM EDTA. The diluted solution, [<sup>125</sup>I]-labeled GH solution (0.05 mL, ca. 10,000 cpm), and rabbit antiserum (1 : 10,000) against rat GH (0.05 mL) were placed in each will of a 96-well plate for RIA and the mixture was incubated for 3 days at 4 °C. Cell membrane fractions containing protein A were added and the mixture was allowed to stand for 20 min and centrifuged. The supernatant fluid was removed and the precipitates were washed with the RIA buffer. The <sup>125</sup>I content in the precipitates was measured. The GH concentration in the sample was calculated from the standard curve made by using the standard GH sample.

**[0257]** The EC<sub>50</sub> values of the test compounds were determined using recurrent calculation from the following equation, where X is the concentration of the test compound, Y is the GH concentration at the given assay, and B is the EC<sub>50</sub> value. C means recurrently calculated GH concentration in the absence of the test compound and A + C means recurrently calculated GH concentration when a maximum amount of the test compound is present.

$$Y = AX/(B + X) + C$$

**[0258]** The culture medium used here consisted of DMEM (Dulbecco's Modified Eagle's Medium) containing 10% horse serum, 2.5% fetal bovine serum, 1% nonessential amino acids, 0.01% streptomycin and penicillin (100 IU/mL). The cultured medium described above was adjusted to pH 7.3 by adding a 25 mM HEPES buffer and the resulting solution was used as the assay medium. A certain amount of the test compound was dissolved in DMSO, at which stage the concentration of the compound was 1000 times higher than the final concentration in the assay, and the aliquot (0.001 mL) was added to the assay medium (1 mL). The resulting mixture was used as the test compound solution. Collagenase (400 mg), DNase type I (1 mg), and BSA (1 g) were dissolved in a 25 mM HEPES buffer (pH 7.4, 40 mL) containing 0.8% NaCl, 0.037% KCl, 0.9% glucose, 0.01% streptomycin, penicillin (100 IU/mL), and 0.7 mM Na<sub>2</sub>HPO<sub>4</sub> and 10 mg/mL aqueous CaCl<sub>2</sub> solution (0.226 mL). The resulting solution was adjusted to a final volume of 50 mL by adding a 25 mM HEPES buffer and sterilized by filtration through a 0.00022 mm filter. The resulting mixture was used as the enzyme solution.

**[0259]** The compound of Example 21, 70, 74 and 91 was evaluated for their GH releasing efficacy under the conditions described above and showed EC<sub>50</sub> values of 4, 5, 0.5 and 1.2 nM, respectively.

#### 45 Experiment 2

##### Biological Activity

**[0260]** The compound of Example 74 (10 mg/kg/day x 2) were administered orally to 11-week-old F 344/N rats (6/group) for 9 days and increase in the weight of each rat was measured. The drug-administered group showed significant increase in the weight of 19.5 ± 2.1 g (p < 0.01), whereas the distilled water-administered group showed 13.5 ± 2.3 g.

##### Formulation Example

##### Preparation of Tablets

**[0261]** The compound of Example 91 (10 mg), lactose (72.5 mg), cornstarch (30 mg), and carboxymethyl cellulose

calcium (5 mg) are mixed, agglomerated with an aqueous solution of hydroxypropyl cellulose (2 mg), and then mixed with magnesium stearate. The resulting mixture is compacted into a tablet of 120 mg.

Industrial Applicability

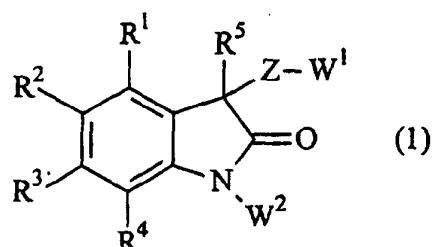
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[0262] The present invention can provide an oxindole derivative or a prodrug thereof, or a pharmaceutically acceptable salt thereof useful for a growth hormone releaser.

10 **Claims**

1. An oxindole derivative of Formula 1, or a pharmaceutically acceptable salt thereof:

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25 wherein

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are the same or different and each is independently hydrogen, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted C<sub>2</sub>-C<sub>6</sub> alkenyl, optionally substituted C<sub>2</sub>-C<sub>6</sub> alkynyl, optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl, an optionally substituted 5- to 7-membered mono- or bi-cyclic heteroaryl group containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms, halogen, cyano, nitro, hydroxy, optionally substituted amino, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, optionally substituted sulfamoyl, optionally substituted carbamoyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonylamino or C<sub>1</sub>-C<sub>6</sub> alkanoylamino, provided that all of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are not simultaneously hydrogen; R<sup>5</sup> is optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl or an optionally substituted 5- to 7-membered mono- or bi-cyclic heteroaryl group containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms;

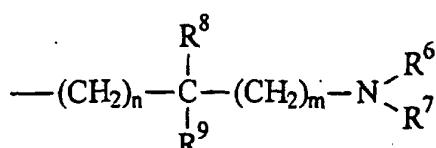
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Z is -O- or -NH-;

one of W<sup>1</sup> and W<sup>2</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or -Y-CON(R<sup>10</sup>)R<sup>11</sup>;

the other of W<sup>1</sup> and W<sup>2</sup> is

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n is 1, 2 or 3; m is 0, 1, 2 or 3;

Y is a single bond or C<sub>1</sub>-C<sub>3</sub> alkylene;

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R<sup>6</sup> and R<sup>7</sup> are the same or different and each is independently hydrogen, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl; or R<sub>6</sub> and R<sub>7</sub> are taken together with the adjacent nitrogen atom to form an optionally substituted 5- to 7-membered mono-cyclic saturated heterocyclic ring containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms;

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R<sup>8</sup> and R<sup>9</sup> are the same or different and each is independently hydrogen or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl; or R<sup>8</sup> and R<sup>9</sup> are taken together with the adjacent carbon atom to form optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkane or an optionally substituted 5- to 7-membered mono-cyclic saturated heterocyclic ring containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms;

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R<sup>8</sup> and R<sup>6</sup> may be taken together to form C<sub>1</sub>-C<sub>5</sub> alkylene in which case R<sup>7</sup> is hydrogen, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and R<sup>9</sup> is hydrogen or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>10</sup> and R<sup>11</sup> are the same or different and each is independently hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl; or R<sup>10</sup> and R<sup>11</sup> are taken together with the adjacent nitrogen atom to form an optionally substituted 5- to 7-membered mono-cyclic saturated heterocyclic ring containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms;

5 wherein:

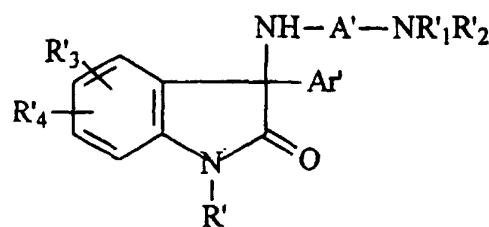
the substituents of an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl or C<sub>2</sub>-C<sub>6</sub> alkynyl group are independently selected from the group consisting of halogen, optionally substituted amino, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, C<sub>6</sub>-C<sub>10</sub> aryl, hydroxy, carboxy, optionally substituted carbamoyl, C<sub>1</sub>-C<sub>6</sub> alkanoyl, C<sub>6</sub>-C<sub>10</sub> aryloxycarbonyl, 5- to 7-membered mono- or bi-cyclic heteroaryl carbonyl (the heteroaryl group containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms), 5- to 7-membered mono-cyclic saturated heterocyclic group-carbonyl (the heterocyclic ring containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms), C<sub>1</sub>-C<sub>6</sub> alkanoylamino, C<sub>1</sub>-C<sub>6</sub> alkylsulfonylamino, optionally substituted ureido, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonylamino, optionally substituted 5- to 7-membered mono-cyclic saturated heterocyclic group (the heterocyclic ring containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms), and optionally substituted sulfamoyl;

10 the substituents of an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl, an optionally substituted 5- to 7-membered mono- or bi-cyclic heteroaryl group having from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms, an optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl group, or an optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkane group, are independently selected from the group consisting of halogen, C<sub>6</sub>-C<sub>10</sub> aryl, a 5- to 7-membered mono- or bi-cyclic heteroaryl group containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, optionally substituted amino, cyano, nitro, hydroxy, mercapto, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, carboxy, optionally substituted sulfamoyl, optionally substituted carbamoyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfamoylamino, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonylamino, C<sub>1</sub>-C<sub>6</sub> alkanoylamino;

15 the substituents of an optionally substituted 5- to 7-membered mono-cyclic saturated heterocyclic group are selected from the group consisting of halogen, C<sub>6</sub>-C<sub>10</sub> aryl, 5- to 7-membered mono- or bi-cyclic heteroaryl (the heteroaryl group containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms), C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl substituted by halogen, C<sub>1</sub>-C<sub>6</sub> alkoxy and/or hydroxy, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, optionally substituted amino, cyano, nitro, hydroxy, mercapto, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, carboxy, optionally substituted sulfamoyl, optionally substituted carbamoyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfamoylamino, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonylamino, C<sub>1</sub>-C<sub>6</sub> alkanoylamino and oxo;

20 the substituents of optionally substituted amino are selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl substituted by hydroxy, and C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> alkoxy, and

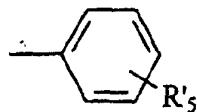
25 the substituents of optionally substituted sulfamoyl, optionally substituted carbamoyl and optionally substituted ureido are selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl substituted by hydroxy and C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> alkoxy; wherein when sulfamoyl, carbamoyl and ureido are substituted by two substituents, the two substituents may be taken together with the adjacent nitrogen atom to form a 5- to 7-membered mono-cyclic saturated heterocyclic group (the heterocyclic ring containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms); other than compounds of formula GB-1,125,671;



55 wherein R' represents hydrogen, lower alkyl, or di-(lower alkyl)amino; A' represents lower alkylene of 2, 3, 4 or 5 carbon atoms, separating the nitrogen atoms to which it is attached by at least 2 carbon atoms; each of R'<sub>1</sub> and R'<sub>2</sub> represents lower alkyl, or R'<sub>1</sub> and R'<sub>2</sub> are combined and together represent 3-oxa-pentamethylene or lower alkylene of 4, 5, 6, 7 or 8 carbon atoms, 4 or 5 of which carbon atoms are in annular position with the nitrogen atom to which they are attached; each of R'<sub>3</sub> and R'<sub>4</sub> represents hydrogen, lower alkyl, lower alkoxy, or halogen;

and Ar' represents benzyl or a group of the formula:

