US006645970B2

(12) **United States Patent**
Albert et al.

(10) **Patent No.: US 6,645,970 B2**
(45) **Date of Patent: Nov. 11, 2003**

(54) **INDOLYLMALEIMIDE DERIVATIVES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/007,368**

(22) Filed: **Nov. 5, 2001**

(65) **Prior Publication Data**

US 2003/0069424 A1 Apr. 10, 2003

Related U.S. Application Data

(60) Provisional application No. 60/246,400, filed on Nov. 7, 2000, and provisional application No. 60/283,705, filed on Apr. 13, 2001.

(51) **Int. Cl.**[7] **A61K 31/498**; A61K 31/475; A61K 31/506; C07D 403/14; C07D 401/14

(52) **U.S. Cl.** **514/266.2**; 514/256; 514/269; 514/272; 514/274; 514/311; 514/312; 514/313; 514/314; 514/307; 514/309; 514/310; 544/284; 544/235; 546/135; 546/139; 546/141; 546/143

(58) **Field of Search** 544/284, 235; 514/266.2, 256, 269, 272, 274, 311, 312, 313, 314, 307, 309, 310; 546/135, 139, 14, 143

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(57) **ABSTRACT**

Indolylmaleimide derivatives comprising either a substituted phenyl, naphthyl, tetrahydronaphthyl, quinazolinyl, quinolyl, isoquinolyl or pyrimidinyl residue have interesting pharmaceutical properties, e.g. in the treatment and/or prevention of T-cell mediated acute or chronic inflammatory diseases or disorders, autoimmune diseases, graft rejection or cancer.

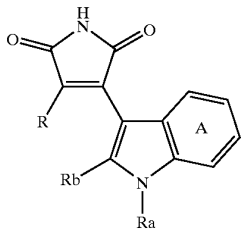
20 Claims, No Drawings

INDOLYLMALEIMIDE DERIVATIVES

This application claims the benefit of provisional application No. 60/246,400 filed Nov. 7, 2000 and of provisional application No. 60/283,705 filed Apr. 13, 2001.

The present invention relates to indolylmaleimide derivatives, process for their production and pharmaceutical compositions containing them.

More particularly the present invention provides a compound of formula I



I

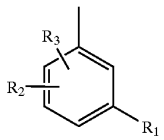
wherein

R_a is H; C_{1-4}alkyl; or C_{1-4}alkyl substituted by OH, NH_2, NHC_{1-4}alkyl or $N(C_{1-4}alkyl)_2$;

R_b is H; or C_{1-4}alkyl;

R is a radical of formula (a), (b), (c), (d), (e) or (f)

(a)



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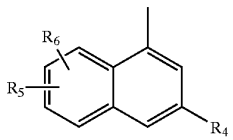

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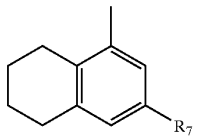

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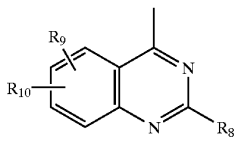

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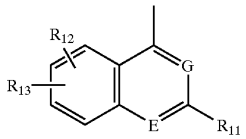

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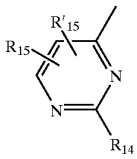


wherein

each of R_1, R_4, R_7, R_8, R_{11} and R_{14} is OH; SH; a heterocyclic residue; $NR_{16}R_{17}$ wherein each of R_{16} and R_{17}, independently, is H or C_{1-4}alkyl or R_{16} and R_{17}form together with the nitrogen atom to which they are bound a heterocyclic residue; or a radical of formula α

$$—X—R_c—Y \quad (\alpha)$$

wherein X is a direct bond, O, S or NR_{18} wherein R_{18} is H or C_{1-4}alkyl,

R_c is C_{1-4}alkylene or C_{1-4}alkylene wherein one CH_2 is replaced by CR_xR_y wherein one of R_x and R_y is H and the other is CH_3, each of R_x and R_y is CH_3 or R_x and R_y form together $—CH_2—CH_2—$, and

