



(86) Date de dépôt PCT/PCT Filing Date: 1998/01/22

(87) Date publication PCT/PCT Publication Date: 1998/07/30

(45) Date de délivrance/Issue Date: 2005/10/04

(85) Entrée phase nationale/National Entry: 1999/07/23

(86) N° demande PCT/PCT Application No.: JP 1998/000234

(87) N° publication PCT/PCT Publication No.: 1998/032757

(30) Priorité/Priority: 1997/01/24 (9/11289) JP

(51) Cl.Int.⁶/Int.Cl.⁶ C07D 487/04, C07D 519/00

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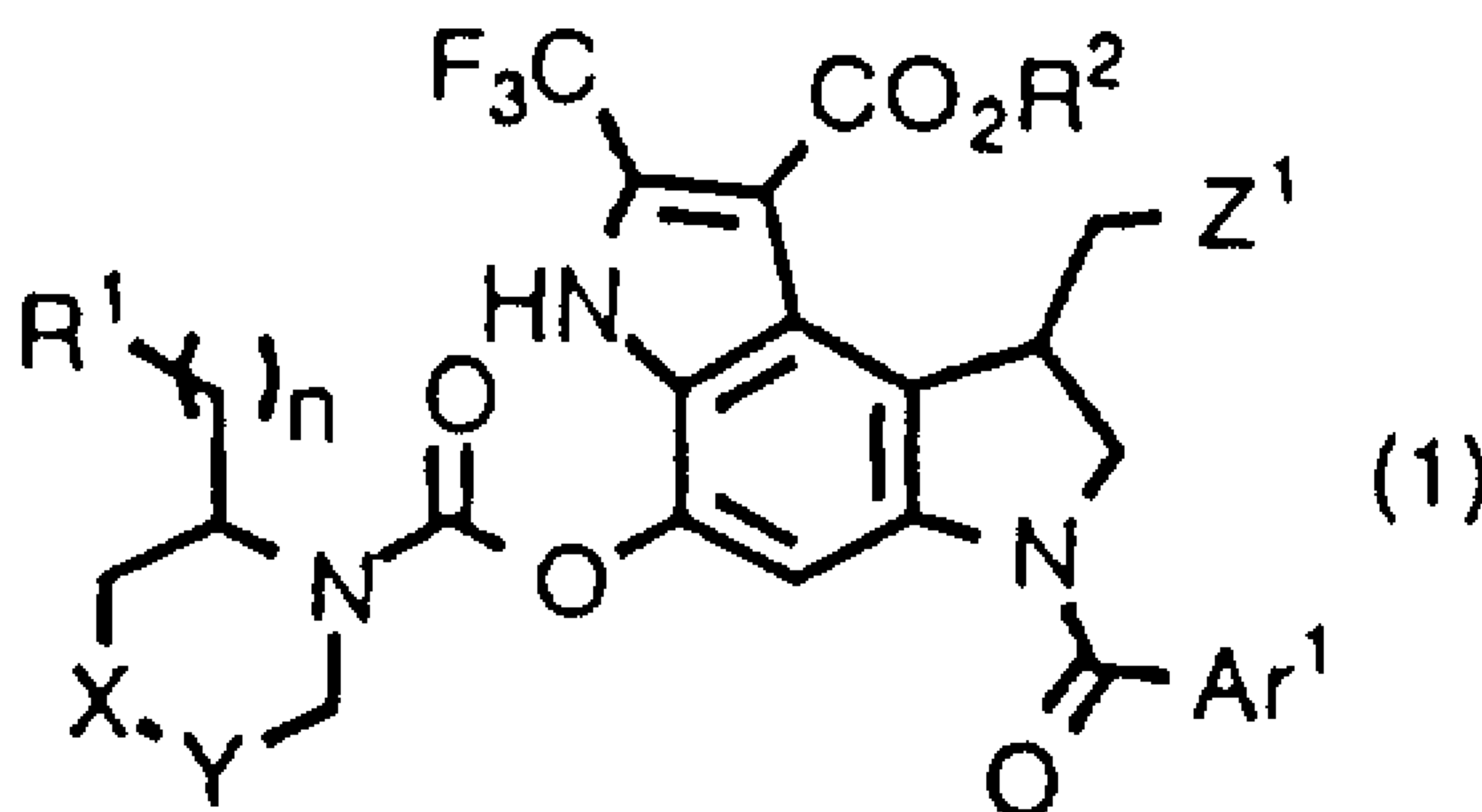
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(54) Titre : DERIVES DE PYRROLOINDOLE ET SUBSTANCES INTERMEDIAIRES POUR LES PRODUIRE

(54) Title: PYRROLOINDOLE DERIVATIVES AND INTERMEDIATES IN PRODUCING THE SAME



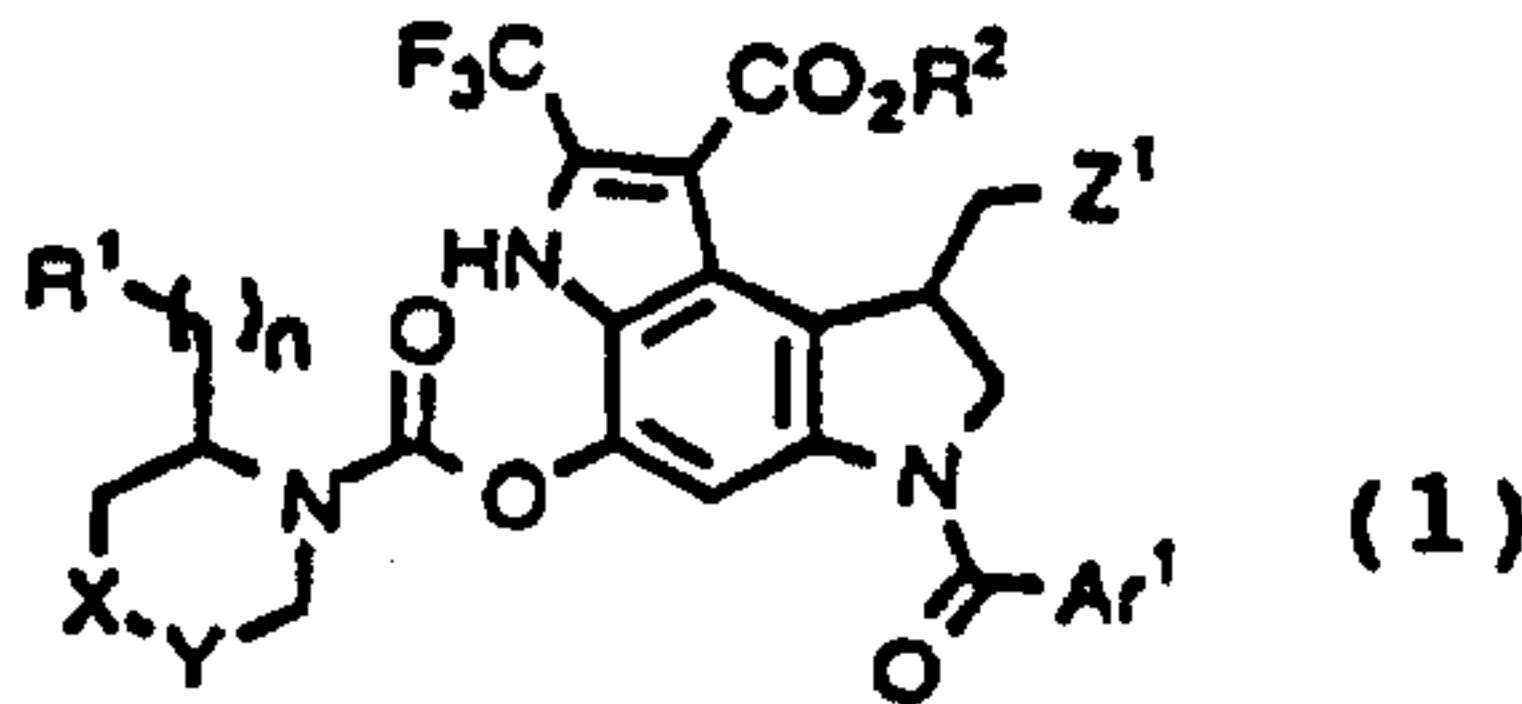
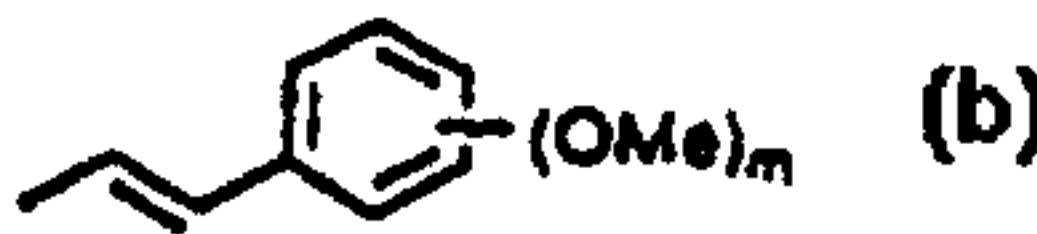
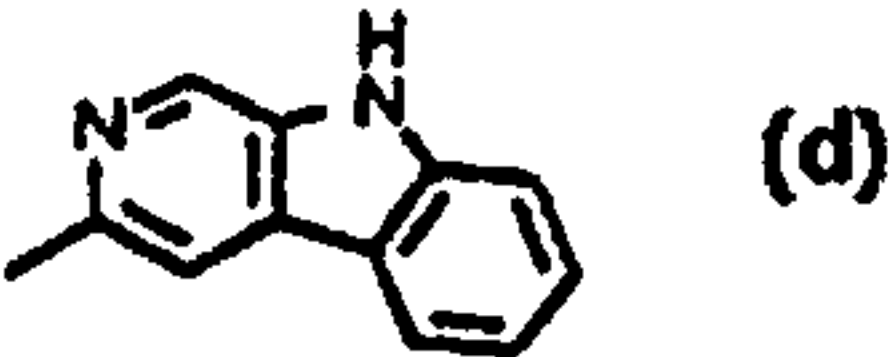
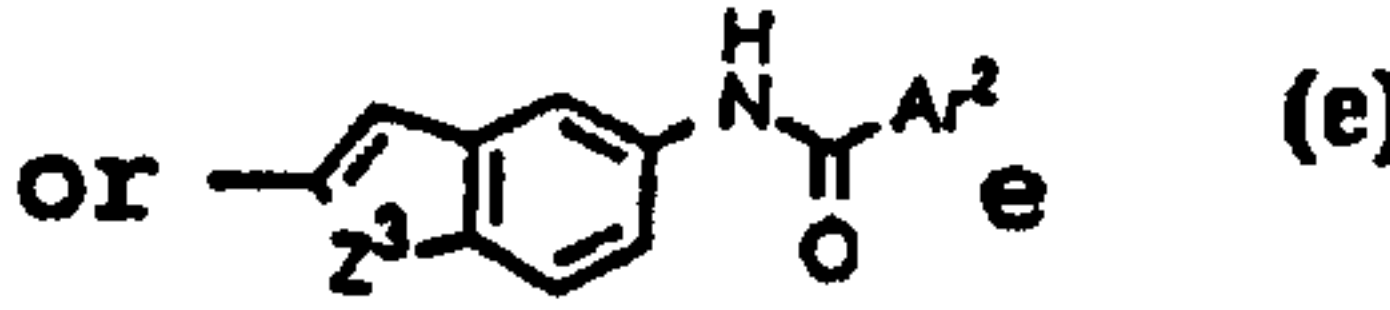
(57) **Abrégé/Abstract:**

Novel carbamoyloxypyrroloindole derivatives represented by general formula (1) and having antimicrobial and antitumor activities, optical isomers thereof and pharmacologically acceptable salts of the same, and intermediates in producing the same, wherein R¹ represents OH or pyrrolidinyl; n is 1 or 2; R² represents lower (C₁₋₄) alkyl; Y-Y or Y-X represents CH₂, CHOH, CH₂-CH₂, O-CH₂ or NMe-CH₂; Z¹ represents Cl or Br; and Ar¹ represents (a), (b), (c), (d) or (e) (wherein Z² and Z³ represent each O or NH; m is an integer of 1 to 4; and Ar₂ represents either of the above a, b, c and d).

PCT

特許協力条約に基づいて公開された国際出願



(51) 国際特許分類6 C07D 487/04, 519/00 // A61K 31/40, 31/47	A1	(11) 国際公開番号 WO98/32757 (43) 国際公開日 1998年7月30日(30.07.98)
(21) 国際出願番号 PCT/JP98/00234 (22) 国際出願日 1998年1月22日(22.01.98) (30) 優先権データ 特願平9/11289 1997年1月24日(24.01.97) JP (71) 出願人 (米国を除くすべての指定国について) 杏林製薬株式会社 (KYORIN PHARMACEUTICAL CO., LTD.)[JP/JP] 〒101 東京都千代田区神田駿河台2丁目5番地 Tokyo, (JP) 財団法人 相模中央化学研究所 (SAGAMI CHEMICAL RESEARCH CENTER)[JP/JP] 〒229 神奈川県相模原市西大沼4丁目4番1号 Kanagawa, (JP) (72) 発明者 ; および (75) 発明者 / 出願人 (米国についてののみ) 福田保路(FUKUDA, Yasumichi)[JP/JP] 〒329-02 栃木県小山市乙女3-21-13-202 Tochigi, (JP) 嶋澤るみ子(SHIMAZAWA, Rumiko)[JP/JP] 〒329-01 栃木県下都賀郡野木町友沼5982-1 杏林製薬卯ノ木家族寮 Tochigi, (JP) 大森康男(OOMORI, Yasuo)[JP/JP] 〒329-01 栃木県下都賀郡野木町友沼5905-280 Tochigi, (JP)		寺島孜郎(TERASHIMA, Shiro)[JP/JP] 〒156 東京都世田谷区経堂2-27-4 Tokyo, (JP) (74) 代理人 弁理士 新部興治, 外(NIIBE, Koji et al.) 〒100 東京都千代田区丸の内2丁目6番2号 丸の内八重洲ビル424号 Tokyo, (JP) (81) 指定国 AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO特許 (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), 欧州特許 (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI特許 (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). 添付公開書類 国際調査報告書 補正書
(54)Title: PYRROLOINDOLE DERIVATIVES AND INTERMEDIATES IN PRODUCING THE SAME (54)発明の名称 ピロロインドール誘導体及びその製造中間体  (1)  (a)  (b)  (c)  (d) or  (e) (57) Abstract Novel carbamoyloxypyrroloindole derivatives represented by general formula (1) and having antimicrobial and antitumor activities, optical isomers thereof and pharmacologically acceptable salts of the same, and intermediates in producing the same, wherein R¹ represents OH or pyrrolidiny; n is 1 or 2; R² represents lower (C₁₋₄) alkyl; Y-Y or Y-X represents CH₂, CHOH, CH₂-CH₂, O-CH₂ or NMe-CH₂; Z¹ represents Cl or Br; and Ar¹ represents (a), (b), (c), (d) or (e) (wherein Z² and Z³ represent each O or NH; m is an integer of 1 to 4; and Ar₂ represents either of the above a, b, c and d).		

SPECIFICATION

PYRROLOINDOLE DERIVATIVES AND INTERMEDIATES
IN PRODUCING THE SAME

TECHNICAL FIELD

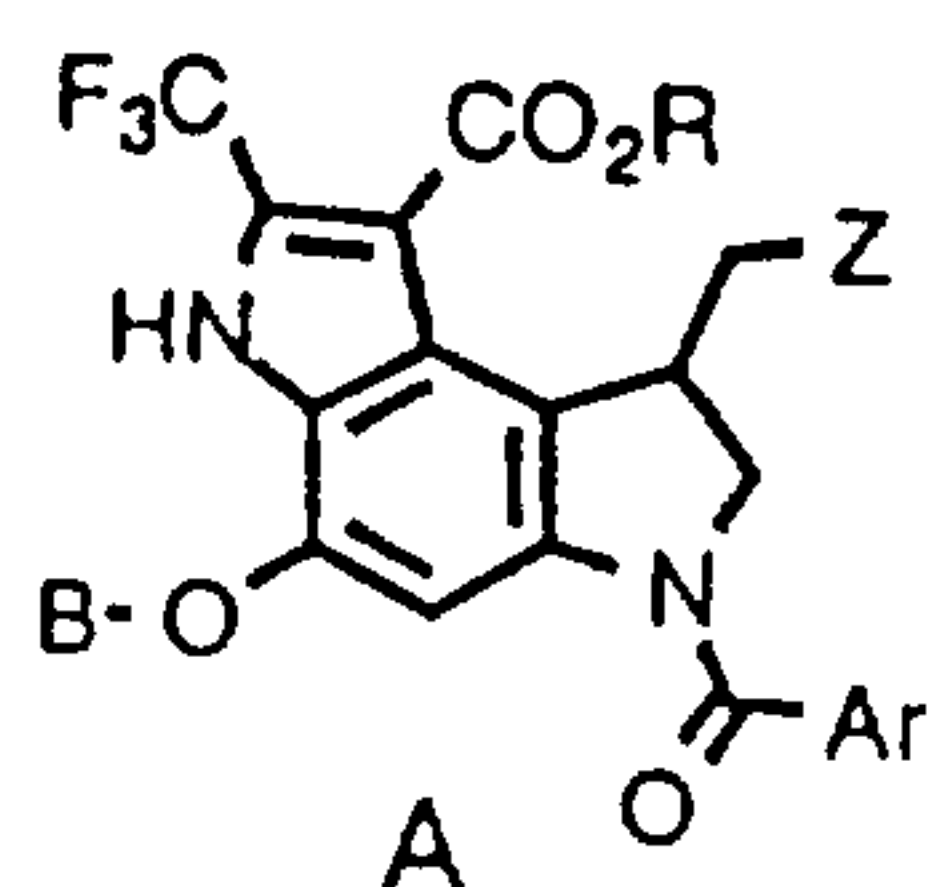
The present invention relates to novel pyrroloindole derivatives having a carbamoyloxy group which have antimicrobial and antitumor activities, optical isomers thereof, and pharmacologically acceptable salts thereof; and intermediates for production thereof.

BACKGROUND ART

CC-1065, which is an antibiotic having antimicrobial activity and antitumor activity, is disclosed in J.Antibiotics, vol.31, p.1211 (1978), and vol.34, p.1119 (1981); and USP 4169888. Duocarmycin A having analogous structure, and analogues thereof are disclosed in WO87/06265; EP0318056; J.Antibiotics, vol.42, p.1229 (1989); and JP-A-4-99774. Derivatives of CC-1065 are disclosed in EP0359454, JP-A-60-193989, and published Japanese translation of PCT application (Kohyo) 2-502005. Derivatives of duocarmycins are disclosed in JP-A-3-7287, JP-A-3-128379, EP0354583, and EP0406749. These are derived by utilizing directly a basic skeleton of a natural substance, or modification of a natural product. Further, a chemically synthesized pyrroloindole derivative having a trifluoromethyl group on the pyrroloindole ring is disclosed

by the inventors of the present invention in JP-A-6-116269.

The inventors of the present invention made comprehensive researches on pyrroloindole derivatives which are effective against solid tumor and is less toxic. Consequently, The inventors found a derivative having a trifluoromethyl group in the pyrroloindole ring, and disclosed it in JP-A-6-116269. In JP-A-6-116269, a prodrug represented by Formula A having a carbamoyl group containing a cyclic amine is disclosed.

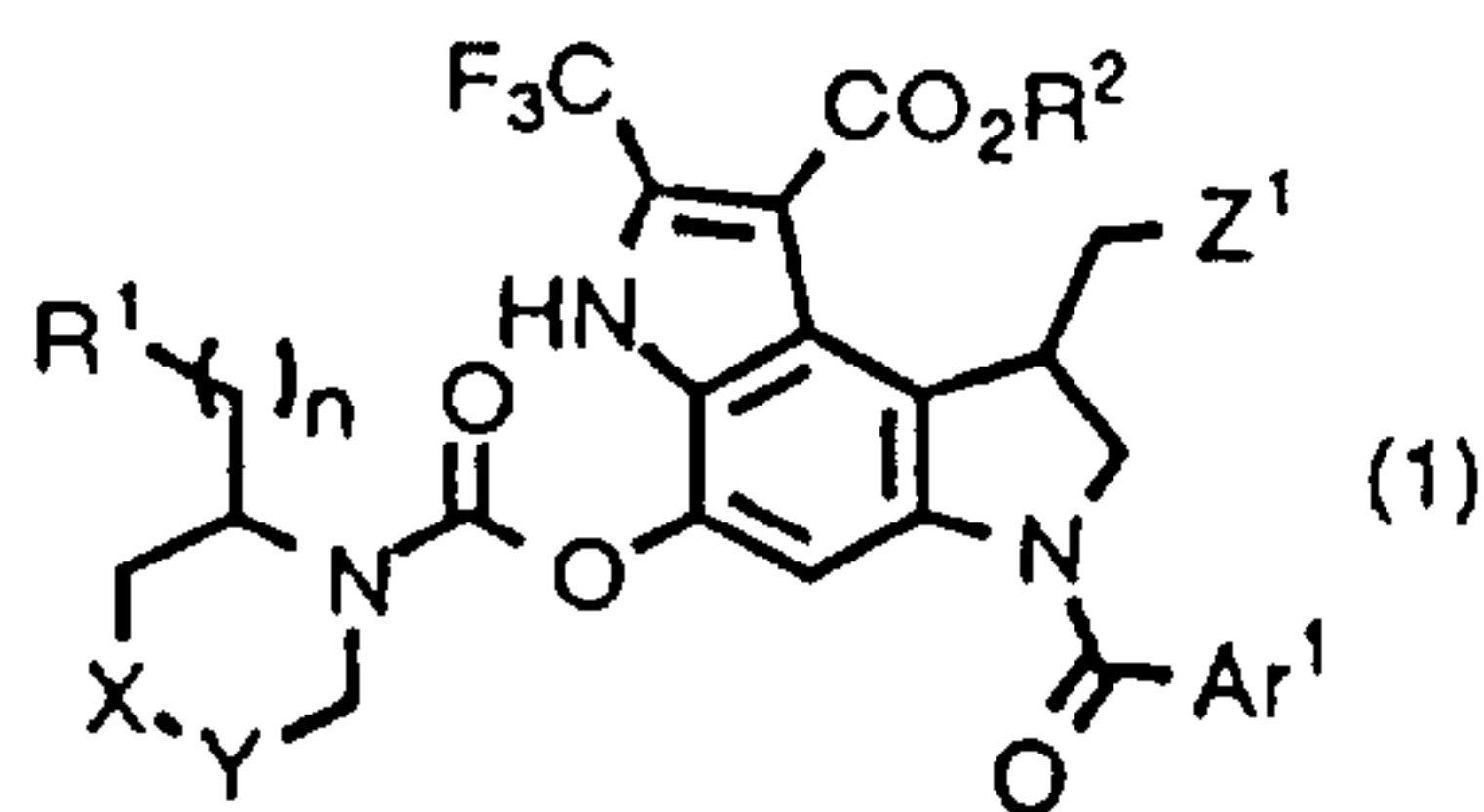


B: MeN NCO, HOCH₂CH₂N NCO, etc.

