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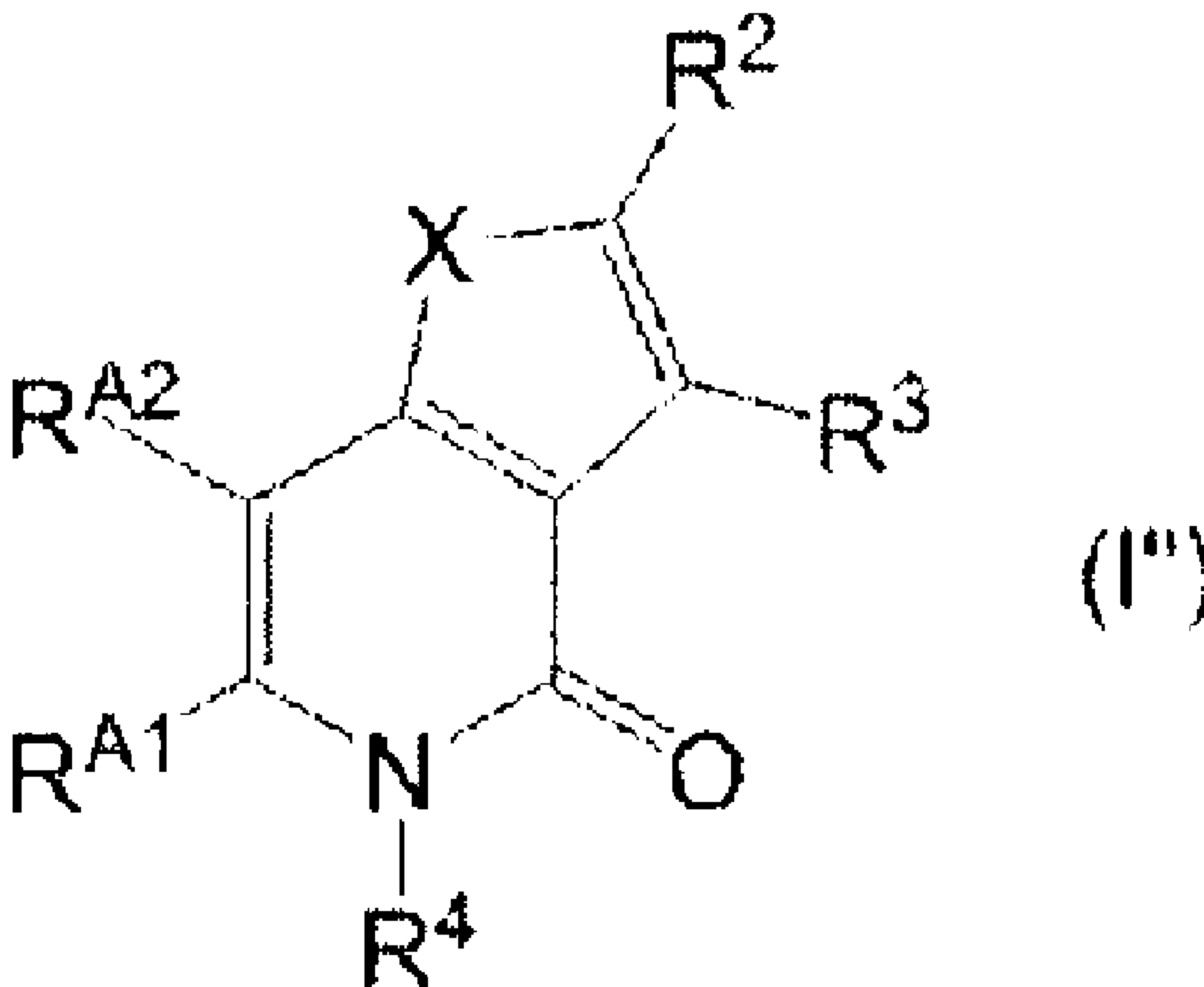
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(54) Titre : DERIVE HETEROCYCLIQUE FUSIONNE ET SON UTILISATION

(54) Title: FUSED HETEROCYCLIC DERIVATIVE AND USE THEREOF



(57) Abrégé/Abstract:

The present invention provides a compound having a superior Smo inhibitory activity and lower toxicity, which is sufficiently satisfactory as a pharmaceutical product. The present invention provides a compound represented by the formula (I) wherein ring A is 5- to 7-membered ring optionally having substituent(s), where substituents are optionally bonded to each other to form a ring; X is O, S or NR¹ (R¹ is a hydrogen atom or a hydrocarbon group optionally having substituent(s)); R² is carbamoyl optionally having substituent(s); and R³ is hydroxy optionally having substituent(s), or a salt thereof.

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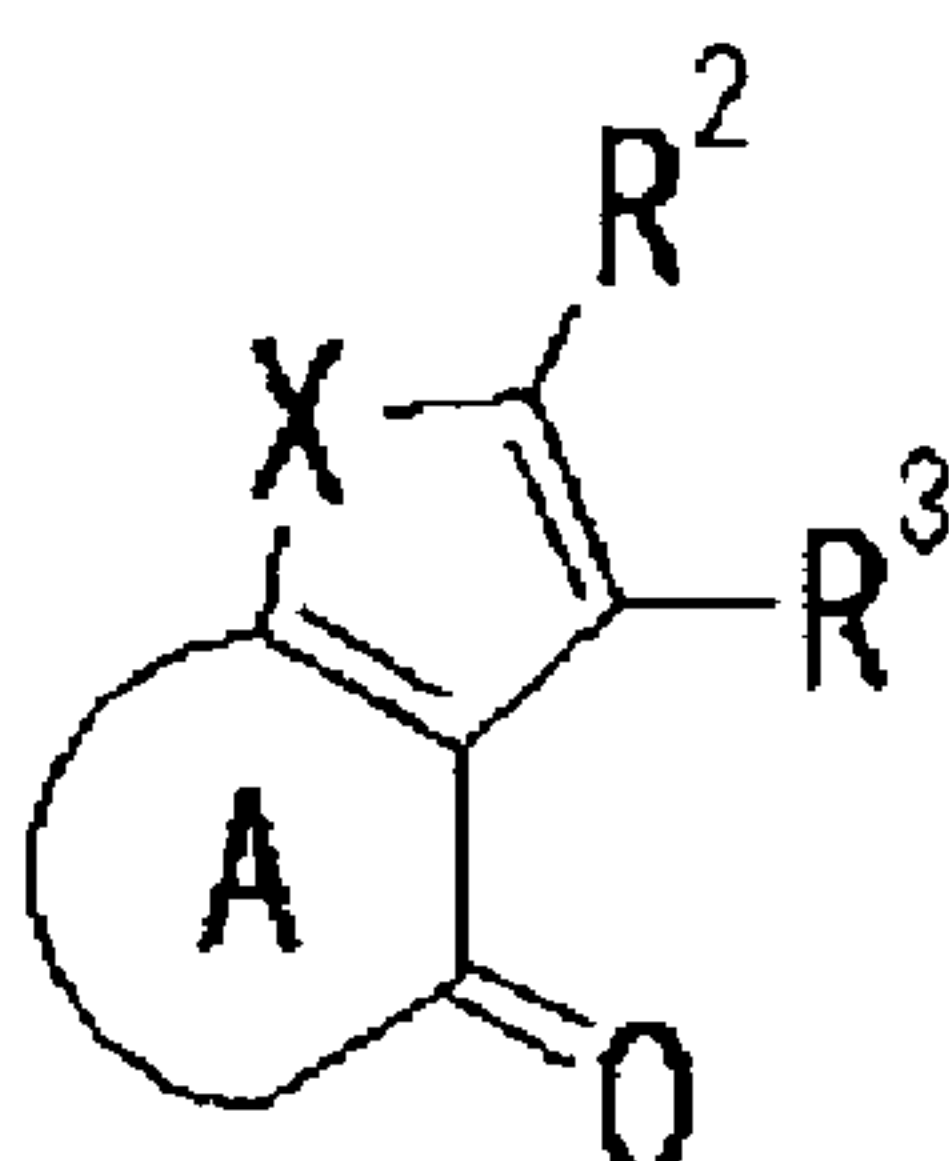
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[Continued on next page]

(54) Title: FUSED HETEROCYCLIC DERIVATIVE AND USE THEREOF



(I)

(57) **Abstract:** The present invention provides a compound having a superior Smo inhibitory activity and lower toxicity, which is sufficiently satisfactory as a pharmaceutical product. The present invention provides a compound represented by the formula (I) wherein ring A is 5- to 7-membered ring optionally having substituent(s), where substituents are optionally bonded to each other to form a ring; X is O, S or NR¹ (R¹ is a hydrogen atom or a hydrocarbon group optionally having substituent(s)); R² is carbamoyl optionally having substituent(s); and R³ is hydroxy optionally having substituent(s), or a salt thereof.

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CECI EST LE TOME __1__ DE __3__

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JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __3__

NOTE: For additional volumes please contact the Canadian Patent Office.

DESCRIPTION**FUSED HETEROCYCLIC DERIVATIVE AND USE THEREOF**

Technical Field

[0001]

5 The present invention relates to a fused heterocyclic derivative and use thereof. More particularly, the present invention relates to a compound having a strong Smo inhibitory activity and useful for the prophylaxis or treatment of cancer and the like, and use thereof.

10 [0002]

(Background of the Invention)

 The study of morphogenesis during the developmental stage has been conducted based on the screening of variant using Drosophila. Hedgehog gene (hh) was found as one of the genes
15 that cause morphological abnormality of Drosophila embryo due to mutation thereof. Hedgehog gene product (Hh) is a secretory protein, which is produced as an about 45 kDa precursor and then divided, due to autolysis, into a 20 kDa N-terminal side domain, which is a main active principle, and a 25 kDa C-
20 terminal side domain. The 20 kDa N-terminal side domain, which is a main active principle, is modified by fatty acid on the N-terminal and cholesterol on the C-terminal thereof. The Hedgehog signal transduction system is formed by the protein group described below. Hh receptor is Patched (Ptch), which is
25 a twelve-transmembrane-type protein. Ptch acts on Smoothed (Smo), which is a seven-transmembrane-type protein, and suppresses the function of Smo in the absence of Hh. When Hh is bound to the receptor Ptch, suppression of Smo is released and Smo is activated. The signal produced by the activation of
30 Smo activates transcription factor Ci, which regulates the expression of the gene group involved in the morphogenesis (non-patent document 1).

 A pathway corresponding to the Drosophila Hedgehog signal transduction system has been confirmed also in mammals. In
35 human, for example, three types of gene products, sonic

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hedgehog (Shh), indian hedgehog (Ihh) and desert hedgehog (Dhh), are known to correspond to *Drosophila* Hh, and undergo post-translational modification as in *Drosophila* Hh (non-patent document 2). In human Shh, a 19 kDa active principle is
5 cleaved out from a 45 kDa precursor protein by autolysis, and fatty acid and cholesterol are added to the N-terminal and C-terminal thereof, respectively (non-patent document 3). Such modification is considered to be essential for the maintenance of Shh activity and, for example, 40 times enhanced activity
10 was achieved by the addition of palmitic acid to *Escherichia coli* recombinant human Shh free of N-terminal modification with fatty acid, and 160 times enhanced activity was achieved by the addition of myristic acid thereto (non-patent document 4). On the other hand, as a human gene corresponding to
15 *Drosophila* Smo, human Smo is known, and as a human gene corresponding to *Drosophila* Ptch, 2 types of Ptch1 and Ptch2 are known. In addition, a transcription factor corresponding to *Drosophila* Ci is considered to be Gli in human, and 3 types of Gli1, Gli2 and Gli3 are known (non-patent document 5).
20 Shh/Ihh/Dhh are each bound to Ptch1 and activate Smo by inhibiting the bond between Ptch1 and Smo. Shh/Ihh/Dhh are also bound to Ptch2, Hipl, Gas1 and Cdo/Boc, besides Ptch1, and regulate the activation of Smo. A signal transduction from Smo induces nuclear localization of Gli1 and Gli2, and
25 activate transcription of Gli1 (non-patent document 6).

The Hedgehog signal is involved in the morphogenesis in the developmental stages also in mammals. In human, for example, patients with Holoprosencephaly, which is a congenital developmental abnormality, showed mutation in Shh
30 (non-patent document 7). Moreover, a natural compound Cyclopamine derived from white hellebore known as a compound inducing Cyclopia in sheep (non-patent document 8) was confirmed to inhibit Smo as action mechanism thereof (non-patent document 9). Furthermore, an Shh knockout mouse was
35 prepared, and its phenotype was found to include Cyclopia,

malformation of extremities (non-patent document 10), and neural plate malformation (non-patent document 11).

Hedgehog signal is inherently a developmental signal, which is promoted in tumor tissues and functions as a cancer cell growth and survival signal. Hedgehog signal is considered to function for the growth and survival of cancer cells in an autocrine mode, or function between cancer cells and cancer interstitial cells in a paracrine mode, in tumor tissues (non-patent document 12). In an autocrine mode, it works for the growth and maintenance of cancer cells, via transcription activation by Gli-1, by abnormal cell cycle control due to increased expression of Cyclin D and decreased expression of p21, promotion of proliferation signal by activation of EGFR pathway and the like. On the other hand, in a paracrine mode, since Shh expressed in cancer cells acts on Smo in cancer interstitial cells, growth factors such as insulin-like growth factor-1, fibroblast growth factor, platelet-derived growth factor and the like are transmitted from cancer interstitial cells to cancer cells, and function for the growth and survival of cancer cells. It is also considered that promotion of VEGF, PDGF pathway and the like by Gli-1 promotes tumor angiogenesis (non-patent document 13). As to the mechanism of promotion of Hedgehog signal, a cancer in which Hedgehog signal is promoted due to mutation of Ptch1 and a cancer which is promoted by overexpression of Shh, which is one of the ligands, have been reported (non-patent document 14). As a cancer in which Hedgehog signal is promoted due to mutation, basal cell cancer and medulloblastoma are known, and mutation of Ptch1 observed in these cancers activates Hedgehog signal in a ligand independent manner (non-patent document 15). As a cancer in which Hedgehog signal is promoted by overexpression of Shh, pancreatic cancer (non-patent document 16) and the like have been reported. In a transgenic mouse in which Shh is forcedly expressed in the pancreas, Hedgehog signal is suggested to be involved not only in the growth and

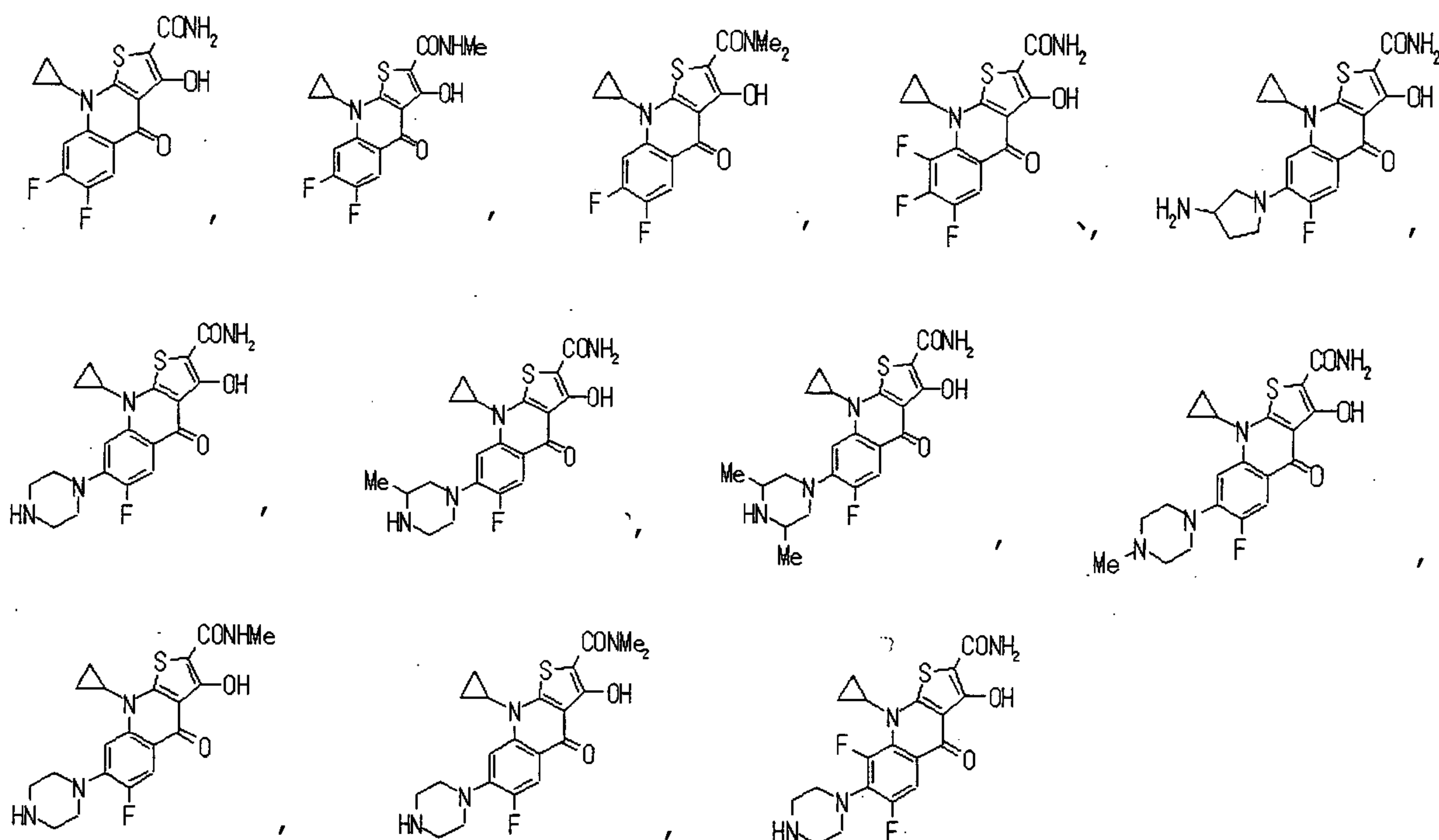
maintenance of cancer, but also carcinogenic process, since a PanIN-like lesion in the initial stages of cancer progress was found in the pancreas (non-patent document 17). Furthermore, Hedgehog signal is considered to function for the growth and survival of cancer stem cells, and play a key role in the metastasis or postoperative recurrence of tumor and the like (non-patent document 18).

As the Hedgehog signal inhibitor, the following are known. Cyclopamine, which is a naturally occurring Smo inhibitory compound, has been reported to show a tumor growth suppressive effect on glioma (non-patent document 19) and the like. As a synthetic low-molecular-weight compound inhibiting Smo, CUR-61414 (non-patent document 20) and SANT-1, 2, 3, 4 (non-patent document 21) have been reported. It has been reported with regard to the Hedgehog signal inhibitory antibody that administration of an anti-Shh antibody to a cancer-bearing nude mouse transplanted with colorectal cancer cell line HT-29 resulted in cancer regression (patent document 1).

[0003]

As a compound similar to the compound described in the present specification, patent document 2 discloses the following compounds having an antibacterial activity.

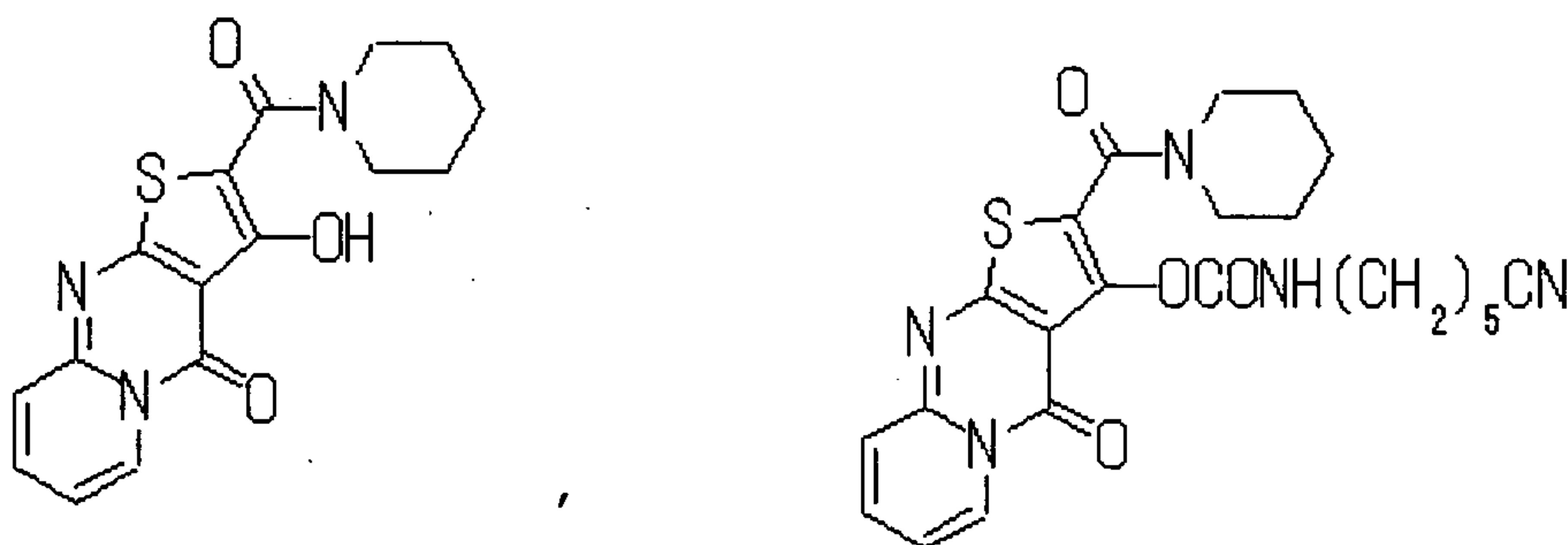
[0004]



[0005]

As a compound having an antibacterial activity, patent document 3 discloses the following compounds.

5 [0006]



[0007]

patent document 1: WO2004/020599

10 patent document 2: JP-A-3-223289

patent document 3: WO93/13664

non-patent document 1: Curr. Opin. Genet. Dev., vol. 12, pages 503-511 (2002)

non-patent document 2: Cell, vol. 103, pages 371-374 (2000)

15 non-patent document 3: J. Biol. Chem., vol. 273, pages 14037-14045 (1998)

non-patent document 4: Biochemistry, vol. 40, pages 4359-4371 (2001)

- non-patent document 5: Nature Rev. Cancer, vol. 2, pages 361-372 (2002)
- non-patent document 6: Curr. Opin. Cell Biol., vol. 19, pages 159-165 (2007)
- 5 non-patent document 7: Nat. Genet., vol. 14, pages 357-360 (1996)
- non-patent document 8: Am. J. Vet. Res., vol. 24, pages 1164-1175 (1963)
- non-patent document 9: Development, vol. 125, pages 3553-3562
10 (1998)
- non-patent document 10: Nature, vol. 383, pages 407-413 (1996)
- non-patent document 11: Cell, vol. 111, pages 63-75 (2002)
- non-patent document 12: Nat. Rev. Drug Discov., vol. 5, pages 1026-1033 (2006)
- 15 non-patent document 13: Clin Cancer Res., vol. 12, pages 5924-5928 (2006)
- non-patent document 14: Nature Rev. Cancer, vol. 3, pages 903-911 (2003)
- non-patent document 15: Am. J. Med. Gen., vol. 123A, pages 5-
20 28 (2003)
- non-patent document 16: Nature, vol. 425, pages 846-851 (2003)
- non-patent document 17: Nature, vol. 425, pages 851-856 (2003)
- non-patent document 18: Trends Cell Biol., vol. 17, pages 438-227 (2007)
- 25 non-patent document 19: Development, vol. 128, pages 5201-5212 (2001)
- non-patent document 20: Proc. Natl. Acad. Sci. U.S.A., vol. 100, pages 4616-4621 (2003)
- non-patent document 21: Proc. Natl. Acad. Sci. U.S.A., vol. 99,
30 pages 14071-14076 (2002)

Disclosure of the Invention

Problems to be Solved by the Invention

[0008]

An object of the present invention is to provide a
35 compound having a superior Smo inhibitory activity, low toxicity

and sufficiently satisfactory as a pharmaceutical product.

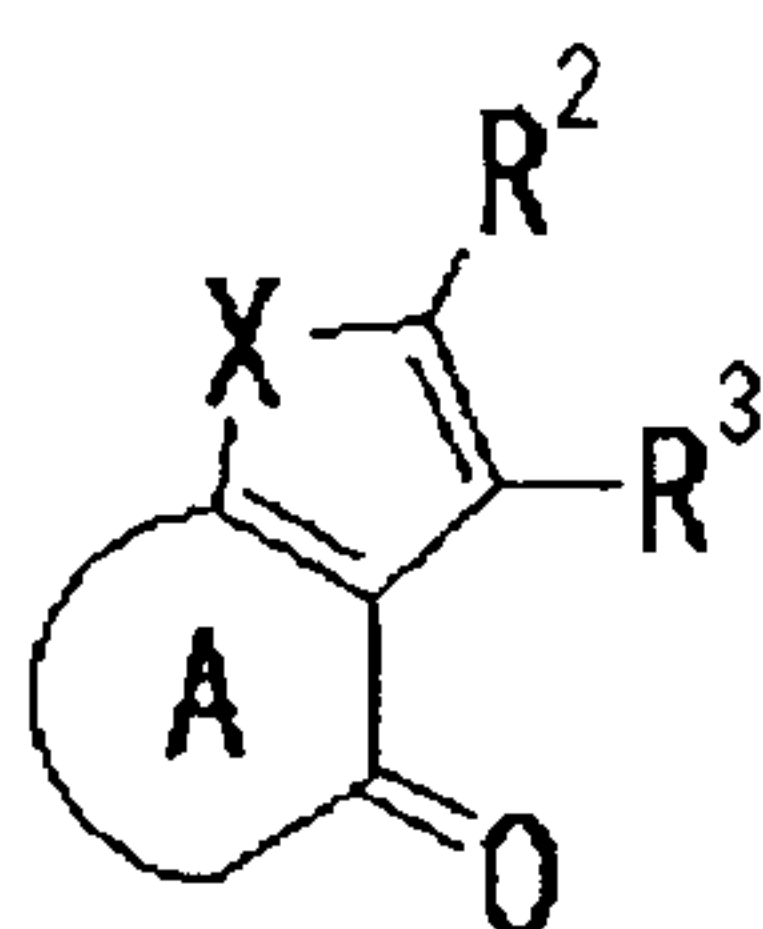
[0009]

The present inventors have conducted intensive studies in an attempt to solve the above-mentioned problems and found that
 5 a compound represented by the following formula and a salt thereof have a superior Smo inhibitory activity, which resulted in the completion of the present invention.

Accordingly, the present invention provides the following.

[1] A compound represented by the formula

10 [0010]



(I)

[0011]

wherein

ring A is a 5- to 7-membered ring optionally having
 15 substituent(s), where substituents are optionally bonded to each other to form a ring;

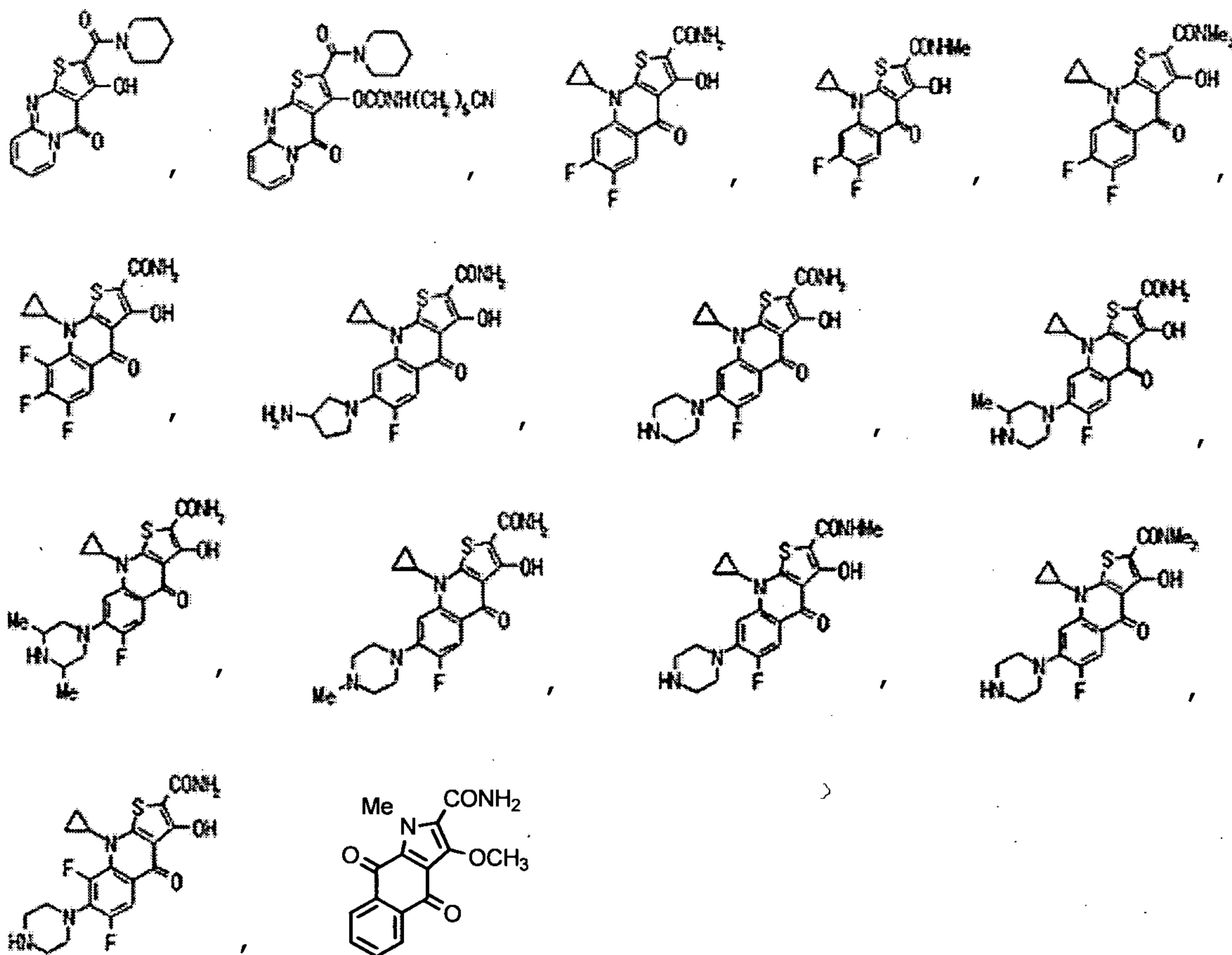
X is O, S or NR¹ (R¹ is a hydrogen atom or a hydrocarbon group optionally having substituent(s));

R² is carbamoyl optionally having substituent(s); and

20 R³ is hydroxy optionally having substituent(s),

except the following compounds;

[0012]

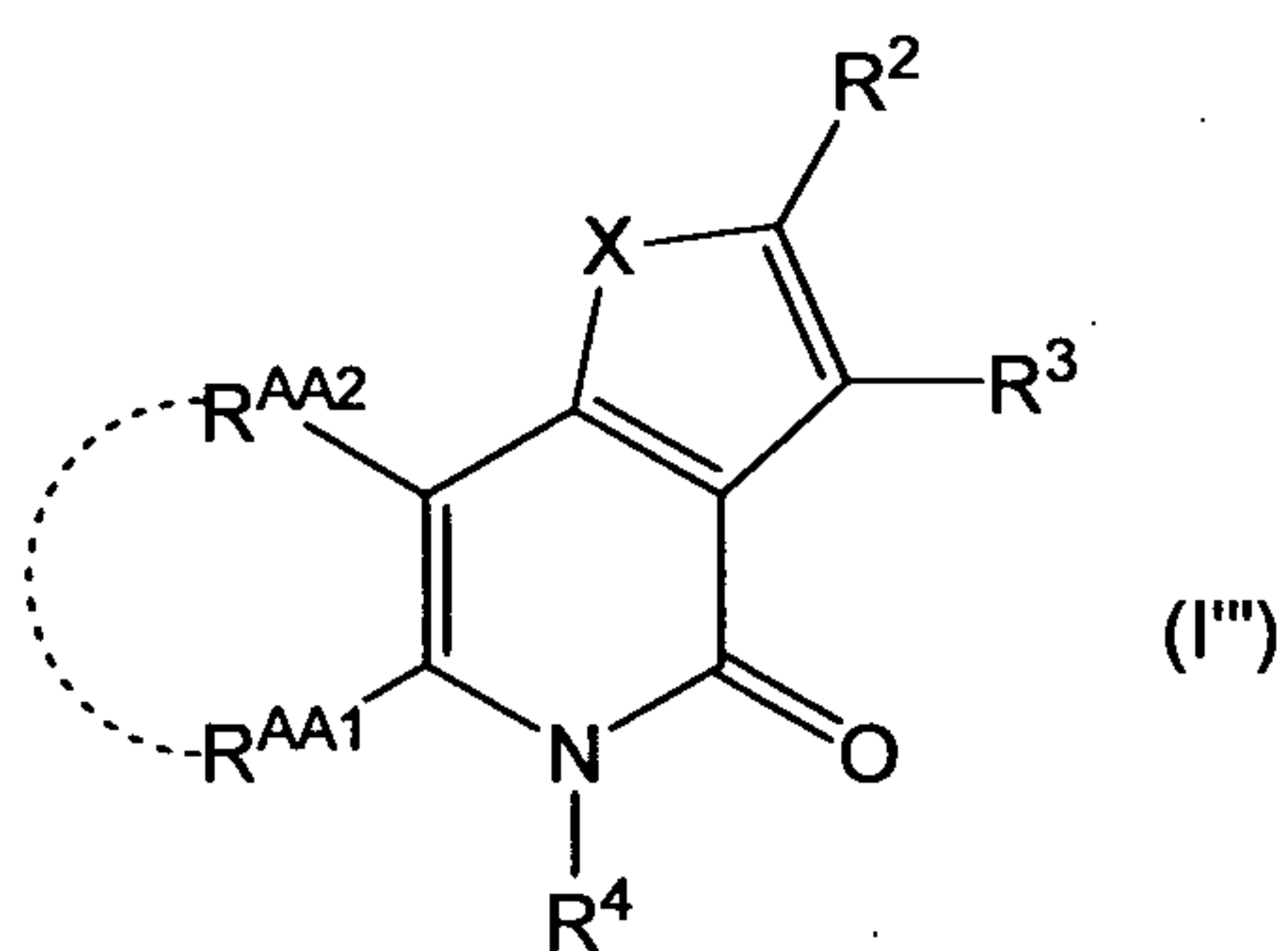


[0013]

(hereinafter sometimes to be abbreviated as compound (I)) or a salt thereof.

5. [2] The compound of the above-mentioned [1], which is represented by the formula

[0014]



[0015]

10 wherein

X, R² and R³ are as defined in the above-mentioned [1],
 R^{AA1} and R^{AA2} are the same or different and each is a hydrogen atom or a substituent, or R^{AA1} and R^{AA2} are optionally bonded to each other to form a 5- to 7-membered ring optionally having

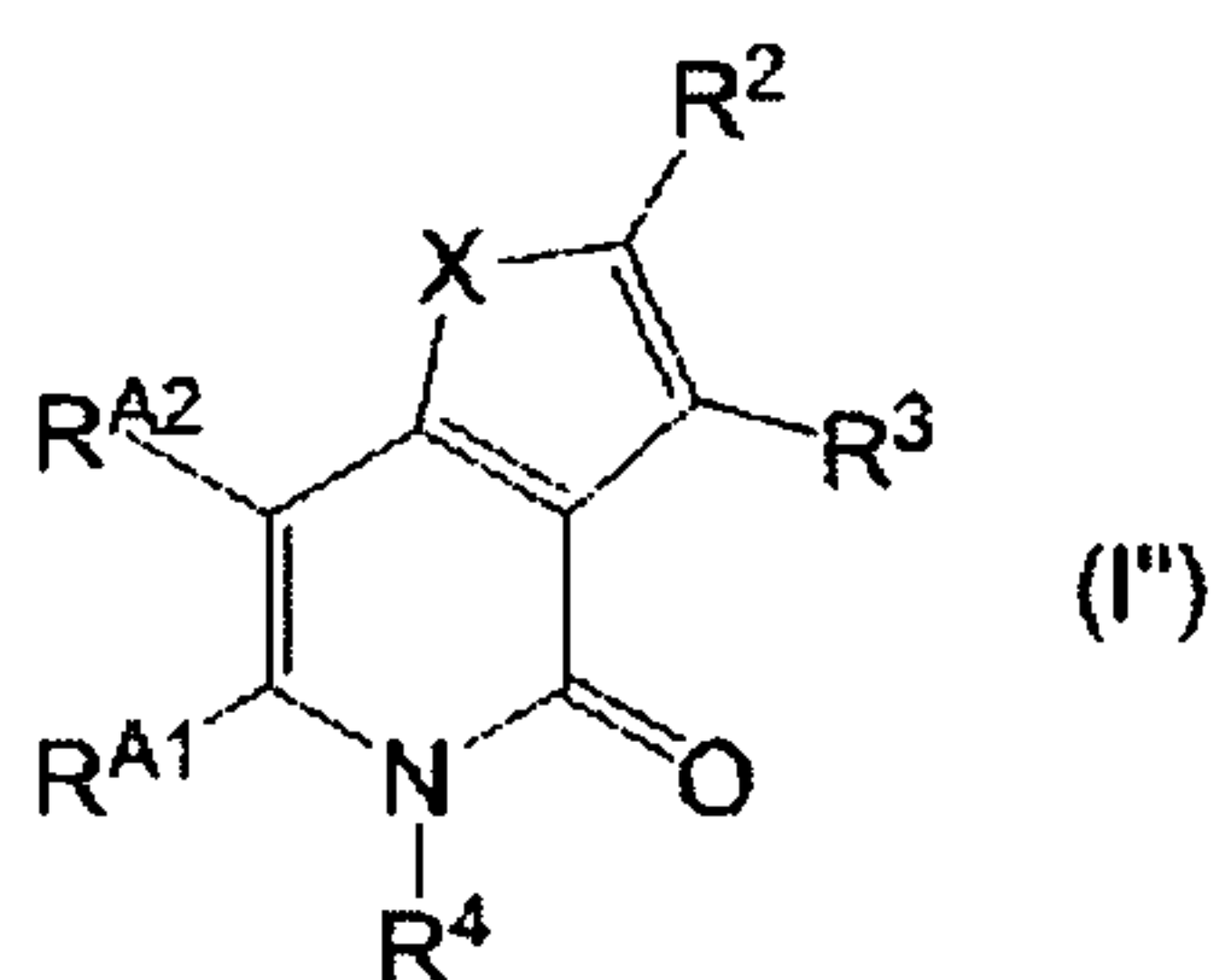
substituent(s), and

R^4 is a hydrogen atom or a hydrocarbon group optionally having substituent(s)

(hereinafter sometimes to be abbreviated as compound (I''').

- 5 [3] The compound of the above-mentioned [2], which is represented by the formula

[0016]



[0017]

10 wherein

X , R^2 and R^3 are as defined in the above-mentioned [1],
 R^{A1} and R^{A2} are the same or different and each is a hydrogen atom or a substituent, and

R^4 is a hydrogen atom or a hydrocarbon group optionally having
 15 substituent(s)

(hereinafter sometimes to be abbreviated as compound (I'')).

[4] The compound of the above-mentioned [3], wherein X is O, S or N(C₁₋₆ alkyl),

R^2 is carbamoyl optionally having substituent(s),

20 R^3 is hydroxy optionally having C₁₋₆ alkyl optionally having substituent(s),

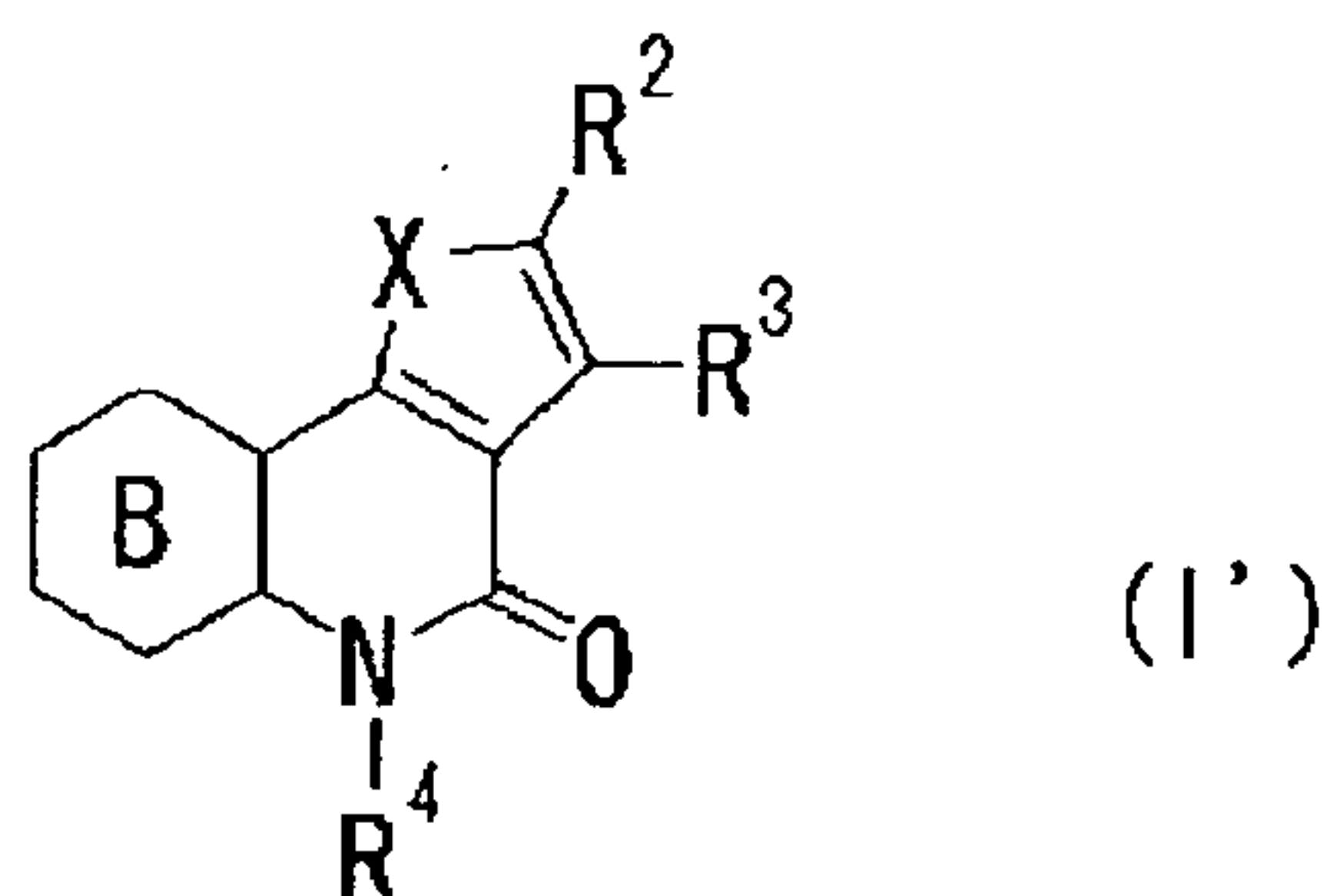
R^{A1} is a hydrogen atom or a C₁₋₆ alkyl group,

R^{A2} is a hydrogen atom or a C₁₋₆ alkyl group, and

R^4 is a hydrogen atom or C₁₋₆ alkyl optionally having
 25 substituent(s).

[5] The compound of the above-mentioned [1], which is represented by the formula

[0018]



[0019]

wherein

X, R² and R³ are as defined in the above-mentioned [1],

5 ring B is a 6-membered ring optionally having substituent(s);
and

R⁴ is a hydrogen atom or a hydrocarbon group optionally having substituent(s)

(hereinafter sometimes to be abbreviated as compound (I')).

10 [6] The compound of the above-mentioned [5], wherein ring B is
a 6-membered ring optionally having substituent(s),

X is O, S or N(C₁₋₆ alkyl),

R² is carbamoyl optionally having substituent(s),

R³ is hydroxy optionally having C₁₋₆ alkyl optionally having
15 substituent(s), and

R⁴ is a hydrogen atom or C₁₋₆ alkyl optionally having
substituent(s).

[7] N-[1-(2-Hydroxyethyl)piperidin-4-yl]-3-methoxy-1-methyl-4-
oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-
20 c]quinoline-2-carboxamide or a salt thereof.

[8] N-[1-(Hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-
oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-
c]quinoline-2-carboxamide or a salt thereof.

[9] 3-Ethoxy-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-
25 methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-
pyrrolo[3,2-c]pyridine-2-carboxamide or a salt thereof.

[10] N-[1-(Hydroxyacetyl)piperidin-4-yl]-1,6-dimethyl-4-oxo-5-
(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-
1H-pyrrolo[3,2-c]pyridine-2-carboxamide or a salt thereof.

30 [11] 6-Ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-

oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide or a salt thereof.

[12] A prodrug of the compound of the above-mentioned [1].

5 [13] A pharmaceutical agent comprising the compound of the above-mentioned [1] or a prodrug thereof.

[14] The pharmaceutical agent of the above-mentioned [13], which is an Smo inhibitor.

[15] The pharmaceutical agent of the above-mentioned [13],
10 which is an agent for the prophylaxis or treatment of cancer.

[16] A method of inhibiting Smo in a mammal, which comprises administering an effective amount of the compound of the above-mentioned [1] or a prodrug thereof to the mammal.

[17] A method for the prophylaxis or treatment of cancer in a
15 mammal, which comprises administering an effective amount of the compound of the above-mentioned [1] or a prodrug thereof to the mammal.

[18] Use of the compound of the above-mentioned [1] or a prodrug thereof for the production of an Smo inhibitor.

20 [19] Use of the compound of the above-mentioned [1] or a prodrug thereof for the production of an agent for the prophylaxis or treatment of cancer.

In the present specification, compound (I) encompasses compound (I'), compound (I'') and compound (I''').

25 [0020]

(Effect of the Invention)

Since the compound of the present invention has a strong Smo inhibitory action, it can provide a clinically useful agent for the prophylaxis or treatment of cancer, a cancer
30 growth inhibitor and a cancer metastasis suppressive agent.

[0021]

(Detailed Description of the Invention)

The present invention is explained in detail in the following.

35 In compound (I), X is O, S or NR¹ (R¹ is a hydrogen atom

or a hydrocarbon group optionally having substituent(s)).

Examples of the "hydrocarbon group optionally having substituent(s)" for R¹ include alkyl optionally having substituent(s), alkenyl optionally having substituent(s),
5 alkynyl optionally having substituent(s), cycloalkyl optionally having substituent(s), aryl optionally having substituent(s) and the like.

[0022]

Examples of the "alkyl" of the above-mentioned "alkyl
10 optionally having substituent(s)" include C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl) and the like.

Examples of the substituent that the above-mentioned "alkyl optionally having substituent(s)" may have include the
15 following "substituent group A" and the like, and 1 to 5 (preferably 1 to 3) substituents may be present at substitutable position(s):

(substituent group A)

(1) halogen atom (e.g., fluorine atom, chlorine atom, bromine
20 atom, iodine atom),

(2) cyano,

(3) C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl) optionally having 1 to 3 substituents selected from

25 (1') C₆₋₁₀ aryl (e.g., phenyl, naphthyl),

(2') amino,

(3') C₁₋₆ alkoxy-carbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino),

(4') hydroxy,

30 (5') C₁₋₆ alkoxy (e.g., methoxy, ethoxy, propoxy), and

(6') heterocyclic group (e.g., pyrrolidinyl, benzodioxolyl),

(4) C₂₋₆ alkenyl (e.g., vinyl, allyl),

(5) C₂₋₆ alkynyl (e.g., ethynyl, propargyl),

(6) C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl,
35 cyclohexyl) optionally having one hydroxy,

- (7) C₆₋₁₀ aryl (e.g., phenyl, naphthyl) optionally having 1 to 3 substituents selected from
- (a) halogen atom (e.g., fluorine atom, chlorine atom),
 - (b) hydroxy,
 - 5 (c) cyano,
 - (d) C₁₋₆ alkyl-sulfonyl (e.g., methylsulfonyl), and
 - (e) C₁₋₆ alkoxy (e.g., methoxy, ethoxy, propoxy) optionally having 1 to 3 halogen atoms (e.g., fluorine atom),
- (8) C₁₋₆ alkyl-carbonyl (e.g., acetyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl) optionally having 1 to 3 substituents selected from
- (1') hydroxy,
 - (2') C₁₋₆ alkoxy (e.g., methoxy, ethoxy),
 - (3') amino,
 - 15 (4') C₁₋₆ alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino),
 - (5') C₁₋₆ alkyl-sulfonyl (e.g., methylsulfonyl), and
 - (6') C₁₋₆ alkyl-carbonyloxy (e.g., methylcarbonyloxy),
- (9) C₆₋₁₀ aryl-carbonyl (e.g., benzoyl, naphthoyl) optionally having 1 to 3 substituents selected from
- (a) halogen atom (e.g., chlorine atom), and
 - (b) C₁₋₆ alkoxy (e.g., methoxy),
- (10) carbamoyl,
- (11) C₁₋₆ alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl) optionally having one hydroxy,
- 25 (12) di-C₁₋₆ alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl),
- (13) C₆₋₁₀ aryl-carbamoyl (e.g., phenylcarbamoyl, naphthylcarbamoyl),
- 30 (14) 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidylcarbonyl, 1-piperazinylcarbonyl, 4-morpholinylcarbonyl, 4-thiomorpholinylcarbonyl, 1-homopiperazinylcarbonyl),
- (15) carboxyl,
- 35 (16) C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl,

- butoxycarbonyl),
- (17) C₆₋₁₀ aryloxy-carbonyl (e.g., phenoxycarbonyl),
- (18) amino optionally having 1 or 2 substituents selected from
- (a) C₁₋₆ alkoxy-carbonyl (e.g., tert-butoxycarbonyl), and
- 5 (b) C₁₋₆ alkyl-carbonyl (e.g., methylcarbonyl) optionally having one hydroxy or C₁₋₆ alkyl-carbonyloxy (e.g., methylcarbonyloxy),
- (19) C₁₋₆ alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino),
- 10 (20) di-C₁₋₆ alkylamino (e.g., dimethylamino, diethylamino, dipropylamino) optionally having one hydroxy,
- (21) C₁₋₆ alkyl-carbonylamino (e.g., acetylamino, ethylcarbonylamino) optionally having 1 to 3 substituents selected from
- 15 (a) C₁₋₆ alkyl-carbonyl-oxy (e.g., methylcarbonyloxy),
- (b) C₁₋₆ alkoxy (e.g., methoxy), and
- (c) hydroxy,
- (22) di-(C₁₋₆ alkyl-carbonyl)amino (e.g., di-(acetyl)amino, di-(ethylcarbonyl)amino, di-(propylcarbonyl)amino),
- 20 (23) C₁₋₆ alkoxy-carbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, tert-butoxycarbonylamino),
- (24) N-C₁₋₆ alkyl-N-(C₁₋₆ alkyl-carbonyl)amino (e.g., N-acetyl-N-methylamino, N-acetyl-N-ethylamino),
- 25 (25) ureido,
- (26) C₁₋₆ alkyl-ureido (e.g., methylureido, ethylureido),
- (27) hydroxy,
- (28) C₁₋₆ alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy) optionally having
- 30 1 to 3 C₆₋₁₀ aryl (e.g., phenyl),
- (29) C₆₋₁₀ aryloxy (e.g., phenoxy, naphthoxy),
- (30) heterocyclic group (e.g., 5- or 6-membered aromatic heterocyclic group such as 1-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-pyrazolyl, 1-imidazolyl, 2-imidazolyl, 2-pyrazinyl, 2-furyl, 2-thiazolyl, 4-pyrimidinyl and the like;
- 35

3- to 8-membered nonaromatic heterocyclic group such as 3-azetidiny, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperidyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 1-morpholinyl, morpholino, 2-tetrahydrofuryl, 5 tetrahydrothiopyran-4-yl, tetrahydropyran-4-yl, 3-azepanyl, 4-azepanyl and the like; a group obtained by fusing a nonaromatic heterocyclic group such as 1,3-benzodioxol-5-yl and the like and a benzene ring) optionally having 1 to 3 (preferably 1 or 2) substituents selected from

10 (1') C₁₋₆ alkyl (e.g., methyl, ethyl, propyl) optionally having 1 to 3 substituents selected from

- (a) halogen atom (e.g., fluorine atom), and
- (b) hydroxy,

(2') hydroxy,

15 (3') oxo,

(4') cyano,

(5') carbamoyl,

(6') C₁₋₆ alkoxy (e.g., methoxy),

(7') C₁₋₆ alkyl-carbamoyl (e.g., methylcarbamoyl),

20 (8') C₁₋₆ alkoxy-carbonyl (e.g., tert-butoxycarbonyl), and

(9') C₁₋₆ alkyl-carbonyl (e.g., acetyl, propionyl) optionally having 1 to 3 substituents selected from

- (a) hydroxy,
- (b) C₁₋₆ alkoxy (e.g., methoxy, ethoxy, propoxy),
- 25 (c) amino,
- (d) C₁₋₆ alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino),
- (e) di-C₁₋₆ alkylamino (e.g., dimethylamino), and
- (f) C₁₋₆ alkyl-carbonyloxy (e.g., methylcarbonyloxy),

30 (31) oxo,

(32) thioxo,

(33) C₁₋₆ alkyl-sulfonyl (e.g., methylsulfonyl),

(34) heterocyclyl-carbonyl (e.g., pyrrolidinylcarbonyl, tetrahydrofurylcarbonyl).

35 [0023]

Examples of the "alkenyl" of the above-mentioned "alkenyl optionally having substituent(s)" include C₂₋₆ alkenyl (e.g., vinyl, allyl) and the like.

Examples of the substituent of the above-mentioned
5 "alkenyl optionally having substituent(s)" include the above-mentioned substituent group A and the like, and 1 to 5 (preferably 1 to 3) substituents may be present at substitutable position(s).

[0024]

10 Examples of the "alkynyl" of the above-mentioned "alkynyl optionally having substituent(s)" include C₂₋₆ alkynyl (e.g., ethynyl, propargyl) and the like.

Examples of the substituent that the above-mentioned
"alkynyl optionally having substituent(s)" may have include
15 the above-mentioned substituent group A and the like, and 1 to 5 (preferably 1 to 3) substituents may be present at substitutable position(s).

[0025]

Examples of the "cycloalkyl" of the above-mentioned
20 "cycloalkyl optionally having substituent(s)" include C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) and the like.

Examples of the substituent that the above-mentioned
"cycloalkyl optionally having substituent(s)" may have include
25 (1) the above-mentioned substituent group A,
(2) C₁₋₆ alkyl optionally having 1 to 3 substituents selected from the above-mentioned substituent group A and the like, and 1 to 5 (preferably 1 to 3) substituents may be present at substitutable position(s).

30 Moreover, the "cycloalkyl optionally having substituent(s)" may be a group obtained by fusing C₃₋₆ cycloalkyl and a benzene ring (e.g., 1,2,3,4-tetrahydronaphthalen-1-yl).

[0026]

35 Examples of the "aryl" of the above-mentioned "aryl

optionally having substituent(s)" include C₆₋₁₀ aryl (e.g., phenyl, naphthyl) and the like.

Examples of the substituent that the above-mentioned "aryl optionally having substituent(s)" may have include

5 (1) the above-mentioned substituent group A (except oxo and thioxo),

(2) C₁₋₆ alkyl optionally having 1 to 3 substituents selected from the above-mentioned substituent group A and the like, and 1 to 5 (preferably 1 to 3) substituents may

10 be present at substitutable position(s).

[0027]

X is preferably O, S or NR^{1'} (R^{1'} is alkyl optionally having substituent(s)), and particularly preferably O, S or N(C₁₋₆ alkyl) (particularly, N(methyl)).

15 [0028]

R² is carbamoyl optionally having substituent(s).

Examples of the "carbamoyl optionally having substituent(s)" for R² include

(1) carbamoyl optionally having 1 or 2 substituent(s) selected

20 from "hydrocarbon group optionally having substituent(s)" and "heterocyclic group optionally having substituent(s)",

(2) cyclic carbamoyl optionally having substituent(s) and the like.

Examples of the above-mentioned "hydrocarbon group

25 optionally having substituent(s)" include those similar to the aforementioned "hydrocarbon group optionally having substituent(s)" for R¹.

Examples of the "heterocyclic group" of the above-mentioned "heterocyclic group optionally having

30 substituent(s)", and the "heterocyclic group" recited as an example of the substituent that the above-mentioned "alkyl optionally having substituent(s)" may have and the like include aromatic heterocyclic group and saturated or unsaturated nonaromatic heterocyclic group (aliphatic

35 heterocyclic group), each containing, as a ring system-

constituting atom (ring atom), 1 to 3 kinds (preferably 1 or 2 kinds) of at least one (preferably 1 to 4, more preferably 1 or 2) hetero atom selected from oxygen atom, sulfur atom (the sulfur atom may be oxidized) and nitrogen atom, and a group
 5 having a bond at carbon atom and the like are used.

Examples of the "aromatic heterocyclic group" include
 (1) 5- or 6-membered monocyclic aromatic heterocyclic group
 such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl,
 thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-
 10 oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl,
 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl,
 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl,
 pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl and the like,
 and
 15 (2) 8- to 12-membered condensed polycyclic aromatic
 heterocyclic group such as benzofuranyl, isobenzofuranyl,
 benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl,
 benzimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl,
 benzothiazolyl, benzopyranyl, 1,2-benzoisothiazolyl, 1H-
 20 benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl,
 quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl,
 purinyl, pteridinyl, carbazolyl, α -carbolinyl, β -carbolinyl, γ -
 carbolinyl, acrydinyl, phenoxazinyl, phenothiazinyl,
 phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl,
 25 phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl,
 pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-
 a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-
 a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-
 triazolo[4,3-b]pyridazinyl and the like,
 30 and the like.

[0029]

Examples of the "nonaromatic heterocyclic group" include
 (1) 3- to 8-membered (preferably 5- or 6-membered) saturated
 or unsaturated (preferably saturated) nonaromatic heterocyclic
 35 group (aliphatic heterocyclic group) such as oxiranyl,

azepanyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thioranyl, piperidyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholinyl, thiomorpholinyl, piperazinyl and the like,

- 5 (2) nonaromatic heterocyclic group wherein the double bond in the above-mentioned monocyclic aromatic heterocyclic group or condensed polycyclic aromatic heterocyclic group is partly or entirely saturated, such as 1,2,3,4-tetrahydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl and the like, and
- 10 (3) a group wherein nonaromatic heterocyclic group such as benzodioxolyl and the like and benzene ring are fused and the like.

Examples of the "substituent" of the above-mentioned "heterocyclic group optionally having substituent(s)" include

15 (1) the above-mentioned substituent group A,

(2) those similar to the above-mentioned "hydrocarbon group optionally having substituent(s)" (preferably C₁₋₆ alkyl optionally having 1 to 3 substituents selected from the above-mentioned substituent group A)

20 and the like, and substituents in a substitutable number may be present at substitutable position(s).

As cyclic carbamoyl of the "cyclic carbamoyl optionally having substituent(s)", 5- to 7-membered cyclic carbamoyl is used, and examples thereof include pyrrolidin-1-ylcarbonyl,

25 piperidin-1-ylcarbonyl, piperazin-1-ylcarbonyl, morpholin-4-ylcarbonyl, thiomorpholin-4-ylcarbonyl, homopiperazin-1-ylcarbonyl and the like.

Examples of the "substituent" of the "cyclic carbamoyl optionally having substituent(s)" include the above-mentioned

30 substituent group A and the like, and 1 to 3 substituents may be present at substitutable position(s).

In addition, the substituents of the cyclic carbamoyl optionally having substituent(s) may be bonded to each other to form a 5- to 7-membered ring. In other words, the 5- to 7-

35 membered ring and cyclic carbamoyl may form a fused ring

system. The fused ring system includes a spiro fused ring system.

Examples of the 5- to 7-membered ring include

- (1) 5- to 7-membered homocyclic ring (e.g., cyclohexane, cyclohexene, cyclohexanediene, cycloheptane, benzene), and
(2) 5- to 7-membered heterocycle (e.g., piperidine, piperazine, morpholine, thiomorpholine, pyridine, pyrazine, pyrimidine, pyridazine, triazine, pyran, dihydropyran, tetrahydropyran, 1,3-dioxole). Among these, cyclohexane ring, benzene ring and 1,3-dioxole ring are preferable.

[0030]

As R^2 ,

(A) carbamoyl optionally having 1 or 2 substituents selected from

- (1) C_{1-6} alkyl optionally having 1 or 2 (preferably 1) substituents selected from

- (1') halogen atom,
(2') cyano,
(3') amino,
(4') C_{1-6} alkylamino,
(5') di- C_{1-6} alkylamino optionally having one hydroxy,
(6') C_{1-6} alkoxy-carbonylamino,
(7') hydroxy,
(8') di- C_{1-6} alkyl-carbamoyl,
(9') 5- to 7-membered cyclic carbamoyl,
(10') heterocyclic group optionally having 1 to 3

(preferably 1) substituents selected from

- (a) hydroxy,
(b) C_{1-6} alkyl optionally having one hydroxy,
(c) oxo,
(d) C_{1-6} alkoxy-carbonyl, and
(e) C_{1-6} alkyl-carbonyl optionally having 1 to 3

(preferably 1) substituents selected from C_{1-6} alkyl-carbonyloxy and hydroxy,

- (11') C_{1-6} alkoxy-carbonyl,

- (12') C₃₋₆ cycloalkyl optionally having one hydroxy,
(13') C₁₋₆ alkoxy,
(14') C₂₋₆ alkynyl,
(15') C₆₋₁₀ aryl optionally having 1 to 3 (preferably 1 or 2)
5 C₁₋₆ alkoxy,
(16') carbamoyl, and
(17') C₁₋₆ alkyl-carbonyl-amino optionally having 1 to 3
(preferably 1) substituents selected from
(a) C₁₋₆ alkyl-carbonyloxy,
10 (b) C₁₋₆ alkoxy, and
(c) hydroxy,
(2) C₃₋₆ cycloalkyl or 1,2,3,4-tetrahydronaphthalenyl optionally
having 1 or 2 substituents selected from
(1') amino optionally having one substituent selected from
15 (a) C₁₋₆ alkoxy-carbonyl, and
(b) C₁₋₆ alkyl-carbonyl optionally having 1 to 3
(preferably 1) substituents selected from hydroxy and C₁₋₆
alkyl-carbonyloxy,
(2') hydroxy,
20 (3') carboxy,
(4') C₁₋₆ alkoxy-carbonyl,
(5') C₁₋₆ alkyl-carbamoyl optionally having one hydroxy,
(6') C₁₋₆ alkyl optionally having one hydroxy, and
(7') C₁₋₆ alkoxy-carbonylamino (e.g., tert-
25 butoxycarbonylamino),
(3) C₆₋₁₀ aryl, and
(4) heterocyclic group optionally having 1 to 4 (preferably 1)
substituents selected from
(1') C₁₋₆ alkyl optionally having 1 to 5 substituents
30 selected from
(a) C₆₋₁₀ aryl,
(b) hydroxy, and
(c) halogen atom,
(2') C₁₋₆ alkyl-carbonyl optionally having 1 to 3 (preferably
35 1) substituents selected from

- (a) C₁₋₆ alkyl-carbonyloxy,
(b) hydroxy,
(c) C₁₋₆ alkoxy,
(d) C₁₋₆ alkyl-sulfonyl, and
5 (e) amino,
(3') C₁₋₆ alkoxy-carbonyl, and
(4') 5- or 6-membered aromatic heterocyclic group optionally
having 1 to 3 (preferably 1) substituents selected from
(a) C₁₋₆ alkyl optionally having 1 to 3 halogen atoms,
10 (b) cyano,
(c) carbamoyl,
(d) C₁₋₆ alkoxy, and
(e) C₁₋₆ alkyl-carbamoyl,
(5') oxo,
15 (6') C₁₋₆ alkyl-carbamoyl,
(7') C₁₋₆ alkyl-sulfonyl,
(8') C₆₋₁₀ aryl optionally having 1 to 3 (preferably 1)
substituents selected from
(a) hydroxy,
20 (b) cyano, and
(c) C₁₋₆ alkyl-sulfonyl,
(9') heterocyclyl-carbonyl, and
(10') C₆₋₁₀ aryloxy-carbonyl (e.g., phenoxycarbonyl),
(B) 5- to 7-membered cyclic carbamoyl optionally having 1 to 3
25 (preferably 1) substituents selected from
(1) C₁₋₆ alkyl optionally having 1 to 3 (preferably 1)
substituents selected from
(a) heterocyclic group,
(b) amino,
30 (c) C₁₋₆ alkoxy, and
(d) C₆₋₁₀ aryl,
(2) amino optionally having one C₁₋₆ alkyl-carbonyl,
(3) N-C₁₋₆ alkyl-N-(C₁₋₆ alkyl-carbonyl)amino,
(4) heterocyclic group,
35 (5) C₁₋₆ alkyl-carbonyl optionally having one substituent

selected from

- (a) hydroxy,
 - (b) C₁₋₆ alkoxy,
 - (c) amino,
 - 5 (d) C₁₋₆ alkylamino,
 - (e) di-C₁₋₆ alkylamino, and
 - (f) C₁₋₆ alkyl-carbonyloxy,
 - (6) C₆₋₁₀ aryl, and
 - (7) oxo, or
 - 10 (C) 5- to 7-membered cyclic carbamoyl fused with 5- to 7-membered ring
- is preferable.

[0031]

R³ is hydroxy optionally having substituent(s). As the
15 "substituent" of the "hydroxy optionally having substituent(s)" for R³, the aforementioned "hydrocarbon group optionally having substituent(s)" for R¹, the aforementioned "heterocyclic group optionally having substituent(s)" and the like can be mentioned.

20 As R³, hydroxy optionally having alkyl optionally having substituent(s) is preferable,

hydroxy optionally having

- (1) C₁₋₆ alkyl optionally having one C₁₋₆ alkoxy,
- (2) C₁₋₆ alkyl optionally having 1 to 5 (preferably 1 to 3)
- 25 halogen atoms,

- (3) C₁₋₆ alkyl optionally having one C₆₋₁₀ aryl, or

- (4) C₁₋₆ alkyl optionally having one heterocyclic group

is more preferable, and

hydroxy substituted by

- 30 (1) C₁₋₆ alkyl optionally having one C₁₋₆ alkoxy,
 - (2) C₁₋₆ alkyl optionally having 1 to 5 (preferably 1 to 3)
- halogen atoms,

- (3) C₁₋₆ alkyl optionally having one C₆₋₁₀ aryl, or

- (4) C₁₋₆ alkyl optionally having one heterocyclic group

35 is still more preferable.

[0032]

Ring A is a 5- to 7-membered ring optionally having substituent(s). As the "5- to 7-membered ring" of the "5- to 7-membered ring optionally having substituent(s)" for ring A,
5 (1) 5- to 7-membered homocyclic ring (e.g., cyclohexane, cyclohexene, cyclohexanediene, cycloheptane, benzene), and
(2) 5- to 7-membered heterocycle (e.g., piperidine, piperazine, morpholine, thiomorpholine, pyridine, pyrazine, pyrimidine, pyridazine, triazine, pyran, dihydropyran, tetrahydropyran,
10 1,3-dioxole)
can be mentioned.

Examples of the "substituent" that the "5- to 7-membered ring" of the "5- to 7-membered ring optionally having substituent(s)" for ring A may have include
15 (1) the above-mentioned substituent group A,
(2) those similar to the above-mentioned "hydrocarbon group optionally having substituent(s)" (preferably, C₁₋₆ alkyl optionally having 1 to 3 substituents selected from the above-mentioned substituent group A)
20 and the like, and substituents in a substitutable number may be present at substitutable position(s).

In addition, as to the "substituent" that the "5- to 7-membered ring" of the "5- to 7-membered ring optionally having substituent(s)" for ring A may have, two substituents are
25 optionally bonded to each other to form a ring. As the ring formed by such "substituents" bonded to each other,
(1) 5- to 7-membered homocyclic ring (e.g., cyclohexane, cyclohexene, cyclohexanediene, cycloheptane, benzene), and
(2) 5- to 7-membered heterocycle (e.g., piperidine, piperazine,
30 morpholine, thiomorpholine, pyridine, pyrazine, pyrimidine, pyridazine, triazine, pyran, dihydropyran, tetrahydropyran, 1,3-dioxole)
can be mentioned.

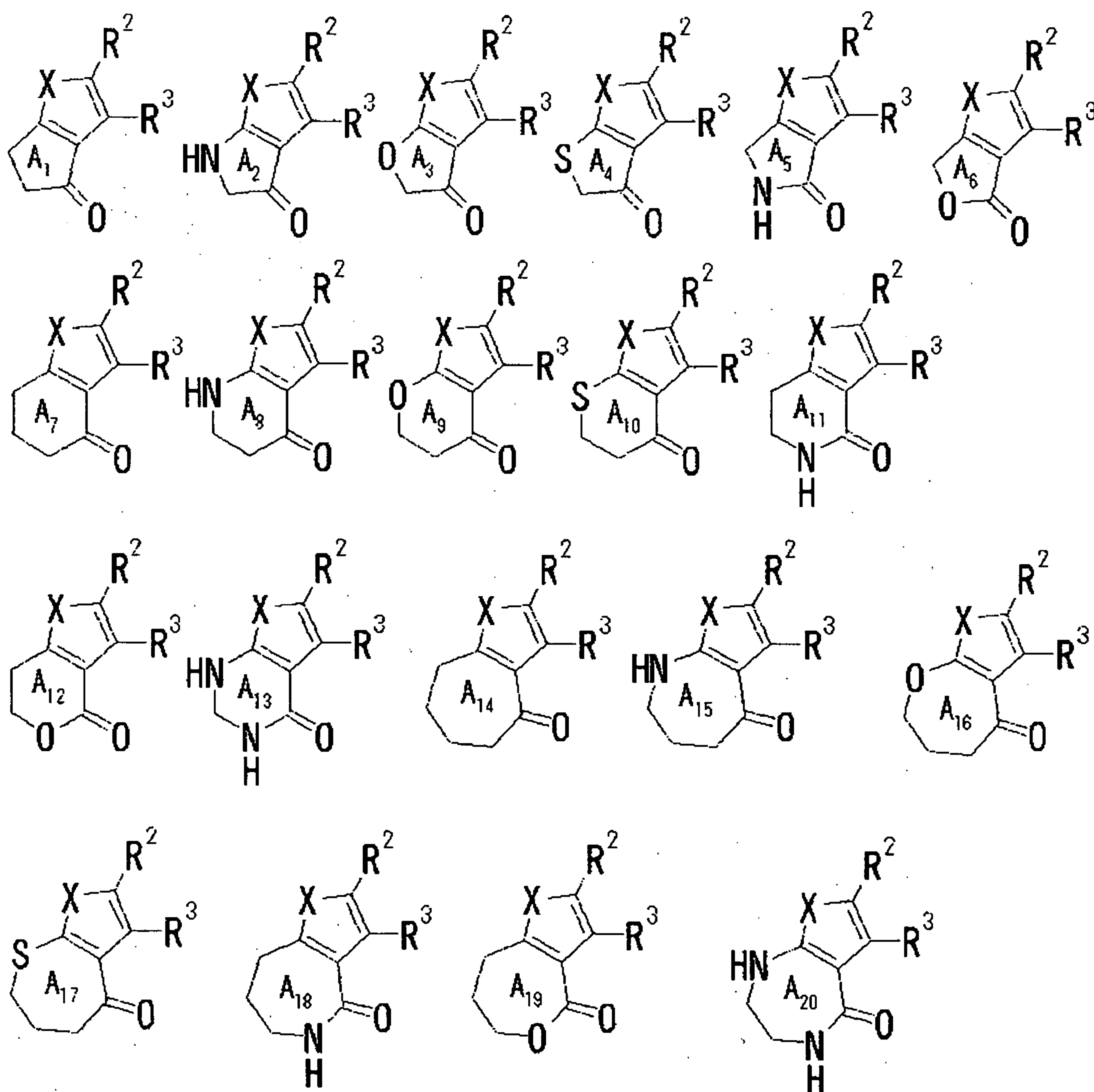
The ring formed by the substituents of ring A, which are
35 bonded to each other, may have substituent(s) and examples of

the substituent include

- (1) the above-mentioned substituent group A,
 - (2) those similar to the above-mentioned "hydrocarbon group optionally having substituent(s)" (preferably C₁₋₆ alkyl optionally having 1 to 3 substituents selected from the above-mentioned substituent group A)
- and the like, and substituents in a substitutable number may be present at substitutable position(s).