Y is bound to the terminal carbon atom and is selected from OH, a heterocyclic residue and $—NR_{19}R_{20}$ wherein each of R_{19} and R_{20} independently is H, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4} alkyl, aryl-C_{1-4}alkyl or C_{1-4}alkyl optionally substituted on the terminal carbon atom by OH, or R_{19} and R_{20} form together with the nitrogen atom to which they are bound a heterocyclic residue;

each of R_2, R_3, R_5, R_6, R_9, R_{10}, R_{12}, R_{13}, R_{15} and R'_{15}, independently, is H, halogen, C_{1-4}alkyl, CF_3, OH, SH, NH_2, C_{1-4}alkoxy, C_{1-4}alkylthio, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)_2$ or CN;

either E is —N═ and G is —CH═ or E is —CH═ and G is —N═; and

ring A is optionally substituted.

Any alkyl or alkyl moiety in e.g. alkoxy may be linear or branched. Halogen may be F, Cl, Br or I, preferably F or Cl. Any aryl may be phenyl or naphthyl, preferably phenyl.

By heterocyclic residue as R_1, R_4, R_7, R_8, R_{11}, R_{14} or Y or formed, respectively, by $NR_{16}R_{17}$ or $NR_{19}R_{20}$, is meant a three to eight, preferably five to eight, membered saturated, unsaturated or aromatic heterocyclic ring comprising 1 or 2 heteroatoms, preferably selected from N, O and S, and optionally substituted. Suitable examples include e.g. pyridyl, e.g. 3- or 4-pyridyl, piperidyl, e.g. piperidin-1-yl, 3- or 4-piperidyl, homopiperidyl, piperazinyl, homopiperazinyl, morpholin-4-yl, imidazolyl, imidazolidinyl, pyrrolyl or pyrrolidinyl, optionally substituted, e.g. mono- or polysubstituted. When the heterocyclic residue is substituted, this may be on one or more ring carbon atoms and/or on a ring nitrogen atom when present. Examples of a substituent on a ring carbon atom include e.g. C_{1-4}alkyl e.g. CH_3;

C_{3-6}cycloalkyl e.g. cyclopropyl, optionally further substituted by C_{1-4}alkyl;

wherein p is 1,2 or 3, preferably 1; CF_3; halogen; OH; NH_2; $—CH_2—NH_2$; $—CH_2—OH$; piperidin-1-yl; pyr-

rolidinyl. Examples of a substituent on a ring nitrogen atom are e.g. C_{1-6}alkyl; acyl, e.g. R'$_x$-CO wherein R'$_x$ is H, C_1alkyl or phenyl optionally substituted by C_{1-4}alkyl, C_{1-4}alkoxy or amino, e.g formyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl—C_{1-4}alkyl; phenyl; phenyl-C_{1-4}alkyl e.g. benzyl; a heterocyclic residue, e.g. as disclosed above, e.g. an aromatic heterocyclic residue comprising 1 or 2 nitrogen atoms; or a residue of formula β

$$—R_{21}—Y' \quad (\beta)$$

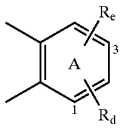
wherein R_{21} is C_{1-4}alkylene or C_{2-4}alkylene interrupted by O and Y' is OH, NH_2, NH(C_{1-4}alkyl) or N(C_{1-4}alkyl)$_2$.

C_{2-4}alkylene interrupted by O may be e.g. —CH_2—CH_2—O—CH_2—CH_2—.

When the substituent on a cyclic nitrogen is a heterocyclic residue, it may be a five or six membered saturated, unsaturated or aromatic heterocyclic ring comprising 1 or 2 heteroatoms, preferably selected from N, O and S. Examples include e.g. 3- or 4-pyridyl, piperidyl, e.g. piperidin-1-yl, 3- or 4-piperidyl, homopiperidyl, piperazinyl, homopiperazinyl, pyrimidinyl, morpholin-4-yl, imidazolyl, imidazolidinyl, pyrrolyl or pyrrolidinyl,

When R_a is substituted C_{1-4}alkyl, the substituent is preferably on the terminal carbon atom.