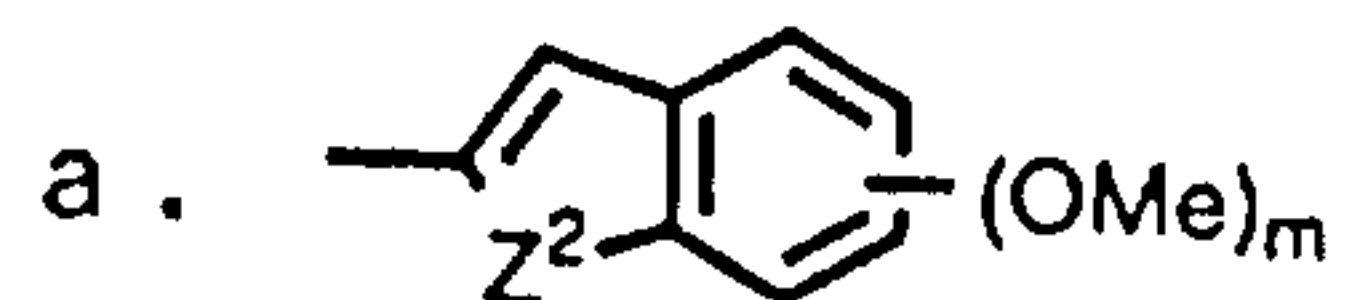
The present invention intends to provide a prodrug which forms an active species (a compound of Formula A in which B is hydrogen) in vivo more readily than the prodrug shown in Examples of JP-A-6-116269, and is effective against solid tumor and is less toxic.

DISCLOSURE OF INVENTION

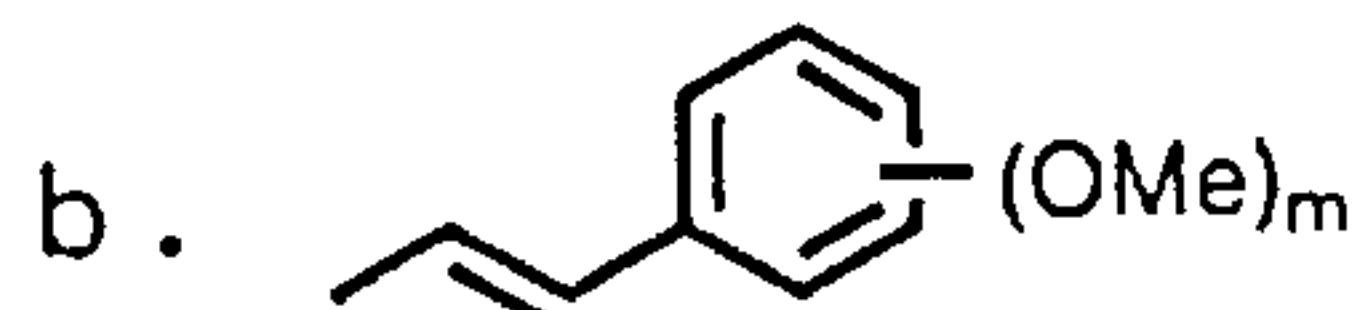
It was found by the inventors of the present invention that the pyrroloindole derivatives having a carbamoyloxy group represented by the following general formula (1) below, optically active isomers thereof, and pharmacologically acceptable salts thereof are useful as the aforementioned prodrug.



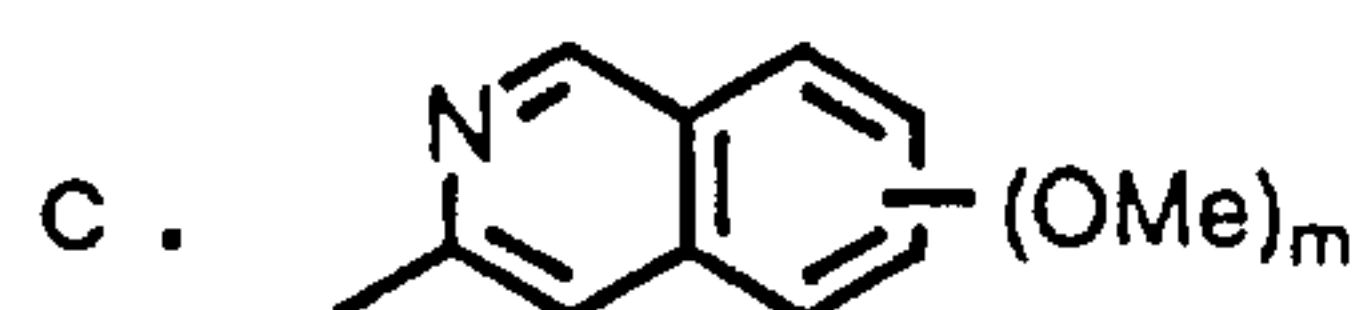
where R^1 is OH, or a pyrrolidinyl group; n is 1 or 2; R^2 is a lower alkyl group of C_1-C_4 ; $X-Y$ or $Y-X$ is CH_2 , $CHOH$, CH_2-CH_2 , $O-CH_2$, or $NMe-CH_2$; Z^1 is Cl or Br; and Ar^1 is



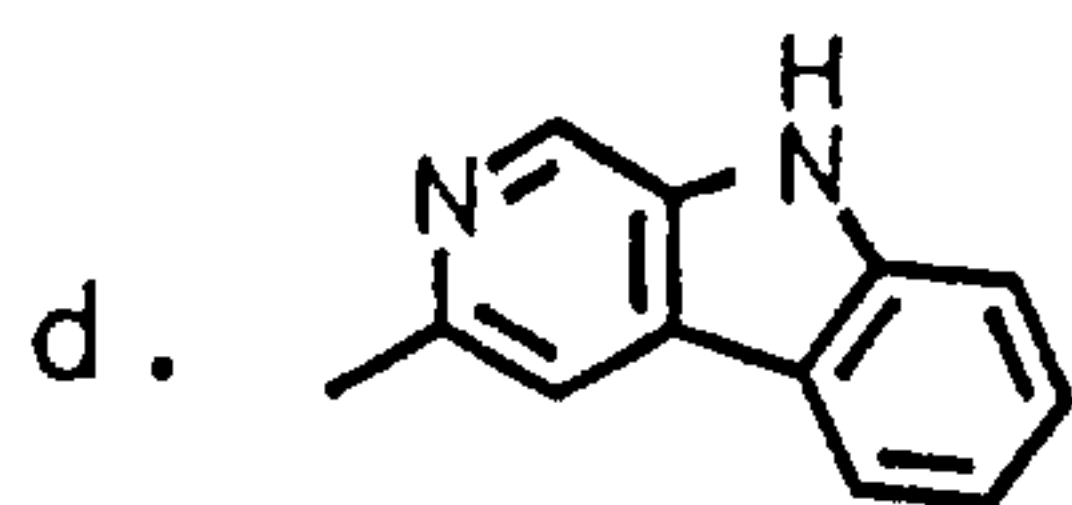
(wherein Z^2 is O or NH, m is 0 or an integer of 1 to 4),



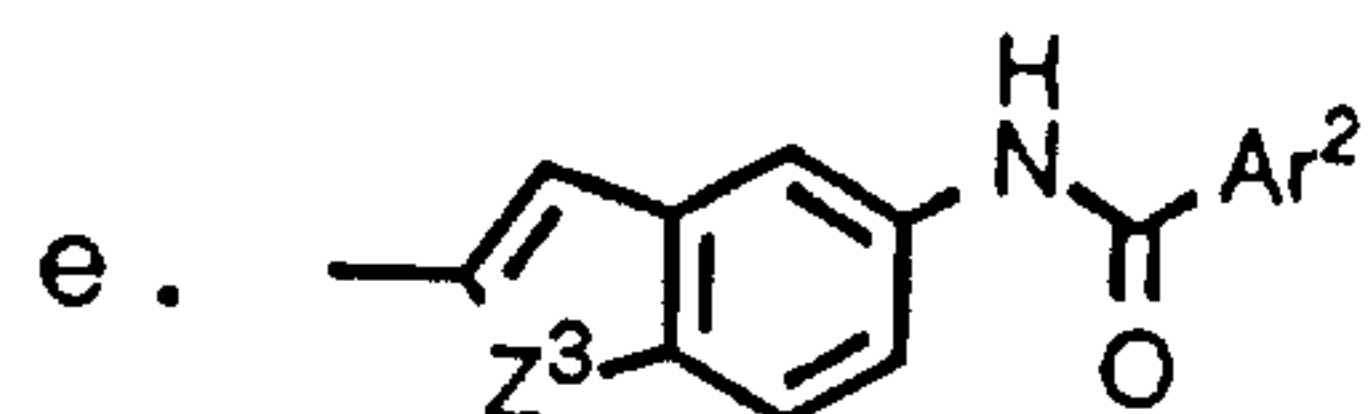
(wherein m is 0 or an integer of 1 to 4),



(wherein m is 0 or an integer of 1 to 4),

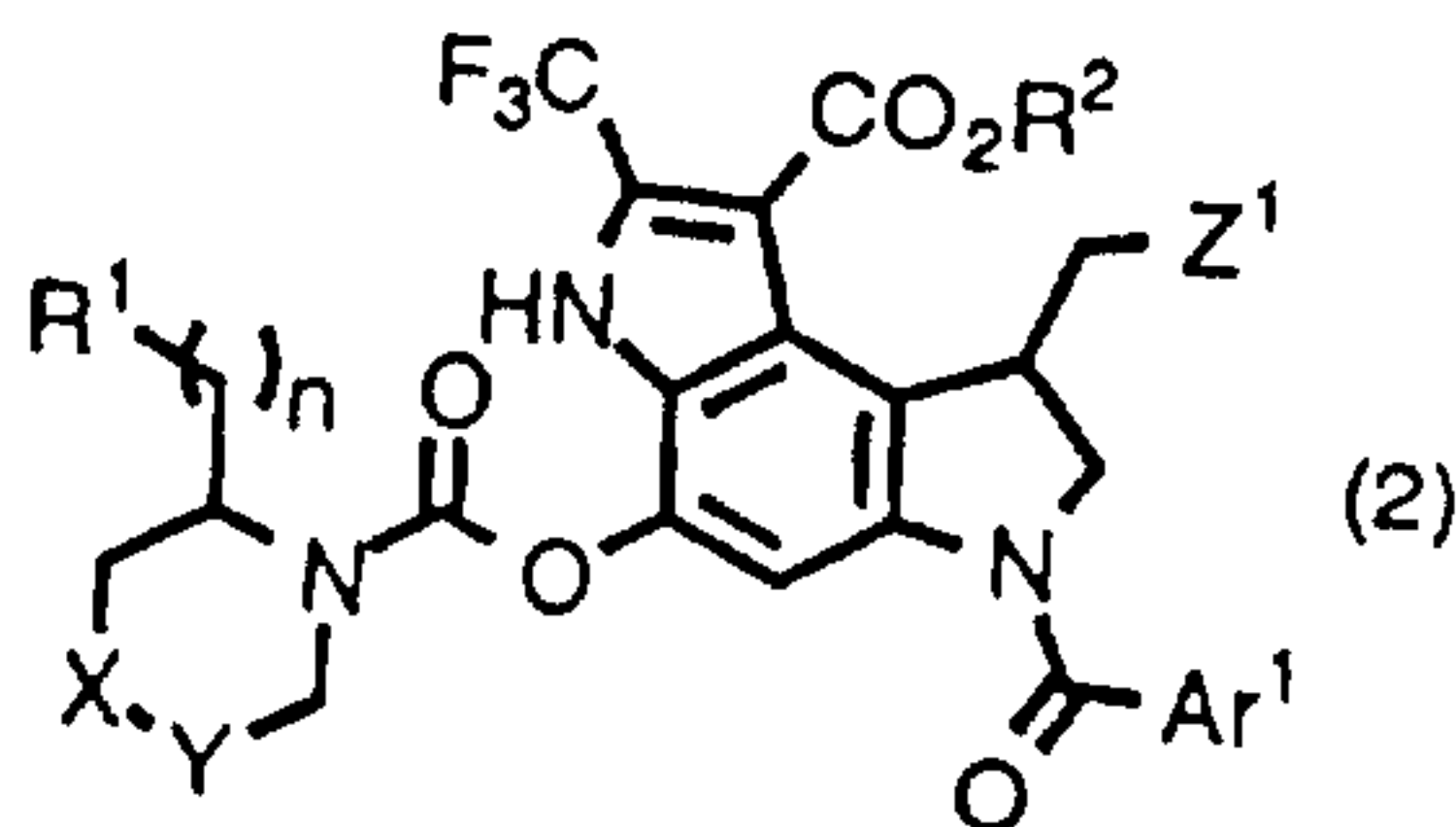


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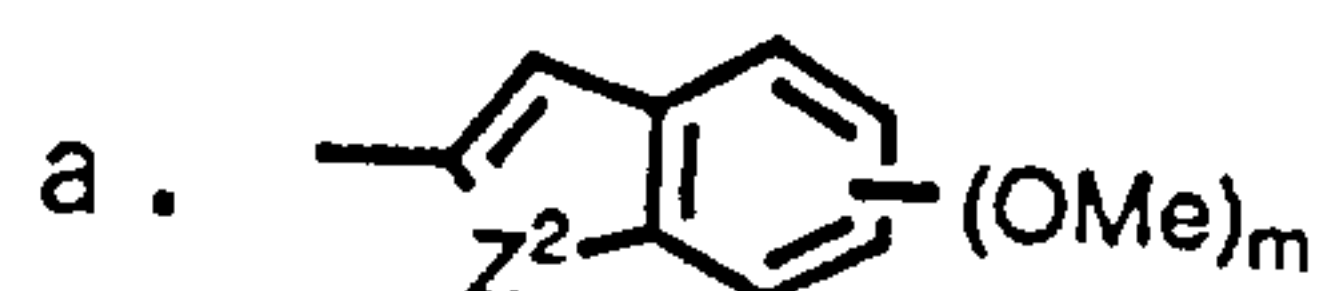


(wherein Z^3 is O or NH; Ar^2 is any of the above groups a, b, c, and d). Consequently the present invention has been completed.

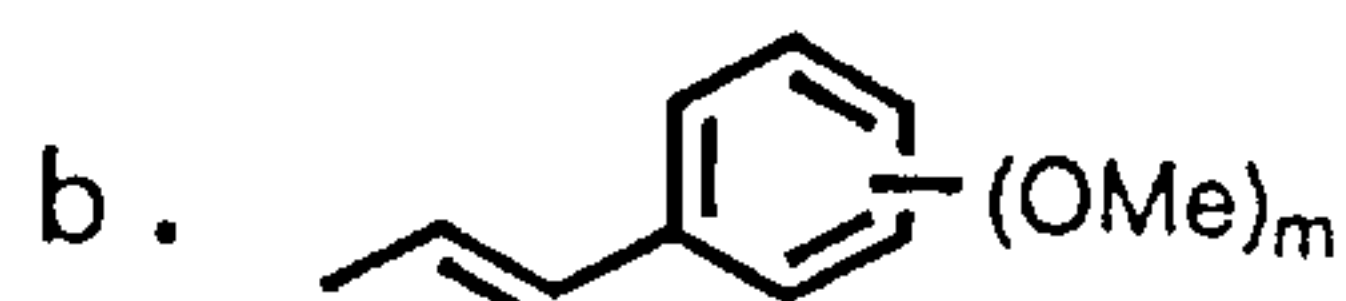
The present invention further relates to protected pyrroloindole derivatives represented by the following general formula (2):



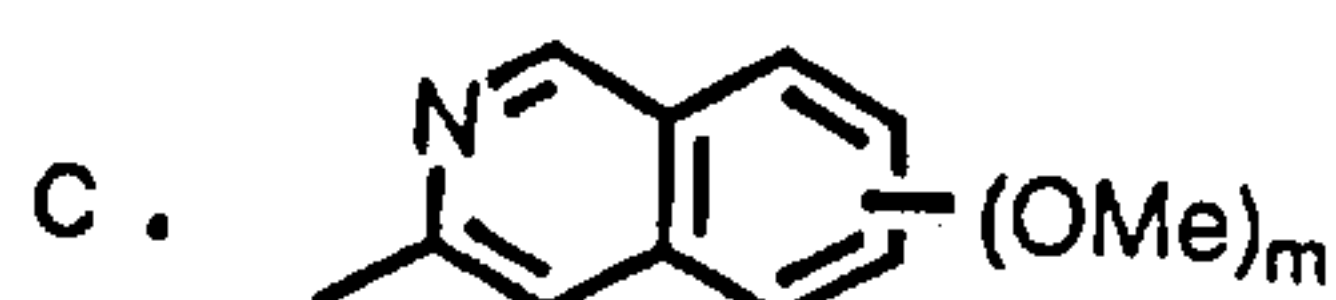
where R^1 is OR^3 (R^3 is a protecting group for the hydroxyl group); n is 1 or 2; R^2 is a lower alkyl of C_1-C_4 ; $X-Y$ is CH_2 , $CHOH$, CH_2-CH_2 , $O-CH_2$, or $NMe-CH_2$; Z^1 is Cl or Br ; and Ar^1 is



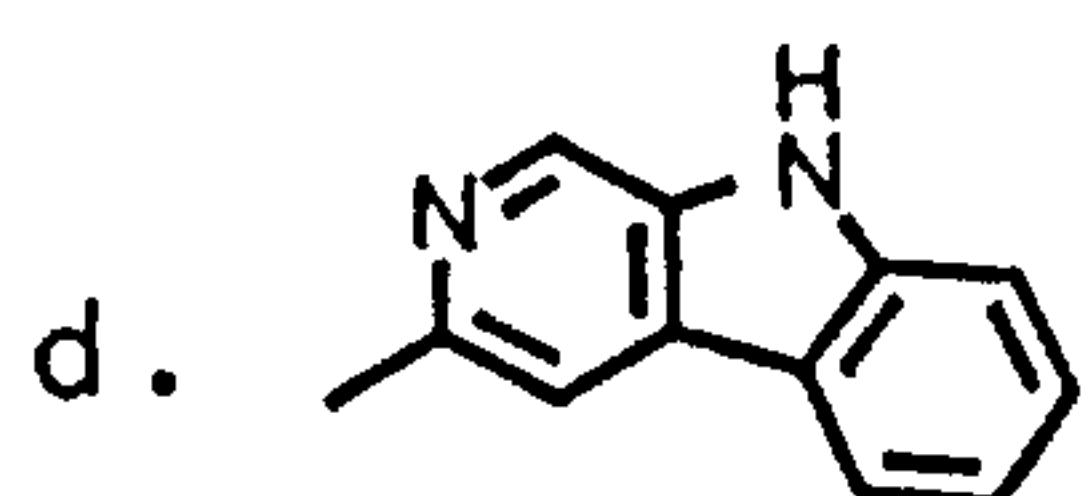
(wherein Z^2 is O or NH , m is 0 or an integer of 1 to 4),



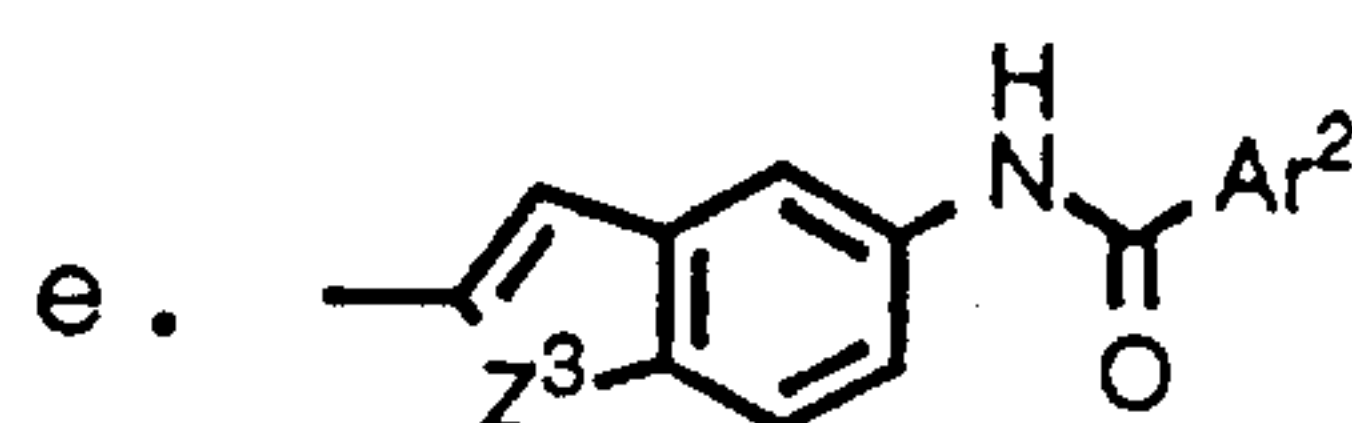
(wherein m is 0 or an integer of 1 to 4),