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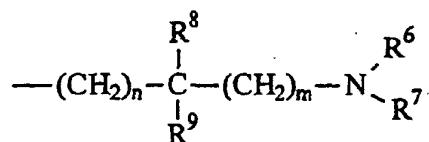
- 10 in which R'5 represents hydrogen, lower alkyl, lower alkoxy, or chlorine.
- 15 2. An oxindole derivative, or a pharmaceutically acceptable salt thereof according to claim 1 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted by halogen, optionally substituted C<sub>2</sub>-C<sub>6</sub> alkenyl, optionally substituted C<sub>2</sub>-C<sub>6</sub> alkynyl, optionally substituted carbamoyl, halogen, cyano, nitro, C<sub>1</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl or C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, provided that all of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are not simultaneously hydrogen;  
wherein the substituents of an optionally substituted C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl or carbamoyl group are as defined in claim 1.
- 20 3. An oxindole derivative, or a pharmaceutically acceptable salt thereof according to claim 1 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently hydrogen, trifluoromethyl, carbamoyl, halogen, 4-carbamoyl-1-butynyl, 4-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbamoyl-1-butynyl, 4-di (C<sub>1</sub>-C<sub>6</sub>)alkylcarbamoyl-1-butynyl, 4-morpholinocarbonyl-1-butynyl, -C≡C-(CH<sub>2</sub>)<sub>k</sub>-Q, wherein k is 1 or 2; Q is hydroxy, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkanoylamino, C<sub>1</sub>-C<sub>6</sub> alkylureido, 2-oxo-1-imidazolidinyl or 2-oxo-1,3-oxazolin-3-yl, provided that all of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are not simultaneously hydrogen.
- 25 4. An oxindole derivative, or a pharmaceutically acceptable salt thereof according to claim 3 wherein both of R<sup>2</sup> and R<sup>4</sup> are hydrogen.
- 30 5. An oxindole derivative, or a pharmaceutically acceptable salt thereof according to claim 1 wherein both of R<sup>2</sup> and R<sup>4</sup> are hydrogen; R<sup>1</sup> is trifluoromethyl, chlorine or bromine; and R<sup>3</sup> is carbamoyl, halogen, 4-carbamoyl-1-butynyl, 4-(C<sub>1</sub>-C<sub>6</sub>)alkylcarbamoyl-1-butynyl, 4-di (C<sub>1</sub>-C<sub>6</sub>)alkylcarbamoyl-1-butynyl, 4-morpholinocarbonyl-1-butynyl, -C≡C-(CH<sub>2</sub>)<sub>k</sub>-Q, wherein k and Q are as defined in claim 3.
- 35 6. An oxindole derivative, or a pharmaceutically acceptable salt thereof according to claim 1 wherein both of R<sup>2</sup> and R<sup>4</sup> are hydrogen; R<sup>1</sup> is trifluoromethyl, chlorine or bromine; and R<sup>3</sup> is carbamoyl.
- 40 7. An oxindole derivative, or a pharmaceutically acceptable salt thereof according to any one of claim 1 to claim 6 wherein R<sup>5</sup> is optionally substituted phenyl or optionally substituted 2-naphthyl; wherein the substituents of optionally substituted phenyl or optionally substituted 2-naphthyl are selected from the group consisting of halogen, C<sub>6</sub>-C<sub>10</sub> aryl, a 5- to 7-membered mono- or bi-cyclic heteroaryl group containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, optionally substituted amino, cyano, nitro, hydroxy, mercapto, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, carboxy, optionally substituted sulfamoyl, optionally substituted carbamoyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonylamino, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonylamino and C<sub>1</sub>-C<sub>6</sub> alkanoylamino; and wherein the substituents of optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted amino, optionally substituted sulfamoyl and optionally substituted carbamoyl are as defined in claim 1.
- 45 8. An oxindole derivative, or a pharmaceutically acceptable salt thereof according to any one of claim 1 to claim 6 wherein R<sup>5</sup> is phenyl optionally substituted by halogen(s) and/or trifluoromethyl(s) or 2-naphthyl optionally substituted by halogen(s) and/or trifluoromethyl(s).
- 50 9. An oxindole derivative, or a pharmaceutically acceptable salt thereof according to any one of claim 1 to claim 8 wherein R<sup>6</sup> and R<sup>7</sup> are independently optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl; or R<sup>6</sup> and R<sup>7</sup> are taken together with the adjacent nitrogen atom to form an optionally substituted 5- to 7-membered mono-cyclic saturated heterocyclic ring containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms;  
wherein the substituents of an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl group, an optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl group, and an optionally substituted 5- to 7-membered mono-cyclic saturated heterocyclic group are as

defined in claim 1.

10. An oxindole derivative, or a pharmaceutically acceptable salt thereof according to any one of claim 1 to claim 9 wherein one of W<sup>1</sup> and W<sup>2</sup> is hydrogen or -CONHR<sup>10</sup>; and the other of W<sup>1</sup> and W<sup>2</sup> is

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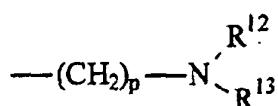
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wherein n, m, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> are as defined in claim 1.

15. 11. An oxindole derivative, or a pharmaceutically acceptable salt thereof according to any one of claim 1 to claim 9 wherein one of W<sup>1</sup> and W<sup>2</sup> is hydrogen; and the other of W<sup>1</sup> and W<sup>2</sup> is

20



wherein p is an integer of 2 to 7; and R<sup>12</sup> and R<sup>13</sup> are independently optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl; wherein the substituents of an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl group are as defined in claim 1.

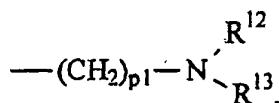
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12. An oxindole derivative, or a pharmaceutically acceptable salt thereof according to any one of claim 1 to claim 9, wherein

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(1) W<sup>1</sup> is hydrogen; and W<sup>2</sup> is

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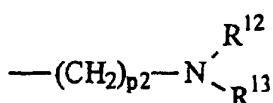


or

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(2) W<sup>2</sup> is hydrogen; and W<sup>1</sup> is

45



50

wherein p1 is an integer of 2 to 7; p2 is an integer of 3 to 7; and R<sup>12</sup> and R<sup>13</sup> are independently optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

wherein the substituents of an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl group are as defined in claim 1.

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13. An oxindole derivative, or a pharmaceutically acceptable salt thereof according to claim 11 or claim 12 wherein R<sup>12</sup> and R<sup>13</sup> are independently methyl or ethyl.

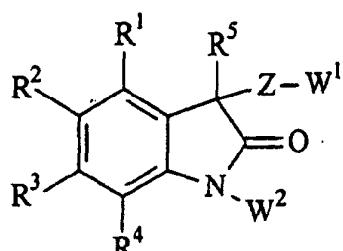
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14. An optical isomer of an oxindole derivative according to any one of the preceding claims, of which the configuration at the C-3 position is equivalent to that of (+)-1-(2-diethylaminoethyl)-4-trifluoromethyl-6-carbamoyl-3-hydroxy-3-(2-chlorophenyl)oxindole, or a pharmaceutically acceptable salt thereof.

15. A medicament containing an oxindole derivative, or a pharmaceutically acceptable salt thereof according to any one of the preceding claims and a pharmaceutically acceptable carrier or diluent.

5 16. An oxindole derivative, or a pharmaceutically acceptable salt thereof according to any one of claim 1 to claim 14 for use in therapy.

17. Use of an oxindole derivative of Formula 1, or a pharmaceutically acceptable salt thereof:



20 wherein

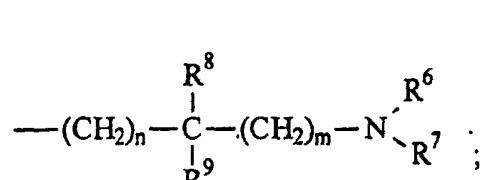
R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are the same or different and each is independently hydrogen, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted C<sub>2</sub>-C<sub>6</sub> alkenyl, optionally substituted C<sub>2</sub>-C<sub>6</sub> alkynyl, optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl, an optionally substituted 5- to 7-membered mono- or bi-cyclic heteroaryl group containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms, halogen, cyano, nitro, hydroxy, optionally substituted amino, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, optionally substituted sulfamoyl, optionally substituted carbamoyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonylamino or C<sub>1</sub>-C<sub>6</sub> alkanoylamino, provided that all of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are not simultaneously hydrogen;

25 R<sup>5</sup> is optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl or an optionally substituted 5- to 7-membered mono- or bi-cyclic heteroaryl group containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms,

30 Z is -O- or -NH-;

one of W<sup>1</sup> and W<sup>2</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or -Y-CON(R<sup>10</sup>)R<sup>11</sup>;

the other of W<sup>1</sup> and W<sup>2</sup> is



35 n is 1, 2 or 3; m is 0, 1, 2 or 3;

Y is a single bond or C<sub>1</sub>-C<sub>3</sub> alkylene;

40 45 R<sup>6</sup> and R<sup>7</sup> are the same or different and each is independently hydrogen, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl; or R<sup>6</sup> and R<sup>7</sup> are taken together with the adjacent nitrogen atom to form an optionally substituted 5- to 7-membered mono-cyclic saturated heterocyclic ring containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms;

50 R<sup>8</sup> and R<sup>9</sup> are the same or different and each is independently hydrogen or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl; or R<sup>8</sup> and R<sup>9</sup> are taken together with the adjacent carbon atom to form an optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkane or an optionally substituted 5- to 7-membered mono-cyclic saturated heterocyclic ring containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms.

55 R<sup>8</sup> and R<sup>6</sup> may be taken together to form C<sub>1</sub>-C<sub>5</sub> alkylene in which case R<sup>7</sup> is hydrogen, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl or optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and R<sup>9</sup> is hydrogen or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>10</sup> and R<sup>11</sup> are the same or different and each is independently hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl; or R<sup>10</sup> and R<sup>11</sup> are taken together with the adjacent nitrogen atom to form an optionally substituted 5- to 7-membered mono-cyclic saturated heterocyclic ring containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms;

wherein:

the substituents of an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl or C<sub>2</sub>-C<sub>6</sub> alkynyl group are independently selected from the group consisting of halogen, optionally substituted amino, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, C<sub>6</sub>-C<sub>10</sub> aryl, hydroxy, carboxy, optionally substituted carbamoyl, C<sub>1</sub>-C<sub>6</sub> alkanoyl, C<sub>6</sub>-C<sub>10</sub> aryl carbonyl, 5- to 7-membered mono- or bi-cyclic heteroaryl carbonyl (the heteroaryl group containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms), 5- to 7-membered monocyclic saturated heterocyclic group-carbonyl (the heterocyclic ring containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms), C<sub>1</sub>-C<sub>6</sub> alkanoylamino, C<sub>1</sub>-C<sub>6</sub> alkylsulfonylamino, optionally substituted ureido, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonylamino, optionally substituted 5- to 7-membered monocyclic saturated heterocyclic group (the heterocyclic ring containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms), and optionally substituted sulfamoyl;

the substituents of an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl, an optionally substituted 5- to 7-membered mono- or bi-cyclic heteroaryl group having from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms, an optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl group, or an optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkane group, are independently selected from the group consisting of halogen, C<sub>6</sub>-C<sub>10</sub> aryl, a 5- to 7-membered mono- or bi-cyclic heteroaryl group containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, optionally substituted amino, cyano, nitro, hydroxy, mercapto, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, carboxy, optionally substituted sulfamoyl, optionally substituted carbamoyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonylamino, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonylamino, C<sub>1</sub>-C<sub>6</sub> alkanoylamino;

the substituents of an optionally substituted 5- to 7-membered mono-cyclic saturated heterocyclic group are selected from the group consisting of halogen, C<sub>6</sub>-C<sub>10</sub> aryl, 5- to 7-membered mono- or bi-cyclic heteroaryl (the heteroaryl group containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms), C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl substituted by halogen, C<sub>1</sub>-C<sub>6</sub> alkoxy and/or hydroxy, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, optionally substituted amino, cyano, nitro, hydroxy, mercapto, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>6</sub> alkoxy carbonyl, carboxy, optionally substituted sulfamoyl, optionally substituted carbamoyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonylamino, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonylamino, C<sub>1</sub>-C<sub>6</sub> alkanoylamino and oxo;

the substituents of optionally substituted amino are selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl substituted by hydroxy, and C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> alkoxy, and

the substituents of optionally substituted sulfamoyl, optionally substituted carbamoyl and optionally substituted ureido are selected from the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl substituted by hydroxy and C<sub>1</sub>-C<sub>6</sub> alkyl substituted by C<sub>1</sub>-C<sub>6</sub> alkoxy; wherein when sulfamoyl, carbamoyl and ureido are substituted by two substituents, the two substituents may be taken together with the adjacent nitrogen atom to form a 5- to 7-membered mono-cyclic saturated heterocyclic group (the heterocyclic ring containing from one to three atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms);