When ring A is substituted, it may be mono- or polysubstituted, preferably monosubstituted, the substituent (s) being selected from the group consisting of e.g. halogen, OH, C_{1-4}alkoxy, e.g. OCH_3, C_{1-4}alkyl, e.g. CH_3, NO_2, CF_3, NH_2, NHC_{1-4}alkyl, N(C_{1-4}alkyl)$_2$ and CN. For example, ring A may be a residue of formula



wherein

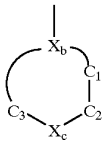
R_d is H; C_{1-4}alkyl; or halogen; and

R_e is OH; NO_2; NH_2; NHC_{1-4}alkyl; or N(C_{1-4}alkyl)$_2$.

When R_a has a CH_2 replaced by CR_xR_Y, it is preferably the CH_2 bearing Y.

Examples of heterocyclic residue as R_1, R_4, R_7, R_8, R_{11}, R_{14} or Y or formed, respectively, by $NR_{16}R_{17}$ or $NR_{19}R_{20}$, include e.g. a residue of formula (γ)

$$(\gamma)$$



wherein

the ring D is a 5, 6 or 7 membered saturated, unsaturated or aromatic ring;

X_b is —N—, —C═ or —CH—;

X_c is —N═, —NR_f—, —CR_f'— or —CHR_f'— wherein R_f is a substituent as indicated above for a ring nitrogen atom, and R_f' is a substituent as indicated above for a ring carbon atom;

the bond between C_1 and C_2 is either saturated or unsaturated;

each of C_1 and C_2, independently, is a carbon atom which is optionally substituted by one or two substituents selected among those indicated above for a ring carbon atom; and

the line between C_3 and X_b and between C_1 and X_b, respectively, represents the number of carbon atoms as required to obtain a 5, 6 or 7 membered ring D.

A preferred residue of formula (γ) is one wherein the ring D forms a 1,4-piperazinyl ring optionally C- and/or N-substituted as indicated.

Representative examples of a residue of formula (γ) are e.g. 3- or 4- pyridyl; piperidin-1-yl; 1-N-(C_{1-4}alkyl)- or —(ω-hydroxy—C_{1-4}alkyl)-3-piperidyl; morpholin-4-yl; imidazolyl; pyrrolidinyl; 1-piperazinyl; 2-C_{1-4}alkyl- or -C_{3-6}cycloalkyl-1-piperazinyl; 3-C_{1-4}alkyl- or —C_{3-6}cycloalkyl-1-piperazinyl; 2,2- or 3,5- or 2,5- or 2,6-di(C_{1-4}alkyl)-1-piperazinyl; 3,4,5-tri-(C_{1-4}alkyl)-1-piperazinyl; 4-N-(C_{1-4}alkyl)- or —(ω-hydroxy-C_{1-4}alkyl)- or —(ω-dimethylamino-C_{1-4}alkyl)-1-piperazinyl; 4-N-pyridin-4-yl-1-piperazinyl; 4-N-phenyl- or —C_{3-6}cycloalkyl-1-piperazinyl; 4-N-(C_{1-4}alkyl)- or —(ω-hydroxy-C_{1-4}alkyl)-3-C_{1-4}alkyl- or —3,3-di(C_{1-4}alkyl)-1-piperazinyl; 4-N-(1-C_{1-4}alkyl-C_{3-6}cycloalkyl)-1-piperazinyl; 4-N-formyl-1-piperazinyl; 4-N-pyrimidin-2-yl-1-piperazinyl; or 4-N-C_{1-4}alkyl-1-homopiperazinyl.

The compounds of formula I may exist in free form or in salt form, e.g. addition salts with e.g. organic or inorganic acids, for example, hydrochloric acid, acetic acid, when R_1, R_4, R_7, R_8, R_{11} or R_{14} and/or R_2, R_3, R_5, R_6, R_9, R_{10}, R_{12}, R_{13} or R_{15} comprises an optionally substituted amino group or a heterocyclic residue which can form acid addition salts.

It will be appreciated that the compounds of formula I may exist in the form of optical isomers, racemates or diastereoisomers. For example, a ring carbon atom bearing a substituent in the heterocyclic residue as R_1, R_4, R_7, R_8, R_{11}, R_{14} or Y or formed, respectively, by $NR_{16}R_{17}$ or $NR_{19}R_{20}$, is asymmetric and may have the D- or L- configuration. It is to be understood that the present invention embraces all enantiomers and their mixtures. Similar considerations apply in relation to starting materials exhibiting asymetric carbon atoms as mentioned.