(wherein m is 0 or an integer of 1 to 4),

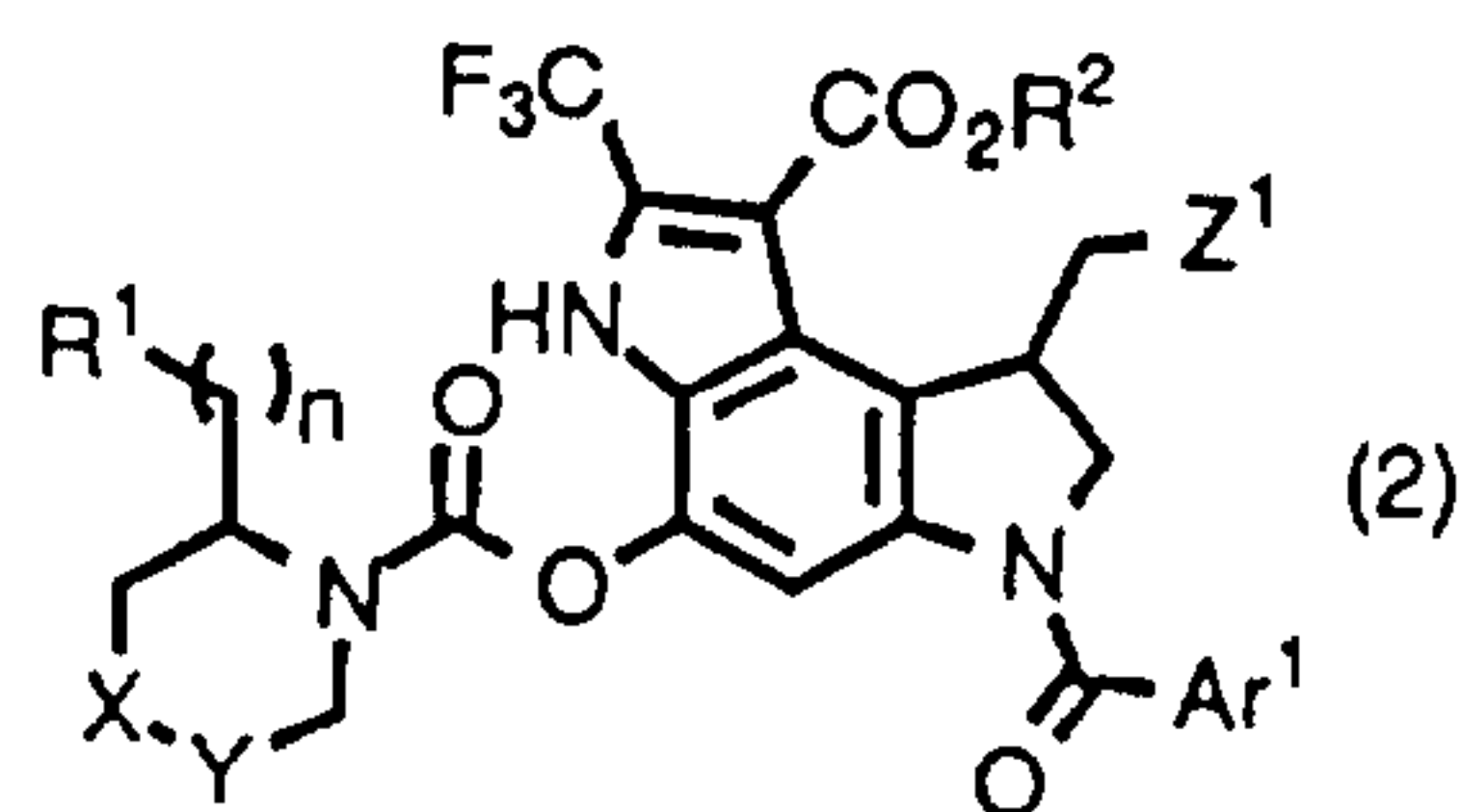


or

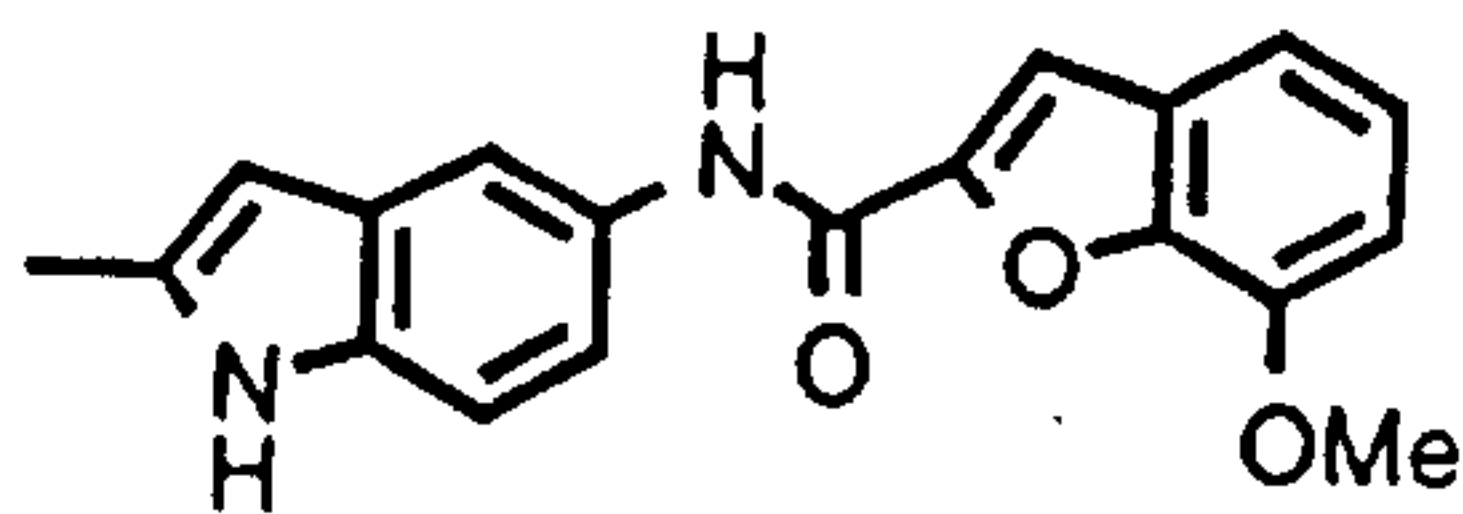


(wherein Z^3 is O or NH ; Ar^2 is any of the above groups of a, b, c, and d), and further relates to protected pyrroloindole derivatives represented by the following general formula

(2):

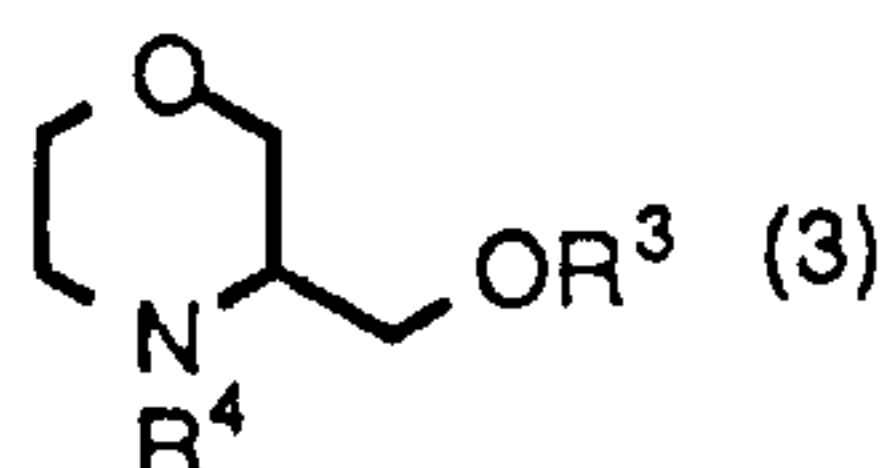


where R^1 is OR^3 (R^3 is a protecting group for the hydroxyl group), n is 1, R^2 is methyl, $X-Y$ is $O-CH_2$, Z^1 is Cl , and Ar^1 is



These derivatives are useful as an intermediate for production of the aforementioned carbamoyl group-containing pyrroloindole derivative.

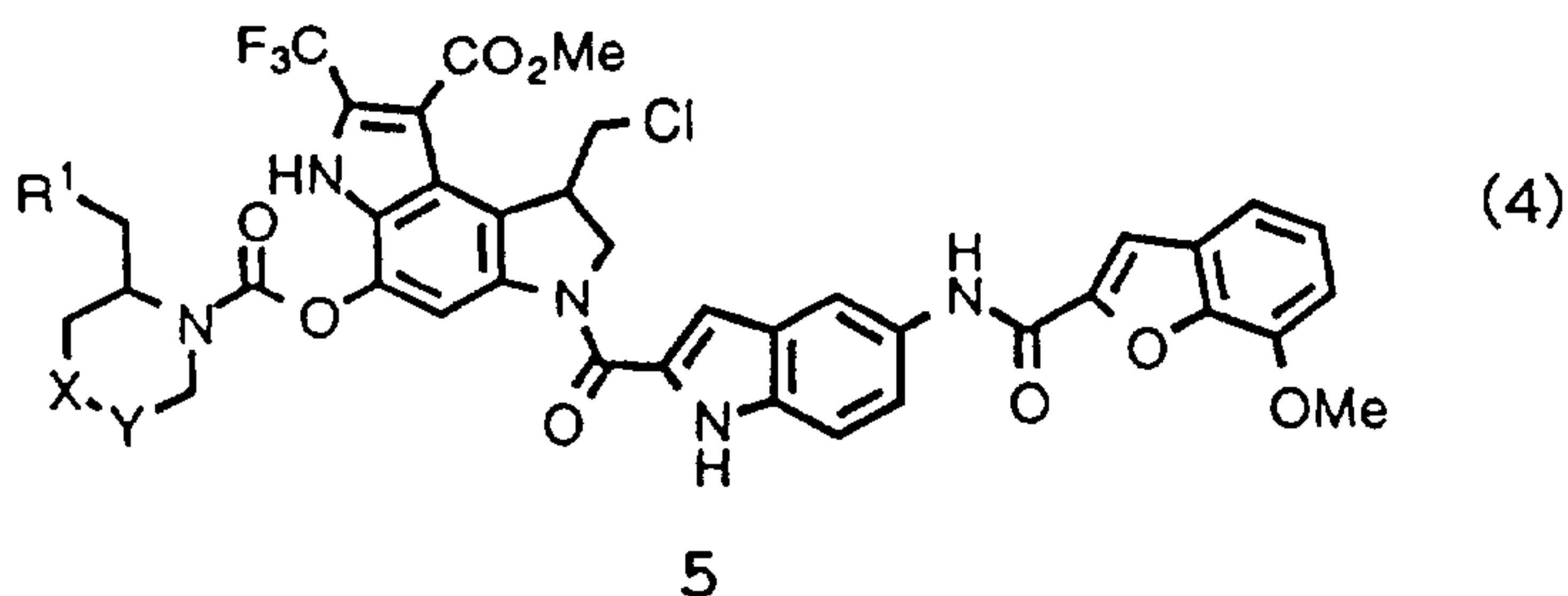
The present invention further relates to an intermediate for production of the aforementioned protected pyrroloindole derivative represented by the following general formula (3), optically active isomers thereof, and salts thereof:



where R^3 is a protecting group for the hydroxyl group, R^4 is a hydrogen atom or a benzyl group.

In the general formulas (1) and (2), the lower alkyl group of C₁-C₄ includes methyl, ethyl, isopropyl, t-butyl, and the like, of which methyl is preferred. The hydroxyl-protecting group represented by R³ includes t-butyldimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyldiphenylsilyl, methoxymethyl, t-butoxymethyl, tetrahydropyranyl, and the like, of which t-butyldimethylsilyl is preferred.

In the present invention, particularly preferred embodiment is represented by the following general formula (4) below:



Of the compounds, preferred are the compound in which R^1 is pyrrolidinyl, and X-Y is CH_2 (Compound I); the compound in which R_1 is OH, and X-Y is CH_2-CH_2 (Compound II); the compound in which R^1 is OH, and X-Y or Y-X is $O-CH_2$ (Compound III); and the compound in which R^1 is OH, and X-Y or Y-X is $NMe-CH_2$ (Compound IV); and optically active isomers of the above compounds. The compounds I-IV and the optically active isomers thereof may be pharmacologically accepted salts, for example, a hydrochloride salt.

The racemic modifications and optically active isomers of the compounds represented by the general formula (1) can be produced by a known process (e.g., JP-A-6-116269). The compound represented by the general formula (1) may be used alone or in combination with a pharmaceutically acceptable auxiliary agent as an antimicrobial or antitumor composition.

For example, the compound represented by the general formula (1) or the salt thereof is dissolved in physiological saline or an aqueous solution of glucose, mannitol, lactose, or the like for use as a medical composition.

Otherwise, a salt of the compound represented by the general formula (1) is freeze-dried in a conventional manner and mixed with sodium chloride or the like for use as a powdery injectable agent. This medical composition may contain an additive known in medical formulation, for example, a pharmaceutically acceptable salt, as necessary.

The solution-type medical composition can be used

as it is. The powdery injectable agent is used after dissolution in distilled water, physiological saline, or an aqueous solution of glucose, mannitol, lactose, or the like for intravenous administration. The medical composition may be administered intra-arterially, intra-abdominally, or intrathoracically, if desired.

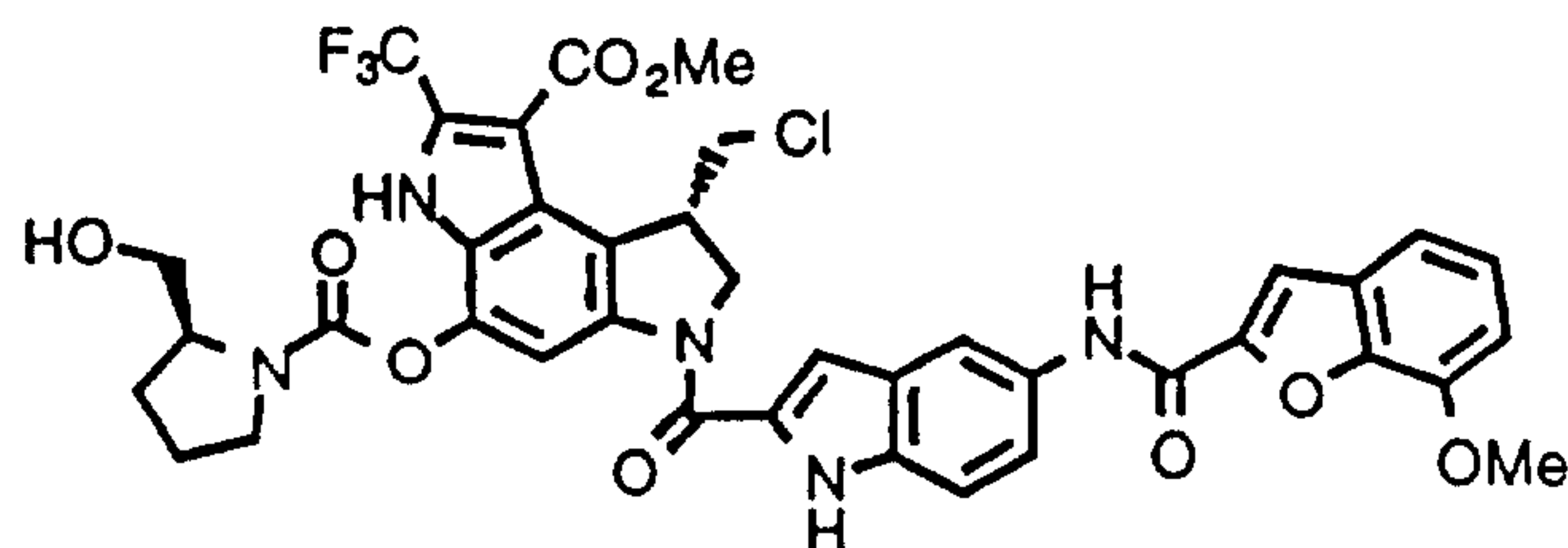
The medical composition may be used also for oral administration as tablets, capsules, powders, granules, ampule-medicine, and so forth, and may contain a medical auxiliary agent conventionally employed in medical formulation.

The dosage depends on the age and the symptom of the patient, ranging from 0.00001 to 100 mg/kg/day for mammals including humans. The administration may be conducted once or several times per day, or intermittently one to four times per week, or once in two to four weeks.

BEST MODE FOR CARRYING OUT THE INVENTION

The advantages of the present invention are described below by reference to Test Examples and Working Examples without limiting the invention thereto.

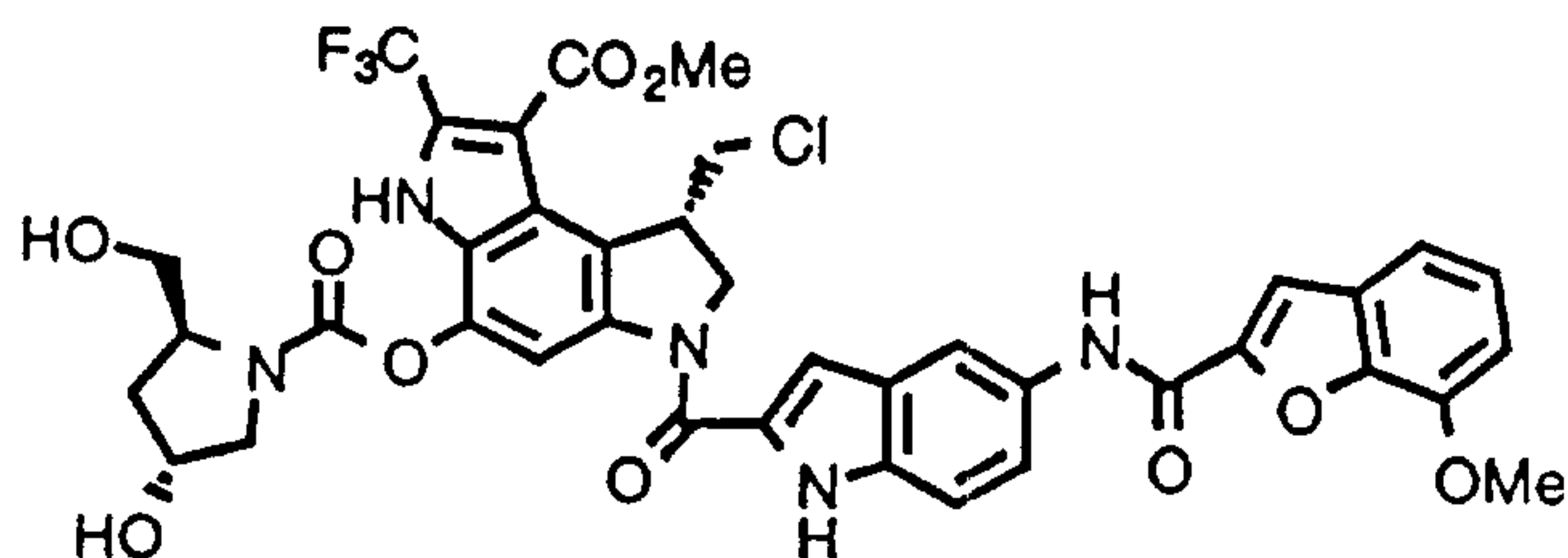
Working Example 1



Methyl (1S)-chloromethyl-5-hydroxy-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (10.2 mg, 15 μ mol) and 4-nitrophenyl chloroformate (7.6 mg, 38 μ mol) were dissolved in 1 mL of tetrahydrofuran, and thereto triethylamine (4.2 μ L, 30 μ mol) was added dropwise with ice cooling. After one hour, (2S)-pyrrolidine-2-methanol (4.4 μ L, 45 μ mol) was added dropwise. The mixture was stirred for two hours, and stirred further for two hours at room temperature. The reaction mixture was poured into 3 mL of saturated aqueous sodium chloride solution and 3 mL of ethyl acetate for extraction. The extracted matter was dried over anhydrous sodium sulfate, and the solvent was evaporated off. The resulting residue was purified by silica gel column chromatography (hexane:acetone = 1:1) to obtain 8.5 mg (70%) of methyl (1S)-chloromethyl-5-{[(2S)-hydroxymethylpyrrolidin-1-ylcarbonyl]oxy}-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate.

NMR(DMSO- d_6) δ : 1.80-2.10(4H,m), 3.30-3.80(6H,m), 3.83-4.20(2H,m), 3.92(3H,s), 4.01(3H,s), 4.42(1H,brs), 4.60(1H,d,J=9.5Hz), 4.79(1H,t,J=9.3Hz), 7.10(1H,dd,J=1.0Hz,8.1Hz), 7.21(1H,d,J=1.5Hz), 7.28(1H,t,J=7.8Hz), 7.37(1H,dd,J=1.0Hz,7.8Hz), 7.50(1H,d,J=8.8Hz), 7.60(1H,dd,J=2.0Hz,9.0Hz), 7.75(1H,s), 8.17(1H,d,J=10.3Hz), 8.21(1H,d,J=1.5Hz), 10.41(1H,s), 11.70(1H,s), 13.06(1H,brs)

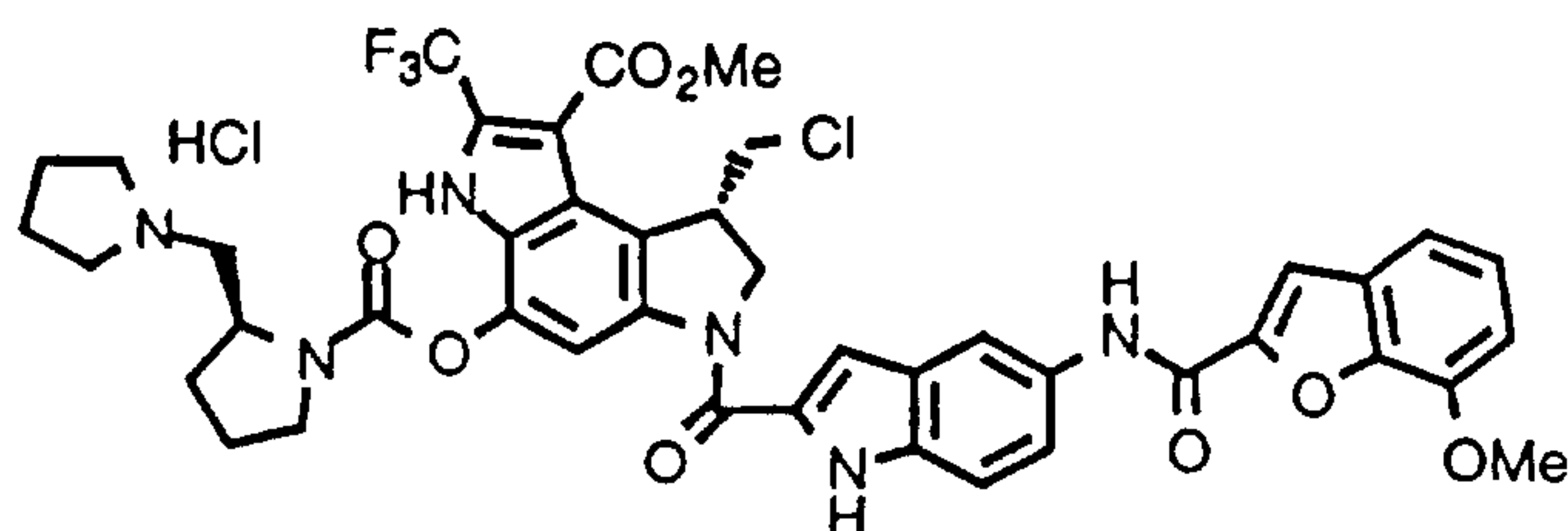
Working Example 2



In the same manner as in Working Example 1, methyl (1S)-chloromethyl-5-hydroxy-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (20.4 mg, 30 μ mol) and (2S,4R)-4-hydroxypyrrolidin-2-methanol (10.5 mg, 90 μ mol) were allowed to react to obtain methyl (1S)-chloromethyl-5-{[(4R)-hydroxy-(2S)-hydroxymethylpyrrolidin-1-ylcarbonyl]oxy}-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (17.3 mg, 70%).