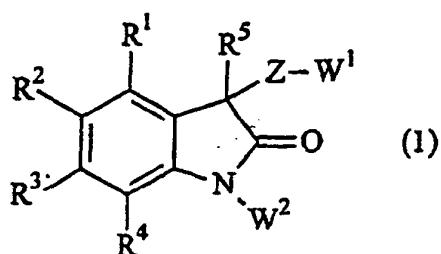
for the manufacture of a medicament which is a growth hormone releaser.

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### Patentansprüche

1. Oxindolderivat der Formel 1 oder ein pharmazeutisch verträgliches Salz davon:

45



wobei

R¹, R², R³ und R⁴ gleich oder verschieden sind und jeweils unabhängig voneinander Wasserstoff, gegebenenfalls

substituiertes C<sub>1</sub>-C<sub>6</sub>-Alkyl, gegebenenfalls substituiertes C<sub>2</sub>-C<sub>6</sub>-Alkenyl, gegebenenfalls substituiertes C<sub>2</sub>-C<sub>6</sub>-Alkinyl, gegebenenfalls substituiertes C<sub>6</sub>-C<sub>10</sub>-Aryl, ein gegebenenfalls substituierter 5- bis 7-gliedriger mono oder bicyclischer Heteroarylrest, der 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält, Halogen, Cyano, Nitro, Hydroxy, gegebenenfalls substituiertes Amino, C<sub>1</sub>-C<sub>6</sub>-Alkoxy, C<sub>1</sub>-C<sub>6</sub>-Alkanoyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxy carbonyl, gegebenenfalls substituiertes Sulfamoyl, gegebenenfalls substituiertes Carbamoyl, C<sub>1</sub>-C<sub>6</sub>-Alkylthio, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonylamino oder C<sub>1</sub>-C<sub>6</sub>-Alkanoylamino sind, mit der Maßgabe, dass die Reste R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> nicht gleichzeitig Wasserstoff sind;

R<sup>5</sup> gegebenenfalls substituiertes C<sub>6</sub>-C<sub>10</sub>-Aryl oder ein gegebenenfalls substituierter 5- bis 7-gliedriger mono- oder bicyclischer Heteroarylrest, der 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält, ist;

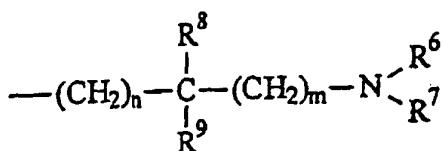
Z gleich -O- oder -NH- ist;

ein Rest W<sup>1</sup> und W<sup>2</sup> Wasserstoff, C<sub>1</sub>-C<sub>6</sub>-Alkyl oder -Y-CON(R<sup>10</sup>)R<sup>11</sup> ist;

der andere Rest W<sup>1</sup> und W<sup>2</sup>

15

20



ist;

n gleich 1, 2 oder 3 ist; m gleich 0, 1, 2 oder 3 ist;

25

Y eine Einfachbindung oder C<sub>1</sub>-C<sub>3</sub>-Alkylen ist;

30

R<sup>6</sup> und R<sup>7</sup> gleich oder verschieden sind und jeweils unabhängig voneinander Wasserstoff, gegebenenfalls substituiertes C<sub>1</sub>-C<sub>6</sub>-Alkyl oder gegebenenfalls substituiertes C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl sind; oder R<sup>6</sup> und R<sup>7</sup> zusammen mit dem benachbarten Stickstoffatom einen gegebenenfalls substituierten 5- bis 7-gliedrigen monocyclischen gesättigten heterocyclischen Ring, der 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält, bilden;

35

R<sup>8</sup> und R<sup>9</sup> gleich oder verschieden sind und jeweils unabhängig voneinander Wasserstoff oder gegebenenfalls substituiertes C<sub>1</sub>-C<sub>6</sub>-Alkyl sind; oder R<sup>8</sup> und R<sup>9</sup> zusammen mit dem benachbarten Kohlenstoffatom gegebenenfalls substituiertes C<sub>3</sub>-C<sub>8</sub>-Cycloalkan oder einen gegebenenfalls substituierten 5- bis 7-gliedrigen monocyclischen gesättigten heterocyclischen Ring, der 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält, bilden;

40

R<sup>8</sup> und R<sup>6</sup> zusammen C<sub>1</sub>-C<sub>5</sub>-Alkylen bilden können, wobei in diesem Fall R<sup>7</sup> Wasserstoff, gegebenenfalls substituiertes C<sub>1</sub>-C<sub>6</sub>-Alkyl oder gegebenenfalls substituiertes C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl ist, und R<sup>9</sup> Wasserstoff oder gegebenenfalls substituiertes C<sub>1</sub>-C<sub>6</sub>-Alkyl ist;

45

R<sup>10</sup> und R<sup>11</sup> gleich oder verschieden sind und jeweils unabhängig voneinander Wasserstoff oder C<sub>1</sub>-C<sub>6</sub>-Alkyl sind; oder R<sup>10</sup> und R<sup>11</sup> zusammen mit dem benachbarten Stickstoffatom einen gegebenenfalls substituierten 5- bis 7-gliedrigen monocyclischen gesättigten heterocyclischen Ring, der 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält, bilden;

wobei:

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die Substituenten des gegebenenfalls substituierten C<sub>1</sub>-C<sub>6</sub>-Alkyl-, C<sub>2</sub>-C<sub>6</sub>-Alkenyl- oder C<sub>2</sub>-C<sub>6</sub>-Alkinylrests unabhängig voneinander ausgewählt sind aus Halogen, gegebenenfalls substituiertem Amino, C<sub>1</sub>-C<sub>6</sub>-Alkoxy, C<sub>1</sub>-C<sub>6</sub>-Alkoxy carbonyl, C<sub>6</sub>-C<sub>10</sub>-Aryl, Hydroxy, Carboxy, gegebenenfalls substituiertem Carbamoyl, C<sub>1</sub>-C<sub>6</sub>-Alkanoyl, C<sub>6</sub>-C<sub>10</sub>-Arylcarbonyl, einem 5- bis 7-gliedrigen mono- oder bicyclischen Heteroarylcarbonyl (wobei der Heteroarylrest 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält), einem 5- bis 7-gliedrigen monocyclischen gesättigten heterocyclischen Rest-Carbonyl (wobei der heterocyclische Ring 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält), C<sub>1</sub>-C<sub>6</sub>-Alkanoylamino, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonylamino; gegebenenfalls substituiertem Ureido, C<sub>1</sub>-C<sub>6</sub>-Alkoxy carbonylamino, gegebenenfalls substituiertem 5- bis 7-gliedrigen monocyclischen gesättigten heterocyclischen Rest (wobei der heterocyclische Ring 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält) und gegebenenfalls substituiertem Sulfamoyl;

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die Substituenten des gegebenenfalls substituierten C<sub>6</sub>-C<sub>10</sub>-Arylrests, des gegebenenfalls substituierten 5- bis 7-gliedrigen mono- oder bicyclischen Heteroarylrests, der 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält, des gegebenenfalls substituierten C<sub>3</sub>-C<sub>8</sub>-Cycloalkylrests oder des

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gegebenenfalls substituierten C<sub>3</sub>-C<sub>8</sub>-Cycloalkanrests unabhängig voneinander ausgewählt sind aus Halogen, C<sub>6</sub>-C<sub>10</sub>-Aryl, einem 5- bis 7-gliedrigen mono- oder bicyclischen Heteroarylrest, der 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält, gegebenenfalls substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl, C<sub>2</sub>-C<sub>6</sub>-Alkenyl, C<sub>2</sub>-C<sub>6</sub>-Alkinyl, gegebenenfalls substituiertem Amino, Cyano, Nitro, Hydroxy, Mercapto, C<sub>1</sub>-C<sub>6</sub>-Alkoxy, C<sub>1</sub>-C<sub>6</sub>-Alkanoyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxy carbonyl, Carboxy, gegebenenfalls substituiertem Sulfamoyl, gegebenenfalls substituiertem Carbamoyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfamoylamino, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonylamino, C<sub>1</sub>-C<sub>6</sub>-Alkanoylamino;

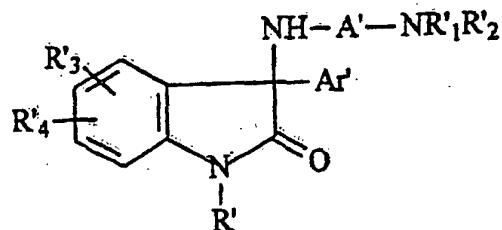
die Substituenten des gegebenenfalls substituierten 5- bis 7-gliedrigen monocyclischen gesättigten heterocyclischen Rests ausgewählt sind aus Halogen, C<sub>6</sub>-C<sub>10</sub>-Aryl, einem 5- bis 7-gliedrigen mono- oder bicyclischen Heteroaryl (wobei der Heteroarylrest 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält), C<sub>1</sub>-C<sub>6</sub>-Alkyl, C<sub>1</sub>-C<sub>6</sub>-Alkyl substituiert mit Halogen, C<sub>1</sub>-C<sub>6</sub>-Alkoxy und/oder Hydroxy, C<sub>2</sub>-C<sub>6</sub>-Alkenyl, C<sub>2</sub>-C<sub>6</sub>-Alkinyl, gegebenenfalls substituiertem Amino, Cyano, Nitro, Hydroxy, Mercapto, C<sub>1</sub>-C<sub>6</sub>-Alkoxy, C<sub>1</sub>-C<sub>6</sub>-Alkanoyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxy carbonyl, Carboxy, gegebenenfalls substituiertem Sulfamoyl, gegebenenfalls substituiertem Carbamoyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfamoylamino, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonylamino, C<sub>1</sub>-C<sub>6</sub>-Alkanoylamino und Oxo;

die Substituenten des gegebenenfalls substituierten Amino ausgewählt sind aus C<sub>1</sub>-C<sub>6</sub>-Alkyl, mit Hydroxy substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl, und mit C<sub>1</sub>-C<sub>6</sub>-Alkoxy substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl; und

die Substituenten des gegebenenfalls substituierten Sulfamoys, gegebenenfalls substituierten Carbamоys und gegebenenfalls substituierten Ureido ausgewählt sind aus C<sub>1</sub>-C<sub>6</sub>-Alkyl, mit Hydroxy substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl und mit C<sub>1</sub>-C<sub>6</sub>-Alkoxy substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl; wobei, wenn Sulfamoyl, Carbamoyl und Ureido durch zwei Substituenten substituiert sind, die zwei Substituenten mit dem benachbarten Stickstoffatom zusammen einen 5- bis 7-gliedrigen monocyclischen gesättigten heterocyclischen Rest (wobei der heterocyclische Ring 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält) bilden können;

mit Ausnahme von Verbindungen der Formel GB-1,125,671;