In the compounds of formula I, the following significances are preferred individually or in any sub-combination:

1. R_a is H or CH_3;
2. R_b is H;
3. Ring A is unsubstituted; or is substituted by methyl in position 7;
4. Preferred heterocyclic residue as formed by $NR_{16}R_{17}$ is e.g. piperazin-1-yl optionally N-substituted, e.g. by C_{1-4}aakyl, ω-hydroxy-C_{1-4}alkyl, ω-dimethylamino-C_{1-4} alkyl, C_{5-6}cycloalkyl, C_{1-4}alkyl-C_{5-6}cycloalkyl, an aromatic heterocyclic residue comprising 1 or 2 nitrogen atoms, e.g. pyridyl or pyrimidin-2-yl, or aresidue of formula β as defined above and/or optionally C-substituted, e.g. by CH_3 e.g. in positions 2, and/or 3 and/or 5 and/or 6 and/or 2,2 or 3,3 or by

e.g. in position 2 or 3; piperidin-1-yl optionally C-substituted, e.g. in position 4, by NH_2, —CH_2—NH_2 or piperidin-1-yl, or in position 3, e.g. by OH or NH_2; or pyrrolidinyl optionally C-substituted in position 3 by OH or NH_2;

5. R_{18} is H or CH_3;

6. R_c is C_{1-4}alkylene or C_{1-4}alkylene wherein the terminal CH_2 is replaced by CR_xR_y wherein R_x and R_y form together —CH_2—CH_2—;

7. X is O;

8. The radical of formula (α) is —O—CH_2—CH_2—Y;

9. Each of R_{19} and R_{20} is H, C_{1-4}alkyl, e.g. methyl, C_{1-4}alkyl substituted on the terminal carbon atom by OH, e.g. —CH_2—CH_2—OH, or cyclopropyl;

10. Preferred heterocyclic residue as formed by $NR_{19}R_{20}$ is e.g. piperazin-1-yl optionally N-substituted by C_{1-4}alkyl or a residue of formula β; piperidin-1-yl; 1-(C_{1-4}alkyl)-piperidin-3-yl; 3- or 4-pyridyl; imidazolyl; pyrrolidinyl; or morpholin-4-yl;

11. Each of R_1, R_4, R_7, R_8, R_{11} or R_{14}, independently, is 1-N-methyl-piperidin-4-yl; 4-methyl-piperazin-1-yl; 4-methyl-1-homopiperazinyl; 4-(2-hydroxyethyl)-piperazin-1-yl; or —X'—$C_{1,2}$ or **3**-alkylene-$NR_{19}R_{20}$ wherein X' is a direct bond, O or NH;

12. In the residue of formula (a) either each of R_2 and R_3 is H or one of R_2 and R_3 is H and the other is F, Cl, CH_3, OH, OCH_3 or CF_3;

13. In the residue of formula (a) R_2 is OH;

14. In the residue of formula (b) either each of R_5 and R_6 is H or one of R_5 and R_6 is H and the other is F, Cl, CH_3, OCH_3 or CF_3;

15. In the residue of formula (b) R_4 is a radical of formula (α) or $NR_{16}R_{17}$;

16. In the residue of formula (d) either each of R_9 and R_{10} is H or one of R_9 and R_{10} is H and the other is F, Cl, CH_3, OCH_3 or CF_3; preferably R_{10} is H and R_9 is in position 5, 6, 7 or 8, preferably in position 6;

17. In the residue of formula (e) each of R_{12} and R_{13} is H;

18. In the residue of formula (e) one of R_{12} and R_{13} is H and the other is F, Cl, CH_3, OCH_3 or CF_3;
when E is —N═ and G is —CH═, preferably R_{13} is H and R_{12} is in position 6 or 7;
when E is —CH═ and G is —N═, preferably R_{13} is H and R_{12} is in position 7;

19. In the residue of formula (f) R_{15} is H, CH_3 or Cl, e.g. in position 5 or 6;

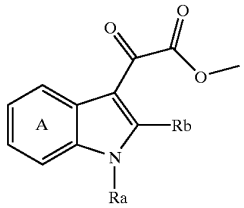
20. In the residue of formula (f) R'_{15} is H or CH_3, e.g. in position 5, preferably H;