Compound (I) specifically has a structure represented by the following formula.

[0033]



[0034]

wherein ring A₁ - ring A₂₀ optionally further have

substituent(s), the substituents are optionally bonded to each other to form a ring, -CH₂-CH₂- part constituting the ring in ring A₁, ring A₇, ring A₈, ring A₉, ring A₁₀, ring A₁₁, ring A₁₂, ring A₁₄, ring A₁₅, ring A₁₆, ring A₁₇, ring A₁₈, ring A₁₉ and ring
 5 A₂₀ is optionally converted to -CH=CH-, -NH-CH₂- part constituting the ring in ring A₂, ring A₅, ring A₈, ring A₁₁, ring A₁₃, ring A₁₅, ring A₁₈ and ring A₂₀ is optionally converted to -N=CH-, and other symbols are as defined above.

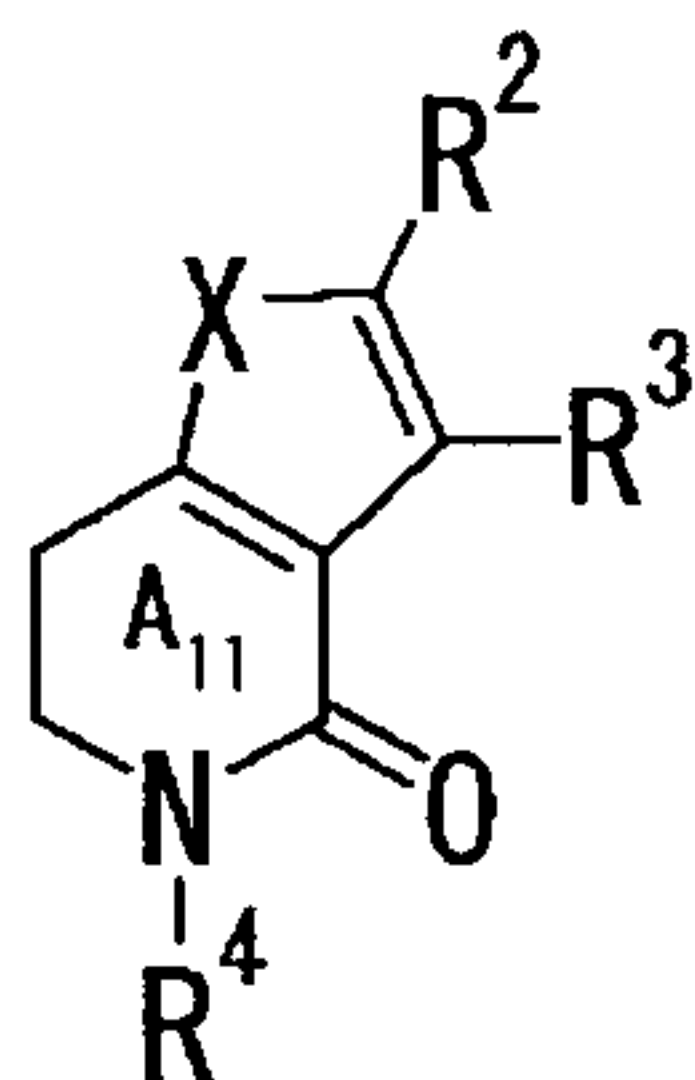
[0035]

10 As the substituent that ring A₁ - ring A₂₀ may have, those similar to the "substituent" that the "5- to 7-membered ring" of the "5- to 7-membered ring optionally having substituent(s)" for ring A may have can be mentioned.

[0036]

15 As compound (I), a compound represented by the formula

[0037]



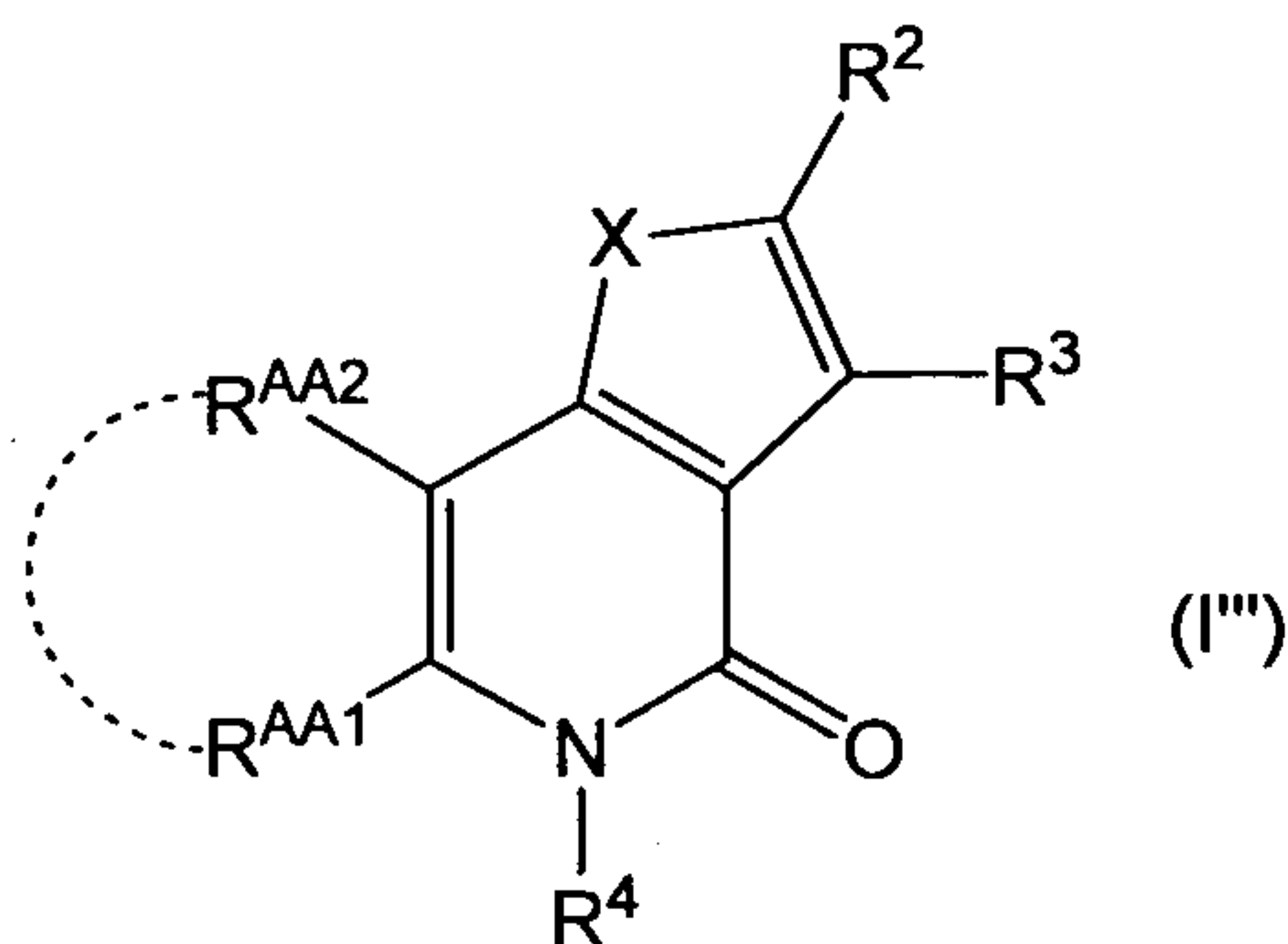
[0038]

20 wherein each symbol is as defined above, is preferable.

[0039]

Of the above-mentioned compounds, compound (I''') represented by the formula

[0040]



25

[0041]

wherein X, R² and R³ are as defined above, R^{AA1} and R^{AA2} are the same or different and each is a hydrogen atom or a substituent, or R^{AA1} and R^{AA2} are optionally bonded to each other to form a 5-
5 to 7-membered ring optionally having substituent(s), and R⁴ is a hydrogen atom or a hydrocarbon group optionally having substituent(s), is preferable.

[0042]

Compound (I''') is explained in detail in the following.

10 X, R² and R³ are as defined above.

R⁴ is a hydrogen atom or a hydrocarbon group optionally having substituent(s). As the "hydrocarbon group optionally having substituent(s)" for R⁴, those similar to the aforementioned "hydrocarbon group optionally having
15 substituent(s)" for R¹ can be mentioned.

As R⁴, a hydrogen atom or alkyl optionally having substituent(s) is preferable. Particularly,

- (1) hydrogen atom,
- (2) C₁₋₆ alkyl optionally having one substituent selected from
 - 20 (1') C₃₋₆ cycloalkyl,
 - (2') C₆₋₁₀ aryl optionally having (i) 1 or 2 C₁₋₆ alkoxy optionally having 1 to 3 halogen atoms or (ii) 1 to 3 halogen atoms,
 - (3') C₁₋₆ alkyl-carbonyl,
 - 25 (4') C₆₋₁₀ aryl-carbonyl optionally having one halogen atom or C₁₋₆ alkoxy,
 - (5') C₁₋₆ alkoxy-carbonyl,
 - (6') C₆₋₁₀ aryl-carbamoyl,
 - (7') heterocyclic group optionally having 1 or 2 C₁₋₆ alkyl
30 optionally having 1 to 3 halogen atoms,
 - (8') C₆₋₁₀ aryloxy,
 - (9') carboxy,
 - (10') cyano, and
 - (11') C₁₋₆ alkoxy optionally having one C₆₋₁₀ aryl,
 - 35 (3) C₁₋₆ alkyl optionally having 1 to 3 halogen atoms

and the like are preferable.

[0043]

(1) R^{AA1} and R^{AA2} are the same or different and each is a hydrogen atom or a substituent. As the substituent, those similar to the aforementioned substituent for ring A can be mentioned.

As R^{AA1} , a hydrogen atom or C_{1-6} alkyl group is preferable.

As R^{AA2} , a hydrogen atom or C_{1-6} alkyl group is preferable.

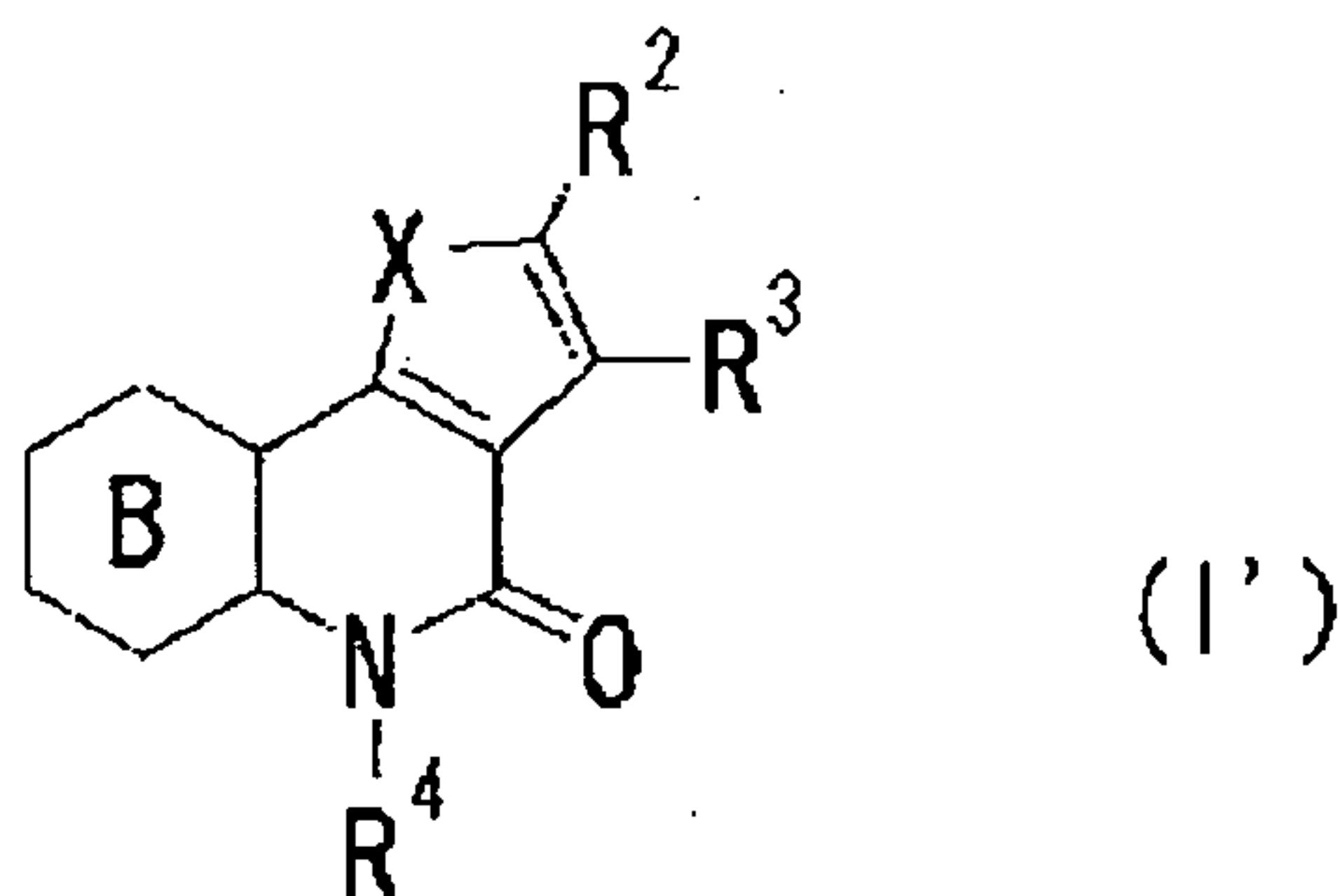
Alternatively,

(2) R^{AA1} and R^{AA2} are bonded to each other to form a 5- to 7-membered ring optionally having substituent(s). As the "5- to 7-membered ring optionally having substituent(s)", those similar to the above-mentioned "5- to 7-membered ring optionally having substituent(s)" for ring A can be mentioned. The 5- to 7-membered ring optionally has a substitutable number of substituents at substitutable positions.

[0044]

In one embodiment, compound (I') represented by the formula

[0045]



[0046]

wherein X, R^2 and R^3 are as defined above, ring B is a 6-membered ring optionally having substituent(s), and R^4 is a hydrogen atom or a hydrocarbon group optionally having substituent(s), in which R^{AA1} and R^{AA2} are bonded to each other to form a 6-membered ring optionally having substituent(s), is preferable from among the above-mentioned compounds (I''').

[0047]

Compound (I') is explained in detail in the following.

[0048]

X, R², R³ and R⁴ are as defined above.

[0049]

- In the formula (I'), preferable examples of R² include
- 5 (A) carbamoyl optionally having 1 or 2 substituents selected from
- (1) C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, n-butyl, 2-methylpropyl, 2,2-dimethylpropyl, 1-methylbutyl, 1-ethylpropyl) optionally having 1 or 2 substituents selected
- 10 from
- (1') halogen atom (e.g., fluorine atom),
- (2') cyano,
- (3') amino,
- (4') C₁₋₆ alkylamino (e.g., isopropylamino),
- 15 (5') di-C₁₋₆ alkylamino (e.g., dimethylamino, diethylamino, di-i-propylamino) optionally having one hydroxy,
- (6') C₁₋₆ alkoxy-carbonylamino (e.g., tert-butoxycarbonylamino),
- (7') hydroxy,
- 20 (8') di-C₁₋₆ alkyl-carbamoyl (e.g., diethylcarbamoyl),
- (9') 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl),
- (10') heterocyclic group (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolyl, 1-imidazolyl, 1-
- 25 piperidyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 1-morpholinyl, morpholino, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-furyl, 2-tetrahydrofuryl, 1,3-benzodioxol-5-yl) optionally having one
- (a) hydroxy,
- 30 (b) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one hydroxy,
- (c) oxo,
- (d) C₁₋₆ alkoxy-carbonyl (e.g., tert-butoxycarbonyl), or
- (e) C₁₋₆ alkyl-carbonyl (e.g., methylcarbonyl) optionally
- 35 having one substituent selected from C₁₋₆ alkyl-carbonyloxy

- (e.g., methylcarbonyloxy) and hydroxy,
- (11') C₁₋₆ alkoxy-carbonyl (e.g., ethoxycarbonyl),
- (12') C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclohexyl) optionally having one hydroxy,
- 5 (13') C₁₋₆ alkoxy (e.g., methoxy, i-propoxy),
- (14') C₂₋₆ alkynyl (e.g., ethynyl),
- (15') C₆₋₁₀ aryl (e.g., phenyl) optionally having 1 or 2 C₁₋₆ alkoxy (e.g., methoxy),
- (16') carbamoyl, and
- 10 (17') C₁₋₆ alkyl-carbonyl-amino (e.g., methylcarbonylamino) optionally having one substituent selected from
- (a) C₁₋₆ alkyl-carbonyl-oxy (e.g., methylcarbonyloxy),
- (b) C₁₋₆ alkoxy (e.g., methoxy), and
- (c) hydroxy,
- 15 (2) C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclohexyl) or 1,2,3,4-tetrahydronaphthalenyl (e.g., 1,2,3,4-tetrahydronaphthalen-1-yl) optionally having 1 or 2 substituents selected from
- (1') amino optionally having one substituent selected from
- (a) C₁₋₆ alkoxy-carbonyl (e.g., tert-butoxycarbonyl), and
- 20 (b) C₁₋₆ alkyl-carbonyl (e.g., methylcarbonyl) optionally having one hydroxy or C₁₋₆ alkyl-carbonyloxy (e.g., methylcarbonyloxy),
- (2') hydroxy,
- (3') carboxy,
- 25 (4') C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl),
- (5') C₁₋₆ alkyl-carbamoyl (e.g., ethylcarbamoyl) optionally having one hydroxy,
- (6') C₁₋₆ alkyl (e.g., methyl) optionally having one hydroxy, and
- 30 (7') C₁₋₆ alkoxy-carbonylamino (e.g., tert-butoxycarbonylamino),
- (3) C₆₋₁₀ aryl (e.g., phenyl), and
- (4) heterocyclic group (e.g., 3-azetidiny, 3-pyrrolidinyl, 4-piperidyl, 2-tetrahydrofuryl, 3-azepanyl, 4-azepanyl,
- 35 tetrahydrothiopyran-4-yl, tetrahydropyran-4-yl) optionally

having 1 to 4 substituents selected from

(1') C₁₋₆ alkyl (e.g., methyl, ethyl, n-propyl) optionally having 1 to 5 substituents selected from

(a) C₆₋₁₀ aryl (e.g., phenyl),

5 (b) hydroxy, and

(c) halogen atom,

(2') C₁₋₆ alkyl-carbonyl (e.g., methylcarbonyl, ethylcarbonyl, i-propylcarbonyl, i-butylcarbonyl) optionally having one substituent selected from

10 (a) C₁₋₆ alkyl-carbonyloxy (e.g., methylcarbonyloxy),

(b) hydroxy,

(c) C₁₋₆ alkoxy (e.g., methoxy),

(d) C₁₋₆ alkyl-sulfonyl (e.g., methylsulfonyl), and

(e) amino,

15 (3') C₁₋₆ alkoxy-carbonyl (e.g., tert-butoxycarbonyl),

(4') 5- or 6-membered aromatic heterocyclic group (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 4-pyrimidinyl) optionally having one substituent selected from

(a) C₁₋₆ alkyl (e.g., methyl) optionally having 1 to 3
20 halogen atoms (e.g., fluorine atom),

(b) cyano,

(c) carbamoyl,

(d) C₁₋₆ alkoxy (e.g., methoxy), and

(e) C₁₋₆ alkyl-carbamoyl (e.g., methylcarbamoyl),

25 (5') oxo,

(6') C₁₋₆ alkyl-carbamoyl (e.g., ethylcarbamoyl),

(7') C₁₋₆ alkyl-sulfonyl (e.g., methylsulfonyl),

(8') C₆₋₁₀ aryl (e.g., phenyl) optionally having one substituent selected from

30 (a) hydroxy,

(b) cyano, and

(c) C₁₋₆ alkyl-sulfonyl (e.g., methylsulfonyl),

(9') heterocycl-yl-carbonyl (e.g., 2-pyrrolidinylcarbonyl, 2-tetrahydrofurylcarbonyl), and

35 (10') C₆₋₁₀ aryloxy-carbonyl (e.g., phenoxycarbonyl),

- (B) 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidylcarbonyl, 1-piperazinylcarbonyl, 1-homopiperazinylcarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl) optionally having
5 one substituent selected from
- (1) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one substituent selected from
- (a) heterocyclic group (e.g., 1-pyrrolidinyl, benzodioxol-5-yl),
10 (b) amino,
(c) C₁₋₆ alkoxy (e.g., methoxy), and
(d) C₆₋₁₀ aryl (e.g., phenyl),
(2) amino optionally having one C₁₋₆ alkyl-carbonyl (e.g., acetyl),
15 (3) N-C₁₋₆ alkyl-N-(C₁₋₆ alkyl-carbonyl)amino (e.g., N-acetyl-N-ethylamino),
(4) heterocyclic group (e.g., 1-pyrrolidinyl, 2-pyridyl),
(5) C₁₋₆ alkyl-carbonyl (e.g., acetyl, propionyl) optionally having one substituent selected from
20 (a) hydroxy,
(b) C₁₋₆ alkoxy (e.g., methoxy, ethoxy),
(c) amino,
(d) C₁₋₆ alkylamino (e.g., isopropylamino),
(e) di-C₁₋₆ alkylamino (e.g., dimethylamino), and
25 (f) C₁₋₆ alkyl-carbonyloxy (e.g., methylcarbonyloxy),
(6) C₆₋₁₀ aryl (e.g., phenyl), and
(7) oxo, and
(C) 5- to 7-membered cyclic carbamoyl fused with 5- to 7-membered ring (e.g., cyclohexane ring, benzene ring, 1,3-dioxolering) (e.g., 1-piperidylcarbonyl).
30

[0050]

In the formula (I'), preferable examples of R³ include hydroxy optionally having

- (1) C₁₋₆ alkyl (e.g., methyl, ethyl, n-butyl) optionally having
35 one

- (a) C₁₋₆ alkoxy (e.g., ethoxy),
(b) C₆₋₁₀ aryl (e.g., phenyl), or
(c) heterocyclic group (e.g., 4-pyridyl, morpholino, 2-tetrahydrofuryl), or
- 5 (2) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)
[preferably, hydroxy substituted by
(1) C₁₋₆ alkyl (e.g., methyl, ethyl, n-butyl) optionally having one
- 10 (a) C₁₋₆ alkoxy (e.g., ethoxy),
(b) C₆₋₁₀ aryl (e.g., phenyl), or
(c) heterocyclic group (e.g., 4-pyridyl, morpholino, 2-tetrahydrofuryl), or
(2) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having 1 to 3
15 halogen atoms (e.g., fluorine atom)].

[0051]

In the formula (I'), preferable examples of R⁴ include

- (1) hydrogen atom,
(2) C₁₋₆ alkyl (e.g., methyl, ethyl, n-propyl, n-butyl, n-pentyl,
20 i-pentyl, 2-ethylbutyl) optionally having one substituent selected from
- (1') C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclohexyl),
(2') C₆₋₁₀ aryl (e.g., phenyl) optionally having (i) one C₁₋₆ alkoxy (e.g., methoxy) optionally having 1 to 3 halogen atoms
25 (e.g., fluorine atom) or (ii) 1 to 3 halogen atoms (e.g., fluorine atom, chlorine atom),
(3') C₁₋₆ alkyl-carbonyl (e.g., methylcarbonyl, tert-butylcarbonyl),
(4') C₆₋₁₀ aryl-carbonyl (e.g., benzoyl),
30 (5') C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl),
(6') C₆₋₁₀ aryl-carbamoyl (e.g., phenylcarbamoyl),
(7') heterocyclic group (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-pyrrolyl, 2-imidazolyl, 2-furyl, 2-tetrahydrofuryl)
35 optionally having 1 or 2 C₁₋₆ alkyl (e.g., methyl) optionally

having 1 to 3 halogen atoms (e.g., fluorine atom),

(8') C₆₋₁₀ aryloxy (e.g., phenoxy),

(9') carboxy,

(10') cyano, and

5 (11') C₁₋₆ alkoxy (e.g., methoxy) optionally having one C₆₋₁₀ aryl (e.g., phenyl), and

(3) C₁₋₆ alkyl (e.g., ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom).

[0052]

10 Ring B is a 6-membered ring optionally having substituent(s). As the "6-membered ring" of the "6-membered ring optionally having substituent(s)",

(1) homocyclic ring (e.g., cyclohexane, cyclohexene, cyclohexanediene, benzene), and

15 (2) heterocycle (e.g., piperidine, piperazine, morpholine, thiomorpholine, pyridine, pyrazine, pyrimidine, pyridazine, triazine, pyran, dihydropyran, tetrahydropyran) can be mentioned.

Examples of the substituent that the ring B may have
20 include

(1) the above-mentioned substituent group A,

(2) C₁₋₆ alkyl optionally having 1 to 3 substituents selected from the above-mentioned substituent group A

and the like, and substituents in a substitutable number may
25 be present at substitutable position(s).

As ring B, cyclohexene ring optionally having substituent(s), benzene ring optionally having substituent(s), or pyridine ring optionally having substituent(s) is preferable, and cyclohexene ring, benzene ring optionally
30 having one halogen atom (e.g., fluorine atom), or pyridine ring is more preferable. Particularly, benzene ring and pyridine ring are preferable.

[0053]

Of compounds (I'), a compound wherein

35 ring B is a 6-membered ring optionally having

substituent(s),

X is O, S or N(C₁₋₆ alkyl),

R² is carbamoyl optionally having substituent(s),

R³ is hydroxy optionally having C₁₋₆ alkyl optionally
5 having substituent(s), and

R⁴ is a hydrogen atom or C₁₋₆ alkyl optionally having
substituent(s)

is preferable.

[0054]

10 Specific examples of preferable compound (I') include the
following.

[Compound (I'-1)]

Compound (I') wherein

X is O, S or N(C₁₋₆ alkyl) (particularly N(methyl));

15 R² is

(A) carbamoyl optionally having 1 or 2 substituents selected
from

(1) C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, 2,2-
dimethylpropyl, 1-methylbutyl) optionally having one
20 substituent selected from

(1') halogen atom (e.g., fluorine atom),

(2') cyano,

(3') amino,

(4') C₁₋₆ alkylamino (e.g., isopropylamino),

25 (5') di-C₁₋₆ alkylamino (e.g., dimethylamino, diethylamino)
optionally having one hydroxy,

(6') C₁₋₆ alkoxy-carbonylamino (e.g., tert-
butoxycarbonylamino),

(7') hydroxy,

30 (8') di-C₁₋₆ alkyl-carbamoyl (e.g., diethylcarbamoyl),

(9') 5- to 7-membered cyclic carbamoyl (e.g., 1-
pyrrolidinylcarbonyl),

(10') heterocyclic group (e.g., 1-pyrrolidinyl, 2-
pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolyl, 1-imidazolyl, 1-
35 piperidyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-

piperazinyl, 1-morpholinyl, 2-pyridyl, 3-pyridyl) optionally having one

(a) hydroxy, or

(b) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one
5 hydroxy, and

(11') C₁₋₆ alkoxy-carbonyl (e.g., ethoxycarbonyl),

(2) C₃₋₆ cycloalkyl (e.g., cyclohexyl) optionally having 1 or 2
substituents selected from

(1') amino, and

10 (2') hydroxy,

(3) C₆₋₁₀ aryl (e.g., phenyl), and

(4) heterocyclic group (e.g., 3-pyrrolidinyl, 4-piperidyl)
optionally having one C₁₋₆ alkyl (e.g., methyl) optionally
having 1 or 2 substituents selected from

15 (a) C₆₋₁₀ aryl (e.g., phenyl), and

(b) hydroxy, or

(B) 5- to 7-membered cyclic carbamoyl (e.g., 1-
pyrrolidinylcarbonyl, 1-piperidylcarbonyl, 1-
homopiperazinylcarbonyl) optionally having one substituent
20 selected from

(1) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one
substituent selected from

(a) heterocyclic group (e.g., 1-pyrrolidinyl, benzodioxol-
5-yl), and

25 (b) amino,

(2) amino,

(3) N-C₁₋₆ alkyl-N-(C₁₋₆ alkyl-carbonyl)amino (e.g., N-acetyl-N-
ethylamino),

(4) heterocyclic group (e.g., 1-pyrrolidinyl), and

30 (5) C₁₋₆ alkyl-carbonyl (e.g., acetyl, propionyl) optionally
having one substituent selected from

(a) hydroxy,

(b) C₁₋₆ alkoxy (e.g., methoxy),

(c) amino, and

35 (d) C₁₋₆ alkylamino (e.g., isopropylamino);

R³ is hydroxy optionally having C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one C₁₋₆ alkoxy (e.g., ethoxy);

R⁴ is

- (1) hydrogen atom, or
- 5 (2) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one substituent selected from
 - (1') C₃₋₆ cycloalkyl (e.g., cyclopropyl),
 - (2') C₆₋₁₀ aryl (e.g., phenyl) optionally having one C₁₋₆ alkoxy (e.g., methoxy),
 - 10 (3') C₁₋₆ alkyl-carbonyl (e.g., tert-butylcarbonyl),
 - (4') C₆₋₁₀ aryl-carbonyl (e.g., benzoyl),
 - (5') C₁₋₆ alkoxy-carbonyl (e.g., ethoxycarbonyl),
 - (6') C₆₋₁₀ aryl-carbamoyl (e.g., phenylcarbamoyl),
 - (7') heterocyclic group (e.g., 2-pyridyl),
 - 15 (8') C₆₋₁₀ aryloxy (e.g., phenoxy), and
 - (9') carboxy; and

ring B is benzene ring.

[0055]

[Compound (I'-2)]

20 Compound (I') wherein

X is O, S or N(C₁₋₆ alkyl) (particularly N(methyl));

R² is

- (A) carbamoyl optionally having 1 or 2 substituents selected from
- 25 (1) C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, 2-methylpropyl, 2,2-dimethylpropyl, 1-methylbutyl) optionally having 1 or 2 substituents selected from
 - (1') halogen atom (e.g., fluorine atom),
 - (2') cyano,
 - 30 (3') amino,
 - (4') C₁₋₆ alkylamino (e.g., isopropylamino),
 - (5') di-C₁₋₆ alkylamino (e.g., dimethylamino, diethylamino) optionally having one hydroxy,
 - (6') C₁₋₆ alkoxy-carbonylamino (e.g., tert-
 - 35 butoxycarbonylamino),

- (7') hydroxy,
- (8') di-C₁₋₆ alkyl-carbamoyl (e.g., diethylcarbamoyl),
- (9') 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl),
- 5 (10') heterocyclic group (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolyl, 1-imidazolyl, 1-piperidyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 1-morpholinyl, 2-pyridyl, 3-pyridyl) optionally having one (a) hydroxy, or (b) C₁₋₆ alkyl (e.g., methyl, ethyl)
- 10 optionally having one hydroxy,
- (11') C₁₋₆ alkoxy-carbonyl (e.g., ethoxycarbonyl), and
- (12') C₃₋₆ cycloalkyl (e.g., cyclohexyl),
- (2) C₃₋₆ cycloalkyl (e.g., cyclohexyl) optionally having 1 or 2 substituents selected from
- 15 (1') amino, and
- (2') hydroxy,
- (3) C₆₋₁₀ aryl (e.g., phenyl), and
- (4) heterocyclic group (e.g., 3-pyrrolidinyl, 4-piperidyl) optionally having one substituent selected from
- 20 (1') C₁₋₆ alkyl (e.g., methyl) optionally having 1 or 2 substituents selected from
- (a) C₆₋₁₀ aryl (e.g., phenyl), and
- (b) hydroxy,
- (2') C₁₋₆ alkyl-carbonyl (e.g., methylcarbonyl) optionally
- 25 having one substituent selected from
- (a) C₁₋₆ alkyl-carbonyloxy (e.g., methylcarbonyloxy), and
- (b) hydroxy,
- (3') C₁₋₆ alkoxy-carbonyl (e.g., tert-butoxycarbonyl), and
- (4') 5- or 6-membered aromatic heterocyclic group (e.g., 4-
- 30 pyridyl), or
- (B) 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidylcarbonyl, 1-homopiperazinylcarbonyl) optionally having one substituent selected from
- 35 (1) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one

substituent selected from

(a) heterocyclic group (e.g., 1-pyrrolidinyl, benzodioxol-5-yl), and

(b) amino,

5 (2) amino,

(3) N-C₁₋₆ alkyl-N-(C₁₋₆ alkyl-carbonyl)amino (e.g., N-acetyl-N-ethylamino),

(4) heterocyclic group (e.g., 1-pyrrolidinyl), and

(5) C₁₋₆ alkyl-carbonyl (e.g., acetyl, propionyl) optionally

10 having one substituent selected from

(a) hydroxy,

(b) C₁₋₆ alkoxy (e.g., methoxy),

(c) amino, and

(d) C₁₋₆ alkylamino (e.g., isopropylamino);

15 R³ is hydroxy optionally having

(1) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one C₁₋₆ alkoxy (e.g., ethoxy), or

(2) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)

20 [preferably, hydroxyl substituted by

(1) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one C₁₋₆ alkoxy (e.g., ethoxy), or

(2) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)];

25 R⁴ is

(1) hydrogen atom, or

(2) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one substituent selected from

(1') C₃₋₆ cycloalkyl (e.g., cyclopropyl),

30 (2') C₆₋₁₀ aryl (e.g., phenyl) optionally having one C₁₋₆ alkoxy (e.g., methoxy),

(3') C₁₋₆ alkyl-carbonyl (e.g., tert-butylcarbonyl),

(4') C₆₋₁₀ aryl-carbonyl (e.g., benzoyl),

(5') C₁₋₆ alkoxy-carbonyl (e.g., ethoxycarbonyl),

35 (6') C₆₋₁₀ aryl-carbamoyl (e.g., phenylcarbamoyl),

(7') heterocyclic group (e.g., 2-pyridyl),
(8') C₆₋₁₀ aryloxy (e.g., phenoxy), and
(9') carboxy; and
ring B is cyclohexene ring or benzene ring (particularly,
5 benzene ring).

[0056]

[Compound (I'-3)]

Compound (I') wherein

X is O, S or N(C₁₋₆ alkyl) (particularly N(methyl));

10 R² is

(A) carbamoyl optionally having 1 or 2 substituents selected
from

(1) C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, n-butyl,
2-methylpropyl, 2,2-dimethylpropyl, 1-methylbutyl, 1-
15 ethylpropyl) optionally having 1 or 2 substituents selected
from

(1') halogen atom (e.g., fluorine atom),
(2') cyano,
(3') amino,
20 (4') C₁₋₆ alkylamino (e.g., isopropylamino),
(5') di-C₁₋₆ alkylamino (e.g., dimethylamino, diethylamino,
di-i-propylamino) optionally having one hydroxy,
(6') C₁₋₆ alkoxy-carbonylamino (e.g., tert-
butoxycarbonylamino),
25 (7') hydroxy,
(8') di-C₁₋₆ alkyl-carbamoyl (e.g., diethylcarbamoyl),
(9') 5- to 7-membered cyclic carbamoyl (e.g., 1-
pyrrolidinylcarbonyl),

(10') heterocyclic group (e.g., 1-pyrrolidinyl, 2-
30 pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolyl, 1-imidazolyl, 1-
piperidyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-
piperazinyl, 1-morpholinyl, morpholino, 2-pyridyl, 3-pyridyl,
4-pyridyl, 2-pyrazinyl, 2-furyl, 2-tetrahydrofuryl, 1,3-
benzodioxol-5-yl) optionally having one

35 (a) hydroxy,

- (b) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one hydroxy,
- (c) oxo,
- (d) C₁₋₆ alkoxy-carbonyl (e.g., tert-butoxycarbonyl), or
- 5 (e) C₁₋₆ alkyl-carbonyl (e.g., methylcarbonyl) optionally having one substituent selected from C₁₋₆ alkyl-carbonyloxy (e.g., methylcarbonyloxy) and hydroxy,
- (11') C₁₋₆ alkoxy-carbonyl (e.g., ethoxycarbonyl),
- (12') C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclohexyl)
- 10 optionally having one hydroxy,
- (13') C₁₋₆ alkoxy (e.g., methoxy, i-propoxy),
- (14') C₂₋₆ alkynyl (e.g., ethynyl),
- (15') C₆₋₁₀ aryl (e.g., phenyl) optionally having 1 or 2 C₁₋₆ alkoxy (e.g., methoxy),
- 15 (16') carbamoyl, and
- (17') C₁₋₆ alkyl-carbonyl-amino (e.g., methylcarbonylamino) optionally having one substituent selected from
- (a) C₁₋₆ alkyl-carbonyl-oxy (e.g., methylcarbonyloxy),
- (b) C₁₋₆ alkoxy (e.g., methoxy), and
- 20 (c) hydroxy,
- (2) C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclohexyl) or 1,2,3,4-tetrahydronaphthalenyl (e.g., 1,2,3,4-tetrahydronaphthalen-1-yl) optionally having 1 or 2 substituents selected from
- (1') amino optionally having one substituent selected from
- 25 (a) C₁₋₆ alkoxy-carbonyl (e.g., tert-butoxycarbonyl), and
- (b) C₁₋₆ alkyl-carbonyl (e.g., methylcarbonyl) optionally having one hydroxy or C₁₋₆ alkyl-carbonyloxy (e.g., methylcarbonyloxy),
- (2') hydroxy,
- 30 (3') carboxy,
- (4') C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl),
- (5') C₁₋₆ alkyl-carbamoyl (e.g., ethylcarbamoyl) optionally having one hydroxy,
- (6') C₁₋₆ alkyl (e.g., methyl) optionally having one hydroxy,
- 35 and

(7') C₁₋₆ alkoxy-carbonylamino (e.g., tert-butoxycarbonylamino),

(3) C₆₋₁₀ aryl (e.g., phenyl), and

(4) heterocyclic group (e.g., 3-azetidiny, 3-pyrrolidinyl, 4-piperidyl, 2-tetrahydrofuryl, 3-azepanyl, 4-azepanyl, tetrahydrothiopyran-4-yl, tetrahydropyran-4-yl) optionally having 1 to 4 substituents selected from

(1') C₁₋₆ alkyl (e.g., methyl, ethyl, n-propyl) optionally having 1 to 5 substituents selected from

10 (a) C₆₋₁₀ aryl (e.g., phenyl),

(b) hydroxy, and

(c) halogen atom,

(2') C₁₋₆ alkyl-carbonyl (e.g., methylcarbonyl, ethylcarbonyl, i-propylcarbonyl, i-butylcarbonyl) optionally having one
15 substituent selected from

(a) C₁₋₆ alkyl-carbonyloxy (e.g., methylcarbonyloxy),

(b) hydroxy,

(c) C₁₋₆ alkoxy (e.g., methoxy),

(d) C₁₋₆ alkyl-sulfonyl (e.g., methylsulfonyl), and

20 (e) amino,

(3') C₁₋₆ alkoxy-carbonyl (e.g., tert-butoxycarbonyl),

(4') 5- or 6-membered aromatic heterocyclic group (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 4-pyrimidinyl) optionally having one substituent selected from

25 (a) C₁₋₆ alkyl (e.g., methyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom),

(b) cyano,

(c) carbamoyl,

(d) C₁₋₆ alkoxy (e.g., methoxy), and

30 (e) C₁₋₆ alkyl-carbamoyl (e.g., methylcarbamoyl),

(5') oxo,

(6') C₁₋₆ alkyl-carbamoyl (e.g., ethylcarbamoyl),

(7') C₁₋₆ alkyl-sulfonyl (e.g., methylsulfonyl),

(8') C₆₋₁₀ aryl (e.g., phenyl) optionally having one
35 substituent selected from

- (a) hydroxy,
(b) cyano, and
(c) C₁₋₆ alkyl-sulfonyl (e.g., methylsulfonyl),
(9') heterocyclyl-carbonyl (e.g., 2-pyrrolidinylcarbonyl, 2-
5 tetrahydrofurylcarbonyl), and
(10') C₆₋₁₀ aryloxy-carbonyl (e.g., phenoxycarbonyl),
(B) 5- to 7-membered cyclic carbamoyl (e.g., 1-
pyrrolidinylcarbonyl, 1-piperidylcarbonyl, 1-
piperazinylcarbonyl, 1-homopiperazinylcarbonyl,
10 morpholinocarbonyl, thiomorpholinocarbonyl) optionally having
one group selected from
(1) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one
substituent selected from
(a) heterocyclic group (e.g., 1-pyrrolidinyl, benzodioxol-5-
15 yl),
(b) amino,
(c) C₁₋₆ alkoxy (e.g., methoxy), and
(d) C₆₋₁₀ aryl (e.g., phenyl),
(2) amino optionally having one C₁₋₆ alkyl-carbonyl (e.g.,
20 acetyl),
(3) N-C₁₋₆ alkyl-N-(C₁₋₆ alkyl-carbonyl)amino (e.g., N-acetyl-N-
ethylamino),
(4) heterocyclic group (e.g., 1-pyrrolidinyl, 2-pyridyl),
(5) C₁₋₆ alkyl-carbonyl (e.g., acetyl, propionyl) optionally
25 having one substituent selected from
(a) hydroxy,
(b) C₁₋₆ alkoxy (e.g., methoxy, ethoxy),
(c) amino,
(d) C₁₋₆ alkylamino (e.g., isopropylamino),
30 (e) di-C₁₋₆ alkylamino (e.g., dimethylamino), and
(f) C₁₋₆ alkyl-carbonyloxy (e.g., methylcarbonyloxy),
(6) C₆₋₁₀ aryl (e.g., phenyl), and
(7) oxo, or
(C) 5- to 7-membered cyclic carbamoyl (e.g., 1-
35 piperidylcarbonyl) fused with 5- to 7-membered ring (e.g.,

- cyclohexane ring, benzene ring, 1,3-dioxole ring);
- R³ is hydroxy optionally having
- (1) C₁₋₆ alkyl (e.g., methyl, ethyl, n-butyl) optionally having one
- 5 (a) C₁₋₆ alkoxy (e.g., ethoxy),
- (b) C₆₋₁₀ aryl (e.g., phenyl), or
- (c) heterocyclic group (e.g., 4-pyridyl, morpholino, 2-tetrahydrofuryl), or
- (2) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having 1 to 3
- 10 halogen atoms (e.g., fluorine atom)
- [preferably, hydroxy substituted by
- (1) C₁₋₆ alkyl (e.g., methyl, ethyl, n-butyl) optionally having one
- (a) C₁₋₆ alkoxy (e.g., ethoxy),
- 15 (b) C₆₋₁₀ aryl (e.g., phenyl), or
- (c) heterocyclic group (e.g., 4-pyridyl, morpholino, 2-tetrahydrofuryl), or
- (2) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having 1 to 3
- halogen atoms (e.g., fluorine atom)];
- 20 R⁴ is
- (1) hydrogen atom,
- (2) C₁₋₆ alkyl (e.g., methyl, ethyl, n-propyl, n-butyl, n-pentyl, i-pentyl, 2-ethylbutyl) optionally having one substituent selected from
- 25 (1') C₃₋₆ cycloalkyl (e.g., cyclopropyl, cyclohexyl),
- (2') C₆₋₁₀ aryl (e.g., phenyl) optionally having (i) one C₁₋₆ alkoxy (e.g., methoxy) optionally having 1 to 3 halogen atoms (e.g., fluorine atom) or (ii) 1 to 3 halogen atoms (e.g., fluorine atom, chlorine atom),
- 30 (3') C₁₋₆ alkyl-carbonyl (e.g., methylcarbonyl, tert-butylcarbonyl),
- (4') C₆₋₁₀ aryl-carbonyl (e.g., benzoyl),
- (5') C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl),
- 35 (6') C₆₋₁₀ aryl-carbamoyl (e.g., phenylcarbamoyl),

(7') heterocyclic group (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-pyrrolyl, 2-imidazolyl, 2-furyl, 2-tetrahydrofuryl) optionally having 1 or 2 C₁₋₆ alkyl (e.g., methyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom),

5 (8') C₆₋₁₀ aryloxy (e.g., phenoxy),

(9') carboxy,

(10') cyano, and

(11') C₁₋₆ alkoxy (e.g., methoxy) optionally having one C₆₋₁₀ aryl (e.g., phenyl), or

10 (3) C₁₋₆ alkyl (e.g., ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom); and

ring B is cyclohexene ring, benzene ring optionally having one halogen atom (e.g., fluorine atom), or pyridine ring (particularly, benzene ring and pyridine ring).

15 [0057]

[Compound (I'-4)]

N-[1-(2-hydroxyethyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide;

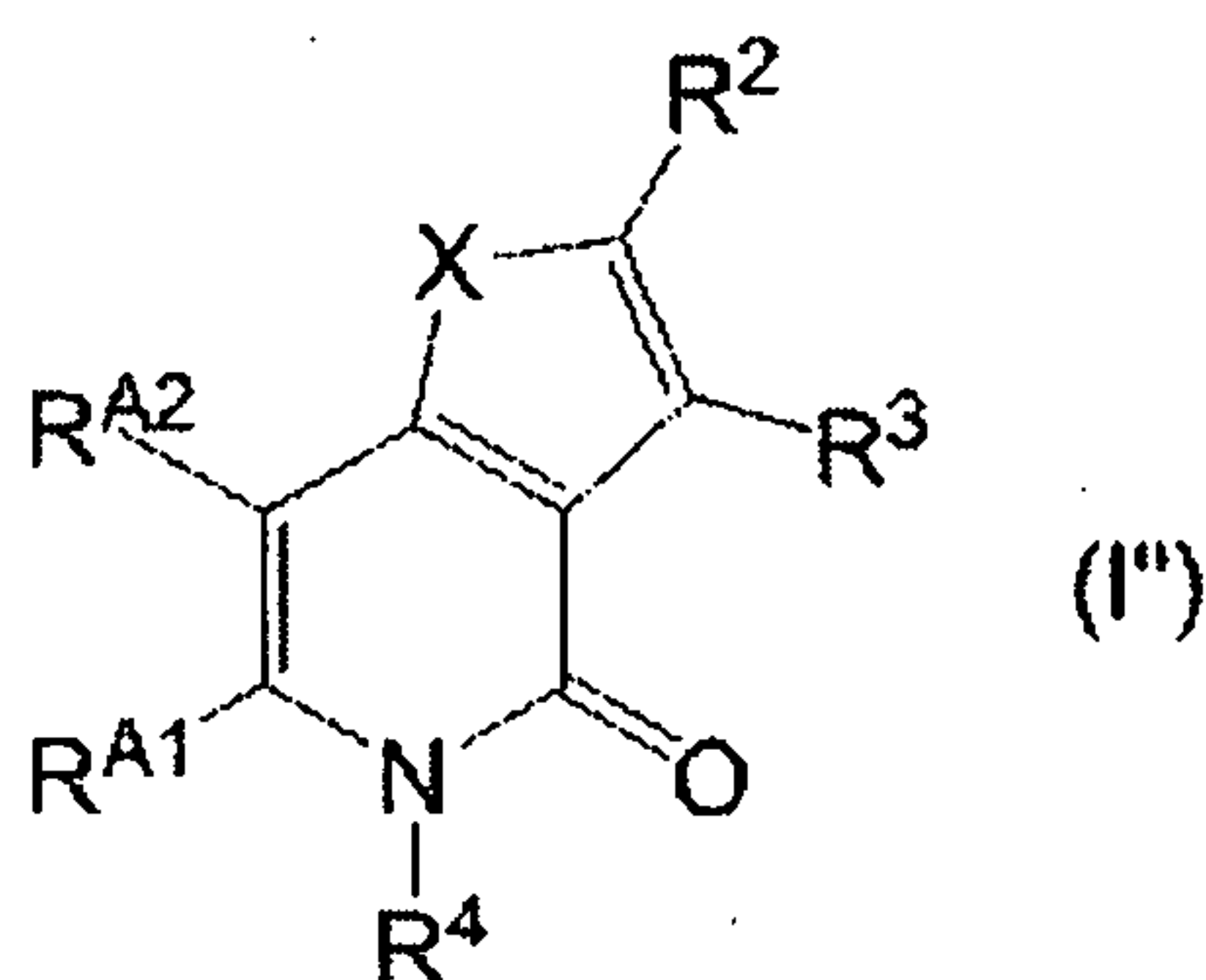
20 N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide;

or a salt thereof.

[0058]

25 In another embodiment, of the above-mentioned compounds (I'''), a compound (I'') represented by the formula

[0059]



30 [0060]

wherein X, R², R³ and R⁴ are as defined above, and R^{A1} and R^{A2} are the same or different and each is a hydrogen atom or a substituent, is preferable.

[0061]

5 In the following, compound (I'') is described in detail.

[0062]

X, R², R³ and R⁴ are as defined above.

[0063]

In the formula (I''), preferable examples of R² is

10 (A) carbamoyl optionally having 1 or 2 substituents selected from

(1) C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, 2-methylpropyl, 2,2-dimethylpropyl, 1-methylbutyl) optionally having 1 or 2 substituents selected from

15 (1') halogen atom (e.g., fluorine atom),

(2') cyano,

(3') amino,

(4') C₁₋₆ alkylamino (e.g., isopropylamino),

(5') di-C₁₋₆ alkylamino (e.g., dimethylamino, diethylamino)

20 optionally having one hydroxy,

(6') C₁₋₆ alkoxy-carbonylamino (e.g., tert-butoxycarbonylamino),

(7') hydroxy,

(8') di-C₁₋₆ alkyl-carbamoyl (e.g., diethylcarbamoyl),

25 (9') 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl),

(10') heterocyclic group (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolyl, 1-imidazolyl, 1-piperidyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 1-morpholinyl, 2-pyridyl, 3-pyridyl, 2-tetrahydrofuryl) optionally having one

(a) hydroxy, or

(b) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one hydroxy,

35 (11') C₁₋₆ alkoxy-carbonyl (e.g., ethoxycarbonyl), and

- (12') C₃₋₆ cycloalkyl (e.g., cyclohexyl),
- (2) C₃₋₆ cycloalkyl (e.g., cyclohexyl) optionally having 1 or 2 substituents selected from
- (1') amino, and
- 5 (2') hydroxy,
- (3) C₆₋₁₀ aryl (e.g., phenyl), and
- (4) heterocyclic group (e.g., 3-pyrrolidinyl, 4-piperidyl, S-oxido-tetrahydrothiopyran-4-yl) optionally having one substituent selected from
- 10 (1') C₁₋₆ alkyl (e.g., methyl) optionally having 1 or 2 substituents selected from
- (a) C₆₋₁₀ aryl (e.g., phenyl), and
- (b) hydroxy,
- (2') C₁₋₆ alkyl-carbonyl (e.g., methylcarbonyl) optionally
- 15 having one substituent selected from
- (a) C₁₋₆ alkyl-carbonyloxy (e.g., methylcarbonyloxy), and
- (b) hydroxy,
- (3') C₁₋₆ alkoxy-carbonyl (e.g., tert-butoxycarbonyl), and
- (4') 5- or 6-membered aromatic heterocyclic group (e.g., 4-
- 20 pyridyl), or
- (B) 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidylcarbonyl, 1-homopiperazinylcarbonyl) optionally having one substituent selected from
- 25 (1) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one substituent selected from
- (a) heterocyclic group (e.g., 1-pyrrolidinyl, benzodioxol-5-yl), and
- (b) amino,
- 30 (2) amino,
- (3) N-C₁₋₆ alkyl-N-(C₁₋₆ alkyl-carbonyl)amino (e.g., N-acetyl-N-ethylamino),
- (4) heterocyclic group (e.g., 1-pyrrolidinyl), and
- (5) C₁₋₆ alkyl-carbonyl (e.g., acetyl, propionyl) optionally
- 35 having one substituent selected from

- (a) hydroxy,
- (b) C₁₋₆ alkoxy (e.g., methoxy),
- (c) amino, and
- (d) C₁₋₆ alkylamino (e.g., isopropylamino).

5 [0064]

In the formula (I''), preferable examples of R³ is hydroxy optionally having

- (1) C₁₋₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl) optionally having one C₁₋₆ alkoxy (e.g., ethoxy), or
- 10 (2) C₁₋₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom) [preferably, hydroxyl substituted by
- (1) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one C₁₋₆ alkoxy (e.g., ethoxy), or
- 15 (2) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)].

[0065]

In the formula (I''), preferable examples of R⁴ is

- (1) hydrogen atom, or
- 20 (2) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one substituent selected from
- (1') C₃₋₆ cycloalkyl (e.g., cyclopropyl),
- (2') C₆₋₁₀ aryl (e.g., phenyl) optionally having (i) 1 or 2 C₁₋₆ alkoxy (e.g., methoxy), or (ii) 1 to 3 halogen atoms (e.g.,
- 25 chlorine atom),
- (3') C₁₋₆ alkyl-carbonyl (e.g., tert-butylcarbonyl),
- (4') C₆₋₁₀ aryl-carbonyl (e.g., benzoyl) optionally having one halogen atom (e.g., chlorine atom) or C₁₋₆ alkoxy (e.g., methoxy),
- 30 (5') C₁₋₆ alkoxy-carbonyl (e.g., ethoxycarbonyl),
- (6') C₆₋₁₀ aryl-carbamoyl (e.g., phenylcarbamoyl),
- (7') heterocyclic group (e.g., 2-pyridyl),
- (8') C₆₋₁₀ aryloxy (e.g., phenoxy), and
- (9') carboxy; and

35 R^{A1} is a hydrogen atom or a C₁₋₆ alkyl group (e.g., methyl,

ethyl, n-propyl).

[0066]

R^{A1} and R^{A2} are the same or different and each is a hydrogen atom or a substituent. As the substituent, those
5 similar to the substituent of the aforementioned ring A can be mentioned.

As R^{A1} , a hydrogen atom or C₁₋₆ alkyl group is preferable.

As R^{A2} , a hydrogen atom or C₁₋₆ alkyl group is preferable.

[0067]

10 Of compounds (I''), a compound wherein

X is O, S or N(C₁₋₆ alkyl),

R^2 is carbamoyl optionally having substituent(s),

R^3 is hydroxy optionally having C₁₋₆ alkyl optionally
having substituent(s),

15 R^{A1} is a hydrogen atom or a C₁₋₆ alkyl group (e.g., methyl, ethyl, n-propyl),

R^{A2} is a hydrogen atom or a C₁₋₆ alkyl group (e.g., methyl), and

R^4 is a hydrogen atom or C₁₋₆ alkyl optionally having
20 substituent(s)
is preferable.

[0068]

Specific examples of preferable compound (I'') include the following.

25 [Compound (I''-1)]

Compound (I'') wherein

X is O, S or N(C₁₋₆ alkyl) (particularly N(methyl));

R^2 is

(A) carbamoyl optionally having 1 or 2 substituents selected
30 from

(1) C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, 2-methylpropyl, 2,2-dimethylpropyl, 1-methylbutyl) optionally
having 1 or 2 substituents selected from

(1') halogen atom (e.g., fluorine atom),

35 (2') cyano,

- (3') amino,
- (4') C₁₋₆ alkylamino (e.g., isopropylamino),
- (5') di-C₁₋₆ alkylamino (e.g., dimethylamino, diethylamino) optionally having one hydroxy,
- 5 (6') C₁₋₆ alkoxy-carbonylamino (e.g., tert-butoxycarbonylamino),
- (7') hydroxy,
- (8') di-C₁₋₆ alkyl-carbamoyl (e.g., diethylcarbamoyl),
- (9') 5- to 7-membered cyclic carbamoyl (e.g., 1-
- 10 pyrrolidinylcarbonyl),
- (10') heterocyclic group (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolyl, 1-imidazolyl, 1-piperidyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 1-morpholinyl, 2-pyridyl, 3-pyridyl) optionally
- 15 having one
- (a) hydroxy, or
- (b) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one hydroxy,
- (11') C₁₋₆ alkoxy-carbonyl (e.g., ethoxycarbonyl), and
- 20 (12') C₃₋₆ cycloalkyl (e.g., cyclohexyl),
- (2) C₃₋₆ cycloalkyl (e.g., cyclohexyl) optionally having 1 or 2 substituents selected from
- (1') amino, and
- (2') hydroxy,
- 25 (3) C₆₋₁₀ aryl (e.g., phenyl), and
- (4) heterocyclic group (e.g., 3-pyrrolidinyl, 4-piperidyl) optionally having one substituent selected from
- (1') C₁₋₆ alkyl (e.g., methyl) optionally having 1 or 2 substituents selected from
- 30 (a) C₆₋₁₀ aryl (e.g., phenyl), and
- (b) hydroxy,
- (2') C₁₋₆ alkyl-carbonyl (e.g., methylcarbonyl) optionally having one substituent selected from
- (a) C₁₋₆ alkyl-carbonyloxy (e.g., methylcarbonyloxy), and
- 35 (b) hydroxy,

(3') C₁₋₆ alkoxy-carbonyl (e.g., tert-butoxycarbonyl), and

(4') 5- or 6-membered aromatic heterocyclic group (e.g., 4-pyridyl), or

(B) 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidylcarbonyl, 1-homopiperazinylcarbonyl) optionally having one group selected from

(1) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one substituent selected from

(a) heterocyclic group (e.g., 1-pyrrolidinyl, benzodioxol-5-yl), and

(b) amino,

(2) amino,

(3) N-C₁₋₆ alkyl-N-(C₁₋₆ alkyl-carbonyl)amino (e.g., N-acetyl-N-ethylamino),

(4) heterocyclic group (e.g., 1-pyrrolidinyl), and

(5) C₁₋₆ alkyl-carbonyl (e.g., acetyl, propionyl) optionally having one substituent selected from

(a) hydroxy,

(b) C₁₋₆ alkoxy (e.g., methoxy),

(c) amino, and

(d) C₁₋₆ alkylamino (e.g., isopropylamino);

R³ is hydroxy optionally having

(1) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one C₁₋₆ alkoxy (e.g., ethoxy), or

(2) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom) [preferably, hydroxy substituted by

(1) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one C₁₋₆ alkoxy (e.g., ethoxy), or

(2) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)];

R⁴ is

(1) hydrogen atom, or

(2) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one

substituent selected from

- (1') C₃₋₆ cycloalkyl (e.g., cyclopropyl),
- (2') C₆₋₁₀ aryl (e.g., phenyl) optionally having one C₁₋₆ alkoxy (e.g., methoxy),
- 5 (3') C₁₋₆ alkyl-carbonyl (e.g., tert-butylcarbonyl),
- (4') C₆₋₁₀ aryl-carbonyl (e.g., benzoyl),
- (5') C₁₋₆ alkoxy-carbonyl (e.g., ethoxycarbonyl),
- (6') C₆₋₁₀ aryl-carbamoyl (e.g., phenylcarbamoyl),
- (7') heterocyclic group (e.g., 2-pyridyl),
- 10 (8') C₆₋₁₀ aryloxy (e.g., phenoxy), and
- (9') carboxy;

R^{A1} is a hydrogen atom or a C₁₋₆ alkyl group (e.g., methyl, ethyl, n-propyl); and

R^{A2} is a hydrogen atom or a C₁₋₆ alkyl group (e.g., methyl).

15 [0069]

[Compound (I''-2)]

Compound (I'') wherein

X is O, S or N(C₁₋₆ alkyl) (particularly N(methyl));

R² is

20 (A) carbamoyl optionally having 1 or 2 substituents selected from

(1) C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, 2-methylpropyl, 2,2-dimethylpropyl, 1-methylbutyl) optionally having 1 or 2 substituents selected from

- 25 (1') halogen atom (e.g., fluorine atom),
- (2') cyano,
- (3') amino,
- (4') C₁₋₆ alkylamino (e.g., isopropylamino),
- (5') di-C₁₋₆ alkylamino (e.g., dimethylamino, diethylamino)
- 30 optionally having one hydroxy,
- (6') C₁₋₆ alkoxy-carbonylamino (e.g., tert-butoxycarbonylamino),
- (7') hydroxy,
- (8') di-C₁₋₆ alkyl-carbamoyl (e.g., diethylcarbamoyl),
- 35 (9') 5- to 7-membered cyclic carbamoyl (e.g., 1-

pyrrolidinylcarbonyl),

(10') heterocyclic group (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolyl, 1-imidazolyl, 1-piperidyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 1-morpholinyl, 2-pyridyl, 3-pyridyl, 2-tetrahydrofuryl) optionally having one

(a) hydroxy, or

(b) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one hydroxy,

10 (11') C₁₋₆ alkoxy-carbonyl (e.g., ethoxycarbonyl), and

(12') C₃₋₆ cycloalkyl (e.g., cyclohexyl),

(2) C₃₋₆ cycloalkyl (e.g., cyclohexyl) optionally having 1 or 2 substituents selected from

(1') amino, and

15 (2') hydroxy,

(3) C₆₋₁₀ aryl (e.g., phenyl), and

(4) heterocyclic group (e.g., 3-pyrrolidinyl, 4-piperidyl, S-oxido-tetrahydrothiopyran-4-yl) optionally having one substituent selected from

20 (1') C₁₋₆ alkyl (e.g., methyl) optionally having 1 or 2 substituents selected from

(a) C₆₋₁₀ aryl (e.g., phenyl), and

(b) hydroxy,

(2') C₁₋₆ alkyl-carbonyl (e.g., methylcarbonyl) optionally
25 having one substituent selected from

(a) C₁₋₆ alkyl-carbonyloxy (e.g., methylcarbonyloxy), and

(b) hydroxy,

(3') C₁₋₆ alkoxy-carbonyl (e.g., tert-butoxycarbonyl), and

(4') 5- or 6-membered aromatic heterocyclic group (e.g., 4-pyridyl), or
30

(B) 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidylcarbonyl, 1-homopiperazinylcarbonyl) optionally having one substituent selected from

35 (1) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one

substituent selected from

(a) heterocyclic group (e.g., 1-pyrrolidinyl, benzodioxol-5-yl), and

(b) amino,

5 (2) amino,

(3) N-C₁₋₆ alkyl-N-(C₁₋₆ alkyl-carbonyl)amino (e.g., N-acetyl-N-ethylamino),

(4) heterocyclic group (e.g., 1-pyrrolidinyl), and

(5) C₁₋₆ alkyl-carbonyl (e.g., acetyl, propionyl) optionally
10 having one substituent selected from

(a) hydroxy,

(b) C₁₋₆ alkoxy (e.g., methoxy),

(c) amino, and

(d) C₁₋₆ alkylamino (e.g., isopropylamino);

15 R³ is hydroxy optionally having

(1) C₁₋₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl)

optionally having one C₁₋₆ alkoxy (e.g., ethoxy), or

(2) C₁₋₆ alkyl (e.g., methyl, ethyl, n-propyl, i-propyl)

optionally having 1 to 3 halogen atoms (e.g., fluorine atom)

20 [preferably, hydroxyl substituted by

(1) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one C₁₋₆ alkoxy (e.g., ethoxy), or

(2) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)];

25 R⁴ is

(1) hydrogen atom, or

(2) C₁₋₆ alkyl (e.g., methyl, ethyl) optionally having one substituent selected from

(1') C₃₋₆ cycloalkyl (e.g., cyclopropyl),

30 (2') C₆₋₁₀ aryl (e.g., phenyl) optionally having (i) 1 or 2

C₁₋₆ alkoxy (e.g., methoxy) or (ii) 1 to 3 halogen atoms (e.g., chlorine atom),

(3') C₁₋₆ alkyl-carbonyl (e.g., tert-butylcarbonyl),

(4') C₆₋₁₀ aryl-carbonyl (e.g., benzoyl) optionally having
35 one halogen atom (e.g., chlorine atom) or C₁₋₆ alkoxy (e.g.,

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methoxy),

(5') C₁₋₆ alkoxy-carbonyl (e.g., ethoxycarbonyl),(6') C₆₋₁₀ aryl-carbamoyl (e.g., phenylcarbamoyl),

(7') heterocyclic group (e.g., 2-pyridyl),

5 (8') C₆₋₁₀ aryloxy (e.g., phenoxy), and

(9') carboxy;

R^{A1} is a hydrogen atom or a C₁₋₆ alkyl group (e.g., methyl, ethyl, n-propyl); and

R^{A2} is a hydrogen atom or a C₁₋₆ alkyl group (e.g., methyl).

10 Of compounds (I"-2), a compound wherein

X is S or N(C₁₋₆ alkyl);

R² is carbamoyl optionally having 1 or 2 substituents selected from

(1) C₁₋₆ alkyl optionally having one substituent selected from15 (1') di-C₁₋₆ alkylamino,

(2') hydroxy, and

(3') heterocyclic group,

(2) C₃₋₆ cycloalkyl optionally substituted by hydroxy, and

(3) heterocyclic group optionally having one substituent

20 selected from

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(1') C₁₋₆ alkyl optionally substituted by hydroxy,

(2') C₁₋₆ alkyl-carbonyl optionally having one substituent selected from

(a) C₁₋₆ alkyl-carbonyloxy, and

5 (b) hydroxy,

(3') C₁₋₆ alkoxy-carbonyl, and

(4') 6-membered aromatic heterocyclic group;

R³ is hydroxy optionally having C₁₋₆ alkyl optionally having 1 to 3 halogen atoms;

10 R⁴ is

(1) hydrogen atom, or

(2) C₁₋₆ alkyl optionally having one substituent selected from

(1') C₆₋₁₀ aryl optionally having (i) 1 or 2 C₁₋₆ alkoxy or (ii) one halogen atom,

15 (2') C₆₋₁₀ aryl-carbonyl optionally having one halogen atom or C₁₋₆ alkoxy;

R^{A1} is a C₁₋₆ alkyl group; and

R^{A2} is a hydrogen atom or a C₁₋₆ alkyl group;

or a salt thereof.

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[0070]

[Compound (I"-3)]

3-ethoxy-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-
 4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-
 5 c]pyridine-2-carboxamide;
 N-[1-(hydroxyacetyl)piperidin-4-yl]-1,6-dimethyl-4-oxo-5-(2-
 oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-
 pyrrolo[3,2-c]pyridine-2-carboxamide;
 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-
 10 (2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-
 1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
 or a salt thereof.

[0071]

When compound (I) is a salt, examples of such salt
 15 include metal salt, ammonium salt, a salt with organic base, a
 salt with inorganic acid, a salt with organic acid, a salt
 with basic or acidic amino acid and the like. Preferable
 examples of the metal salt include alkali metal salt such as
 sodium salt, potassium salt and the like; alkaline earth metal
 20 salt such as calcium salt, magnesium salt, barium salt and the
 like; aluminum salt and the like. Preferable examples of the
 salt with organic base include a salt with trimethylamine,
 triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine,
 diethanolamine, triethanolamine, cyclohexylamine,
 25 dicyclohexylamine, N,N'-dibenzylethylenediamine and the like.
 Preferable examples of the salt with inorganic acid include a

salt with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. Preferable examples of the salt with organic acid include a salt with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. Preferable examples of the salt with basic amino acid include a salt with arginine, lysine, ornithine and the like, and preferable examples of the salt with acidic amino acid include a salt with aspartic acid, glutamic acid and the like.

Of these, a pharmaceutically acceptable salt is preferable. For example, when a compound has an acidic functional group, an inorganic salt such as alkali metal salt (e.g., sodium salt, potassium salt etc.), alkaline earth metal salt (e.g., calcium salt, magnesium salt etc.) and the like, ammonium salt etc., and when a compound has a basic functional group, for example, a salt with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, or a salt with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like can be mentioned.

[0072]

The production method of the compound of the present invention is described in the following.

In each of the following production methods, when alkylation reaction, amidation reaction (condensation reaction), esterification reaction, reduction reaction, reductive amination reaction, amination reaction, halogenation reaction, oxidation reaction and the like are performed, these reactions are performed according to known methods. Examples of such methods include the methods described in Organic Functional Group Preparations, 2nd edition, Academic Press,

Inc. (1989), Comprehensive Organic Transformations, VCH Publishers Inc. (1989) and the like, and the like. Protection and deprotection reactions are performed according to known methods, for example, the methods described in Protective
5 Groups in Organic Synthesis, 3rd edition, John Wiley and Sons, Inc. (1999) or a method analogous thereto.

[0073]

The solvents indicated in generic terms, which are used in the following reactions are explained in the following.

10 Examples of the "alcohols" include methanol, ethanol, 1-propanol, 2-propanol, tert-butyl alcohol and the like.

Examples of the "ethers" include diethyl ether, diisopropyl ether, diphenyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like.

15 Examples of the "esters" include ethyl acetate, methyl acetate, tert-butyl acetate and the like.

Examples of the "hydrocarbons" include benzene, toluene, xylene, cyclohexane, hexane, pentane and the like.

20 Examples of the "amides" include N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide and the like.

25 Examples of the "halogenated hydrocarbons" include dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, tetrachloroethylene, chlorobenzene and the like.

Examples of the "nitriles" include acetonitrile, propionitrile and the like.

Examples of the "ketones" include acetone, 2-butanone and the like.

30 Examples of the "organic acids" include formic acid, acetic acid, propionic acid, trifluoroacetic acid, methanesulfonic acid and the like.

Examples of the "aromatic amines" include pyridine, 2,6-lutidine, quinoline and the like.

35 Examples of the "sulfoxides" include dimethyl sulfoxide

and the like.

In the present production methods, a starting material compound and a production intermediate may be salts. As such salt, those similar to the salts of the aforementioned
5 compound (I) can be mentioned.

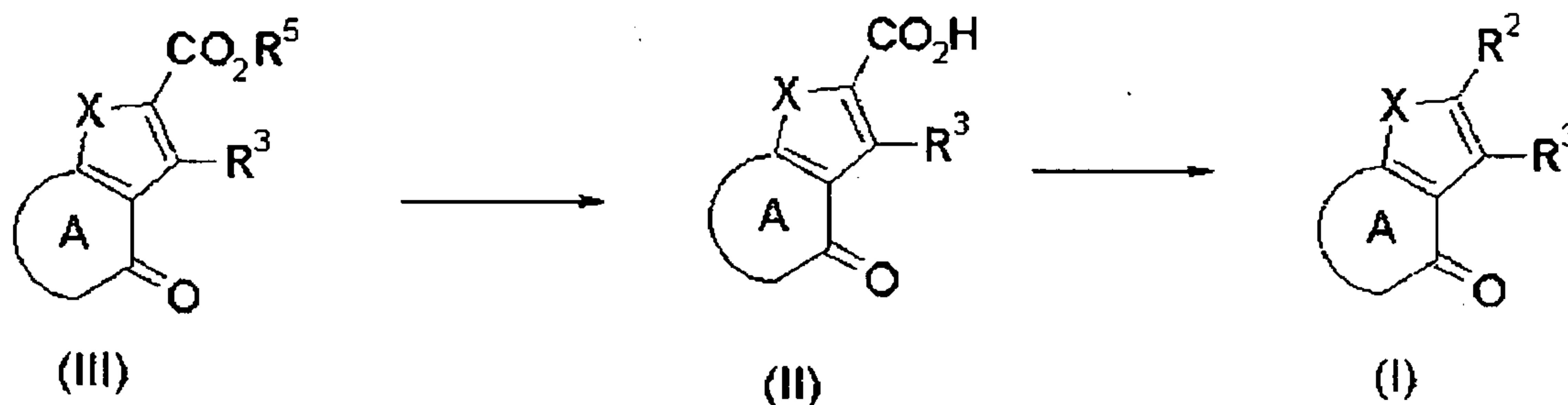
[0074]

Compound (I) can be produced, for example, by [Method A] shown below or a method analogous thereto.

[Method A]

10 Compound (III) is hydrolyzed and the obtained compound (II) is condensed with amine, whereby compound (I) can be produced.

[0075]



15 [0076]

wherein R^5 is C_{1-6} alkyl or benzyl, and other symbols are as defined above.

Examples of C_{1-6} alkyl for R^5 include methyl, ethyl and the like, preferably ethyl.

20 Compound (III) can be produced according to the production methods of compound (IIIa) and compound (IIIb) shown below.

Compound (III) can be converted to compound (II) by hydrolysis under acidic or basic conditions in a solvent that
25 does not adversely influence the reaction. Particularly, when R^5 is benzyl, a catalytic hydrogenation reaction in a solvent that does not adversely influence the reaction can be used.