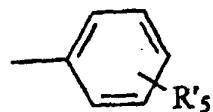
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wobei R' Wasserstoff, ein Niederalkylrest oder Di(niederalkyl)amino ist; A' ein Niederalkylenrest mit 2, 3, 4 oder 5 Kohlenstoffatomen ist, der die Stickstoffatom, an die er gebunden ist, durch mindestens 2 Kohlenstoffatome trennt; jeweils von R'<sub>1</sub> und R'<sub>2</sub> ein Niederalkylrest ist oder R'<sub>1</sub> und R'<sub>2</sub> kombiniert sind und zusammen 3-Oxapentamethylen oder ein Niederalkylenrest mit 4, 5, 6, 7 oder 8 Kohlenstoffatomen sind, wobei 4 oder 5 der Kohlenstoffatome in einer ringförmigen Position mit dem Stickstoffatom, an das sie gebunden sind, sind; jeweils von R'<sub>3</sub> und R'<sub>4</sub> Wasserstoff, ein Niederalkylrest, ein Niederalkoxyrest oder Halogen ist; und Ar' Benzyl oder ein Rest der Formel:

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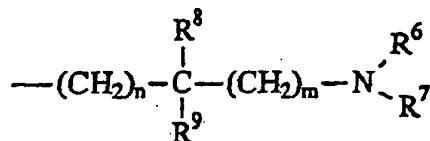
ist, in der R'<sub>5</sub> Wasserstoff, ein Niederalkylrest, ein Niederalkoxyrest oder Chlor ist.

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2. Oxindolderivat oder ein pharmazeutisch verträgliches Salz davon nach Anspruch 1, wobei R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> unabhängig voneinander Wasserstoff, gegebenenfalls mit Halogen substituiertes C<sub>1</sub>-C<sub>6</sub>-Alkyl, gegebenenfalls substituiertes C<sub>2</sub>-C<sub>6</sub>-Alkenyl, gegebenenfalls substituiertes C<sub>2</sub>-C<sub>6</sub>-Alkinyl, gegebenenfalls substituiertes Carbamoyl, Halogen, Cyano, Nitro, C<sub>1</sub>-C<sub>6</sub>-Alkanoyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxy carbonyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfinyl oder C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonyl ist, mit der Maßgabe, dass nicht alle Reste R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> gleichzeitig Wasserstoff sind; wobei die Substituenten des gegebenenfalls substituierten C<sub>2</sub>-C<sub>6</sub>-Alkenyl-, C<sub>2</sub>-C<sub>6</sub>-Alkinyl- oder Carbamoylrests

wie in Anspruch 1 definiert sind.

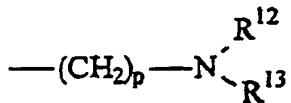
3. Oxindolderivat oder ein pharmazeutisch verträgliches Salz davon nach Anspruch 1, wobei R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> unabhängig voneinander Wasserstoff, Trifluormethyl, Carbamoyl, Halogen, 4-Carbamoyl-1-butinyl, 4-(C<sub>1</sub>-C<sub>6</sub>)-Alkylcarbamoyl-1-butinyl, 4-Di-(C<sub>1</sub>-C<sub>6</sub>)-Alkylcarbamoyl-1-butinyl, 4-Morpholincarbonyl-1-butinyl, -C≡C-(CH<sub>2</sub>)<sub>k</sub>-Q ist, wobei k gleich 1 oder 2 ist; Q Hydroxy, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub>-Alkanoylamino, C<sub>1</sub>-C<sub>6</sub>-Alkylureido, 2-Oxo-1-imidazolidinyl oder 2-Oxo-1,3-oxazolin-3-yl ist; mit der Maßgabe, dass nicht alle Reste R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> gleichzeitig Wasserstoff sind.
- 10 4. Oxindolderivat oder ein pharmazeutisch verträgliches Salz davon nach Anspruch 3, wobei beide Reste R<sup>2</sup> und R<sup>4</sup> Wasserstoff sind.
- 5 5. Oxindolderivat oder ein pharmazeutisch verträgliches Salz davon nach Anspruch 1, wobei beide Reste R<sup>2</sup> und R<sup>4</sup> Wasserstoff sind; R<sup>1</sup> Trifluormethyl, Chlor oder Brom ist; und R<sup>3</sup> Carbamoyl, Halogen, 4-Carbamoyl-1-butinyl, 4-(C<sub>1</sub>-C<sub>6</sub>)-Alkylcarbamoyl-1-butinyl, 4-Di-(C<sub>1</sub>-C<sub>6</sub>)-Alkylcarbamoyl-1-butinyl, 4-Morpholincarbonyl-1-butinyl, -C≡C-(CH<sub>2</sub>)<sub>k</sub>-Q ist, wobei k und Q wie in Anspruch 3 definiert sind.
- 15 6. Oxindolderivat oder ein pharmazeutisch verträgliches Salz davon nach Anspruch 1, wobei beide Reste R<sup>2</sup> und R<sup>4</sup> Wasserstoff sind; R<sup>1</sup> Trifluormethyl, Chlor oder Brom ist; und R<sup>3</sup> Carbamoyl ist.
- 20 7. Oxindolderivat oder ein pharmazeutisch verträgliches Salz davon nach einem der Ansprüche 1 bis 6, wobei R<sup>5</sup> gegebenenfalls substituiertes Phenyl oder gegebenenfalls substituiertes 2-Naphthyl ist; wobei die Substituenten des gegebenenfalls substituierten Phenyls oder gegebenenfalls substituierten 2-Naphthyls ausgewählt sind aus Halogen, C<sub>6</sub>-C<sub>10</sub>-Aryl, einem 5- bis 7-gliedrigen mono- oder bicyclischen Heteroarylrest, der 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält, gegebenenfalls substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl, C<sub>2</sub>-C<sub>6</sub>-Alkenyl, C<sub>2</sub>-C<sub>6</sub>-Alkinyl, gegebenenfalls substituiertem Amino, Cyano, Nitro, Hydroxy, Mercapto, C<sub>1</sub>-C<sub>6</sub>-Alkoxy, C<sub>1</sub>-C<sub>6</sub>-Alkanoyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxy carbonyl, Carboxy, gegebenenfalls substituiertem Sulfamoyl, gegebenenfalls substituiertem Carbamoyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonylamino, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonyl amino und C<sub>1</sub>-C<sub>6</sub>-Alkanoylamino; und wobei die Substituenten des gegebenenfalls substituierten C<sub>1</sub>-C<sub>6</sub>-Alkyls, gegebenenfalls substituierten Amino, gegebenenfalls substituierten Sulfamoyls und gegebenenfalls substituierten Carbamoyls wie in Anspruch 1 definiert sind.
- 25 8. Oxindolderivat oder ein pharmazeutisch verträgliches Salz davon nach einem der Ansprüche 1 bis 6, wobei R<sup>5</sup> Phenyl gegebenenfalls substituiert mit Halogen(en) und/oder Trifluormethyl(en) oder 2-Naphthyl gegebenenfalls substituiert mit Halogen(en) und/oder Trifluormethyl(en) ist.
- 30 9. Oxindolderivat oder ein pharmazeutisch verträgliches Salz davon nach einem der Ansprüche 1 bis 8, wobei R<sup>6</sup> und R<sup>7</sup> unabhängig voneinander gegebenenfalls substituiertes C<sub>1</sub>-C<sub>6</sub>-Alkyl oder gegebenenfalls substituiertes C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl sind; oder R<sup>6</sup> und R<sup>7</sup> zusammen mit dem benachbarten Stickstoffatom einen gegebenenfalls substituierten 5- bis 7-gliedrigen monocyclischen gesättigten heterocyclischen Ring, der 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält, bilden; wobei die Substituenten des gegebenenfalls substituierten C<sub>1</sub>-C<sub>6</sub>-Alkylrests, des gegebenenfalls substituierten C<sub>3</sub>-C<sub>8</sub>-Cycloalkylrests und des gegebenenfalls substituierten 5- bis 7-gliedrigen monocyclischen gesättigten heterocyclischen Rests wie in Anspruch 1 definiert sind.
- 35 10. Oxindolderivat oder ein pharmazeutisch verträgliches Salz davon nach einem der Ansprüche 1 bis 9, wobei einer der Reste W<sup>1</sup> und W<sup>2</sup> Wasserstoff oder -CONHR<sup>10</sup> ist; und der andere Rest W<sup>1</sup> und W<sup>2</sup>



ist, wobei n, m, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup> und R<sup>10</sup> wie in Anspruch 1 definiert sind.

11. Oxindolderivat oder ein pharmazeutisch verträgliches Salz davon nach einem der Ansprüche 1 bis 9, wobei einer der Reste W<sup>1</sup> und W<sup>2</sup> Wasserstoff ist; und der andere Rest W<sup>1</sup> und W<sup>2</sup>

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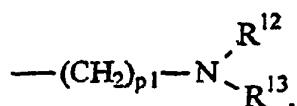
10 ist, wobei p eine ganze Zahl von 2 bis 7 ist; und R<sup>12</sup> und R<sup>13</sup> unabhängig voneinander gegebenenfalls substituiertes C<sub>1</sub>-C<sub>6</sub>-Alkyl sind; wobei die Substituenten des gegebenenfalls substituierten C<sub>1</sub>-C<sub>6</sub>-Alkylrests wie in Anspruch 1 definiert sind.

12. Oxindolderivat oder ein pharmazeutisch verträgliches Salz davon nach einem der Ansprüche 1 bis 9, wobei

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- (1) W<sup>1</sup> Wasserstoff ist; und W<sup>2</sup>

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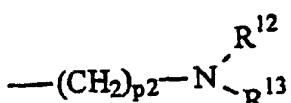


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ist, oder

- (2) W<sup>2</sup> Wasserstoff ist; und W<sup>1</sup>

30



35

ist,

wobei p1 eine ganze Zahl von 2 bis 7 ist; p2 eine ganze Zahl von 3 bis 7 ist; und R<sup>12</sup> und R<sup>13</sup> unabhängig voneinander gegebenenfalls substituiertes C<sub>1</sub>-C<sub>6</sub>-Alkyl sind; wobei die Substituenten des gegebenenfalls substituierten C<sub>1</sub>-C<sub>6</sub>-Alkylrests wie in Anspruch 1 definiert sind.