NMR (DMSO- d_6) δ : 1.80-2.20 (2H, m), 3.34-3.80 (6H, m), 3.90-4.35 (2H, m), 3.92 (3H, s), 4.01 (3H, s), 4.35-4.50 (2H, m), 4.60 (1H, d, J=11.2 Hz), 4.75-4.81 (1H, m), 5.08-5.15 (1H, m), 7.10 (1H, d, J=8.3 Hz), 7.21 (1H, d, J=1.5 Hz), 7.28 (1H, t, J=7.8 Hz), 7.37 (1H, d, 7.8 Hz), 7.50 (1H, d, J=8.8 Hz), 7.60 (1H, dd, J=1.5 Hz, 8.8 Hz), 7.75 (1H, s), 8.18-8.30 (2H, m), 10.41 (1H, s), 11.71 (1H, s), 13.09 (1H, brs)

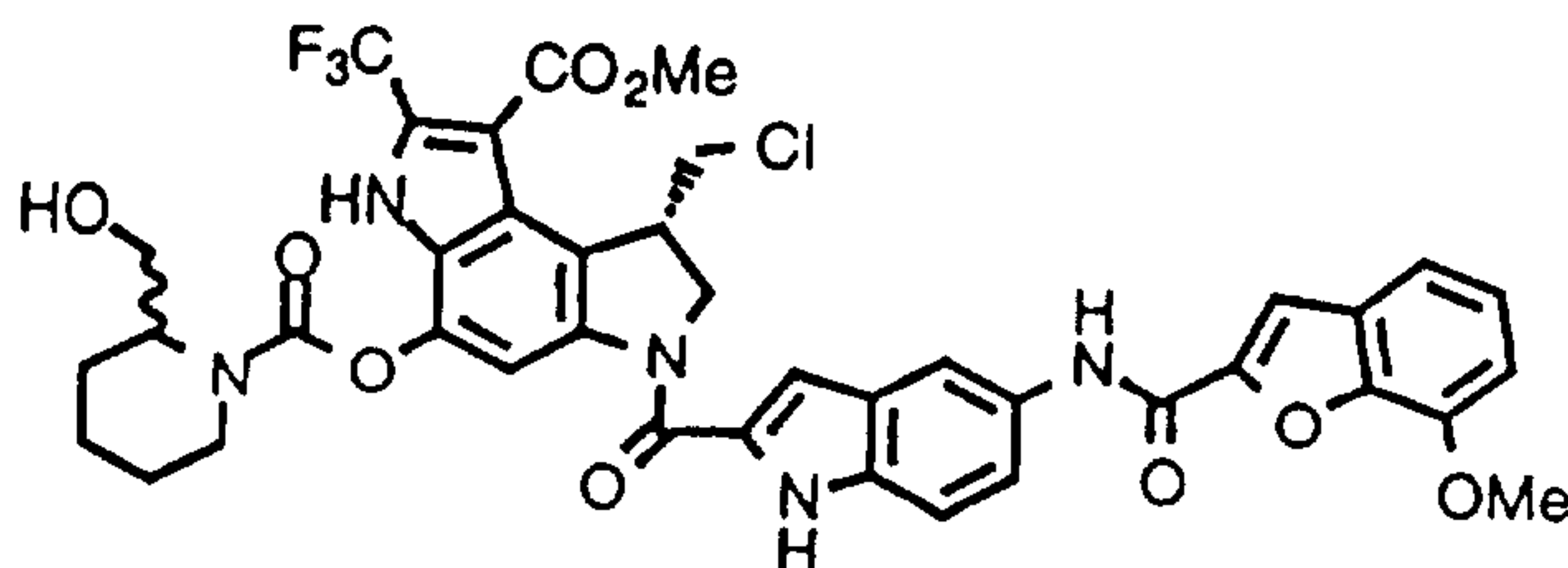
Working Example 3



In the same manner as in Working Example 1, methyl (1S)-chloromethyl-5-hydroxy-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (20.4 mg, 30 μ mol) and (2S)-(pyrrolidin-1-ylmethyl)pyrrolidine (13.9 mg, 90 μ mol) were allowed to react to obtain methyl (1S)-chloromethyl-5-([(2S)-(pyrrolidin-1-ylmethyl)pyrrolidin-1-ylcarbonyl]oxy)-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate. The resulting reaction product was treated with 3M-HCl in methanol (0.5 mL)-ethyl acetate (0.05 mL) to obtain 18.2 mg (68%) of the hydrochloride.

NMR(DMSO- d_6) δ : 1.80-2.30 (8H,m), 2.95-4.05 (10H,m), 3.91 (3H,s), 4.00 (3H,s), 4.28 (1H,m), 4.41 (1H,m), 4.61 (1H,m), 4.80 (1H,m), 7.10 (1H,d,J=8.3Hz), 7.22 (1H,s), 7.28 (1H,t,J=7.8Hz), 7.37 (1H,d,J=7.8Hz), 7.51 (1H,d,J=8.8Hz), 7.61 (1H,dd,J=1.5Hz,8.8Hz), 7.76 (1H,s), 8.19-8.31 (2H,m), 9.71 (1H,brs), 10.43 (1H,s), 11.67 (1H,s), 13.20 (1H,brs)

Working Example 4

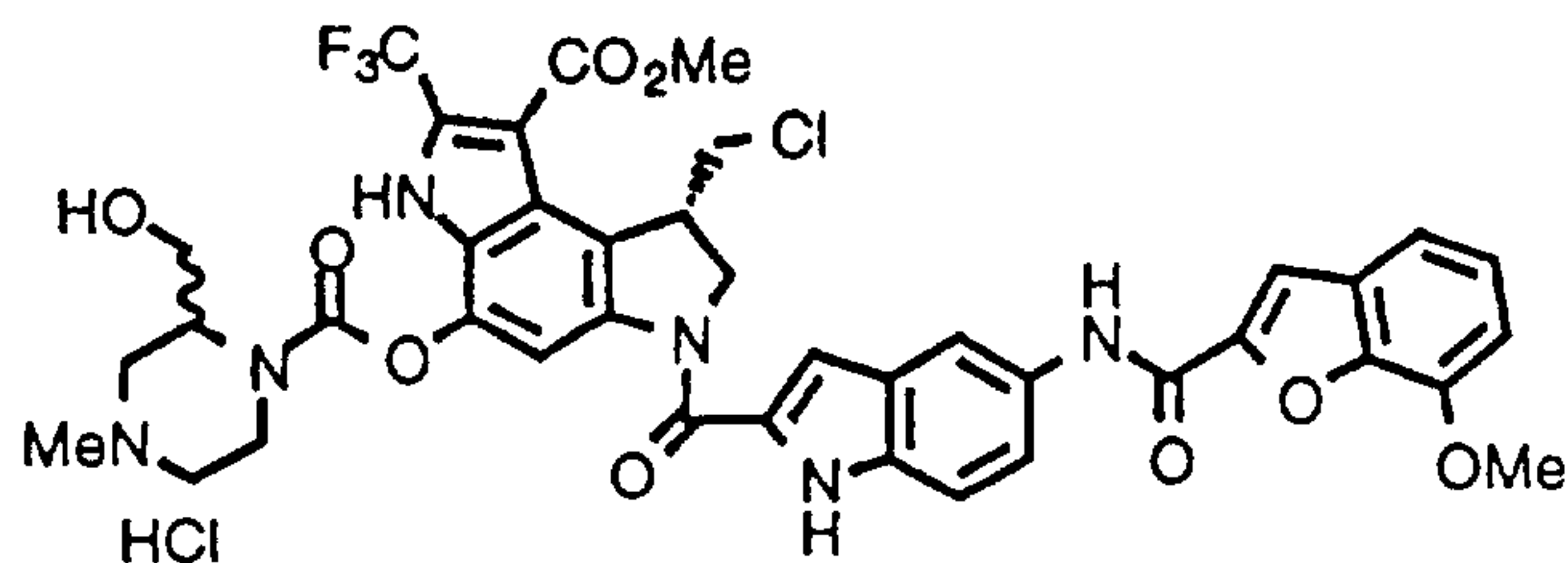


In the same manner as in Working Example 1, methyl (1S)-chloromethyl-5-hydroxy-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-

1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (13.6 mg, 20 μ mol) and (2RS)-piperidine-2-methanol (6.9 mg, 60 μ mol) were allowed to react to obtain methyl (1S)-chloromethyl-5-{[(2RS)-hydroxymethylpiperidin-1-ylcarbonyl]oxy}-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (12.5 mg, 76%).

NMR(DMSO- d_6) δ : 1.40-1.85(6H,m), 3.25-3.95(8H,m), 3.91(3H,s), 4.00(3H,s), 4.42(1H,m), 4.60(1H,d,J=10.7Hz), 4.80(1H,t,J=9.8Hz), 7.10(1H,d,J=8.3Hz), 7.21(1H,s), 7.28(1H,t,J=7.8Hz), 7.36(1H,d,J=7.8Hz), 7.49(1H,d,J=8.8Hz), 7.60(1H,dd,J=2.0Hz,9.3Hz), 7.75(1H,s), 8.21(2H,m), 10.41(1H,s), 11.74(1H,s)

Working Example 5

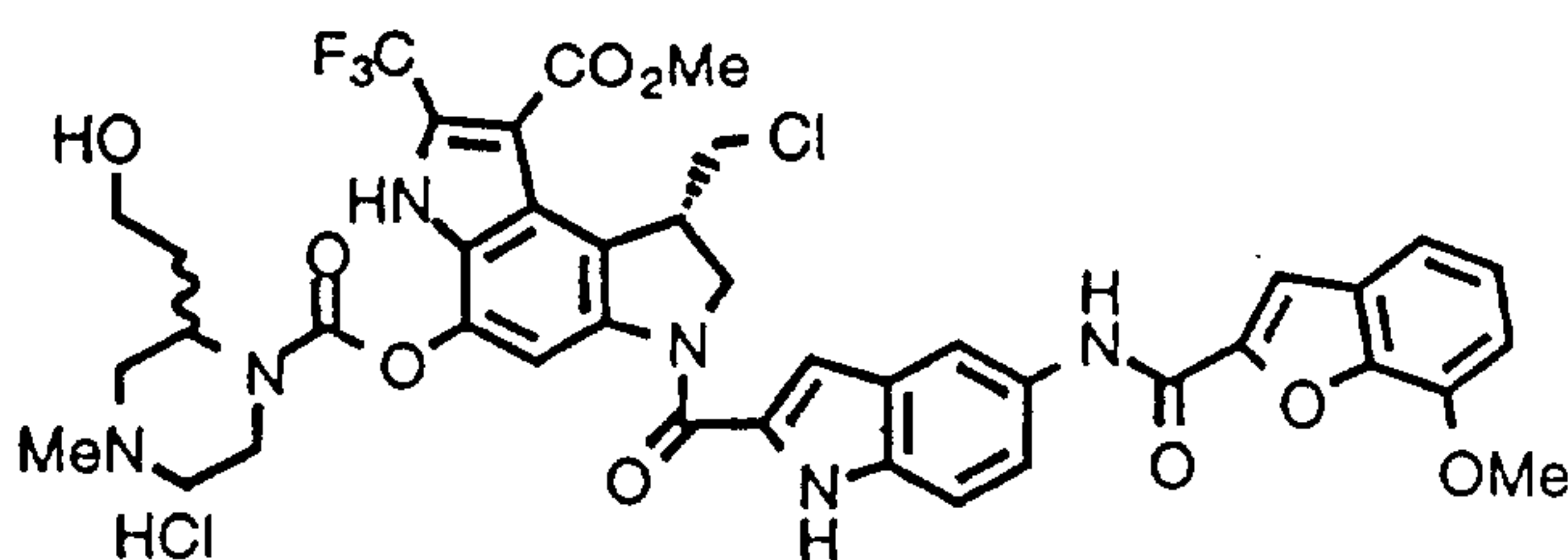


In the same manner as in Working Example 3, methyl (1S)-chloromethyl-5-hydroxy-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (27.2 mg, 40 μ mol) and (2RS)-4-methylpiperazine-2-methanol (13.0 mg, 100 μ mol) were allowed to react and the resulting product was treated to obtain hydrochloride of methyl (1S)-chloromethyl-5-{[(2RS)-hydroxymethyl-4-methylpiperazin-1-ylcarbonyl]oxy}-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino

-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (18.8 mg, 54%).

NMR(DMSO- d_6) δ : 2.88(3H,s), 3.05-3.95(10H,m), 3.92(3H,s), 4.00(3H,s), 4.14(1H,m), 4.20-4.50(2H,m), 4.61(1H,d,J=11.2Hz), 4.81(1H,t,J=9.3Hz), 7.10(1H,d,J=7.8Hz), 7.22(1H,s), 7.28(1H,t,J=7.8Hz), 7.36(1H,d,J=7.8Hz), 7.50(1H,d,J=9.3Hz), 7.61(1H,d,J=10.3Hz), 7.76(1H,s), 8.21-8.31(2H,m), 10.00(1H,br), 10.43(1H,s), 11.66(1H,br), 13.11(1H,brs)

Working Example 6

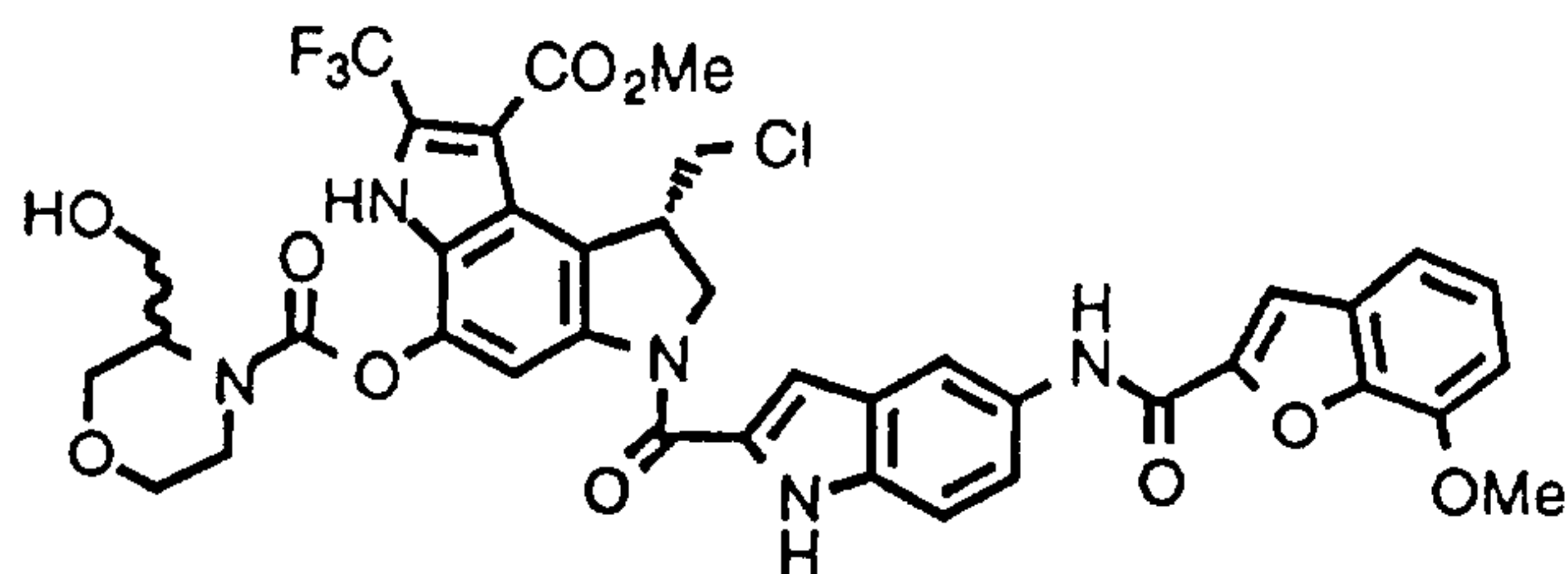


In the same manner as in Working Example 3, methyl (1S)-chloromethyl-5-hydroxy-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (20.4 mg, 30 μ mol) and (2RS)-4-methylpiperazine-2-ethanol (12.4 mg, 90 μ mol) were allowed to react and the resulting product was treated to obtain hydrochloride of methyl (1S)-chloromethyl-5-[(2RS)-hydroxyethyl-4-methylpiperazin-1-ylcarbonyl]oxy-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (16.5 mg, 62%).

NMR(DMSO- d_6) δ : 1.80-2.50(2H,m), 2.86(3H,s), 3.05-3.95(10H,m), 3.92(3H,s), 4.00(3H,s), 4.08(1H,m), 4.43(1H,m),

4.59 (1H,m) , 4.80 (1H,m) , 4.94 (1H,m) , 7.10 (1H,d,J=7.8Hz) ,
 7.22 (1H,d,J=2.0Hz) , 7.28 (1H,t,J=7.8Hz) ,
 7.37 (1H,dd,J=1.0Hz,8.8Hz) , 7.50 (1H,d,J=8.8Hz) ,
 7.61 (1H,dd,J=2.0Hz,8.8Hz) , 7.76 (1H,s) , 8.21-8.32 (2H,m) ,
 10.05 (1H,brs) , 10.43 (1H,s) , 11.67 (1H,s) , 13.17 (1H,brs)

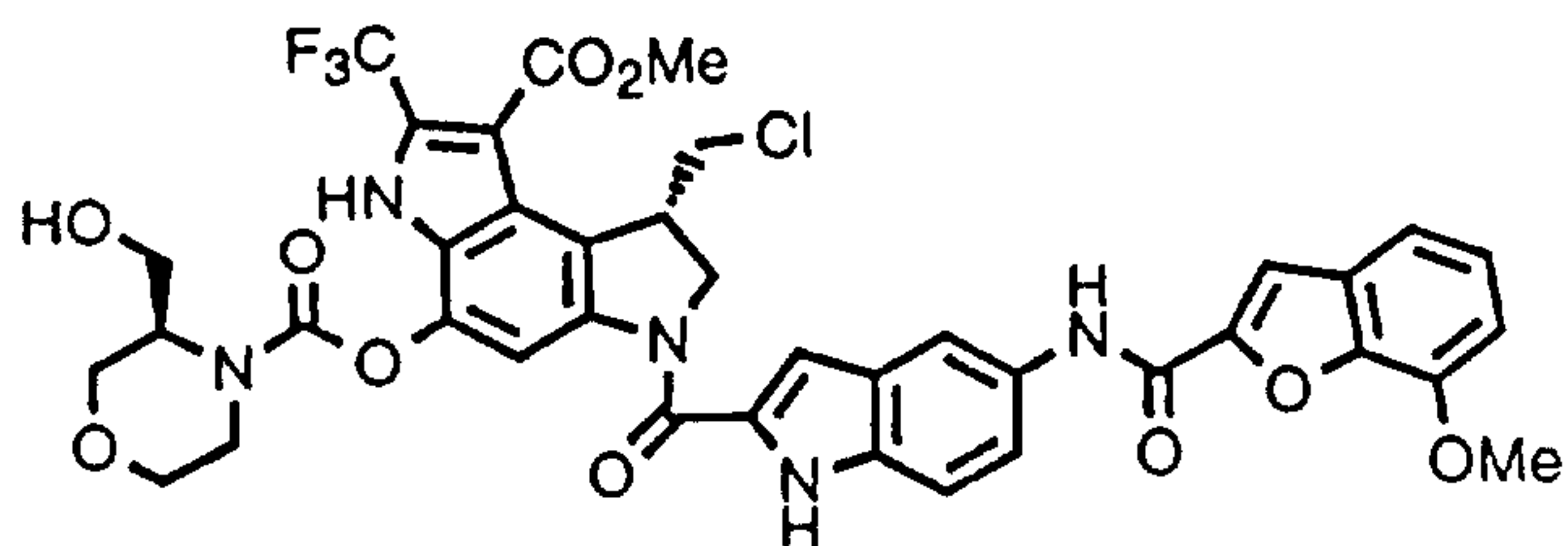
Working Example 7



In the same manner as in Working Example 1, methyl (1S)-chloromethyl-5-hydroxy-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (20.4 mg, 30 μ mol) and (3RS)-morpholine-3-methanol (10.5 mg, 90 μ mol) were allowed to react to obtain methyl (1S)-chloromethyl-5-[[(3RS)-hydroxymethylmorpholin-4-ylcarbonyl]oxy]-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (17.5 mg, 71%).