As the acid used for hydrolysis, hydrochloric acid, sulfuric acid and the like can be mentioned, and as the base,
30 sodium hydroxide, potassium hydroxide, lithium hydroxide and

the like can be mentioned. The amount thereof is generally 1 to 20 molar equivalent, preferably 1 to 10 molar equivalents, per 1 mol of compound (III).

Examples of the catalyst used for the catalytic hydrogenation reaction include Raney-nickel, platinum oxide, or palladium, ruthenium, rhodium, iridium and the like on activated carbon, barium sulfate, calcium carbonate and the like. The amount thereof is generally 0.01 to 1 molar equivalent, preferably 0.05 to 0.5 molar equivalent, per 1 mol of compound (III).

As the hydrogen source, hydrogen, cyclohexene, hydrazine, ammonium formate and the like are used.

Examples of the solvent that does not adversely influence the reaction include ethers, alcohols, hydrocarbons, ketones, nitriles, amides, esters, water and the like, with preference given to alcohols, ethers and water. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 100°C, preferably 20 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0077]

The condensation reaction of compound (II) and amine can be performed in a solvent that does not adversely influence the reaction and using, for example, a condensation agent.

The amine to be used in this reaction can be condensed with carboxy group of compound (II) to form a "carbamoyl optionally having substituent(s)" for R². Such amine may be a commercially available one, or can be produced from the corresponding starting material compound by a method known per se.

Examples of the condensation agent include carbodiimide (e.g., dicyclohexylcarbodiimide (DCCD), water-soluble carbodiimide (WSCD) and the like), phosphate ester (e.g.,

diethyl cyanophosphonate, diethyl chlorophosphonate, diphenyl phosphoroazide and the like), BOP reagent (1H-benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP)), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ),
 5 carbonyldiimidazole and the like, with preference given to WSCD.

The amount of each of the amine and condensation agent to be used is generally 1 to 10 molar equivalents, preferably 1 to 2 molar equivalents, per 1 mol of compound (II).

10 Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, ketones, nitriles, amides, esters and the like, with preference given to ethers and amides. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

15 The reaction temperature is generally 0 to 100°C, preferably 20 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

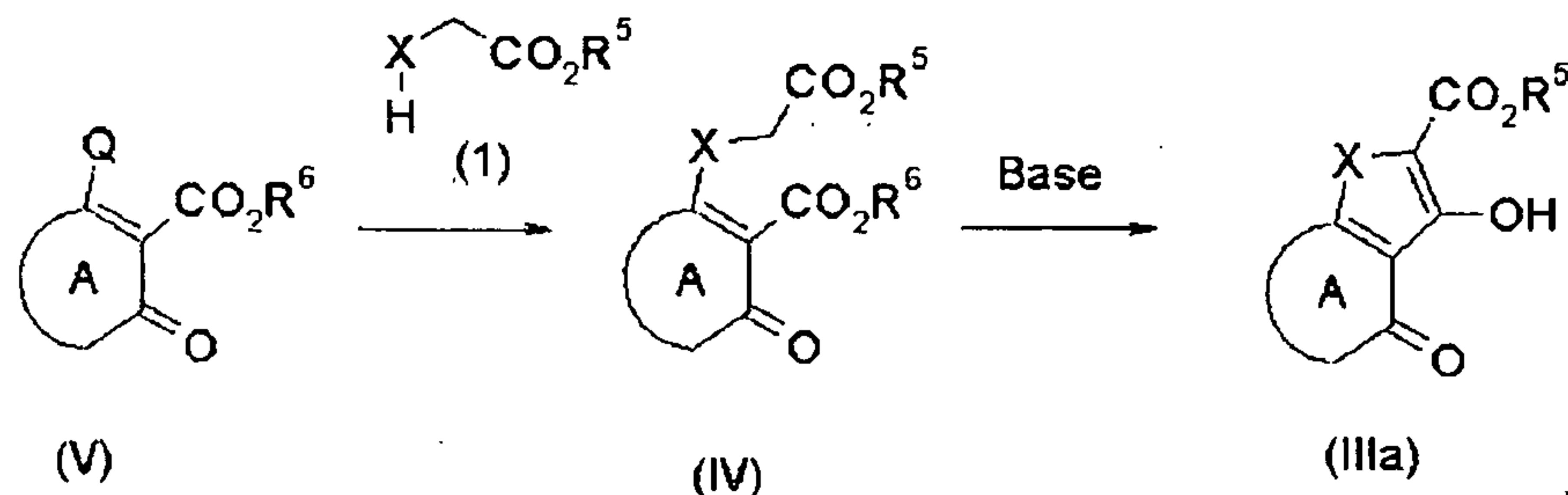
[0078]

20 In compounds (III), compound (IIIa) wherein R³ is hydroxy can be produced, for example, [Method B] shown below or a method analogous thereto.

[Method B]

Compound (V) is reacted with compound (1) and the
 25 obtained compound (IV) is treated with a base to give compound (IIIa).

[0079]



[0080]

30 wherein Q is a leaving group, R⁶ is C₁₋₆ alkyl, and other symbols are as defined above.

Examples of the leaving group for Q include halogen atom (e.g., chlorine, bromine, iodine), optionally halogenated C₁₋₆ alkylsulfonyloxy (e.g., methylsulfonyloxy, ethylsulfonyloxy, trifluoromethylsulfonyloxy), C₆₋₁₀ arylsulfonyloxy optionally
5 having C₁₋₆ alkyl (e.g., benzenesulfonyloxy, 4-toluenesulfonyloxy), methylmercapto, methanesulfonyl and the like, with preference given to halogen atom.

Examples of the C₁₋₆ alkyl for R⁶ include methyl, ethyl and the like.

10 Compound (V) can be produced according to the production methods of compound (Va) and compound (Va-2) shown below.

The reaction of compound (V) and compound (1) can be performed in the presence of a base as necessary and in a solvent that does not adversely influence the reaction.

15 Compound (1) may be a commercially available one, or can be produced from the corresponding starting material compound by a method known per se.

The amount of compound (1) to be used is generally 1 to 20 molar equivalents, preferably 1 to 10 molar equivalents,
20 per 1 mol of compound (V). Examples of the base to be used as necessary include sodium hydride, sodium methoxide, sodium ethoxide, sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine and the like. The amount thereof to be
25 used is generally 1 to 20 molar equivalents, preferably 2 to 10 molar equivalents, per 1 mol of compound (V).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, amides, esters and the like, with preference given to ethers and
30 amides. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 100°C, preferably 20 to 90°C.

The reaction time is generally 0.5 to 100 hr, preferably
35 1 to 48 hr.

[0081]

Compound (IV) can be converted to compound (IIIa) using a base in a solvent that does not adversely influence the reaction.

5 Examples of the base include sodium methoxide, sodium ethoxide, sodium hydroxide, triethylamine and the like and the amount thereof to be used is generally 1 to 20 molar equivalents, preferably 2 to 10 molar equivalents, per 1 mol of compound (IV).

10 Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, amides, esters and the like, with preference given to ethers and amides. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

15 The reaction temperature is generally 0 to 100°C, preferably 20 to 90°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

Compound (V) can be directly converted to compound (IIIa) without isolating compound (IV).

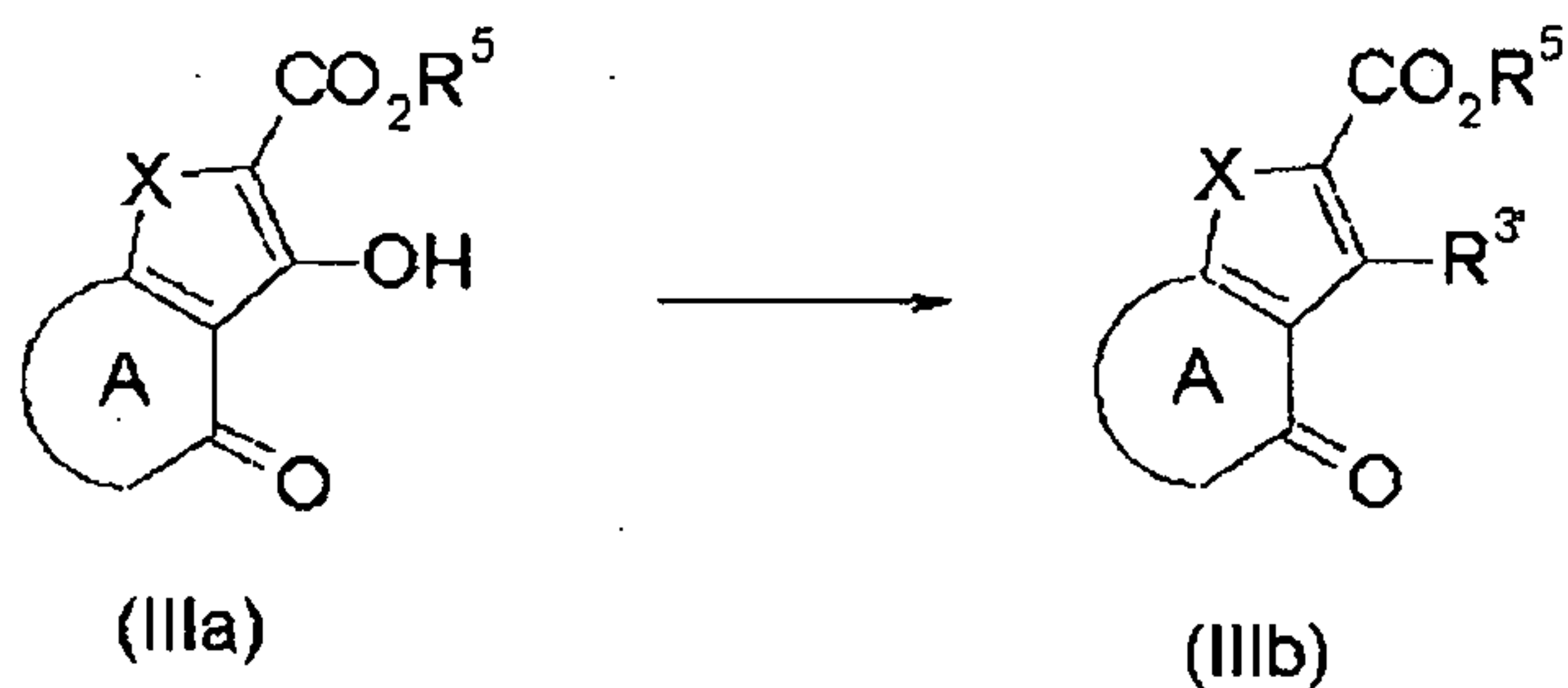
[0082]

In compound (III), compound (IIIb) wherein R^3 is alkoxy optionally having substituent(s) can be produced, for example, by [Method C] shown below or a method analogous thereto.

25 [Method C]

Compound (IIIa) is reacted with halogenated alkyl, sulfate ester, methanesulfonate ester optionally substituted by halogen atom(s) and the like to give compound (IIIb).

[0083]



30

[0084]

wherein R^{3'} is alkoxy optionally having substituent(s), and other symbols are as defined above.

The "alkoxy optionally having substituent(s)" for R^{3'} means "hydroxy substituted by alkyl optionally having substituent(s)" encompassed in the "hydroxy optionally having substituent(s)" for R³.

The reaction between compound (IIIa) and halogenated alkyl, sulfate ester, methanesulfonate ester optionally substituted by halogen atom(s) and the like can be performed in the presence of a base in a solvent that does not adversely influence the reaction.

The halogenated alkyl, sulfate ester and methanesulfonate ester optionally substituted by halogen atom(s) used in this reaction can alkylate the hydroxyl group of compound (IIIa) to form "alkoxy optionally having substituent(s)" for R^{3'}. Such halogenated alkyl, sulfate ester, sulfate ester and methanesulfonate ester optionally substituted by halogen atom(s) may be commercially available ones, or can be produced from the corresponding starting material compound by a method known per se.

The amount of halogenated alkyl and the like to be used is generally 1 to 3 molar equivalents, preferably 1 to 2 molar equivalents, per 1 mol of compound (IIIa). Examples of the base to be used include sodium methoxide, sodium ethoxide, cesium carbonate, sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the like, and the amount thereof to be used is generally 1 to 5 molar equivalents, preferably 1 to 3 molar equivalents, per 1 mol of compound (IIIa).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, esters and the like, with preference given to ethers and amides. Two or more kinds of the above-mentioned

solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 100°C, preferably 20 to 90°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

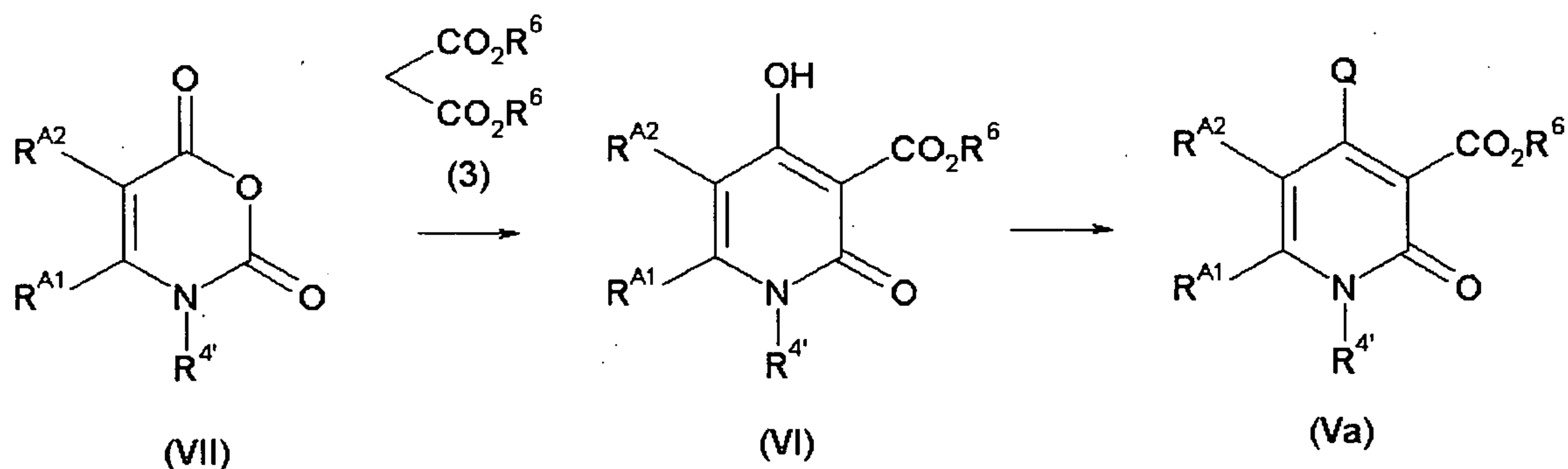
[0085]

Of compounds (V), 2-oxonicotinate ester (Va) wherein ring A is pyridine ring or fused pyridine ring can be produced, for example, by [Method D] shown below or a method analogous thereto.

[Method D]

Compound (VII) is reacted with malonate ester (3) and hydroxy of the obtained compound (VI) is converted to a leaving group Q to give compound (Va).

[0086]



[0087]

wherein R^{4'} is hydrocarbon group optionally having substituent(s), and other symbols are as defined above.

As the "hydrocarbon group optionally having substituent(s)" for R^{4'}, those similar to the "hydrocarbon group optionally having substituent(s)" for R⁴ can be mentioned.

[0088]

The reaction of compound (VII) and malonate ester (3) can be performed in the presence of a base in a solvent that does not adversely influence the reaction.

Malonate ester (3) may be a commercially available one, or can be produced from the corresponding starting material compound by a method known per se.

The amount of malonate ester (3) to be used is generally 1 to 2 molar equivalents, preferably 1 to 1.5 molar equivalents, per 1 mol of compound (VII). Examples of the base to be used include sodium hydride, sodium methoxide, sodium ethoxide, sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine, DBU and the like and the amount thereof to be used is generally 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents, per 1 mol of compound (VII).

10 Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, ketones, nitriles, amides and the like, with preference given to ethers and amides. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

15 The reaction temperature is generally 0 to 100°C, preferably 0 to 80°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0089]

20 Conversion of hydroxy of compound (VI) to leaving group Q can be performed by, for example, using a halogenating reagent and a sulfonylation reagent in a solvent that does not adversely influence the reaction or without solvent and in the presence of a base as necessary.

25 Examples of the halogenating reagent include thionyl chloride, phosphoryl chloride, phosphorus pentachloride, phosphorus tribromide and the like.

The amount of the halogenating reagent to be used is generally 1 to 20 molar equivalents, preferably 2 to 10 molar equivalents, per 1 mol of compound (VI).

30 The reaction temperature is generally 0 to 130°C, preferably 20 to 130°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

35 Examples of the sulfonylation reagent include

trifluoromethanesulfonic acid anhydride, methanesulfonyl halide, benzenesulfonyl halide and the like and the amount thereof to be used is generally 1 to 2 molar equivalents, preferably 1 to 1.5 molar equivalents, per 1 mol of compound (VI). Examples of the base to be used as necessary include triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine and the like and the amount thereof to be used is generally 2 to 5 molar equivalents, preferably 2 to 3 molar equivalents, per 1 mol of compound (VI).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, amides, esters and the like, with preference given to ethers and amides. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -10 to 100°C, preferably 0 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

Compound (VII) to be the starting material in [Method D] can be synthesized by a known method, for example, the method described in Journal of Heterocyclic Chemistry, vol. 12, pages 565-572 (1975).

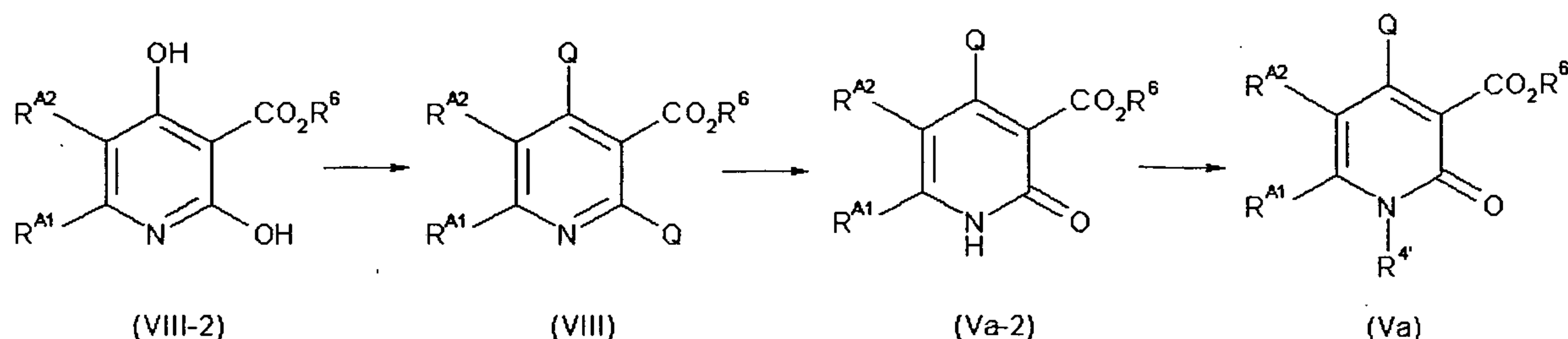
[0090]

Also, compound (Va) can be produced, for example, by [Method E] shown below or a method analogous thereto.

[Method E]

The hydroxy of compound (VIII-2) is converted to leaving group Q, and the obtained compound (VIII) is hydrolyzed to give compound (Va-2). This compound (Va-2) is reacted with halogenated hydrocarbon and the like to give compound (Va).

[0091]



[0092]

wherein each symbol is as defined above.

Compound (VIII) can be produced according to the synthesis method of compound (Va) in the aforementioned [Method D]. The amount of the halogenating reagent and the sulfonylation reagent to be used can be increased as necessary.

[0093]

Hydrolysis of compound (VIII) can be performed, for example, after once substituting leaving group Q with acetoxy or alkoxy or directly under alkaline conditions or acidic conditions, in a solvent that does not adversely influence the reaction.

When the leaving group Q is once substituted with acetoxy or alkoxy, for example, sodium acetate, sodium methoxide, sodium ethoxide and the like can be used and the amount thereof to be used is generally 1 to 20 molar equivalents, preferably 1 to 5 molar equivalents, per 1 mol of compound (VIII).

For direct hydrolysis under acidic conditions, for example, acetic acid, hydrochloric acid, sulfuric acid, methanesulfonic acid and the like can be used as an acid.

For direct hydrolysis under alkaline conditions, for example, aqueous sodium hydroxide solution, aqueous potassium hydroxide solution, aqueous lithium hydroxide solution and the like can be used as a base.

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, water and the like, with preference given to ethers, amides and water. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate

ratio.

The reaction temperature is generally 0 to 130°C, preferably 20 to 130°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0094]

Compound (Va-2) can be converted to compound (Va) by reacting compound (Va-2) with a compound represented by the formula $R^{4'}-Q'$ wherein $R^{4'}$ is as defined above and Q' is a leaving group, in a solvent that does not adversely influence the reaction or without solvent in the presence of a base as necessary.

Examples of the leaving group for Q' include halogen atom (e.g., chlorine, bromine, iodine), optionally halogenated C_{1-6} alkylsulfonyloxy (e.g., methylsulfonyloxy, ethylsulfonyloxy, trifluoromethylsulfonyloxy), C_{6-10} arylsulfonyloxy optionally having C_{1-6} alkyl (e.g., benzenesulfonyloxy, 4-toluenesulfonyloxy), methylmercapto, methanesulfonyl and the like, with preference given to halogen atom.

The amount of the compound represented by the formula $R^{4'}-Q'$ to be used is generally 1 to 20 molar equivalents, preferably 2 to 10 molar equivalents, per 1 mol of compound (Va-2).

Examples of the base to be used as necessary include triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine, sodium hydride, potassium carbonate, cesium carbonate, potassium tert-butoxide, sodium tert-butoxide and the like, with preference given to sodium tert-butoxide, and the amount thereof to be used is generally 2 to 5 molar equivalents, preferably 2 to 3 molar equivalents, per 1 mol of compound (Va-2).

Preferably, tetrabutylammonium bromide or the like is added to the reaction.

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, amides,

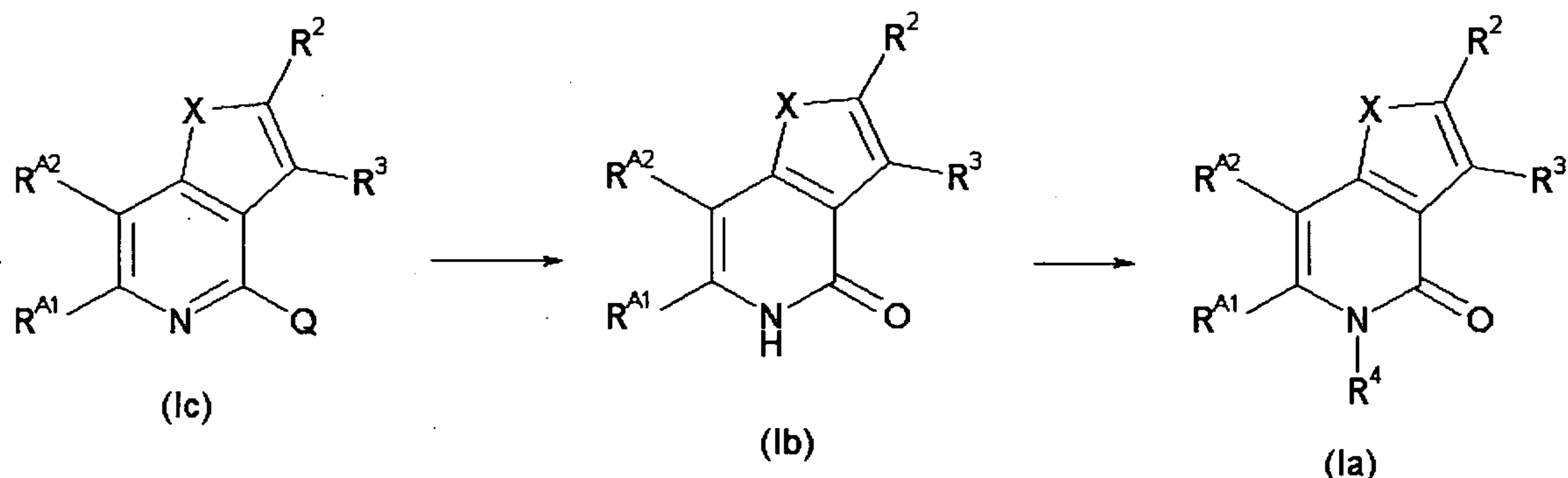
The reaction temperature is generally -10 to 100°C,
5 preferably 0 to 60°C.

[0095]

[0096]

[Method F]

20 [0097]



The reaction from compound (Ib) to compound (Ia) can be performed according to the reaction from compound (Va-2) to compound (Va) in [Method E].

Compound (Ic) can be produced according to the production method of compound (Ica) and compound (Icb) shown below.

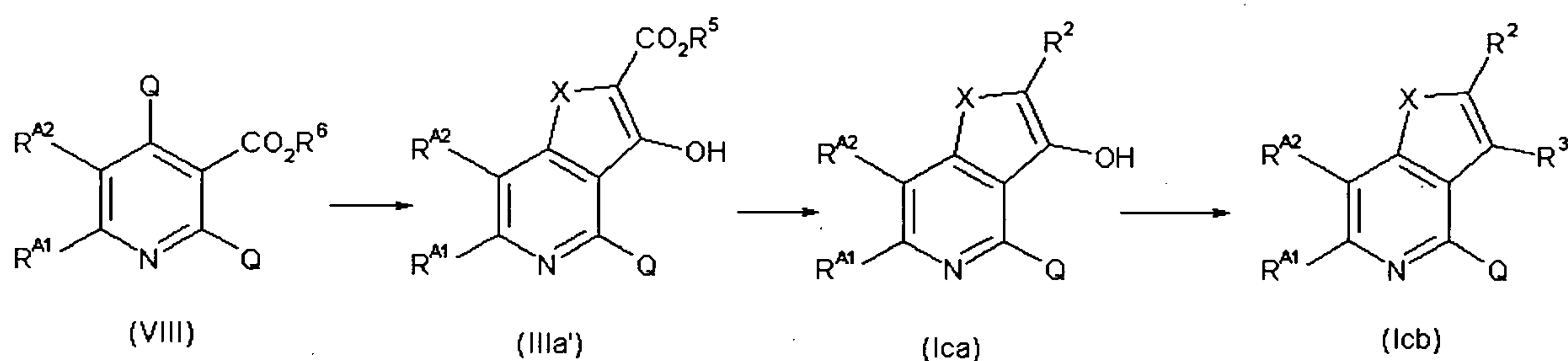
[0099]

In compounds (Ic), compound (Ica) wherein R^3 is hydroxy and compound (Icb) wherein R^3 is alkoxy optionally having substituent(s) (shown by $R^{3'}$ in the following formula (Icb)) can be produced, for example, by [Method G] shown below or a method analogous thereto.

[Method G]

Compound (Ica) and compound (Icb) can be produced from compound (VIII) by reactions according to [Method A], [Method B] and [Method C].

[0100]



[0101]

wherein each symbol is as defined above.

The reaction from compound (VIII) to compound (IIIa') can be performed according to [Method B].

The reaction from compound (IIIa') to compound (Ica) can be performed according to [Method A].

The reaction from compound (Ica) to compound (Icb) can be performed according to [Method C].

[0102]

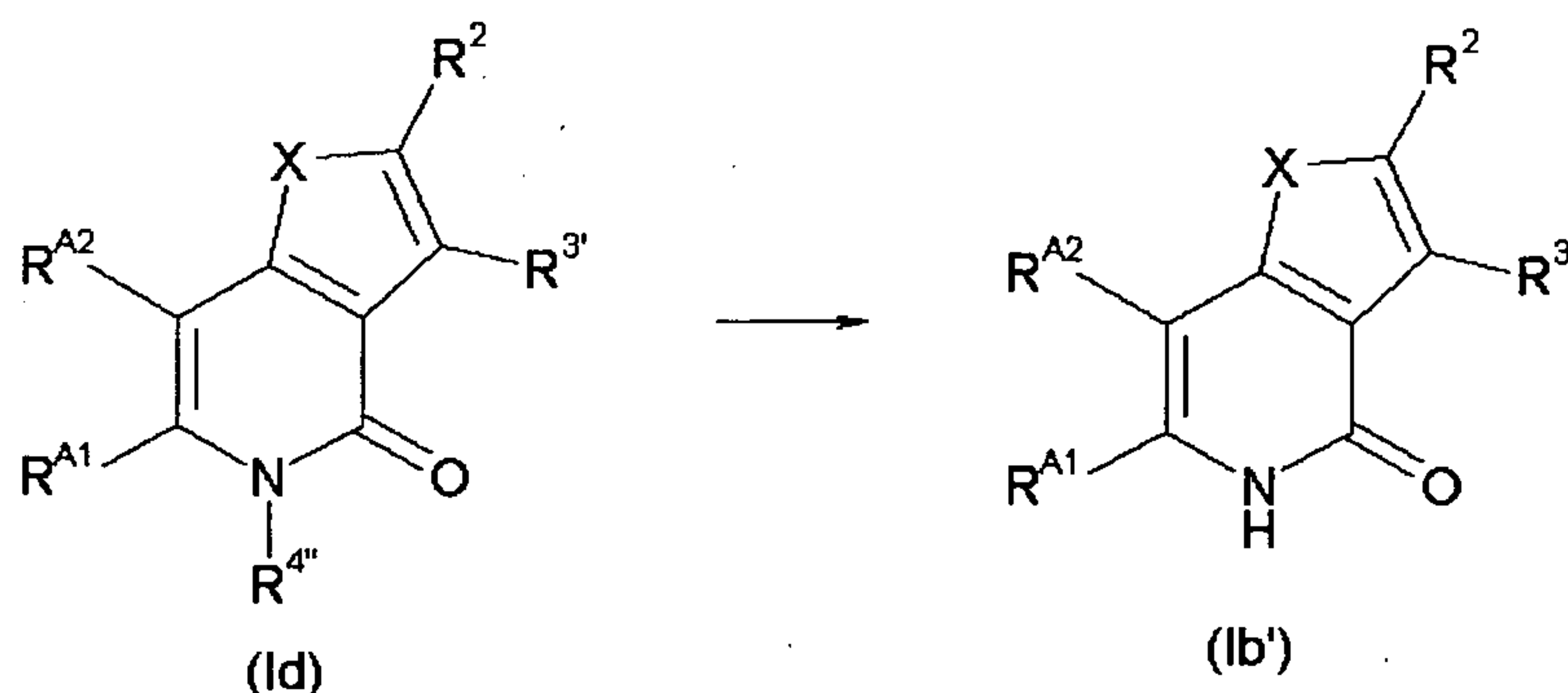
Also, compound (Ib) can be produced, for example, [Method H] shown below or a method analogous thereto.

[Method H]

Of compounds (Ib), compound (Ib') wherein R^3 is alkoxy optionally having substituent(s) (shown by $R^{3'}$ in the following formula (Ib')) can be produced by removing $R^{4''}$ from compound (Id) wherein R^3 is alkoxy optionally having substituent(s) (shown by $R^{3'}$ in the following formula (Id)) and R^4 is phenacyl

optionally having substituent(s), methoxymethyl, 4-methoxybenzyl or 2,4-dimethoxybenzyl (shown by $R^{4''}$ in the following formula (Id)) from among compounds (Ia).

[0103]



[0104]

wherein $R^{4''}$ is phenacyl optionally having substituent(s), methoxymethyl, 4-methoxybenzyl or 2,4-dimethoxybenzyl, and other symbols are as defined above.

10 [0105]

When $R^{4''}$ is phenacyl optionally having substituent(s), conversion of compound (Id) to compound (Ib') can be performed, for example, in the presence of metal such as zinc and the like under acidic conditions in a solvent that does not
15 adversely influence the reaction. The amount of zinc to be used is generally 1 to 20 molar equivalents, preferably 1 to 10 molar equivalents, per 1 mol of compound (Id). As acid, hydrochloric acid, sulfuric acid and the like are used.

Examples of the solvent that does not adversely influence
20 the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, water and the like, with preference given to ethers, amides and water. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

25 The reaction temperature is generally 20 to 120°C, preferably 20 to 100°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 24 hr.

[0106]

When R^{4''} is methoxymethyl, conversion of compound (Id) to compound (Ib') can be performed under acidic conditions in a solvent that does not adversely influence the reaction. As acid, hydrochloric acid, sulfuric acid and the like can be
5 used.

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, water and the like, with preference given to ethers, amides and water. Two or more kinds of the above-
10 mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 120°C, preferably 20 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably
15 1 to 24 hr.

[0107]

When R^{4''} is 4-methoxybenzyl, conversion of compound (Id) to compound (Ib') can be performed under strong acidic conditions in a solvent that does not adversely influence the
20 reaction. As acid, trifluoroacetic acid, trifluoromethanesulfonic acid and the like can be used. In this case, anisole can be used as a cation scavenger in an amount of generally 1 to 20 molar equivalents, preferably 1 to 5 molar equivalents, per 1 mol of compound (Id).

25 Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, and the like, preferably ethers and amides. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

30 The reaction temperature is generally 0 to 120°C, preferably 20 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 24 hr.

[0108]

35 When R^{4''} is 2,4-dimethoxybenzyl, conversion of compound

(Id) to compound (Ib') can be performed in the presence of an oxidant such as cerium (IV) diammonium nitrate (CAN), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and the like in a solvent that does not adversely influence the reaction.

5 The amount of the oxidant to be used is generally 1 to 20 molar equivalents, preferably 1 to 5 molar equivalents, per 1 mol of compound (Id).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones,
10 nitriles, amides, water and the like, with preference given to ethers, nitriles, amides and water. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 120°C,
15 preferably 20 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 24 hr.

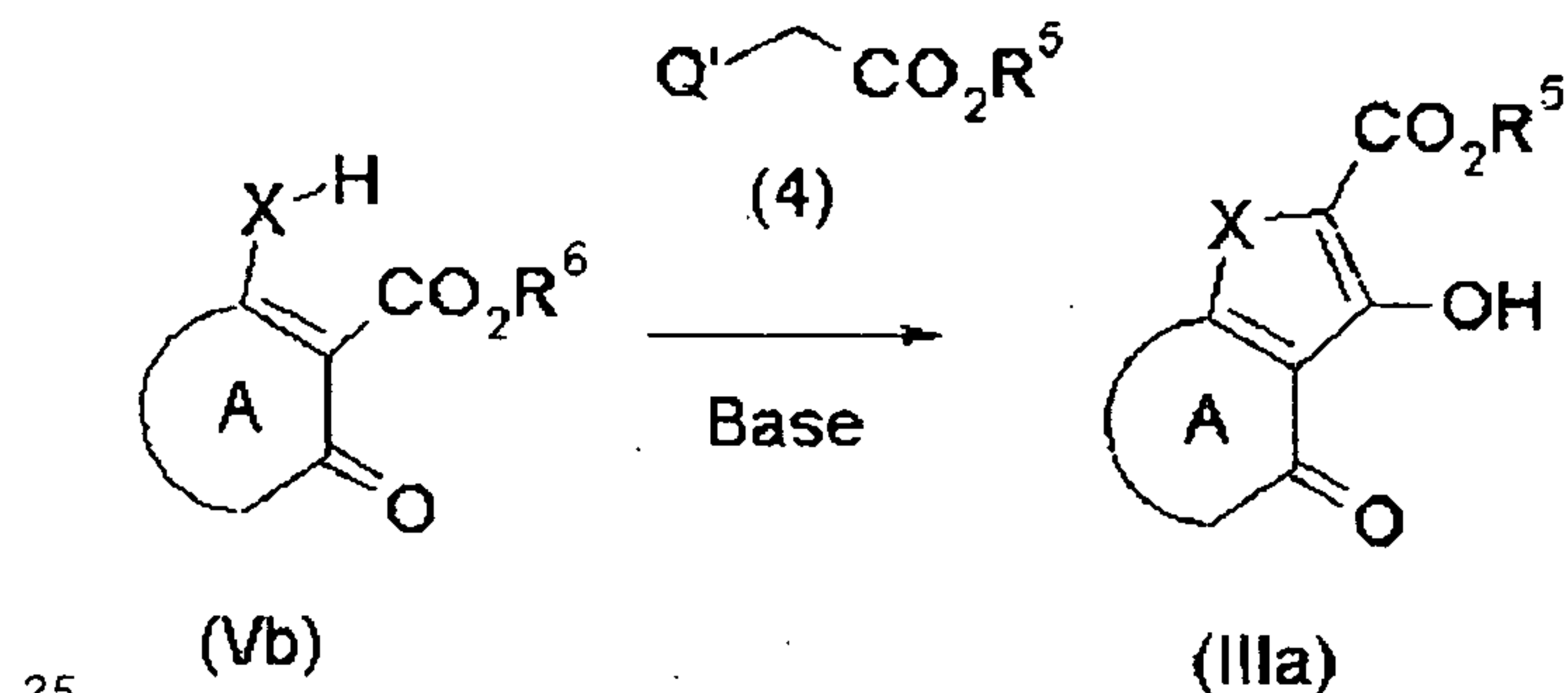
[0109]

Also, compound (IIIa) can be produced, for example, by
20 [Method I] shown below or a method analogous thereto.

[Method I]

Compound (Vb) is reacted with compound (4) to give compound (IIIa).

[0110]



[0111]

wherein Q' is a leaving group, and other symbols are as defined above.

Examples of the leaving group for Q' include those
30 similar to the leaving group for the aforementioned Q, with

preference given to halogen atom.

Compound (4) may be a commercially available reagent, or can be synthesized by a method known *per se*.

Compound (Vb), for example, 6-amino-2,4-dioxo-1,2,3,4-
5 tetrahydropyrimidine-5-carboxylate derivative and the like, to be the starting material in [Method I] can be synthesized by a known method, for example, the method described in Journal of Chemical Society of Japan, vol. 46, pages 3849-3853 (1973). For example, 2-mercapto-4-oxo-1,4-dihydroquinoline-3-
10 carboxylate derivative and the like can be synthesized by a known method, for example, the method described in Journal of Heterocyclic Chemistry, vol. 27, pages 839-843 (1990).

The reaction between compound (Vb) and compound (4) can be performed in the presence of a base in a solvent that does
15 not adversely influence the reaction.

The amount of compound (4) to be used is generally 1 to 3 molar equivalents, preferably 1 to 2 molar equivalents, per 1 mol of compound (Vb). Examples of the base include sodium methoxide, sodium ethoxide, sodium carbonate, sodium hydrogen
20 carbonate, sodium hydroxide, triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine and the like and the amount thereof to be used is generally 2 to 5 molar equivalents, preferably 2 to 3 molar equivalents, per 1 mol of compound (Vb).

25 Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, water and the like, with preference given to ethers, amides and water. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate
30 ratio.

The reaction temperature is generally 20 to 120°C, preferably 20 to 100°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 24 hr.

35 [0112]

A compound within the scope of the present invention can also be produced by applying a means known *per se* to compound (I) for introduction of substituents and conversion of functional groups. For conversion of substituents, a known
5 conventional method can be used. For example, conversion to carboxy by hydrolysis of ester, conversion to carbamoyl by amidation of carboxy, conversion to hydroxymethyl by reduction of carboxy, conversion to alcohol compound by reduction or alkylation of carbonyl, reductive amination of carbonyl,
10 oximation of carbonyl, acylation, ureation, sulfonylation or alkylation of amino, substitution and amination of active halogen by amine, amination of nitro by reduction, alkylation of hydroxy, substitution and amination of hydroxy and the like can be mentioned. When a reactive substituent that causes non-
15 objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction,
20 whereby the compound within the scope of the present invention can also be produced.

In the above-mentioned production method, when the starting compound or the compound of the present invention has an amino group, a carboxyl group, a hydroxy group or a
25 mercapto group as a substituent, a protecting group generally used in peptide chemistry and the like may be introduced into these groups. The protecting group can be removed according to a conventional method in any step in each scheme.

[0113]

30 Compound (I) can be isolated and purified by a means known *per se*, such as phase transfer, concentration, solvent extraction, fractionation, liquid conversion, crystallization, recrystallization, chromatography and the like. When compound (I) is obtained as a free compound, it can be converted to a
35 desired salt by a method known *per se* or a method analogous

thereto. Conversely, when the compound is obtained as a salt, it can be converted to a free form or other desired salt by a method known *per se* or a method analogous thereto.

[0114]

5 Compound (I) may be used as a prodrug. A prodrug of compound (I) means a compound converted to compound (I) by a reaction due to an enzyme, a gastric acid, etc. under the physiological condition in the living body, that is, a compound converted to compound (I) by oxidation, reduction,
10 hydrolysis, etc. due to an enzyme, a compound converted to compound (I) by hydrolysis etc. due to gastric acid, and the like.

[0115]

A prodrug of compound (I) may be a compound obtained by
15 subjecting an amino in compound (I) to an acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino in compound (I) to eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation,
20 pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation); a compound obtained by subjecting hydroxy in compound (I) to acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting hydroxy in the compound (I) of the present invention to acetylation,
25 palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminomethylcarbonylation); a compound obtained by subjecting carboxy in compound (I) to esterification or amidation (e.g., a compound obtained by subjecting carboxy in
30 compound (I) to ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl
35 esterification, cyclohexyloxycarbonyl ethyl esterification or

methylation) and the like. Any one of these compounds can be produced from compound (I) by a method known *per se*.

[0116]

A prodrug of compound (I) may also be a compound
5 converted into compound (I) under physiological conditions, such as those described in IYAKUHIN no KAIHATSU (Development of Pharmaceuticals), Vol. 7, Design of Molecules, p.163-198, Published by HIROKAWA SHOTEN (1990).

[0117]

10 When compound (I) has an isomer such as optical isomer, stereoisomer, positional isomer, rotational isomer and the like, any isomer and a mixture thereof are encompassed in compound (I). For example, when compound (I) has an optical isomer, an optical isomer resolved from a racemate is also encompassed in compound
15 (I). Such isomers can be obtained as independent products by a synthesis means or a separation means (concentration, solvent extraction, column chromatography, recrystallization and the like) known *per se*.

[0118]

20 Compound (I) may be a crystal, and both a single crystal and crystal mixtures are encompassed in compound (I). Crystals can be produced by crystallization according to crystallization methods known *per se*.

Compound (I) may also be a cocrystal.

25 Compound (I) may be a hydrate, a non-hydrate, a solvate or a non-solvate, both of which are encompassed in compound (I) and the like.

A compound labeled with an isotope (e.g., ^2H , ^3H , ^{14}C , ^{35}S , ^{125}I etc.) is also encompassed in compound (I).

30 [0119]

Compound (I) of the present invention, or a salt thereof, or a prodrug thereof (sometimes to be abbreviated as "the compound of the present invention" in the present specification) interacts, for example, with human Smo protein
35 and changes the steric structure thereof, whereby formation of

a complex with a protein involved in the signal transduction in the cytoplasm is inhibited and the Hedgehog signal transduction system is inhibited. Alternatively, the compound of the present invention interacts with human Smo protein and
5 directly inhibits formation of a complex of human Smo protein with a protein involved in the Hedgehog signal transduction system in the cytoplasm, whereby the Hedgehog signal transduction system is inhibited. Alternatively, the compound of the present invention interacts with a site of an Smo
10 protein, for example, phosphorylation site and the like, which is modified by a protein involved in the Hedgehog signal transduction system, whereby modification such as phosphorylation of Smo and the like is inhibited and the Hedgehog signal transduction system is inhibited.

15 Inhibition of the Hedgehog signal transduction system can be measured, for example, by quantifying a decrease in the expression level of a reporter gene connected to the downstream of the Gli binding site based on the fluorescence intensity according to Experimental Example 1. Alternatively,
20 it can be measured by quantifying the expression of Gli-1 mRNA in a cell extract by quantitative PCR method and the like. A compound that inhibits Hedgehog signal targets Smo, which can be confirmed, for example, by binding fluorescence-labeled Cyclopamine and a test compound to cells expressing Smo,
25 measuring the fluorescence level of the cell, and comparing the value with that without addition of a test compound to find a decrease.

[0120]

Accordingly, the compound of the present invention is
30 useful as an Smo inhibitor for mammals (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human, etc.). The compound of the present invention is used as a pharmaceutical agent such as an agent for the prophylaxis or treatment of diseases possibly influenced by Smo, for example,
35 cancer [e.g., colorectal cancer (e.g., colon cancer, rectal

cancer, anal cancer, familial colorectal cancer, hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor, etc.), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, malignant mesothelioma, etc.), mesothelioma, 5 pancreatic cancer (e.g., pancreatic duct cancer, pancreatic endocrine tumor, etc.), pharyngeal cancer, laryngeal cancer, esophageal cancer, gastric cancer (e.g., papillary adenocarcinoma, mucinous adenocarcinoma, adenosquamous cancer, etc.), duodenal cancer, small intestinal cancer, breast cancer 10 (e.g., invasive ductal breast carcinoma, ductal cancer in situ, inflammatory breast cancer, etc.), ovarian cancer (e.g., ovarian epithelial cancer, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor, etc.), testicular tumor, prostate cancer (e.g., hormone- 15 dependent prostate cancer, non-hormone dependent prostate cancer, etc.), liver cancer (e.g., hepatocellular carcinoma, primary liver cancer, extrahepatic bile duct cancer, etc.), thyroid cancer (e.g., medullary thyroid cancer, etc.), kidney cancer (e.g., renal cell carcinoma, renal pelvis and ureter 20 transitional cell cancer, etc.), uterus cancer (e.g., cervical cancer, cancer of uterine body, uterine sarcoma, etc.), brain tumor (e.g., medulloblastoma, glioma, pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, pituitary adenoma, etc.), retinoblastoma, skin 25 cancer (e.g., basal cell carcinoma, malignant melanoma, etc.), sarcoma (e.g., rhabdomyosarcoma, leiomyosarcoma, soft tissue sarcoma, etc.), malignant bone tumor, urinary bladder cancer, blood cancer (e.g., multiple myeloma, leukemia, malignant lymphoma, Hodgkin's disease, chronic myeloproliferative disorder, 30 etc.), cancer unknown primary etc.], a cancer growth inhibitor, a cancer metastasis inhibitor, an apoptosis promoter and the like. Among these, the compound of the present invention is effective, for example, for brain tumor, skin cancer, lung cancer, pancreatic cancer, cancer of the bile duct, prostate 35 cancer, esophagus cancer, gastric cancer, colorectal cancer,

sarcoma and breast cancer. Especially, the compound of the present invention is effective for glioma, medulloblastoma, basal cell tumor, small cell lung cancer, pancreatic cancer, cancer of the bile duct, prostate cancer, esophagus cancer, 5 gastric cancer, colorectal cancer, rhabdomyosarcoma and breast cancer.

[0121]

The compound of the present invention can be administered orally or parenterally as it is or in a mixture with a 10 pharmacologically acceptable carrier.

The dosage form of the compound of the present invention for oral administration is, for example, tablet (including sugar-coated tablet, film-coated tablet), pill, granule, powder, capsule (including soft capsule, microcapsule), syrup, emulsion, 15 suspension and the like, and the dosage form for parenteral administration is, for example, injection, injecting agent, instillation, suppository and the like. In addition, it is effective to make a sustained release preparation by combining the compound with a suitable base (e.g., polymer of butyric acid, 20 polymer of glycolic acid, copolymer of butyric acid-glycolic acid, a mixture of a polymer of butyric acid and a polymer of glycolic acid, polyglycerol fatty acid ester etc.).

[0122]

As a method for producing the compound of the present 25 invention in the above-mentioned dosage form, a known production method generally used in the pertinent field can be employed. When the above-mentioned dosage form is produced, suitable amounts of additives such as excipient, binder, disintegrant, lubricant, sweetening agent, surfactant, suspending agent, 30 emulsifier and the like, generally used in the pharmaceutical field, are appropriately added as necessary for production.

[0123]

When the compound of the present invention is prepared into a tablet, for example, it can be produced by adding an 35 excipient, a binder, a disintegrant, a lubricant and the like,

and when a pill or a granule is to be prepared, it can be produced by adding an excipient, a binder, a disintegrant and the like. When a powder or a capsule is to be prepared, it can be produced by adding an excipient and the like, when a syrup is to be prepared, it can be produced by adding a sweetener and the like, and when an emulsion or a suspension is to be prepared, it can be produced by adding a suspending agent, a surfactant, an emulsifier and the like.

[0124]

10 Examples of the excipient include lactose, sucrose, glucose, starch, sucrose, microcrystalline cellulose, powdered glycyrrhiza, mannitol, sodium hydrogen carbonate, calcium phosphate, calcium sulfate and the like.

15 Examples of the binder include 5 - 10 wt% starch liquid paste, 10 - 20 wt% gum arabic solution or gelatin solution, 1 - 5 wt% tragacanth solution, carboxymethyl cellulose solution, sodium alginate solution, glycerin and the like.

 Examples of the disintegrant include starch, calcium carbonate and the like.

20 Examples of the lubricant include magnesium stearate, stearic acid, calcium stearate, purified talc and the like.

 Examples of the sweetener include glucose, fructose, invert sugar, sorbitol, xylitol, glycerin, simple syrup and the like.

25 Examples of the surfactant include sodium lauryl sulfate, polysorbate 80, sorbitan monofatty acid ester, polyoxyl 40 stearate and the like.

 Examples of the suspending agent include gum arabic, sodium alginate, sodium carboxymethyl cellulose, methyl
30 cellulose, bentonite and the like.

 Examples of the emulsifier include gum arabic, tragacanth, gelatin, polysorbate 80 and the like.

[0125]

Furthermore, when the compound of the present invention is
35 produced in the above-mentioned dosage form, a suitable amount

of a colorant, a preservative, an aromatic, a corrigent, a stabilizer, a thickening agent and the like typically used in the field of preparation can be added on demand.

[0126]

5 As the injection, intravenous injection as well as subcutaneous injection, intracutaneous injection, intramuscular injection, instillation and the like are mentioned, and as the sustained release preparation, an iontophoresis transdermal agent and the like are mentioned.

10 [0127]

Such injections are prepared by methods known per se, or by dissolving, suspending or emulsifying the compound of the present invention in a sterilized aqueous or oily liquid. As an aqueous liquid for injection, physiological saline, isotonic
15 solutions containing glucose or other auxiliary drugs (e.g., D-sorbitol, D-mannitol, sodium chloride and the like) and the like can be mentioned, and they can be used in combination with suitable solubilizing agents, such as alcohols (e.g., ethanol), polyalcohols (e.g., propylene glycol, polyethylene glycol),
20 nonionic surfactants (e.g., polysorbate 80, HCO-50) and the like. As an oily liquid, sesame oil, soybean oil and the like can be mentioned, which may be used in combination with solubilizing agents such as benzyl benzoate, benzyl alcohol and the like. In addition, buffers (e.g., phosphate buffer, sodium acetate
25 buffer), soothing agents (e.g., benzalkonium chloride, procaine hydrochloride and the like), stabilizers (e.g., human serum albumin, polyethylene glycol and the like), preservatives (e.g., benzyl alcohol, phenol and the like) and the like can be blended. A prepared injection is generally filled in an ampoule.

30 [0128]

While the content of the compound of the present invention in the pharmaceutical agent of the present invention varies depending on the form of the pharmaceutical preparation, it is generally about 0.01 to 100 wt%, preferably about 2 to 85 wt%,
35 more preferably about 5 to 70 wt%, relative to the entire

preparation.

[0129]

While the content of the additive in the pharmaceutical agent of the present invention varies depending on the form of the pharmaceutical preparation, it is generally about 1 to 99.9 wt%, preferably about 10 to 90 wt%, relative to the entire preparation.

[0130]

The compound of the present invention is stable and low toxic, and can be used safely. While the daily dose varies depending on the condition and body weight of patients, the kind of compound, administration route and the like, in the case of, for example, oral administration to patients for the treatment of cancer, the daily dose to an adult (body weight about 60 kg) is about 1 to 1000 mg, preferably about 3 to 300 mg, more preferably about 10 to 200 mg, as an active ingredient (the compound of the present invention), which can be given in a single administration or administered in 2 or 3 portions a day.

[0131]

When the compound of the present invention is administered parenterally, it is generally administered in the form of a liquid (e.g., injection). While the dose varies depending on the subject of administration, target organ, symptom, administration method and the like, it is, for example, about 0.01 mg to about 100 mg, preferably about 0.01 to about 50 mg, more preferably about 0.01 to about 20 mg, in the form of an injection, relative to 1 kg body weight, which is preferably given by intravenous injection.

[0132]

The compound of the present invention can be used concurrently with other drugs. To be specific, the compound of the present invention can be used together with medicaments such as hormonal therapeutic agents, chemotherapeutic agents, immunotherapeutic agents, pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors

and the like. In the following, the drugs that can be used in combination with the compound of the present invention are abbreviated as concomitant drugs.

[0133]

5 Examples of the "hormonal therapeutic agents" include fosfestrol, diethylstilbestrol, chlorotrianisene, medroxyprogesterone acetate, megestrol acetate, chlormadinone acetate, cyproterone acetate, danazol, allylestrenol, gestrinone, mepartricin, raloxifene, ormeloxifene,
10 levormeloxifene, anti-estrogens (e.g., tamoxifen citrate, toremifene citrate, and the like), pill preparations, mepitiostane, testrolactone, aminoglutethimide, LH-RH agonists (e.g., goserelin acetate, buserelin, leuprorelin, and the like), droloxifene, epitiostanol, ethinylestradiol sulfonate,
15 aromatase inhibitors (e.g., fadrozole hydrochloride, anastrozole, retrozole, exemestane, vorozole, formestane, and the like), anti-androgens (e.g., flutamide, bicartamide, nilutamide, and the like), 5 α -reductase inhibitors (e.g., finasteride, epristeride, and the like), adrenal cortex
20 hormone drugs (e.g., dexamethasone, prednisolone, betamethasone, triamcinolone, and the like), androgen synthesis inhibitors (e.g., abiraterone, and the like), retinoid and drugs that retard retinoid metabolism (e.g., liarozole, and the like), thyroid hormone, and DDS (Drug
25 Delivery System) preparations thereof, and the like.

[0134]

 Examples of the "chemotherapeutic agents" include alkylating agents, antimetabolites, anticancer antibiotics, plant-derived anticancer agents, and the like.

30 [0135]

 Examples of the "alkylating agents" include nitrogen mustard, nitrogen mustard-N-oxide hydrochloride, chlorambutyl, cyclophosphamide, ifosfamide, thiotepa, carboquone, improsulfan tosylate, busulfan, nimustine hydrochloride,
35 mitobronitol, melphalan, dacarbazine, ranimustine, sodium

estramustine phosphate, triethylenemelamine, carmustine, lomustine, streptozocin, pipobroman, etoglucid, carboplatin, cisplatin, miboplatin, nedaplatin, oxaliplatin, altretamine, ambamustine, dibrospidium hydrochloride, fotemustine, 5 prednimustine, pumitepa, ribomustin, temozolomide, treosulphan, trophosphamide, zinostatin stimalamer, adozelesin, cystemustine, bizelesin, DDS (Drug Delivery System) preparations thereof, and the like.

[0136]

10 Examples of the "antimetabolites" include mercaptopurine, 6-mercaptopurine riboside, thioinosine, methotrexate, pemetrexed, enocitabine, cytarabine, cytarabine ocfosfate, ancitabine hydrochloride, 5-FU drugs (e.g., fluorouracil, tegafur, UFT, doxifluridine, carmofur, gallocitabine, emitefur, 15 capecitabine, and the like), aminopterin, nelzarabine, leucovorin calcium, tabloid, butocine, calcium folinate, levofolinate calcium, cladribine, emitefur, fludarabine, gemcitabine, hydroxycarbamide, pentostatin, piritrexim, idoxuridine, mitoguazone, thiazophrine, ambamustine, 20 bendamustine, DDS preparations thereof, and the like.

[0137]

Examples of the "anticancer antibiotics" include actinomycin-D, actinomycin-C, mitomycin-C, chromomycin-A3, bleomycin hydrochloride, bleomycin sulfate, peplomycin sulfate, 25 daunorubicin hydrochloride, doxorubicin hydrochloride, aclarubicin hydrochloride, pirarubicin hydrochloride, epirubicin hydrochloride, neocarzinostatin, mithramycin, sarcomycin, carzinophilin, mitotane, zorubicin hydrochloride, mitoxantrone hydrochloride, idarubicin hydrochloride, DDS 30 preparations thereof, and the like.

[0138]

Examples of the "plant-derived anticancer agents" include etoposide, etoposide phosphate, vinblastine sulfate, vincristine sulfate, vindesine sulfate, teniposide, paclitaxel, 35 docetaxel, vinorelbine, DDS preparations thereof, and the like.

[0139]

Examples of the "immunotherapeutic agents (BRM)" include picibanil, krestin, sizofiran, lentinan, ubenimex, interferons, interleukins, macrophage colony-stimulating factor, 5 granulocyte colony-stimulating factor, erythropoietin, lymphotoxin, BCG vaccine, *Corynebacterium parvum*, levamisole, polysaccharide K, procodazole, anti-CTLA4 antibody, and the like.

[0140]

10 Example of the "cell growth factors" in the "pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors" include any substances that promote cell proliferation, which are normally peptides having not more than 20,000 molecular weight that are 15 capable of exhibiting their activity at low concentrations by binding to a receptor, including (1) EGF (epidermal growth factor) or substances possessing substantially the same activity as EGF [e.g., TGF α , and the like], (2) insulin or substances possessing substantially the same activity as 20 insulin [e.g., insulin, IGF (insulin-like growth factor)-1, IGF-2, and the like], (3) FGF (fibroblast growth factor) or substances possessing substantially the same activity as FGF [e.g., acidic FGF, basic FGF, KGF (keratinocyte growth factor), FGF-10, and the like], and (4) other cell growth factors [e.g., 25 CSF (colony stimulating factor), EPO (erythropoietin), IL-2 (interleukin-2), NGF (nerve growth factor), PDGF (platelet-derived growth factor), TGF β (transforming growth factor β), HGF (hepatocyte growth factor), VEGF (vascular endothelial growth factor), heregulin, angiopoietin, and the like].

30 [0141]

Examples of the "cell growth factor receptors" include any receptors capable of binding to the aforementioned cell growth factors, including EGF receptor, heregulin receptor (HER3, etc.), insulin receptor, IGF receptor-1, IGF receptor-2, 35 FGF receptor-1 or FGF receptor-2, VEGF receptor, angiopoietin

receptor (Tie2 etc.), PDGF receptor, and the like.

[0142]

As the "pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors", EGF inhibitor, TGF α inhibitor, heregulin inhibitor, insulin inhibitor, IGF inhibitor, FGF inhibitor, KGF inhibitor, CSF inhibitor, EPO inhibitor, IL-2 inhibitor, NGF inhibitor, PDGF inhibitor, TGF β inhibitor, HGF inhibitor, VEGF inhibitor, angiopoietin inhibitor, EGF receptor inhibitor, HER2 inhibitor, HER4 inhibitor, insulin receptor inhibitor, IGF-1 receptor inhibitor, IGF-2 receptor inhibitor, FGF receptor-1 inhibitor, FGF receptor-2 inhibitor, FGF receptor-3 inhibitor, FGF receptor-4 inhibitor, VEGF receptor inhibitor, Tie-2 inhibitor, PDGF receptor inhibitor, Abl inhibitor, Raf inhibitor, FLT3 inhibitor, c-Kit inhibitor, Src inhibitor, PKC inhibitor, Trk inhibitor, Ret inhibitor, mTOR inhibitor, Aurora inhibitor, PLK inhibitor, MEK(MEK1/2) inhibitor, MET inhibitor, CDK inhibitor, Akt inhibitor, ERK inhibitor and the like are used. More specifically, anti-VEGF antibody (Bevacizumab etc.), anti-HER2 antibody (Trastuzumab, Pertuzumab etc.), anti-EGFR antibody (Cetuximab, Panitumumab, Matuzumab, Nimotuzumab etc.), anti-VEGFR antibody, anti-HGF antibody, Imatinib mesylate, Erlotinib, Gefitinib, Sorafenib, Sunitinib, Dasatinib, Lapatinib, Vatalanib, 4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-7-[3-(1-pyrrolidinyl)propoxy]quinazoline (AZD-2171), Lestaurtinib, Pazopanib, Canertinib, Tandutinib, 3-(4-bromo-2,6-difluorobenzyloxy)-5-[3-[4-(1-pyrrolidinyl)butyl]ureido]isothiazole-4-carboxamide (CP-547632), Axitinib, N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(pyridin-4-ylmethylamino)pyridine-3-carboxamide (AMG-706), Nilotinib, 6-[4-(4-ethylpiperazin-1-ylmethyl)phenyl]-N-[1(R)-phenylethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (AEE-788), Vandetanib, Temsirolimus, Everolimus, Enzastaurin, N-[4-[4-(4-methylpiperazin-1-yl)-6-(3-methyl-1H-pyrazol-5-ylamino)pyrimidin-2-ylsulfanyl]phenyl]cyclopropanecarboxamide

(VX-680), phosphoric acid 2-[N-[3-[4-[5-[N-(3-fluorophenyl)carbamoylmethyl]-1H-pyrazol-3-ylamino]quinazolin-7-yloxy]propyl]-N-ethylamino]ethyl ester (AZD-1152), 4-[9-chloro-7-(2,6-difluorophenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-ylamino]benzoic acid (MLN-8054), N-[2-methoxy-5-[(E)-2-(2,4,6-trimethoxyphenyl)vinylsulfonylmethyl]phenyl]glycine sodium salt (ON-1910Na), 4-[8-cyclopentyl-7(R)-ethyl-5-methyl-6-oxo-5,6,7,8-tetrahydropteridin-2-ylamino]-3-methoxy-N-(1-methylpiperidin-4-yl)benzamide (BI-2536), 5-(4-bromo-2-chlorophenylamino)-4-fluoro-1-methyl-1H-benzimidazole-6-carbohydroxamic acid 2-hydroxyethyl ester (AZD-6244), N-[2(R),3-dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzamide (PD-0325901), Everolimus (RAD001) and the like are used.

[0143]

In addition to the aforementioned drugs, L-asparaginase, aceglatone, procarbazine hydrochloride, protoporphyrin-cobalt complex salt, mercuric hematoporphyrin-sodium, topoisomerase I inhibitors (e.g., irinotecan, topotecan, and the like), topoisomerase II inhibitors (e.g., sobuzoxane, and the like), differentiation inducers (e.g., retinoid, vitamin D, and the like), other angiogenesis inhibitors (e.g., humagillin, shark extract, COX-2 inhibitor, and the like), α -blockers (e.g., tamsulosin hydrochloride, and the like), bisphosphonic acids (e.g., pamidronate, zoledronate, and the like), thalidomide, 5-azacytidine, decitabine, proteasome inhibitor (e.g., bortezomib, and the like), antitumor antibody such as anti-CD20 antibody and the like, toxin labeled antibody and the like can also be used.

[0144]

By combining the compound of the present invention and a concomitant drug, a superior effect such as

- (1) the dose can be reduced as compared to single administration of the compound of the present invention or a concomitant drug,
- (2) the drug to be combined with the compound of the present invention can be selected according to the condition of patients (mild case, severe case and the like),

(3) the period of treatment can be set longer,
(4) a sustained treatment effect can be designed,
(5) a synergistic effect can be afforded by a combined use of
the compound of the present invention and a concomitant drug,
5 and the like, can be achieved.

[0145]

In the present specification, the compound of the present invention and a concomitant drug used in combination are referred to as the "combination agent of the present invention".

10 For use of the combination agent of the present invention, the administration time of the compound of the present invention and the concomitant drug is not restricted, and the compound of the present invention and the concomitant drug can be administered to an administration subject simultaneously, or may
15 be administered at different times. The dosage of the concomitant drug may be determined according to the dose clinically set, and can be appropriately selected depending on the administration subject, administration route, disease, combination and the like.

20 [0146]

Examples of the administration mode of the combined use of the compound of the present invention and the concomitant drug include the following methods: (1) The compound of the present invention and the concomitant drug are simultaneously produced
25 to give a single preparation, which is then administered. (2) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered simultaneously by the same administration route. (3) The compound of the present invention and the concomitant
30 drug are separately produced to give two kinds of preparations which are administered by the same administration route at different times. (4) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered simultaneously by
35 different administration routes. (5) The compound of the present

invention and the concomitant drug are separately produced to give two kinds of preparations which are administered by different administration routes at different times (e.g., the compound of the present invention and the concomitant drug are administered in this order, or in the reverse order). The dose of the concomitant drug is appropriately determined in accordance with its clinical dose, and the ratio of the compound of the present invention and the concomitant drug is appropriately determined depending on the administration subject, administration route, target disease, symptom, combination, and the like. For example, when the administration subject is human, the concomitant drug is used in 0.01 to 100 (parts by weight), relative to 1 part by weight of the compound of the present invention.

15 [0147]

The combination agent of the present invention has low toxicity and, for example, the compound of the present invention and/or the above-mentioned concomitant drug can be mixed, according to a method known *per se*, with a pharmacologically acceptable carrier to give pharmaceutical compositions, such as tablets (including sugar-coated tablet, film-coated tablet), powders, granules, capsules (including soft capsule), solutions, injections, suppositories, sustained release agents and the like, which can be safely administered orally or parenterally (e.g., local, rectum, venous, and the like). An injection can be administered by intravenous, intramuscular, subcutaneous or intra-organ administration, or directly to the lesion.

[0148]

As a pharmacologically acceptable carrier which may be used for preparing the combination agent of the present invention, those similar to the aforementioned pharmacologically acceptable carriers, that can be used for the production of the pharmaceutical agent of the present invention, can be mentioned. Where necessary, the aforementioned additives that can be used for the production of the pharmaceutical agent of the present

invention, such as preservatives, antioxidants, colorants, sweetening agents, adsorbents, wetting agents and the like can also be appropriately used in appropriate amounts.

[0149]

5 The compounding ratio of the compound of the present invention to the concomitant drug in the combination agent of the present invention can be appropriately set depending on the administration subject, administration route, diseases and the like.

10 For example, the content of the compound of the present invention in the combination agent of the present invention varies depending on the dosage form, and is usually from about 0.01 to 100% by weight, preferably from about 0.1 to 50% by weight, further preferably from about 0.5 to 20% by weight,
15 based on the entire preparation.

 The content of the concomitant drug in the combination agent of the present invention varies depending on the dosage form, and is usually from about 0.01 to 90% by weight, preferably from about 0.1 to 50% by weight, further preferably
20 from about 0.5 to 20% by weight, based on the entire preparation.

 The content of additives in the combination agent of the present invention varies depending on the dosage form, and is usually from about 1 to 99.99% by weight, preferably from about 10 to 90% by weight, based on the entire preparation.

25 When the compound of the present invention and the concomitant drug are separately prepared, the same content may be adopted.

[0150]

 These preparations can be produced by a method known *per se*, which is generally employed in the preparation process.
30

 For example, the compound of the present invention and the concomitant drug can be made into an aqueous injection together with a dispersing agent (e.g., Tween 80 (manufactured by Atlas Powder, US), HCO 60 (manufactured by Nikko Chemicals),
35 polyethylene glycol, carboxymethylcellulose, sodium alginate,

hydroxypropylmethylcellulose, dextrin and the like), a stabilizer (e.g., ascorbic acid, sodium pyrosulfite, and the like), a surfactant (e.g., Polysorbate 80, macrogol and the like), a solubilizer (e.g., glycerin, ethanol and the like), a
5 buffer (e.g., phosphoric acid and alkali metal salt thereof, citric acid and alkali metal salt thereof, and the like), an isotonizing agent (e.g., sodium chloride, potassium chloride, mannitol, sorbitol, glucose and the like), a pH adjuster (e.g., hydrochloric acid, sodium hydroxide and the like), a
10 preservative (e.g., ethyl paraoxybenzoate, benzoic acid, methylparaben, propylparaben, benzyl alcohol and the like), a dissolving agent (e.g., conc. glycerin, meglumine and the like), a solubilizing agent (e.g., propylene glycol, sucrose and the like), a soothing agent (e.g., glucose, benzyl alcohol and the
15 like), and the like, or can be dissolved, suspended or emulsified in a vegetable oil such as olive oil, sesame oil, cotton seed oil, corn oil and the like or a solubilizing agent such as propylene glycol and the like and prepared into an oily injection, whereby an injection is afforded.

20 [0151]

In addition, an excipient (e.g., lactose, sucrose, starch and the like), a disintegrating agent (e.g., starch, calcium carbonate and the like), a binder (e.g., starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone,
25 hydroxypropylcellulose and the like), a lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000 and the like) and the like may be added to the compound of the present invention or the concomitant drug, and the mixture can be compression-molded, according to a method known per se then if desirable,
30 the molded product can be coated by a method known per se for the purpose of masking of taste, enteric property or durability, to give a preparation for oral administration. As the coating agent, for example, hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene
35 glycol, Tween 80, Pluronic F68, cellulose acetate phthalate,

hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudoragit (methacrylic acid-acrylic acid copolymer, manufactured by Rohm, DE), pigment (e.g., iron oxide red, titanium dioxide, etc.) and the like can be used. The
5 preparation for oral administration may be any of an immediate-release preparation and a sustained release preparation.

[0152]

Moreover, the compound of the present invention and the concomitant drug can be made into an oily or aqueous solid,
10 semisolid or liquid suppository according to a method known per se, by mixing them with an oily substrate, aqueous substrate or aqueous gel substrate. As the above-mentioned oily substrate, for example, glycerides of higher fatty acid [e.g., cacao butter, Witepsols (manufactured by Dynamit Nobel, Germany), etc.],
15 glycerides of medium chain fatty acid [e.g., Miglyols (manufactured by Dynamit Nobel, Germany), etc.], or vegetable oils (e.g., sesame oil, soybean oil, cotton seed oil and the like), and the like are mentioned. Furthermore, as the aqueous substrate, for example, polyethylene glycol, propylene glycol
20 and the like are mentioned, and as the aqueous gel substrate, for example, natural gums, cellulose derivatives, vinyl polymers, acrylic acid polymers and the like are mentioned.

[0153]

As the above-mentioned sustained release preparation,
25 sustained release microcapsules and the like are mentioned. The sustained release microcapsule can be produced by a method known per se, for example, a method shown in the following [2].

[0154]

The compound of the present invention is preferably molded
30 into a preparation for oral administration such as a solid preparation (e.g., powder, granule, tablet, capsule) and the like, or molded into a preparation for rectal administration such as a suppository and the like. Particularly, a preparation for oral administration is preferable.

35 The concomitant drug can be made into the above-mentioned

drug form depending on the kind of the drug.

[0155]

[1] An injection of the compound of the present invention or the concomitant drug, and preparation thereof, [2] a sustained
5 release preparation or immediate-release preparation of the compound of the present invention or the concomitant drug, and preparation thereof, [3] a sublingual, buccal or intraoral quick integrating agent of the compound of the present
invention or the concomitant drug, and preparation thereof,
10 will be described below specifically.

[0156]

[1] Injection and preparation thereof

An injection prepared by dissolving the compound of the present invention or the concomitant drug into water is
15 preferable. This injection may be allowed to contain a benzoate and/or salicylate.

The injection is obtained by dissolving the compound of the present invention or the concomitant drug, and if desirable, a benzoate and/or salicylate, into water.

20 [0157]

As the above-mentioned salts of benzoic acid and salicylic acid, for example, salts of alkali metals such as sodium, potassium and the like, salts of alkaline earth metals such as calcium, magnesium and the like, ammonium salts,
25 meglumine salts, salts with organic bases such as tromethamol and the like, etc. are listed.

[0158]

The concentration of the compound of the present invention or the concomitant drug in an injection is from 0.5
30 to 50 w/v%, preferably from about 3 to 20 w/v%. The concentration of a benzoate or/and salicylate is from 0.5 to 50 w/v%, preferably from about 3 to 20 w/v%.

[0159]

The injection of the present invention appropriately
35 contains additives usually used in an injection, for example,

a stabilizer (e.g., ascorbic acid, sodium pyrosulfite and the like), a surfactant (e.g., Polysorbate 80, macrogol and the like), a solubilizer (e.g., glycerin, ethanol and the like), a buffer (e.g., phosphoric acid and alkali metal salt thereof, citric acid and alkali metal salt thereof, and the like), an isotonizing agent (e.g., sodium chloride, potassium chloride and the like), a dispersing agent (e.g., hydroxypropylmethylcellulose, dextrin), a pH regulator (e.g., hydrochloric acid, sodium hydroxide and the like), a preservative (e.g., ethyl parahydroxybenzoate, benzoic acid and the like), a dissolving agent (e.g., conc. glycerin, meglumine and the like), a solubilizing agent (e.g., propylene glycol, sucrose and the like), a soothing agent (e.g., glucose, benzyl alcohol and the like), and the like. These additives are generally blended in a proportion usually used in an injection.