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13. Oxindolderivat oder ein pharmazeutisch verträgliches Salz davon nach Anspruch 11 oder Anspruch 12, wobei R<sup>12</sup> und R<sup>13</sup> unabhängig voneinander Methyl oder Ethyl sind.

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14. Optisches Isomer eines Oxindolderivats nach einem der vorstehenden Ansprüche, dessen Konfiguration an der C-3-Position zu der von (+)-1-(2-Diethylaminoethyl)-4-trifluormethyl-6-carbamoyl-3-hydroxy-3-(2-chlorphenyl)-oxindol oder ein pharmazeutisch verträgliches Salz davon äquivalent ist.

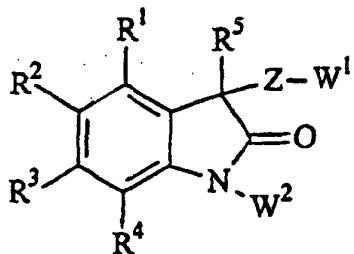
15. Arzneimittel, das ein Oxindolderivat oder ein pharmazeutisch verträgliches Salz davon nach einem der vorstehenden Ansprüche und einen pharmazeutisch verträglichen Träger oder Verdünnungsmittel enthält.

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16. Oxindolderivat oder ein pharmazeutisch verträgliches Salz davon nach einem der Ansprüche 1 bis 14 zur Verwendung bei einer Therapie.

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17. Verwendung eines Oxindolderivats der Formel 1 oder eines pharmazeutisch verträglichen Salzes davon



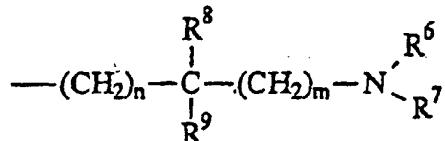
wobei

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> gleich oder verschieden sind und jeweils unabhängig voneinander Wasserstoff, gegebenenfalls substituiertes C<sub>1</sub>-C<sub>6</sub>-Alkyl, gegebenenfalls substituiertes C<sub>2</sub>-C<sub>6</sub>-Alkenyl, gegebenenfalls substituiertes C<sub>2</sub>-C<sub>6</sub>-Alkinyl, gegebenenfalls substituiertes C<sub>6</sub>-C<sub>10</sub>-Aryl, ein gegebenenfalls substituierter 5- bis 7-gliedriger mono-oder bicyclischer Heteroarylrest, der 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält, Halogen, Cyano, Nitro, Hydroxy, gegebenenfalls substituiertes Amino, C<sub>1</sub>-C<sub>6</sub>-Alkoxy, C<sub>1</sub>-C<sub>6</sub>-Alkanoyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxy carbonyl, gegebenenfalls substituiertes Sulfamoyl, gegebenenfalls substituiertes Carbamoyl, C<sub>1</sub>-C<sub>6</sub>-Alkylthio, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonylamino oder C<sub>1</sub>-C<sub>6</sub>-Alkanoylamino ist, mit der Maßgabe, dass die Reste R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> nicht gleichzeitig Wasserstoff sind;

15 R<sup>5</sup> gegebenenfalls substituiertes C<sub>6</sub>-C<sub>10</sub>-Aryl oder ein gegebenenfalls substituierter 5-bis 7-gliedriger mono- oder bicyclischer Heteroarylrest, der 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält, ist;

20 Z gleich -O- oder -NH- ist;

25 einer der Reste W<sup>1</sup> und W<sup>2</sup> Wasserstoff, C<sub>1</sub>-C<sub>6</sub>-Alkyl oder -Y-CON(R<sup>10</sup>)R<sup>11</sup> ist; der andere Rest W<sup>1</sup> und W<sup>2</sup>



35 ist;

n gleich 1, 2 oder 3 ist; m gleich 0, 1, 2 oder 3 ist;

Y eine Einfachbindung oder C<sub>1</sub>-C<sub>3</sub>-Alkylen ist;

40 R<sup>6</sup> und R<sup>7</sup> gleich oder verschieden sind und jeweils unabhängig voneinander Wasserstoff, gegebenenfalls substituiertes C<sub>1</sub>-C<sub>6</sub>-Alkyl oder gegebenenfalls substituiertes C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl sind; oder R<sup>6</sup> und R<sup>7</sup> zusammen mit dem benachbarten Stickstoffatom einen gegebenenfalls substituierten 5- bis 7-gliedrigen monocyclischen gesättigten heterocyclischen Ring, der 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält, bilden;

45 R<sup>8</sup> und R<sup>9</sup> gleich oder verschieden sind und jeweils unabhängig voneinander Wasserstoff oder gegebenenfalls substituiertes C<sub>1</sub>-C<sub>6</sub>-Alkyl sind; oder R<sup>8</sup> und R<sup>9</sup> zusammen mit dem benachbarten Kohlenstoffatom ein gegebenenfalls substituiertes C<sub>3</sub>-C<sub>8</sub>-Cycloalkan oder einen gegebenenfalls substituierten 5- bis 7-gliedrigen monocyclischen gesättigten heterocyclischen Ring, der 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält, bilden;

50 R<sup>8</sup> und R<sup>6</sup> zusammen ein C<sub>1</sub>-C<sub>5</sub>-Alkylen bilden können, wobei in diesem Fall R<sup>7</sup> Wasserstoff, gegebenenfalls substituiertes C<sub>1</sub>-C<sub>6</sub>-Alkyl oder gegebenenfalls substituiertes C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl ist, und R<sup>9</sup> Wasserstoff oder gegebenenfalls substituiertes C<sub>1</sub>-C<sub>6</sub>-Alkyl ist;

55 R<sup>10</sup> und R<sup>11</sup> gleich oder verschieden sind und jeweils unabhängig voneinander Wasserstoff oder C<sub>1</sub>-C<sub>6</sub>-Alkyl sind; oder R<sup>10</sup> und R<sup>11</sup> zusammen mit dem benachbarten Stickstoffatom einen gegebenenfalls substituierten 5- bis 7-gliedrigen monocyclischen gesättigten heterocyclischen Ring, der 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält, bilden;

wobei:

die Substituenten des gegebenenfalls substituierten C<sub>1</sub>-C<sub>6</sub>-Alkyl-, C<sub>2</sub>-C<sub>6</sub>-Alkenyl- oder C<sub>2</sub>-C<sub>6</sub>-Alkinylrests un-

abhängig voneinander ausgewählt sind aus Halogen, gegebenenfalls substituiertem Amino, C<sub>1</sub>-C<sub>6</sub>-Alkoxy, C<sub>1</sub>-C<sub>6</sub>-Alkoxycarbonyl, C<sub>6</sub>-C<sub>10</sub>-Aryl, Hydroxy, Carboxy, gegebenenfalls substituiertem Carbamoyl, C<sub>1</sub>-C<sub>6</sub>-Alkanoyl, C<sub>6</sub>-C<sub>10</sub>-Arylcarbonyl, einem 5- bis 7-gliedrigen mono- oder bicyclischen Heteroarylcarbonyl (wobei der Heteroarylrest 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält), einem 5- bis 7-gliedrigen monocyclischen gesättigten heterocyclischen Rest-Carbonyl (wobei der heterocyclische Ring 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält); C<sub>1</sub>-C<sub>6</sub>-Alkanoylamino, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonylamino, gegebenenfalls substituiertem Ureido, C<sub>1</sub>-C<sub>6</sub>-Alkoxycarbonylamino, gegebenenfalls substituiertem 5- bis 7-gliedrigen monocyclischen gesättigten heterocyclischen Rest (wobei der heterocyclische Ring 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält), und gegebenenfalls substituiertem Sulfamoyl;

5 die Substituenten des gegebenenfalls substituierten C<sub>1</sub>-C<sub>6</sub>-Arylrests, des gegebenenfalls substituierten 5- bis 7-gliedrigen mono- oder bicyclischen Heteroarylrests, der 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält, des gegebenenfalls substituierten C<sub>3</sub>-C<sub>8</sub>-Cycloalkylrests oder des gegebenenfalls substituierten Cycloalkanrests unabhängig voneinander ausgewählt sind aus Halogen, C<sub>6</sub>-C<sub>10</sub>-Aryl, einem 5- bis 7-gliedrigen mono- oder bicyclischen Heteroarylrest, der 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält, gegebenenfalls substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl, C<sub>2</sub>-C<sub>6</sub>-Alkenyl, C<sub>2</sub>-C<sub>6</sub>-Alkinyl, gegebenenfalls substituiertem Amino, Cyano, Nitro, Hydroxy, Mercapto, C<sub>1</sub>-C<sub>6</sub>-Alkoxy, C<sub>1</sub>-C<sub>6</sub>-Alkanoyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxycarbonyl, Carboxy, gegebenenfalls substituiertem Sulfamoyl, gegebenenfalls substituiertem Carbamoyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonylamino, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonylamino, C<sub>1</sub>-C<sub>6</sub>-Alkanoylamino;

10 die Substituenten des gegebenenfalls substituierten 5- bis 7-gliedrigen monocyclischen gesättigten heterocyclischen Rests ausgewählt sind aus Halogen, C<sub>6</sub>-C<sub>10</sub>-Aryl, einem 5- bis 7-gliedrigen mono- oder bicyclischen Heteroaryl (wobei der Heteroarylrest 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält), C<sub>1</sub>-C<sub>6</sub>-Alkyl, C<sub>1</sub>-C<sub>6</sub>-Alkyl substituiert mit Halogen, C<sub>1</sub>-C<sub>6</sub>-Alkoxy und/oder Hydroxy, C<sub>2</sub>-C<sub>6</sub>-Alkenyl, C<sub>2</sub>-C<sub>6</sub>-Alkinyl, gegebenenfalls substituiertem Amino, Cyano, Nitro, Hydroxy, Mercapto, C<sub>1</sub>-C<sub>6</sub>-Alkoxy, C<sub>1</sub>-C<sub>6</sub>-Alkanoyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxycarbonyl, Carboxy, gegebenenfalls substituiertem Sulfamoyl, gegebenenfalls substituiertem Carbamoyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonylamino, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonylamino, C<sub>1</sub>-C<sub>6</sub>-Alkanoylamino und Oxo;

15 die Substituenten des gegebenenfalls substituierten Amino ausgewählt sind aus C<sub>1</sub>-C<sub>6</sub>-Alkyl, mit Hydroxy substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl, und mit C<sub>1</sub>-C<sub>6</sub>-Alkoxy substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl; und

20 die Substituenten des gegebenenfalls substituierten Sulfamoyls, gegebenenfalls substituierten Carbamoyls und gegebenenfalls substituierten Ureido ausgewählt sind aus C<sub>1</sub>-C<sub>6</sub>-Alkyl, mit Hydroxy substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl und mit C<sub>1</sub>-C<sub>6</sub>-Alkoxy substituiertem C<sub>1</sub>-C<sub>6</sub>-Alkyl; wobei, wenn Sulfamoyl, Carbamoyl und Ureido durch zwei Substituenten substituiert sind, die zwei Substituenten zusammen mit dem benachbarten Stickstoffatom einen 5- bis 7-gliedrigen monocyclischen gesättigten heterocyclischen Rest (wobei der heterocyclische Ring 1 bis 3 Atome, ausgewählt aus Stickstoff-, Schwefel- und Sauerstoffatomen, enthält) bilden können;

25

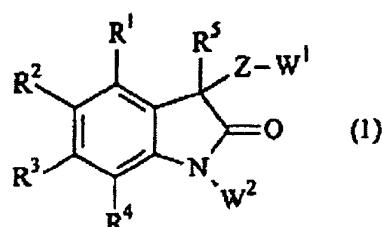
zur Herstellung eines Medikaments, welches ein Wachstumshormonreleaser ist.