NMR(DMSO- d_6) δ : 3.15-4.05 (11H,m) , 3.92 (3H,s) ,
 4.00 (3H,s) , 4.29 (1H,m) , 4.43 (1H,m) , 4.61 (1H,d,J=10.7Hz) ,
 4.80 (1H,t,J=9.3Hz) , 7.10 (1H,d,J=7.3Hz) , 7.22 (1H,d,J=2.0Hz) ,
 7.28 (1H,t,J=8.3Hz) , 7.36 (1H,d,J=7.8Hz) , 7.49 (1H,d,J=8.8Hz) ,
 7.60 (1H,dd,J=2.0Hz,8.8Hz) , 7.75 (1H,s) , 8.21 (2H,m) ,
 10.41 (1H,s) , 11.73 (1H,s) , 13.08 (1H,brs)

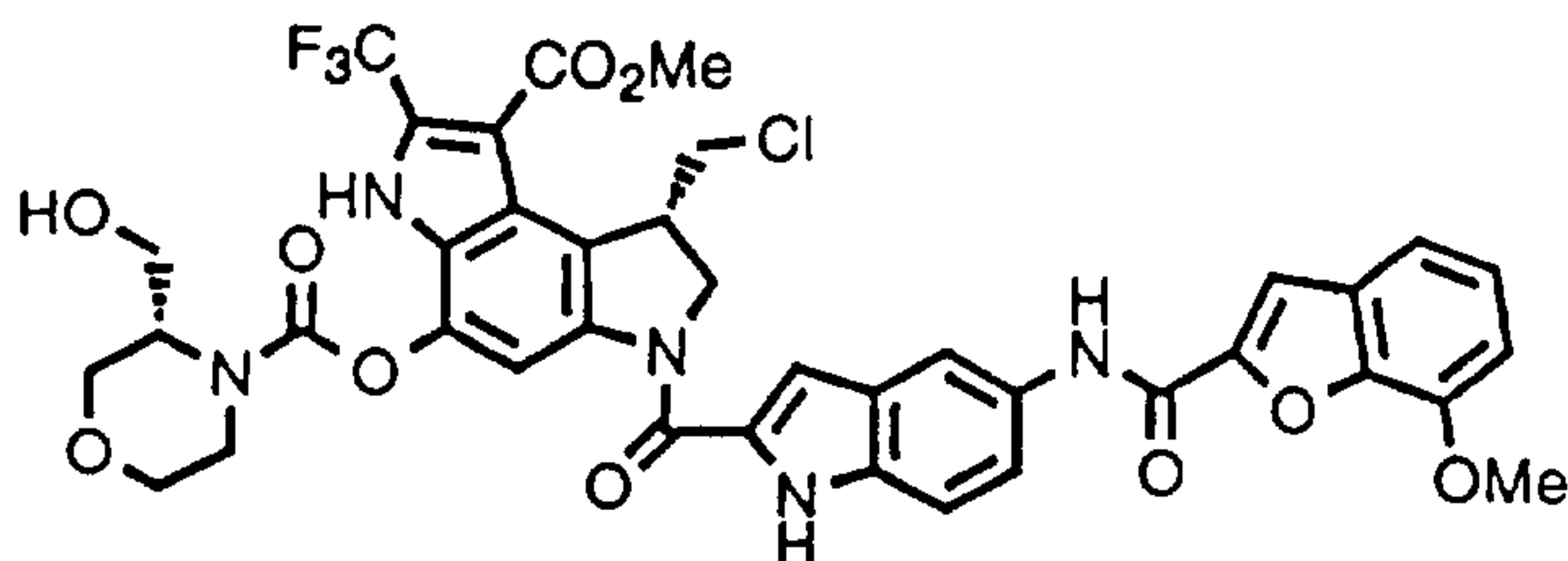
Working Example 8



In the same manner as in Working Example 1, methyl (1S)-chloromethyl-5-hydroxy-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (81.7 mg, 0.12 mmol) and (3R)-morpholine-3-methanol (42.2 mg, 0.36 mmol) were allowed to react to obtain methyl (1S)-chloromethyl-5-([(3R)-hydroxymethylmorpholin-4-ylcarbonyl]oxy)-3-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (62.9 mg, 64%).

NMR(DMSO- d_6) δ : 3.15-4.15(11H,m), 3.91(3H,s), 4.00(3H,s), 4.30(1H,m), 4.42(1H,m), 4.60(1H,d,J=10.7Hz), 4.80(1H,t,J=10.3Hz), 7.10(1H,d,J=7.3Hz), 7.22(1H,s), 7.28(1H,t,J=7.8Hz), 7.37(1H,d,J=7.8Hz), 7.49(1H,d,J=8.5Hz), 7.60(1H,dd,J=2.0Hz,9.0Hz), 7.76(1H,s), 8.21(2H,s), 10.42(1H,s), 11.74(1H,brs), 12.78,13.09(total 1H,brs $\times$ 2, in each rotamer)

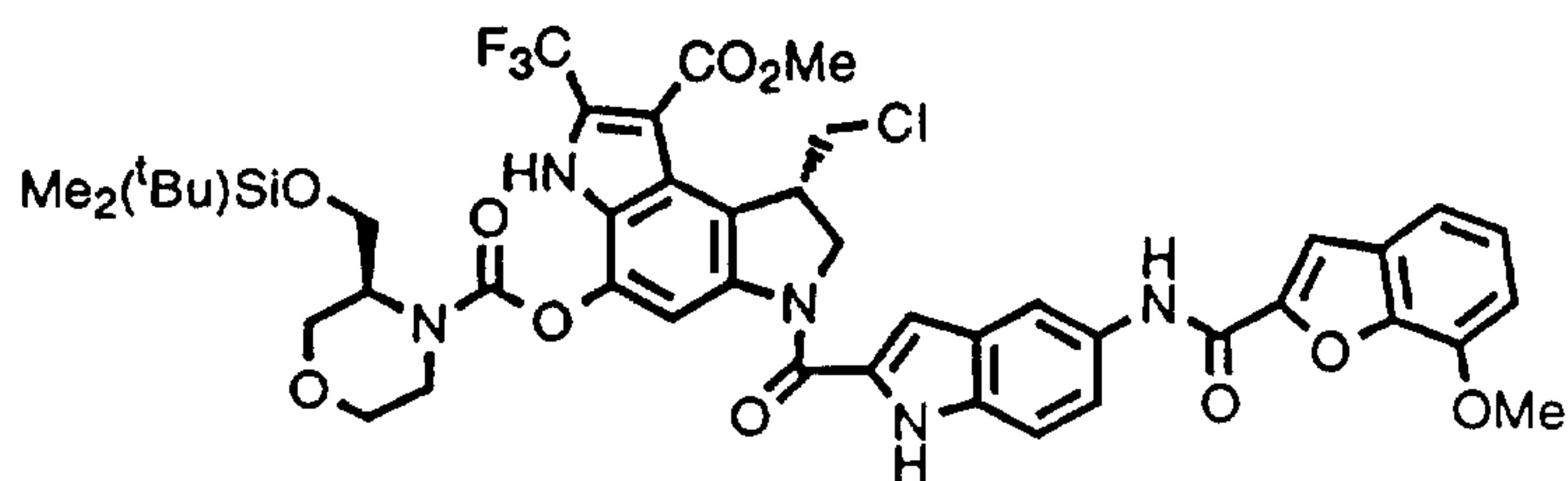
Working Example 9



In the same manner as in Working Example 1, methyl (1S)-chloromethyl-5-hydroxy-3-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (81.7 mg, 0.12 mmol) and (3S)-morpholine-3-methanol (42.2 mg, 0.36 mmol) were allowed to react to obtain methyl (1S)-chloromethyl-5-[[(3S)-hydroxymethylmorpholin-4-ylcarbonyl]oxy]-3-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (69.7 mg, 70%).

NMR(DMSO- d_6) δ : 3.10-4.15(11H,m), 3.91(3H,s), 4.00(3H,s), 4.28(1H,m), 4.43(1H,m), 4.60(1H,d,J=11.0Hz), 4.80(1H,t,J=10.5Hz), 7.10(1H,d,J=7.3Hz), 7.23(1H,d,J=2.0Hz), 7.28(1H,t,J=7.8Hz), 7.37(1H,d,J=7.8Hz), 7.49(1H,d,J=9.0Hz), 7.60(1H,dd,J=2.0Hz,8.8Hz), 7.76(1H,s), 8.21(2H,m), 10.42(1H,s), 11.73(1H,s), 12.85,13.11(total 1H,brs $\times$ 2, in each rotamer).

Working Example 10

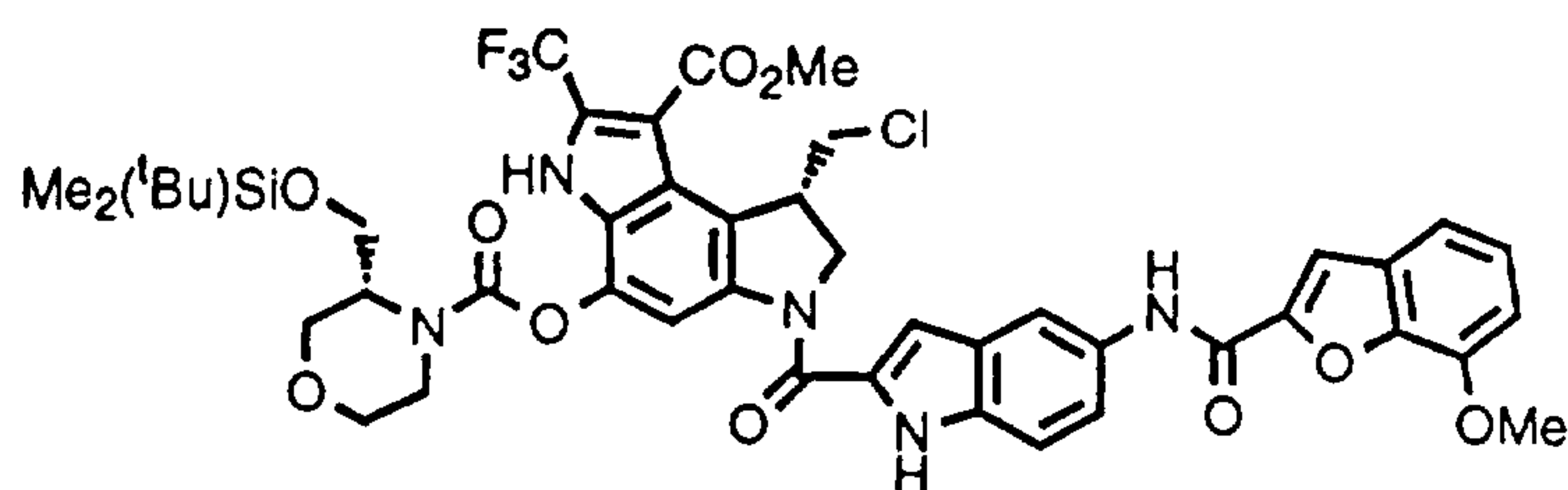


Methyl (1S)-chloromethyl-5-hydroxy-3-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (1.02 g, 1.5 mmol) and 4-nitrophenyl chloroformate (0.51 g, 2.55 mmol) were dissolved

in 50 mL of tetrahydrofuran, and thereto triethylamine (313.6 μ L, 2.25 mmol) was added dropwise with ice cooling. After 1.5 hours, (3S)-3-(t-butyldimethylsilyloxy)-methymorpholine hydrochloride (0.80 g, 3.0 mmol) and triethylamine (0.52 mL, 3.75 mmol) were added thereto. The mixture was stirred overnight. The reaction mixture was diluted with 50 mL of ethyl acetate, washed with saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. After the solvent was evaporated off, the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 1:1) to obtain methyl (1S)-chloromethyl-5-{[(3S)-(t-butyldimethylsilyloxy)-methymorpholin-4-ylcarbonyl]oxy}-3-[5-[7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (1.08 g, 77%).

NMR(DMSO- d_6) δ : 0.04, 0.07 (total 6H, s $\times$ 2, in each rotamer), 0.85, 0.86 (total 9H, s $\times$ 2, in each rotamer), 3.15-4.10 (10H, m), 3.91 (3H, s), 4.00 (3H, s), 4.19 (1H, m), 4.40 (1H, m), 4.59 (1H, d, J=11.2 Hz), 4.80 (1H, t, J=10.7 Hz), 7.10 (1H, d, J=7.8 Hz), 7.22 (1H, s), 7.28 (1H, t, J=8.1 Hz), 7.37 (1H, d, J=7.6 Hz), 7.50 (1H, d, J=8.8 Hz), 7.60 (1H, dd, J=2.0 Hz, 9.0 Hz), 7.76 (1H, s), 8.17 (2H, m), 10.42 (1H, s), 11.69 (1H, s), 13.09 (1H, brs)

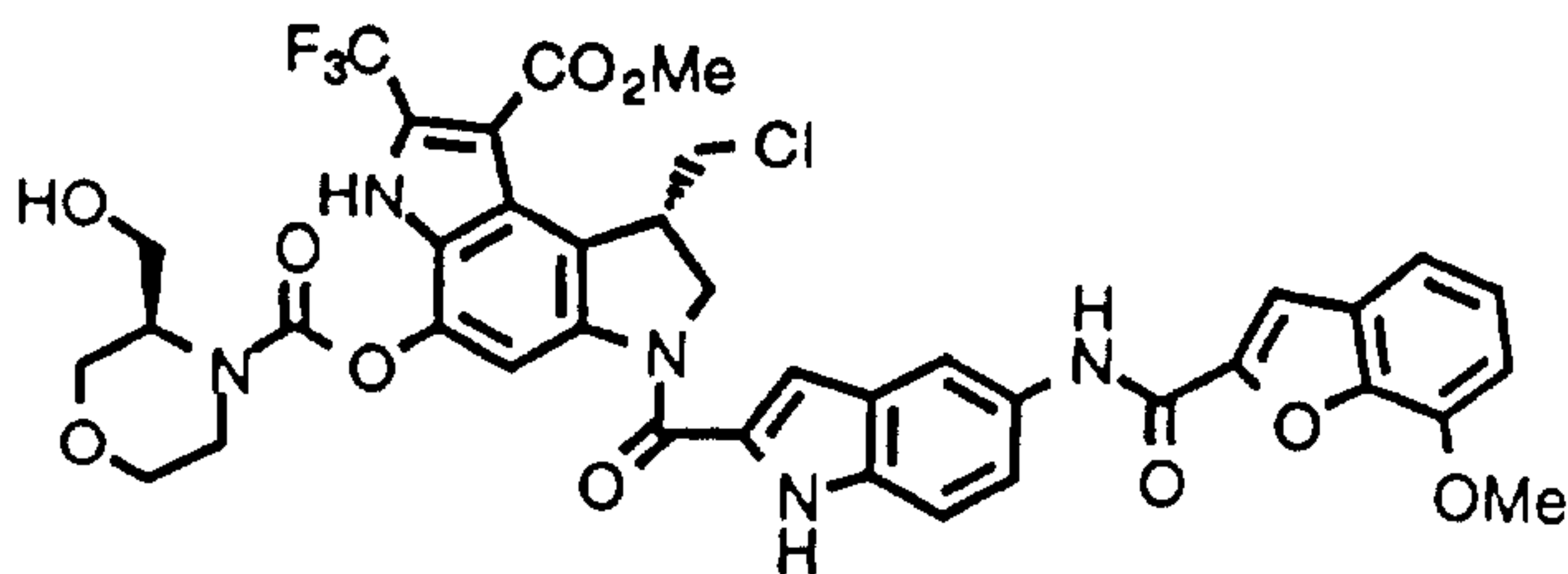
Working Example 11



In the same manner as in Working Example 10, methyl (1S)-chloromethyl-5-hydroxy-3-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (1.36 g, 2.0 mmol) and (3R)-3-(t-butyldimethylsilyloxy)-methyldmorpholine hydrochloride (1.07 g, 4.0 mmol) were allowed to react to obtain methyl (1S)-chloromethyl-5-[(3R)-(t-butyldimethylsilyloxy)-methyldmorpholin-4-ylcarbonyl]oxy-3-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (1.58 g, 84%).

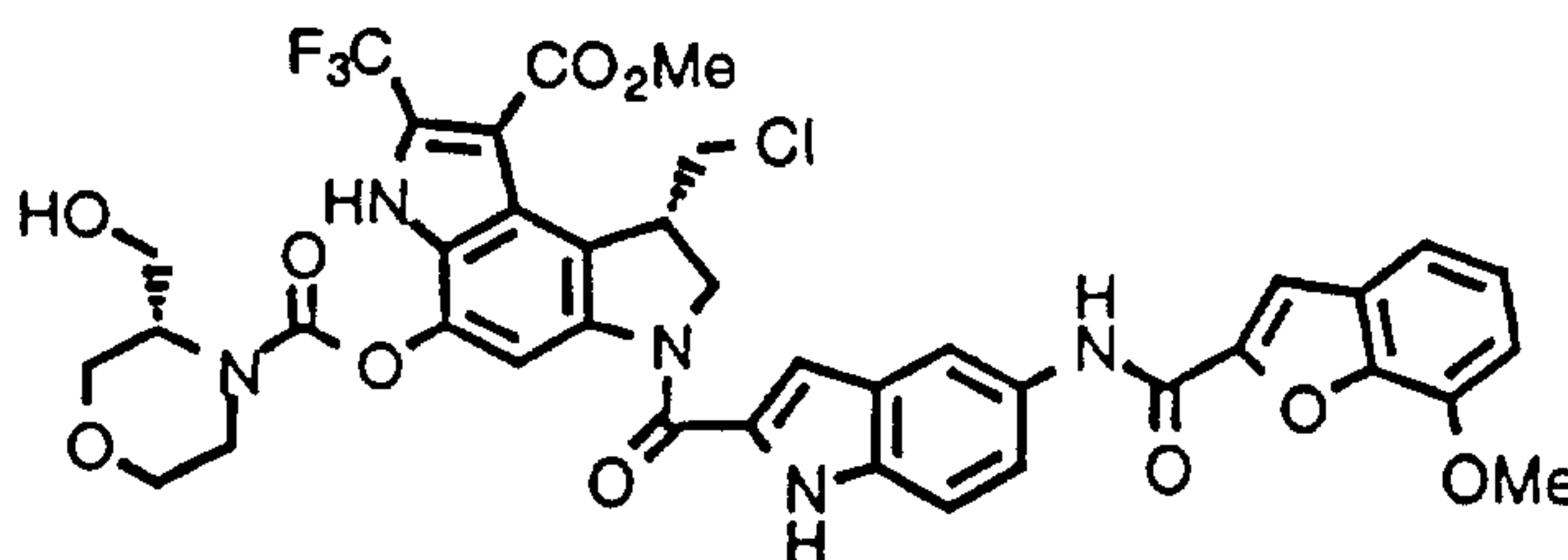
NMR (DMSO- d_6) δ : 0.07, 0.08 (total 6H, s $\times$ 2, in each rotamer), 0.867, 0.874 (total 9H, s $\times$ 2, in each rotamer), 3.15-4.10 (10H, m), 3.91 (3H, s), 4.00 (3H, s), 4.21 (1H, m), 4.41 (1H, m), 4.59 (1H, d, J=10.5 Hz), 4.80 (1H, t, J=10.2 Hz), 7.10 (1H, d, J=7.6 Hz), 7.22 (1H, s), 7.28 (1H, t, J=7.8 Hz), 7.37 (1H, d, J=7.8 Hz), 7.50 (1H, d, J=8.8 Hz), 7.60 (1H, dd, J=2.0 Hz, 8.8 Hz), 7.76 (1H, s), 8.18 (1H, s), 8.20 (1H, s), 10.42 (1H, s), 11.69 (1H, s), 13.08 (1H, brs)

Working Example 12



Methyl (1S)-chloromethyl-5-[(3S)-(t-butyl dimethylsilyloxy)methylmorpholin-4-ylcarbonyl)oxy]-3-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (1.03 g, 1.1 mmol) was suspended in 2 mL of ethyl acetate and 8 mL of isopropanol. Thereto, 5.5 mL of 1N hydrochloric acid in isopropyl alcohol was added, and the mixture was stirred at room temperature for one hour. The reaction mixture was cooled by ice. Thereto, 10 mL of isopropyl ether was added and the mixture was stirred for 15 minutes. The formed crystalline matter was collected by filtration, and washed with isopropyl ether to obtain methyl (1S)-chloromethyl-5-[[(3R)-hydroxymethylmorpholin-4-ylcarbonyl]oxy]-3-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (0.83 g, 92%) as colorless crystals. This substance is the same as the one obtained in Working Example 8.

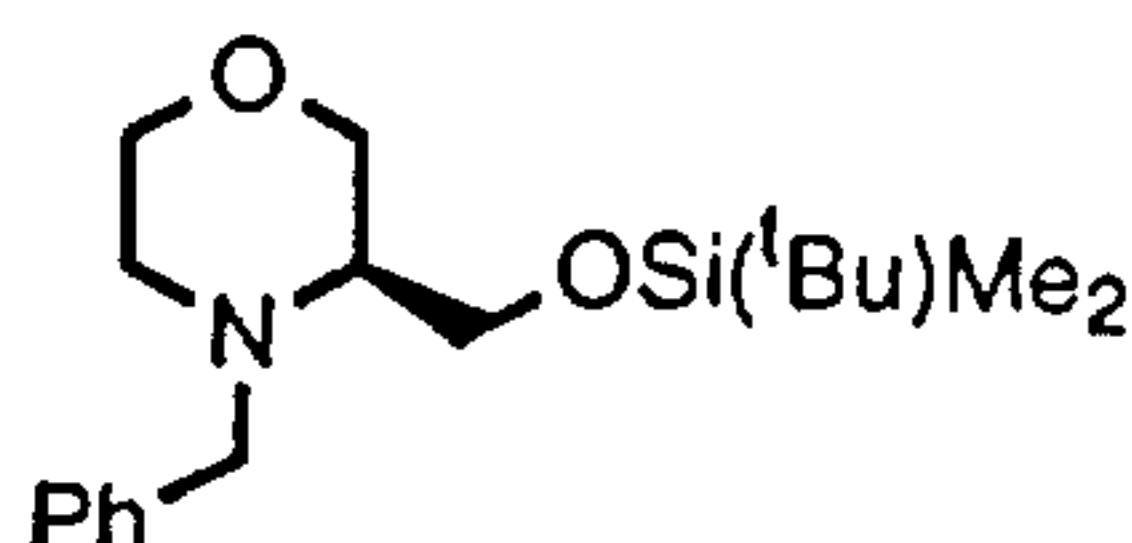
Working Example 13



In the same manner as in Working Example 12, methyl (1S)-chloromethyl-5-[[(3R)-(t-butyl dimethylsilyloxy)-

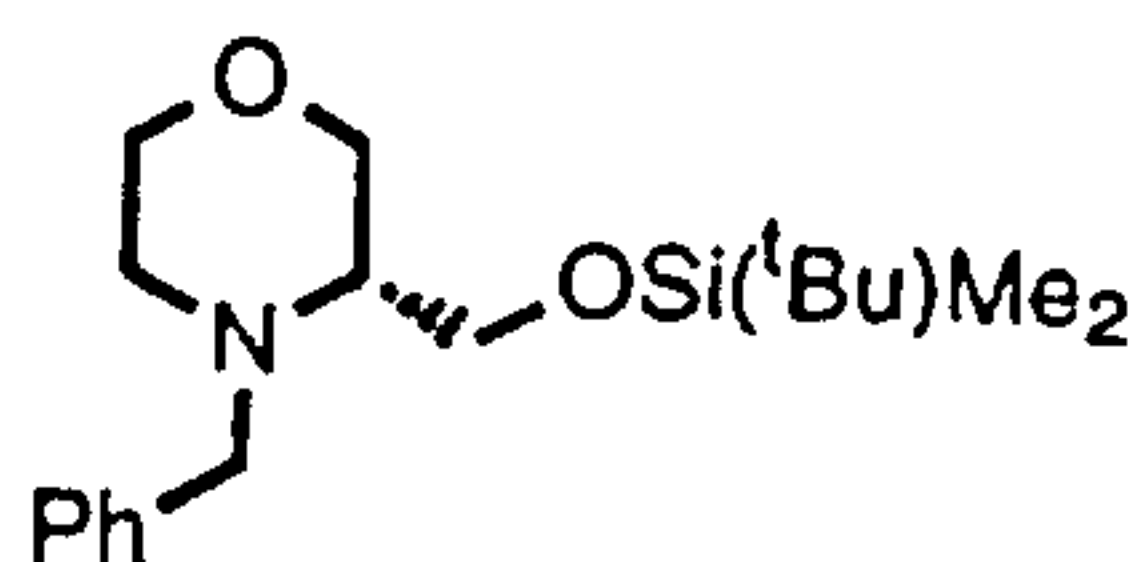
methylmorpholin-4-ylcarbonyl]oxy}-3-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (1.41 g, 1.5 mmol) was treated to obtain methyl (1S)-chloromethyl-5-{[(3S)-hydroxymethylmorpholin-4-ylcarbonyl]oxy}-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate (1.20 g, 97%) as colorless crystals. This substance is the same as the one obtained in Working Example 9.