[0160]

It is advantageous that pH of an injection be controlled from pH 2 to 12, preferably from pH 2.5 to 8.0, by addition of a pH regulator.

An injection is obtained by dissolving the compound of the present invention or the concomitant drug and if desirable, a benzoate and/or a salicylate, and if necessary, the above-mentioned additives into water. These may be dissolved in any order, and can be appropriately dissolved in the same manner as in a conventional method of producing an injection.

[0161]

An aqueous solution for injection may be advantageously heated, alternatively, for example, filter sterilization, high pressure heat sterilization and the like can be conducted in the same manner as for a usual injection, to provide an injection.

It may be advantageous that an aqueous solution for injection is subjected to high pressure heat sterilization at 100 to 121°C for 5 to 30 min.

Further, a preparation endowed with an antibacterial property of a solution may also be produced so that it can be used as a preparation which is divided and administered multiple-times.

5 [0162]

[2] Sustained release preparation or immediate-release preparation, and preparation thereof

A sustained release preparation is preferable which is obtained, if desirable, by coating a nucleus containing the
10 compound of the present invention or the concomitant drug with a film agent such as a water-insoluble substance, swellable polymer and the like. For example, a sustained release preparation for oral administration of once administration per day type is preferable.

15 [0163]

As the water-insoluble substance used in a film agent, there are listed, for example, cellulose ethers such as ethylcellulose, butylcellulose and the like, cellulose esters such as cellulose acetate, cellulose propionate and the like,
20 polyvinyl esters such as polyvinyl acetate, polyvinyl butyrate and the like, acrylic acid/methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylate/cinnamoethyl methacrylate/aminoalkyl methacrylate copolymers, polyacrylic acid, polymethacrylic acid, methacrylic acid alkylamide
25 copolymers, poly(methyl methacrylate), polymethacrylate, polymethacrylamide, aminoalkyl methacrylate copolymers, poly(methacrylic anhydride), glycidyl methacrylate copolymer, particularly, acrylic acid-based polymers such as Eudoragit (manufactured by Rohm Pharma) such as Eudoragit RS-100, RL-100,
30 RS-30D, RL-30D, RL-PO, RS-PO (ethyl acrylate/methyl methacrylate/trimethylchloride methacrylate/ethyl ammonium copolymer), Eudoragit NE-30D (methyl methacrylate/ethyl acrylate copolymer), and the like, hydrogenated oils such as hydrogenated castor oil (e.g., Lubri wax (manufactured by
35 Freund Corporation) and the like), waxes such as carnauba wax,

fatty acid glycerin ester, paraffin and the like, polyglycerin fatty acid esters, and the like.

[0164]

As the swellable polymer, polymers having an acidic dissociating group and showing pH dependent swell are preferable, and polymers having an acidic dissociating group, which manifest small swelling in acidic regions such as in stomach and large swelling in neutral regions such as in small intestine and large intestine, are preferable.

As such a polymer having an acidic dissociating group and showing pH dependent swell, cross-linkable polyacrylic acid polymers such as, for example, Carbomer 934P, 940, 941, 974P, 980, 1342 and the like, polycarbophil, calcium polycarbophil (all of which are manufactured by BF Goodrich), Hiviswako 103, 104, 105, 304 (all are manufactured by Wako Pure Chemical Industries, Ltd.), and the like, are listed.

[0165]

The film agent used in a sustained release preparation may further contain a hydrophilic substance.

As the hydrophilic substance, for example, polysaccharides which may contain a sulfate group such as pullulan, dextrin, alkali metal alginate and the like, polysaccharides having a hydroxyalkyl or carboxyalkyl such as hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose sodium and the like, methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, polyethylene glycol and the like can be mentioned.

[0166]

The content of a water-insoluble substance in the film agent of a sustained release preparation is from about 30 to about 90% (w/w), preferably from about 35 to about 80% (w/w), further preferably from about 40 to about 75% (w/w), the content of a swellable polymer is from about 3 to about 30% (w/w), preferably from about 3 to about 15% (w/w). The film agent may further contain a hydrophilic substance, and in

which case, the content of a hydrophilic substance in the film agent is about 50% (w/w) or less, preferably about 5 to about 40% (w/w), further preferably from about 5 to about 35% (w/w). This % (w/w) indicates % by weight based on a film agent composition which is obtained by removing a solvent (e.g., water, lower alcohols such as methanol, ethanol and the like) from a film agent solution.

[0167]

The sustained release preparation is produced by preparing a nucleus containing a drugs as exemplified below, then, coating the resulted nucleus with a film agent solution prepared by heat-solving a water-insoluble substance, swellable polymer and the like or by dissolving or dispersing it in a solvent.

[0168]

I. Preparation of nucleus containing drug

The form of nucleus containing a drug to be coated with a film agent (hereinafter, sometimes simply referred to as nucleus) is not particularly restricted, and preferably, the nucleus is formed into particles such as a granule or fine particle.

When the nucleus is composed of granules or fine particles, the average particle size thereof is preferably from about 150 to about 2000 μm , further preferably, from about 500 to about 1400 μm .

Preparation of the nucleus can be effected by a usual production method. For example, a suitable excipient, binding agent, disintegrating agent, lubricant, stabilizer and the like are mixed with a drug, and the mixture is subjected to a wet extrusion granulating method, fluidized bed granulating method or the like, to prepare a nucleus.

The content of drugs in a nucleus is from about 0.5 to about 95% (w/w), preferably from about 5.0 to about 80% (w/w), further preferably from about 30 to about 70% (w/w).

[0169]

As the excipient contained in the nucleus, for example, saccharides such as sucrose, lactose, mannitol, glucose and the like, starch, crystalline cellulose, calcium phosphate, corn starch and the like are used. Among them, crystalline
5 cellulose, corn starch are preferable.

[0170]

As the binding agent, for example, polyvinyl alcohol, hydroxypropylcellulose, polyethylene glycol, polyvinyl pyrrolidone, Pluronic F68, gum Arabic, gelatin, starch and the
10 like are used. As the disintegrating agent, for example, carboxymethylcellulose calcium (ECG505), croscarmellose sodium (Ac-Di-Sol), crosslinked polyvinylpyrrolidone (Crospovidone), low substituted hydroxypropylcellulose (L-HPC) and the like are used. Among them, hydroxypropylcellulose,
15 polyvinylpyrrolidone, lower substituted hydroxypropylcellulose are preferable. As the lubricant and coagulation inhibitor, for example, talc, magnesium stearate and inorganic salts thereof are used, and as the lubricant, polyethylene glycol and the like are used. As the stabilizer, acids such as
20 tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like, are used.

[0171]

A nucleus can also be prepared by, in addition to the above-mentioned productions method, for example, a rolling
25 granulation method in which a drug or a mixture of a drug with an excipient, lubricant and the like is added portionwise onto an inert carrier particle which is the core of the nucleus while spraying a binder dissolved in a suitable solvent such as water, lower alcohol (e.g., methanol, ethanol and the like)
30 and the like, a pan coating method, a fluidized bed coating method or a melt granulating method. As the inert carrier particle, for example, those made of sucrose, lactose, starch, crystalline cellulose or waxes can be used, and the average particle size thereof is preferably from about 100 μm to about
35 1500 μm .

[0172]

For separating a drug contained in a nucleus and a film agent, the surface of the nucleus may be coated with a protective agent. As the protective agent, for example, the above-mentioned hydrophilic substances, water-insoluble substances and the like are used. As the protective agent, preferably polyethylene glycol, and polysaccharides having a hydroxyalkyl or carboxyalkyl are used, more preferably, hydroxypropylmethylcellulose and hydroxypropylcellulose are used. The protective agent may contain, as stabilizer, acids such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like, and lubricants such as talc and the like. When the protective agent is used, the coating amount is from about 1 to about 15% (w/w), preferably from about 1 to about 10% (w/w), further preferably from about 2 to about 8% (w/w), based on the nucleus.

[0173]

The protective agent can be coated by a usual coating method, and specifically, the protective agent can be coated by spray-coating the nucleus, for example, by a fluidized bed coating method, pan coating method and the like.

[0174]

II. Coating of nucleus with film agent

A nucleus obtained in the above-mentioned step I is coated with a film agent solution obtained by heat-solving the above-mentioned water-insoluble substance and pH-dependent swellable polymer, and a hydrophilic substance, or by dissolving or dispersing them in a solvent, to give a sustained release preparation.

As the method for coating a nucleus with a film agent solution, for example, a spray coating method and the like are listed.

The composition ratio of a water-insoluble substance, swellable polymer or hydrophilic substance in a film agent solution is appropriately selected so that the contents of

these components in a coated film are the above-mentioned contents, respectively.

The coating amount of a film agent is from about 1 to about 90% (w/w), preferably from about 5 to about 50% (w/w),
5 further preferably from about 5 to about 35% (w/w), based on a nucleus (not including coating amount of protective agent).

[0175]

As the solvent in a film agent solution, water or an organic solvent can be used alone or in admixture thereof. In
10 the case of use in admixture, the mixing ratio of water to an organic solvent (water/organic solvent: by weight) can be varied in the range from 1 to 100%, and preferably from 1 to about 30%. The organic solvent is not particularly restricted providing it dissolves a water-insoluble substance, and for
15 example, lower alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol, n-butyl alcohol and the like, lower alkanone such as acetone and the like, acetonitrile, chloroform, methylene chloride and the like are used. Among them, lower alcohols are preferable, and ethyl alcohol and
20 isopropyl alcohol are particularly preferable. Water, and a mixture of water with an organic solvent are preferably used as a solvent for a film agent. In this case, if necessary, an acid such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like may also be added into
25 a film agent solution for stabilizing the film agent solution.

[0176]

An operation of coating by spray coating can be effected by a usual coating method, and specifically, it can be effected by coating a film agent solution onto a nucleus by a
30 fluidized bed coating method, pan coating method and the like. In this case, if necessary, talc, titanium oxide, magnesium stearate, calcium stearate, light anhydrous silicic acid and the like may also be added as a lubricant, and glycerin fatty acid ester, hydrogenated castor oil, triethyl citrate, cetyl
35 alcohol, stearyl alcohol and the like may also be added as a

plasticizer.

[0177]

After coating with a film agent, if necessary, an antistatic agent such as talc and the like may be mixed.

5 The immediate-release preparation may be liquid (solution, suspension, emulsion and the like) or solid (particle, pill, tablet and the like). As the immediate-release preparation, oral administration agents and parenteral administration agents such as an injection and the like are used, and oral
10 administration agents are preferable.

[0178]

The immediate-release preparation, usually, may contain, in addition to an active component drug, also carriers, additives and excipients conventionally used in the
15 pharmaceutical field (hereinafter, sometimes abbreviated as excipient). The excipient used is not particularly restricted providing it is an excipient ordinarily used as a preparation excipient. For example, as the excipient for an oral solid preparation, lactose, starch, corn starch, crystalline
20 cellulose (Avicel PH101, manufactured by Asahi Kasei Corporation, and the like), powder sugar, granulated sugar, mannitol, light anhydrous silicic acid, magnesium carbonate, calcium carbonate, L-cysteine and the like are listed, and preferably, corn starch and mannitol and the like are listed.
25 These excipients can be used alone or in combination of two or more. The content of the excipient is, for example, from about 4.5 to about 99.4 w/w%, preferably from about 20 to about 98.5 w/w%, further preferably from about 30 to about 97 w/w%, based on the total amount of the immediate-release preparation.

30 [0179]

The content of a drug in the immediate-release preparation can be appropriately selected in the range from about 0.5 to about 95w/w%, preferably from about 1 to about 60w/w% based on the total amount of the immediate-release
35 preparation.

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[0180]

When the immediate-release preparation is an oral solid preparation, it usually contains, in addition to the above-mentioned components, also a disintegrating agent. As this
5 disintegrating agent, for example, carboxymethylcellulose calcium (ECG-505, manufactured by Gotoku Yakuhin), croscarmellose sodium (e.g., Actisol, manufactured by Asahi Kasei Corporation), crospovidone (e.g., Kollidon CL, manufactured by BASF), low substituted hydroxypropylcellulose (manufactured by
10 Shin-Etsu Chemical Co., Ltd.), carboxymethylstarch (manufactured by Matsutani Kagaku K.K.), carboxymethylstarch sodium (Exprotab, manufactured by Kimura Sangyo), partially pregelatinized starch (PCS, manufactured by Asahi Kasei Corporation), and the like are used, and for example, those
15 which disintegrate a granule by absorbing water in contact with water, causing swelling, or making a channel between an effective ingredient and an excipient constituting the nucleus, can be used. These disintegrating agents can be used alone or in combination of two or more. The amount of the
20 disintegrating agent used is appropriately selected depending on the kind and blending amount of a drug used, design of releasing property, and the like, and for example, from about 0.05 to about 30 w/w%, preferably from about 0.5 to about 15 w/w%, based on the total amount of the immediate-release
25 preparation.

[0181]

When the immediate-release preparation is an oral solid preparation, it may further contain, in addition to the above-mentioned composition, if desired, additives conventional in
30 solid preparations. As such an additive, there are used, for example, a binder (e.g., sucrose, gelatin, gum Arabic powder, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, polyvinylpyrrolidone, pullulan, dextrin and the like), a
35 lubricant (e.g., polyethylene glycol, magnesium stearate, talc,

light anhydrous silicic acid (e.g., Aerosil (manufactured by Nippon Aerosil))), a surfactant (e.g., anionic surfactants such as sodium alkylsulfate and the like, nonionic surfactants such as polyoxyethylene fatty acid ester and polyoxyethylene sorbitan fatty acid ester, polyoxyethylene castor oil derivatives and the like), a colorant (e.g., tar coloring matter, caramel, iron oxide red, titanium oxide, riboflavins), if necessary, an appetizing agent (e.g., sweetening agent, flavoring agent and the like), an adsorbent, preservative, wetting agent, antistatic agent, and the like. Further, as the stabilizer, an organic acid such as tartaric acid, citric acid, succinic acid, fumaric acid and the like may also be added.

[0182]

As the above-mentioned binder, hydroxypropylcellulose, polyethylene glycol and polyvinylpyrrolidone and the like are preferably used.

[0183]

The immediate-release preparation can be prepared by, based on a usual technology of producing preparations, mixing the above-mentioned components, and if necessary, further kneading the mixture, and molding it. The above-mentioned mixing is conducted by generally used methods, for example, mixing, kneading and the like. Specifically, when a immediate-release preparation is formed, for example, into a particle, it can be prepared, according to the same means as in the above-mentioned method for preparing a nucleus of a sustained release preparation, by mixing the components using a vertical granulator, universal kneader (manufactured by Hata Tekkosho), fluidized bed granulator FD-5S (manufactured by Powrex Corporation), and the like, and then, granulating the mixture by a wet extrusion granulation method, fluidized bed granulation method and the like.

[0184]

Thus obtained immediate-release preparation and sustained release preparation may be themselves made into products or

made into products appropriately together with preparation excipients and the like, separately, by an ordinary method, then, may be administered simultaneously or may be administered in combination at any administration interval, or
5 they may be themselves made into one preparation for oral administration (e.g., granule, fine particle, tablet, capsule and the like) or made into one preparation for oral administration appropriately together with preparation excipients and the like. It may also be permissible that they
10 are made into granules or fine particles, and filled in the same capsule to be used as a preparation for oral administration.

[0185]

[3] Sublingual, buccal or intraoral quick disintegrating agent
15 and preparation thereof

Sublingual, buccal or intraoral quick disintegrating agents may be a solid preparation such as tablet and the like, or may be an oral mucosa membrane patch (film).

As the sublingual, buccal or intraoral quick
20 disintegrating agent, a preparation containing the compound of the present invention or the concomitant drug and an excipient is preferable. It may contain also auxiliary agents such as a lubricant, isotonizing agent, hydrophilic carrier, water-dispersible polymer, stabilizer and the like. Further, for
25 easy absorption and increased *in vivo* use efficiency, β -cyclodextrin or β -cyclodextrin derivatives (e.g., hydroxypropyl- β -cyclodextrin and the like) and the like may also be contained.

[0186]

30 As the above-mentioned excipient, lactose, sucrose, D-mannitol, starch, crystalline cellulose, light anhydrous silicic acid and the like are listed. As the lubricant, magnesium stearate, calcium stearate, talc, colloidal silica and the like are listed, and particularly, magnesium stearate
35 and colloidal silica are preferable. As the isotonizing agent,

sodium chloride, glucose, fructose, mannitol, sorbitol, lactose, saccharose, glycerin, urea and the like are listed, and particularly, mannitol is preferable. As the hydrophilic carrier, swellable hydrophilic carriers such as crystalline
5 cellulose, ethylcellulose, crosslinkable polyvinylpyrrolidone, light anhydrous silicic acid, silicic acid, dicalcium phosphate, calcium carbonate and the like are listed, and particularly, crystalline cellulose (e.g., microcrystalline cellulose and the like) is preferable. As the water-
10 dispersible polymer, gums (e.g., gum tragacanth, acacia gum, cyamopsis gum), alginates (e.g., sodium alginate), cellulose derivatives (e.g., methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose), gelatin, water-soluble starch,
15 polyacrylic acids (e.g., Carbomer), polymethacrylic acid, polyvinyl alcohol, polyethylene glycol, polyvinylpyrrolidone, polycarbophil, ascorbic acid, palmitates and the like are listed, and hydroxypropylmethylcellulose, polyacrylic acid, alginate, gelatin, carboxymethylcellulose,
20 polyvinylpyrrolidone, polyethylene glycol and the like are preferable. Particularly, hydroxypropylmethylcellulose is preferable. As the stabilizer, cysteine, thiosorbitol, tartaric acid, citric acid, sodium carbonate, ascorbic acid, glycine, sodium sulfite and the like are listed, and
25 particularly, citric acid and ascorbic acid are preferable.

[0187]

The sublingual, buccal or intraoral quick disintegrating agent can be produced by mixing the compound of the present invention or the concomitant drug and an excipient by a method
30 known *per se*. Further, if desired, the above-mentioned auxiliary agents such as a lubricant, isotonizing agent, hydrophilic carrier, water-dispersible polymer, stabilizer, colorant, sweetening agent, preservative and the like may be mixed. The sublingual, buccal or intraoral quick
35 disintegrating agent is obtained by mixing the above-mentioned

components simultaneously or at a time interval, then
subjecting the mixture to tablet-making molding under pressure.
For obtaining suitable hardness, it may also be permissible
that the materials are moistened by using a solvent such as
5 water, alcohol and the like if desired before and after the
tablet making process, and after the molding, the materials
are dried, to obtain a product.

[0188]

In the case of molding into a mucosa membrane patch
10 (film), the compound of the present invention or the
concomitant drug and the above-mentioned water-dispersible
polymer (preferably, hydroxypropylcellulose,
hydroxypropylmethylcellulose), excipient and the like are
dissolved in a solvent such as water and the like, and the
15 resulted solution is cast to give a film. Further, additives
such as a plasticizer, stabilizer, antioxidant, preservative,
colorant, buffer, sweetening agent and the like may also be
added. For imparting suitable elasticity to the film, glycols
such as polyethylene glycol, propylene glycol and the like may
20 be contained, or for enhancing adhesion of the film to an
intraoral mucosa membrane lining, a bio-adhesive polymer (e.g.,
polycarbophil, carbopol) may also be contained. In the casting,
a solution is poured on the non-adhesive surface, spread to
uniform thickness (preferably, about 10 to 1000 micron) by an
25 application tool such as a doctor blade and the like, then,
the solution is dried to form a film. It may be advantageous
that thus formed film is dried at room temperature or under
heat, and cut into a desired area.

[0189]

30 As the preferable intraoral quick disintegrating agent,
there are listed solid quick scattering dose agents composed
of a network body comprising the compound of the present
invention or the concomitant drug, and a water-soluble or
water-diffusible carrier which is inert to the compound of the
35 present invention or concomitant drug, are listed. This

network body is obtained by sublimating a solvent from the solid composition constituted of a solution prepared by dissolving the compound of the present invention or the concomitant drug in a suitable solvent.

5 [0190]

It is preferable that the composition of an intraoral quick disintegrating agent contains a matrix forming agent and a secondary component, in addition to the compound of the present invention or the concomitant drug.

10 [0191]

Examples of the matrix forming agent include gelatins, dextrans, animal proteins or vegetable proteins such as soybean, wheat and psyllium seed protein and the like; rubber substances such as gum Arabic, guar gum, agar, xanthan and the like; polysaccharides; alginic acids; carboxymethylcelluloses; carageenans; dextrans; pectines; synthetic polymers such as polyvinylpyrrolidone and the like; substances derived from a gelatin-gum Arabic complex, and the like. Further, saccharides such as mannitol, dextrose, lactose, galactose, trehalose and the like; cyclic saccharides such as cyclodextrin and the like; inorganic salts such as sodium phosphate, sodium chloride and aluminum silicate and the like; amino acids having 2 to 12 carbon atoms such as glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine, L-phenylalanine and the like, are contained.

[0192]

One or more of the matrix forming agents can be introduced in a solution or suspension before solidification. Such as matrix forming agent may be present in addition to a surfactant, or may be present while a surfactant being excluded. The matrix forming agents aid to maintain the compound of the present invention or the concomitant drug in the solution or suspension in diffused condition, in addition to formation of the matrix.

35 [0193]

The composition may contain secondary components such as a preservative, antioxidant, surfactant, thickening agent, colorant, pH controlling agent, flavoring agent, sweetening agent, food taste masking agent and the like. As the suitable
5 colorant, there are listed red, black and yellow iron oxides, and FD & C dyes such as FD & C Blue 2, FD & C Red 40 and the like manufactured by Ellis and Everard. Examples of the suitable flavoring agent include mint, raspberry, licorice, orange, lemon, grapefruit, caramel, vanilla, cherry, grape
10 flavor and combinations thereof. Examples of the suitable pH controlling agent include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Examples of the suitable sweetening agent include aspartame, acesulfame K and thaumatin and the like. Examples of the suitable food
15 taste masking agent include sodium bicarbonate, ion exchange resin, cyclodextrin-inclusion compounds, adsorbent substances and microcapsulated apomorphine.

[0194]

The preparation contains the compound of the present
20 invention or the concomitant drug in an amount usually from about 0.1 to about 50% by weight, preferably from about 0.1 to about 30% by weight, and preferable are preparations (such as the above-mentioned sublingual agent, buccal and the like) which can dissolve 90% or more of the compound of the present
25 invention or the concomitant drug (into water) within the time range of about 1 to about 60 min, preferably of about 1 to about 15 min, more preferably of about 2 to about 5 min, and intraoral quick disintegrating preparations which are disintegrated within the range of 1 to 60 sec, preferably of 1
30 to 30 sec, further preferably of 1 to 10 sec, after placed in an oral cavity.

[0195]

The content of the above-mentioned excipient in the whole preparation is from about 10 to about 99% by weight,
35 preferably from about 30 to about 90% by weight. The content

of β -cyclodextrin or β -cyclodextrin derivative in the whole preparation is from 0 to about 30% by weight. The content of the lubricant in the whole preparation is from about 0.01 to about 10% by weight, preferably from about 1 to about 5% by weight. The content of the isotonizing agent in the whole preparation is from about 0.1 to about 90% by weight, preferably, from about 10 to about 70% by weight. The content of the hydrophilic carrier in the whole preparation is from about 0.1 to about 50% by weight, preferably, from about 10 to about 30% by weight. The content of the water-dispersible polymer in the whole preparation is from about 0.1 to about 30% by weight, preferably, from about 10 to about 25% by weight. The content of the stabilizer in the whole preparation is from about 0.1 to about 10% by weight, preferably, from about 1 to 5% by weight. The above-mentioned preparation may further contain additives such as a colorant, sweetening agent, preservative and the like, if necessary.

[0196]

The dosage of a combination agent of the present invention differs depending on the kind of a compound of the present invention, age, body weight, condition, drug form, administration method, administration period and the like, and for example, for one cancer patient (adult, body weight: about 60 kg), the combination agent is administered intravenously, at a dose of about 0.01 to about 1000 mg/kg/day, preferably about 0.01 to about 100 mg/kg/day, more preferably about 0.1 to about 100 mg/kg/day, particularly about 0.1 to about 50 mg/kg/day, especially about 1.5 to about 30 mg/kg/day, in terms of the compound of the present invention or the concomitant drug, respectively, once or several times in division a day. Of course, since the dose as described above varies depending on various conditions, amounts smaller than the above-mentioned dosage may sometimes be sufficient, further, amounts over that range sometimes have to be administered.

[0197]

The amount of the concomitant drug can be set at any value unless side effects are problematical. The daily dosage in terms of the concomitant drug differs depending on the severity of the symptom, age, sex, body weight, sensitivity difference of the administration subject, administration period, interval, and nature, pharmacy, kind of the pharmaceutical preparation, kind of effective ingredient, and the like, and not particularly restricted, and the amount of a drug is, in the case of oral administration for example, usually from about 0.001 to 2000 mg, preferably from about 0.01 to 500 mg, further preferably from about 0.1 to 100 mg, per 1 kg body weight of a mammal, which is usually administered once to 4-times in division a day.

[0198]

In administration of a combination agent of the present invention, the compound of the present invention may be administered after administration of the concomitant drug or the concomitant drug may be administered after administration of the compound of the present invention, though they may be administered simultaneously. When administered at a time interval, the interval differs depending on the effective ingredient to be administered, drug form and administration method, and for example, when the concomitant drug is administered first, a method in which the compound of the present invention is administered within time range of from 1 min to 3 days, preferably from 10 min to 1 day, more preferably from 15 min to 1 hr after administration of the concomitant drug is exemplified. When the compound of the present invention is administered first, a method in which the concomitant drug is administered within time range of from 1 min to 1 day, preferably from 10 min to 6 hrs, more preferably from 15 min to 1 hr after administration of the compound of the present invention is exemplified.

[0199]

In a preferable administration method, for example, the concomitant drug which has been molded into an oral

administration preparation is administered orally at a daily dose of about 0.001 to 200 mg/kg, and about 15 min later, the compound of the present invention which has been molded into an oral administration preparation is administered orally at a
5 daily dose of about 0.005 to 100 mg/kg.

[0200]

Furthermore, the compound of the present invention or the combination agent of the present invention can be used concurrently with a non-drug therapy. To be precise, the
10 compound of the present invention or the combination agent of the present invention can be combined with a non-drug therapy such as (1) surgery, (2) hypertensive chemotherapy using angiotensin II etc., (3) gene therapy, (4) thermotherapy, (5) cryotherapy, (6) laser cauterization, (7) radiotherapy, and the
15 like.

[0201]

For example, by using the compound of the present invention or the combination agent of the present invention before or after an surgery and the like, or before or after a
20 combined treatment of two or three kinds thereof, effects such as prevention of emergence of resistance, prolongation of Disease-Free Survival, suppression of cancer metastasis or recurrence, prolongation of life and the like can be afforded.

[0202]

25 In addition, it is possible to combine a treatment with the compound of the present invention or the combination agent of the present invention with a supportive therapy [(i) administration of antibiotic (e.g., β -lactam type such as pansporin and the like, macrolide type such as clarithromycin
30 and the like etc.) for the complication with various infectious diseases, (ii) administration of high-calorie transfusion, amino acid preparation or general vitamin preparation for the improvement of malnutrition, (iii) administration of morphine for pain mitigation, (iv) administration of a pharmaceutical
35 agent for ameliorating side effects such as nausea, vomiting,

anorexia, diarrhea, leucopenia, thrombocytopenia, decreased hemoglobin concentration, hair loss, hepatopathy, renopathy, DIC, fever and the like and (v) administration of a pharmaceutical agent for suppressing multiple drug resistance of cancer and the
5 like].

[0203]

Preferably, the compound of the present invention or the combination agent of the present invention is administered orally (including sustained-release preparations), intravenously
10 (including boluses, infusions and clathrates), subcutaneously and intramuscularly (including boluses, infusions and sustained-release preparations), transdermally, intratumorally or proximally before or after the above-described treatment is conducted.

15 [0204]

As a period for administering the compound of the present invention or the combination agent of the present invention before the surgery, etc., for example, it can be administrated 1-time about 30 min to 24 hrs before the surgery, etc., or in 1
20 to 3 cycles about 3 months to 6 months before the surgery, etc. In this way, the surgery, etc. can be conducted easily because, for example, a cancer tissue would be reduced by administering the compound of the present invention or the combination agent of the present invention before the surgery, and the like.

25 [0205]

As a period for administering the compound of the present invention or the combination agent of the present invention after the surgery, etc., for example, it can be administrated repeatedly per a few weeks to 3 months, about 30 min to 24 hrs
30 after the surgery, and the like. In this way, it enhances the effect of the surgery, etc. by administering the compound of the present invention or the combination agent of the present invention after the surgery, and the like.

35 **Examples**

[0206]

The present invention is explained in detail in the following by referring to Reference Examples, Examples, Formulation Examples and Experimental Examples, which are not
5 to be construed as limitative.

[0207]

In the Reference Examples and Examples, the purity of the compounds was measured under the following HPLC conditions.
measurement device: SHIMADZU Corporation LC-10 Avp system
10 column: CAPSEL PAK C18UG120 S-3 μ m, 2.0 X 50 mm
solvent: Solution A; 0.1% trifluoroacetic acid-containing water,
Solution B; 0.1% trifluoroacetic acid-containing acetonitrile
15 gradient cycle: 0.00 min (Solution A/Solution B=90/10), 4.00 min (Solution A/Solution B=5/95), 5.50 min (Solution A/Solution B=5/95), 5.51 min (Solution A/Solution B=90/10), 8.00 min (Solution A/Solution B=90/10)
injection volume: 2 μ l
20 flow rate: 0.5 ml/min
detection method: UV 220 nm

In the Reference Examples and Examples, the purification of the compounds by preparative HPLC was performed under the following conditions.

25 1) measurement device: Gilson Company Inc., High Throughput Purification System
column: YMC CombiPrep ODS-A, S-5 μ m, 50 X 20 mm
detection method: UV 220 nm
solvent: Solution A; 0.1% trifluoroacetic acid-containing
30 water,

Solution B; 0.1% trifluoroacetic acid-containing acetonitrile
gradient cycle: representative example 0.00 min (Solution A/Solution B=98/2), 1.00 min (Solution A/Solution B=98/2),
35 5.20 min (Solution A/Solution B=0/100), 6.40 min (Solution

A/Solution B=0/100), 6.50 min (Solution A/Solution B=98/2),
6.60 min (Solution A/Solution B=98/2), flow rate: 25 mL/min,
or 0.00 min (Solution A/Solution B= 90/10), 1.00 min (Solution
A/Solution B= 90/10), 4.00 min (Solution A/Solution B= 10/95),
5 8.50 min (Solution A/Solution B= 10/95), 8.60 min (Solution
A/Solution B= 90/10), 8.70 min (Solution A/Solution B= 90/10)
flow rate: 20 ml/min

2) measurement device: Gilson Company Inc., High Throughput
Purification System

10 column: YMC CombiPrep, ProC18 RS, S-5 μ m, 20 X 50 mm (YMC)
solvent: SOLUTION A; 10 mM ammonium carbonate-containing water,
SOLUTION B; acetonitrile
gradient cycle: 0.00 min (SOLUTION A/SOLUTION B=95/5), 2.00
min (SOLUTION A/SOLUTION B=95/5), 4.02 min (SOLUTION
15 A/SOLUTION B=5/95), 6.40 min (SOLUTION A/SOLUTION B=5/95),
6.50 min (SOLUTION A/SOLUTION B=95/5), 8.00 min (SOLUTION
A/SOLUTION B=95/5)

3) measurement device: Gilson Company Inc., High Throughput
Purification System

20 column: YMC CombiPrep, ProC18 RS, S-5 μ m, 20 X 50 mm (YMC)
solvent: SOLUTION A; 0.1% trifluoroacetic acid-containing
water,
SOLUTION B; 0.1% trifluoroacetic acid-containing
acetonitrile

25 gradient cycle: 0.00 min (SOLUTION A/SOLUTION B=98/2), 1.00
min (SOLUTION A/SOLUTION B=98/2), 5.20 min (SOLUTION
A/SOLUTION B=60/40), 5.40 min (SOLUTION A/SOLUTION B=5/95),
6.40 min (SOLUTION A/SOLUTION B=5/95), 6.50 min (SOLUTION
A/SOLUTION B=98/2), 6.60 min (SOLUTION A/SOLUTION B=98/2)

30 injection volume: 500 μ l, flow rate: 20 ml/min, detection
method: UV 220 nm, 254 nm

In the Reference Examples and Examples, mass spectrum
(MS) was measured under the following conditions.

measurement device: Micromass platform II or Waters ZMD
35 ionization method: Atmospheric Pressure Chemical Ionization:

APCI or electron impact ionization method (Electron Spray Ionization: ESI)

In the Reference Examples and Examples, HPLC-mass spectrum (LC-MS) was measured under the following conditions.

5 1) measurement device: Micromass ZMD, Agilent Technologies HP1100 and 1200 LC/MSD

column: CAPCELL PAK C18UG120, S-3 μ m, 1.5 X 35 mm

solvent: SOLUTION A; 0.05% trifluoroacetic acid-containing water,

10 SOLUTION B; 0.04% trifluoroacetic acid-containing acetonitrile

gradient cycle: 0.00 min (Solution A/Solution B=90/10), 2.00

min (Solution A/Solution B=5/95), 2.75 min (Solution

A/Solution B=5/95), 2.76 min (Solution A/Solution B=90/10),

15 3.45 min (Solution A/Solution B=90/10)

injection volume: 2 μ l

flow rate: 0.5 ml/min

detection method: UV 220 nm

ionization method: electron impact ionization method (Electron

20 Spray Ionization: ESI)

2) measurement device: Waters, 4-ch LC/MS system with MUX

column: CAPCELL PAK C18 UG-120, S-3 μ m, 1.5 X 35 mm (Shiseido Co., Ltd.)

solvent: SOLUTION A; 5 mM ammonium acetate-containing water,

25 SOLUTION B; 5 mM ammonium acetate-containing acetonitrile

gradient cycle: gradient: 0.00 min (SOLUTION A/SOLUTION

B=100/0), 2.00 min (SOLUTION A/SOLUTION B=0/100), 3.00 min

(SOLUTION A/SOLUTION B=0/100), 3.01 min (SOLUTION A/SOLUTION

30 B=100/0), 3.30 min (SOLUTION A/SOLUTION B=100/0)

injection volume: 2 μ L, flow rate: 0.5 mL/min, detection

method: UV 220 nm

ionization method: electrospray ionization method (ESI)

measurement mode: full scan (positive+negative ions)

35 measured mass value range: m/z=150 - 750

¹H-NMR spectrum was measured using tetramethylsilane as the internal standard, using BRUKER AVANCE DPX-300 (300 MHz), AV300 (300MHz), AV400 (400 MHz) and VARIAN Mercury-300 (300 MHz), and all δ values are expressed in ppm.

5 As the Microwave reaction apparatus, Emrys Optimizer, Biotage Japan Ltd. was used.

Unless otherwise specified, the numerical value of mixed solvent shows a volume mixing ratio of each solvent. Unless otherwise specified, % means weight %. While the room
10 temperature (ambient temperature) in the present specification means a temperature of from about 10°C to about 35°C, it is not particularly strictly limited.

[0208]

Other abbreviations used in the specification mean the
15 following:

s: singlet

d: doublet

t: triplet

q: quartet

20 m: multiplet

sext: sextet

br: broad

J: coupling constant

Hz: Hertz

25 CDCl₃: deuterated chloroform

DMSO-d₆: dimethyl sulfoxide-d₆

CD₃OD: deuterated methanol

¹H-NMR: proton nuclear magnetic resonance

LC/MS: liquid chromatography-mass spectrometry spectrum

30 DMF: N,N-dimethylformamide

DMSO: dimethyl sulfoxide

THF: tetrahydrofuran

WSCD: water-soluble carbodiimide (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) hydrochloride

35 HOBt: 1-hydroxybenzotriazole

Boc: tert-butoxycarbonyl

K₂CO₃: potassium carbonate

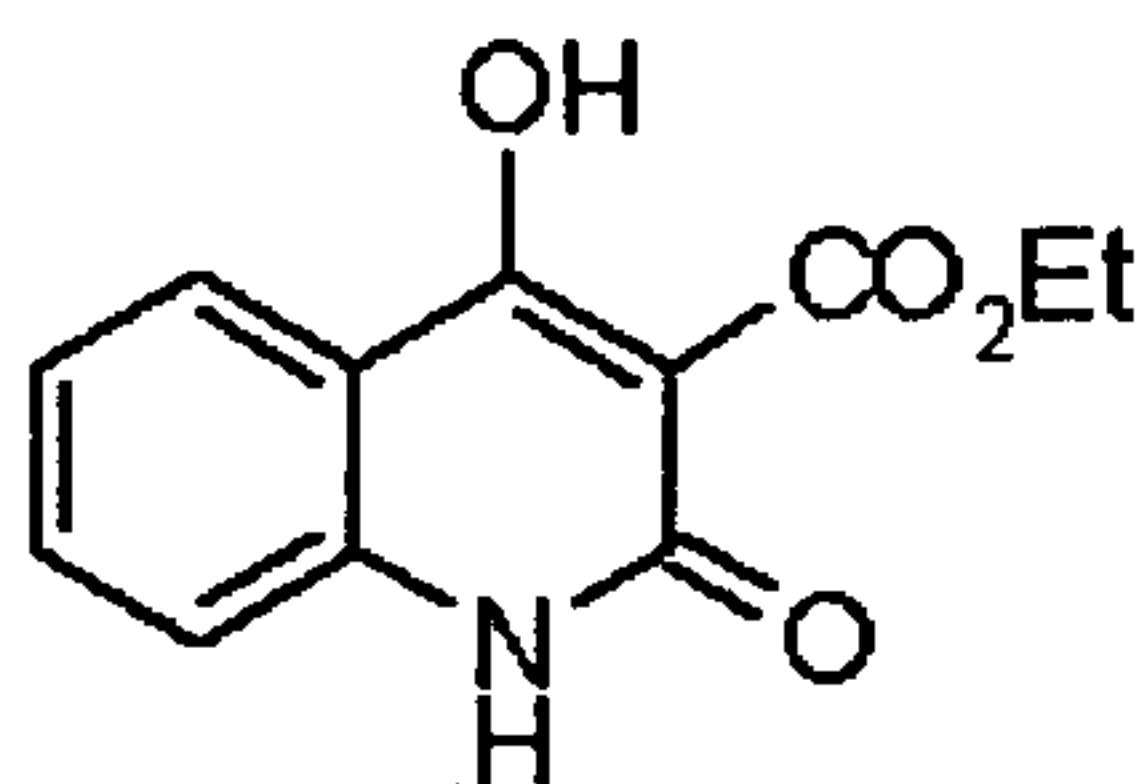
M: mol concentration

[0209]

5 Reference Example 1

Production of ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate

[0210]



10 [0211]

To a solution of methyl anthranilate (121 g, 0.8 mol) and diethyl malonate (128 g, 0.8 mol) in ethanol (900 mL) was added a 20% solution (274 g) of sodium ethoxide in ethanol, and the mixture was stirred at room temperature for 30 min.

15 Ethanol was evaporated, and the mixture was stirred at 140°C for 12 hr. After cooling, the obtained solid was washed with diethyl ether, and dissolved in water. Insoluble materials were filtered off, the filtrate was acidified with 5N hydrochloric acid, and the precipitated solid was collected by
20 filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (161 g, 86%) as a pale-yellow powder.

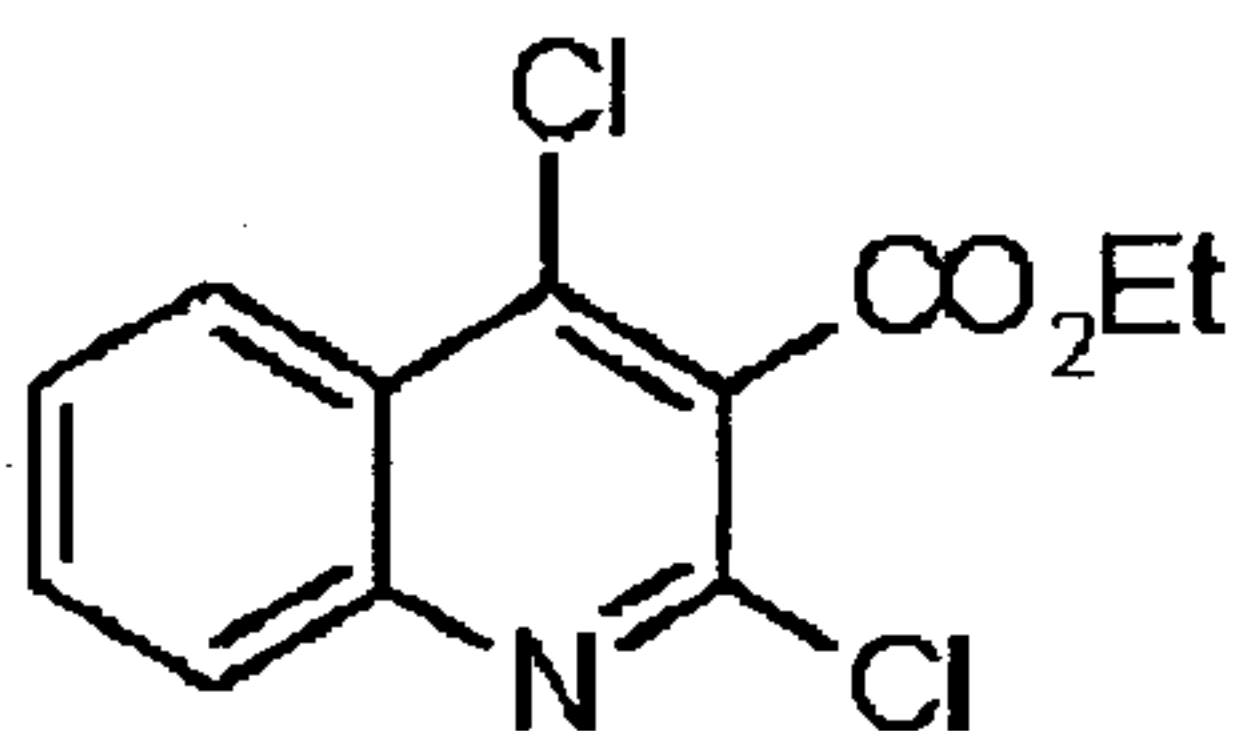
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.31 (3H, t, J = 7.1 Hz), 4.34 (2H, q, J = 7.1 Hz), 7.19-7.29 (2H, m), 7.63 (1H, td, J = 7.8, 1.2
25 Hz), 7.94 (1H, d, J = 8.1 Hz), 11.51 (1H, br s), 13.40 (1H, br s).

[0212]

Reference Example 2

Production of ethyl 2,4-dichloroquinoline-3-carboxylate

30 [0213]



[0214]

A mixture of the compound of Reference Example 1 (75 g, 0.32 mol) and phosphorus oxychloride (200 mL) was stirred at 110°C for 6 hr. After cooling, the reaction mixture was concentrated under reduced pressure, the residue was dissolved in a small amount of ethyl acetate and the mixture was poured into ice water. The obtained mixture was extracted with ethyl acetate, and the extract was washed successively with 1N aqueous sodium hydroxide solution, water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=1/5) to give the title compound (68 g, 79%) as a white solid.

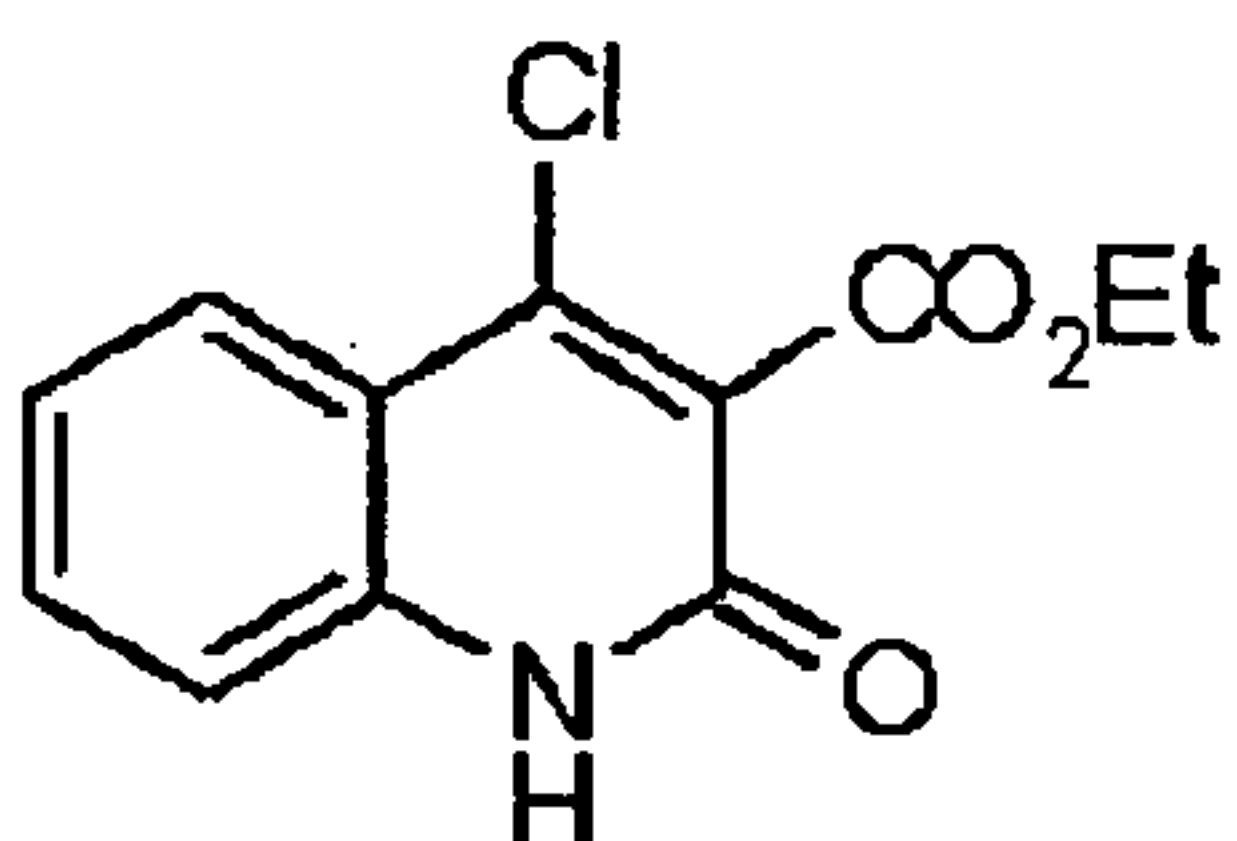
¹H-NMR (300 MHz, CDCl₃) δ: 1.47 (3H, t, J = 7.2 Hz), 4.54 (2H, q, J = 7.2 Hz), 7.71 (1H, t, J = 7.5 Hz), 7.85 (1H, t, J = 7.5 Hz), 8.06 (1H, d, J = 8.2 Hz), 8.24 (1H, d, J = 8.2 Hz).

[0215]

Reference Example 3

Production of ethyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate

[0216]



[0217]

A mixture of the compound of Reference Example 2 (68.0 g, 0.25 mol) and sodium acetate (21.7 g, 0.26 mol) in acetic acid (200 mL) was stirred at 120°C for 20 hr. After cooling, the reaction mixture was added to water, and the precipitated solid was collected by filtration. The obtained solid was

washed with water, and dried under reduced pressure to give the title compound (58.8 g, 94%) as a white solid.

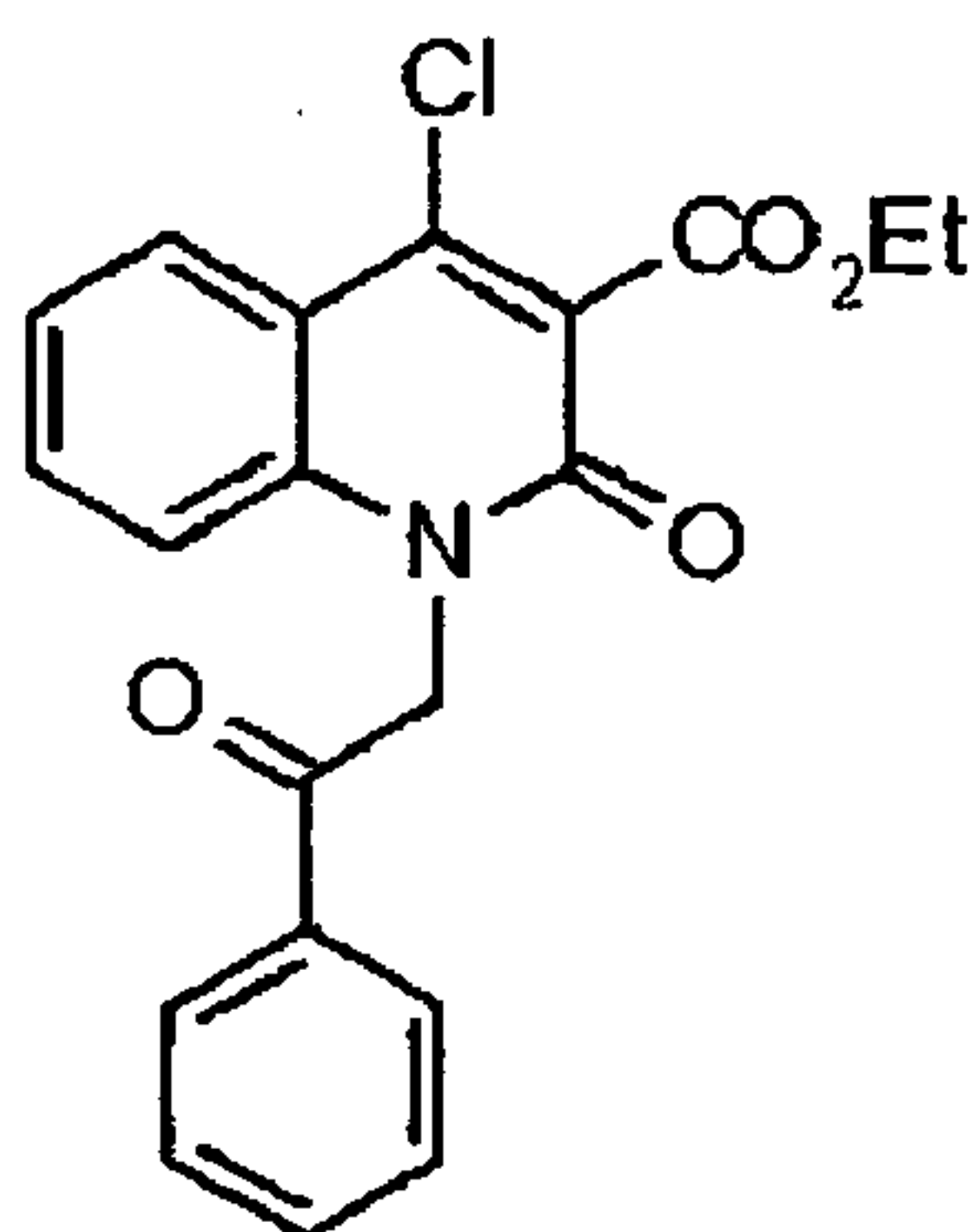
¹H-NMR (300 MHz, CDCl₃) δ: 1.46 (3H, t, J = 7.2 Hz), 4.53 (2H, q, J = 7.2 Hz), 7.34 (1H, t, J = 7.8 Hz), 7.43 (1H, d, J = 8.1 Hz), 7.63 (1H, t, J = 7.8 Hz), 8.00 (1H, d, J = 8.1 Hz), 12.41 (1H, br s).

[0218]

Reference Example 4

Production of ethyl 4-chloro-2-oxo-1-(2-oxo-2-phenylethyl)-
1,2-dihydroquinoline-3-carboxylate

[0219]



[0220]

To a solution of the compound of Reference Example 3 (10.0 g, 39.7 mmol) in DMF (160 mL) was added sodium hydride (60% in oil, 1.7 g, 41.7 mmol) under ice-cooling, and the mixture was stirred for 15 min. Phenacyl bromide (8.7 g, 43.7 mmol) was added to the obtained mixture under ice-cooling, and the mixture was stirred for 1 hr. The reaction mixture was added to water (1.5 L), and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluate; ethyl acetate/hexane=1/2 - 1/1) to give the title compound (10.5 g, 71%) as a pale-yellow solid.

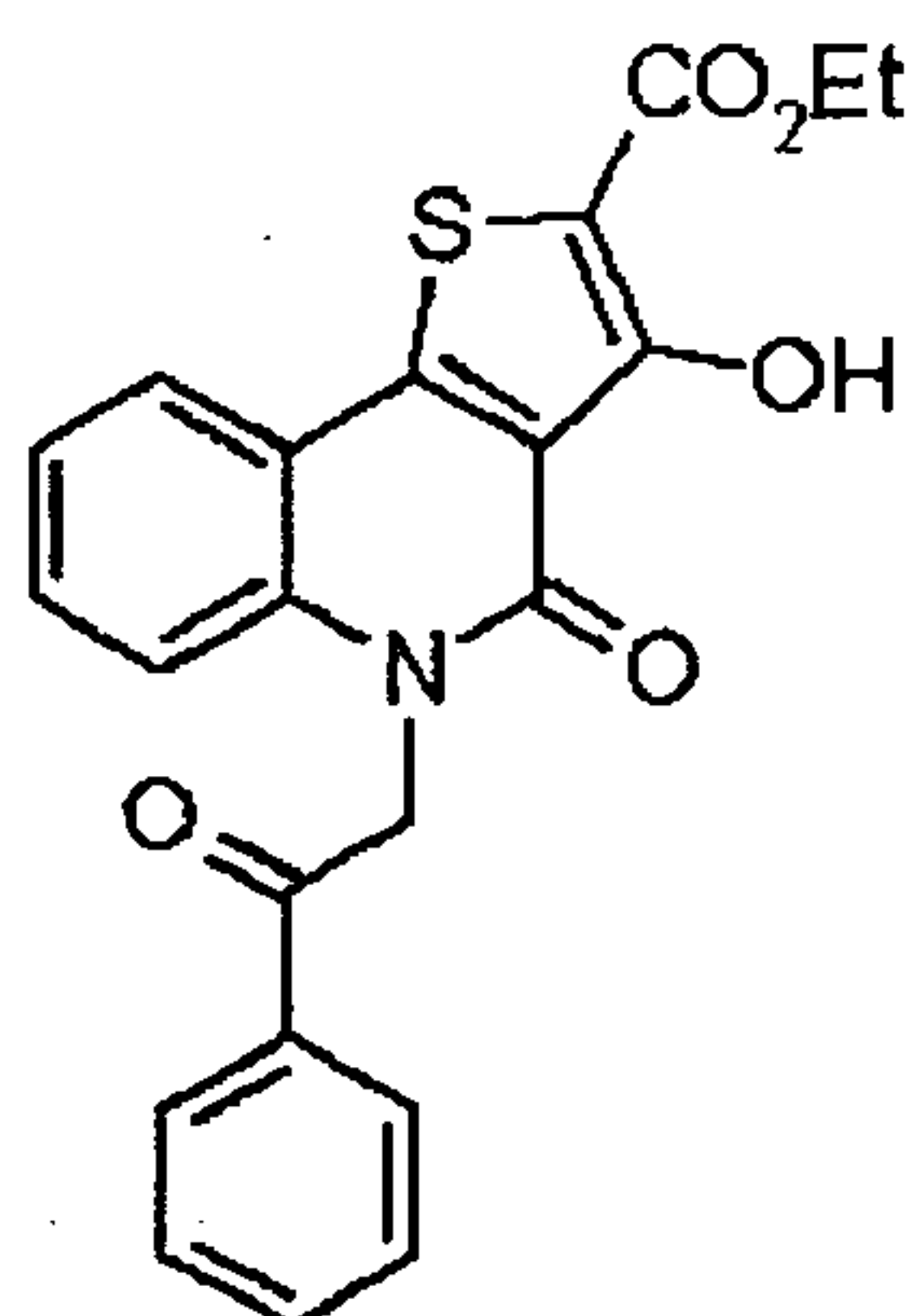
¹H-NMR (300 MHz, CDCl₃) δ: 1.42 (3H, t, J = 7.2 Hz), 4.47 (2H, q, J = 7.2 Hz), 5.80 (2H, s), 7.02 (1H, d, J = 8.1 Hz), 7.34 (1H, t, J = 7.8 Hz), 7.53-7.60 (3H, m), 7.65-7.70 (1H, m), 8.06-8.13 (3H, m).

[0221]

Reference Example 5

Production of ethyl 3-hydroxy-4-oxo-5-(2-oxo-2-phenylethyl)-
4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

5 [0222]



[0223]

A 20% solution (17.2 g, 50.5 mmol) of sodium ethoxide in ethanol was diluted with ethanol (50 mL), ethyl thioglycolate
10 (6.1 g, 50.5 mmol) was added to the obtained solution, and the mixture was stirred at room temperature for 5 min. The compound of Reference Example 4 (9.3 g, 25.3 mmol) was added to the mixture, and the mixture was stirred at room temperature for 18 hr. The reaction mixture was diluted with
15 ice water (50 mL), 2N hydrochloric acid (30 mL) was added and the mixture was stirred for 30 min. The precipitated solid was collected by filtration, washed with water and diethyl ether, and dried under reduced pressure to give the title compound (10.0 g, 96%) as a white powder.

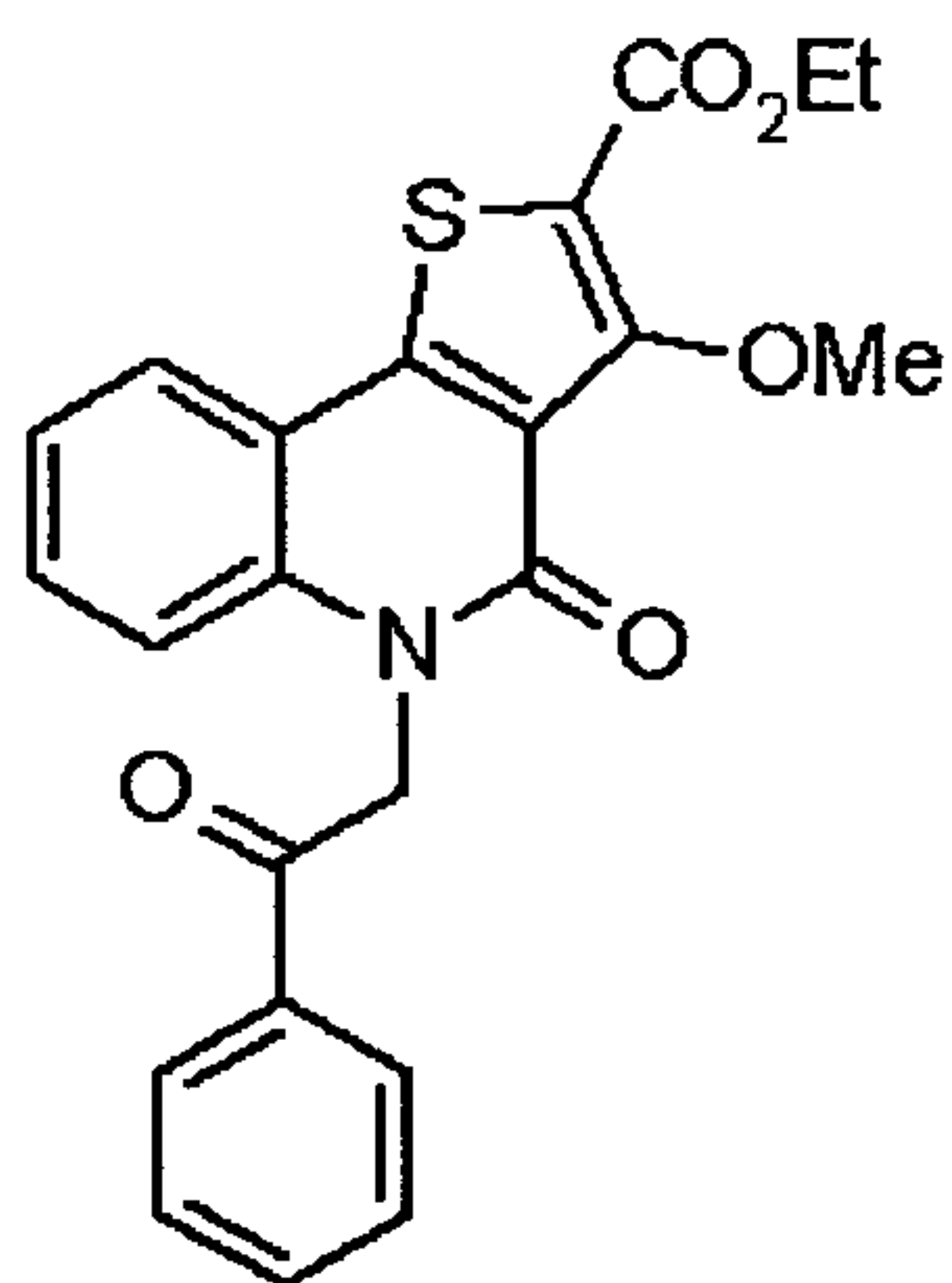
20 ¹H-NMR (300 MHz, DMSO-d₆) δ: 1.32 (3H, t, J = 7.0 Hz), 4.25-4.35 (2H, m), 6.01 (2H, s), 7.40 (1H, t, J = 7.2 Hz), 7.55-7.67 (4H, m), 7.77 (1H, t, J = 7.5 Hz), 8.00-8.07 (1H, m), 8.07-8.19 (2H, m), 10.40-10.65 (1H, br).

[0224]

25 Reference Example 6

Production of ethyl 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-
4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0225]



[0226]

A mixture of the compound of Reference Example 5 (7.0 g, 17.1 mmol) and DBU (4.3 g, 18.3 mmol) in DMF (150 mL) was stirred at room temperature for 10 min, and iodomethane (4.0 g, 28.0 mmol) was added. The mixture was stirred at room temperature for 4 hr, and concentrated under reduced pressure. The residue was diluted with water, and extracted twice with ethyl acetate-THF mixed solution. The extract was combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethyl acetate-diethyl ether mixed solution, and dried under reduced pressure to give the title compound (5.7 g, 79%) as a pale-green powder.

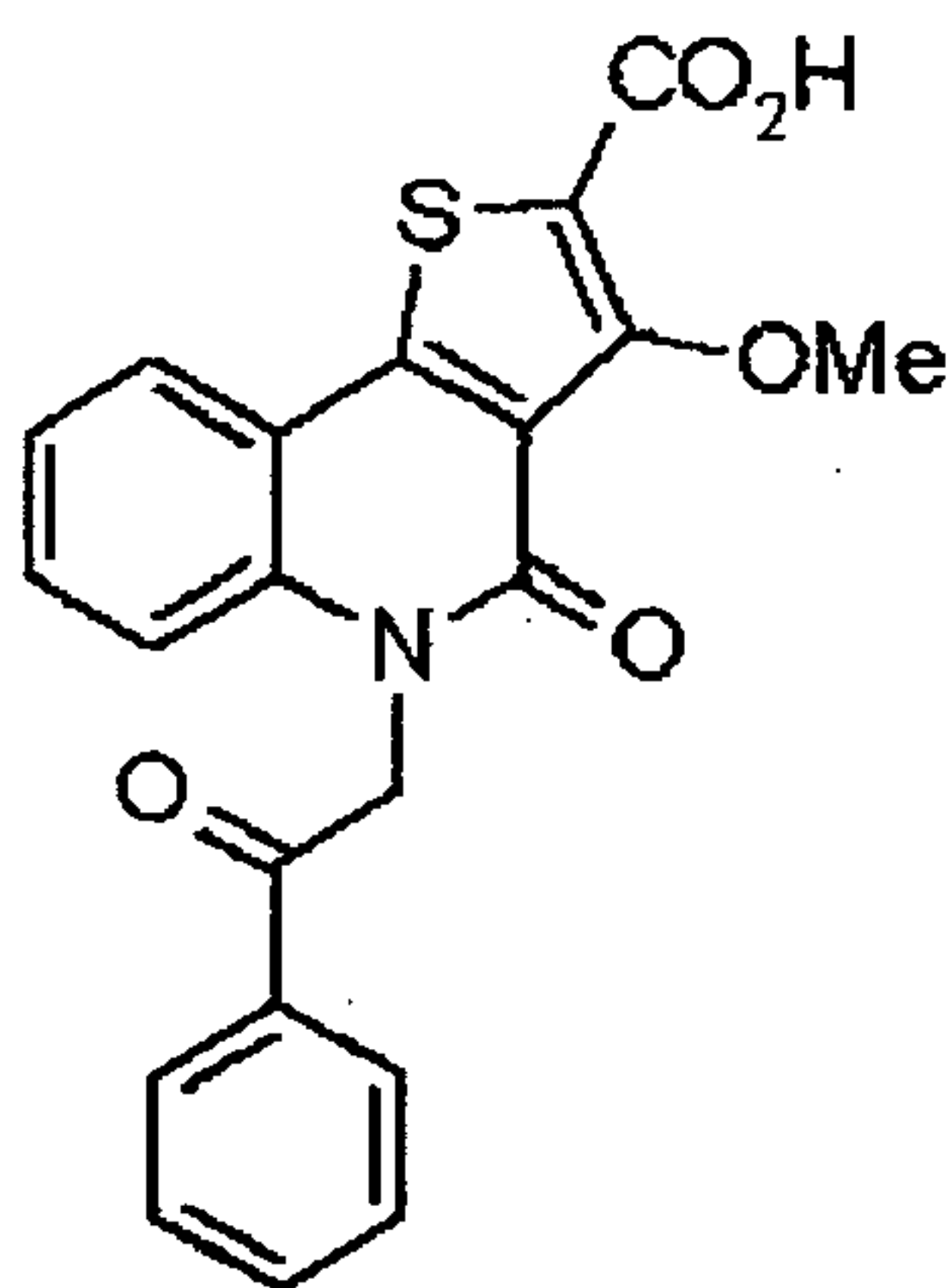
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.34 (3H, t, J = 7.1 Hz), 3.95 (3H, s), 4.34 (2H, q, J = 7.1 Hz), 5.98 (2H, s), 7.37 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.7 Hz), 7.57-7.67 (3H, m), 7.76 (1H, t, J = 7.5 Hz), 8.06 (1H, d, J = 7.8 Hz), 8.16-8.19 (2H, m).

[0227]

Reference Example 7

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0228]



[0229]

A mixed solution of the compound of Reference Example 6 (5.7 g, 13.5 mmol) and 2N aqueous sodium hydroxide solution (60 mL) in THF (200 mL)-ethanol (100 mL) was stirred at room temperature for 18 hr. The reaction mixture was neutralized with 2N hydrochloric acid (60 mL), and the precipitated solid was collected by filtration. The obtained solid was washed successively with water and diethyl ether, and dried under reduced pressure to give the title compound (4.2 g, 79%) as a pale-pink powder.

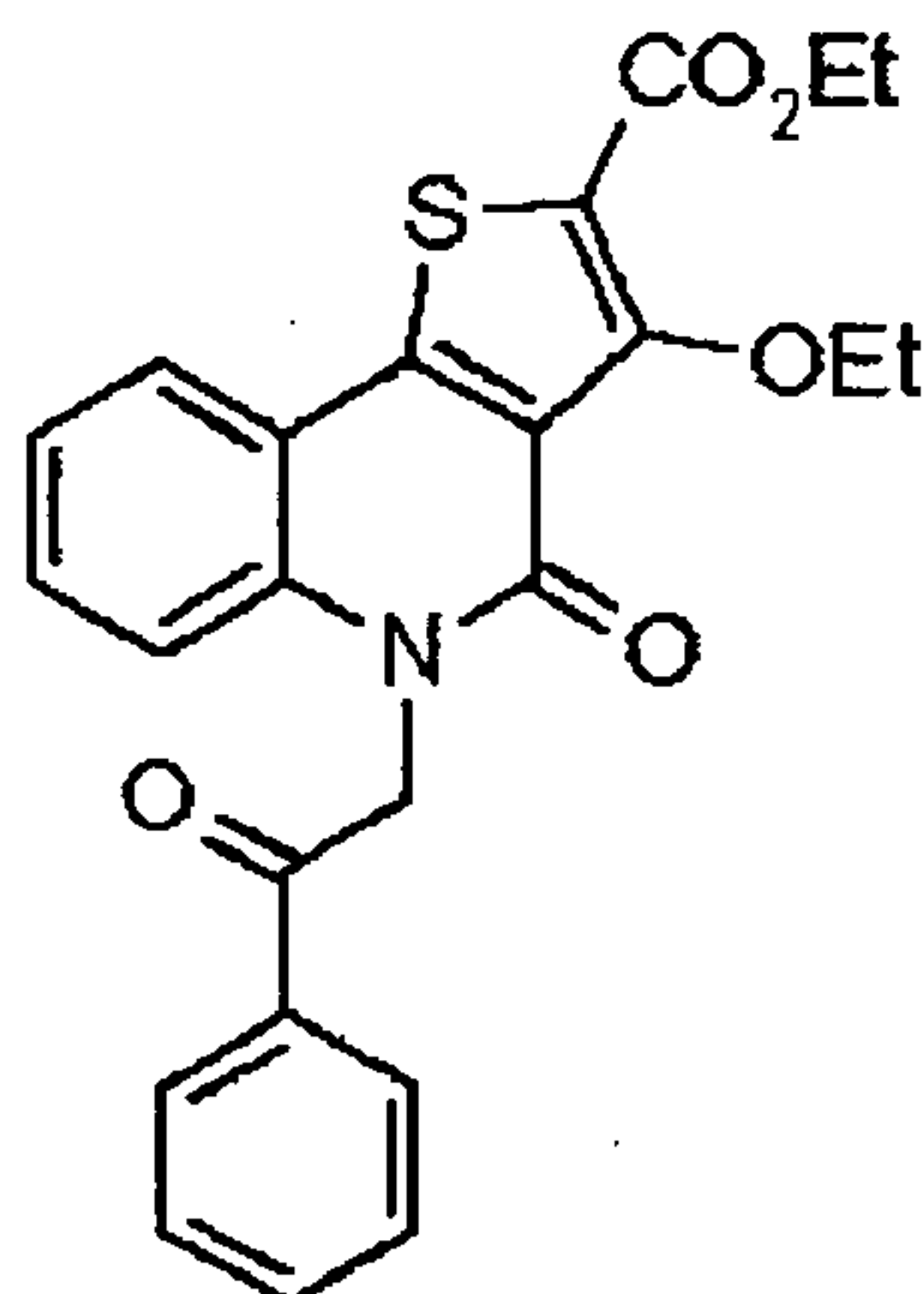
¹H-NMR (300 MHz, DMSO-d₆) δ: 3.93 (3H, s), 5.98 (2H, s), 7.35 (1H, t, J = 7.8 Hz), 7.48 (1H, d, J = 8.7 Hz), 7.56-7.67 (3H, m), 7.77 (1H, t, J = 7.2 Hz), 8.04 (1H, dd, J = 8.1, 1.2 Hz), 8.16-8.19 (2H, m).

[0230]

Reference Example 8

Production of ethyl 3-ethoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

20 [0231]



[0232]

In the same manner as in Reference Example 6, the title compound (461 mg, 87%) was obtained as a white powder from the compound (500 mg, 1.22 mmol) of Reference Example 5, DBU (280 mg, 1.84 mmol) and iodoethane (302 mg, 1.84 mmol).