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#### Revendications

1. Dérivé d'oxindole de formule 1, ou un sel pharmaceutiquement acceptable de ce dérivé :

45



55

dans lequel

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> sont identiques ou différents, et chacun représente indépendamment un atome d'hydrogène, les groupes alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué, alcényle en C<sub>2</sub>-C<sub>6</sub> éventuellement substitué, alcyne en

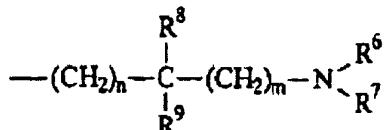
5  $C_2-C_6$  éventuellement substitué, aryle en  $C_6-C_{10}$  éventuellement substitué, un groupe hétéroaryle monocyclique ou bicyclique de 5 à 7 chaînons comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène, un atome d'halogène, les groupes cyano, nitro, hydroxyle, amino éventuellement substitué, alcoxy en  $C_1-C_6$ , alcanoyle en  $C_1-C_6$ , alcoxycarbonyle en  $C_1-C_6$ , sulfamoyle éventuellement substitué, carbamoyle, alkylthio en  $C_1-C_6$ , alkylsulfinylo en  $C_1-C_6$ , alkylsulfonylo en  $C_1-C_6$ , alkylsulfonylamino en  $C_1-C_6$  ou alcanoyle-amino en  $C_1-C_6$ , sous réserve que R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> ne représentent pas tous simultanément un atome d'hydrogène ;

10 R<sup>5</sup> représente un groupe aryle en  $C_6-C_{10}$  éventuellement substitué ou un groupe hétéroaryle monocyclique ou bicyclique de 5 à 7 chaînons comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène ;

15 Z représente -O- ou -NH-;

l'un des groupes parmi W<sup>1</sup> et W<sup>2</sup> représente un atome d'hydrogène, un groupe alkyle en  $C_1-C_6$  ou -Y-CON(R<sup>10</sup>)R<sup>11</sup>;

l'autre groupe parmi W<sup>1</sup> et W<sup>2</sup> représente



n vaut 1, 2 ou 3 ; m vaut 0, 1, 2 ou 3 ;

Y représente une liaison simple ou un groupe alkylène en  $C_1-C_3$  ;

25 R<sup>6</sup> et R<sup>7</sup> sont identiques ou différents, et chacun représente indépendamment un atome d'hydrogène ou les groupes alkyle en  $C_1-C_6$  éventuellement substitué ou cycloalkyle en  $C_3-C_8$  éventuellement substitué ; ou R<sup>6</sup> et R<sup>7</sup>, pris conjointement avec l'atome d'azote adjacent, forment un hétérocycle saturé monocyclique de 5 à 7 chaînons éventuellement substitué qui comporte de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène ;

30 R<sup>8</sup> et R<sup>9</sup> sont identiques ou différents, et chacun représente indépendamment un atome d'hydrogène ou un groupe alkyle en  $C_1-C_6$  éventuellement substitué ; ou R<sup>8</sup> et R<sup>9</sup>, pris conjointement avec l'atome de carbone adjacent, forment un cycloalcane en  $C_3-C_8$  éventuellement substitué ou un hétérocycle saturé monocyclique de 5 à 7 chaînons éventuellement substitué qui comporte de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène ;

35 R<sup>8</sup> et R<sup>6</sup> peuvent être pris conjointement afin de former un alkylène en  $C_1-C_5$ , auquel cas R<sup>7</sup> représente un atome d'hydrogène, les groupes alkyle en  $C_1-C_6$  éventuellement substitué ou cycloalkyle en  $C_3-C_8$  éventuellement substitué, et R<sup>9</sup> représente un atome d'hydrogène ou un groupe alkyle en  $C_1-C_6$  éventuellement substitué ;

40 R<sup>10</sup> et R<sup>11</sup> sont identiques ou différents, et chacun représente indépendamment un atome d'hydrogène ou un groupe alkyle en  $C_1-C_6$  éventuellement substitué ; ou R<sup>10</sup> et R<sup>11</sup>, pris conjointement avec l'atome d'azote adjacent, forment un hétérocycle saturé monocyclique de 5 à 7 chaînons éventuellement substitué qui comporte de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène ;

dans lequel :

45 les substituants d'un groupe alkyle en  $C_1-C_6$ , alcényle en  $C_2-C_6$  ou alcyne en  $C_2-C_6$ , éventuellement substitué, sont indépendamment choisis dans le groupe comprenant un atome d'halogène, les groupes amino éventuellement substitué, alcoxy en  $C_1-C_6$ , alcoxycarbonyle en  $C_1-C_6$ , aryle en  $C_6-C_{10}$ , hydroxyle, carboxyle, carbamoyle éventuellement substitué, alcanoyle en  $C_1-C_6$ , arylcarbonyle en  $C_6-C_{10}$ , hétéroarylcarbonyle monocyclique ou bicyclique de 5 à 7 chaînons (le groupe hétéroaryle comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre ou d'oxygène), hétérocycle carbonylé saturé monocyclique de 5 à 7 chaînons (l'hétérocycle comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène), alcanoyle-amino en  $C_1-C_6$ , alkylsulfonylamino en  $C_1-C_6$ , uréido éventuellement substitué, alcoxycarbonylamino en  $C_1-C_6$ , hétérocycle saturé monocyclique de 5 à 7 chaînons éventuellement substitué (l'hétérocycle comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène), et sulfamoyle éventuellement substitué ;

50 les substituants d'un groupe aryle en  $C_6-C_{10}$  éventuellement substitué, d'un groupe hétéroaryle monocyclique ou bicyclique de 5 à 7 chaînons éventuellement substitué comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène, d'un groupe cycloalkyle en  $C_3-C_8$  éventuellement substitué ou d'un groupe cycloalcane en  $C_3-C_8$  éventuellement substitué, sont indépendamment choisis dans

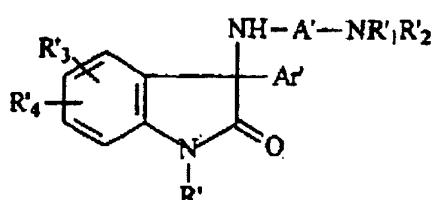
le groupe comprenant un atome d'halogène, les groupes aryle en C<sub>6</sub>-C<sub>10</sub>, hétéroaryle monocyclique ou bicyclique de 5 à 7 chaînons comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène, alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué, alcényle en C<sub>2</sub>-C<sub>6</sub>, alcyne en C<sub>2</sub>-C<sub>6</sub>, amino éventuellement substitué, cyano, nitro, hydroxyle, mercapto, alcoxy en C<sub>1</sub>-C<sub>6</sub>, alcanoyle en C<sub>1</sub>-C<sub>6</sub>, alcoxycarbonyle en C<sub>1</sub>-C<sub>6</sub>, carboxyle, sulfamoyle éventuellement substitué, carbamoyle éventuellement substitué, alkylsulfamoylamino en C<sub>1</sub>-C<sub>6</sub>, alkylsulfinyle en C<sub>1</sub>-C<sub>6</sub>, alkylsulfonyle en C<sub>1</sub>-C<sub>6</sub>, alkylsulfamoylamino en C<sub>1</sub>-C<sub>6</sub>, alcanoylamino en C<sub>1</sub>-C<sub>6</sub> ;

les substituants d'un groupe hétérocyclique saturé monocyclique de 5 à 7 chaînons éventuellement substitué sont choisis dans le groupe comprenant un atome d'halogène, les groupes aryle en C<sub>6</sub>-C<sub>10</sub>, hétéroaryle monocyclique ou bicyclique de 5 à 7 chaînons (le groupe hétéroaryle comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène), alkyle en C<sub>1</sub>-C<sub>6</sub>, alkyle en C<sub>1</sub>-C<sub>6</sub> substitué par un atome d'halogène, un groupe alcoxy en C<sub>1</sub>-C<sub>6</sub> et/ou un groupe hydroxyle, alcényle en C<sub>2</sub>-C<sub>6</sub>, alcyne en C<sub>2</sub>-C<sub>6</sub>, amino éventuellement substitué, cyano, nitro, hydroxyle, mercapto, alcoxy en C<sub>1</sub>-C<sub>6</sub>, alcanoyle en C<sub>1</sub>-C<sub>6</sub>, alcoxycarbonyle en C<sub>1</sub>-C<sub>6</sub>, carboxyle, sulfamoyle éventuellement substitué, carbamoyle éventuellement substitué, alkylsulfamoylamino en C<sub>1</sub>-C<sub>6</sub>, alkylsulfinyle en C<sub>1</sub>-C<sub>6</sub>, alkylsulfonyle en C<sub>1</sub>-C<sub>6</sub>, alkylsulfamoylamino en C<sub>1</sub>-C<sub>6</sub>, alcanoylamino en C<sub>1</sub>-C<sub>6</sub> ;

les substituants du groupe amino éventuellement substitué sont choisis dans le groupe comprenant les groupes alkyle en C<sub>1</sub>-C<sub>6</sub>, alkyle en C<sub>1</sub>-C<sub>6</sub> substitué par un groupe hydroxyle et alkyle en C<sub>1</sub>-C<sub>6</sub> substitué par un groupe alcoxy en C<sub>1</sub>-C<sub>6</sub>, et

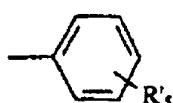
les substituants des groupes sulfamoyle éventuellement substitué, carbamoyle éventuellement substitué et uréido éventuellement substitué sont choisis dans le groupe comprenant les groupes alkyle en C<sub>1</sub>-C<sub>6</sub>, alkyle en C<sub>1</sub>-C<sub>6</sub> substitué par un groupe hydroxyle et alkyle en C<sub>1</sub>-C<sub>6</sub> substitué par un groupe alcoxy en C<sub>1</sub>-C<sub>6</sub>, dans lesquels lorsque les groupes sulfamoyle, carbamoyle et uréido sont substitués par deux substituants, les deux substituants peuvent être pris conjointement avec l'atome d'azote adjacent afin de former un groupe hétérocyclique saturé monocyclique ou bicyclique de 5 à 7 chaînons (l'hétérocycle comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène) ;

différent des composés de formule GB-1 125 671 ;



40 dans lequel R' représente un atome d'hydrogène, un groupe alkyle inférieur ou di(alkyle inférieur)amino ; A' représente un alkylène inférieur de 2, 3, 4 ou 5 atomes de carbone, séparant les atomes d'azote auxquels il est lié par au moins 2 atomes de carbone ; chacun de R'<sub>1</sub> et R'<sub>2</sub> représente un groupe alkyle inférieur, ou R'<sub>1</sub> et R'<sub>2</sub> sont réunis et représentent conjointement un groupe 3-oxapentaméthylène ou un alkylène inférieur de 4, 5, 6, 7 ou 8 atomes de carbone, 4 ou 5 de ces atomes de carbone forment un cycle avec l'atome d'azote auquel ils sont liés ;

45 chacun de R'<sub>3</sub> et R'<sub>4</sub> représente un atome d'hydrogène, un groupe alkyle inférieur, un groupe alcoxy inférieur ou un atome d'halogène ; et Ar' représente un groupe benzyle ou un groupe de formule:



dans lequel R'<sub>5</sub> représente un atome d'hydrogène, un groupe alkyle inférieur, un groupe alcoxy inférieur ou un atome de chlore.