Working Example 14



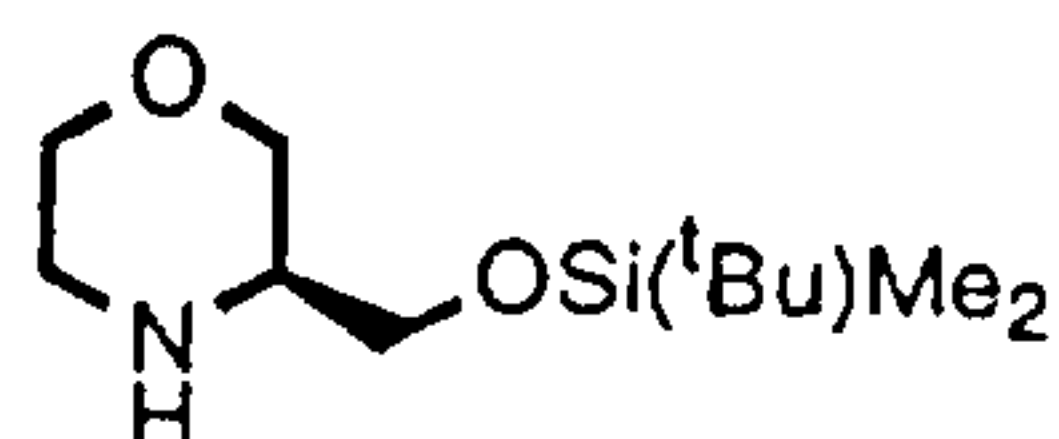
(3R)-4-Benzylmorpholine-3-methanol (1.04 g, 5.0 mmol), t-butyldimethylchlorosilane (0.83 g, 5.5 mol), and imidazole (0.41 g, 6.0 mmol) were allowed to react in 5 mL of dichloromethane at room temperature overnight. The reaction product was purified by silica gel column chromatography (hexane:ethyl acetate = 5:1) to obtain (3S)-3-(t-butyldimethylsilyloxy)methyl-4-benzylmorpholine (1.53 g, 95%) as a colorless oil.

Working Example 15



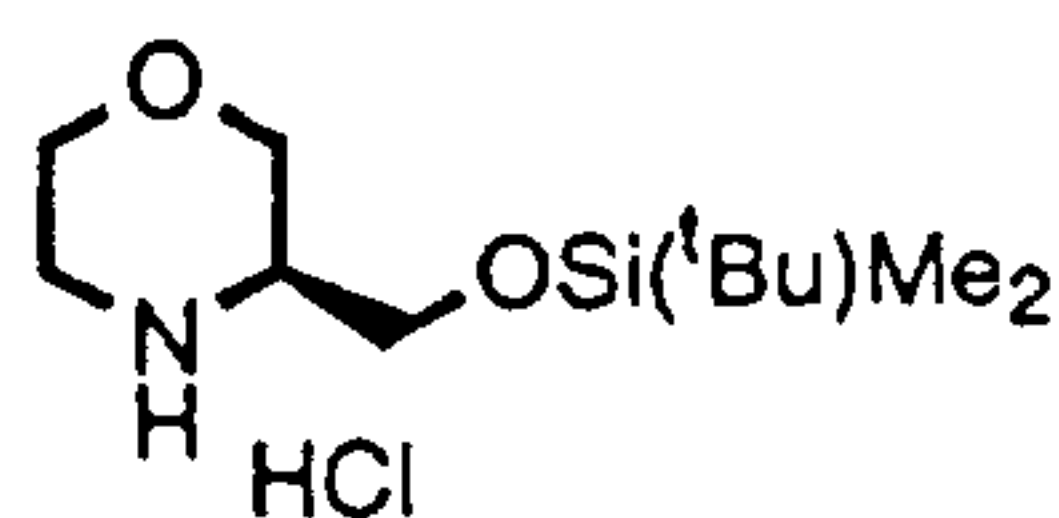
In the same manner as in Working Example 14, (3S)-4-benzylmorpholine-3-methanol (1.24 g, 6.0 mmol) was treated to obtain (3R)-3-(t-butyldimethylsilyloxy)methyl-4-benzylmorpholine (1.82 g, 94%) as a colorless oil.

Working Example 16



(3R)-Morpholine-3-methanol (84.8 mg, 0.72 mmol), t-butyldimethylchlorosilane (0.11 g, 0.72 mmol), and imidazole (59.1 mg, 0.87 mmol) were allowed to react in 1 mL of dichloromethane at room temperature for 2 hours. The reaction product was purified by silica gel chromatography (dichloromethane:methanol:acetone = 15:1:0.5) to obtain (3S)-3-(t-butyldimethylsilyloxy)methylmorpholine (0.15 g, 92%) as a colorless oil.

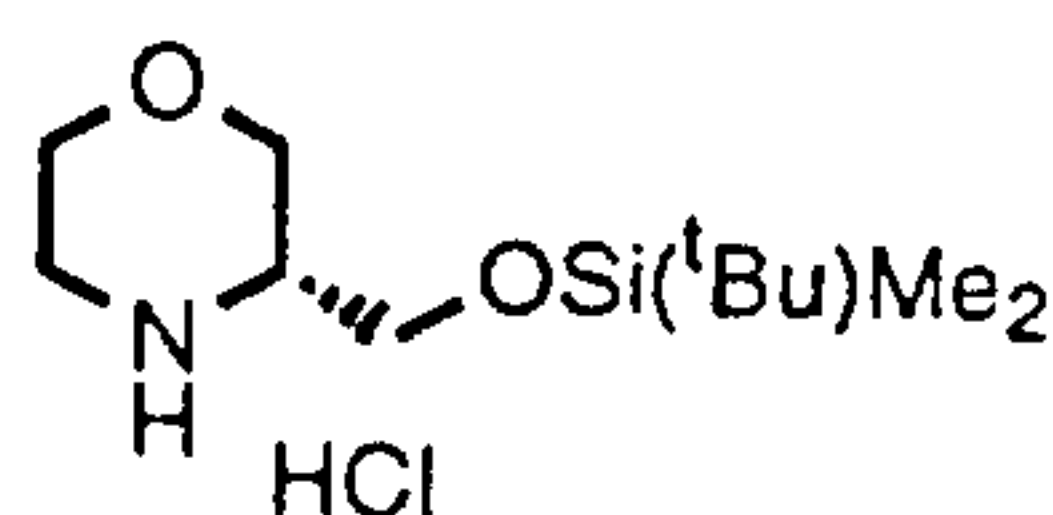
Working Example 17



(3S)-3-(t-Butyldimethylsilyloxy)methyl-4-benzylmorpholine (1.19 g, 3.7 mmol) was treated for hydrogenation in the presence of 10% palladium-carbon (0.36 g) in 5 mL of ethanol and 0.32 mL of chloroform for 4 hours (one atmosphere). The catalyst was removed by filtration, and the filtrate was concentrated. The precipitated

crystalline matter was washed with ether to obtain (3S)-3-(t-butyldimethylsilyloxy)methylmorpholine hydrochloride (0.96 g (96%) .

Working Example 18



In the same manner as in working Example 17, (3R)-3-(t-butyldimethylsilyloxy)methyl-4-benzylmorpholine (1.82 g, 5.6 mmol) was treated to obtain (3R)-3-(t-butyldimethylsilyloxy)methylmorpholine hydrochloride (1.13 g, 74%) .

Test Example 1

Decomposition reaction under chemical conditions:

A buffer solution of pH 7.4 was prepared by mixing suitably an aqueous 0.1M citric acid solution and an aqueous 0.2M disodium hydrogenphosphate solution. The buffer solution was diluted tenfold with water. This buffer solution was further dissolved in N,N-dimethylacetamide at a concentration of 50 v/v%, and its pH was adjusted to 7.4 by adding suitable amount of aqueous 0.1M citric acid solution to prepare a buffer solution. The test compounds were dissolved respectively in the buffer solution at a concentration of 5 μ M to prepare the test sample solutions. The test sample solutions were placed respectively in a glass vial, and the glass vials were kept at 37°C in a thermostat.

The change of the concentration of remaining test compounds with lapse of time was determined quantitatively intermittently by high performance liquid chromatography (HPLC) to measure the half life ($t_{1/2}$: hours). Table 1 shows the test results.

Table 1

Test compound	Half life ($t_{1/2}$: hours)	Test compound	Half life ($t_{1/2}$: hours)
Example 1	>8	Example 5	1.7 *
Example 2	>8	Example 6	5.8 *
Example 3	1.0	Example 7	1.7 *
Example 4	>8 *		

* Average of the half lives of the diastereomers

The compounds of the present invention decomposes rapidly in the buffer solution of pH 7.4 to form the active species.

Test Example 2

Evaluation with mouse bearing M5076/ADR cells (adriamycin-resistant strain) transplanted subcutaneously:

M5076/ADR cells (adriamycin-resistant strain) were transplanted subcutaneously at the axillary region of female mice (BDFI strain, 8 week age) in an amount of 3.0×10^6 cells for an individual mouse. Nine days after the transplantation, the test compound solution was injected once into the tail vein. After 13 days from the injection, the tumor was excised and weighed. The antitumor activity was

evaluated by the ratio (T/C) of the average tumor weight (T) of the administrated group to the average tumor weight (C) of control group to which solvent was administrated. Table 2 shows the effects.

Table 2

Test compound	Dose (mg/kg)	T/C
Example 4	1.0	0.01
Example 5	1.0	0.01
Example 6	1.0	0.02

The compounds of the present invention showed excellent antitumor effect against M5076/ADR cells (adriamycin-resistant strain).

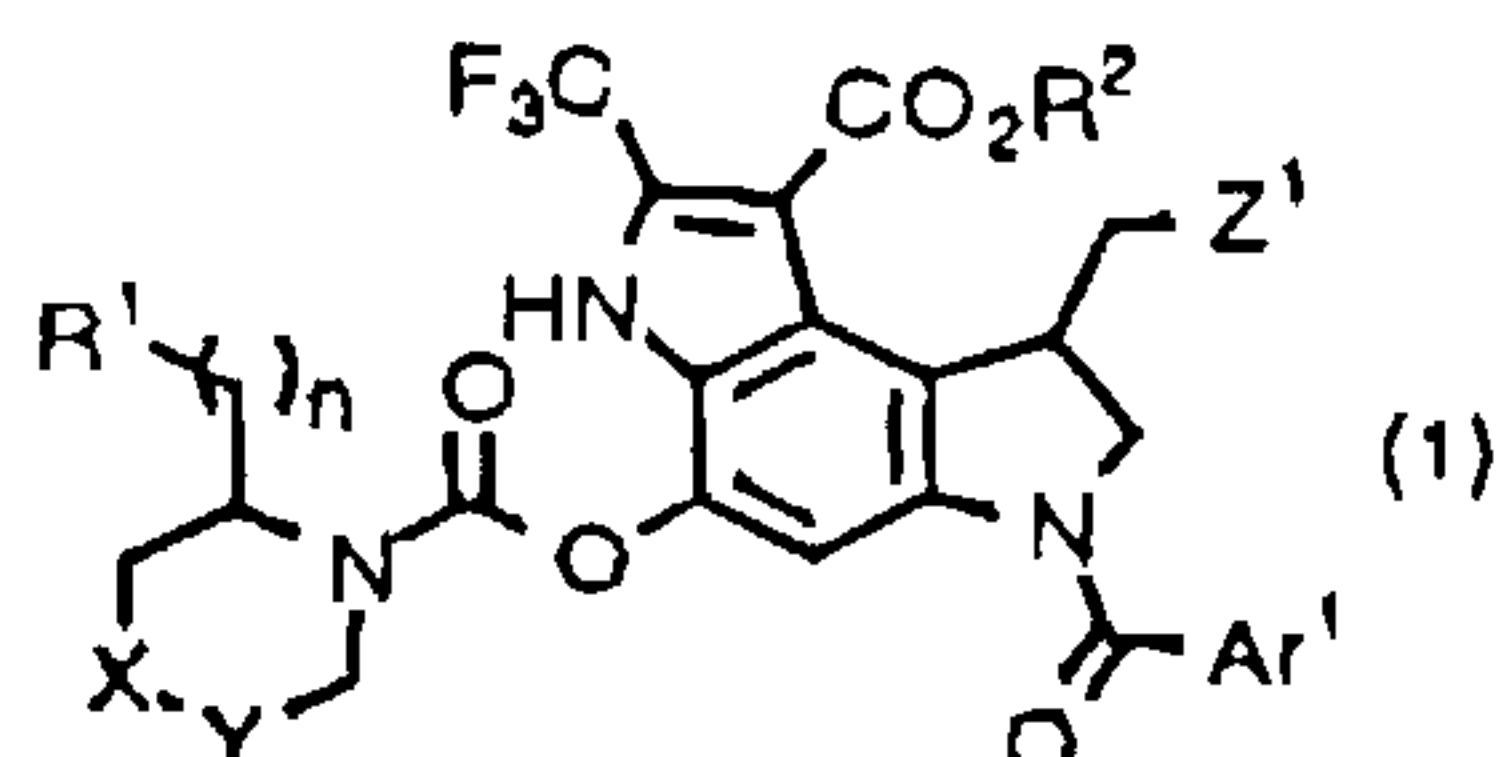
INDUSTRIAL APPLICABILITY

The pyrroloindole derivative of the present invention, which has a carbamoyloxy group comprising a cyclic amine having hydroxyalkyl or pyrrolidinylalkyl at α -position to the nitrogen of the carbamoyl group, decomposes at an appropriate rate in vivo or under chemical conditions to produce active species, although carbamoyl groups comprising a cyclic amine are generally stable. Such a prodrug have firstly produced according to the present invention. The prodrug compounds of the present invention are effective against solid tumor, and are less toxic and exhibit antitumor activity in a broad safety range. Therefore the chemotherapy for patients with cancer can be

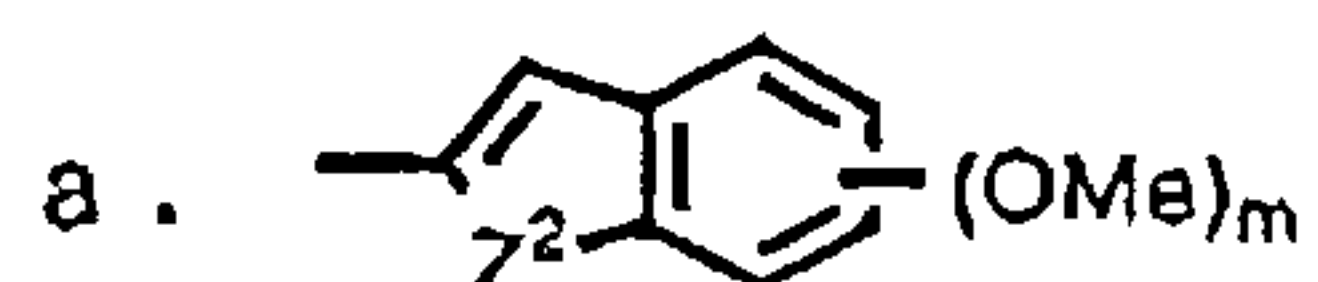
conducted with less adverse effects.

CLAIMS

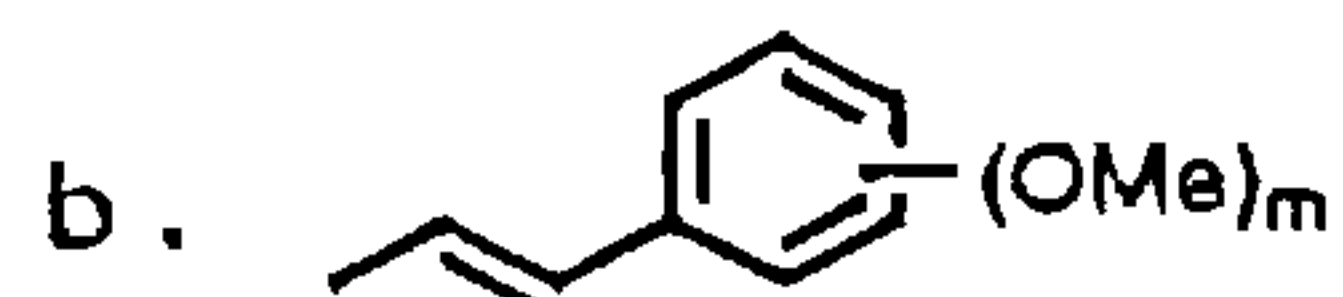
1. A pyrroloindole derivative having a carbamoyloxy group represented by the following general formula (1) below, an optically active isomer thereof, and a pharmacologically acceptable salt thereof:



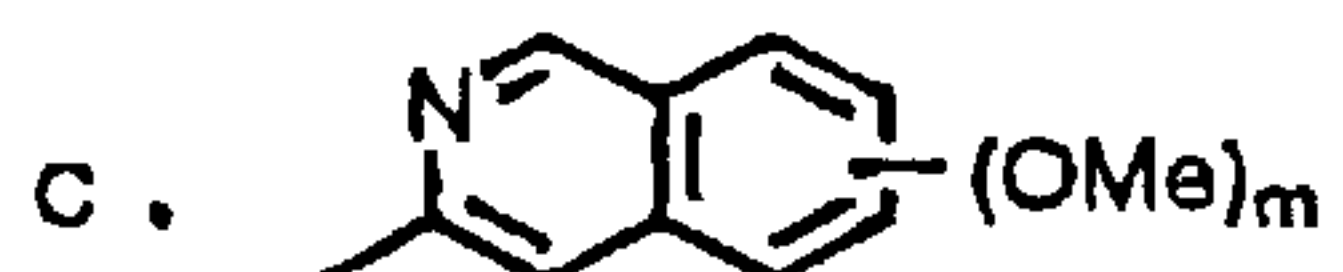
where R^1 is OH, or a pyrrolidinyl group; n is 1 or 2; R^2 is a lower alkyl group of C_1-C_4 ; $X-Y$ or $Y-X$ is CH_2 , $CHOH$, CH_2-CH_2 , $O-CH_2$, or $NMe-CH_2$; Z^1 is Cl or Br; and Ar^1 is



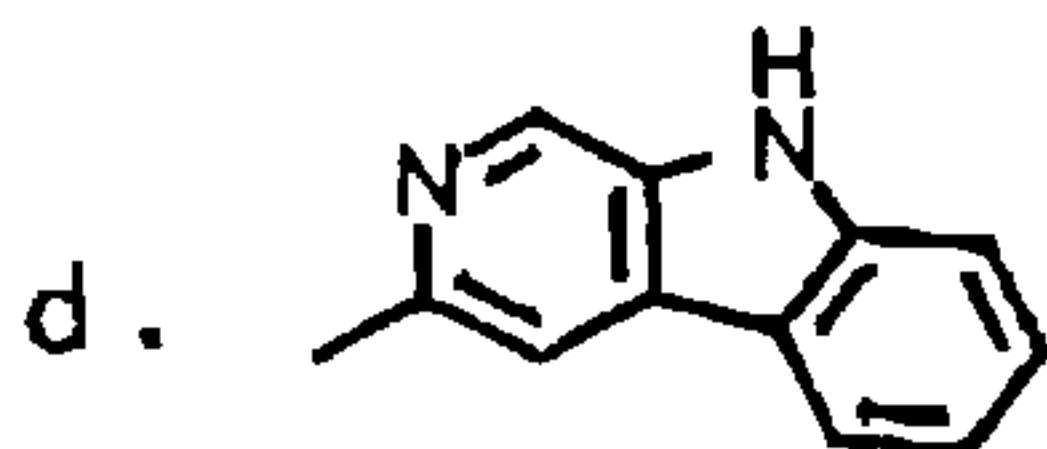
wherein Z^2 is O or NH, m is 0 or an integer of 1 to 4,