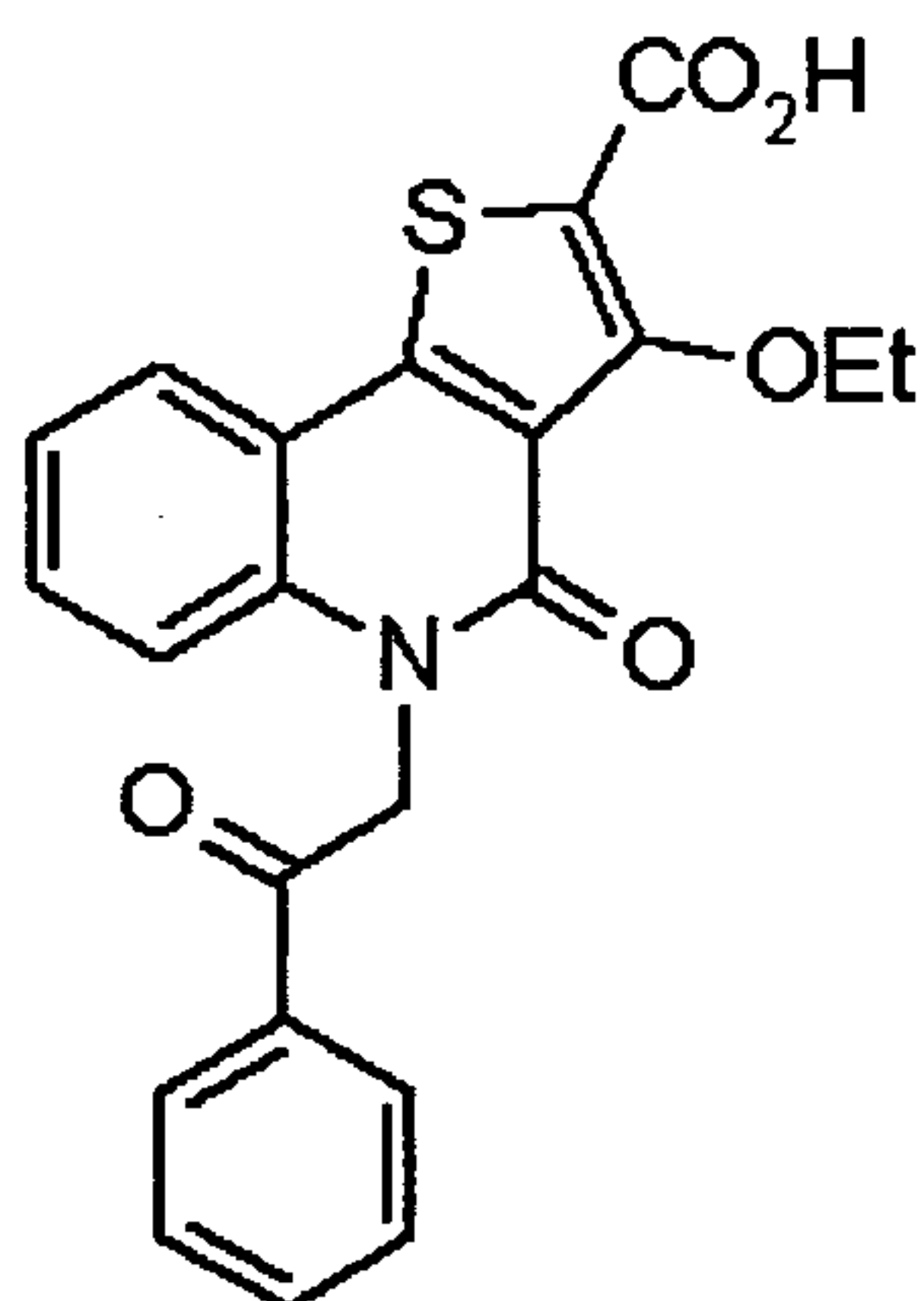
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.34 (6H, t, J = 7.0 Hz), 4.21 (2H, q, J = 7.0 Hz), 4.34 (2H, q, J = 7.0 Hz), 5.98 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.57-7.67 (3H, m), 7.76 (1H, t, J = 7.2 Hz), 8.06 (1H, dd, J = 7.8, 1.2 Hz), 8.16-8.19 (2H, m).

[0233]

Reference Example 9

Production of 3-ethoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

15 [0234]



[0235]

In the same manner as in Reference Example 7, the title compound (392 mg, 95%) was obtained as a pale-pink powder from the compound (440 mg, 1.01 mmol) of Reference Example 8.

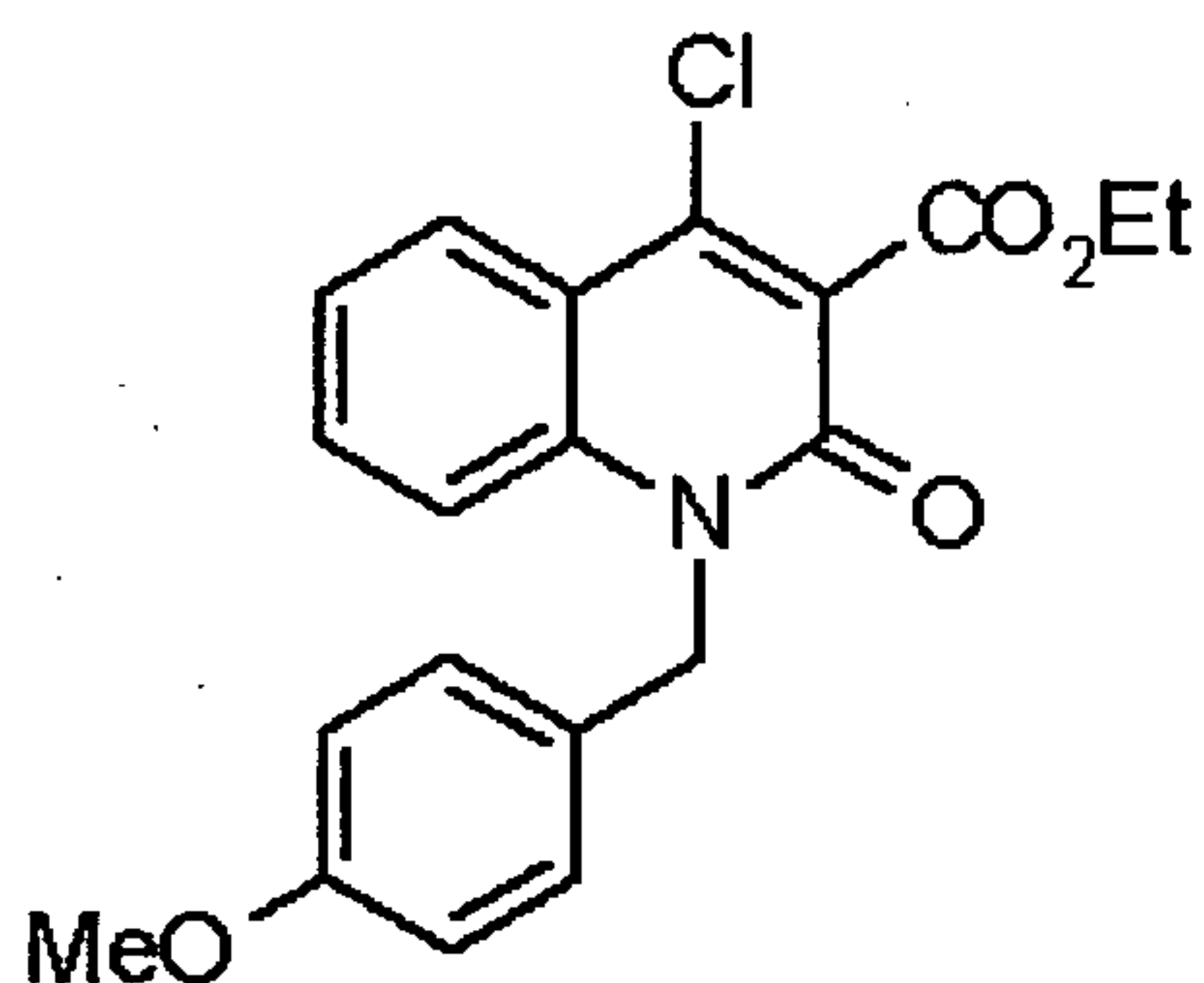
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.33 (3H, t, J = 7.0 Hz), 4.20 (2H, q, J = 7.0 Hz), 6.00 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.47 (1H, d, J = 8.4 Hz), 7.56-7.67 (3H, m), 7.77 (1H, t, J = 7.5 Hz), 8.04 (1H, dd, J = 7.8, 1.2 Hz), 8.16-8.19 (2H, m).

25 [0236]

Reference Example 10

Production of ethyl 4-chloro-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxylate

[0237]



[0238]

In the same manner as in Reference Example 4, the title compound (10.8 g, 79%) was obtained as a white powder from the compound (10.0 g, 39.8 mmol) of Reference Example 3 and 4-methoxybenzyl chloride (7.48 mL, 47.8 mmol).

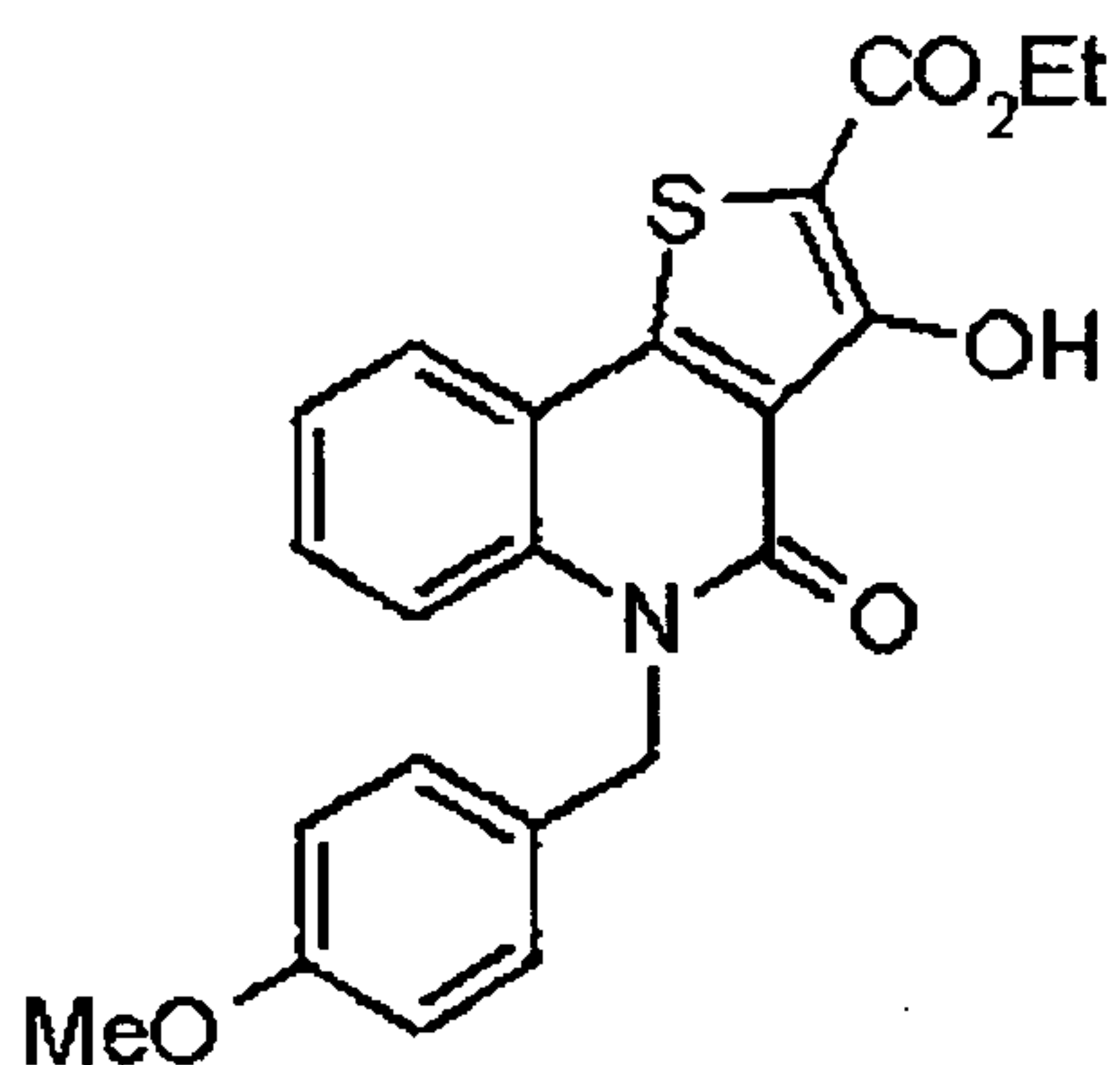
$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ : 1.34 (3H, t, $J = 7.1$ Hz), 3.70 (3H, s), 4.40 (2H, q, $J = 7.1$ Hz), 5.48 (2H, s), 6.89 (2H, d, $J = 8.7$ Hz), 7.19 (2H, d, $J = 8.7$ Hz), 7.42 (1H, t, $J = 7.8$ Hz), 7.61 (1H, d, $J = 8.7$ Hz), 7.69–7.75 (1H, m), 8.04 (1H, dd, $J = 7.8, 1.2$ Hz).

[0239]

Reference Example 11

Production of ethyl 3-hydroxy-5-(4-methoxybenzyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0240]



[0241]

In the same manner as in Reference Example 5, the title compound (10.4 g, 88%) was obtained as a white powder from the compound (10.6 g, 31.0 mmol) of Reference Example 10.

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ : 1.32 (3H, t, $J = 7.0$ Hz), 3.70 (3H, s), 4.32 (2H, q, $J = 7.0$ Hz), 5.53 (2H, s), 6.87 (2H, d, $J =$

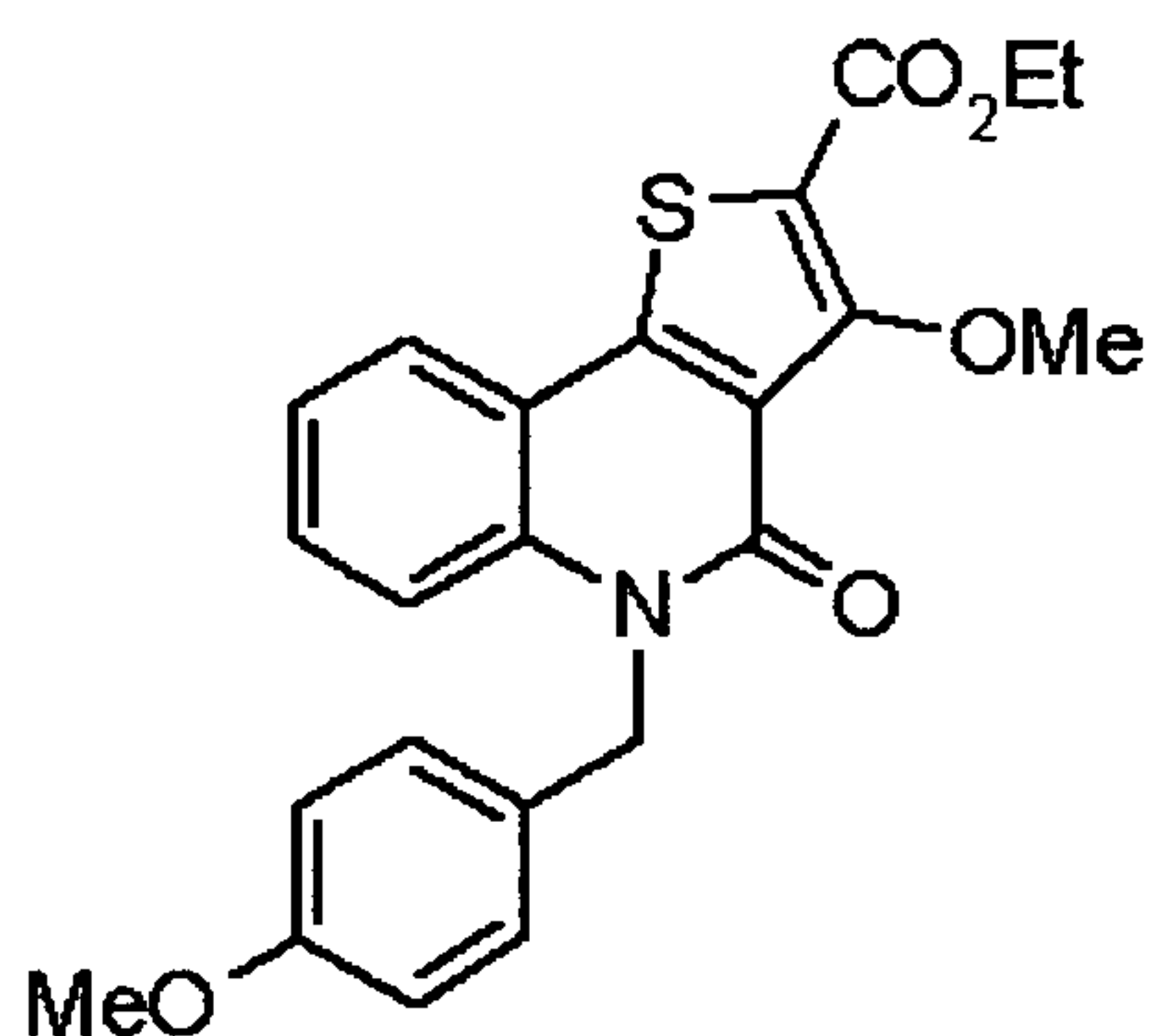
8.9 Hz), 7.23 (2H, d, $J = 8.9$ Hz), 7.34–7.39 (1H, m), 7.58–7.66 (2H, m), 8.00–8.03 (1H, m), 10.77 (1H, s).

[0242]

Reference Example 12

- 5 Production of ethyl 3-methoxy-5-(4-methoxybenzyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0243]



[0244]

- 10 In the same manner as in Reference Example 6, the title compound (5.2 g, 64%) was obtained as a white powder from the compound (7.5 g, 19.8 mmol) of Reference Example 11.

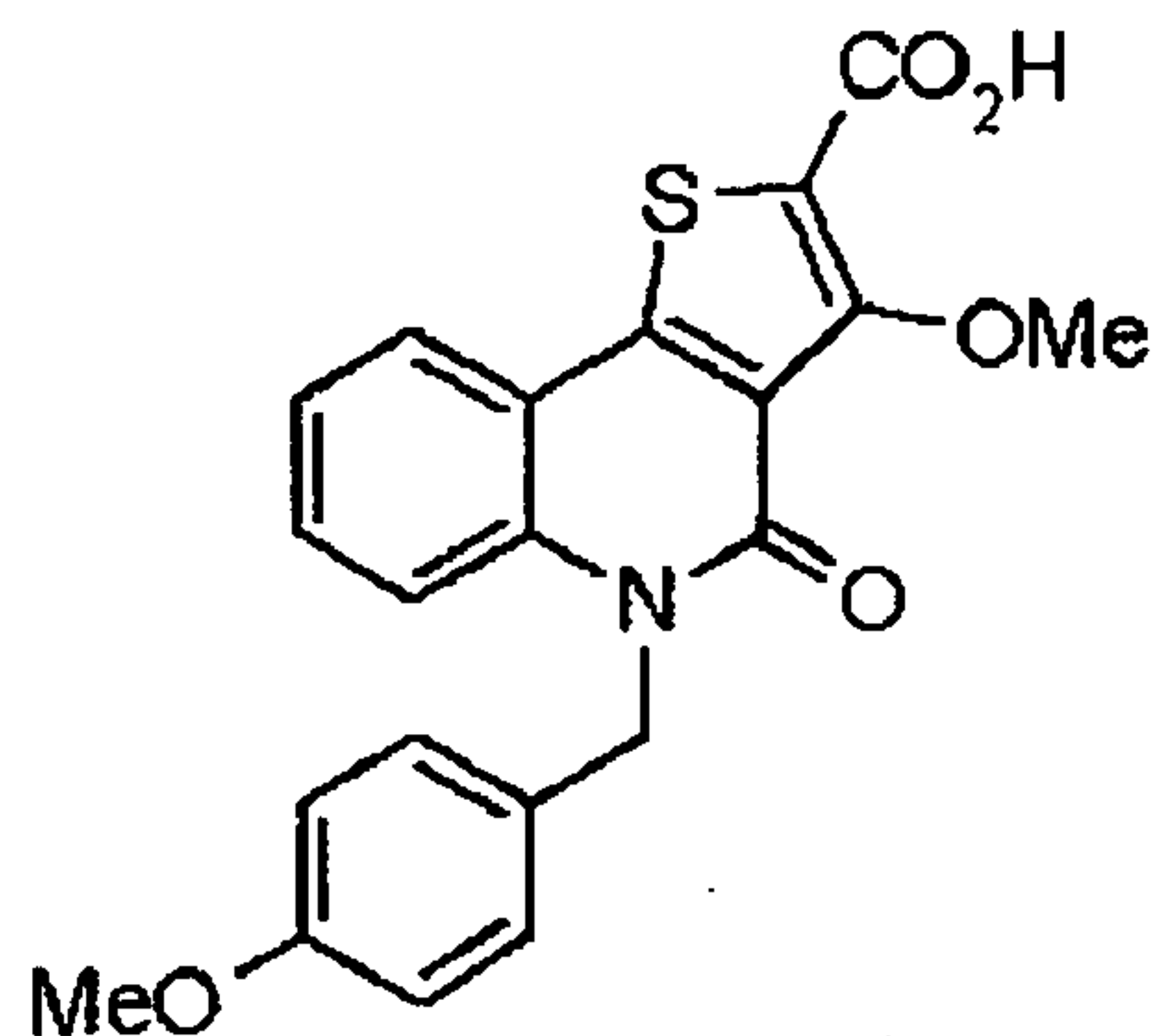
$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ : 1.34 (3H, t, $J = 7.1$ Hz), 3.70 (3H, s), 4.01 (3H, s), 4.34 (2H, q, $J = 7.1$ Hz), 5.50 (2H, s), 6.87
 15 (2H, d, $J = 8.7$ Hz), 7.20 (2H, d, $J = 8.7$ Hz), 7.27–7.32 (1H, m), 7.48–7.60 (2H, m), 8.01 (1H, dd, $J = 7.7, 1.4$ Hz).

[0245]

Reference Example 13

- Production of 3-methoxy-5-(4-methoxybenzyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid
 20

[0246]



[0247]

In the same manner as in Reference Example 7, the title compound (4.75 g, 98%) was obtained as a white powder from the compound (5.0 g, 12.3 mmol) of Reference Example 12.

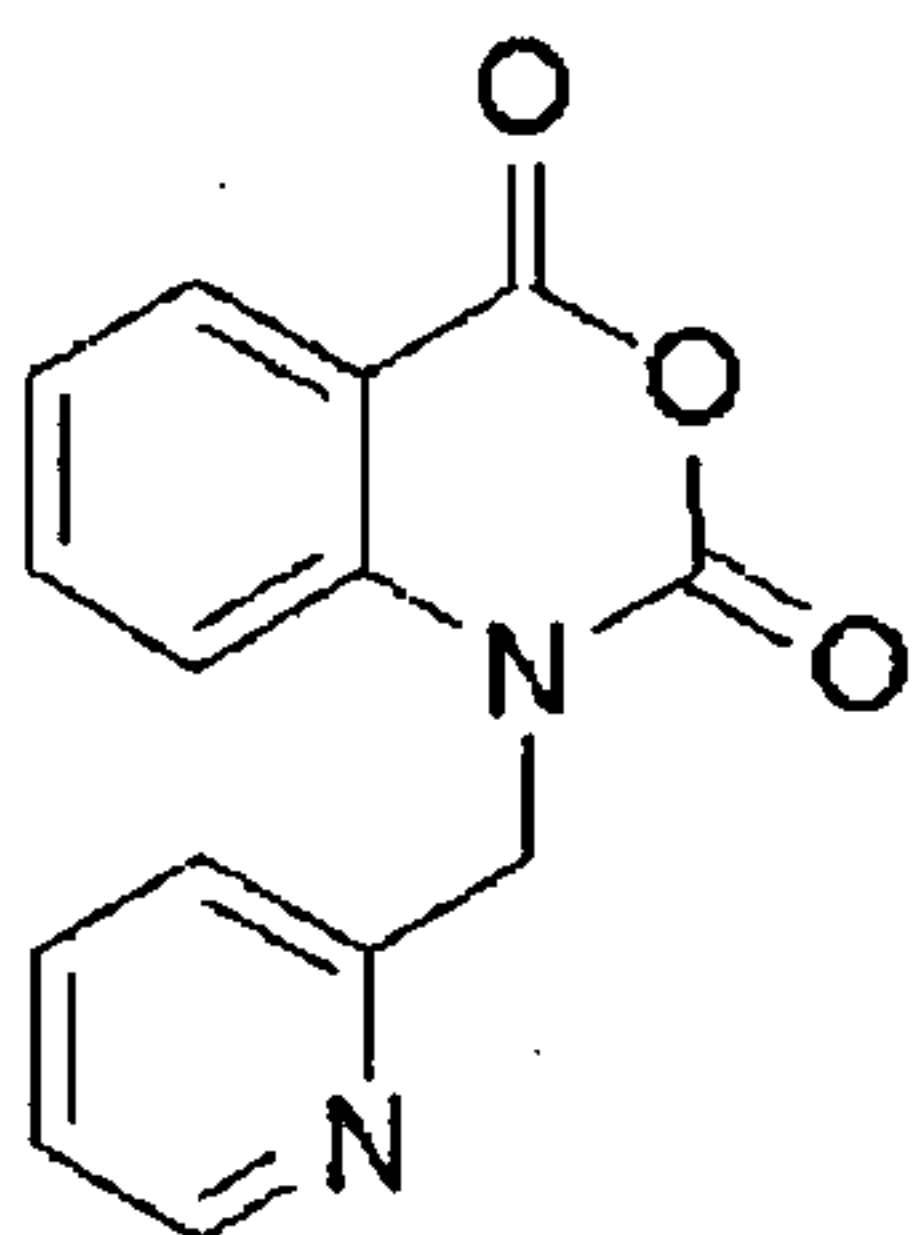
¹H-NMR (300 MHz, DMSO-d₆) δ: 3.70 (3H, s), 3.93 (3H, s), 5.51
5 (2H, s), 6.87 (2H, d, J = 8.7 Hz), 7.20 (2H, d, J = 8.7 Hz),
7.27-7.32 (1H, m), 7.48-7.59 (2H, m), 7.99 (1H, dd, J = 7.8,
1.2 Hz), 13.40 (1H, s).

[0248]

Reference Example 14

10 Production of 1-(pyridin-2-ylmethyl)-2H-3,1-benzoxazine-
2,4(1H)-dione

[0249]



[0250]

15 To a solution of isatoic anhydride (25.4 g, 0.156 mol) in
DMF (300 mL) were added 2-(chloromethyl)pyridine hydrochloride
(28.1 g, 0.171 mol) and sodium hydride (66% in oil, 12.5 g,
0.34 mol) under ice-cooling. The obtained mixture was stirred
at room temperature for 42 hr. Water (750 mL) was added to the
20 reaction mixture and the mixture was ice-cooled. The
precipitated solid was collected by filtration, and
recrystallized from acetone-diisopropyl ether to give the
title compound (13.4 g, 34%).

¹H-NMR (300 MHz, DMSO-d₆) δ: 5.36 (2H, s), 7.24-7.34 (3H, m),
25 7.49 (1H, d, J = 8.1 Hz), 7.73 (1H, ddd, J = 8.6, 7.2, 1.5 Hz),
7.77 (1H, td, J = 7.7, 1.6 Hz), 8.03 (1H, dd, J = 7.8, 1.8 Hz),
8.50 (1H, ddd, J = 4.9, 1.7, 1.0 Hz).

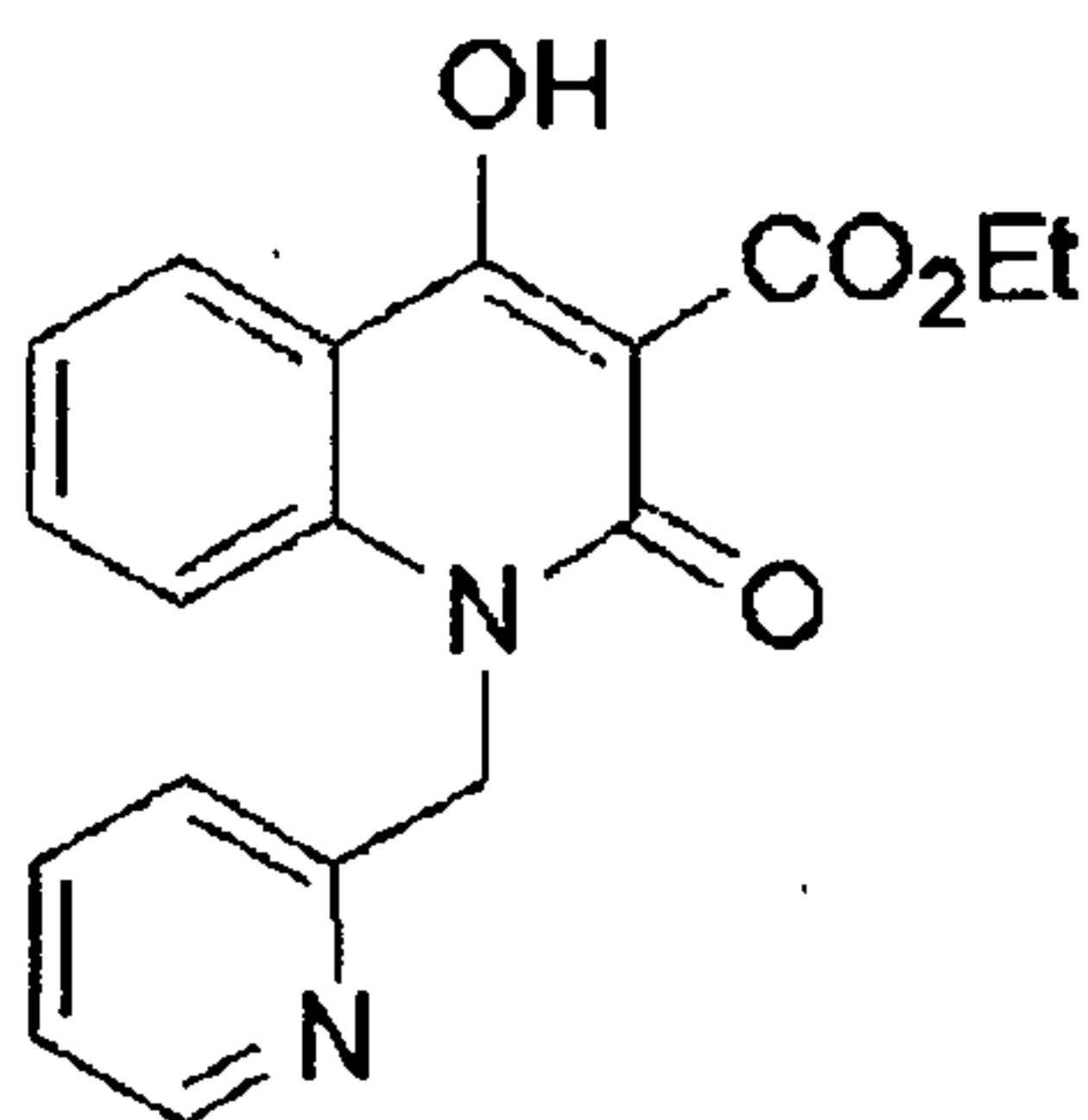
[0251]

Reference Example 15

30 Production of ethyl 4-hydroxy-2-oxo-1-(pyridin-2-ylmethyl)-

1,2-dihydroquinoline-3-carboxylate

[0252]



[0253]

5 To a solution of diethyl malonate (15.6 g, 97.4 mmol) in DMF (90 mL) was added sodium hydride (66% in oil, 2.60 g, 72 mmol) under ice-cooling, and the mixture was stirred at the same temperature for 10 min. The compound of Reference Example 14 (16.5 g, 64.9 mmol) was added to the obtained mixture by
10 small portions, and the mixture was stirred at 120°C for 6 hr. The reaction mixture was concentrated under reduced pressure, ice water was added to the residue and the mixture was washed with diethyl ether. The aqueous layer was weakly basified with 5N hydrochloric acid (8 mL) under ice-cooling. The
15 precipitated crystals were collected by filtration, washed with water, and recrystallized from ethyl acetate-diisopropyl ether to give the title compound (12.8 g, 60%).

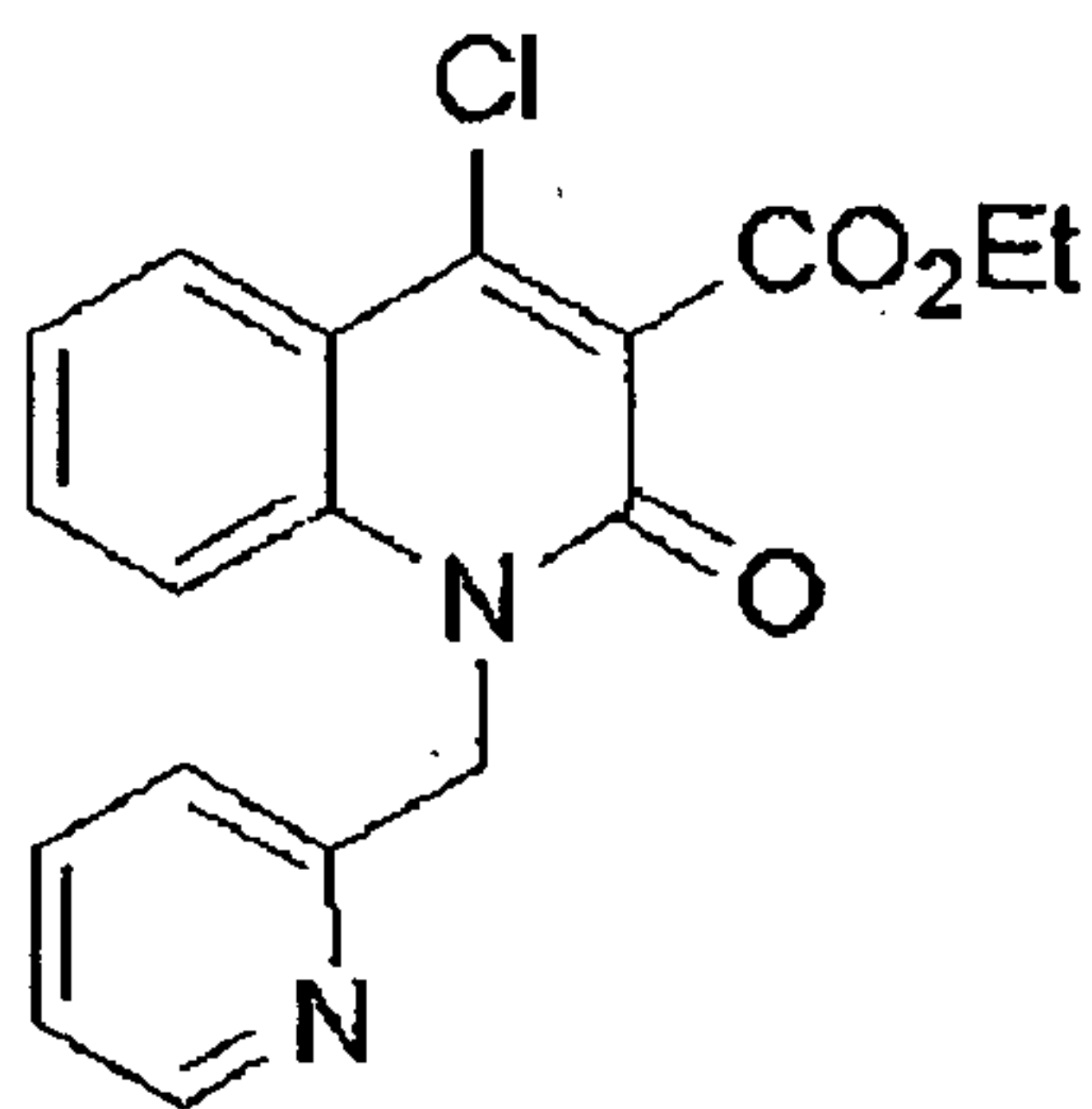
¹H-NMR (300 MHz, CDCl₃) δ: 1.50 (3H, t, J = 7.1 Hz), 4.53 (2H, q, J = 7.1 Hz), 5.61 (2H, br s), 7.12-7.18 (2H, m), 7.18-7.25 (1H, m), 7.36 (1H, d, J = 8.7 Hz), 7.51-7.59 (2H, m), 8.18 (1H, dd, J = 8.3, 1.7 Hz), 8.56 (1H, dd, J = 5.3, 2.0 Hz), 14.53 (1H, s).

[0254]

Reference Example 16

25 Production of ethyl 4-chloro-2-oxo-1-(pyridin-2-ylmethyl)-1,2-dihydroquinoline-3-carboxylate

[0255]



[0256]

To a mixture of the compound of Reference Example 15 (16.1 g, 49.6 mmol) and toluene (50 mL) was added phosphorus
 5 oxychloride (12 mL, 0.13 mol), and the mixture was stirred at 110°C for 1 hr. The reaction mixture was allowed to cool, and the solvent was removed by decantation. Water was added to the residue and the mixture was washed with diethyl ether. The aqueous layer was neutralized with sodium carbonate and
 10 extracted twice with chloroform. The combined organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=1/1 - 3/1) and crystallized from ethyl
 15 acetate-hexane to give the title compound (2.54 g, 15%).

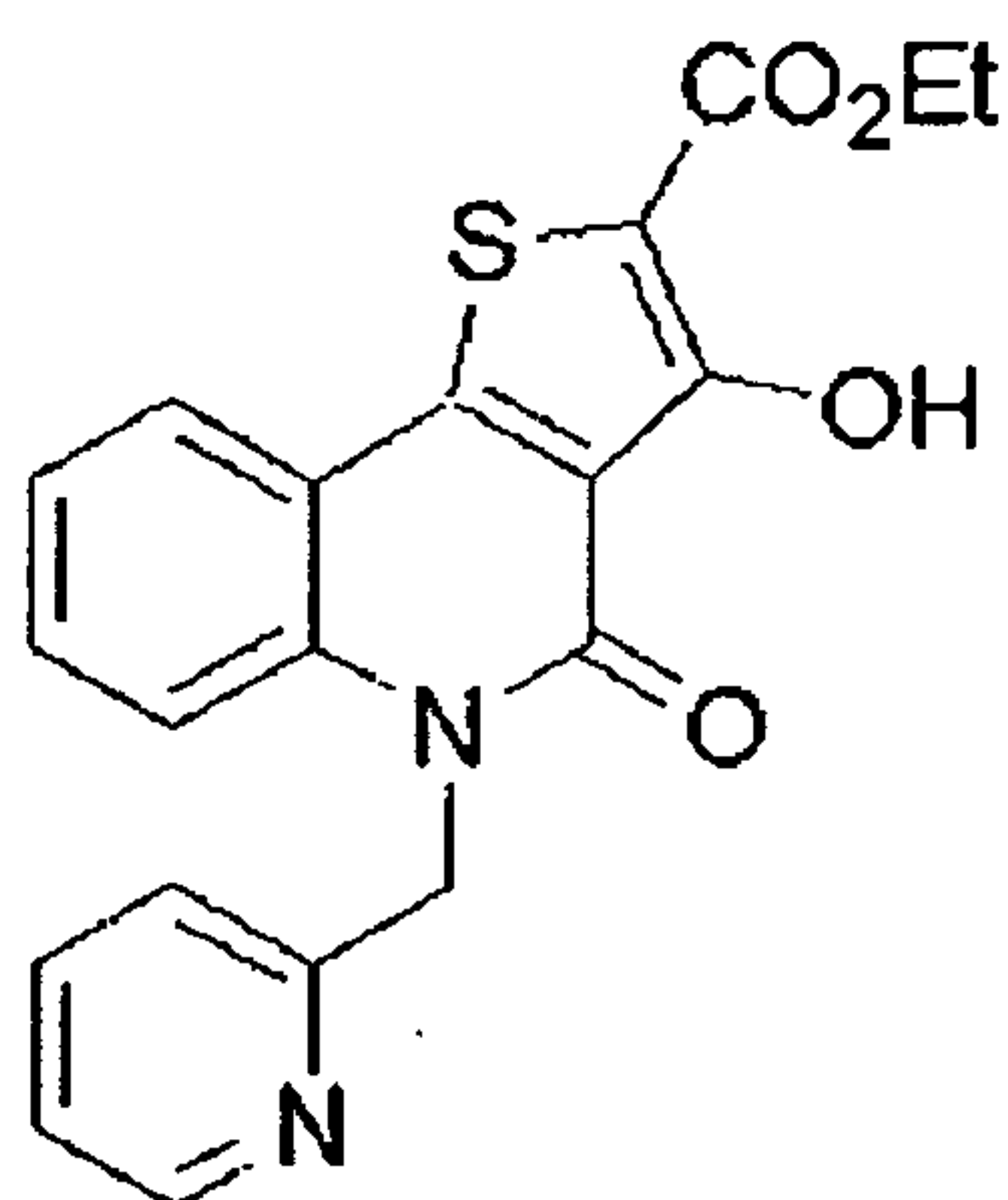
¹H-NMR (300 MHz, CDCl₃) δ: 1.44 (3H, t, J = 7.2 Hz), 4.50 (2H, q, J = 7.2 Hz), 5.64 (2H, br s), 7.15-7.26 (2H, m), 7.31 (1H, ddd, J = 8.2, 5.9, 2.3 Hz), 7.52-7.63 (3H, m), 8.06 (1H, dt, J = 7.8, 0.8 Hz), 8.56 (1H, ddd, J = 4.7, 1.9, 0.8 Hz).

20 [0257]

Reference Example 17

Production of ethyl 3-hydroxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0258]



[0259]

A 20% solution (4.51 g, 13 mmol) of sodium ethoxide in ethanol was diluted with ethanol (15 mL), and ethyl
 5 thioglycolate (1.74 mL, 15.9 mmol) was added to the obtained solution. The mixture was stirred at room temperature for 10 min. The compound of Reference Example 16 (2.27 g, 6.62 mmol) was added to the mixture, and the mixture was stirred at room temperature for 5.5 hr. The reaction mixture was neutralized
 10 with ice water and 2N hydrochloric acid (3.2 mL) under ice-cooling, and extracted twice with chloroform. The combined organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The obtained solid was washed with ethanol to give
 15 the title compound (2.50 g, 99%).

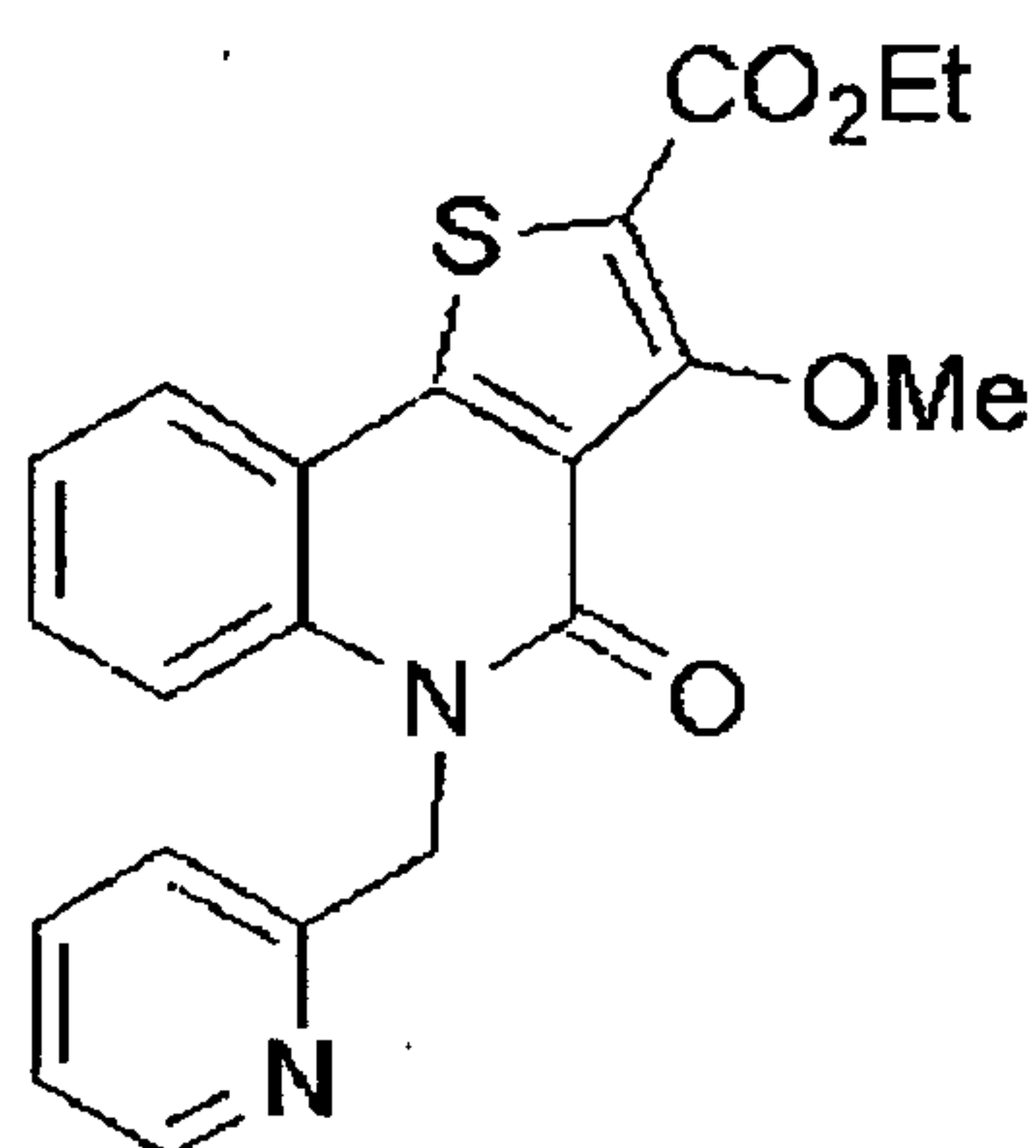
¹H-NMR (300 MHz, CDCl₃) δ: 1.43 (3H, t, J = 7.1 Hz), 4.43 (2H, q, J = 7.1 Hz), 5.69 (2H, br s), 7.16-7.24 (2H, m), 7.25-7.32 (1H, m), 7.49 (1H, ddd, J = 8.6, 7.1, 1.5 Hz), 7.57 (1H, d, J = 8.1 Hz), 7.60 (1H, td, J = 7.7, 1.8 Hz), 7.82 (1H, dd, J = 8.1, 1.5 Hz), 8.57 (1H, ddd, J = 4.9, 1.6, 0.8 Hz), 10.68 (1H, s).

[0260]

Reference Example 18

Production of ethyl 3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

25 [0261]



[0262]

To a suspension of the compound of Reference Example 17 (2.26 g, 5.94 mmol) in DMF (20 mL) was added DBU (1.06 mL, 7.09 mmol), and iodomethane (0.74 mL, 12 mmol) was added to the obtained solution. The obtained mixture was stirred at room temperature for 14 hr, water was added, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with water, 0.5N sodium hydroxide solution and water, dried by passing through basic silica gel (eluted with ethyl acetate), and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (1.16 g, 50%).

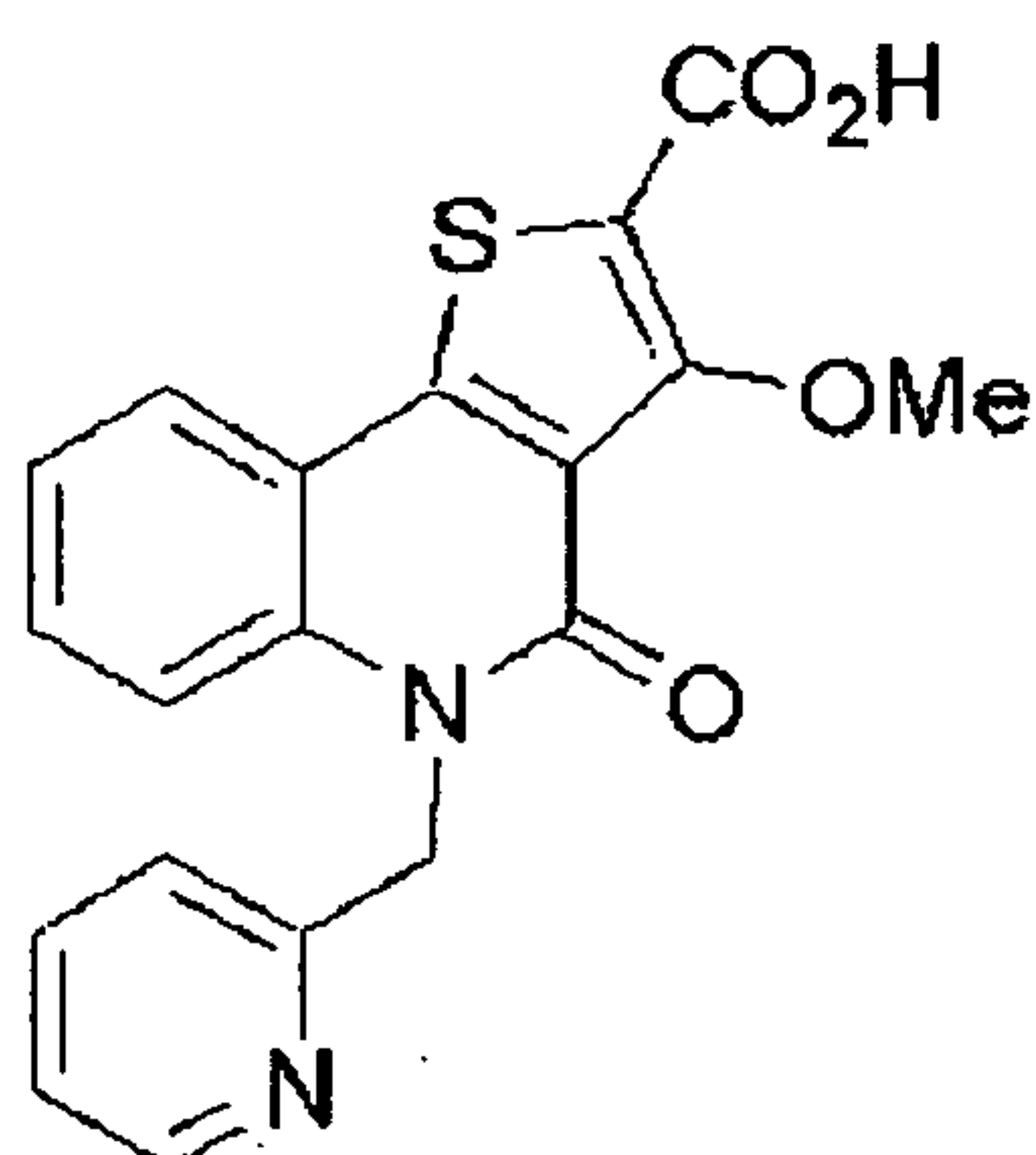
¹H-NMR (300 MHz, CDCl₃) δ: 1.43 (3H, t, J = 7.1 Hz), 4.17 (3H, s), 4.41 (2H, q, J = 7.1 Hz), 5.70 (2H, br s), 7.14-7.26 (3H, m), 7.45 (1H, ddd, J = 8.6, 7.0, 1.6 Hz), 7.51 (1H, dd, J = 8.6, 0.8 Hz), 7.57 (1H, td, J = 7.7, 1.8 Hz), 7.83 (1H, ddd, J = 7.7, 1.5, 0.3 Hz), 8.57 (1H, ddd, J = 5.0, 2.0, 0.9 Hz).

[0263]

20 Reference Example 19

Production of 3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0264]



[0265]

To a suspension of the compound of Reference Example 18 (1.21 g, 3.07 mmol) in THF (10 mL) and ethanol (10 mL) was added 5N aqueous sodium hydroxide solution (1.2 mL, 6.0 mmol). The obtained mixture was stirred at room temperature for 45 min, ethanol (5 mL) was added and the mixture was further stirred for 135 min. The reaction mixture was ice-cooled, neutralized with 1N hydrochloric acid (6.0 mL), and chloroform and water were added. The organic layer was separated, and the aqueous layer was extracted twice with chloroform. The combined organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was recrystallized from chloroform-diisopropyl ether to give the title compound (1.11 g, 99%).

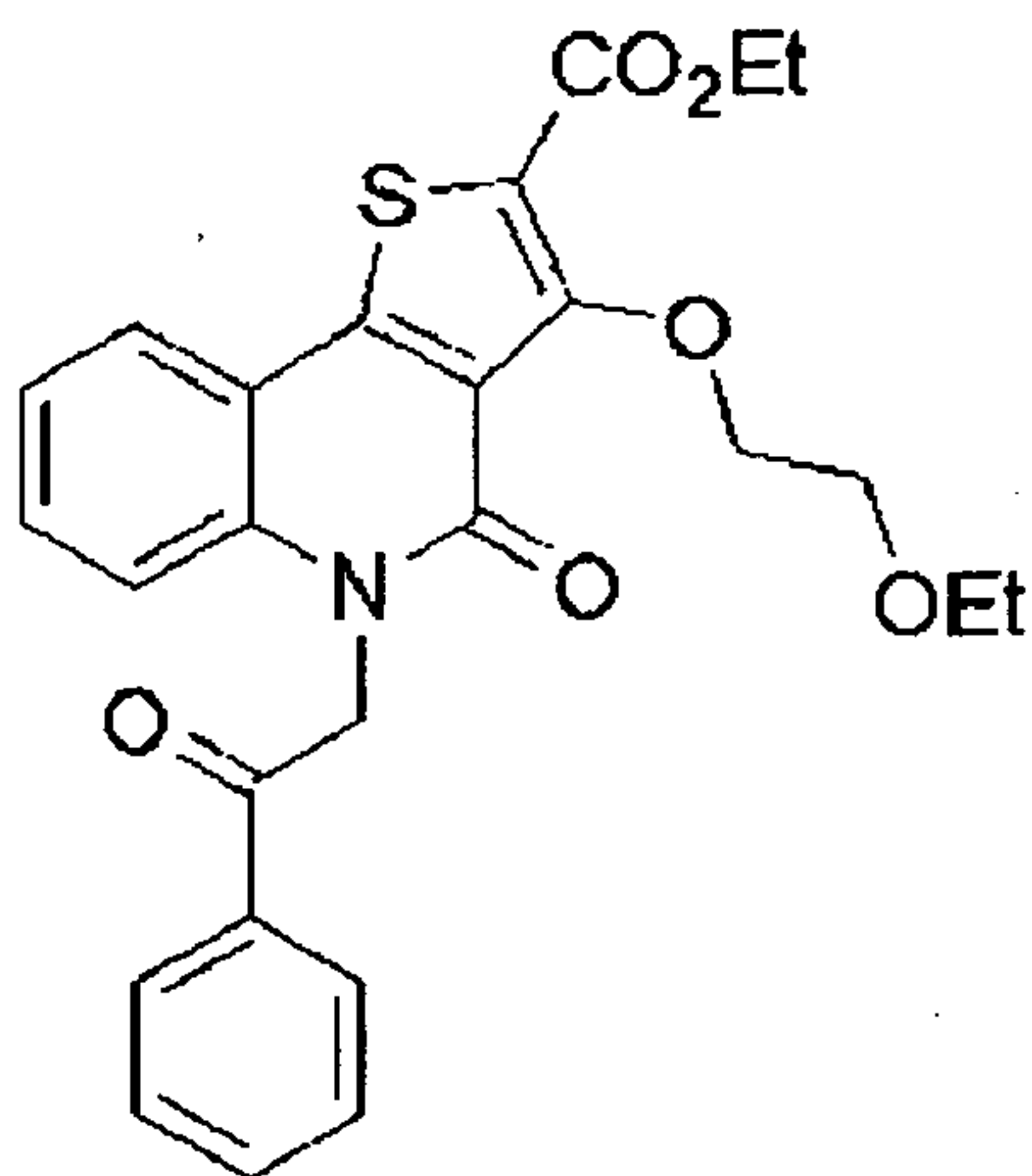
¹H-NMR (300 MHz, DMSO-d₆) δ: 3.96 (3H, s), 5.65 (2H, s), 7.23-7.33 (3H, m), 7.43 (1H, d, J = 8.7 Hz), 7.54 (1H, ddd, J = 8.6, 7.3, 1.4 Hz), 7.73 (1H, td, J = 7.7, 1.9 Hz), 7.97-8.02 (1H, m), 8.45-8.48 (1H, m), 13.38 (1H, br s).

20 [0266]

Reference Example 20

Production of ethyl 3-(2-ethoxyethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0267]



[0268]

To a suspension of the compound of Reference Example 5 (1.35 g, 3.31 mmol) in DMF (20 mL) were added DBU (1.48 mL, 9.90 mmol) and 2-bromoethylethylether (1.12 mL, 9.93 mmol), and the mixture was stirred at 60°C for 30 hr. Chloroform and water were added to the reaction mixture, the organic layer was separated and the aqueous layer was extracted with chloroform. The combined organic layer was washed with 0.5N sodium hydroxide solution and water, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=1/3 - 2/3) and recrystallized from dichloromethane-diisopropyl ether to give the title compound (1.36 g, 86%).

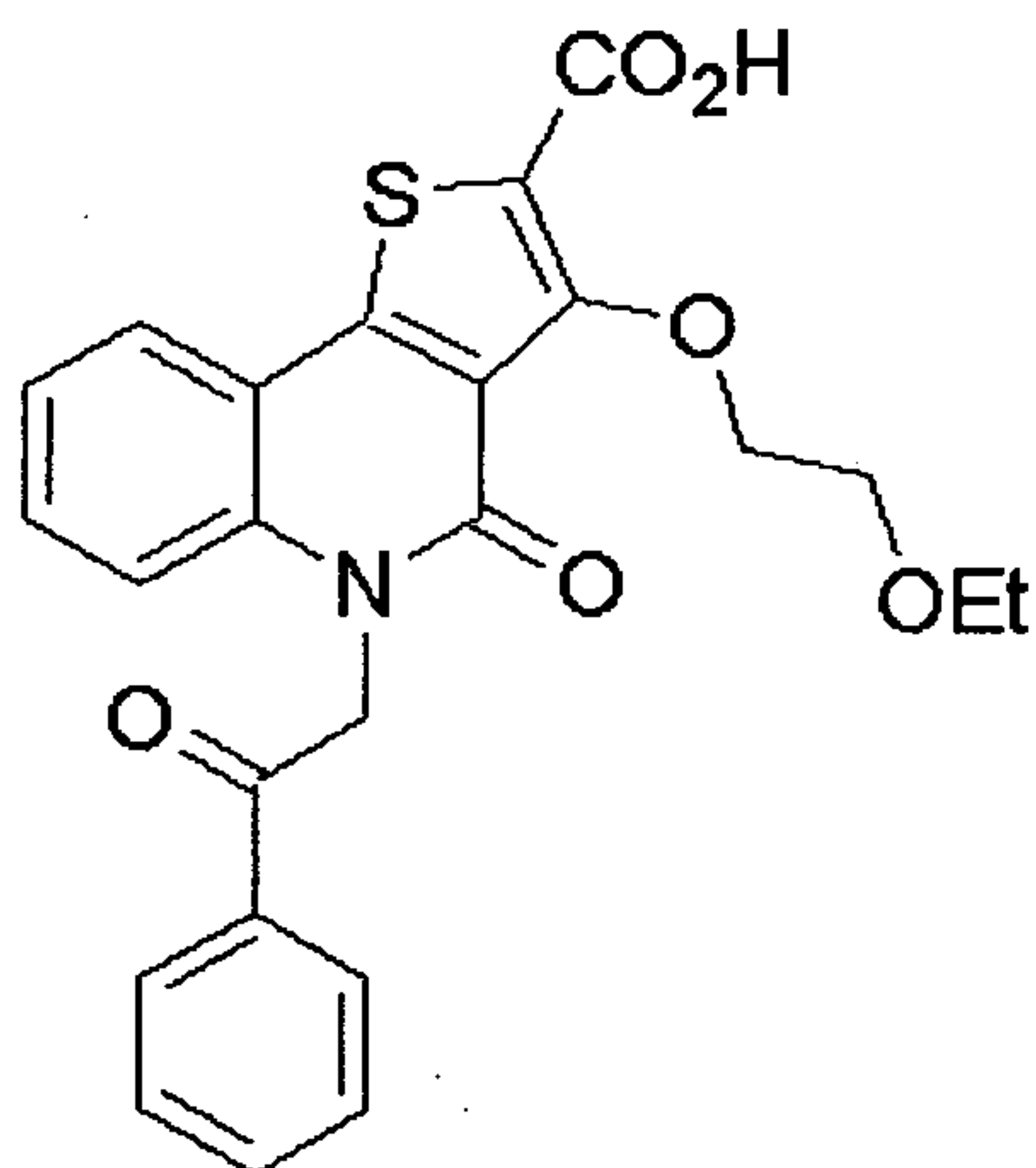
¹H-NMR (300 MHz, CDCl₃) δ: 1.17 (3H, t, J = 7.1 Hz), 1.43 (3H, t, J = 7.1 Hz), 3.56 (2H, q, J = 7.1 Hz), 3.89 (2H, dd, J = 5.5, 4.6 Hz), 4.40 (2H, q, J = 7.1 Hz), 4.45 (2H, dd, J = 5.5, 4.6 Hz), 5.85 (2H, s), 6.97 (1H, d, J = 8.1 Hz), 7.21-7.28 (1H, m), 7.45 (1H, ddd, J = 8.7, 7.2, 1.4 Hz), 7.51-7.58 (2H, m), 7.63-7.69 (1H, m), 7.86 (1H, dd, J = 7.8, 1.5 Hz), 8.07-8.12 (2H, m).

[0269]

Reference Example 21

Production of 3-(2-ethoxyethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0270]



[0271]

To a suspension of the compound of Reference Example 20 (1.20 g, 2.50 mmol) in THF (16 mL) and ethanol (16 mL) was
 5 added 5N aqueous sodium hydroxide solution (1.0 mL, 5.0 mmol). The obtained mixture was stirred at room temperature for 3 hr. The reaction mixture was acidified with 1N hydrochloric acid, and water was added. The precipitated crystals were collected
 10 by filtration and washed with water to give the title compound (1.09 g, 97%).

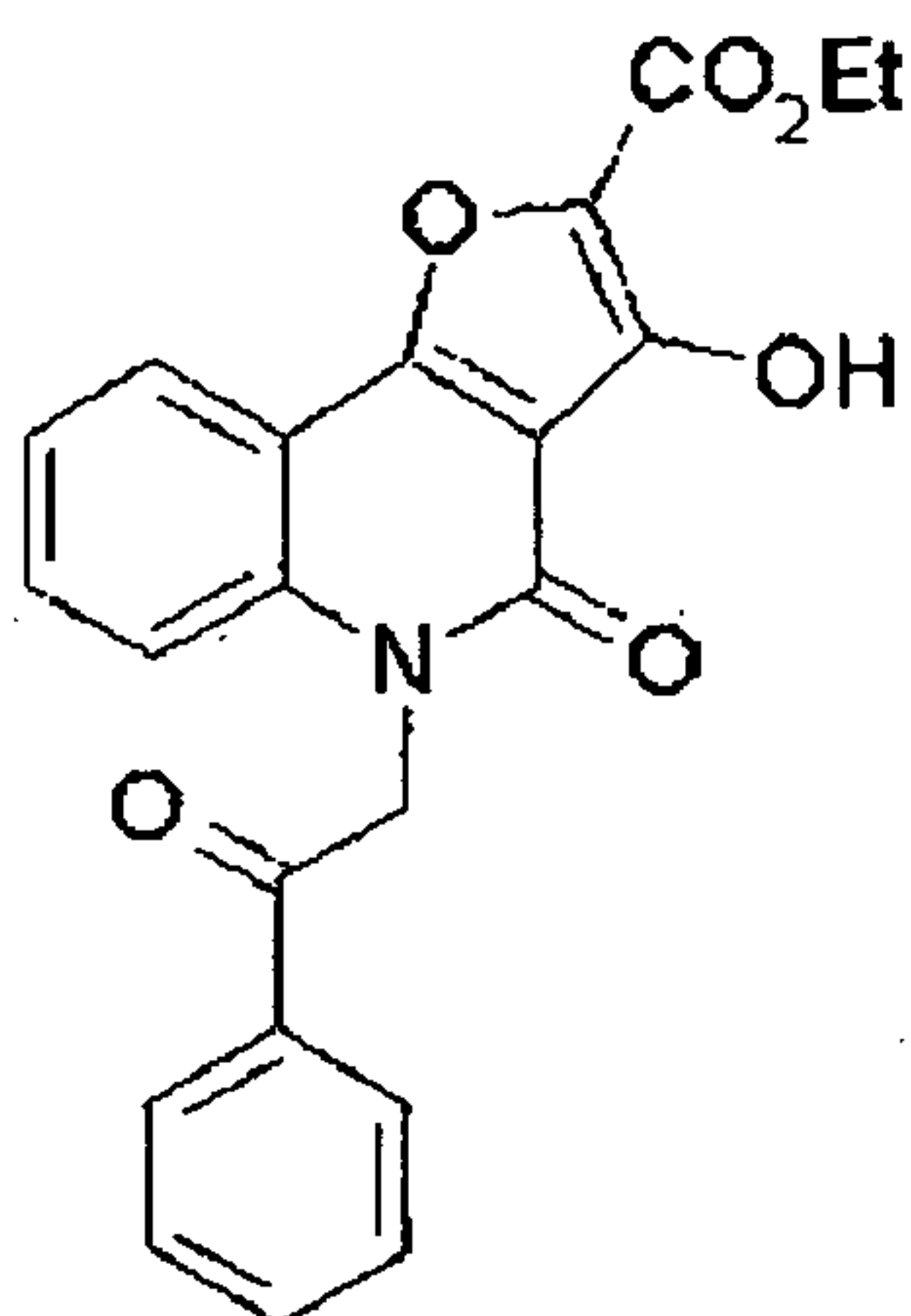
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.01 (3H, t, J = 6.9 Hz), 3.40 (2H, q, J = 6.9 Hz), 3.71 (2H, t, J = 5.0 Hz), 4.30 (2H, t, J = 5.0 Hz), 5.97 (2H, s), 7.33 (1H, t, J = 7.7 Hz), 7.46 (1H, d, J = 8.7 Hz), 7.54-7.66 (3H, m), 7.76 (1H, t, J = 7.2 Hz), 8.02 (1H,
 15 d, J = 7.8 Hz), 8.16 (2H, d, J = 7.5 Hz), 13.27 (1H, br s).

[0272]

Reference Example 22

Production of ethyl 3-hydroxy-4-oxo-5-(2-oxo-2-phenylethyl)-
 4,5-dihydrofuro[3,2-c]quinoline-2-carboxylate

20 [0273]



[0274]

In the same manner as in Reference Example 5, the title compound (1.10 g, 69%) was obtained as a white powder from the compound of Reference Example 4 (1.50 g, 4.06 mmol), a 20% solution (2.76 g, 8.11 mmol) of sodium ethoxide in ethanol and ethyl glycolate (1.01 g, 9.73 mmol).

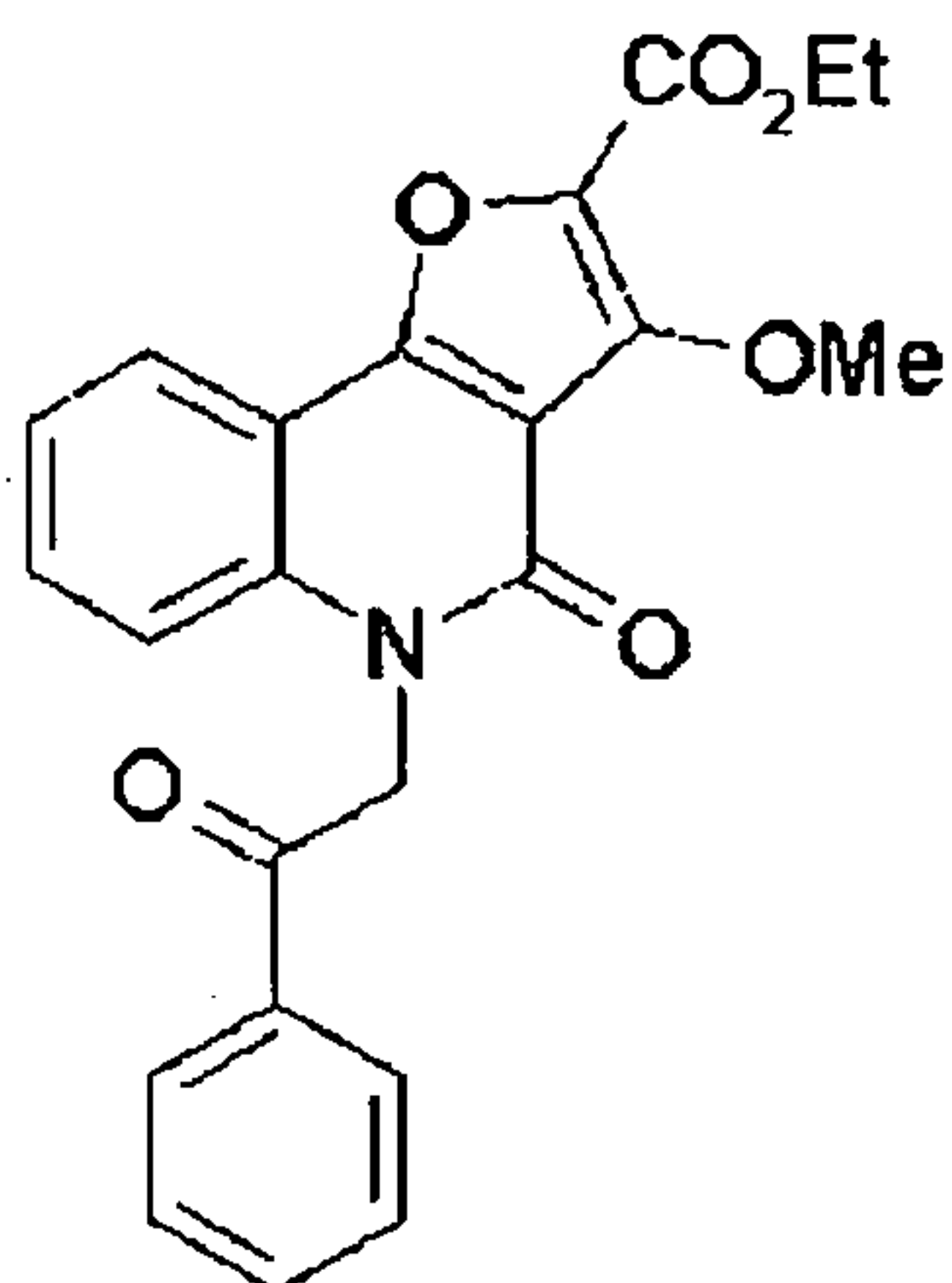
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.34 (3H, t, J = 7.1 Hz), 4.35 (2H, q, J = 7.1 Hz), 5.96 (2H, s), 7.39 (1H, t, J = 7.7 Hz), 7.51 (1H, d, J = 8.4 Hz), 7.60-7.67 (3H, m), 7.74-7.79 (1H, m), 8.05 (1H, dd, J = 7.7, 1.4 Hz), 8.15-8.18 (2H, m), 9.80-11.10 (1H, br).

[0275]

Reference Example 23

15 Production of ethyl 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrofuro[3,2-c]quinoline-2-carboxylate

[0276]



[0277]

20 In the same manner as in Reference Example 6, the title compound (250 mg, 23%) was obtained as a white powder from the

compound of Reference Example 22 (1.05 g, 2.68 mmol), DBU (612 mg, 4.02 mmol) and iodomethane (250 μ L, 4.02 mmol).