21. R is a radical of formula (d), (e) or (f).

The present invention also includes a process for the preparation of a compound of formula I which process comprises

a) reacting a compound of formula II

(II)



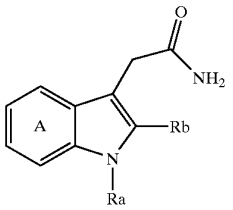
wherein R_a, R_b and ring A are as defined above, with a compound of formula III

$$R—CH_2—CO—NH_2 \quad (III)$$

wherein R is as defined above,

b) reacting a compound of formula IV

(IV)



wherein R_a, R_b and ring A are as defined above, with a compound of formula V

$$R—CO—CO—OCH_3 \quad (V)$$

wherein R is as defined above; or

c) converting in a compound of formula I a substituent R_1, R_4, R_7, R_8, R_{11} or R_{14} into another substituent R_1, R_4, R_7, R_8, R_{11} or R_{14}

and, where required, converting the resulting compound of formula I obtained in free form to a salt form or vice versa, as appropriate.

Process steps a) and (b) may conveniently be effected in the presence of a strong base, e.g. t-BuOK. When compounds of formula III or V comprising an OH group which should not participate to the reaction are used, such OH group is in protected form. The OH-protecting group may be removed according to methods known in the art at the end of condensation step a) or b). Process step c) may be carried out according to known methods: for example when R_1, R_4, R_7, R_8, R_{11}, or R_{14} comprises a final OH group, this OH group may be replaced by the desired —$NR_{16}R_{17}$ or —$NR_{19}R_{20}$.

Compounds of formula II may be prepared by reacting the corresponding indol compound with an oxalyl halogenide, e.g. chloride, or with a monoalkyl oxalyl chloride under basic conditions, e.g. as disclosed in Example 28.

Compounds of formula III or V, used as starting materials, may be prepared in accordance with known methods, e.g. by introducing the desired substituent R_1, R_4, R_7, R_8, R_{11} or R_{14}, respectively, in a compound of formula III' or V'

$$R'—CH_2—CO—NH_2 \quad (III')$$

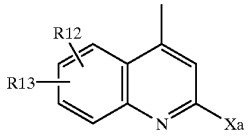
$$R''—CO—CO—OCH_3 \quad (V')$$

wherein each of R' or R" is respectively a radical of formula (a), (b), (c), (d), (e) or (f), each of which comprising a leaving group, e.g. halogen, in place of R_1, R_4, R_7, R_8, R_{11}, or R_{14}.

Alternatively, compounds of formula III wherein R is a radical of formula (a), (b) or (c), R_1, R_4 or R_7 being a radical of formula (α), may be prepared in accordance with known methods by reacting a compound of formula III' wherein R' is respectively a radical of formula (a), (b) or (c), each of which comprising OH in place of R_1, R_4or R_7, with a compound of formula X_a—X—R_c—Y wherein X_a is a leaving group, e.g. Cl, and X, R_c or Y are as defined above.

Compounds of formula I wherein R is a radical of formula (e) wherein E is —N═, G is —CH═ and R_{11} is —O—R_c—Y or —S—R_c—Y may also be prepared by reacting together a compound of formula II as defined above with a compound of formula III' wherein R' is a radical of formula (e')

(e')



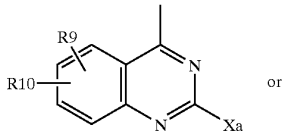
wherein R_{12} and R_{13} are as defined above and X_a is a leaving group, e.g. halogen, and with a compound of formula VI

$$R'_{11}H \qquad (VI)$$

wherein R'_{11} is —O—R_c—Y or —S—R_c—Y. This reaction may be carried out in accordance with know methods, e.g. as disclosed in Example 28 below.

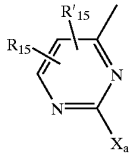
Compounds of formula I wherein R is a radical of formula (d) or (f) wherein R_8 or R_{14} is —O—R_c—Y or —S—R_c—Y may also be prepared by reacting together a compound of formula II as defined above with a compound of formula III' wherein R" is a radical of formula (d') or (f')

(d')



or

(f')



wherein R_9, R_{10}, R_{15} and R'_{15} are as defined above and X_a is a leaving group, e.g. halogen, and with a compound of formula VI'

$$A—H \qquad (VI)$$

wherein A is —O—R_c—Y or —S—R_c—Y. This reaction may be carried out in accordance with know methods.