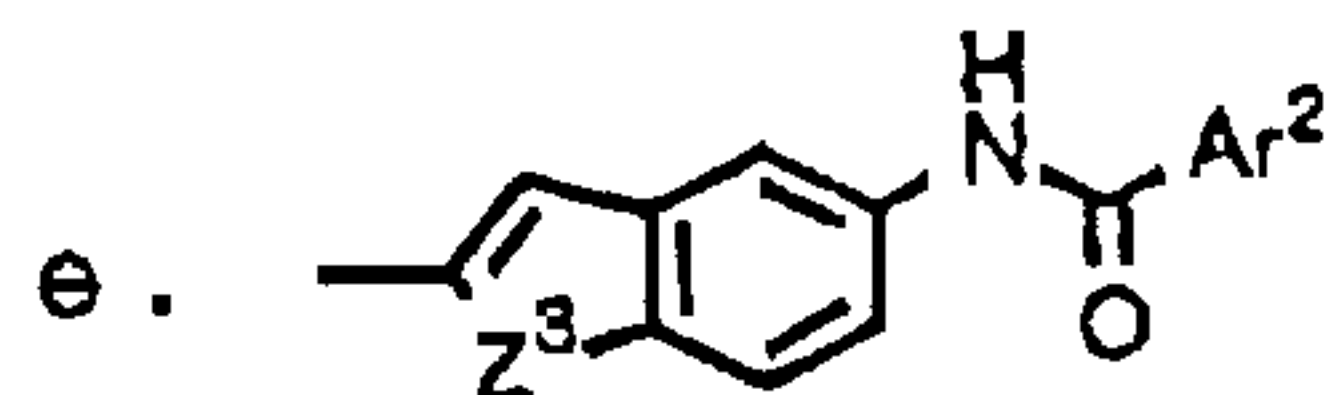
wherein m is 0 or an integer of 1 to 4,



wherein m is 0 or an integer of 1 to 4,



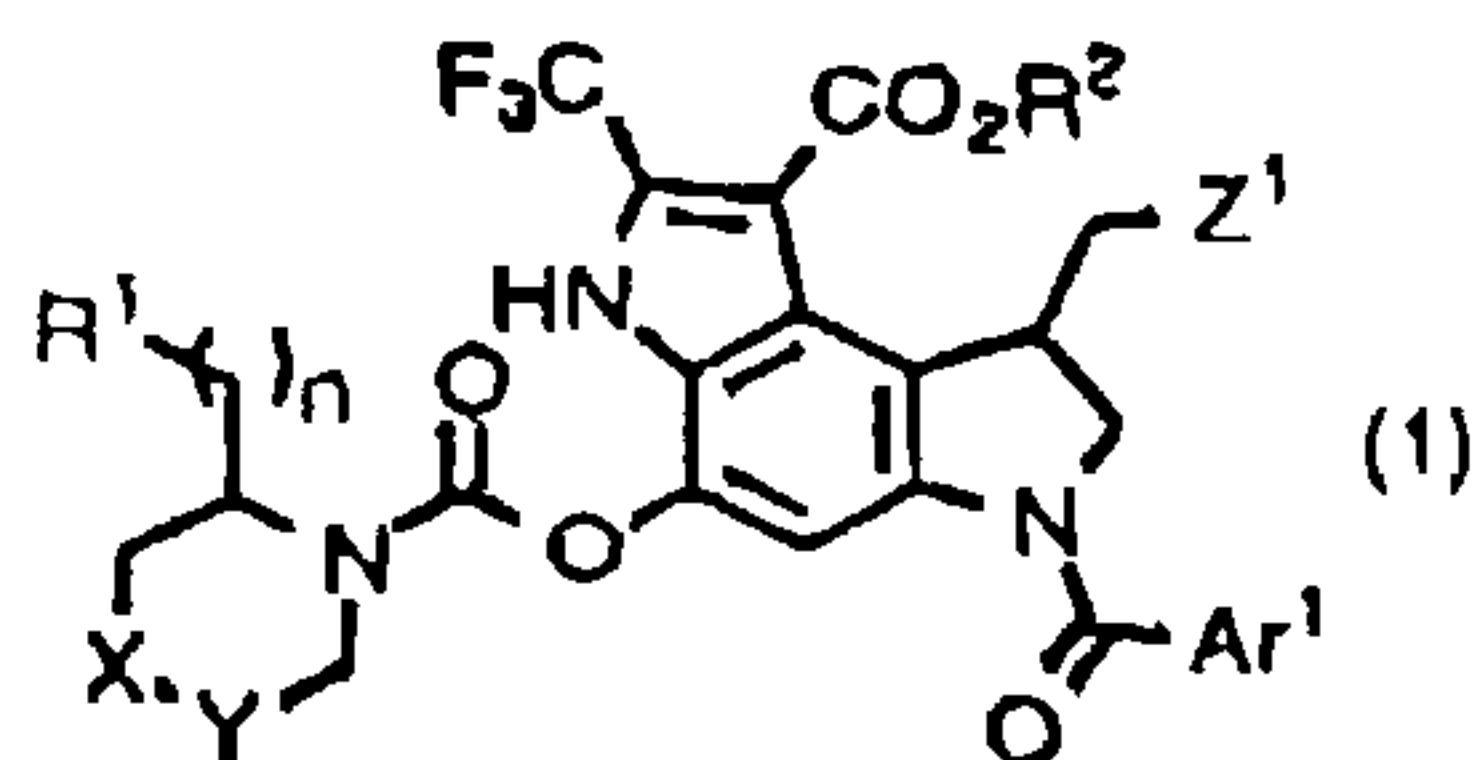
or



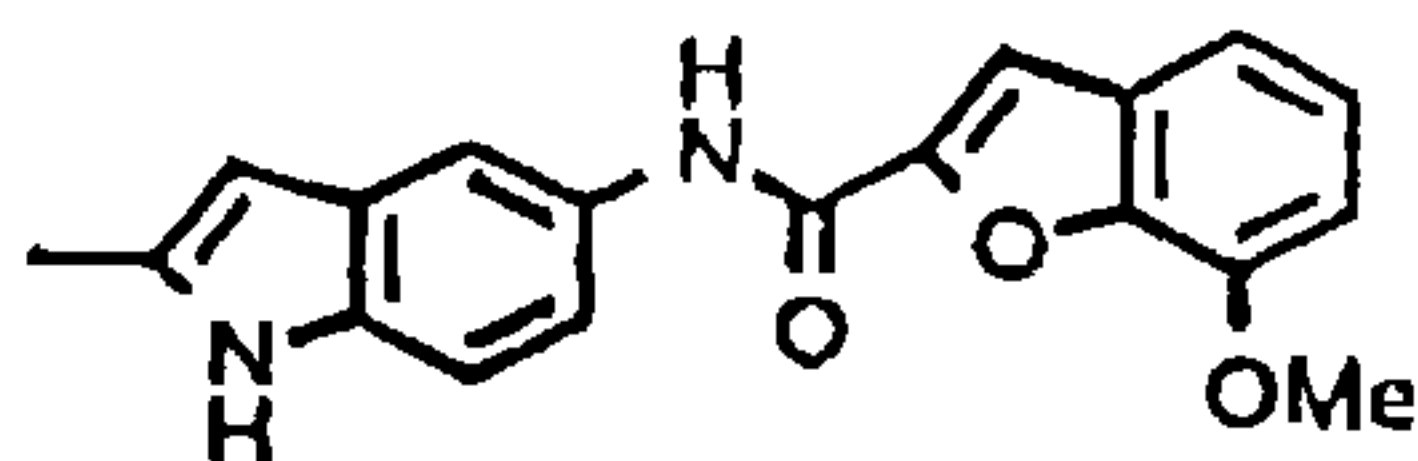
wherein Z^3 is O or NH; Ar^2 is any of the above groups a, b,

c, and d.

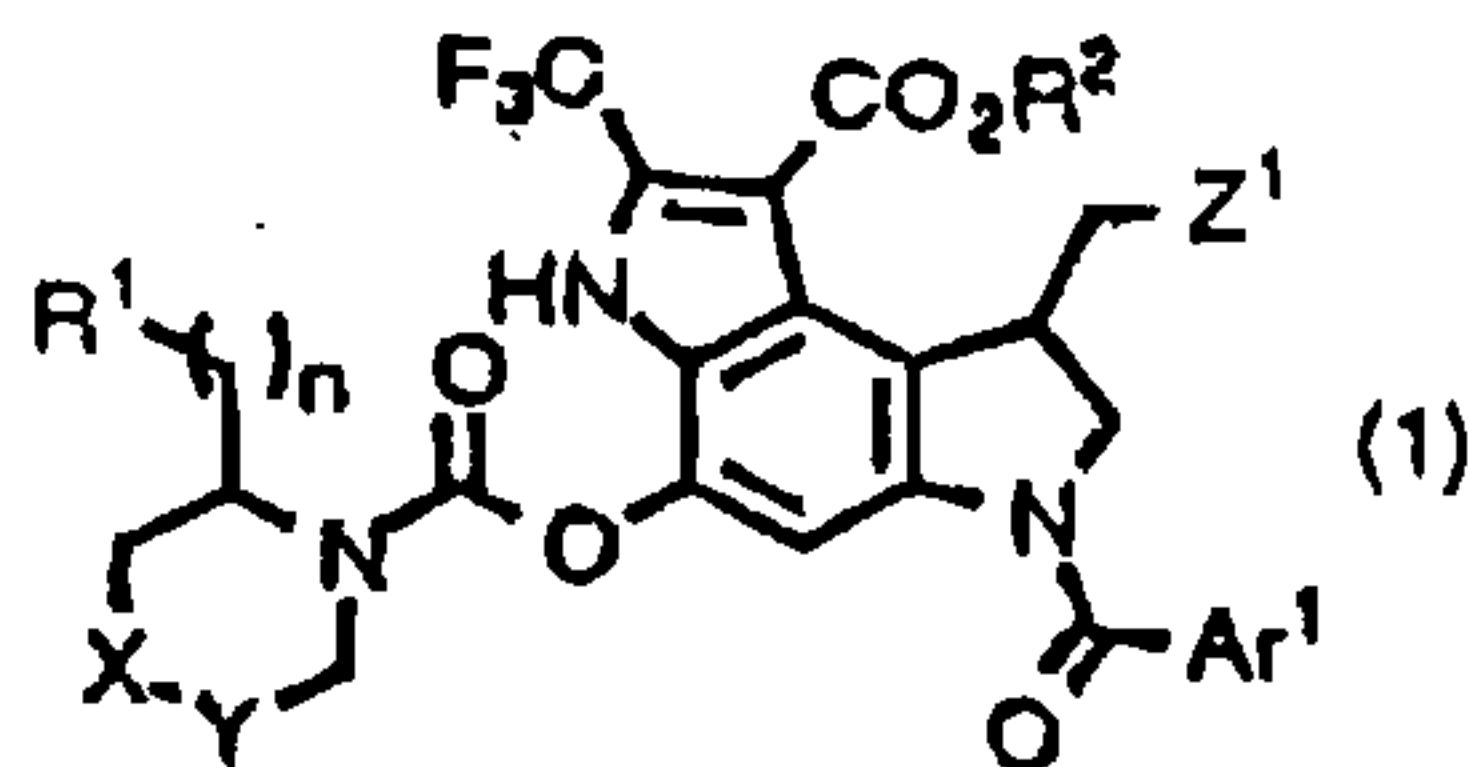
2. The pyrroloindole derivative having a carbamoyloxy group according to claim 1 represented by the following general formula (1) below, the optically active isomer thereof, and the pharmacologically acceptable salt thereof:



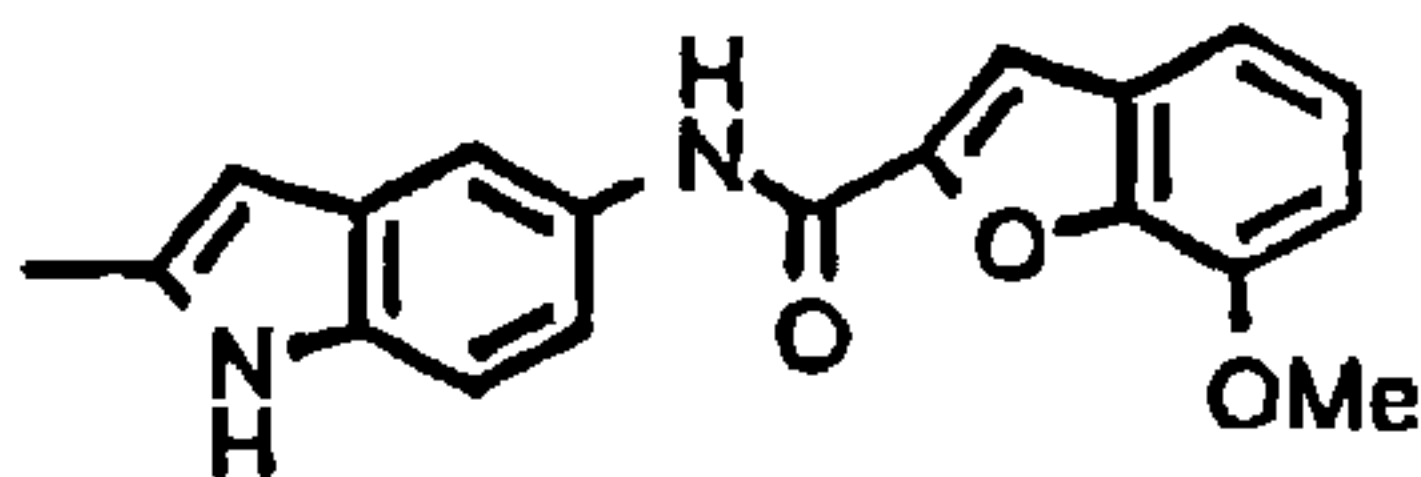
where R^1 is a pyrrolidinyl group, n is 1, R^2 is methyl, $X-Y$ is CH_2 , Z^1 is Cl, and Ar^1 is



3. The pyrroloindole derivative having a carbamoyloxy group according to claim 1 represented by the following general formula (1) below, and the optically active isomer thereof:

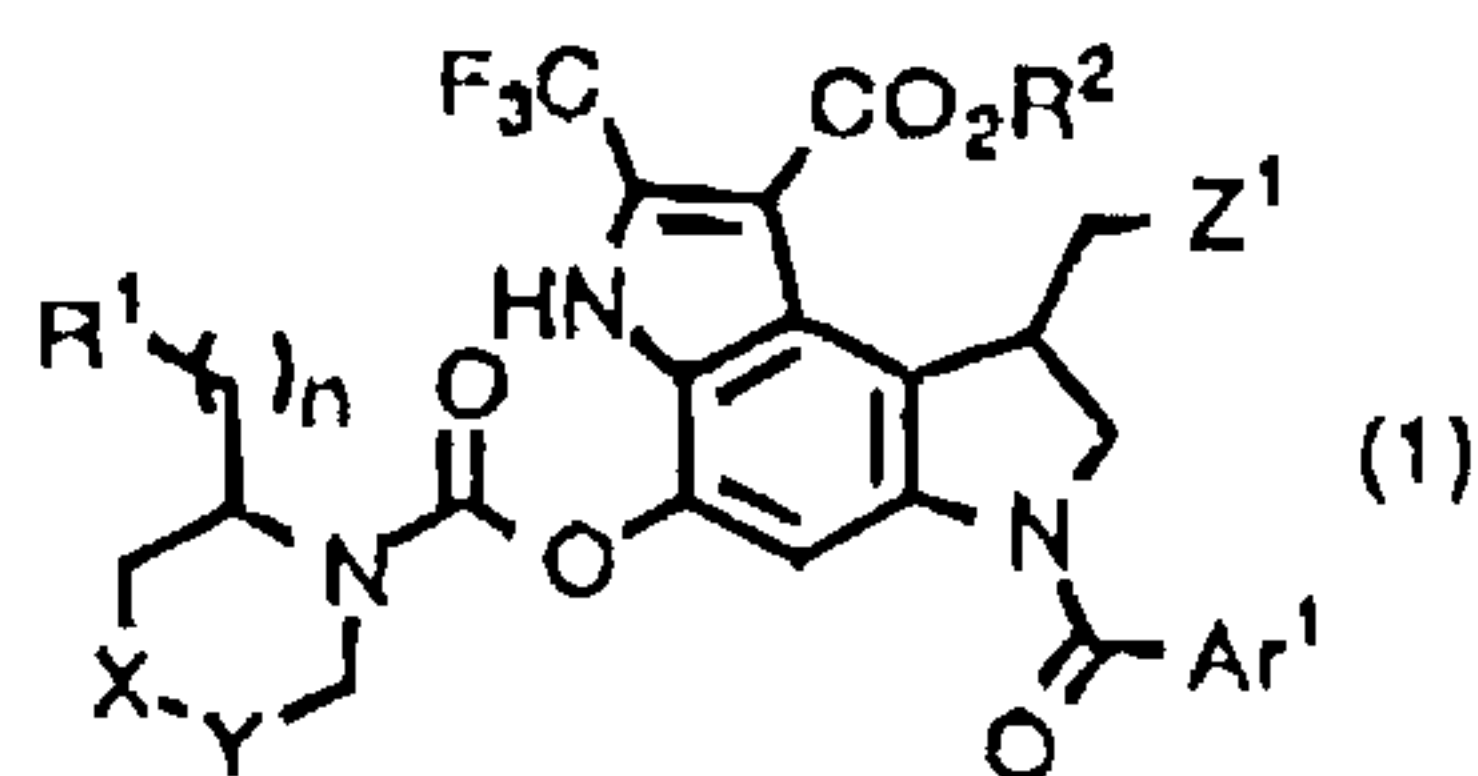


where R^1 is OH, n is 1, R^2 is methyl, $X-Y$ is CH_2-CH_2 , Z^1 is Cl, and Ar^1 is

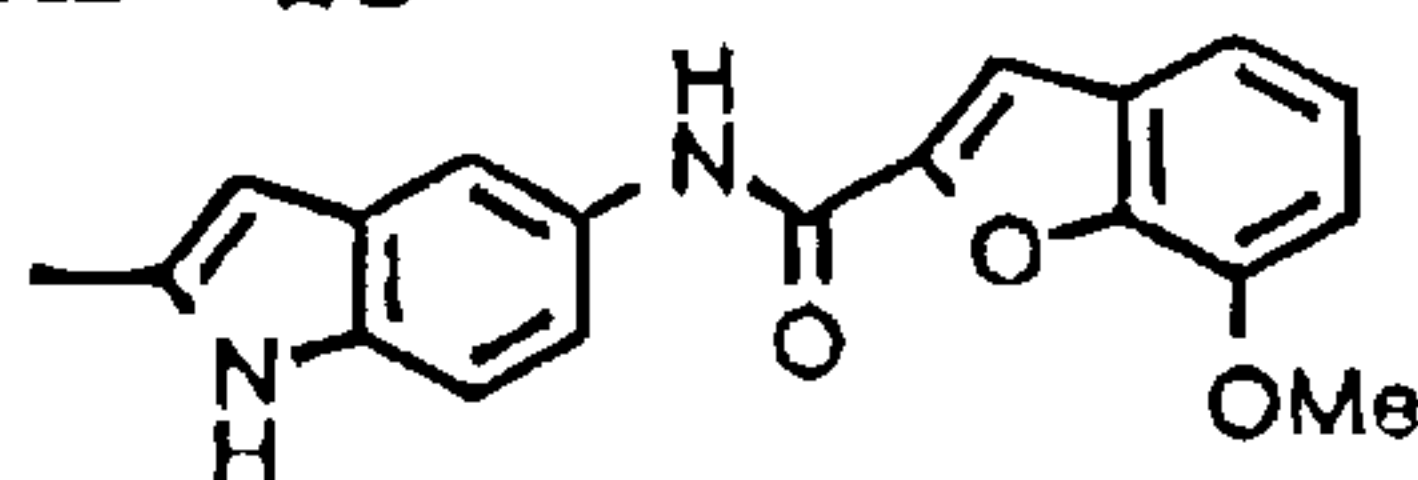


4. The pyrroloindole derivative having a carbamoyloxy group according to claim 1 represented by the following

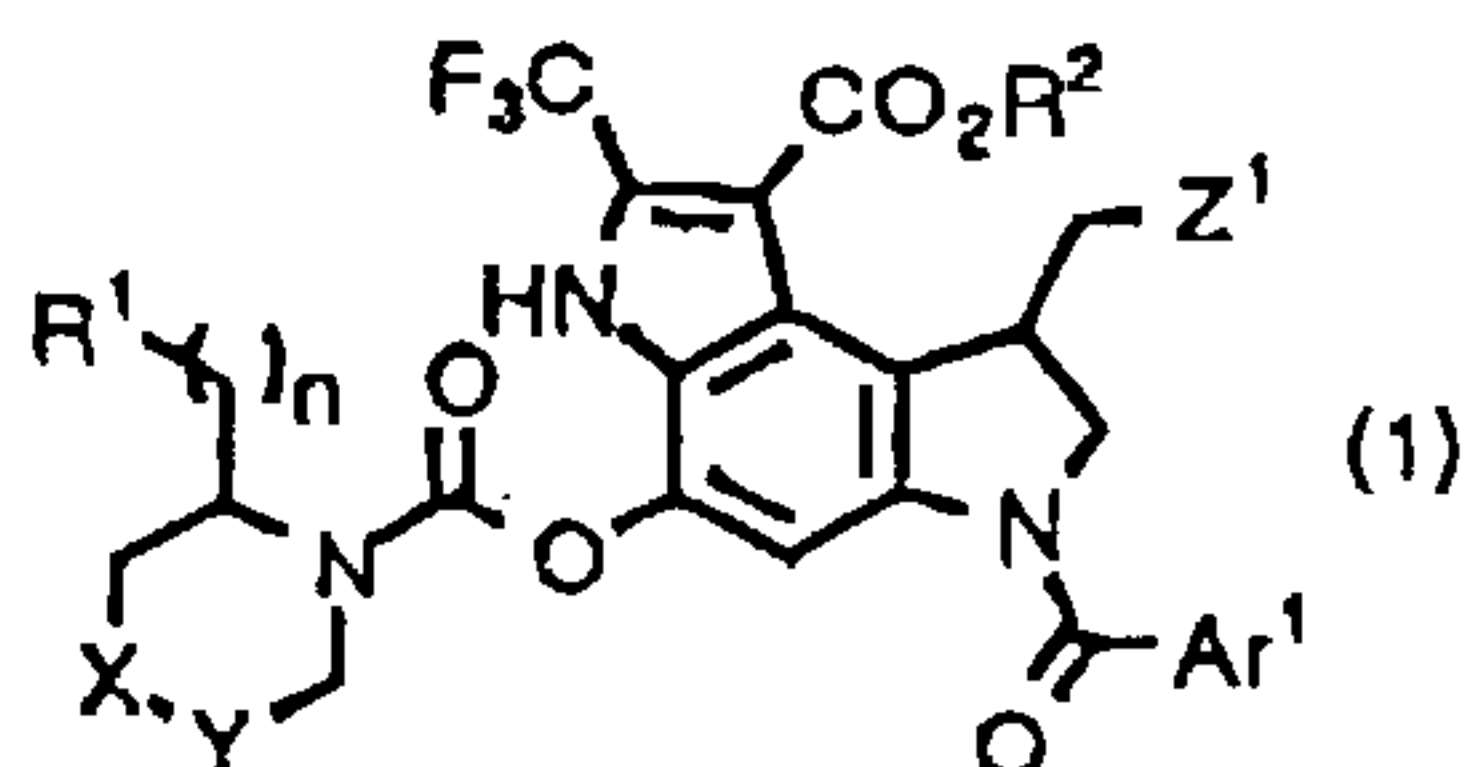
general formula (1) below and the optically active isomer thereof:



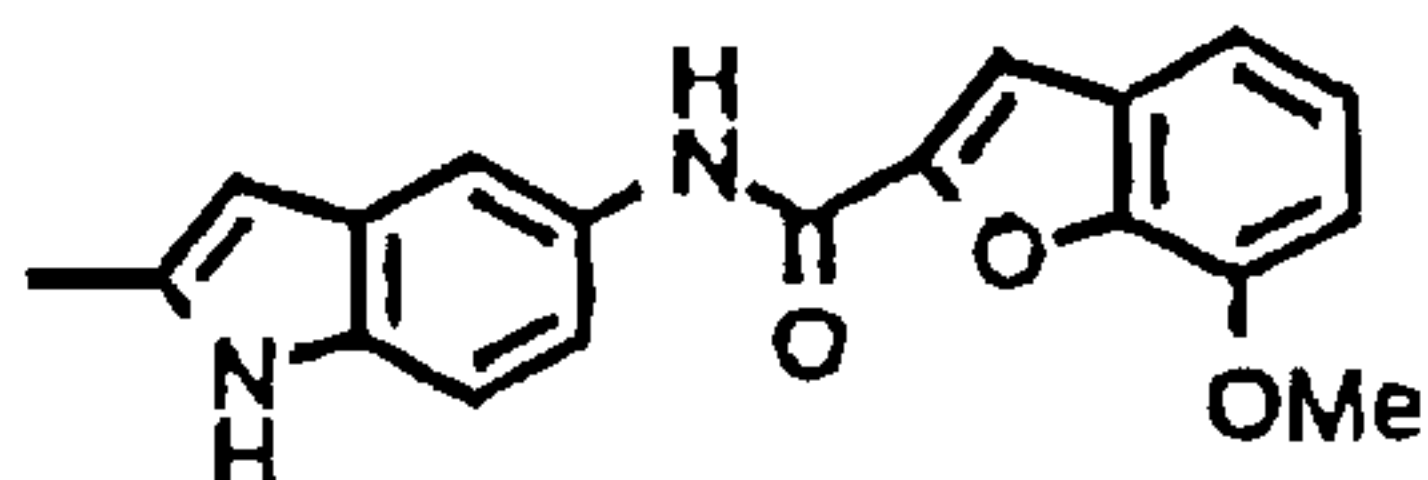
where R^1 is OH, n is 1, R^2 is methyl, X-Y or Y-X is O-CH₂, Z^1 is Cl, and Ar^1 is



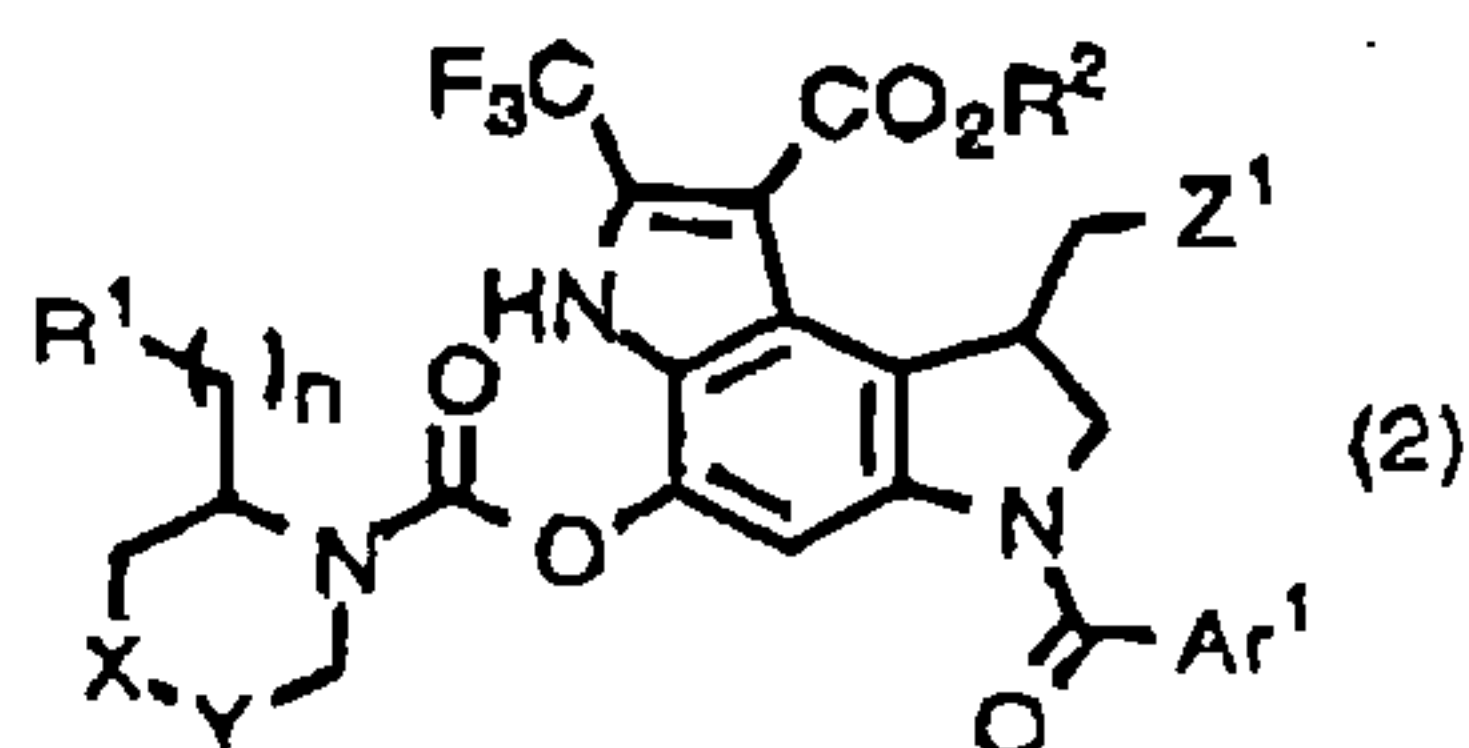
5. The pyrroloindole derivative having a carbamoyloxy group according to claim 1 represented by the following general formula (1) below, the optically active isomer thereof, and the pharmacologically acceptable salt thereof:



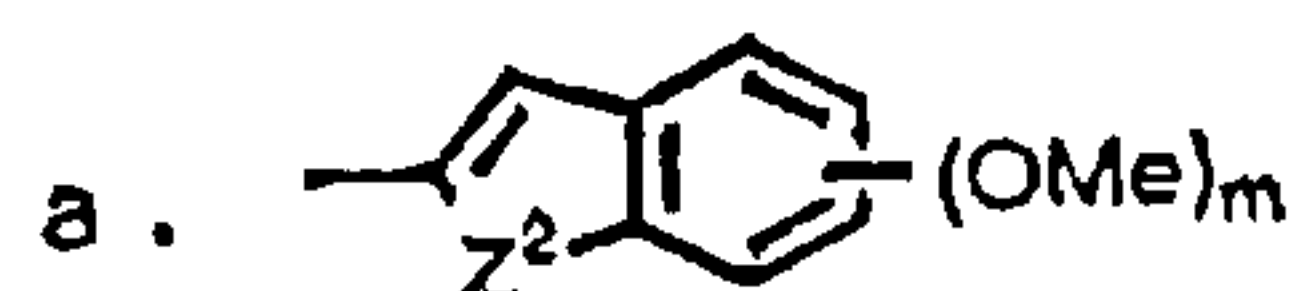
where R^1 is OH, n is 1, R^2 is methyl, X-Y or Y-X is NMe-CH₂, Z^1 is Cl, and Ar^1 is



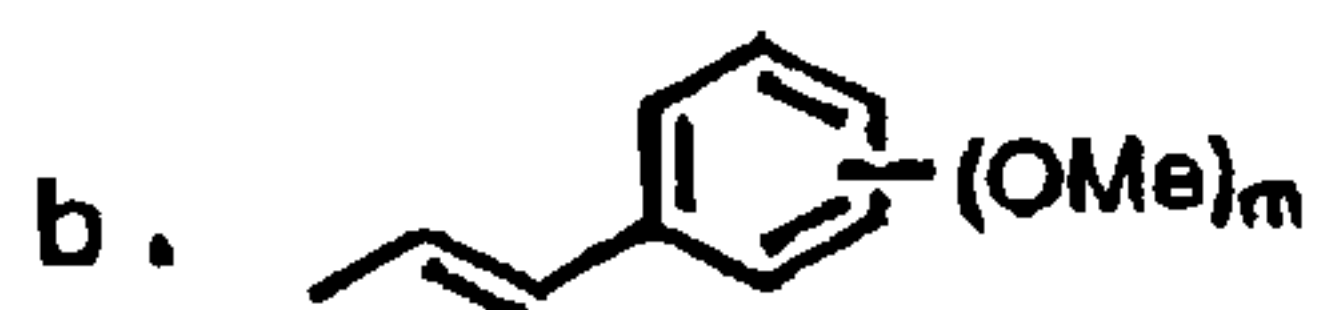
6. A protected pyrroloindole derivative represented by the following general formula (2):



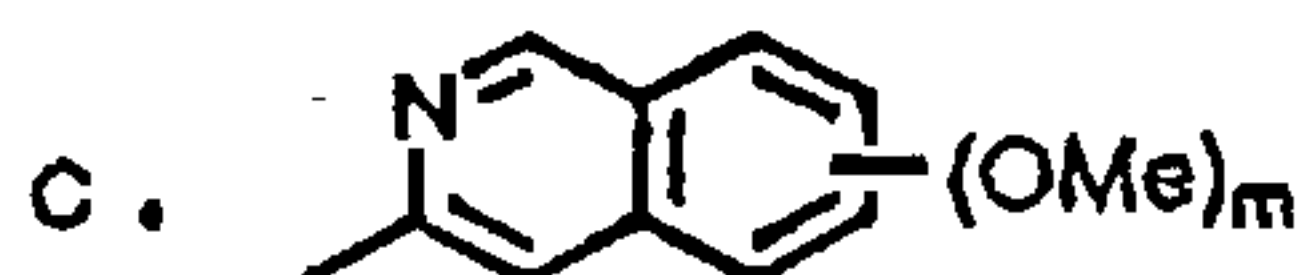
where R^1 is OR^3 wherein R^3 is a protecting group for the hydroxyl group; n is 1 or 2; R^2 is a lower alkyl of C_1-C_4 ; $X-Y$ is CH_2 , $CHOH$, CH_2-CH_2 , $O-CH_2$, or $NMe-CH_2$; Z^1 is Cl or Br; and Ar^1 is



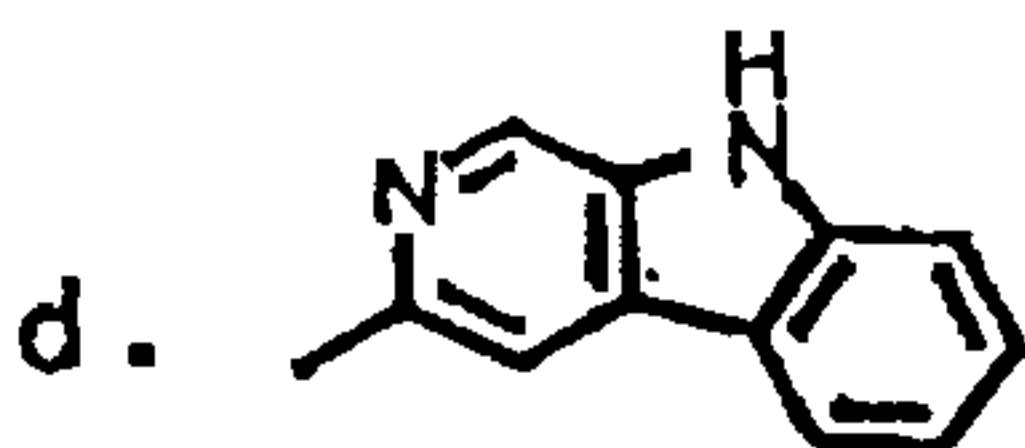
wherein Z^2 is O or NH, m is 0 or an integer of 1 to 4,



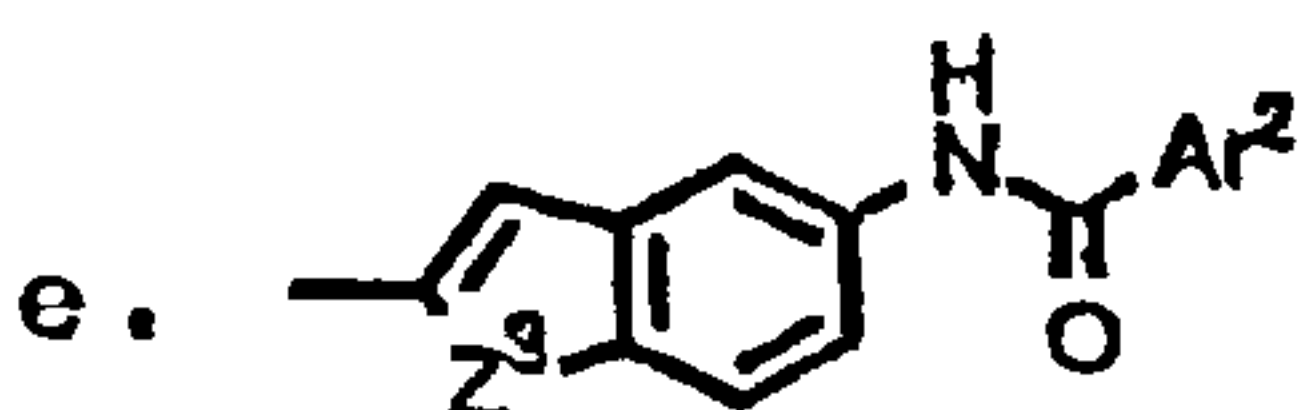
wherein m is 0 or an integer of 1 to 4,



wherein m is 0 or an integer of 1 to 4,



or



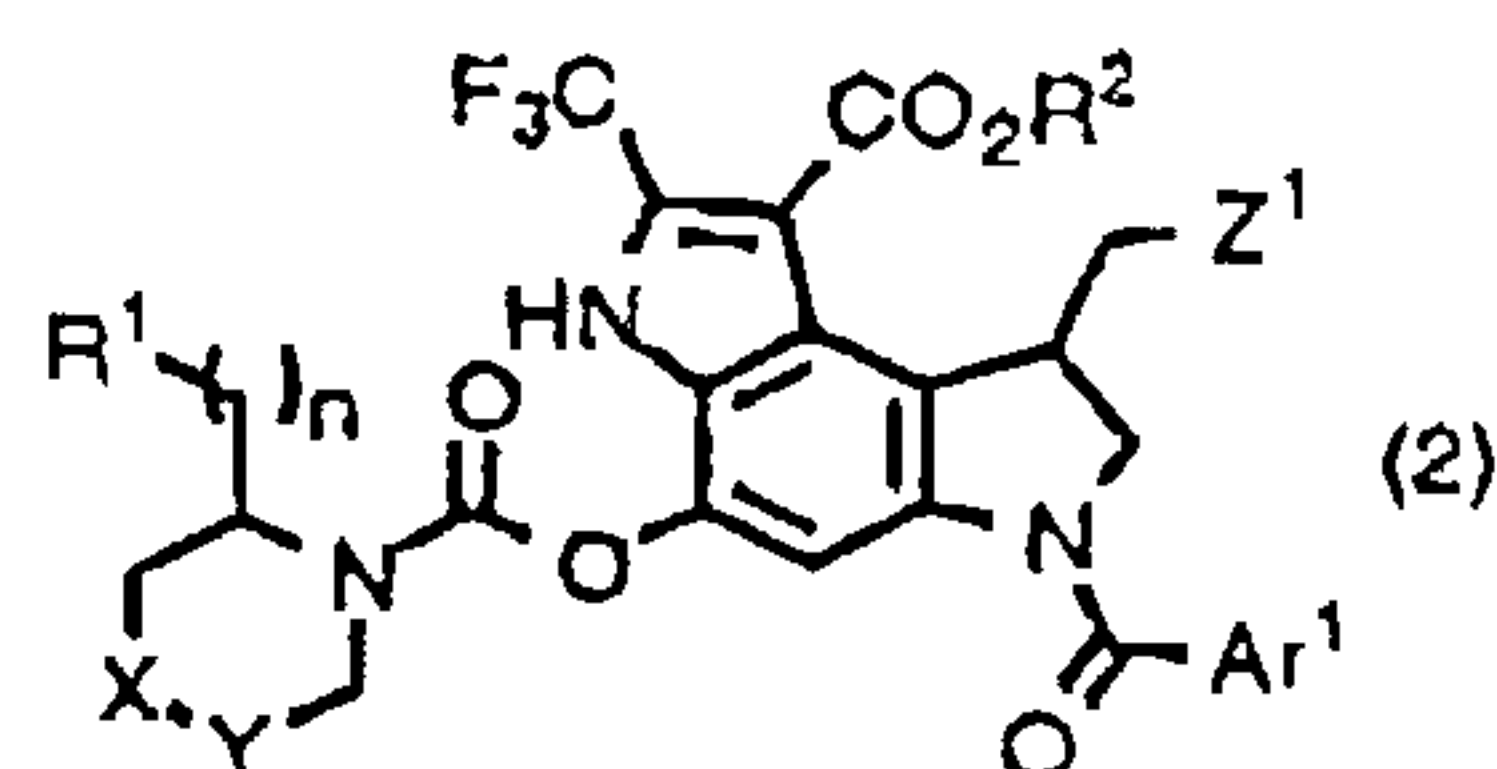
wherein Z^3 is O or NH; Ar^2 is any of the above groups of a, b, c, and d).

English translation of the annex to the IPER

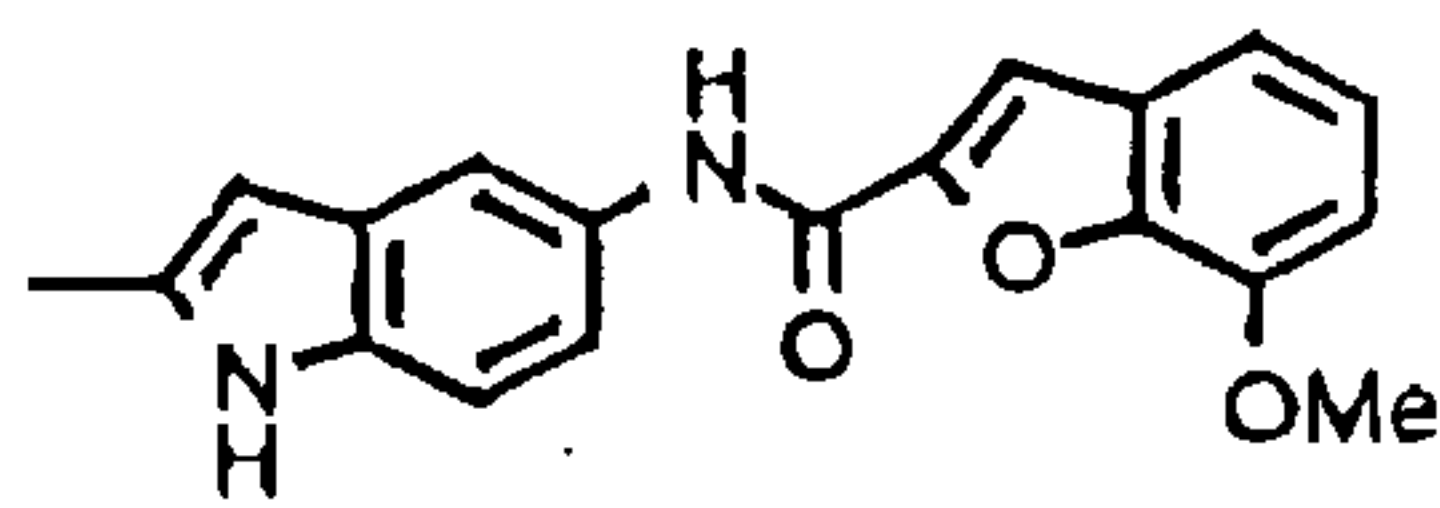
CLAIMS IN THE AMENDMENT

[Filed on October 29, 1998 under PCT Article 34:
Claim 8 has been amended; the other claims are not changed
(one page)]

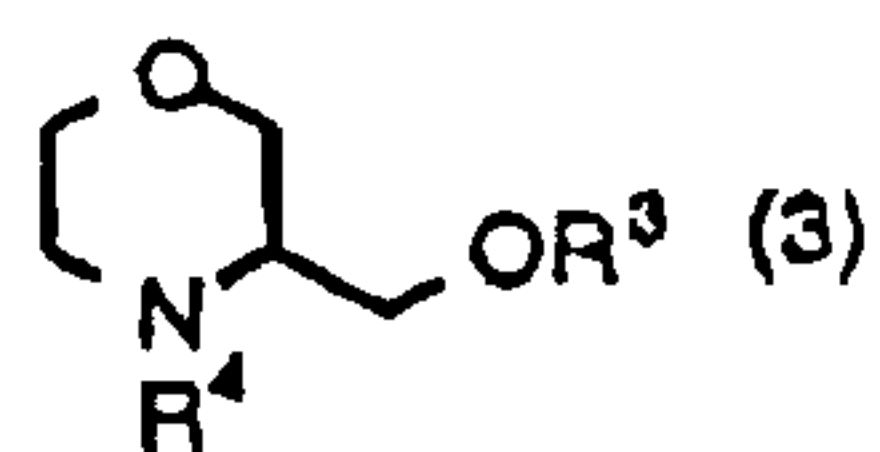
7. The protected pyrroloindole derivative according to claim 6 represented by the following general formula (2):



where R^1 is OR^3 wherein R^3 is a protecting group for the hydroxyl group, n is 1, R^2 is methyl, $X-Y$ is $O-CH_2$, Z^1 is Cl, and Ar^1 is



8. (Amended) A morpholine derivative represented by the following general formula (3), an optical isomer thereof, and a salt thereof:



wherein R^3 is a *t*-butyldimethylsilyl group and R^4 is a hydrogen atom or a benzyl group.