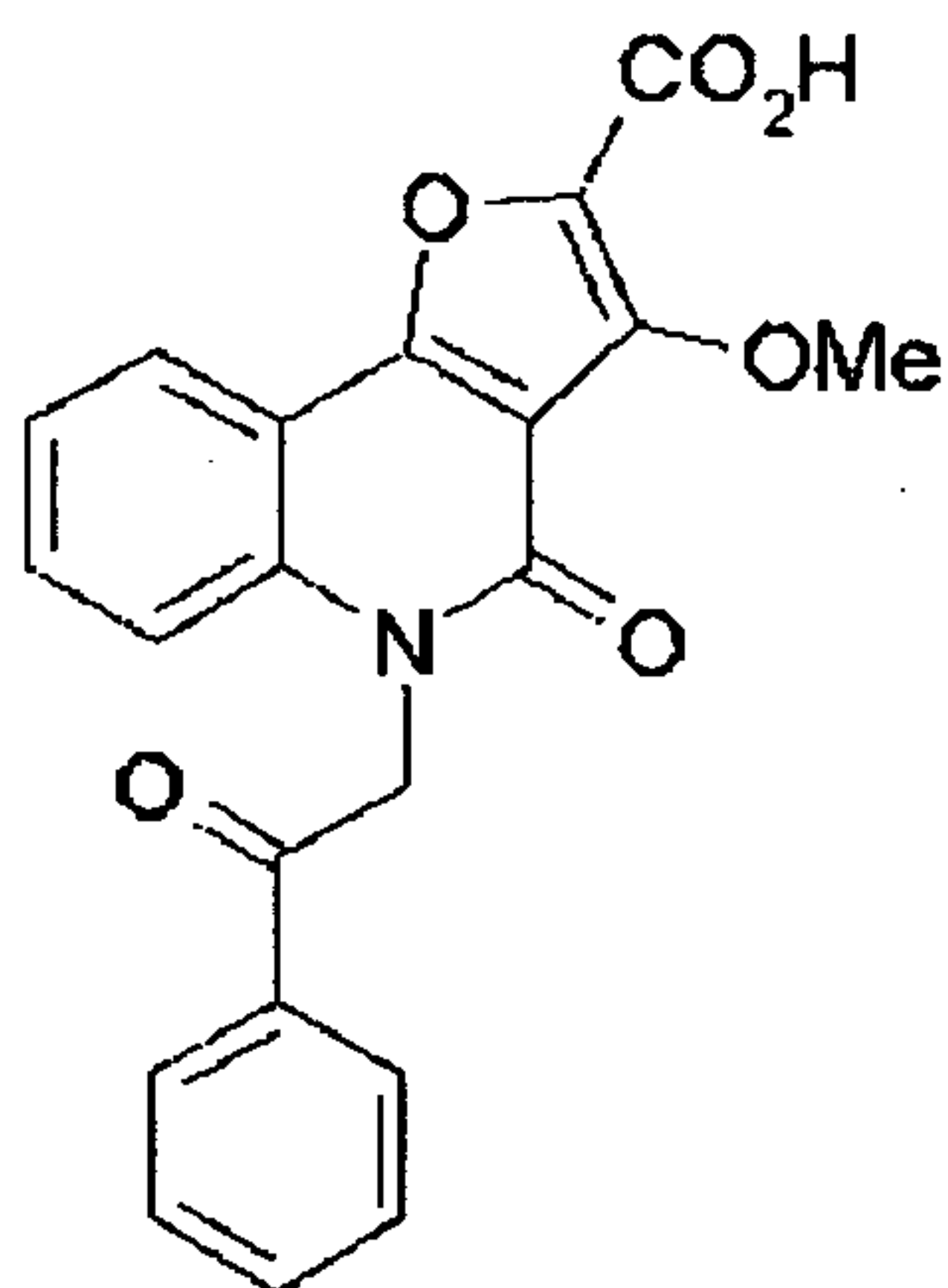
$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ : 1.35 (3H, t, $J = 7.1$ Hz), 4.14 (3H, s), 4.37 (2H, q, $J = 7.1$ Hz), 5.99 (2H, s), 7.39–7.45 (1H, m),
 5 7.55 (1H, d, $J = 8.7$ Hz), 7.62–7.68 (3H, m), 7.74–7.80 (1H, m),
 8.09 (1H, dd, $J = 7.8, 1.5$ Hz), 8.16–8.18 (2H, m).

[0278]

Reference Example 24

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-
 10 dihydrofuro[3,2-c]quinoline-2-carboxylic acid

[0279]



[0280]

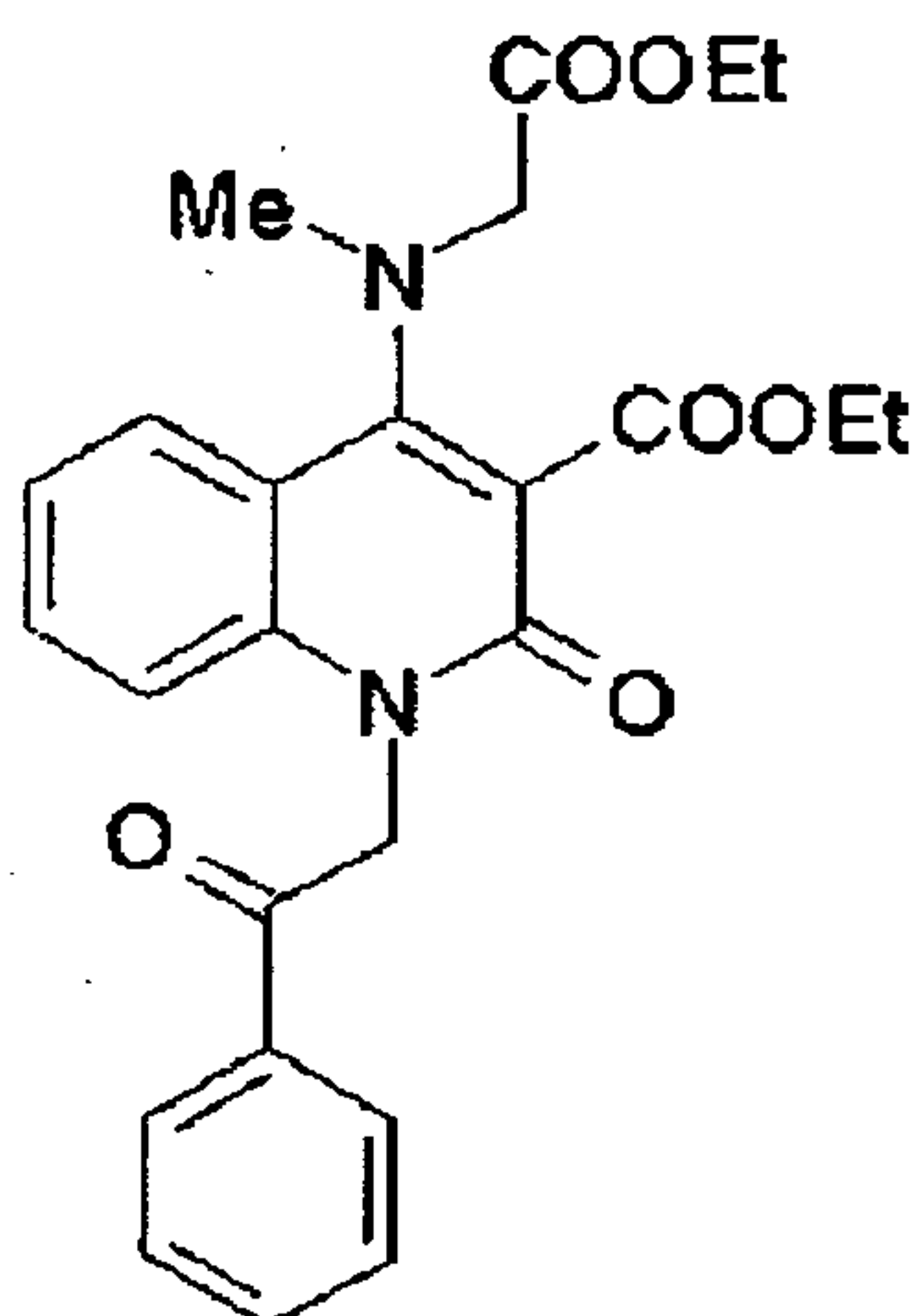
In the same manner as in Reference Example 7, the title
 15 compound (160 mg, 72%) was obtained as a white powder from the
 compound of Reference Example 23 (240 mg, 0.592 mmol), 8N
 aqueous sodium hydroxide solution (1.0 mL) and ethanol (14 mL).
 $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ : 4.12 (3H, s), 5.99 (2H, s), 7.42
 (1H, t, $J = 7.6$ Hz), 7.54 (1H, d, $J = 7.8$ Hz), 7.62–7.67 (3H,
 20 m), 7.77 (1H, t, $J = 7.8$ Hz), 8.07 (1H, dd, $J = 7.6, 1.5$ Hz),
 8.16–8.18 (2H, m), 12.60–14.10 (1H, br).

[0281]

Reference Example 25

Production of ethyl 4-[(2-ethoxy-2-oxoethyl)(methyl)amino]-2-
 25 oxo-1-(2-oxo-2-phenylethyl)-1,2-dihydroquinoline-3-carboxylate

[0282]



[0283]

A mixture of the compound of Reference Example 4 (24.1 g, 65.2 mmol), sarcosine ethyl ester hydrochloride (12.0 g, 78.2 mmol), triethylamine (18.1 mL, 130 mmol) and ethanol (200 mL) was stirred at 85°C for 15 hr, sarcosine ethyl ester hydrochloride (3.00 g, 19.6 mmol) and triethylamine (18.1 mL, 130 mmol) were further added, and the mixture was stirred at 85°C for 7 hr. After cooling, water was added to the reaction mixture, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (24.6 g, 84%) as a white powder.

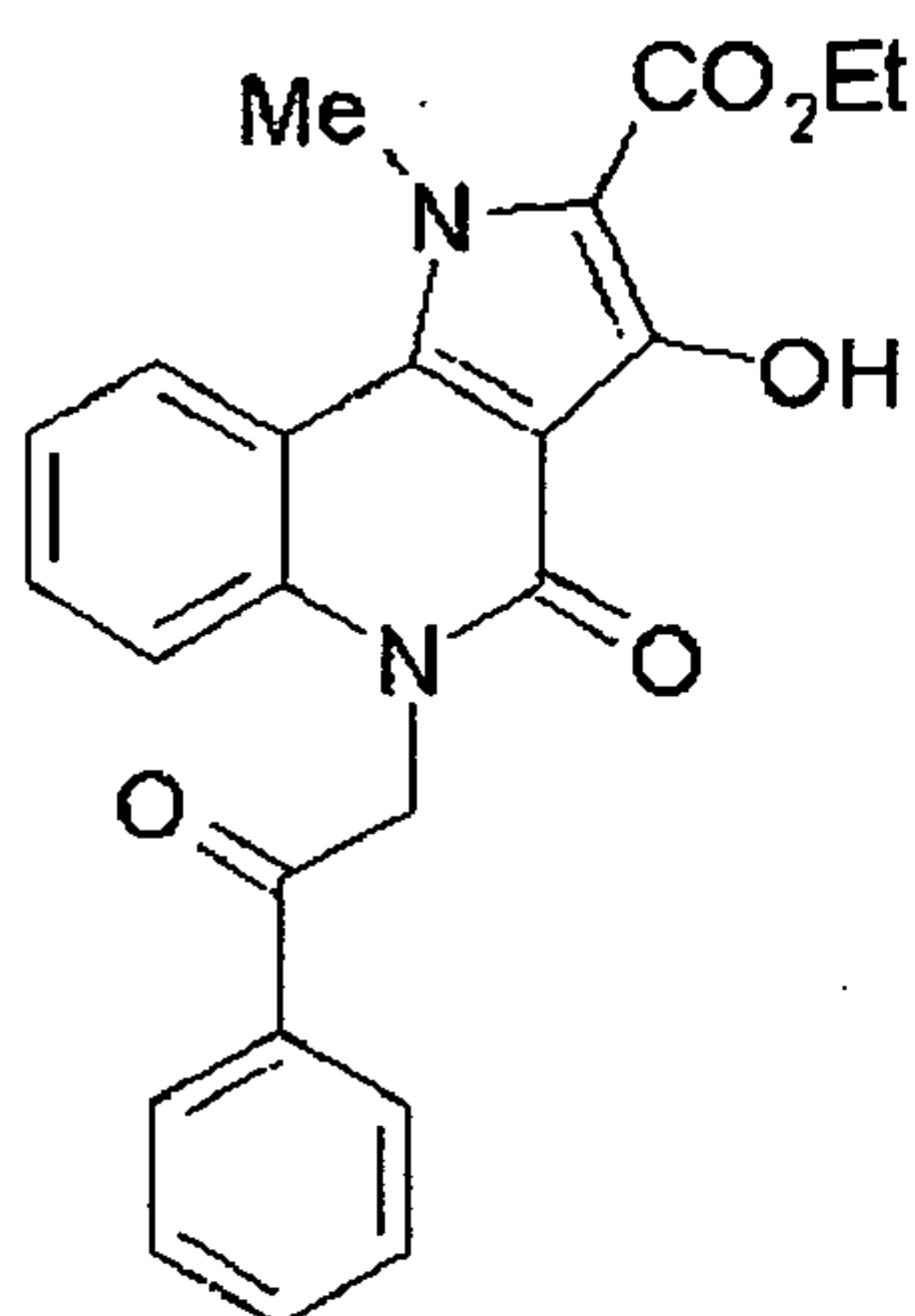
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.21-1.31 (6H, m), 2.93 (3H, s), 3.95 (2H, s), 4.15-4.31 (4H, m), 5.87 (2H, s), 7.31 (1H, t, J = 7.8 Hz), 7.40 (1H, d, J = 8.4 Hz), 7.55-7.65 (3H, m), 7.72-7.78 (1H, m), 8.05 (1H, dd, J = 7.8, 1.5 Hz), 8.12-8.15 (2H, m).

[0284]

20 Reference Example 26

Production of ethyl 3-hydroxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate

[0285]



[0286]

A mixture of the compound of Reference Example 25 (1.25 g, 2.77 mmol), a 20% solution (1.23 g, 3.33 mmol) of sodium
 5 ethoxide in ethanol and ethanol (25 mL) was stirred at 55°C for 15 hr. The reaction mixture was diluted with water, 1N hydrochloric acid (5 mL) was added and the mixture was stirred for 30 min. The precipitated solid was collected by filtration, washed with water, ethanol and ethyl acetate, and
 10 recrystallized from dimethylformamide-ethanol to give the title compound (760 mg, 68%) as a white powder.

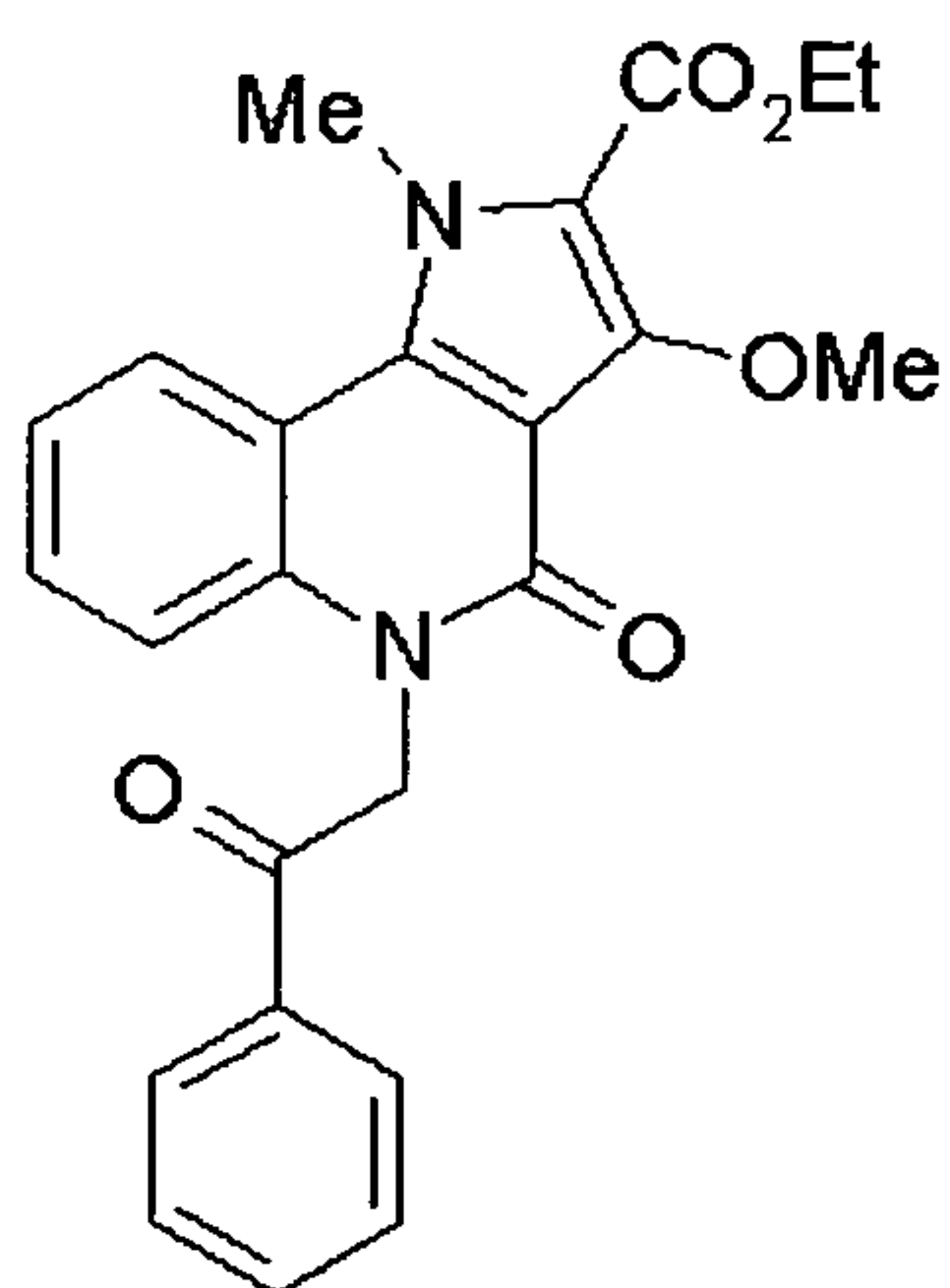
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.33 (3H, t, J = 7.2 Hz), 4.30-4.38 (5H, m), 5.93 (2H, s), 7.30-7.40 (2H, m), 7.48-7.53 (1H, m), 7.61-7.66 (2H, m), 7.73-7.79 (1H, m), 8.15-8.18 (2H, m), 8.34-
 15 8.37 (1H, m), 9.00 (1H, s).

[0287]

Reference Example 27

Production of ethyl 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-
 20 carboxylate

[0288]



[0289]

In the same manner as in Reference Example 6, the title compound (420 mg, 55%) was obtained as a white powder from the compound of Reference Example 26 (740 mg, 1.83 mmol), DBU (410 μ L, 2.74 mmol) and iodomethane (171 μ L, 2.74 mmol).

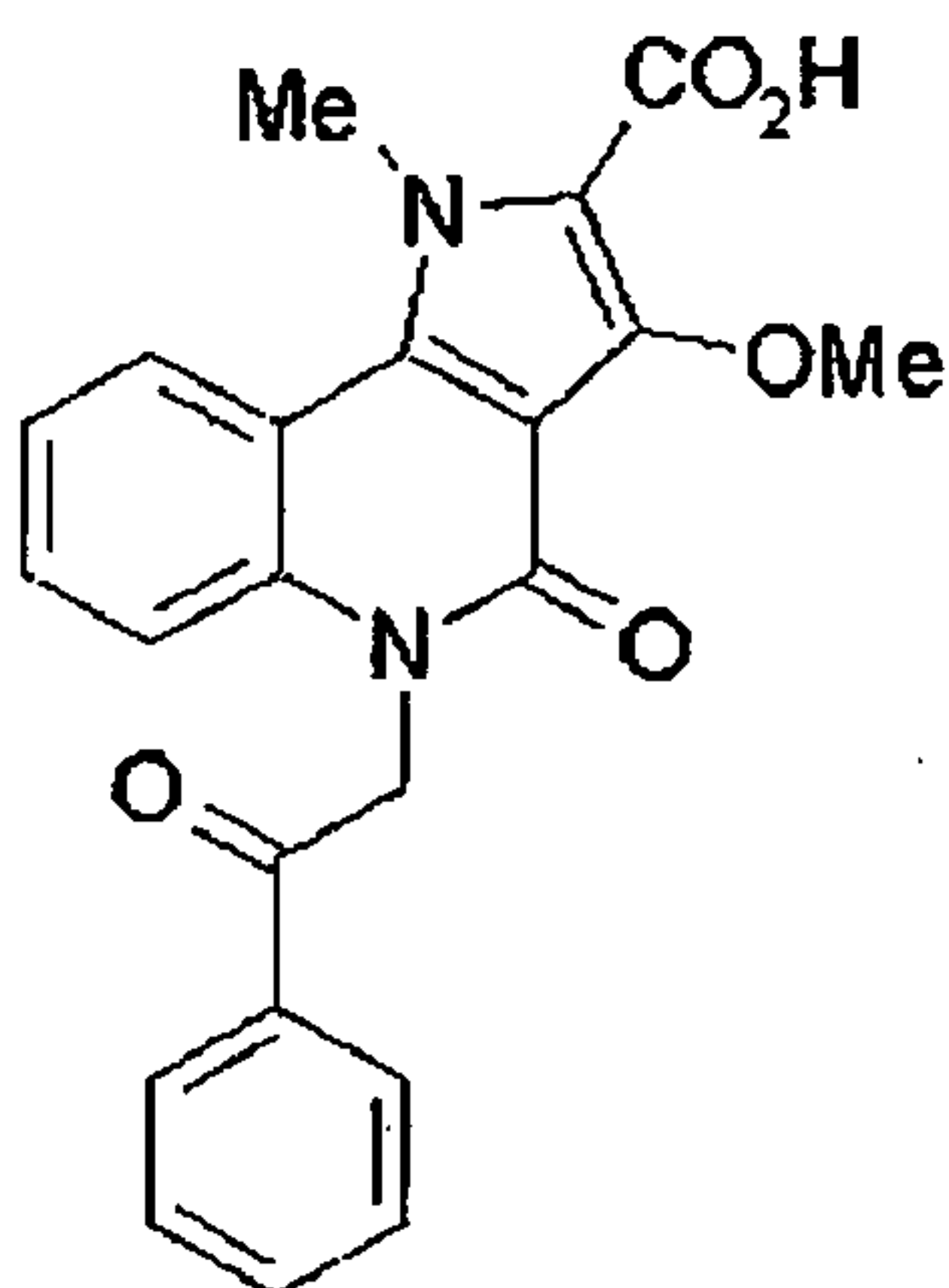
$^1\text{H-NMR}$ (300 MHz, DMSO- d_6) δ : 1.35 (3H, t, $J = 7.1$ Hz), 3.89 (3H, s), 4.29–4.37 (5H, m), 5.96 (2H, s), 7.30–7.40 (2H, m), 7.48–7.53 (1H, m), 7.61–7.66 (2H, m), 7.73–7.78 (1H, m), 8.15–8.18 (2H, m), 8.38 (1H, dd, $J = 8.3, 1.4$ Hz).

[0290]

Reference Example 28

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylic acid

[0291]



[0292]

In the same manner as in Reference Example 7, the title compound (345 mg, 91%) was obtained as a white powder from the compound of Reference Example 27 (405 mg, 0.968 mmol), 8N

aqueous sodium hydroxide solution (1.5 mL) and ethanol (15 mL).

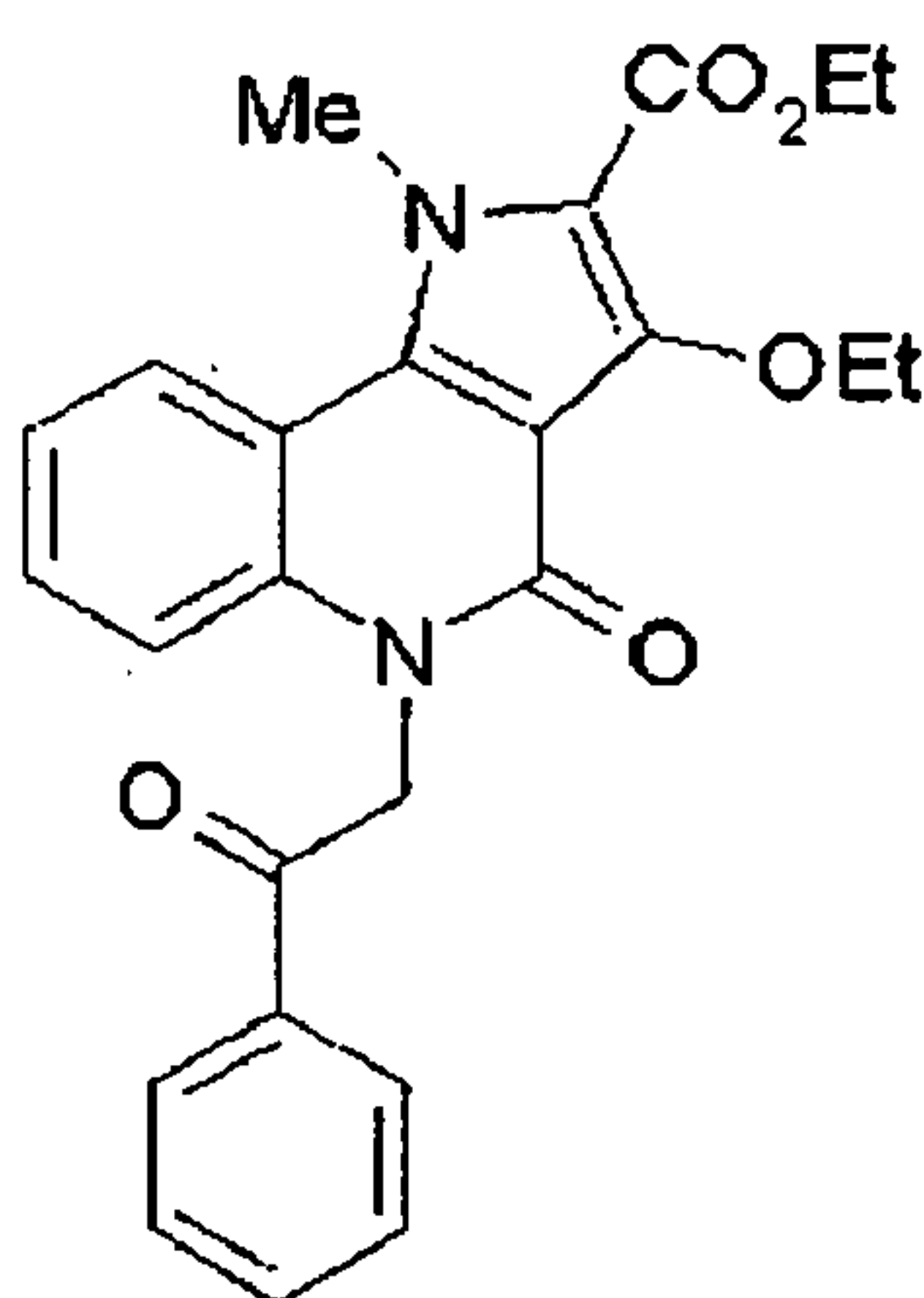
¹H-NMR (300 MHz, DMSO-d₆) δ: 3.88 (3H, s), 4.31 (3H, s), 5.95 (2H, s), 7.29-7.39 (2H, m), 7.46-7.52 (1H, m), 7.61-7.66 (2H, m), 7.73-7.78 (1H, m), 8.16-8.18 (2H, m), 8.38 (1H, dd, J = 8.3, 1.1 Hz), 12.92 (1H, s).

[0293]

Reference Example 29

Production of ethyl 3-ethoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate

[0294]



[0295]

In the same manner as in Reference Example 6, the title compound (2.10 g, quant.) was obtained as a white powder from the compound (1.90 g, 4.70 mmol) of Reference Example 26, DBU (1.05 mL, 7.05 mmol) and iodoethane (564 μL, 7.05 mmol).

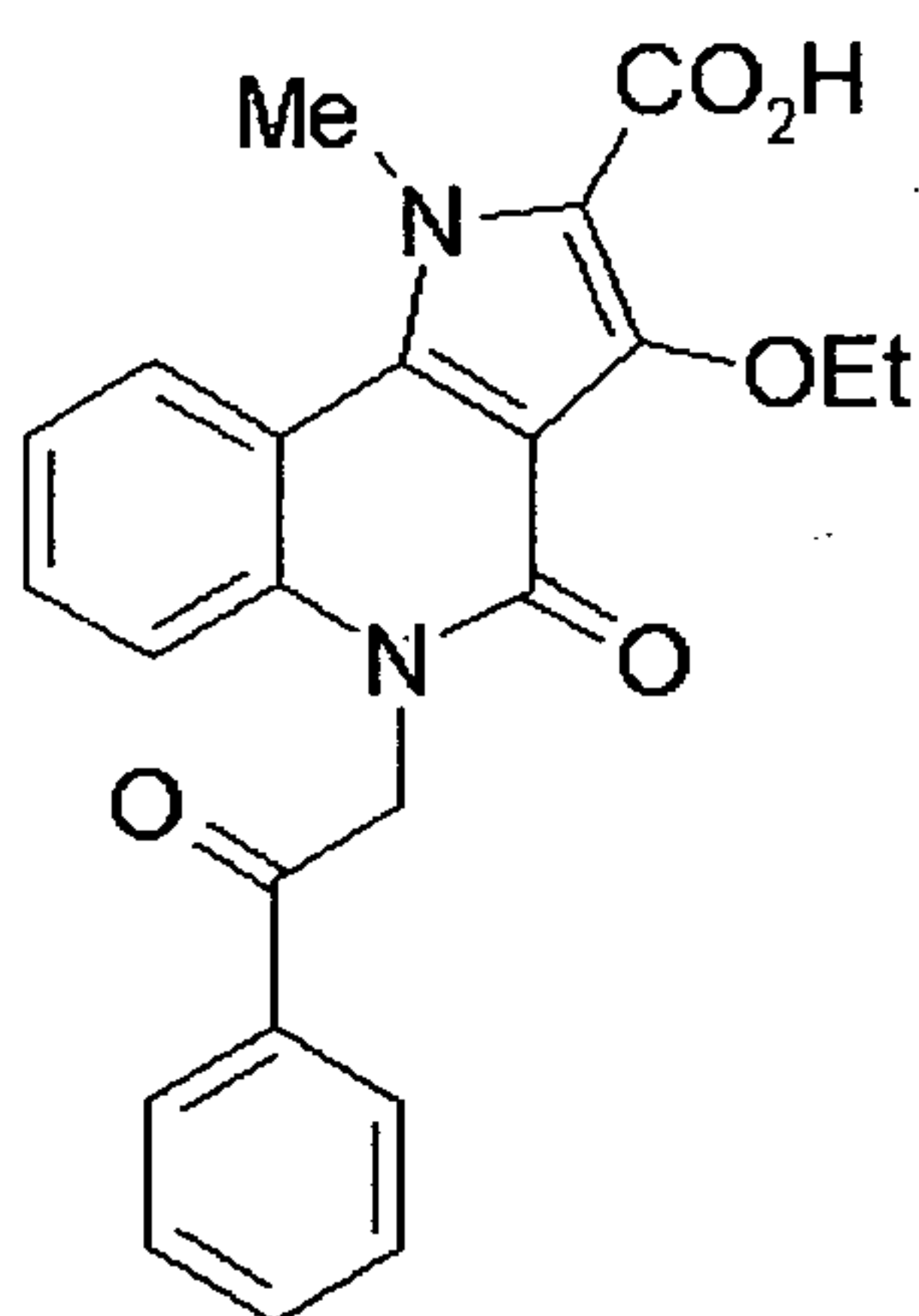
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.27-1.37 (6H, m), 4.16 (2H, q, J = 6.9 Hz), 4.29-4.36 (5H, m), 5.95 (2H, s), 7.27-7.39 (2H, m), 7.50 (1H, t, J = 8.0 Hz), 7.63 (2H, t, J = 7.3 Hz), 7.76 (1H, t, J = 7.4 Hz), 8.17 (2H, d, J = 7.3 Hz), 8.38 (1H, d, J = 8.1 Hz).

[0296]

Reference Example 30

Production of 3-ethoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylic acid

[0297]



[0298]

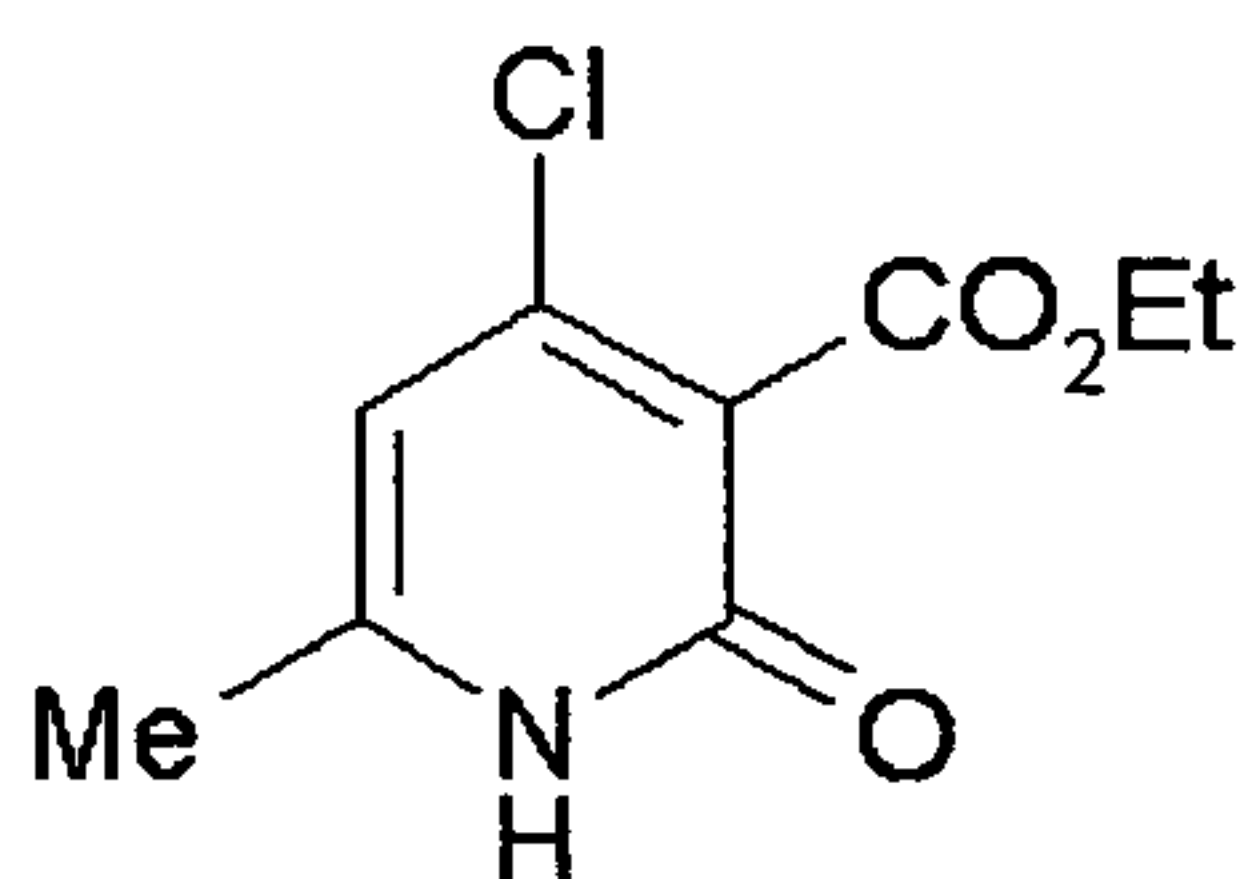
In the same manner as in Reference Example 7, the title compound (1.62 g, 89%) was obtained as a white powder from the compound of Reference Example 29 (1.95 g, 4.51 mmol), 8N aqueous sodium hydroxide solution (2.0 mL) and ethanol (14 mL). ¹H-NMR (300 MHz, DMSO-d₆) δ: 1.27 (3H, t, J = 7.0 Hz), 4.16 (2H, q, J = 7.0 Hz), 4.31 (3H, s), 5.95 (2H, s), 7.27-7.39 (2H, m), 7.49 (1H, t, J = 7.4 Hz), 7.63 (2H, t, J = 7.4 Hz), 7.76 (1H, t, J = 7.4 Hz), 8.15-8.18 (2H, m), 8.38 (1H, d, J = 7.2 Hz), 12.83 (1H, s).

[0299]

Reference Example 31

Production of ethyl 4-chloro-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate

[0300]



[0301]

A mixture of ethyl 4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (3.00 g, 15.2 mmol), phosphorus oxychloride (7.75 mL), n-butyltriethylammonium chloride (13.8 g, 60.8 mmol) and acetonitrile (60 mL) was stirred at 40°C for 30 min and under refluxing conditions for 30 min. After cooling, the reaction mixture was concentrated under reduced pressure, water was added to the residue and the mixture was

extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethyl acetate-hexane mixed solution, and dried under reduced pressure to
 5 give the title compound (1.45 g, 44%) as a white powder.

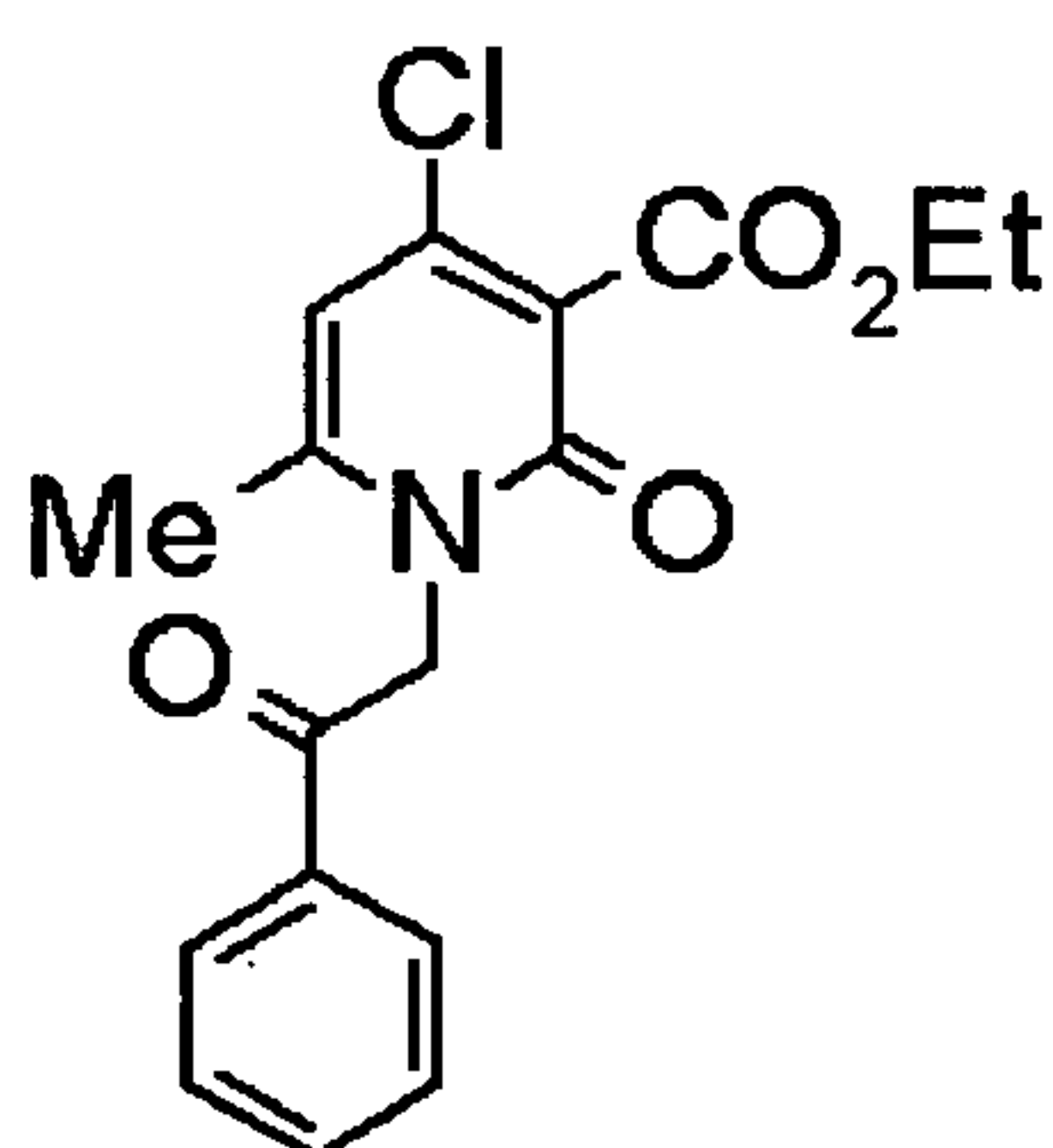
$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ : 1.26 (3H, t, $J = 7.0$ Hz), 2.20 (3H, s), 4.25 (2H, q, $J = 7.0$ Hz), 6.26 (1H, s), 12.29 (1H, s).

[0302]

Reference Example 32

10 Production of ethyl 4-chloro-6-methyl-2-oxo-1-(2-oxo-2-phenylethyl)-1,2-dihydropyridine-3-carboxylate

[0303]



[0304]

15 A mixture of the compound of Reference Example 31 (9.00 g, 41.7 mmol), potassium carbonate (17.3 g, 125 mmol), phenacyl bromide (16.6 g, 83.5 mmol) and DMF (100 mL) was stirred at room temperature for 15 hr. The reaction mixture was poured into water (100 mL), and the mixture was extracted with ethyl
 20 acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=1/9 - 7/3) to give the title compound (3.18 g, 23%) as a white powder.

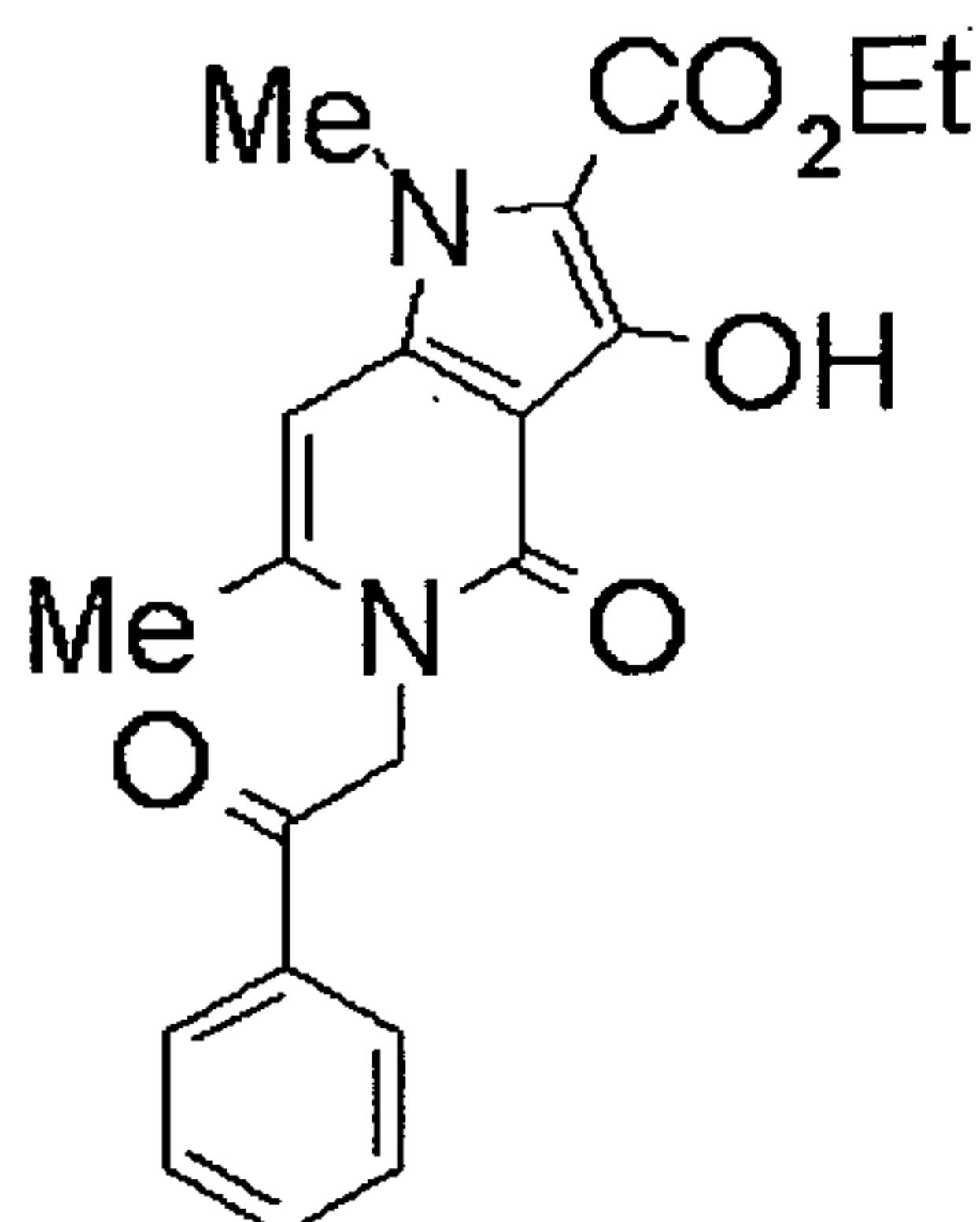
25 $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ : 1.25 (3H, t, $J = 7.0$ Hz), 2.30 (3H, s), 4.25 (2H, q, $J = 7.0$ Hz), 5.63 (2H, s), 6.54 (1H, d, $J = 0.6$ Hz), 7.61 (2H, t, $J = 7.5$ Hz), 7.72-7.78 (1H, m), 8.07-8.10 (2H, m).

[0305]

30 Reference Example 33

Production of ethyl 3-hydroxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0306]



[0307]

A mixture of the compound of Reference Example 32 (2.00 g, 5.99 mmol), sarcosine ethyl ester hydrochloride (1.84 g, 12.0 mmol), triethylamine (4.98 mL, 36.0 mmol) and ethanol (20 mL) was stirred at 80°C for 15 hr, a 20% solution (3.5 mL) of sodium ethoxide in ethanol was added, and the mixture was stirred at 100°C for 24 hr. After cooling, the reaction mixture was diluted with water (50 mL), 6N hydrochloric acid was added to adjust to pH 3 - 4, and the mixture was stirred for 30 min. The precipitated solid was collected by filtration, and washed with water and ethyl acetate/THF to give the title compound (1.50 g, 68%) as a white powder.

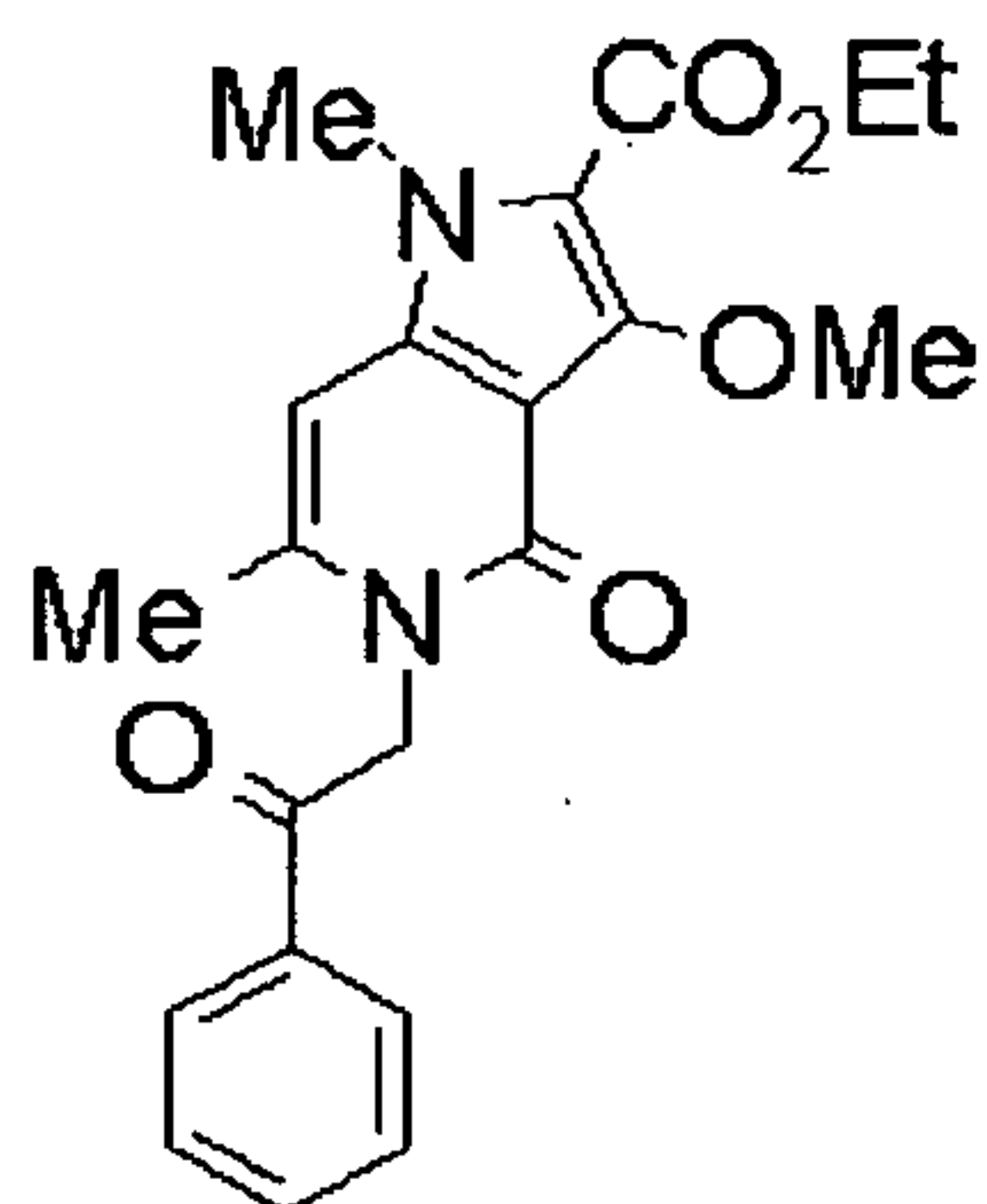
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.31 (3 H, t, J=7.1 Hz), 2.26 (3 H, s), 3.77 (3 H, s), 4.30 (2 H, q, J=7.0 Hz), 5.57 (2 H, s), 6.52 (1 H, s), 7.54-7.67 (2 H, m), 7.69-7.79 (1 H, m), 8.03-8.18 (2 H, m), 8.90 (1 H, s).

[0308]

Reference Example 34

Production of ethyl 3-methoxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0309]



[0310]

In the same manner as in Reference Example 6, the title compound (390 mg, 26%) was obtained as a white powder from the compound of Reference Example 33 (1.45 g, 3.94 mmol), DBU (882 μ L, 5.90 mmol) and iodomethane (367 μ L, 5.90 mmol).

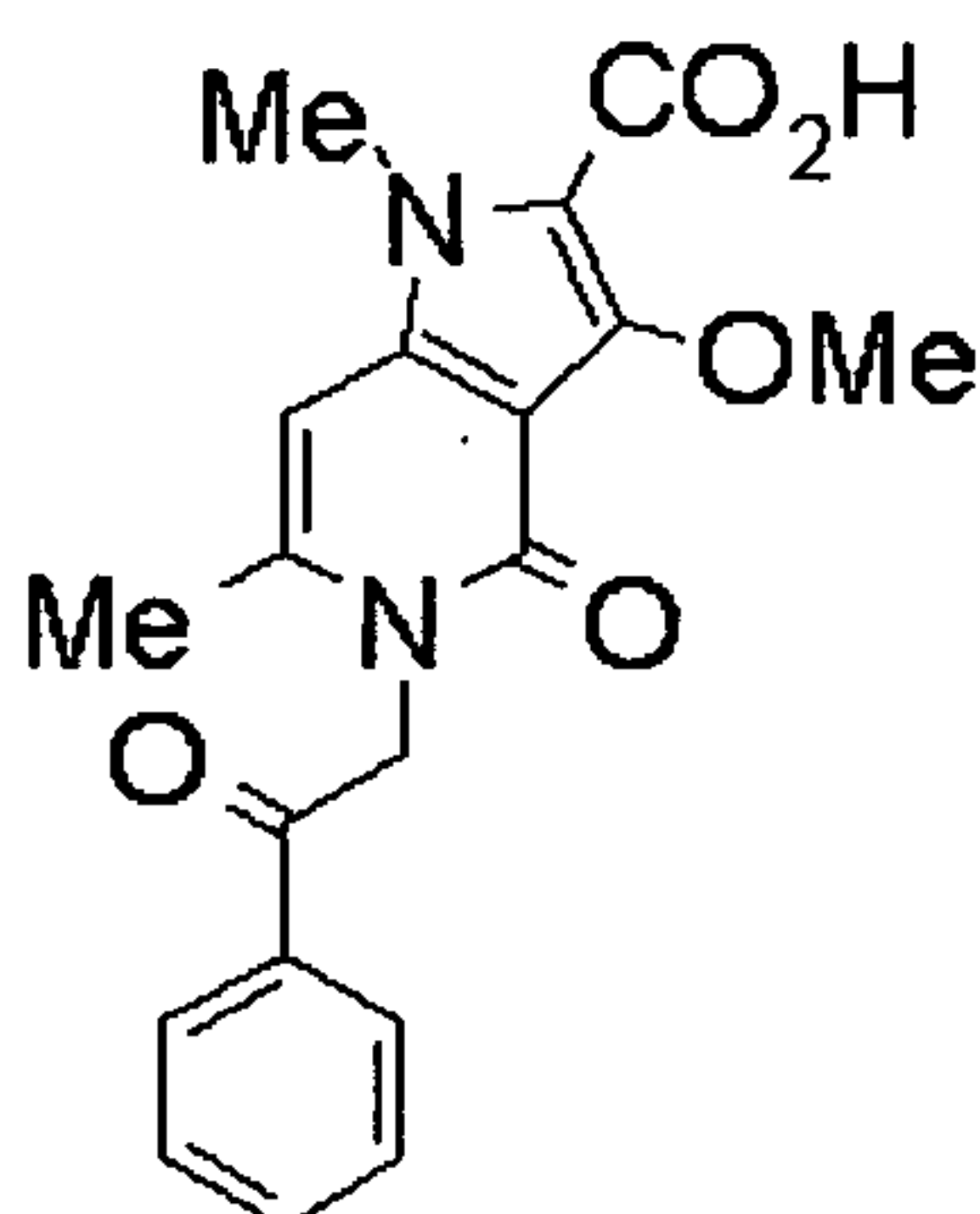
$^1\text{H-NMR}$ (300 MHz, DMSO- d_6) δ : 1.30 (3 H, t, $J=7.1$ Hz), 2.28 (3 H, s), 3.81 (3 H, s), 3.86 (3 H, s), 4.27 (2 H, q, $J=7.0$ Hz), 5.60 (2 H, s), 6.59 (1 H, s), 7.54–7.66 (2 H, m), 7.69–7.79 (1 H, m), 8.05–8.16 (2 H, m).

[0311]

Reference Example 35

Production of 3-methoxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0312]



[0313]

In the same manner as in Reference Example 7, the title compound (305 mg, 89%) was obtained as a white powder from the compound of Reference Example 34 (370 mg, 0.968 mmol), 8N aqueous sodium hydroxide solution (1 mL) and ethanol (7 mL).

$^1\text{H-NMR}$ (300 MHz, DMSO- d_6) δ : 2.28 (3 H, s), 3.81 (3 H, s), 3.86

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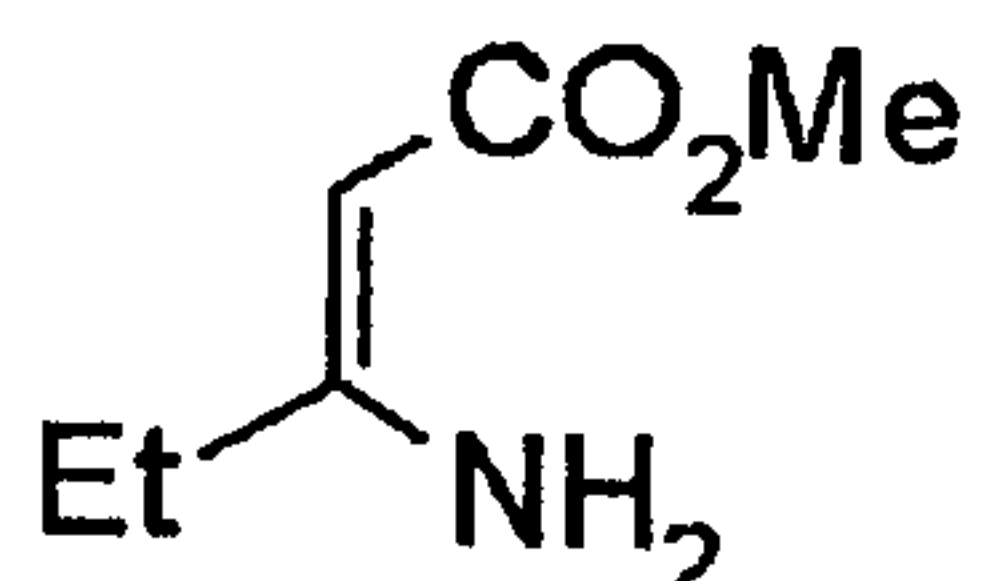
(3 H, s), 5.60 (2 H, s), 6.58 (1 H, s), 7.61 (2 H, t, J=7.4 Hz), 7.74 (1 H, t, J=7.3 Hz), 8.11 (2 H, d, J=7.7 Hz), 12.50 (1 H, br s).

[0314]

5 Reference Example 36

Production of methyl (2Z)-3-aminopenta-2-enoate

[0315]



[0316]

10 A mixture of methyl 3-oxovalerate (75.0 g, 576 mmol), ammonium acetate (222 g, 2.88 mol) and methanol (750 mL) was stirred at room temperature for 3 days. The mixture was concentrated under reduced pressure, water (500 mL) was added to the residue and the mixture was extracted with ethyl
15 acetate (200 mL). The extract was washed with brine, dried over magnesium sulfate, concentrated under reduced pressure, and dried to give the title compound (68.5 g, 92%) as a pale-yellow oil.

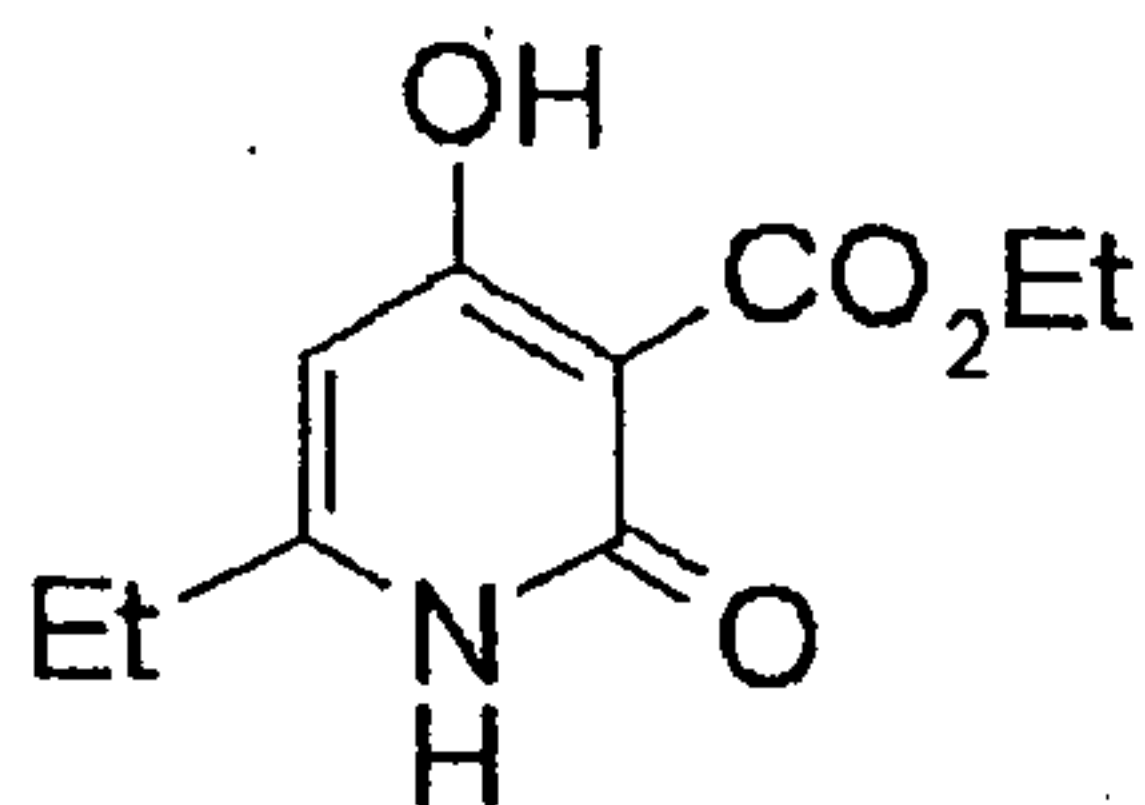
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.06 (3 H, t, J=7.6 Hz), 2.09 (2 H, q, J=7.6 Hz), 3.49 (3 H, s), 4.34 (1 H, s), 6.94 (1 H, s), 7.72 (1 H, br s).

[0317]

Reference Example 37

Production of ethyl 6-ethyl-4-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylate
25

[0318]



[0319]

To a solution of the compound of Reference Example 36
30 (50.0 g, 387 mmol) and diethyl malonate (58.8 mL, 387 mmol) in

ethanol (400 mL) was added a 20% solution (133 g) of sodium ethoxide in ethanol, and the mixture was stirred at 150°C for 15 hr while evaporating ethanol. After cooling, the obtained solid was collected by filtration, washed with ethyl acetate, and dissolved in water. Insoluble material was filtered off, the filtrate was acidified with 5N hydrochloric acid, and the precipitated solid was collected by filtration. The obtained solid was washed with water and ethyl acetate-hexane to give the title compound (36.4 g, 45%) as a white powder.

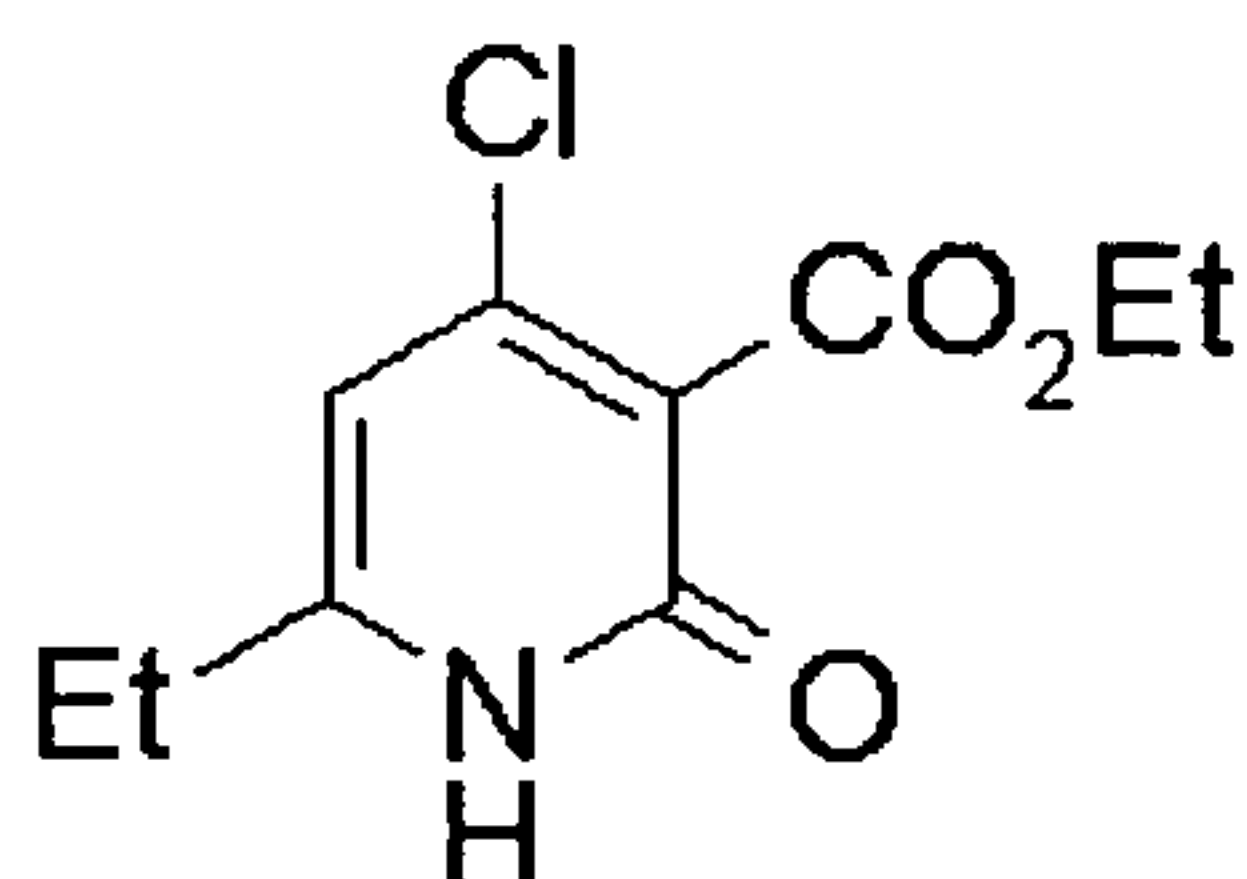
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.12 (3 H, t, J=7.6 Hz), 1.26 (3 H, t, J=7.1 Hz), 2.42 (2 H, q, J=7.6 Hz), 4.25 (2 H, q, J=7.0 Hz), 5.79 (1 H, s), 11.37 (1 H, brs), 12.57 (1 H, s).

[0320]

Reference Example 38

Production of ethyl 4-chloro-6-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylate

[0321]



[0322]

A mixture of the compound of Reference Example 37 (15.0 g, 71.0 mmol) and phosphorus oxychloride (19.9 mL, 213 mmol) was stirred at 80°C for 30 min. The mixture was concentrated under reduced pressure, ice water was added to the residue, and the precipitated solid was collected by filtration, and washed with water and ethyl acetate to give the title compound (9.80 g, 60%) as a white solid.

¹H-NMR (300 MHz, DMSO-d₆) δ: 1.15 (3 H, t, J=7.5 Hz), 1.26 (3 H, t, J=7.0 Hz), 2.44-2.55 (2 H, m), 4.25 (2 H, q, J=7.1 Hz), 6.26 (1 H, s), 12.28 (1 H, s).

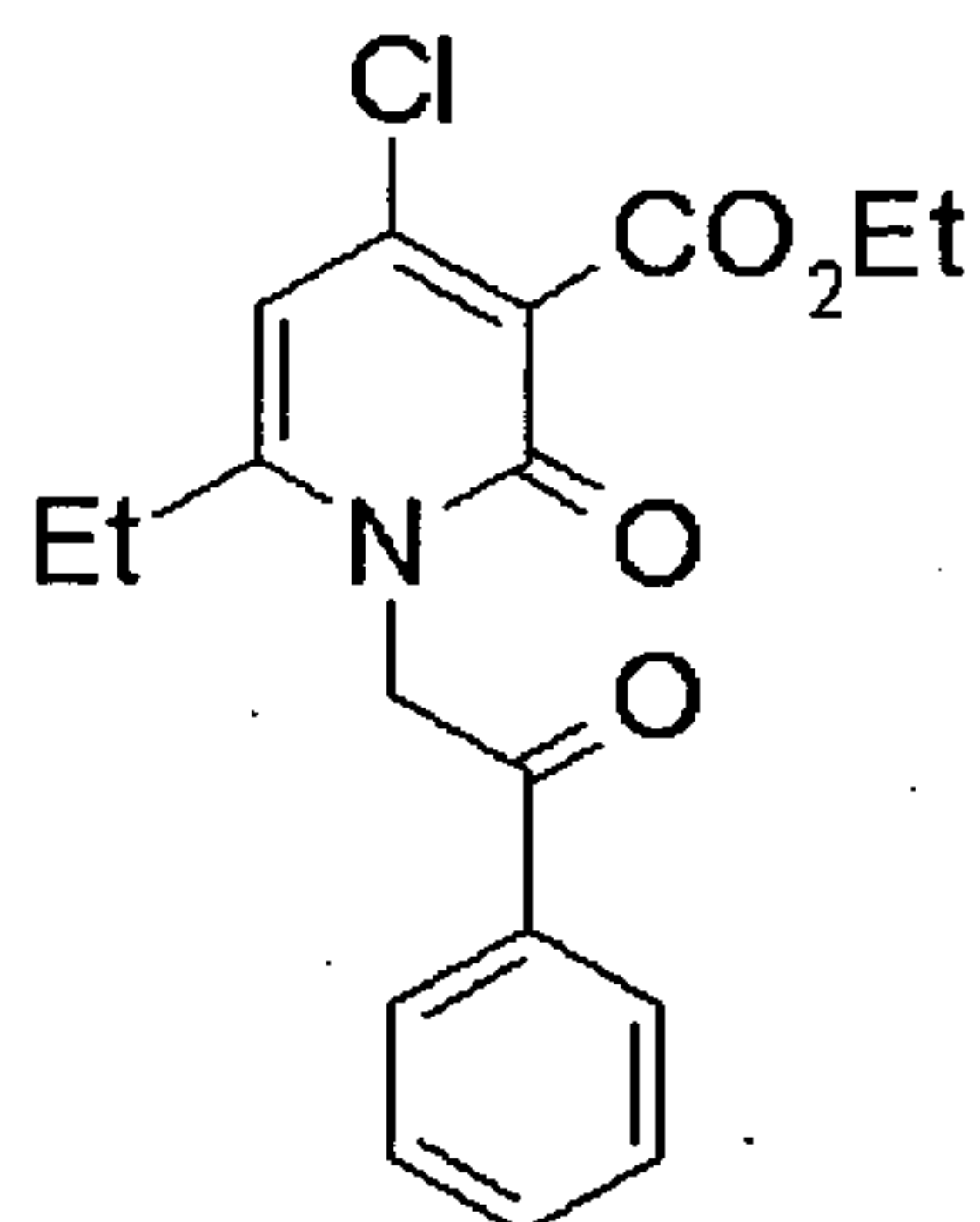
[0323]

Reference Example 39

Production of ethyl 4-chloro-6-ethyl-2-oxo-1-(2-oxo-2-

phenylethyl)-1,2-dihydropyridine-3-carboxylate

[0324]



[0325]

5 In the same manner as in Reference Example 32, the title compound (1.00 g, 7%) was obtained as a white powder from the compound of Reference Example 38 (9.50 g, 41.4 mmol), potassium carbonate (13.7 g, 99.2 mmol), phenacyl bromide (9.88 g, 49.6 mmol) and DMF (100 mL).

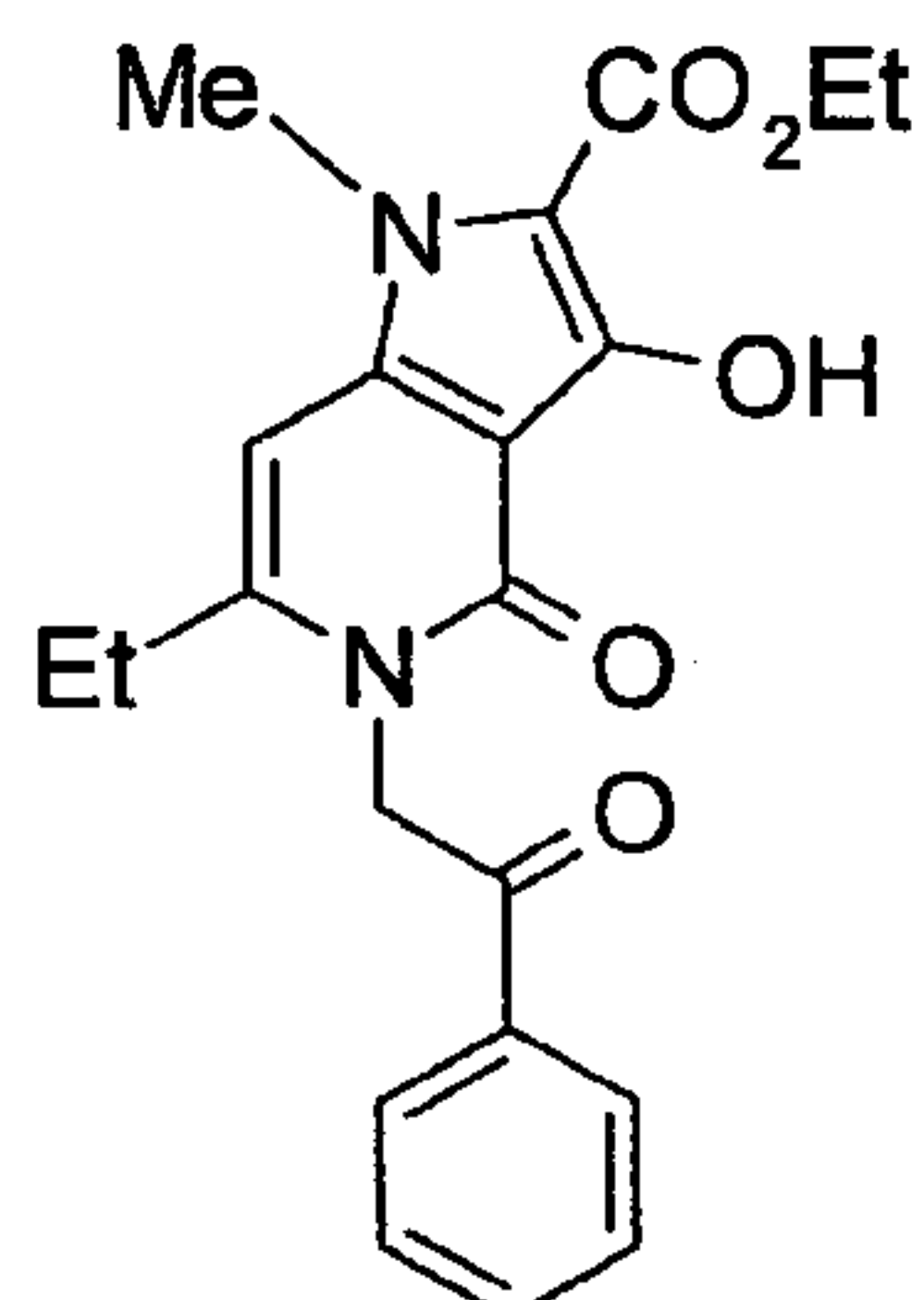
10 ¹H-NMR (300 MHz, DMSO-d₆) δ: 1.14 (3 H, t, J=7.4 Hz), 1.24 (3 H, t, J=7.1 Hz), 2.62 (2 H, q, J=7.4 Hz), 4.25 (2 H, q, J=7.1 Hz), 5.61 (2 H, s), 6.44 (1 H, s), 7.54-7.66 (2 H, m), 7.70-7.79 (1 H, m), 8.05-8.13 (2 H, m).