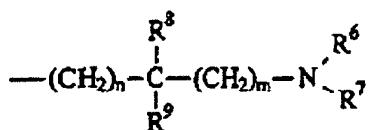
- 55
2. Dérivé d'oxindole ou un sel pharmaceutiquement acceptable de ce dérivé selon la revendication 1, dans lequel R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> représentent indépendamment un atome d'hydrogène ou un atome d'halogène, les groupes alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué par un atome d'halogène, alcényle en C<sub>2</sub>-C<sub>6</sub> éventuellement substitué, alcyne

en C<sub>2</sub>-C<sub>6</sub> éventuellement substitué, carbamoyle éventuellement substitué, cyano, nitro, alcanoyle en C<sub>1</sub>-C<sub>6</sub>, alcoxycarbonyle en C<sub>1</sub>-C<sub>6</sub>, alkylsulfinyle en C<sub>1</sub>-C<sub>6</sub>, alkylsulfonyle en C<sub>1</sub>-C<sub>6</sub>, sous réserve que R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> ne représentent pas tous simultanément un atome d'hydrogène ;

5 dans lequel les substituants d'un groupe alcényle en C<sub>2</sub>-C<sub>6</sub>, alcynyle en C<sub>2</sub>-C<sub>6</sub> ou carbamoyle, éventuellement substitué, ont les significations indiquées dans la revendication 1.

- 3. Dérivé d'oxindole ou un sel pharmaceutiquement acceptable de ce dérivé selon la revendication 1, dans lequel R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> représentent indépendamment un atome d'hydrogène ou un atome d'halogène, les groupes trifluorométhyle, carbamoyle, 4-carbamoyl-1-butynyle, 4-(alkyle en C<sub>1</sub>-C<sub>6</sub>)carbamoyl-1-butynyle, 4-di(alkyle en C<sub>1</sub>-C<sub>6</sub>)carbamoyl-1-butynyle, 4-morpholinocarbonyl-1-butynyle, -C≡C-(CH<sub>2</sub>)<sub>k</sub>-Q dans lequel k vaut 1 ou 2 ; Q représente un groupe hydroxyle, alkylsulfonyle en C<sub>1</sub>-C<sub>6</sub>, alcanoyleamino en C<sub>1</sub>-C<sub>6</sub>, alkyluréido en C<sub>1</sub>-C<sub>6</sub>, 2-oxo-1-imidazolidinyle ou 2-oxo-1,3-oxazolin-3-yle, sous réserve que R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> ne représentent pas tous simultanément un atome d'hydrogène.
- 4. Dérivé d'oxindole ou un sel pharmaceutiquement acceptable de ce dérivé selon la revendication 3, dans lequel R<sup>2</sup> et R<sup>4</sup> représentent tous deux un atome d'hydrogène.
- 5. Dérivé d'oxindole ou un sel pharmaceutiquement acceptable de ce dérivé selon la revendication 1, dans lequel R<sup>2</sup> et R<sup>4</sup> représentent tous deux un atome d'hydrogène, R<sup>1</sup> représente un groupe trifluorométhyle, un atome de chlore ou un atome de brome ; et R<sup>3</sup> représente un atome d'halogène, un groupe carbamoyle, 4-carbamoyl-1-butynyle, 4-(alkyle en C<sub>1</sub>-C<sub>6</sub>)carbamoyl-1-butynyle, 4-di(alkyle en C<sub>1</sub>-C<sub>6</sub>)carbamoyl-1-butynyle, 4-morpholinocarbonyl-1-butynyle, -C≡C-(CH<sub>2</sub>)<sub>k</sub>-Q dans lequel k et Q ont les significations indiquées dans la revendication 3.
- 6. Dérivé d'oxindole ou un sel pharmaceutiquement acceptable de ce dérivé selon la revendication 1, dans lequel R<sup>2</sup> et R<sup>4</sup> représentent tous deux un atome d'hydrogène, R<sup>1</sup> représente un groupe trifluorométhyle, un atome de chlore ou un atome de brome ; et R<sup>3</sup> représente un groupe carbamoyle.
- 7. Dérivé d'oxindole ou un sel pharmaceutiquement acceptable de ce dérivé selon l'une quelconque des revendications 1 à 6, dans lequel R<sup>5</sup> représente un groupe phényle éventuellement substitué ou un groupe 2-naphtyle éventuellement substitué ; dans lequel les substituants des groupes phényle et 2-naphtyle éventuellement substitués sont choisis dans le groupe comprenant un atome d'halogène, les groupes aryle en C<sub>6</sub>-C<sub>10</sub>, hétéroaryle monocyclique ou bicyclique de 5 à 7 chaînons comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène, alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué, alcényle en C<sub>2</sub>-C<sub>6</sub> éventuellement substitué, alcynyle en C<sub>2</sub>-C<sub>6</sub> éventuellement substitué, amino éventuellement substitué, cyano, nitro, hydroxyle, mercapto, alcoxy en C<sub>1</sub>-C<sub>6</sub>, alcanoyle en C<sub>1</sub>-C<sub>6</sub>, alcoxycarbonyle en C<sub>1</sub>-C<sub>6</sub>, carboxyle, sulfamoyle éventuellement substitué, carbamoyle éventuellement substitué, alkylsulfamoylamino en C<sub>1</sub>-C<sub>6</sub>, alkylsulfinyle en C<sub>1</sub>-C<sub>6</sub>, alkylsulfonyle en C<sub>1</sub>-C<sub>6</sub>, alkylsulfonylamino en C<sub>1</sub>-C<sub>6</sub> et alcanoyleamino en C<sub>1</sub>-C<sub>6</sub>; et dans lequel les substituants des groupes alkyle en C<sub>1</sub>-C<sub>6</sub>, amino, sulfamoyle et carbamoyle, éventuellement substitués, ont les significations indiquées dans la revendication 1.
- 8. Dérivé d'oxindole ou un sel pharmaceutiquement acceptable de ce dérivé selon l'une quelconque des revendications 1 à 6, dans lequel R<sup>5</sup> représente un groupe phényle éventuellement substitué par un ou plusieurs atomes d'halogène et/ou un ou plusieurs groupes trifluorométhyle, ou R<sup>5</sup> représente un groupe 2-naphtyle éventuellement substitué par un ou plusieurs atomes d'halogène et/ou un ou plusieurs groupes trifluorométhyle.
- 9. Dérivé d'oxindole ou un sel pharmaceutiquement acceptable de ce dérivé selon l'une quelconque des revendications 1 à 8, dans lequel R<sup>6</sup> et R<sup>7</sup> représentent indépendamment un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué ou un groupe cycloalkyle en C<sub>3</sub>-C<sub>8</sub> éventuellement substitué ; ou R<sup>6</sup> et R<sup>7</sup>, pris conjointement avec l'atome d'azote adjacent, forment un hétérocycle saturé monocyclique de 5 à 7 chaînons éventuellement substitué qui comporte de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène ; dans lequel les substituants d'un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué, d'un groupe cycloalkyle en C<sub>3</sub>-C<sub>8</sub> éventuellement substitué et d'un groupe hétérocyclique saturé monocyclique éventuellement substitué de 5 à 7 chaînons ont les significations indiquées dans la revendication 1.
- 10. Dérivé d'oxindole ou un sel pharmaceutiquement acceptable de ce dérivé selon l'une quelconque des revendications 1 à 9, dans lequel l'un des groupes parmi W<sup>1</sup> et W<sup>2</sup> représente un atome d'hydrogène ou -CONHR<sup>10</sup> ; et l'autre groupe parmi W<sup>1</sup> et W<sup>2</sup> représente

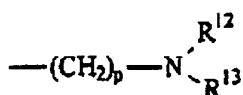
5



dans lequel n, m, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, et R<sup>10</sup> ont les significations indiquées dans la revendication 1.

- 10 11. Dérivé d'oxindole ou un sel pharmaceutiquement acceptable de ce dérivé selon l'une quelconque des revendications 1 à 9, dans lequel l'un des groupes parmi W<sup>1</sup> et W<sup>2</sup> représente un atome d'hydrogène ; et l'autre groupe parmi W<sup>1</sup> et W<sup>2</sup> représente

15

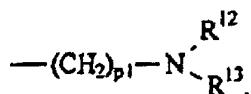


- 20 dans lequel p représente un nombre entier de 2 à 7 ; et R<sup>12</sup> et R<sup>13</sup> représentent indépendamment un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué ;  
dans lequel les substituants d'un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué ont les significations indiquées dans la revendication 1.

- 25 12. Dérivé d'oxindole ou un sel pharmaceutiquement acceptable de ce dérivé selon l'une quelconque des revendications 1 à 9,  
dans lequel

(1) W<sup>1</sup> représente un atome d'hydrogène et W<sup>2</sup> représente

30

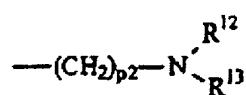


35

ou

(2) W<sup>2</sup> représente un atome d'hydrogène et W<sup>1</sup> représente

40



45

dans lequel p1 représente un nombre entier de 2 à 7 ; p2 représente un nombre entier de 3 à 7 ; et R<sup>12</sup> et R<sup>13</sup> représentent indépendamment un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué ;  
dans lequel les substituants d'un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué ont les significations indiquées dans la revendication 1.

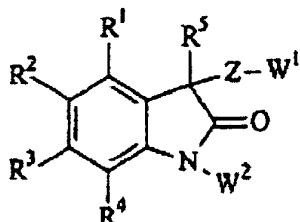
13. Dérivé d'oxindole ou un sel pharmaceutiquement acceptable de ce dérivé selon la revendication 11 ou la revendication 12, dans lequel R<sup>12</sup> et R<sup>13</sup> représentent indépendamment un groupe méthyle ou un groupe éthyle.