Insofar as the production of the starting materials is not particularly described, the compounds are known or may be prepared analogously to methods known in the art or as described hereafter.

The following Examples are illustrative of the invention.

RT=room temperature

THF=tetrahydrofuran

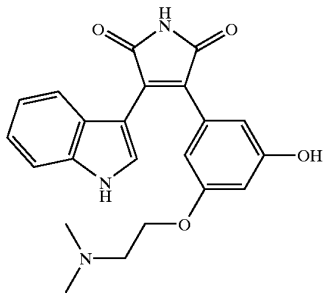
FCC=flash column chromatography

TBAF=tetrabutyl ammonium fluoride

BINAP=2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

EXAMPLE 1

3-(1.H.-Indol-3-yl)-4-[3-(2-dimethylamino-ethoxy)-5-hydroxy-phenyl]-pyrrole-2,5-dione



A solution of 400 mg (0.58 mmol) of 3-(1.H.-indol-3-yl)-4-[3-(2-methanesulfonyloxy-ethoxy)-5-triphenylmethoxy-phenyl]-pyrrole-2,5-dione in 5 mL of 33% dimethylamine in ethanol is stirred overnight at RT. The reaction mixture is diluted with ethyl acetate. The resulting mixture is washed with saturated aqueous sodium bicarbonate. The layers are separated and the aqueous layer is extracted with three portions of ethyl acetate. The combined organic solution is washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue is filtered through a plug of silica gel (70:30 ethyl acetate/methanol) to afford 3-(1.H.-Indol-3-yl)-4-[3-(2-dimethylamino-ethoxy)-5-triphenylmethoxy-phenyl]-pyrrole-2,5-dione, which is immediately used in the next step without further purification.

To a solution of 370 mg (0.58 mmol) of 3-(1.H.-Indol-3-yl)-4-[3-(2-dimethylamino-ethoxy)-5-triphenylmethoxy-phenyl]-pyrrole-2,5-dione in 5 mL of methanol is added 251 mg (1.46 mmol) of para-toluenesulfonic acid. After stirring for 2 h at room temperature, the mixture is diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate. The aqueous layer is extracted with three portions of ethyl acetate. The combined organic layers are washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue is purified by column chromatography on silica gel (7:3 ethyl acetate/methanol) to afford the title compound as an orange foam.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.89 (s, 1H), 11.00 (s, 1H), 9.45 (s, 1H), 7.98 (s, 1H), 7.43 (d, J=8.0 Hz, 1H), 7.08 (t, J=7.4 Hz, 1H), 6.78 (t, J=7.4 Hz, 1H), 6.50 (m, 2H), 6.34 (s, 1H), 6.30 (s, 1H), 3.69 (t, J=5.9 Hz, 2H), 2.35 (t, J=5.9 Hz, 2H), 2.06 (s, 6H); MS (EI, negative ionization) m/z 390 $[M-H]^-$, (EI, positive ionization) m/z 392 $[M+H]^+$

3-(1.H.-Indol-3-yl)-4-[3-(2-methanesulfonyloxy-ethoxy)-5-hydroxy-phenyl]-pyrrole-2,5-dione, used as starting material, may be prepared as follows:

a) [3-(2-Triisopropylsilyloxy-ethoxy)-5-hydroxy-phenyl]-acetic Acid Methyl Ester

A mixture of 9.39 g (51.5 mmol) of (3,5-dihydroxy-phenyl)-acetic acid methyl ester (prepared according to U. Eder, G. Sauer, G. Haffer, G. Neef, R. Wiechert, U.S. Pat. No. 4,066,674), 11.38 g (61.8 mmol) of 1-bromo-2-triisopropylsilyloxy-ethane and 14.50 g (51.5 mmol) of cesium carbonate is stirred at RT for 1 hour and at 60° C. for another hour. The reaction mixture is then treated with saturated aqueous sodium carbonate and extracted with ethyl acetate. The layers are separated and the organic layer is

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