[0326]

15 Reference Example 40

Production of ethyl 6-ethyl-3-hydroxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0327]



20

[0328]

A mixture of the compound of Reference Example 39 (950 mg, 2.73 mmol), sarcosine ethyl ester hydrochloride (839 mg, 5.46

mmol), triethylamine (2.27 mL, 16.4 mmol) and ethanol (10 mL) was stirred at 80°C for 10 hr, triethylamine (2.27 mL, 16.4 mmol) was further added, and the mixture was stirred at 100°C for 15 hr. After cooling, water was added to the reaction mixture, and the mixture was acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed successively with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluate; ethyl acetate/methanol=10/1) to give the title compound (698 mg, 67%) as a brown solid.

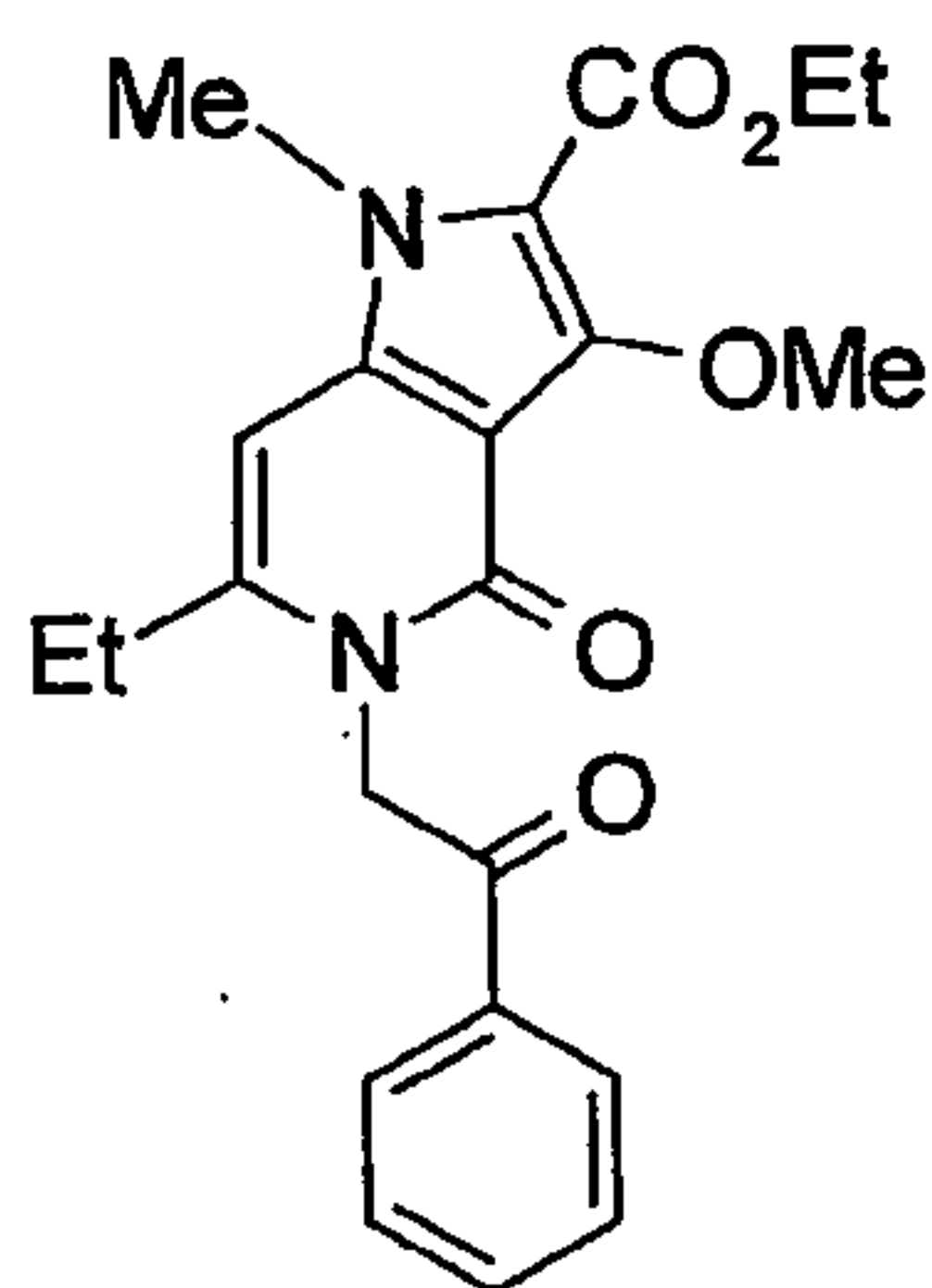
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.18 (3 H, t, J=7.4 Hz), 1.31 (3 H, t, J=7.1 Hz), 2.56 (2 H, q, J=7.6 Hz), 3.80 (3 H, s), 4.30 (2 H, q, J=7.2 Hz), 5.55 (2 H, s), 6.43 (1 H, s), 7.60 (2 H, t, J=7.6 Hz), 7.68-7.79 (1 H, m), 8.00-8.21 (2 H, m), 8.90 (1 H, s).

[0329]

Reference Example 41

Production of ethyl 6-ethyl-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0330]



[0331]

In the same manner as in Reference Example 6, the title compound (156 mg, 23%) was obtained as a white powder from the compound of Reference Example 40 (650 mg, 1.70 mmol).

¹H-NMR (300 MHz, DMSO-d₆) δ: 1.19 (3 H, t, J=7.3 Hz), 1.30 (3 H, t, J=7.1 Hz), 2.58 (2 H, q, J=7.4 Hz), 3.84 (3 H, s), 3.85 (3

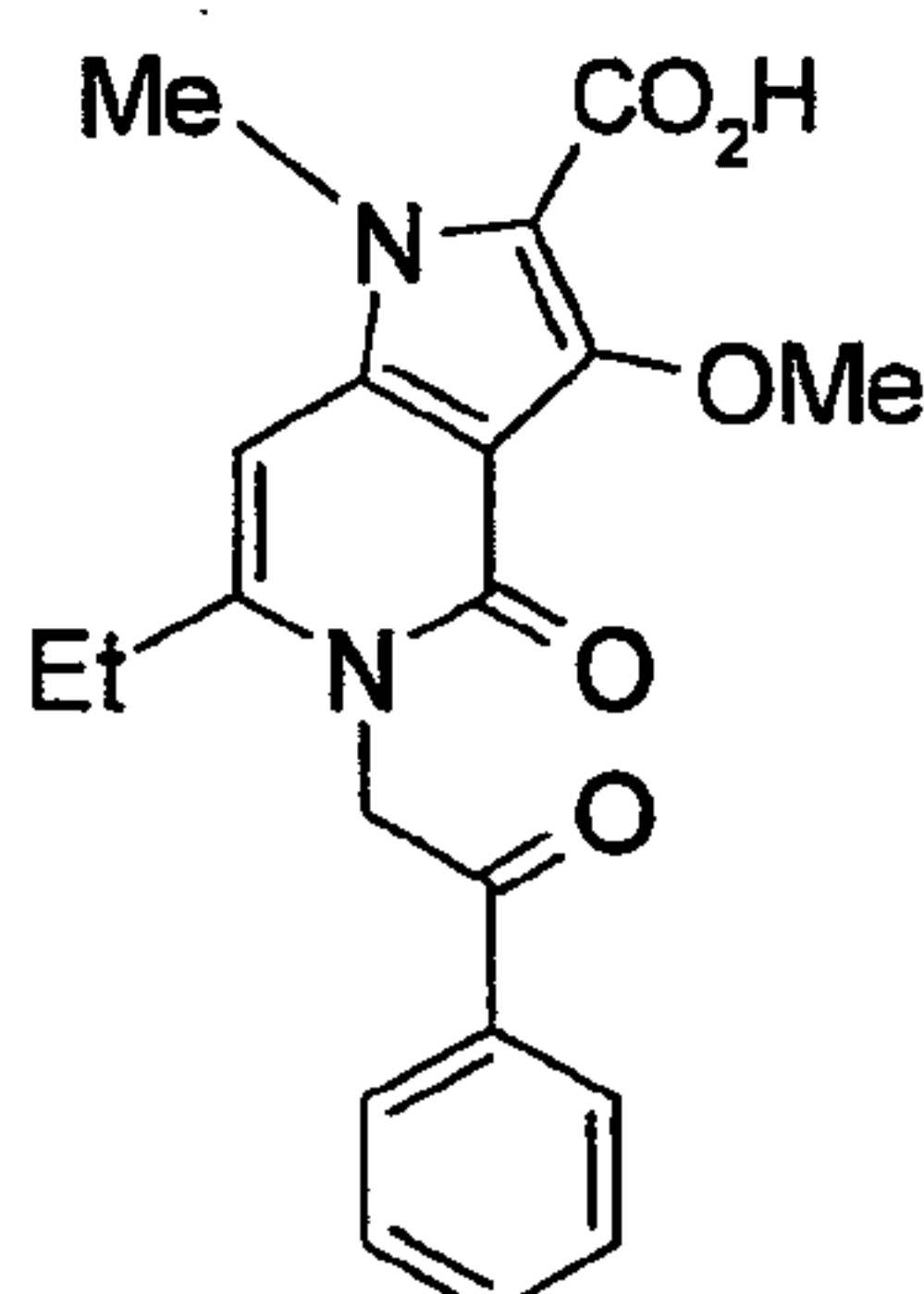
H, s), 4.27 (2 H, q, J=7.0 Hz), 5.58 (2 H, s), 6.50 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.67-7.82 (1 H, m), 8.03-8.19 (2 H, m).

[0332]

5 Reference Example 42

Production of 6-ethyl-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0333]



10

[0334]

In the same manner as in Reference Example 7, the title compound (110 mg, 79%) was obtained as a white powder from the compound of Reference Example 41 (150 mg, 0.378 mmol).

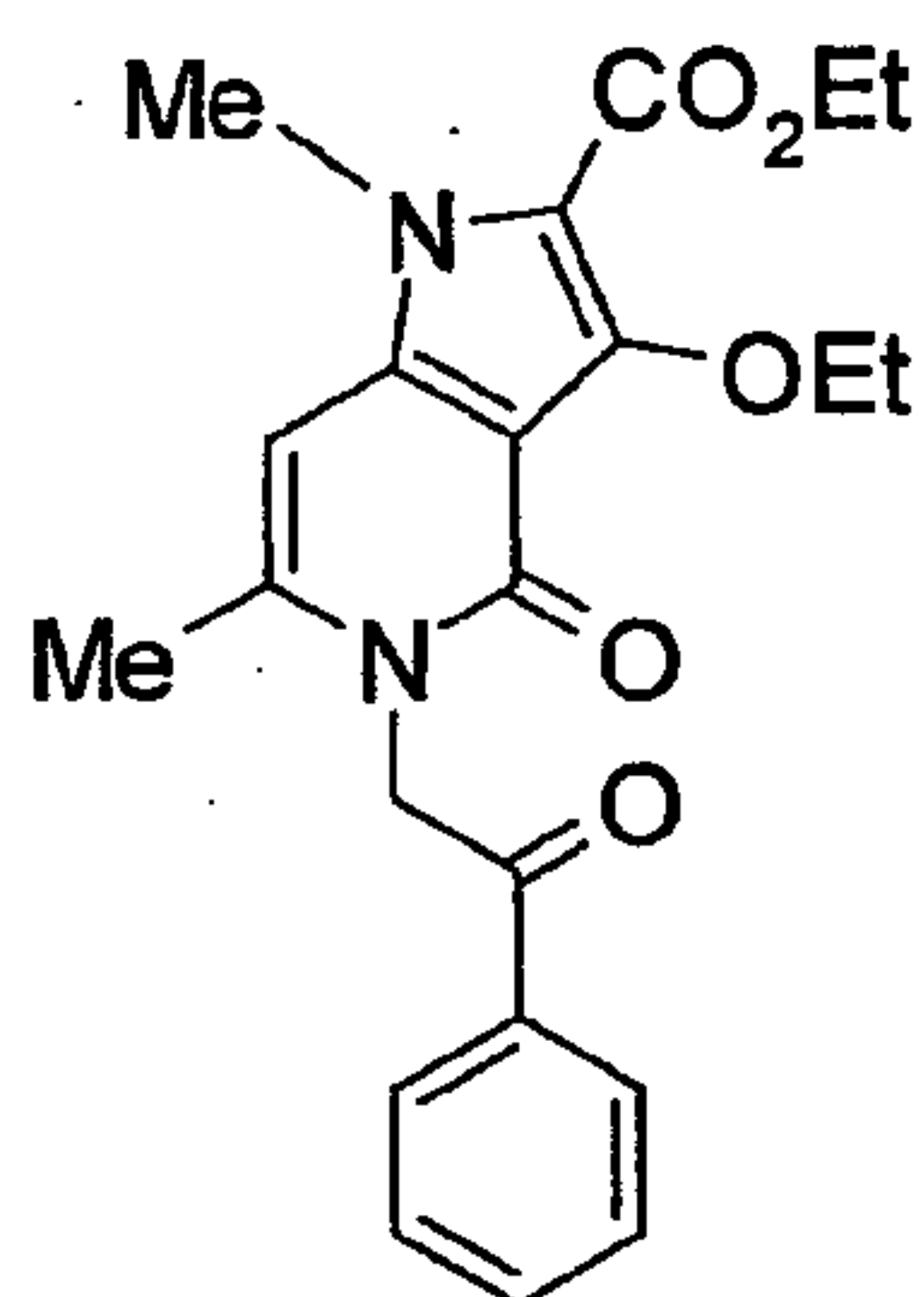
15 ¹H-NMR (300 MHz, DMSO-d₆) δ: 1.19 (3 H, t, J=7.3 Hz), 2.57 (2 H, q, J=7.3 Hz), 3.84 (3 H, s), 3.85 (3 H, s), 5.58 (2 H, s), 6.48 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.67-7.86 (1 H, m), 7.97-8.31 (2 H, m), 12.51 (1 H, br s).

[0335]

20 Reference Example 43

Production of ethyl 3-ethoxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0336]



[0337]

In the same manner as in Reference Example 6, the title compound (560 mg, 52%) was obtained as a white powder from the compound of Reference Example 33 (1.00 g, 2.71 mmol) and iodoethane (326 μ L, 4.07 mmol).

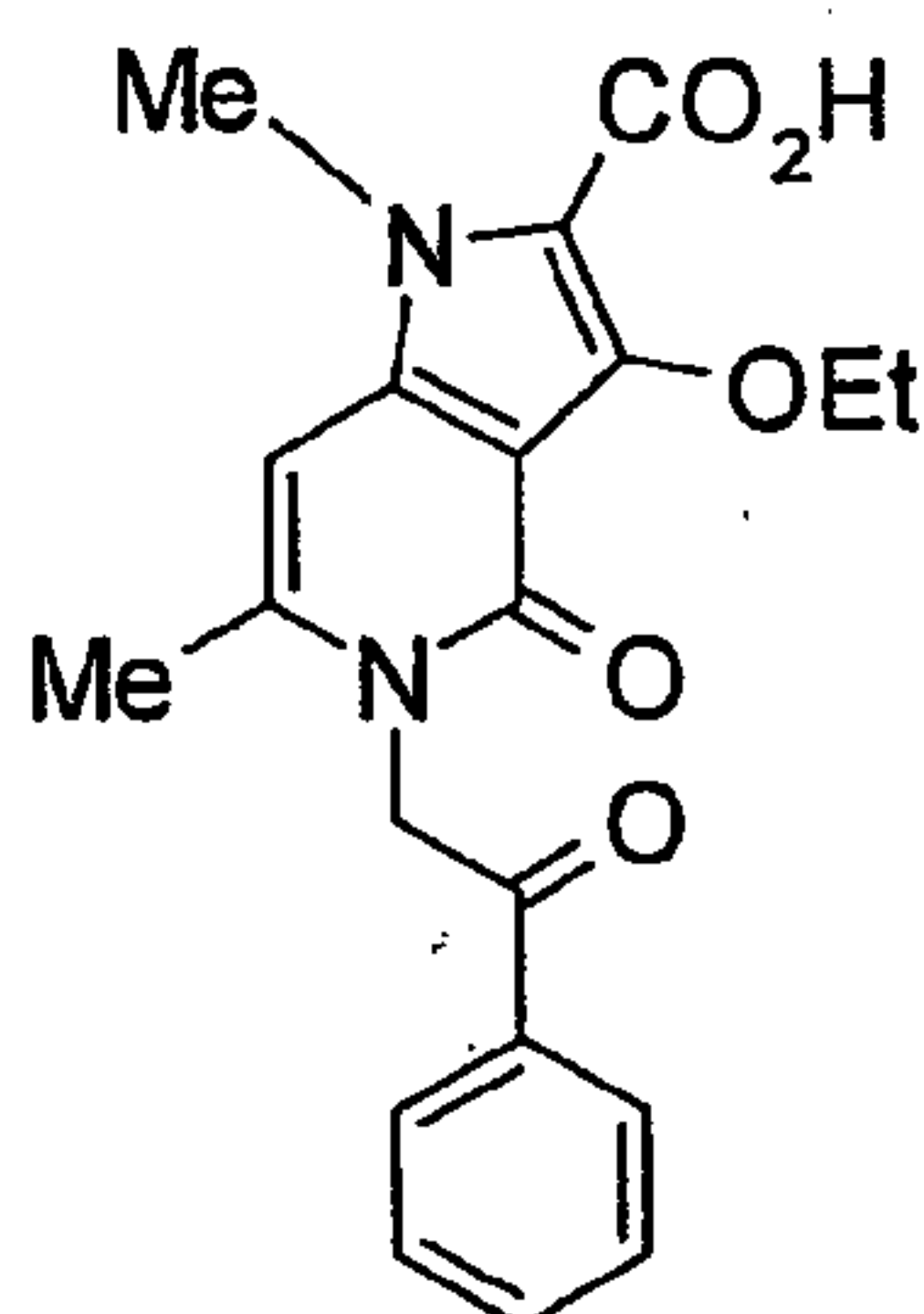
$^1\text{H-NMR}$ (300 MHz, DMSO- d_6) δ : 1.24 (3 H, t, $J=7.0$ Hz), 1.30 (3 H, t, $J=7.1$ Hz), 2.28 (3 H, s), 3.81 (3 H, s), 4.15 (2 H, q, $J=7.0$ Hz), 4.26 (2 H, q, $J=7.1$ Hz), 5.60 (2 H, s), 6.58 (1 H, s), 7.61 (2 H, t, $J=7.6$ Hz), 7.69–7.78 (1 H, m), 8.06–8.14 (2 H, m).

[0338]

Reference Example 44

Production of 3-ethoxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0339]



[0340]

In the same manner as in Reference Example 7, the title compound (380 mg, 74%) was obtained as a white powder from the compound of Reference Example 43 (550 mg, 1.39 mmol).

$^1\text{H-NMR}$ (300 MHz, DMSO- d_6) δ : 1.22 (3 H, t, $J=7.0$ Hz), 2.28 (3 H, s), 3.81 (3 H, s), 4.15 (2 H, q, $J=7.0$ Hz), 4.26 (2 H, q, $J=7.1$ Hz), 5.60 (2 H, s), 6.58 (1 H, s), 7.61 (2 H, t, $J=7.6$ Hz), 7.69–7.78 (1 H, m), 8.06–8.14 (2 H, m).

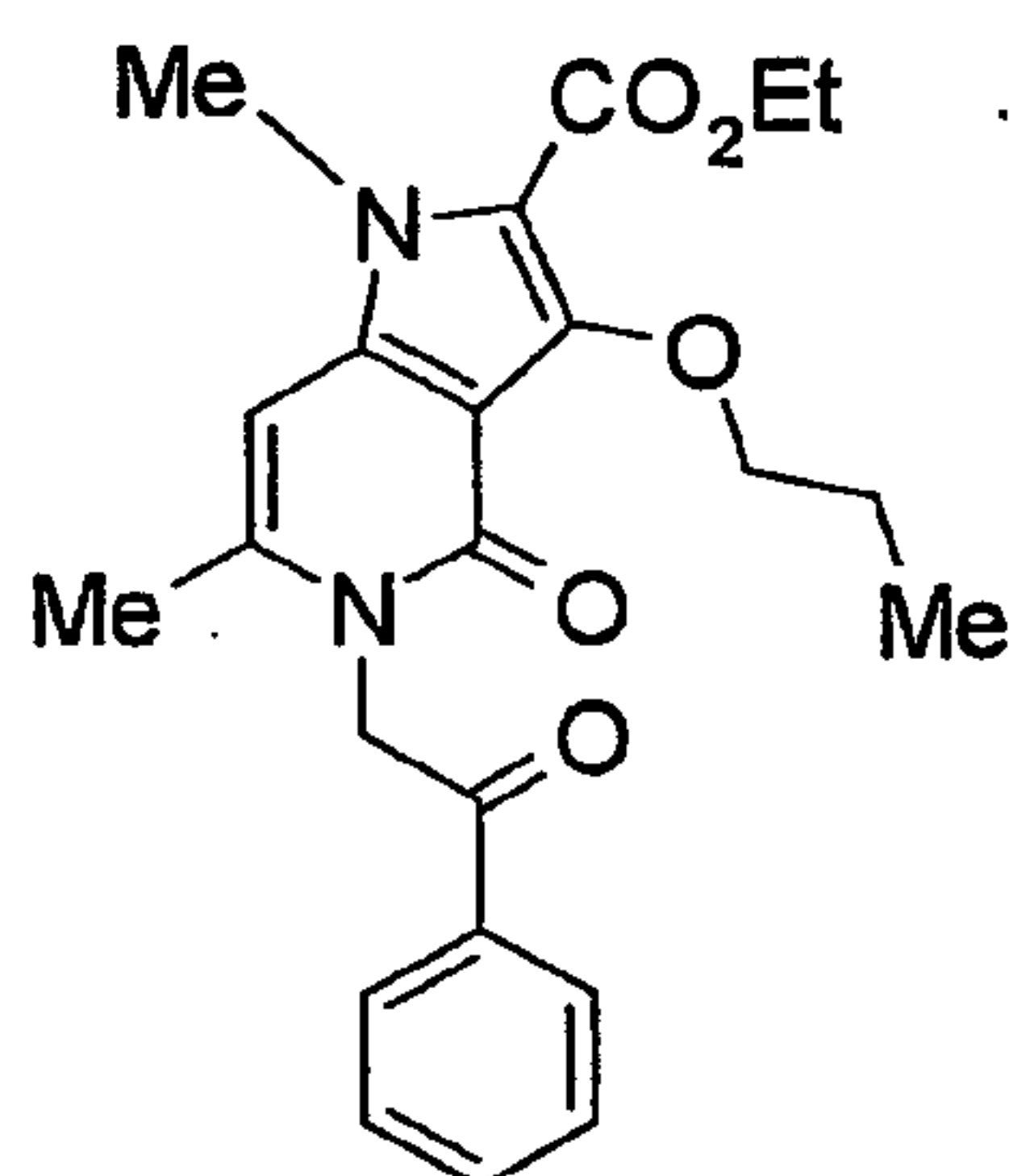
s), 3.81 (3 H, s), 4.16 (2 H, q, J=7.0 Hz), 5.60 (2 H, s), 6.57 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.69-7.79 (1 H, m), 8.03-8.16 (2 H, m), 12.38 (1 H, br s).

[0341]

5 Reference Example 45

Production of ethyl 1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-propoxy-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0342]



10

[0343]

In the same manner as in Reference Example 6, the title compound (152 mg, 18%) was obtained as a white powder from the compound (750 mg, 2.04 mmol) of Reference Example 33 and 1-bromopropane (277 μ L, 3.05 mmol).

$^1\text{H-NMR}$ (300 MHz, DMSO- d_6) δ : 0.94 (3 H, t, J=7.5 Hz), 1.30 (3 H, t, J=7.1 Hz), 1.57-1.73 (2 H, m), 2.28 (3 H, s), 3.80 (3 H, s), 4.08 (2 H, t, J=6.5 Hz), 4.26 (2 H, q, J=7.1 Hz), 5.60 (2 H, s), 6.58 (1 H, s), 7.56-7.66 (2 H, m), 7.69-7.78 (1 H, m), 8.06-8.15 (2 H, m).

20

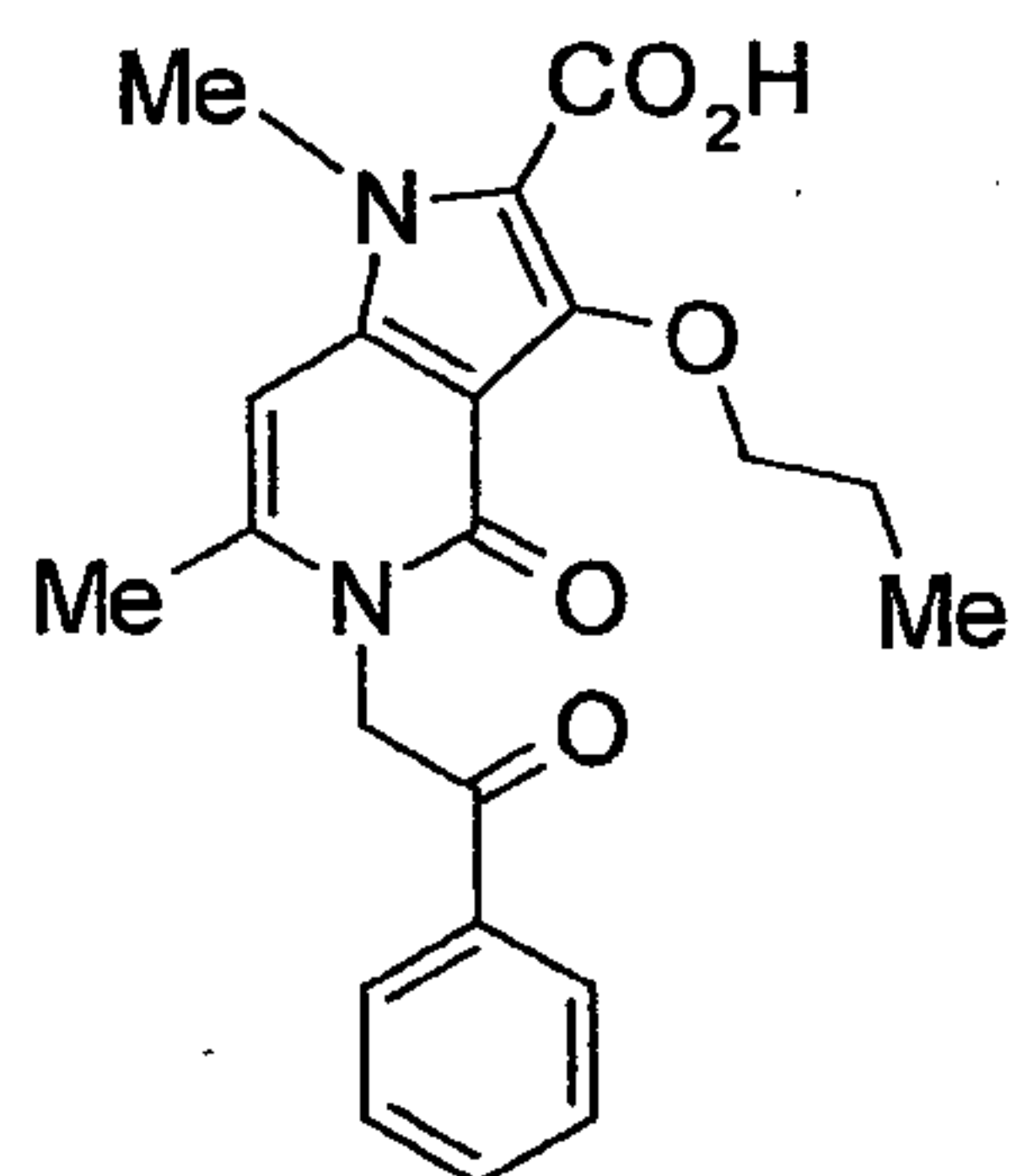
[0344]

Reference Example 46

Production of 1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-propoxy-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

25

[0345]



[0346]

In the same manner as in Reference Example 7, the title compound (105 mg, 81%) was obtained as a white powder from the compound of Reference Example 45 (140 mg, 0.341 mmol).

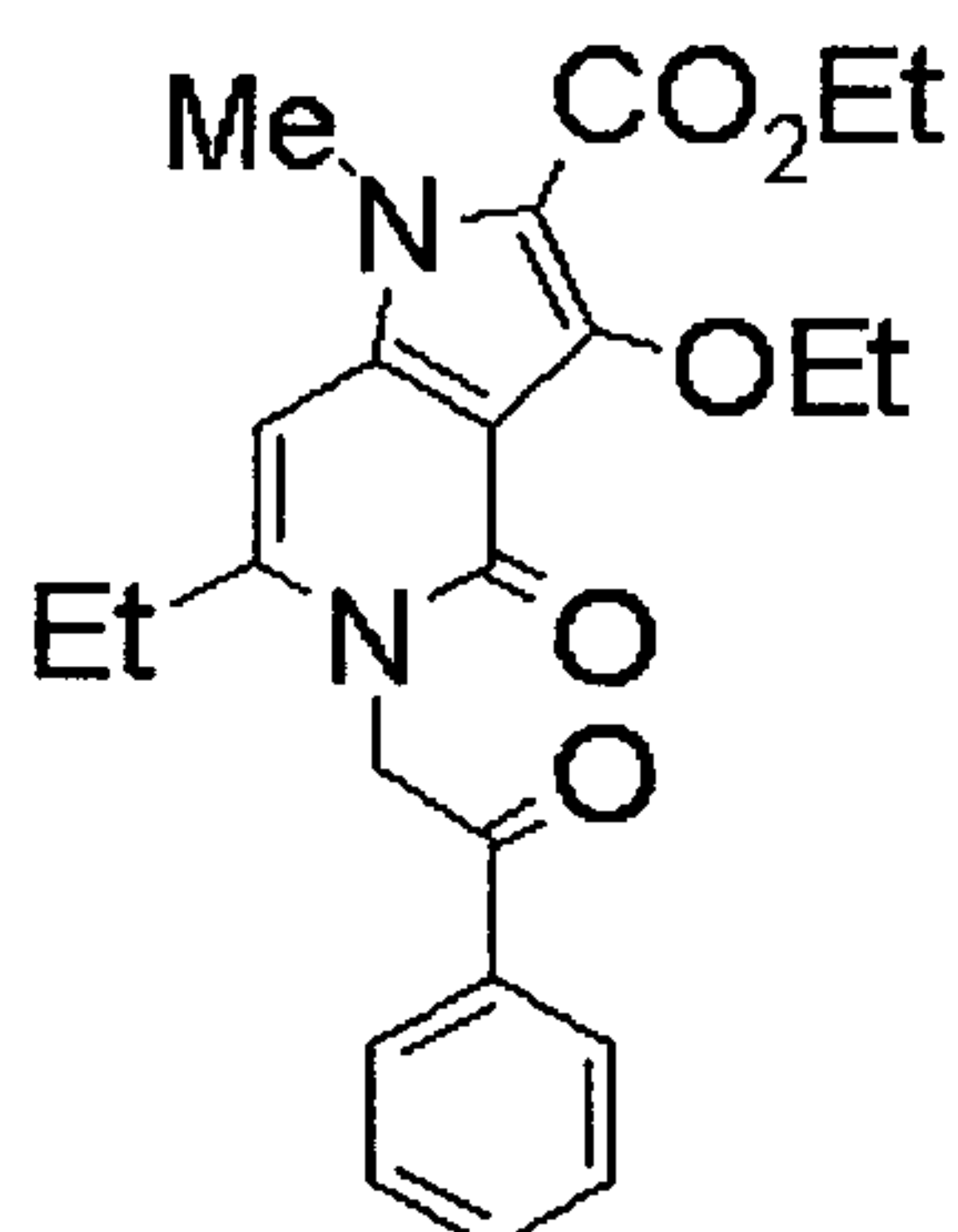
¹H-NMR (300 MHz, DMSO-d₆) δ: 0.88-0.94 (3 H, m), 1.58-1.67 (2 H, m), 2.27 (3 H, s), 3.81 (3 H, s), 4.08 (2 H, t, J=6.6 Hz), 5.60 (2 H, s), 6.57 (1 H, s), 7.55-7.65 (2 H, m), 7.69-7.77 (1 H, m), 8.06-8.14 (2 H, m).

10 [0347]

Reference Example 47

Production of ethyl 6-ethyl-3-ethoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

15 [0348]



[0349]

A mixture of the compound of Reference Example 40 (330 mg, 0.863 mmol), potassium carbonate (715 mg, 5.18 mmol), iodoethane (138 μL, 1.73 mmol) and DMF (5 mL) was stirred at room temperature for 15 hr. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extract was combined, washed with saturated brine, dried over

magnesium sulfate, and concentrated under reduced pressure.

The residue was collected by filtration, and dried to give the title compound (189 mg, 46%) as a white powder.

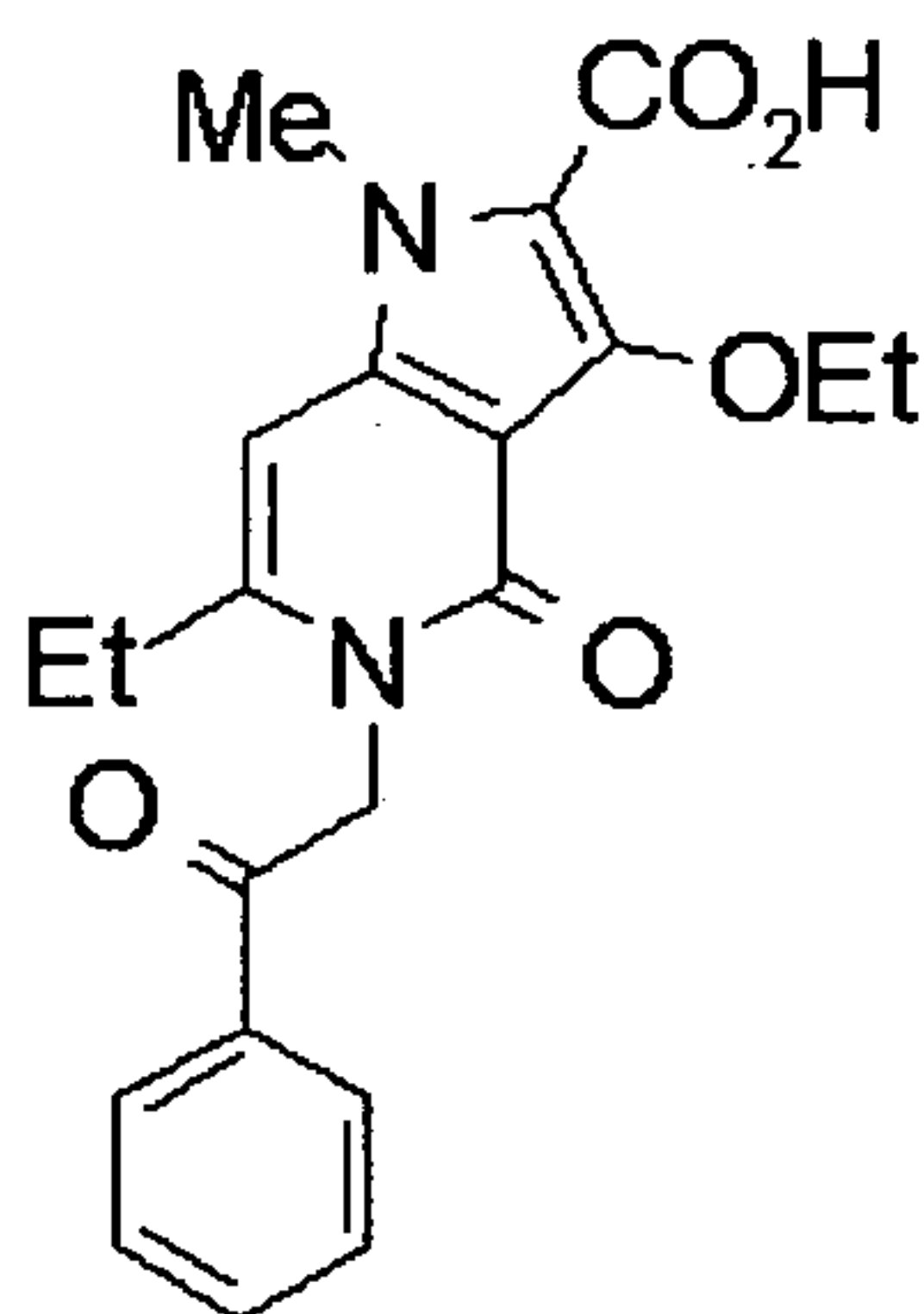
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.13-1.35 (9 H, m), 2.57 (2 H, q, J=7.2 Hz), 3.84 (3 H, s), 4.10-4.19 (2 H, m), 4.26 (2 H, q, J=7.2 Hz), 5.58 (2 H, s), 6.49 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.70-7.77 (1 H, m), 8.07-8.14 (2 H, m).

[0350]

Reference Example 48

10 Production of 3-ethoxy-6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0351]



15 [0352]

A solution of the compound of Reference Example 47 (160 mg, 0.390 mmol) and 8N aqueous sodium hydroxide solution (1 mL) in ethanol (7 mL) was stirred at 60°C for 1 hr. The reaction mixture was diluted with water, acidified with 6N hydrochloric acid, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (74.0 mg, 50%) as a white powder.

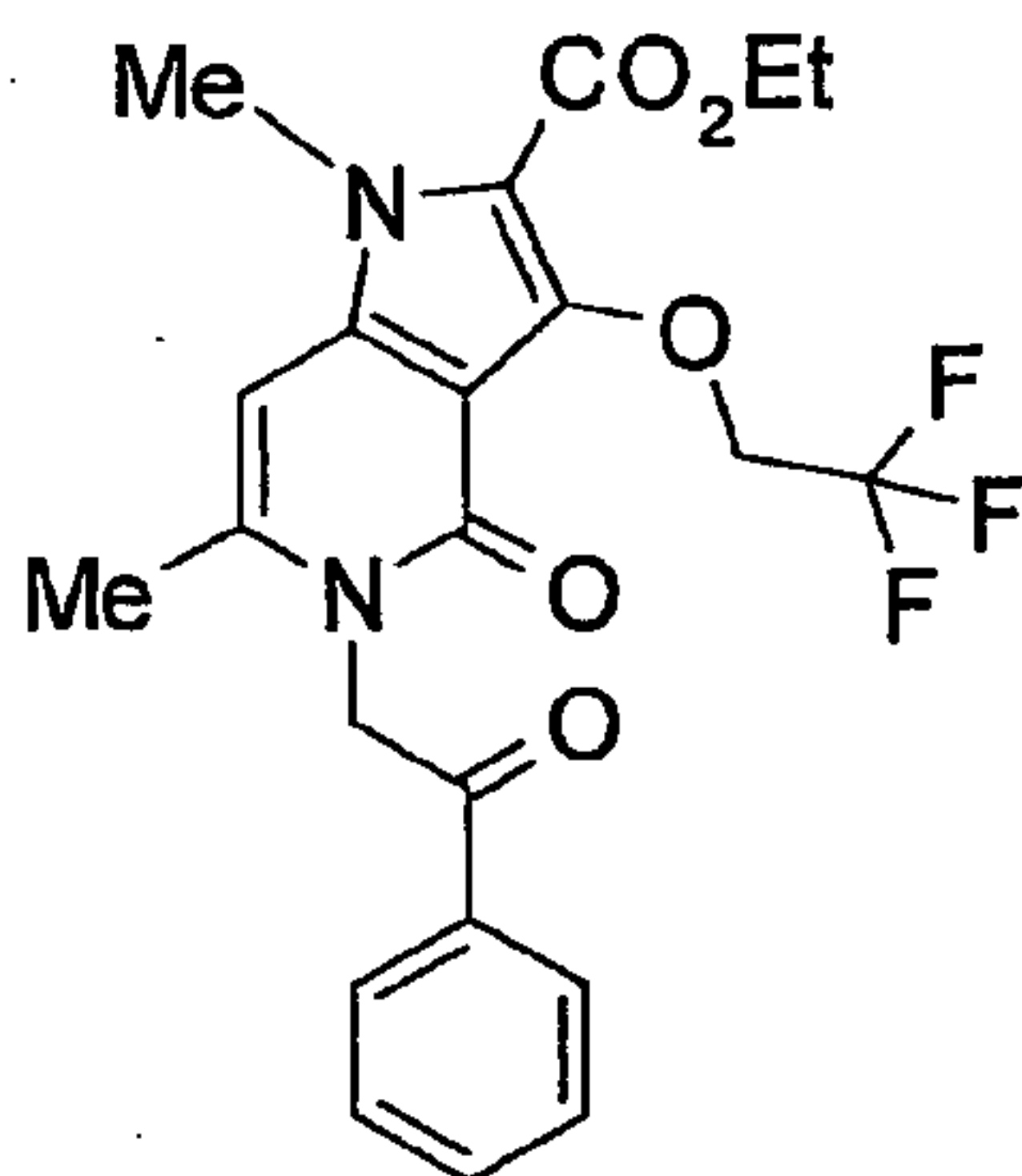
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.13-1.25 (6 H, m), 2.57 (2 H, q, J=7.3 Hz), 3.84 (3 H, s), 4.15 (2 H, q, J=7.0 Hz), 5.57 (2 H, s), 6.47 (1 H, s), 7.61 (2 H, t, J=7.5 Hz), 7.69-7.78 (1 H, m), 8.08-8.15 (2 H, m), 12.35 (1 H, br s).

[0353]

Reference Example 49

Production of ethyl 1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0354]



5

[0355]

A mixture of the compound of Reference Example 33 (750 mg, 2.04 mmol), 1,1,1-trifluoro-2-iodoethane (603 μ L, 6.12 mmol), potassium fluoride (119 mg, 2.04 mmol) and dimethyl sulfoxide
 10 (10 mL) was stirred at 100°C for 15 hr. The reaction mixture was diluted with water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel
 15 chromatography (eluate; ethyl acetate) to give the title compound (125 mg, 14%) as a white solid.

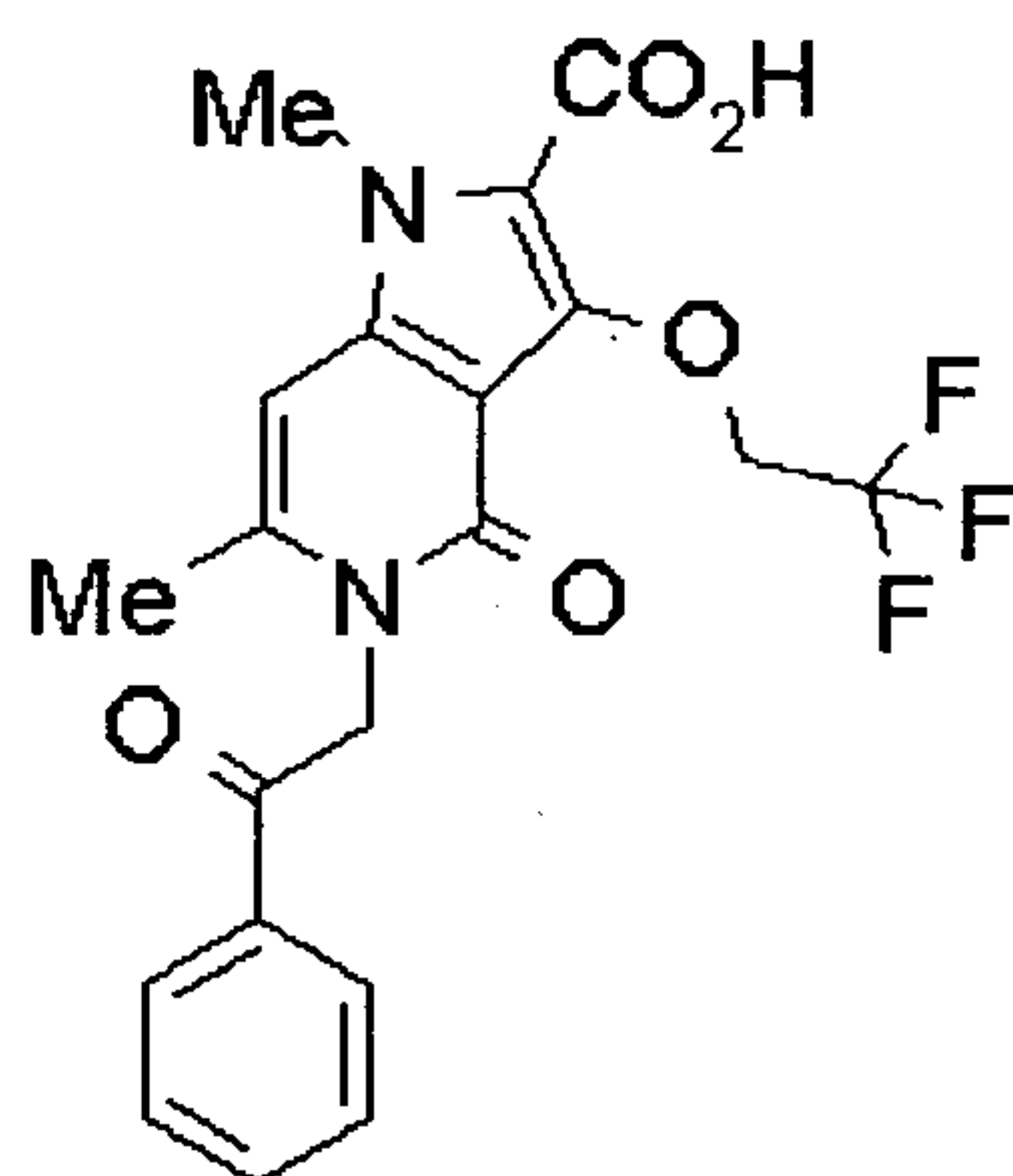
$^1\text{H-NMR}$ (300 MHz, DMSO- d_6) δ : 1.28 (3 H, t, $J=7.2$ Hz), 2.30 (3 H, s), 3.83 (3 H, s), 4.19-4.31 (2 H, m), 4.84 (2 H, q, $J=9.3$ Hz), 5.64 (2 H, s), 6.66 (1 H, s), 7.57-7.66 (2 H, m), 7.69-7.79 (1
 20 H, m), 8.07-8.15 (2 H, m).

[0356]

Reference Example 50

Production of 1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-
 25 2-carboxylic acid

[0357]



[0358]

A solution of the compound of Reference Example 49 (110 mg, 0.244 mmol) and 8N aqueous sodium hydroxide solution (1 mL) in ethanol (7 mL) was stirred at 60°C for 1 hr. The reaction mixture was diluted with water and acidified with 6N hydrochloric acid, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (78.0 mg, 76%) as a white powder.

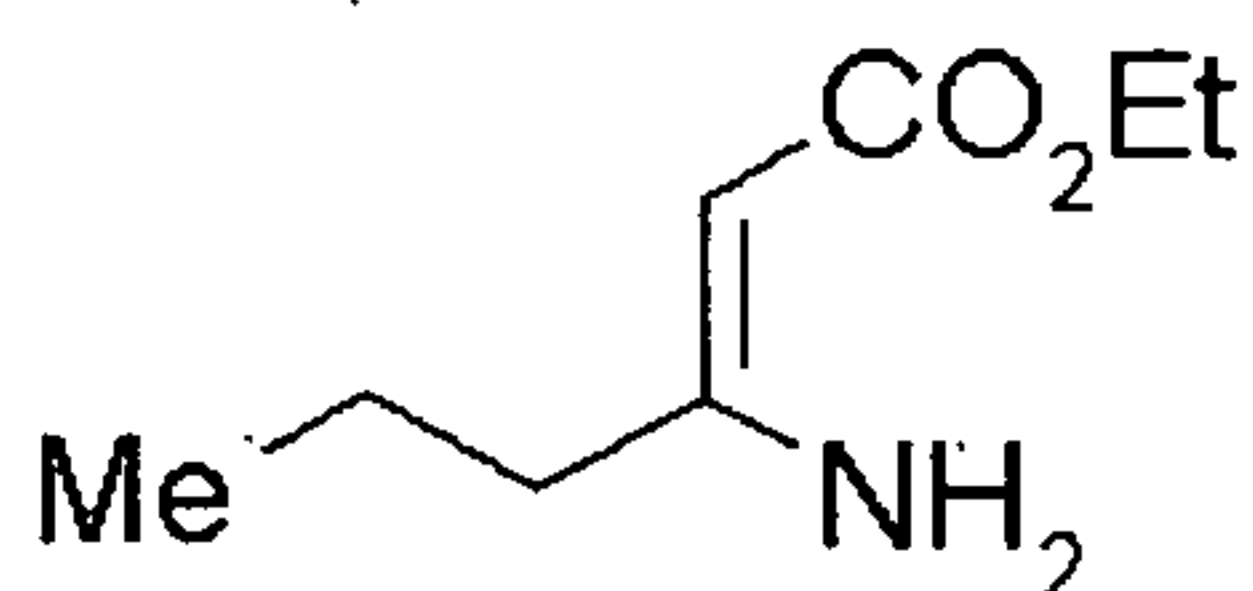
¹H-NMR (300 MHz, DMSO-d₆) δ: 2.29 (3 H, s), 3.83 (3 H, s), 4.82 (2 H, q, J=9.3 Hz), 5.63 (2 H, s), 6.64 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.70-7.78 (1 H, m), 8.07-8.15 (2 H, m), 12.57 (1 H, br s).

[0359]

Reference Example 51

Production of ethyl (2Z)-3-aminohept-2-enoate

[0360]



[0361]

In the same manner as in Reference Example 36, the title compound (109 g, quant.) was obtained as a pale-yellow oil from ethyl 3-oxohexanoate (100 g, 632 mmol), ammonium acetate (244 g, 3.16 mmol) and methanol (750 mL).

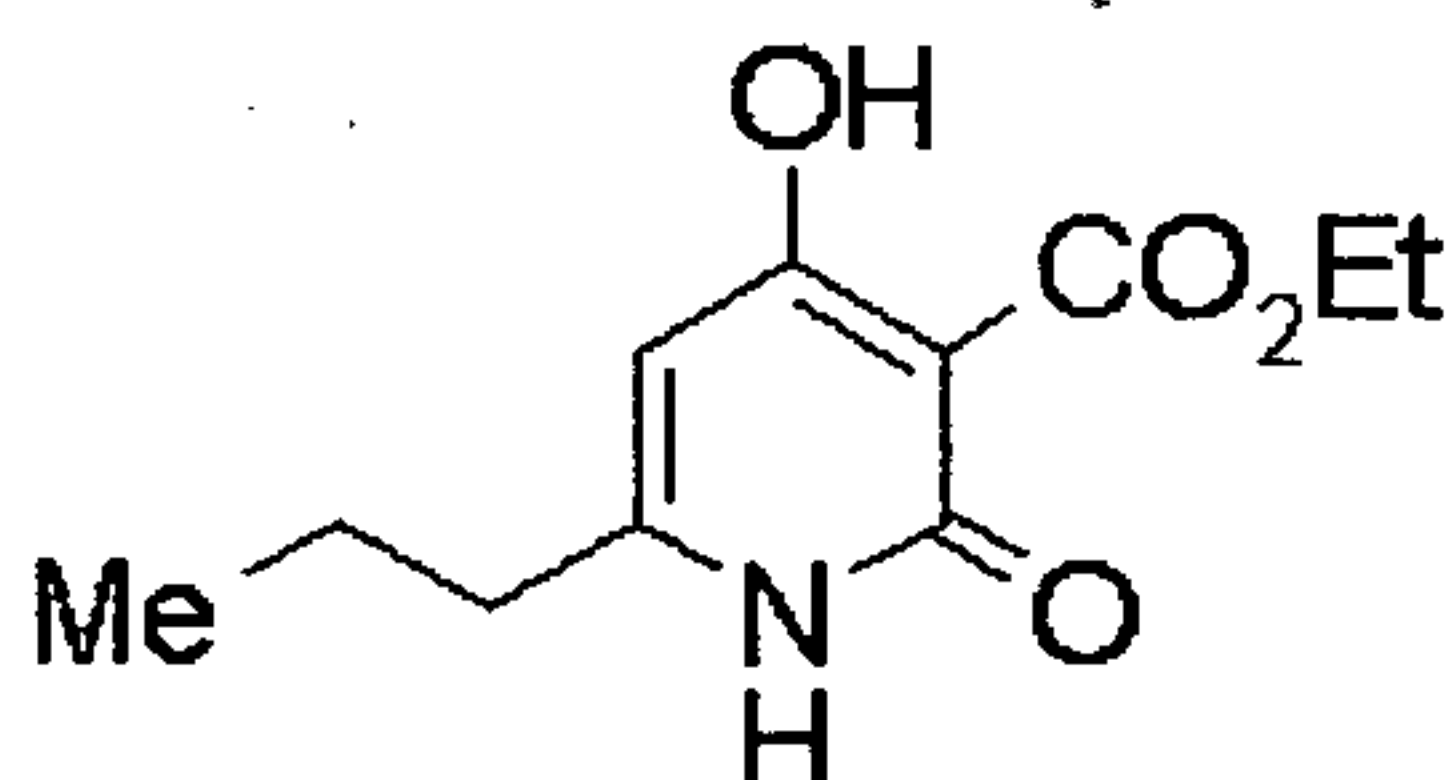
¹H-NMR (300 MHz, DMSO-d₆) δ: 0.87 (3 H, t, J=7.4 Hz), 1.11-1.17 (3 H, m), 1.42-1.58 (2 H, m), 2.00-2.07 (2 H, m), 3.96 (2 H, q, J=7.2 Hz), 4.30 (1 H, s), 6.90 (1 H, br s), 7.73 (1 H, br s).

[0362]

Reference Example 52

Production of ethyl 4-hydroxy-2-oxo-6-n-propyl-1,2-dihydropyridine-3-carboxylate

5 [0363]



[0364]

In the same manner as in Reference Example 37, the title compound (27.5 g, 34%) was obtained as a white powder from the
10 compound of Reference Example 51 (50.0 g, 0.387 mmol), diethyl malonate (58.8 mL, 387 mmol) and ethanol (400 mL).

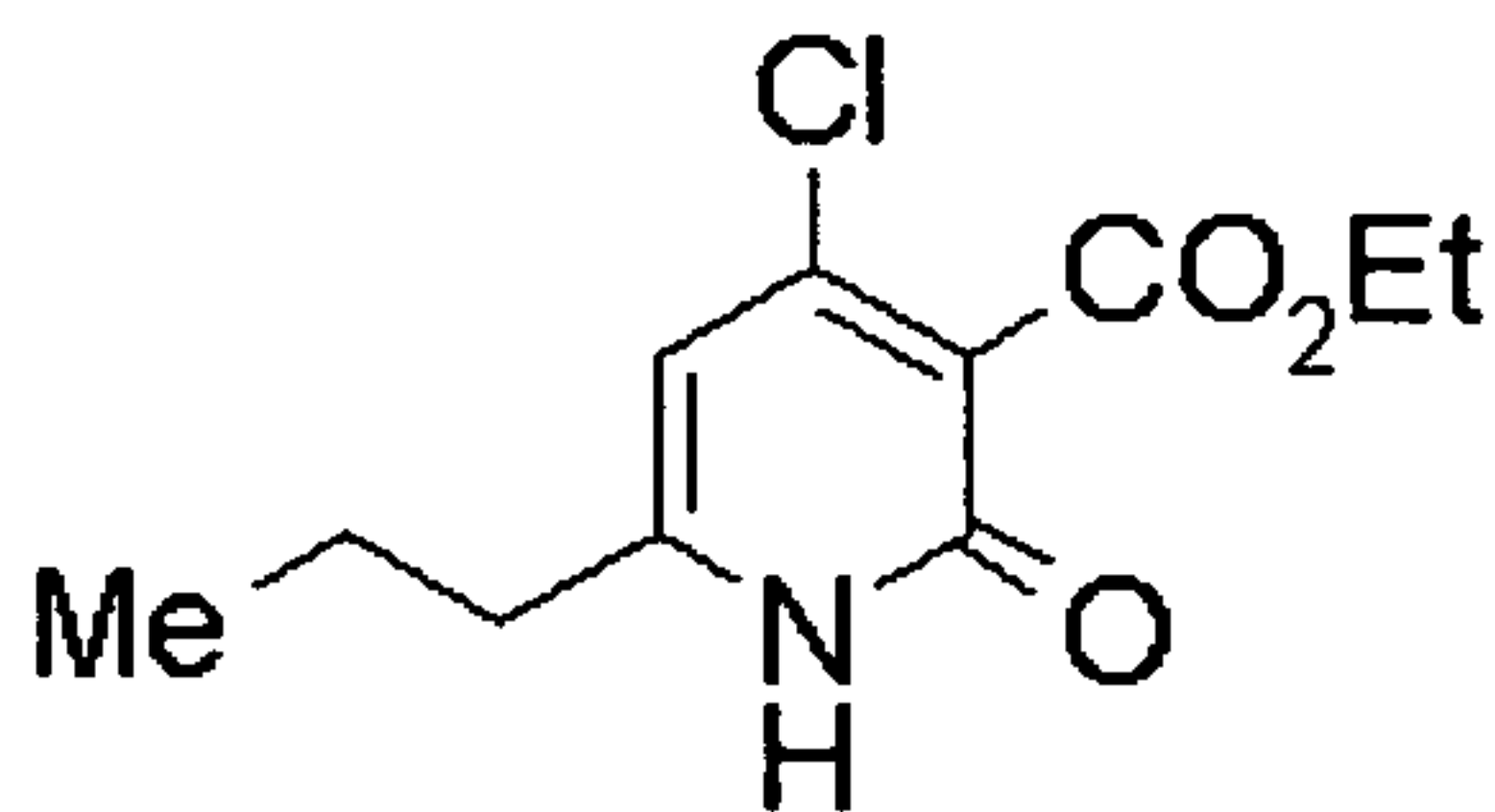
¹H-NMR (300 MHz, DMSO-d₆) δ: 0.87 (3 H, t, J=7.4 Hz), 1.26 (3 H, t, J=7.2 Hz), 1.49-1.65 (2 H, m), 2.38 (2 H, t), 4.25 (2 H, q, J=7.0 Hz), 5.79 (1 H, s), 11.37 (1 H, s), 12.56 (1 H, s).

15 [0365]

Reference Example 53

Production of ethyl 4-chloro-2-oxo-6-propyl-1,2-dihydropyridine-3-carboxylate

[0366]



20

[0367]

A mixture of the compound of Reference Example 52 (37.0 g, 164 mmol) and phosphorus oxychloride (45.9 mL, 493 mmol) was stirred at 80°C for 30 min. The mixture was concentrated under
25 reduced pressure, and ice water was added to the residue. The precipitated solid was collected by filtration, and washed with water and ethyl acetate to give the title compound (17.6 g, 44%) as a white solid.

¹H-NMR (300 MHz, DMSO-d₆) δ: 0.87 (3 H, t, J=7.4 Hz), 1.26 (3 H,

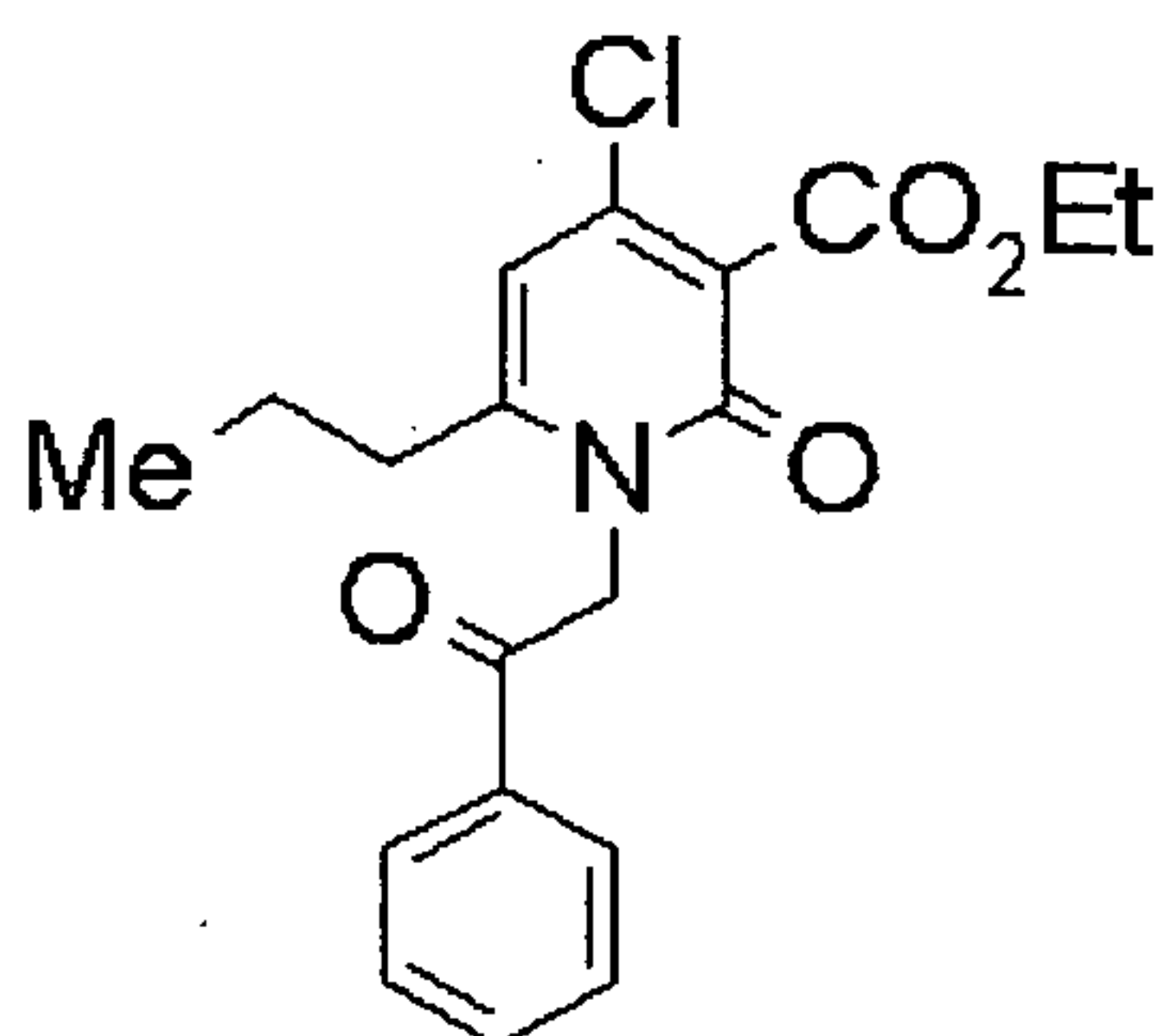
t, J=7.1 Hz), 1.52-1.65 (2 H, m), 2.40-2.48 (2 H, m), 4.25 (2 H, q, J=7.1 Hz), 6.27 (1 H, s), 12.17 (1 H, br s).

[0368]

Reference Example 54

- 5 Production of ethyl 4-chloro-2-oxo-1-(2-oxo-2-phenylethyl)-6-propyl-1,2-dihydropyridine-3-carboxylate

[0369]



[0370]

- 10 In the same manner as in Reference Example 4, the title compound (7.15 g, 28%) was obtained as a white powder from the compound of Reference Example 53 (17.0 g, 69.8 mmol), sodium hydride (60% in oil, 3.07 g, 76.7 mmol), phenacyl bromide (16.7 g, 83.8 mmol) and DMF (150 mL).

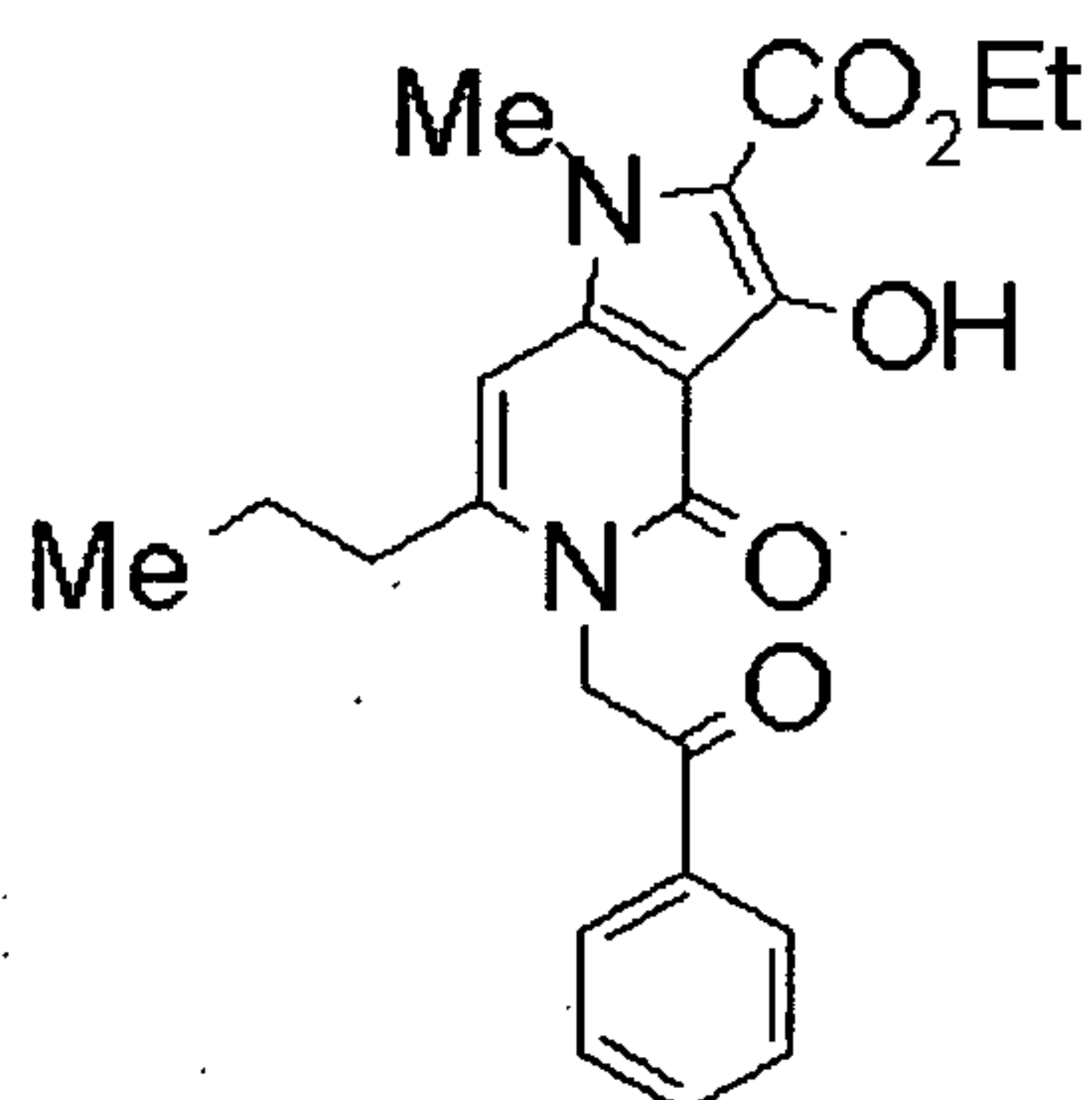
- 15 ¹H-NMR (300 MHz, DMSO-d₆) δ: 0.91 (3 H, t, J=7.3 Hz), 1.24 (3 H, t, J=7.1 Hz), 1.47-1.64 (2 H, m), 2.55-2.66 (2 H, m), 4.24 (2 H, q, J=7.1 Hz), 5.59 (2 H, s), 6.47 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.70-7.80 (1 H, m), 8.06-8.17 (2 H, m).

[0371]

- 20 Reference Example 55

Production of ethyl 3-hydroxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-6-propyl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0372]



[0373]

A mixture of the compound of Reference Example 54 (7.00 g, 19.3 mmol), sarcosine ethyl ester hydrochloride (5.94 g, 38.7 mmol), triethylamine (29.7 mL, 193 mmol) and ethanol (100 mL) was stirred for 2 days under refluxing conditions. The mixture was concentrated under reduced pressure, water (200 mL) was added to the residue, and the mixture was acidified with 5N hydrochloric acid (3 mL). The precipitated solid was collected by filtration, and washed with water and hexane-ethyl acetate to give the title compound (5.70 g, 74%) as a white solid.

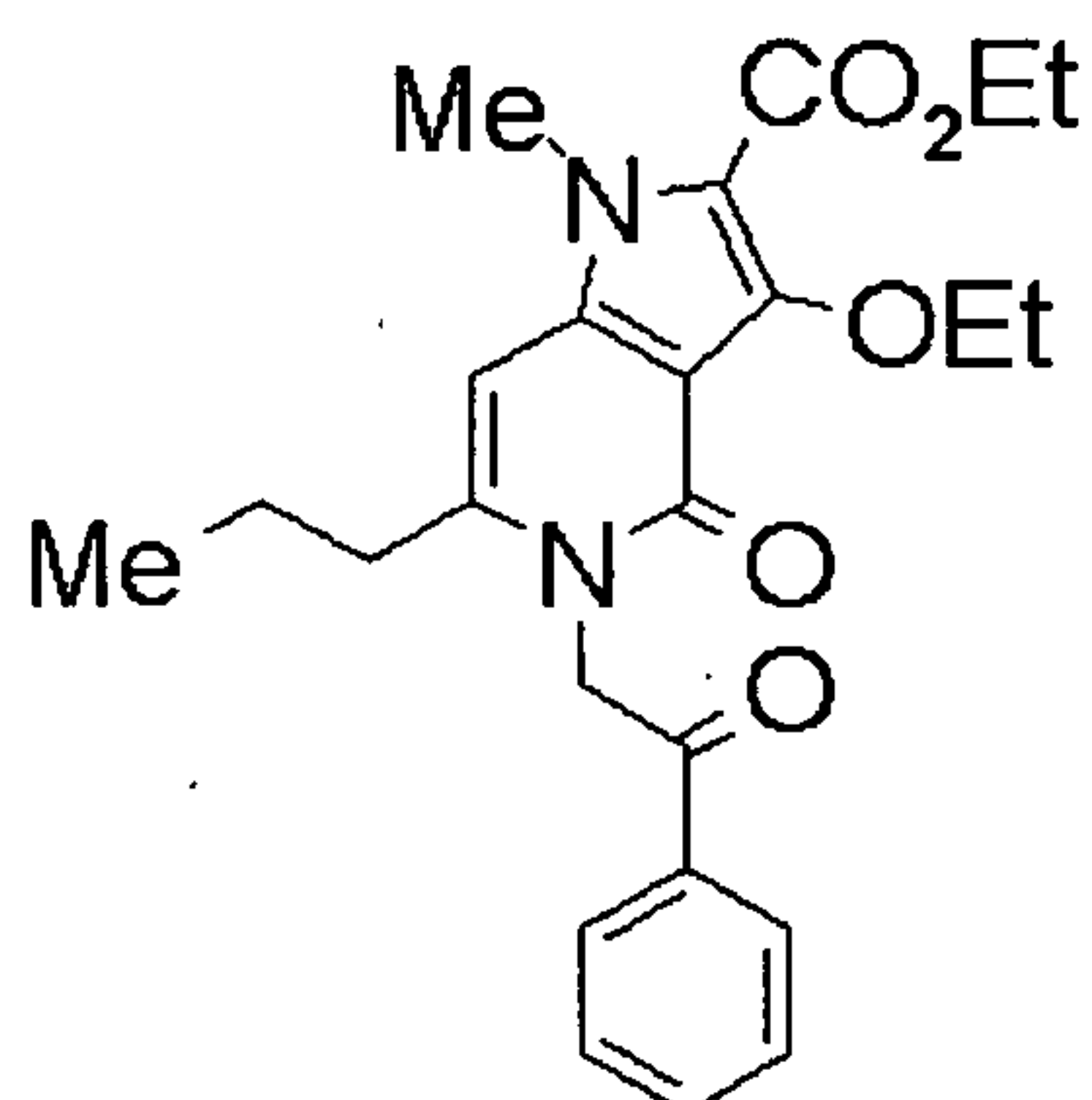
¹H-NMR (300 MHz, DMSO-d₆) δ: 0.92 (3 H, t, J=7.3 Hz), 1.31 (3 H, t, J=7.1 Hz), 1.50-1.65 (2 H, m), 2.49-2.57 (2 H, m), 3.78 (3 H, s), 4.30 (2 H, q, J=7.1 Hz), 5.52 (2 H, s), 6.45 (1 H, s), 7.60 (2 H, t, J=7.5 Hz), 7.68-7.78 (1 H, m), 8.07-8.15 (2 H, m), 8.90 (1 H, br s).