- 55 14. Isomère optique d'un dérivé d'oxindole selon l'une quelconque des revendications précédentes, dont la configuration de l'atome de carbone en position 3 est équivalente à celle du (+)-1-(2-diéthylaminoéthyl)-4-trifluorométhyl-6-carbamoyl-3-hydroxy-3-(2-chlorophényl)oxindole, ou un sel pharmaceutiquement acceptable de ce dérivé.

15. Médicament contenant un dérivé d'oxindole ou un sel pharmaceutiquement acceptable de ce dérivé selon l'une quelconque des revendications précédentes et un excipient ou un diluant pharmaceutiquement acceptable.

5 16. Dérivé d'oxindole ou un sel pharmaceutiquement acceptable de ce dérivé selon l'une quelconque des revendications 1 à 14, destiné à être utilisé en thérapie.

10 17. Utilisation d'un dérivé d'oxindole de formule 1 ou d'un sel pharmaceutiquement acceptable de ce dérivé :



20 dans lequel

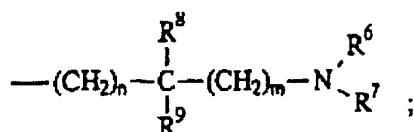
R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> sont identiques ou différents, et chacun représente indépendamment un atome d'hydrogène, les groupes alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué, alcényle en C<sub>2</sub>-C<sub>6</sub> éventuellement substitué, alcyne en C<sub>2</sub>-C<sub>6</sub> éventuellement substitué, aryle en C<sub>6</sub>-C<sub>10</sub> éventuellement substitué, un groupe hétéroaryle monocyclique ou bicyclique de 5 à 7 chaînons comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène, un atome d'halogène, les groupes cyano, nitro, hydroxyle, les groupes amino éventuellement substitué, alcoxy en C<sub>1</sub>-C<sub>6</sub>, alcanoyle en C<sub>1</sub>-C<sub>6</sub>, alcoxycarbonyle en C<sub>1</sub>-C<sub>6</sub>, sulfamoyle éventuellement substitué, carbamoyle, alkylthio en C<sub>1</sub>-C<sub>6</sub>, alkylsulfinyle en C<sub>1</sub>-C<sub>6</sub>, alkylsulfonyle en C<sub>1</sub>-C<sub>6</sub>, alkylsulfonylamino en C<sub>1</sub>-C<sub>6</sub> ou alcanoylamino en C<sub>1</sub>-C<sub>6</sub>, sous réserve que R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> ne représentent pas tous simultanément un atome d'hydrogène ;

30 R<sup>5</sup> représente un groupe aryle en C<sub>6</sub>-C<sub>10</sub> éventuellement substitué ou un groupe hétéroaryle monocyclique ou bicyclique de 5 à 7 chaînons comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène ;

Z représente -O- ou -NH- ;

l'un des groupes parmi W<sup>1</sup> et W<sup>2</sup> représente un atome d'hydrogène, un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> ou -Y-CON(R<sup>10</sup>)R<sup>11</sup> ;

35 l'autre groupe parmi W<sup>1</sup> et W<sup>2</sup> représente



40 n vaut 1, 2 ou 3 ; m vaut 0, 1, 2 ou 3 ;

Y représente une liaison simple ou un groupe alkylène en C<sub>1</sub>-C<sub>3</sub> ;

45 R<sup>6</sup> et R<sup>7</sup> sont identiques ou différents, et chacun représente indépendamment un atome d'hydrogène ou les groupes alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué ou cycloalkyle en C<sub>3</sub>-C<sub>8</sub> éventuellement substitué ; ou R<sup>6</sup> et R<sup>7</sup>, pris conjointement avec l'atome d'azote adjacent, forment un hétérocycle saturé monocyclique de 5 à 7 chaînons éventuellement substitué qui comporte de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène ;

50 R<sup>8</sup> et R<sup>9</sup> sont identiques ou différents, et chacun représente indépendamment un atome d'hydrogène ou un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué ; ou R<sup>8</sup> et R<sup>9</sup>, pris conjointement avec l'atome de carbone adjacent, forment un cycloalcane en C<sub>3</sub>-C<sub>8</sub> éventuellement substitué ou un hétérocycle saturé monocyclique de 5 à 7 chaînons éventuellement substitué qui comporte de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène ;

55 R<sup>8</sup> et R<sup>6</sup> peuvent être pris conjointement afin de former un alkylène en C<sub>1</sub>-C<sub>5</sub>, auquel cas R<sup>7</sup> représente un

atome d'hydrogène, les groupes alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué ou cycloalkyle en C<sub>3</sub>-C<sub>8</sub> éventuellement substitué, et R<sup>9</sup> représente un atome d'hydrogène ou un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué ;

R<sup>10</sup> et R<sup>11</sup> sont identiques ou différents, et chacun représente indépendamment un atome d'hydrogène ou un groupe alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué ; ou R<sup>10</sup> et R<sup>11</sup>, pris conjointement avec l'atome d'azote adjacent, forment un hétérocycle saturé monocyclique de 5 à 7 chaînons éventuellement substitué qui comporte de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène ; dans lequel :

les substituants d'un groupe alkyle en C<sub>1</sub>-C<sub>6</sub>, alcényle en C<sub>2</sub>-C<sub>6</sub> ou alcynyle en C<sub>2</sub>-C<sub>6</sub> éventuellement substitué sont indépendamment choisis dans le groupe comprenant un atome d'halogène, les groupes amino éventuellement substitué, alcoxy en C<sub>1</sub>-C<sub>6</sub>, alcoxycarbonyle en C<sub>1</sub>-C<sub>6</sub>, aryle en C<sub>6</sub>-C<sub>10</sub>, hydroxyle, carboxyle, carbamoyle éventuellement substitué, alcanoyle en C<sub>1</sub>-C<sub>6</sub>, arylcarbonyle en C<sub>6</sub>-C<sub>10</sub>, hétéroarylcarbonyle monocyclique ou bicyclique de 5 à 7 chaînons (le groupe hétéroaryle comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre ou d'oxygène), un groupe hétérocyclique carbonylé saturé monocyclique de 5 à 7 chaînons (l'hétérocycle comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène), un groupe hétérocyclique saturé monocylique de 5 à 7 chaînons éventuellement substitué (l'hétérocycle comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène), et sulfamoyle éventuellement substitué ;

les substituants d'un groupe aryle en C<sub>6</sub>-C<sub>10</sub> éventuellement substitué, d'un groupe hétéroaryle monocyclique ou bicyclique de 5 à 7 chaînons éventuellement substitué comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène, d'un groupe cycloalkyle en C<sub>3</sub>-C<sub>8</sub> éventuellement substitué ou d'un groupe cycloalcane en C<sub>3</sub>-C<sub>8</sub> éventuellement substitué, sont indépendamment choisis dans le groupe comprenant un atome d'halogène, les groupes aryle en C<sub>6</sub>-C<sub>10</sub>, hétéroaryle monocyclique ou bicyclique de 5 à 7 chaînons comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène, alkyle en C<sub>1</sub>-C<sub>6</sub> éventuellement substitué, alcényle en C<sub>2</sub>-C<sub>6</sub>, alcynyle en C<sub>2</sub>-C<sub>6</sub>, amino éventuellement substitué, cyano, nitro, hydroxyle, mercapto, alcoxy en C<sub>1</sub>-C<sub>6</sub>, alcanoyle en C<sub>1</sub>-C<sub>6</sub>, alcoxycarbonyle en C<sub>1</sub>-C<sub>6</sub>, carboxyle, sulfamoyle éventuellement substitué, carbamoyle éventuellement substitué, alkylsulfamoylamino en C<sub>1</sub>-C<sub>6</sub>, alkylsulfinyle en C<sub>1</sub>-C<sub>6</sub>, alkylsulfonyle en C<sub>1</sub>-C<sub>6</sub>, alkylsulfonylamino en C<sub>1</sub>-C<sub>6</sub>, alcanoyle en C<sub>1</sub>-C<sub>6</sub> ;

les substituants d'un groupe hétérocyclique saturé monocylique de 5 à 7 chaînons éventuellement substitué sont choisis dans le groupe comprenant un atome d'halogène, les groupes aryle en C<sub>6</sub>-C<sub>10</sub>, hétéroaryle monocyclique ou bicyclique de 5 à 7 chaînons (le groupe hétéroaryle comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène), alkyle en C<sub>1</sub>-C<sub>6</sub>, alkyl en C<sub>1</sub>-C<sub>6</sub> substitué par un atome d'halogène, un groupe alcoxy en C<sub>1</sub>-C<sub>6</sub> et/ou un groupe hydroxyle, alcényle en C<sub>2</sub>-C<sub>6</sub>, alcynyle en C<sub>2</sub>-C<sub>6</sub>, amino éventuellement substitué, cyano, nitro, hydroxyle, mercapto, alcoxy en C<sub>1</sub>-C<sub>6</sub>, alcanoyle en C<sub>1</sub>-C<sub>6</sub>, alcoxycarbonyle en C<sub>1</sub>-C<sub>6</sub>, carboxyle, sulfamoyle éventuellement substitué, carbamoyle éventuellement substitué, alkylsulfamoylamino en C<sub>1</sub>-C<sub>6</sub>, alkylsulfinyle en C<sub>1</sub>-C<sub>6</sub>, alkylsulfonyle en C<sub>1</sub>-C<sub>6</sub>, alkylsulfonylamino en C<sub>1</sub>-C<sub>6</sub>, alcanoyle en C<sub>1</sub>-C<sub>6</sub> ;

les substituants du groupe amino éventuellement substitué sont choisis dans le groupe comprenant les groupes alkyle en C<sub>1</sub>-C<sub>6</sub>, alkyl en C<sub>1</sub>-C<sub>6</sub> substitué par un groupe hydroxyle et alkyle en C<sub>1</sub>-C<sub>6</sub> substitué par un groupe alcoxy en C<sub>1</sub>-C<sub>6</sub>, et

les substituants des groupes sulfamoyle éventuellement substitué, carbamoyle éventuellement substitué et uréido éventuellement substitué sont choisis dans le groupe comprenant les groupes alkyle en C<sub>1</sub>-C<sub>6</sub>, alkyl en C<sub>1</sub>-C<sub>6</sub> substitué par un groupe hydroxyle et alkyle en C<sub>1</sub>-C<sub>6</sub> substitué par un groupe alcoxy en C<sub>1</sub>-C<sub>6</sub>, dans lesquels lorsque les groupes sulfamoyle, carbamoyle et uréido sont substitués par deux substituants, les deux substituants peuvent être pris conjointement avec l'atome d'azote adjacent afin de former un groupe hétérocyclique saturé monocyclique ou bicyclique de 5 à 7 chaînons (l'hétérocycle comportant de 1 à 3 atomes choisis dans le groupe comprenant les atomes d'azote, de soufre et d'oxygène) ;

pour la fabrication d'un médicament qui est un agent de libération de l'hormone de croissance.