[0374]

Reference Example 56

Production of ethyl 3-ethoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-6-propyl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0375]



[0376]

A mixture of the compound of Reference Example 55 (1.00 g, 8.08 mmol), diethyl sulfate (397 μ L, 3.03 mmol), potassium carbonate (1.05 g, 7.57 mmol) and acetone (20 mL) was stirred
5 for 15 hr under refluxing conditions. Water (30 mL) was added to the mixture, and the precipitated solid was collected by filtration, and washed with water and ethyl acetate-hexane to give the title compound (876 mg, 82%) as a white solid.

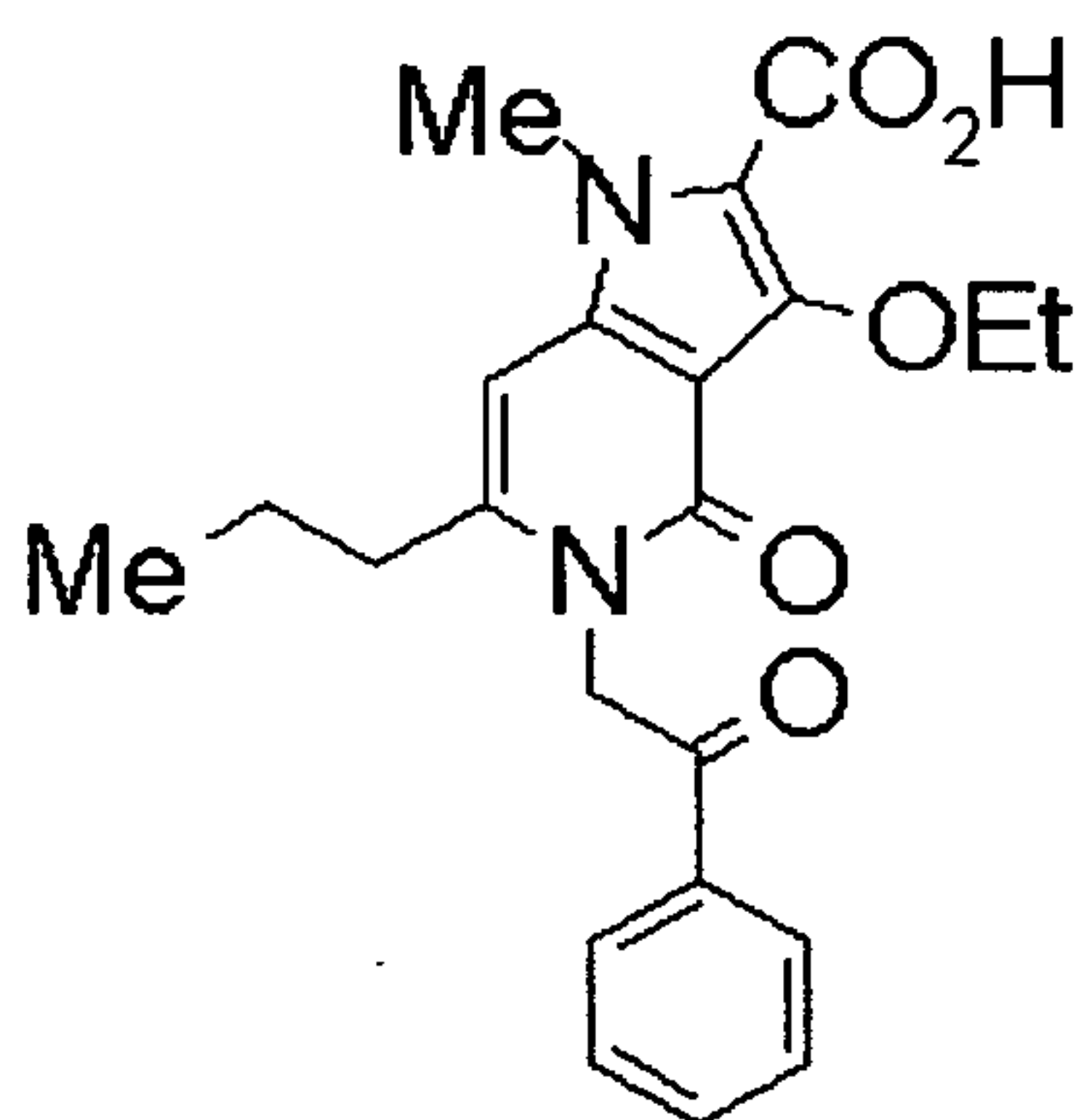
$^1\text{H-NMR}$ (300 MHz, DMSO- d_6) δ : 0.93 (3 H, t, $J=7.4$ Hz), 1.23 (3 H, t, $J=7.0$ Hz), 1.30 (3 H, t, $J=7.1$ Hz), 1.52-1.66 (2 H, m),
10 2.51-2.58 (2 H, m), 3.83 (3 H, s), 4.14 (2 H, q, $J=7.1$ Hz), 4.26 (2 H, q, $J=7.1$ Hz), 5.54 (2 H, s), 6.51 (1 H, s), 7.61 (2 H, t, $J=7.6$ Hz), 7.69-7.77 (1 H, m), 8.08-8.15 (2 H, m).

[0377]

15 Reference Example 57

Production of 3-ethoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-6-propyl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0378]



[0379]

A solution of the compound of Reference Example 56 (850 mg, 2.00 mmol) and 8N aqueous sodium hydroxide solution (2 mL) in ethanol (14 mL) was stirred at 60°C for 30 min. The
25 reaction mixture was diluted with water, acidified with 5N hydrochloric acid, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (705 mg, 89%) as a white powder.

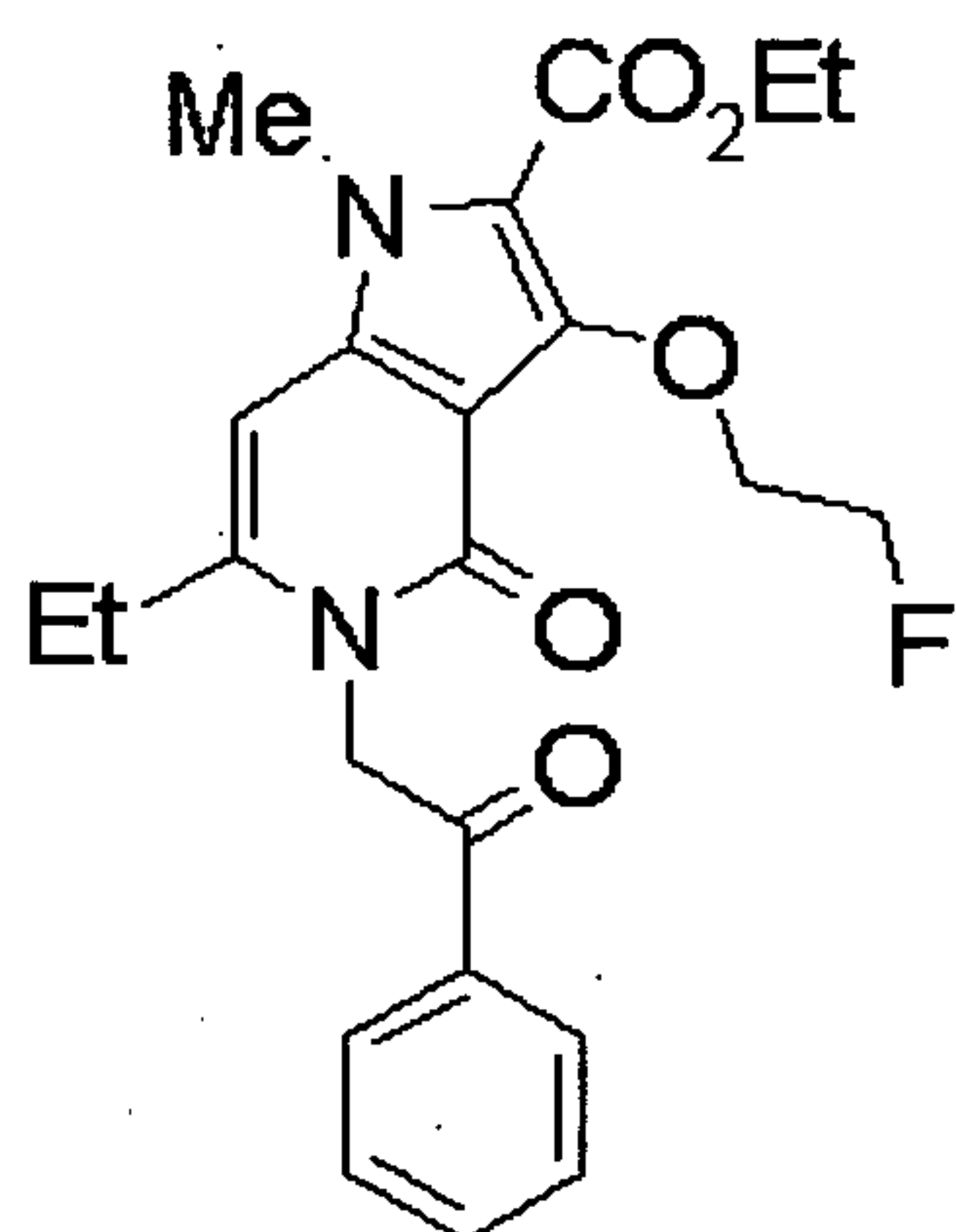
¹H-NMR (300 MHz, DMSO-d₆) δ: 0.93 (3 H, t, J=7.4 Hz), 1.21 (3 H, t, J=7.0 Hz), 1.50-1.66 (2 H, m), 2.50-2.58 (2 H, m), 3.83 (3 H, s), 4.15 (2 H, q, J=7.1 Hz), 5.54 (2 H, s), 6.50 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.69-7.78 (1 H, m), 8.08-8.16 (2 H, m), 12.42 (1 H, br s).

[0380]

Reference Example 58

Production of ethyl 6-ethyl-3-(2-fluoroethoxy)-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0381]



[0382]

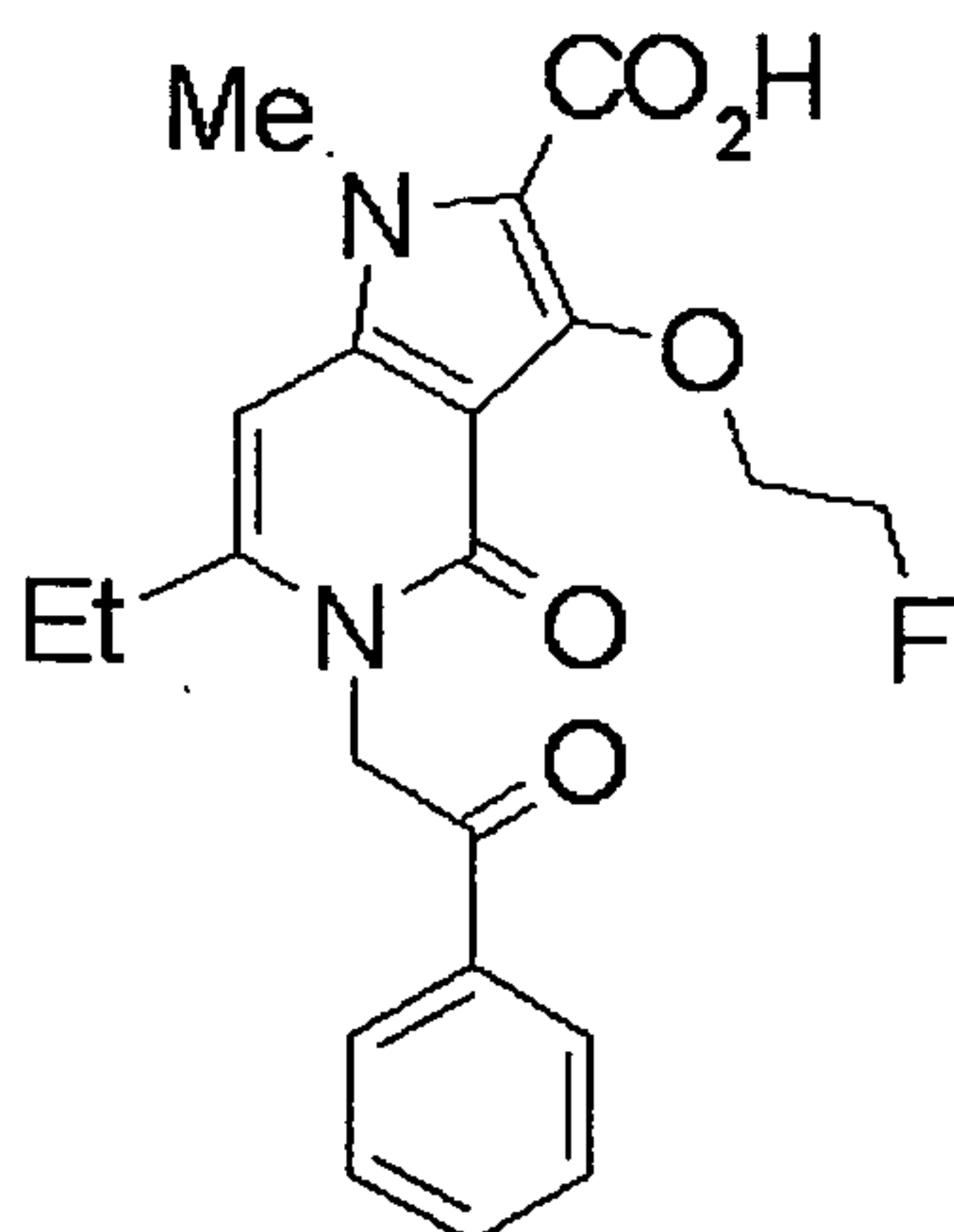
In the same manner as in Reference Example 6, the title compound (649 mg, 77%) was obtained as a white powder from the compound of Reference Example 40 (750 mg, 1.96 mmol), DBU (440 μL, 2.94 mmol) and 1-fluoro-2-iodoethane (512 mg, 2.94 mmol). ¹H-NMR (300 MHz, DMSO-d₆) δ: 1.19 (3 H, t, J=7.3 Hz), 1.30 (3 H, t, J=7.1 Hz), 2.58 (2 H, q, J=7.3 Hz), 3.85 (3 H, s), 4.26 (2 H, q, J=7.1 Hz), 4.32-4.36 (1 H, m), 4.42-4.47 (1 H, m), 4.53-4.59 (1 H, m), 4.69-4.75 (1 H, m), 5.58 (2 H, s), 6.51 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.70-7.77 (1 H, m), 8.08-8.14 (2 H, m).

[0383]

Reference Example 59

Production of 6-ethyl-3-(2-fluoroethoxy)-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0384]



[0385]

A solution of the compound of Reference Example 58 (620
 5 mg, 1.45 mmol) and 8N aqueous sodium hydroxide solution (1 mL)
 in ethanol (7 mL) was stirred at 60°C for 30 min. The reaction
 mixture was diluted with water, acidified with 5N hydrochloric
 acid, and the precipitated solid was collected by filtration.
 The obtained solid was washed with water, and dried under
 10 reduced pressure to give the title compound (470 mg, 56%) as a
 white powder.

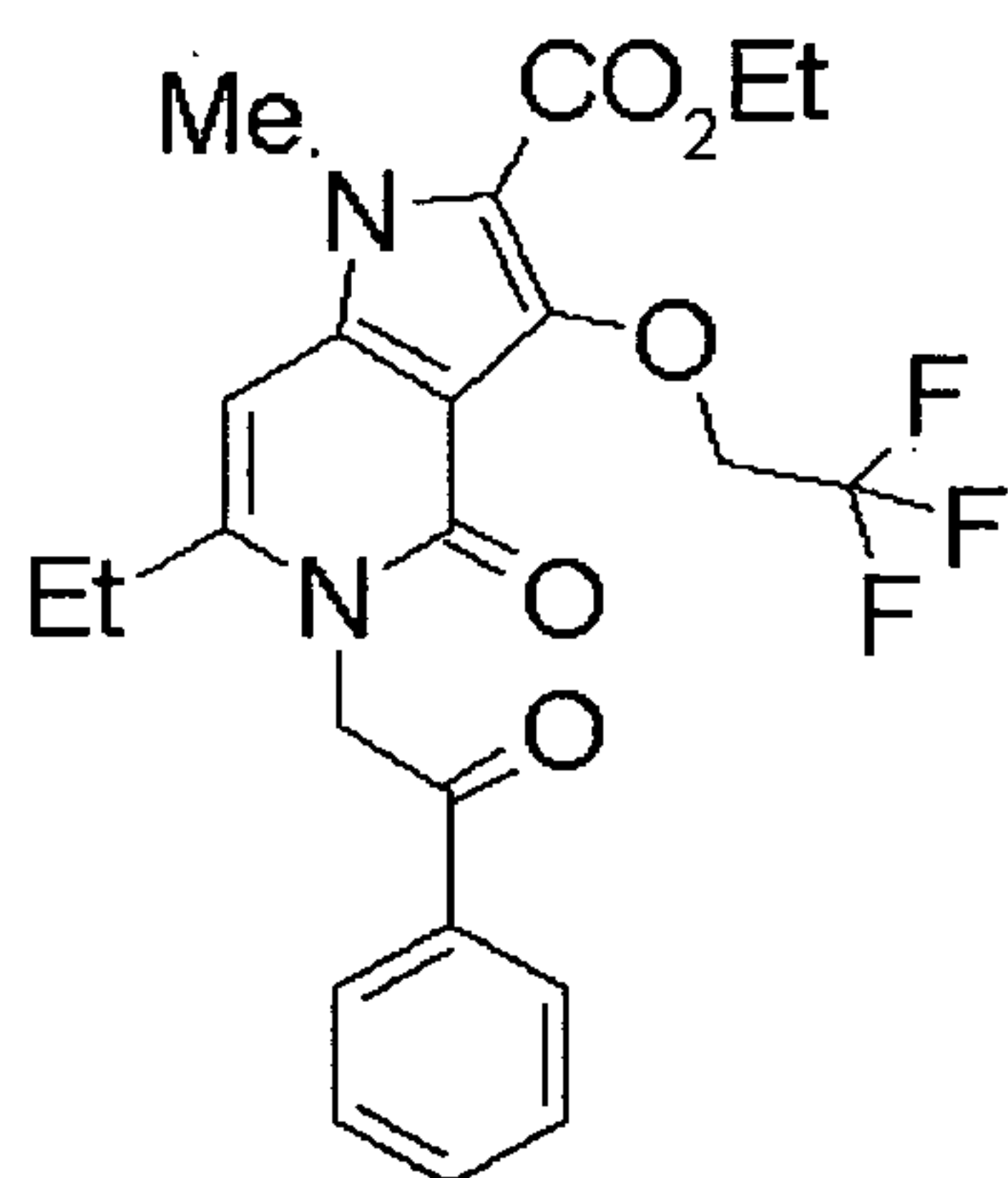
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.19 (3 H, t, J=7.4 Hz), 2.58 (2 H,
 q, J=7.4 Hz), 3.85 (3 H, s), 4.32-4.36 (1 H, m), 4.42-4.47 (1
 H, m), 4.54-4.59 (1 H, m), 4.70-4.74 (1 H, m), 5.58 (2 H, s),
 15 6.50 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.70-7.77 (1 H, m),
 8.09-8.15 (2 H, m), 12.48 (1 H, br s).

[0386]

Reference Example 60

Production of ethyl 6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-
 20 phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-
 pyrrolo[3,2-c]pyridine-2-carboxylate

[0387]



[0388]

A mixture of the compound of Reference Example 40 (1.00 g, 2.61 mmol), 1,1,1-trifluoro-2-iodoethane (1.29 mL, 13.1 mmol), cesium carbonate (4.27 g, 13.1 mmol) and dimethyl sulfoxide (10 mL) was stirred at 100°C for 5 hr. The reaction mixture was filtered, the filtrate was diluted with 1N hydrochloric acid (30 mL), and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; hexane/ethyl acetate=9/1 - 0/10) to give the title compound (278 mg, 23%) as a white solid.

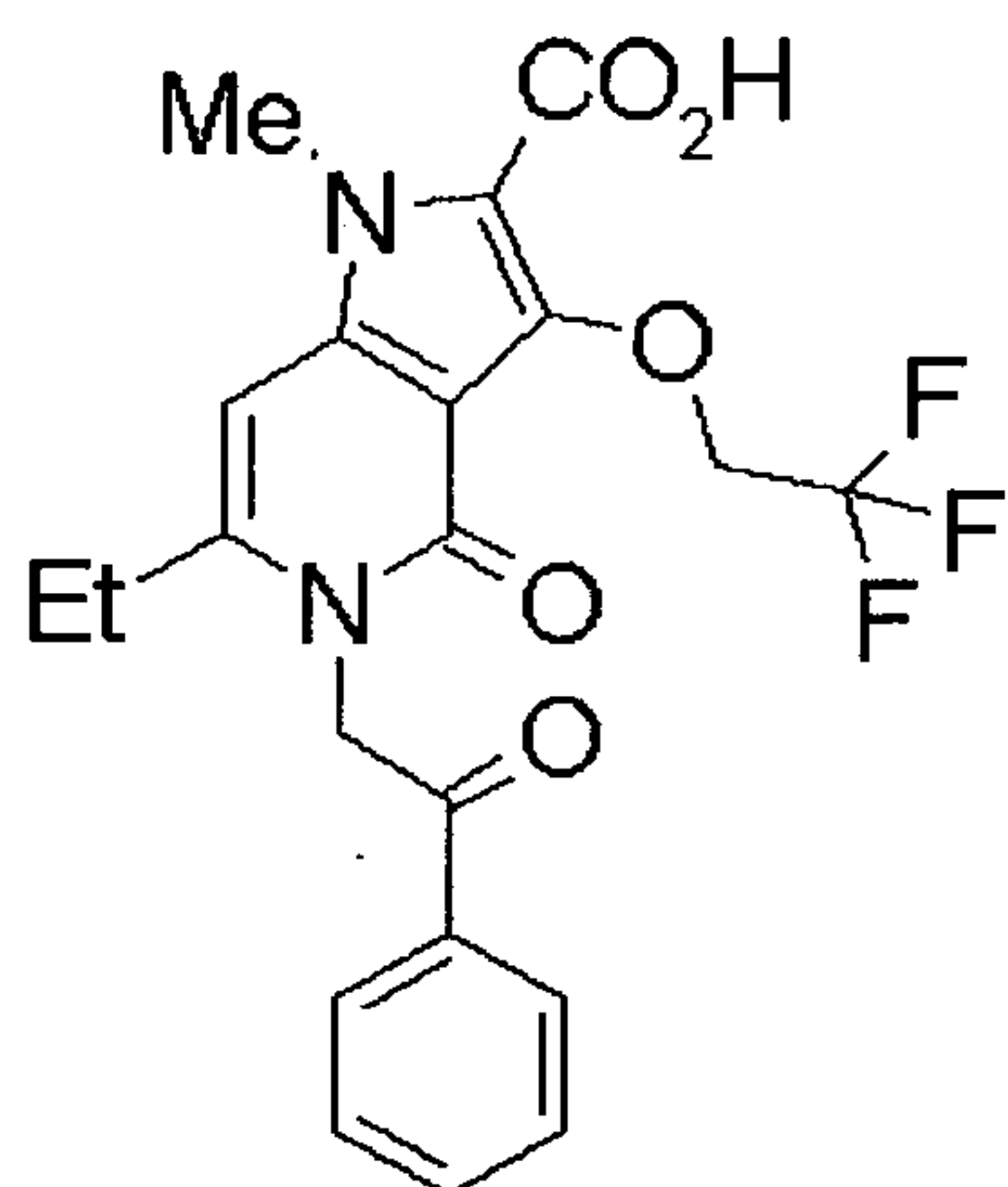
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.19 (3 H, t, J=7.4 Hz), 1.28 (3 H, t, J=7.1 Hz), 2.59 (2 H, q, J=7.4 Hz), 3.86 (3 H, s), 4.26 (2 H, q, J=7.1 Hz), 4.83 (2 H, q, J=9.3 Hz), 5.62 (2 H, s), 6.56 (1 H, s), 7.61 (2 H, t, J=7.5 Hz), 7.70-7.78 (1 H, m), 8.08-8.14 (2 H, m).

[0389]

20 Reference Example 61

Production of 6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0390]



[0391]

A solution of the compound of Reference Example 60 (270 mg, 0.581 mmol) and 8N aqueous sodium hydroxide solution (1 mL) in ethanol (7 mL) was stirred at 60°C for 1 hr. The reaction mixture was diluted with water, acidified with 5N hydrochloric acid, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (235 mg, 93%) as a white powder.

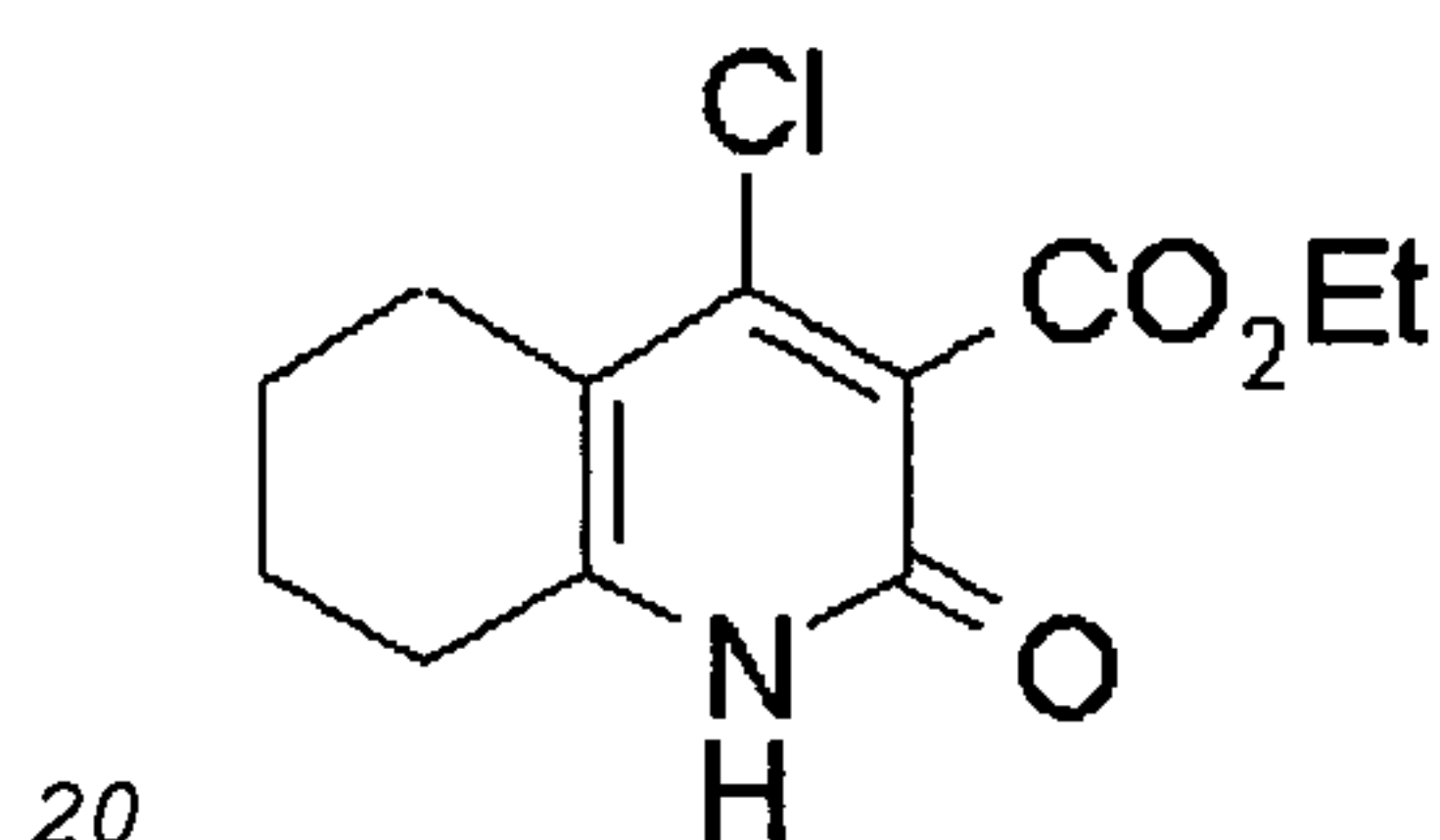
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.19 (3 H, t, J=7.4 Hz), 2.58 (2 H, q, J=7.4 Hz), 3.86 (3 H, s), 4.82 (2 H, q, J=9.2 Hz), 5.61 (2 H, s), 6.54 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.70-7.77 (1 H, m), 8.07-8.16 (2 H, m), 12.74 (1 H, br s).

15 [0392]

Reference Example 62

Production of ethyl 4-chloro-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylate

[0393]



20

[0394]

A mixture of ethyl 4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylate (26.0 g, 110 mmol) and phosphorus oxychloride (51.3 mL) was stirred at 130°C for 1.5 hr. After cooling, the reaction mixture was concentrated under

reduced pressure, and ice was added to the residue. The mixture was neutralized with saturated sodium hydrogen carbonate solution, and extracted with ethyl acetate. The extract was washed successively with saturated sodium hydrogen carbonate solution, water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was collected by filtration, and washed with ethyl acetate-hexane to give the title compound (4.65 g, 17%) as a white solid.

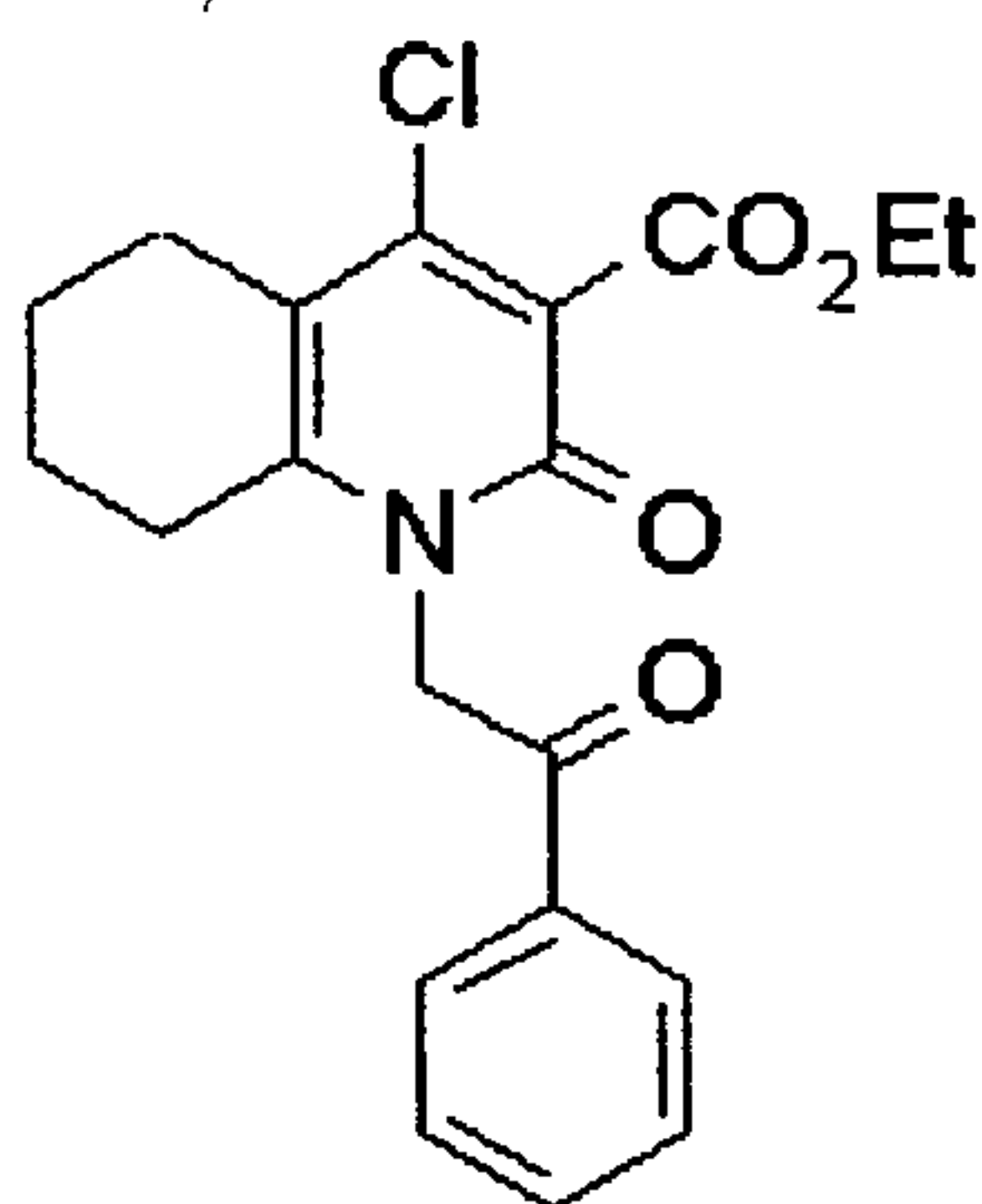
10 ^1H -NMR (300 MHz, DMSO- d_6) δ : 1.25 (3 H, t, $J=7.1$ Hz), 1.61-1.74 (4 H, m), 2.37-2.45 (2 H, m), 2.51-2.57 (2 H, m), 4.24 (2 H, q, $J=7.2$ Hz), 12.09 (1 H, s).

[0395]

Reference Example 63

15 Production of ethyl 4-chloro-2-oxo-1-(2-oxo-2-phenylethyl)-1,2,5,6,7,8-hexahydroquinoline-3-carboxylate

[0396]



[0397]

20 In the same manner as in Reference Example 4, the title compound (710 mg, 16%) was obtained as a white powder from the compound of Reference Example 62 (3.00 g, 11.7 mmol), sodium hydride (60% in oil, 516 mg, 12.9 mmol) and phenacyl bromide (2.57 g, 12.9 mmol).

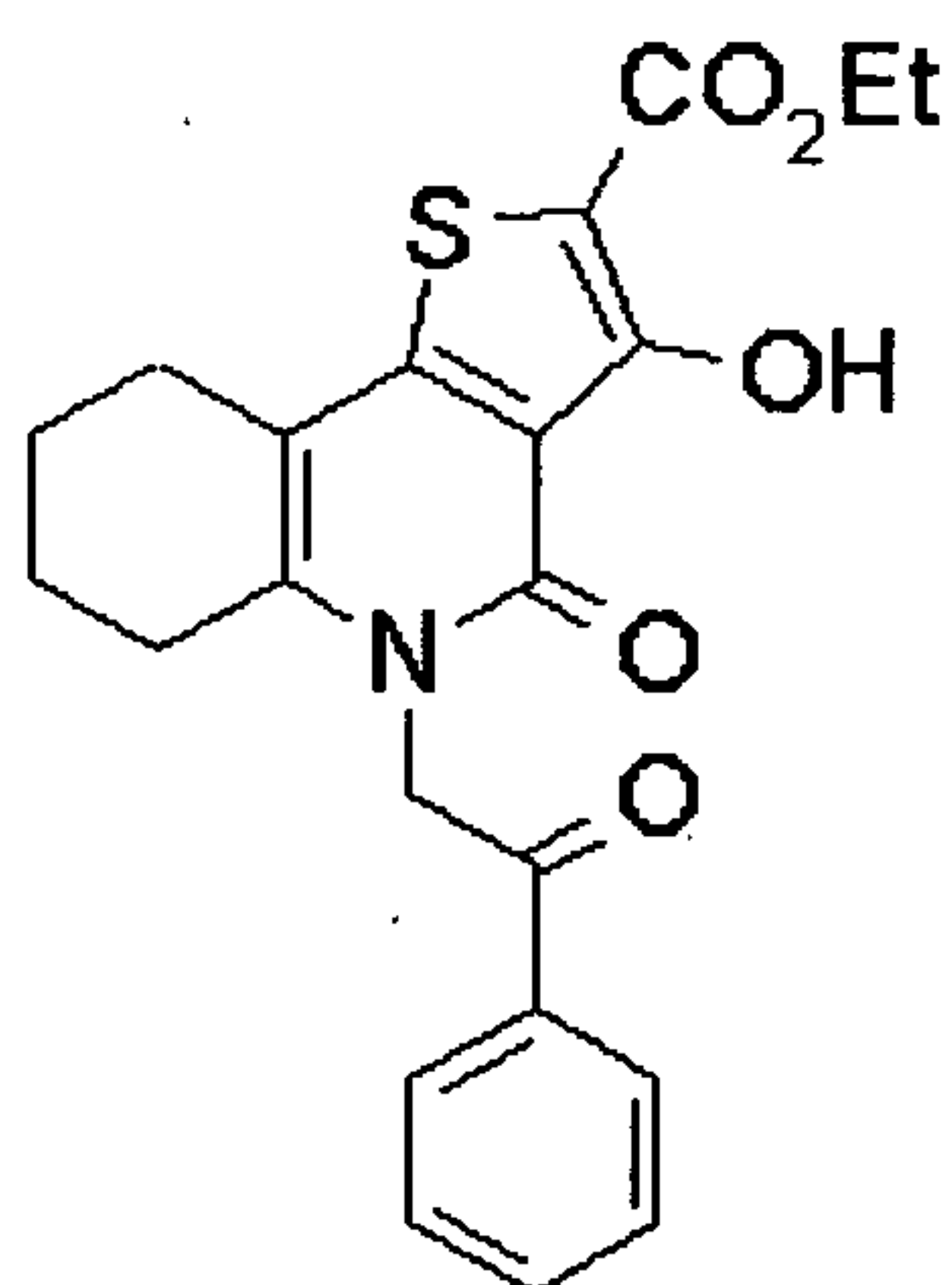
25 ^1H -NMR (300 MHz, DMSO- d_6) δ : 1.25 (3H, t, $J = 7.1$ Hz), 1.60-1.80 (4H, m), 2.50-2.65 (4H, m), 4.26 (2H, q, $J = 7.1$ Hz), 5.66 (2H, s), 7.61 (2H, t, $J = 7.4$ Hz), 7.74 (1H, t, $J = 7.4$ Hz), 8.09 (2H, d, $J = 7.4$ Hz).

[0398]

Reference Example 64

Production of ethyl 3-hydroxy-4-oxo-5-(2-oxo-2-phenylethyl)-
4,5,6,7,8,9-hexahydrothieno[3,2-c]quinoline-2-carboxylate

[0399]



5

[0400]

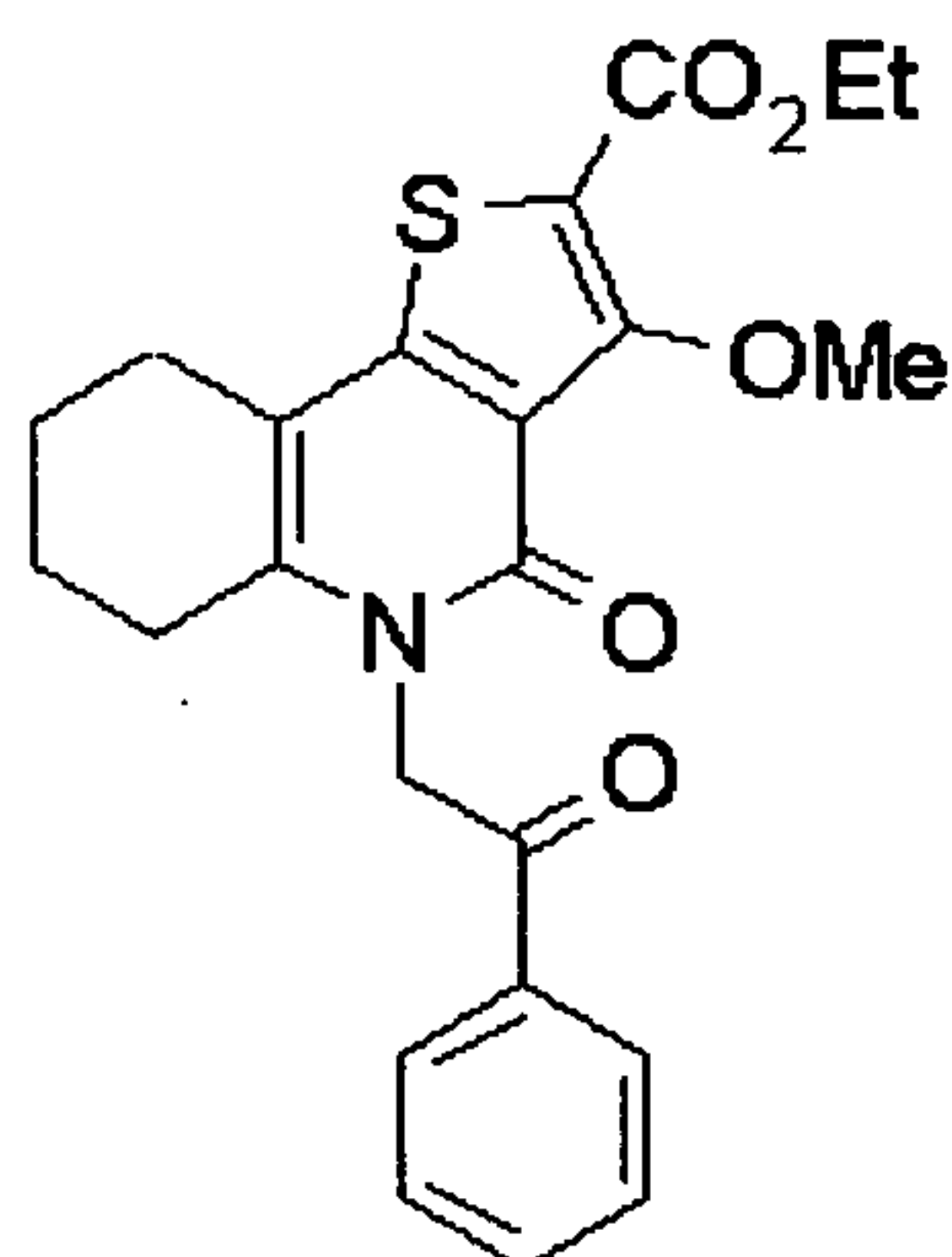
In the same manner as in Reference Example 5, the title compound (751 mg, 100%) was obtained as a white powder from the compound of Reference Example 63 (690 mg, 1.85 mmol), 20%
10 solution (1.26 g, 3.69 mmol) of sodium ethoxide in ethanol, ethyl thioglycolate (486 μ L, 4.43 mmol) and ethanol (15 mL). $^1\text{H-NMR}$ (300 MHz, DMSO- d_6) δ : 1.29 (3H, t, $J = 7.0$ Hz), 1.65–1.85 (4H, m), 2.50–2.65 (4H, m), 4.28 (2H, q, $J = 7.0$ Hz), 5.72 (2H, s), 7.62 (2H, t, $J = 7.7$ Hz), 7.73–7.78 (1H, m), 8.10–8.13 (2H,
15 m), 10.39 (1H, s).

[0401]

Reference Example 65

Production of ethyl 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-
4,5,6,7,8,9-hexahydrothieno[3,2-c]quinoline-2-carboxylate

20 [0402]



[0403]

In the same manner as in Reference Example 6, the title compound (238 mg, 31%) was obtained as a white powder from the compound of Reference Example 64 (740 mg, 1.80 mmol),

5 iodomethane (168 μ L, 2.70 mmol), DBU (404 μ L, 2.70 mmol) and DMF (15 mL).

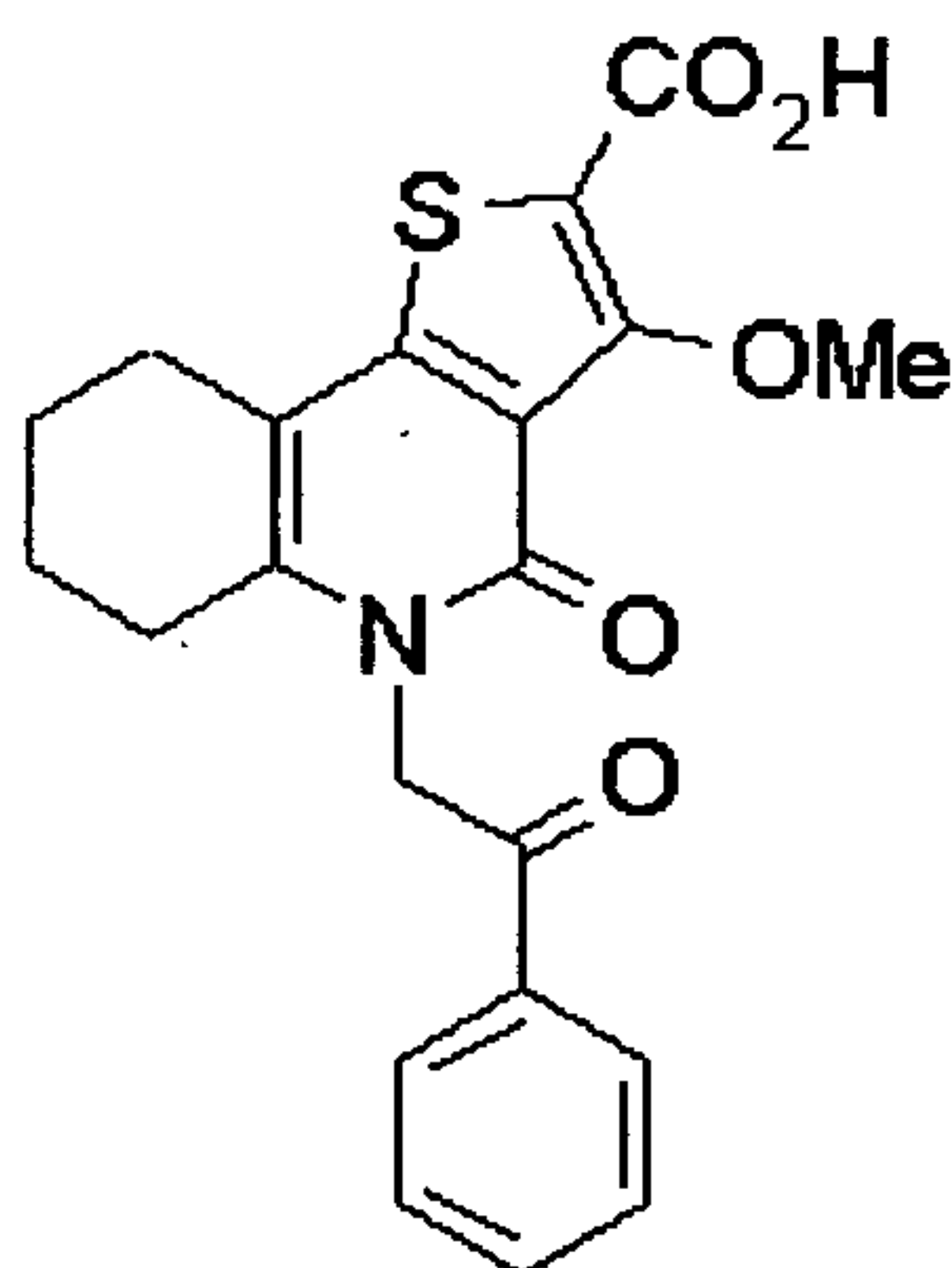
^1H -NMR (300 MHz, DMSO- d_6) δ : 1.31 (3H, t, J = 7.0 Hz), 1.65-1.85 (4H, m), 2.45-2.65 (4H, m), 3.89 (3H, s), 4.29 (2H, q, J = 7.0 Hz), 5.67 (2H, s), 7.62 (2H, t, J = 7.4 Hz), 7.75 (1H, t, J = 7.4 Hz), 8.11 (2H, d, J = 7.4 Hz).

[0404]

Reference Example 66

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5,6,7,8,9-hexahydrothieno[3,2-c]quinoline-2-carboxylic acid

15 [0405]



[0406]

A solution of the compound of Reference Example 65 (220 mg, 0.517 mmol) and 8N aqueous sodium hydroxide solution (1 mL) in ethanol (7 mL) was stirred at 60°C for 1 hr. The reaction mixture was acidified with 6N hydrochloric acid (1.5 mL), and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (162 mg, 79%) as a

25 white powder.

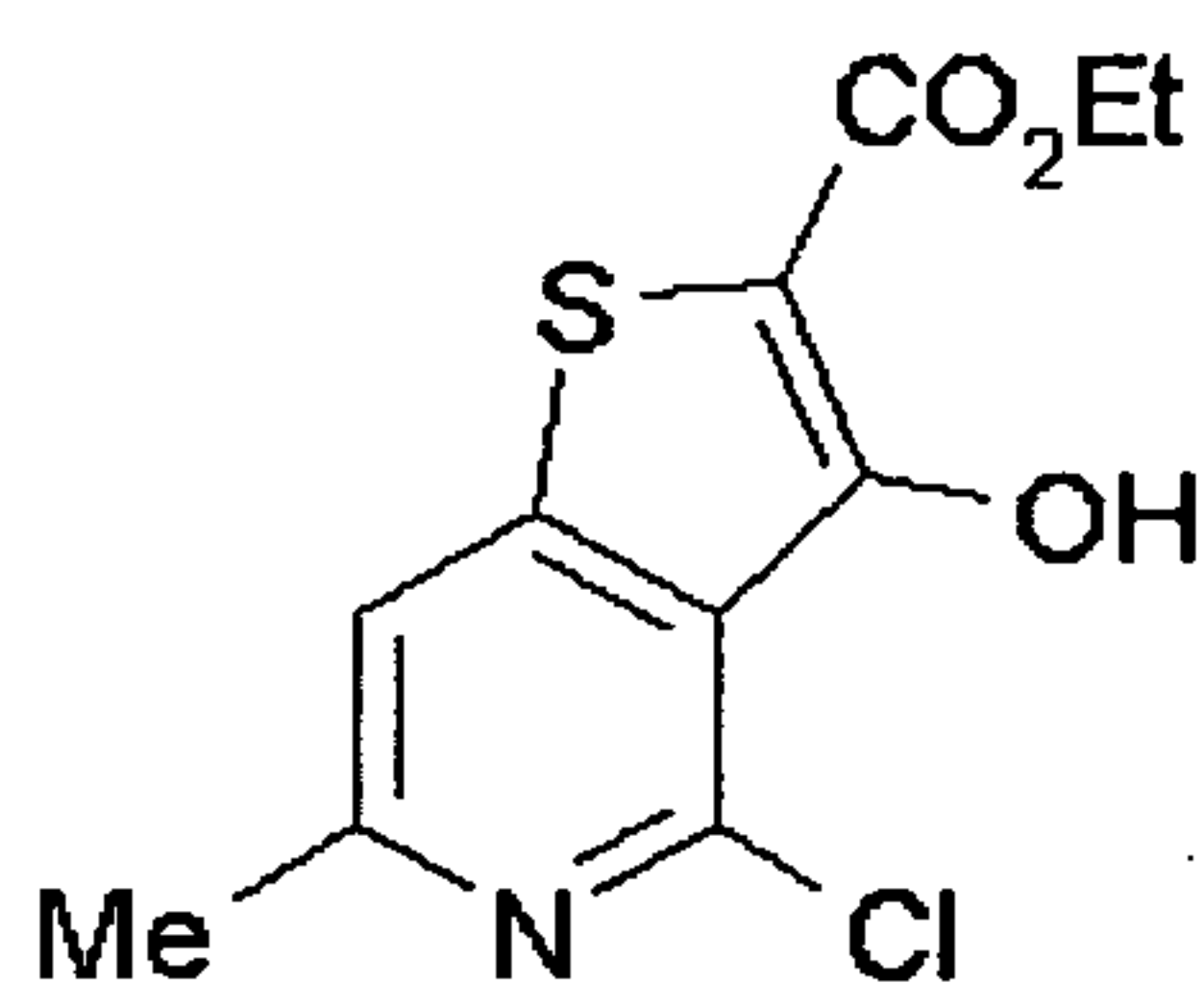
^1H -NMR (300 MHz, DMSO- d_6) δ : 1.66-1.88 (4H, m), 2.52-2.61 (4H, m), 3.86 (3H, s), 5.66 (2H, s), 7.62 (2H, t, J = 7.6 Hz), 7.70-7.79 (1H, m), 8.03-8.11 (2H, m), 13.12 (1H, s).

[0407]

Reference Example 67

Production of ethyl 4-chloro-3-hydroxy-6-methylthieno[3,2-c]pyridine-2-carboxylate

5 [0408]



[0409]

To a suspension of ethyl 2,4-dichloro-6-methylpyridine-3-carboxylate (10.0 g, 42.7 mmol) in acetonitrile (45 mL) were
10 added potassium carbonate (8.85 g, 64.1 mmol) and ethyl thioglycolate (4.68 mL, 42.7 mmol), and the mixture was stirred for 15 hr under refluxing conditions. The reaction mixture was diluted with water (150 mL), 6N hydrochloric acid (15mL) was added and the mixture was stirred for 30 min. The
15 precipitated solid was collected by filtration, washed with water and ethanol-diisopropyl ether (1/1), and dried under reduced pressure to give the title compound (10.9 g, 94%) as a white powder.

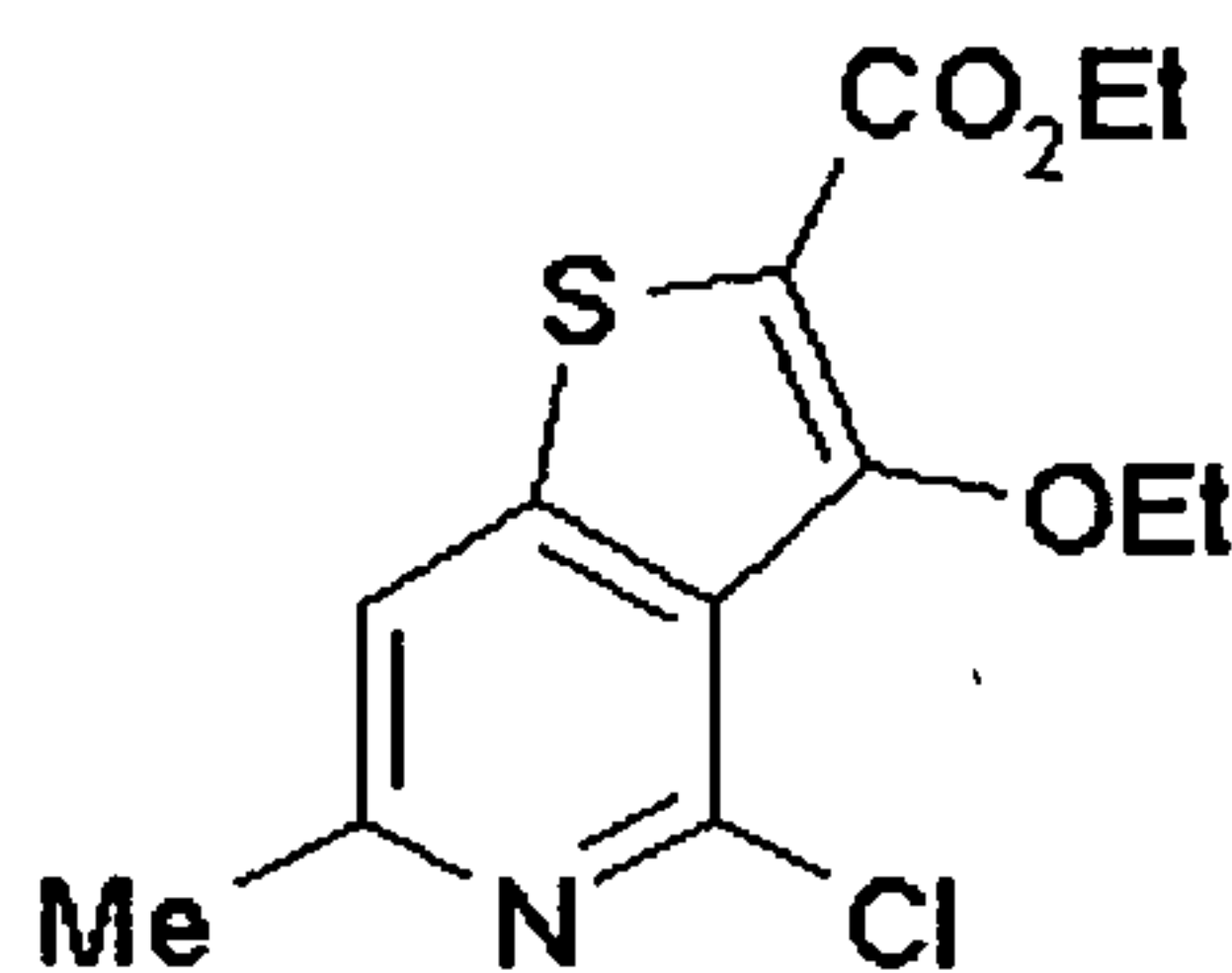
¹H-NMR (300 MHz, DMSO-d₆) δ:1.32 (3H, t, J = 7.1 Hz), 2.54 (3H, s),
20 4.36 (2H, q, J = 7.1 Hz), 7.87 (1H, s), 10.75 (1H, s).

[0410]

Reference Example 68

Production of ethyl 4-chloro-3-ethoxy-6-methylthieno[3,2-c]pyridine-2-carboxylate

25 [0411]



[0412]

In the same manner as in Reference Example 6, the title compound (4.30 g, 78%) was obtained as a white powder from the compound of Reference Example 67 (4.97 g, 18.3 mmol), DBU (4.10 mL, 27.4 mmol) and iodoethane (2.19 mL, 27.4 mmol).

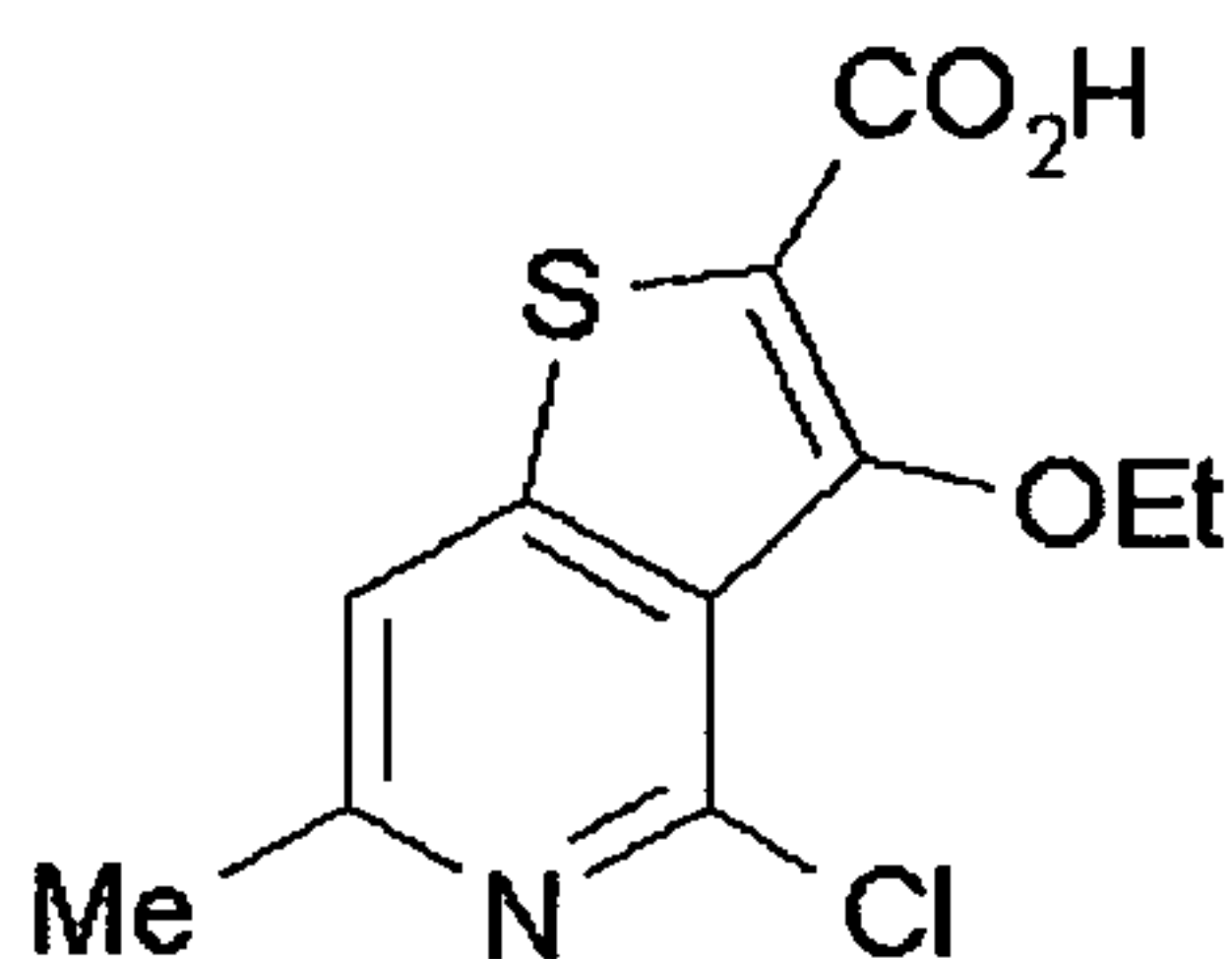
5 $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ : 1.33 (3H, t, $J = 7.2$ Hz), 1.43 (3H, t, $J = 7.1$ Hz), 2.54 (3H, s), 4.25 (2H, q, $J = 7.0$ Hz), 4.34 (2H, q, $J = 7.1$ Hz), 7.92 (1H, s).

[0413]

Reference Example 69

10 Production of 4-chloro-3-ethoxy-6-methylthieno[3,2-c]pyridine-2-carboxylic acid

[0414]



[0415]

15 A mixed solution of the compound of Reference Example 68 (4.30 g, 14.3 mmol) and 8N aqueous sodium hydroxide solution (15 mL) in THF (22 mL)-ethanol (22 mL) was stirred for 5 hr under refluxing conditions. The reaction mixture was acidified with 6N hydrochloric acid (22 mL) and the precipitated solid
20 was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (3.80 g, 97%) as a white powder.

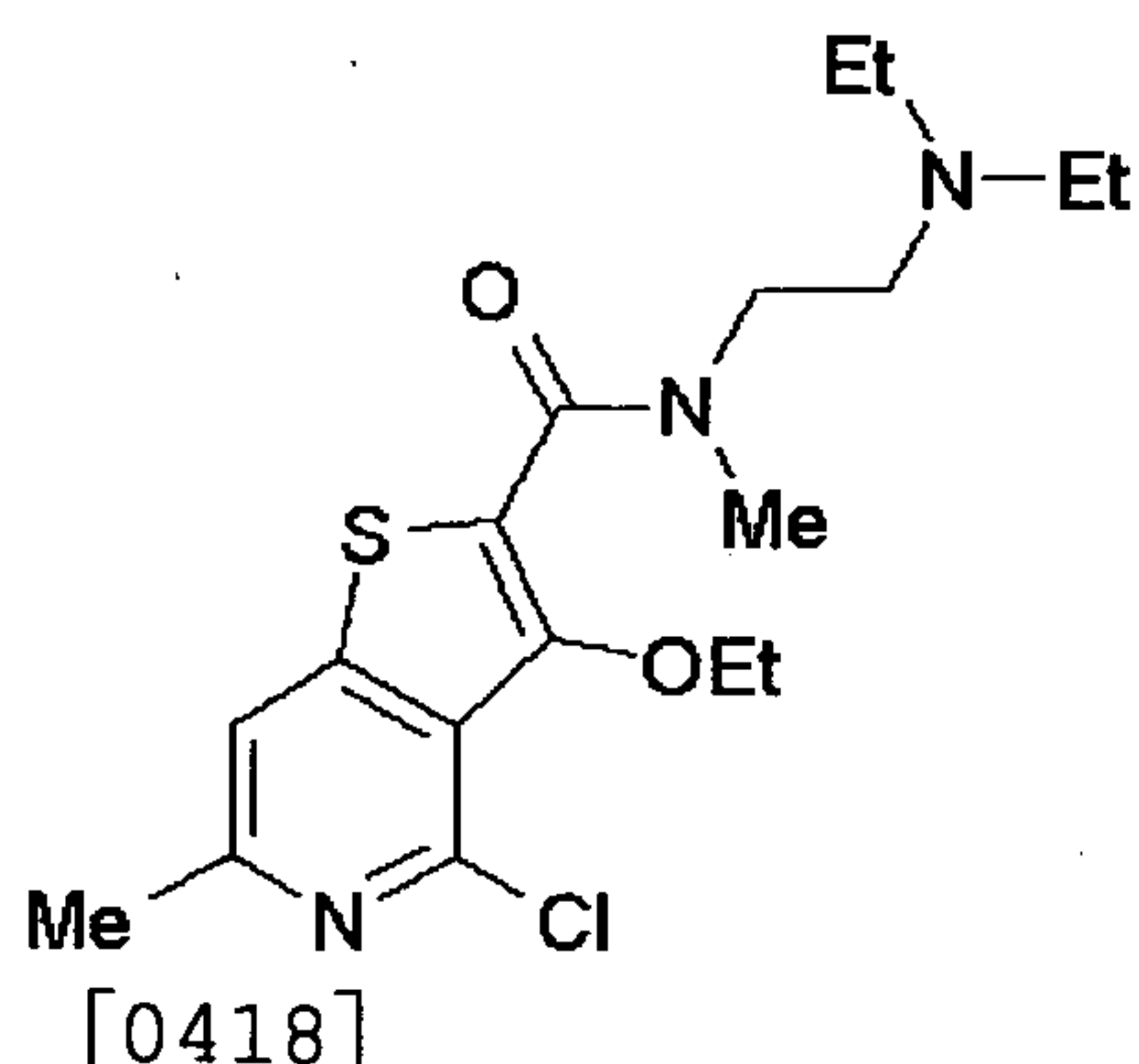
$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ : 1.40 (3H, t, $J = 6.9$ Hz), 2.54 (3H, s), 4.26 (2H, q, $J = 6.9$ Hz), 7.90 (1H, s), 13.65 (1H, s).

25 [0416]

Reference Example 70

Production of 4-chloro-N-[2-(diethylamino)ethyl]-3-ethoxy-N,6-dimethylthieno[3,2-c]pyridine-2-carboxamide

[0417]



In the same manner as in Example 25, the title compound (800 mg, 59%) was obtained as a colorless oil from the compound of Reference Example 69 (1.00 g, 3.68 mmol) and N,N-diethyl-N'-methylethane-1,2-diamine (773 μ L, 4.78 mmol).

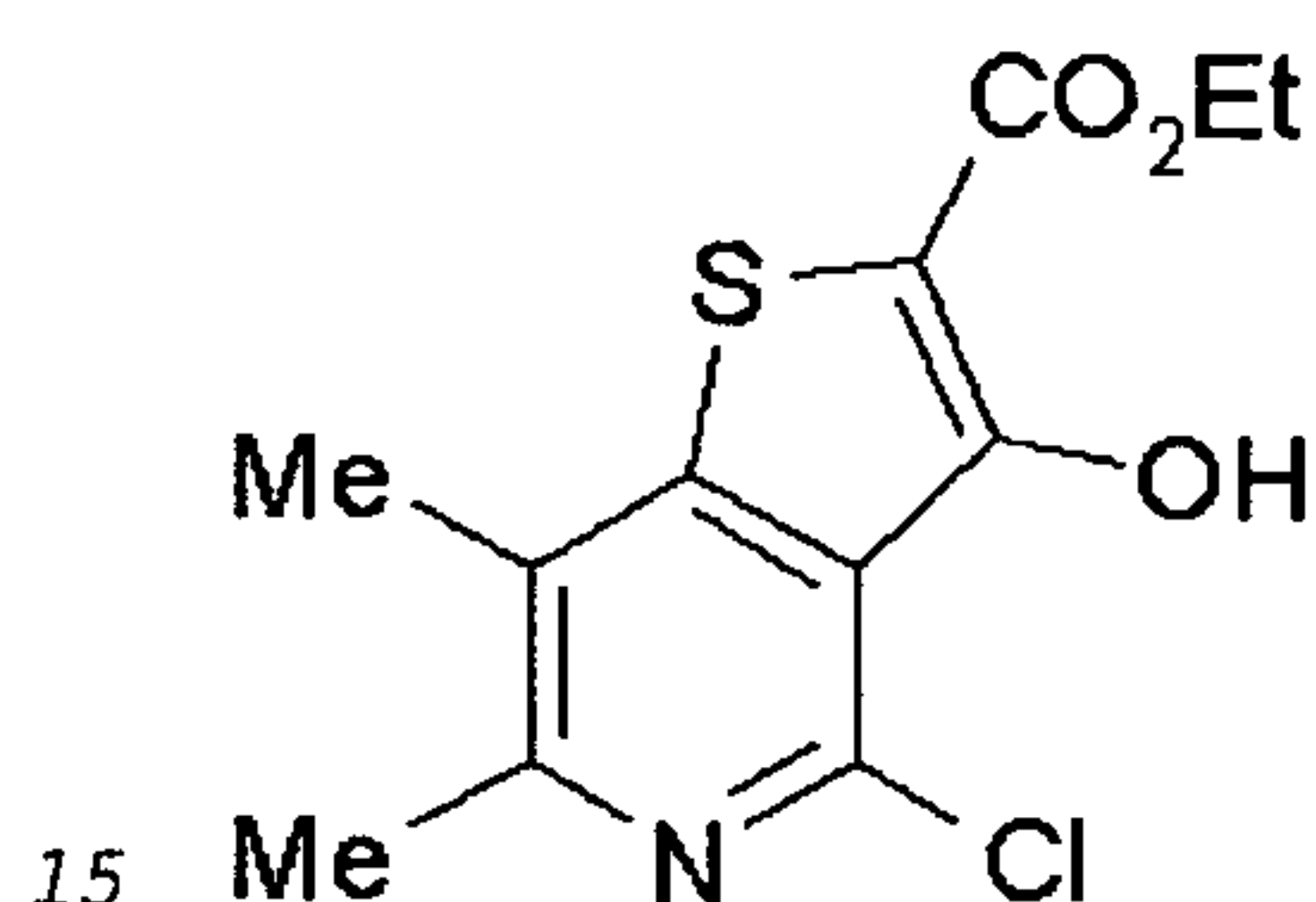
$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ : 0.65–1.10 (6H, m), 1.33 (3H, t, $J = 6.9$ Hz), 2.20–2.70 (6H, m), 2.53 (3H, s), 3.04 (3H, s), 3.35–3.65 (2H, m), 4.05–4.20 (2H, m), 7.89 (1H, s).

[0419]

Reference Example 71

Production of ethyl 4-chloro-3-hydroxy-6,7-dimethylthieno[3,2-c]pyridine-2-carboxylate

[0420]



A 20% solution (1.73 g, 5.08 mmol) of sodium ethoxide in ethanol was diluted with ethanol (5 mL), and ethyl thioglycolate (610 mg, 5.08 mmol) was added. Ethyl 2,4-dichloro-5,6-dimethylpyridine-3-carboxylate (630 mg, 2.54 mmol) was added to the mixture, and the mixture was stirred at room temperature for 18 hr. 2N Hydrochloric acid (3 mL) was added to the reaction mixture and the mixture was partitioned between brine and ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated. The obtained solid was washed with diisopropyl ether-hexane, and dried under

reduced pressure to give the title compound (374 mg, 52%) as a white powder.

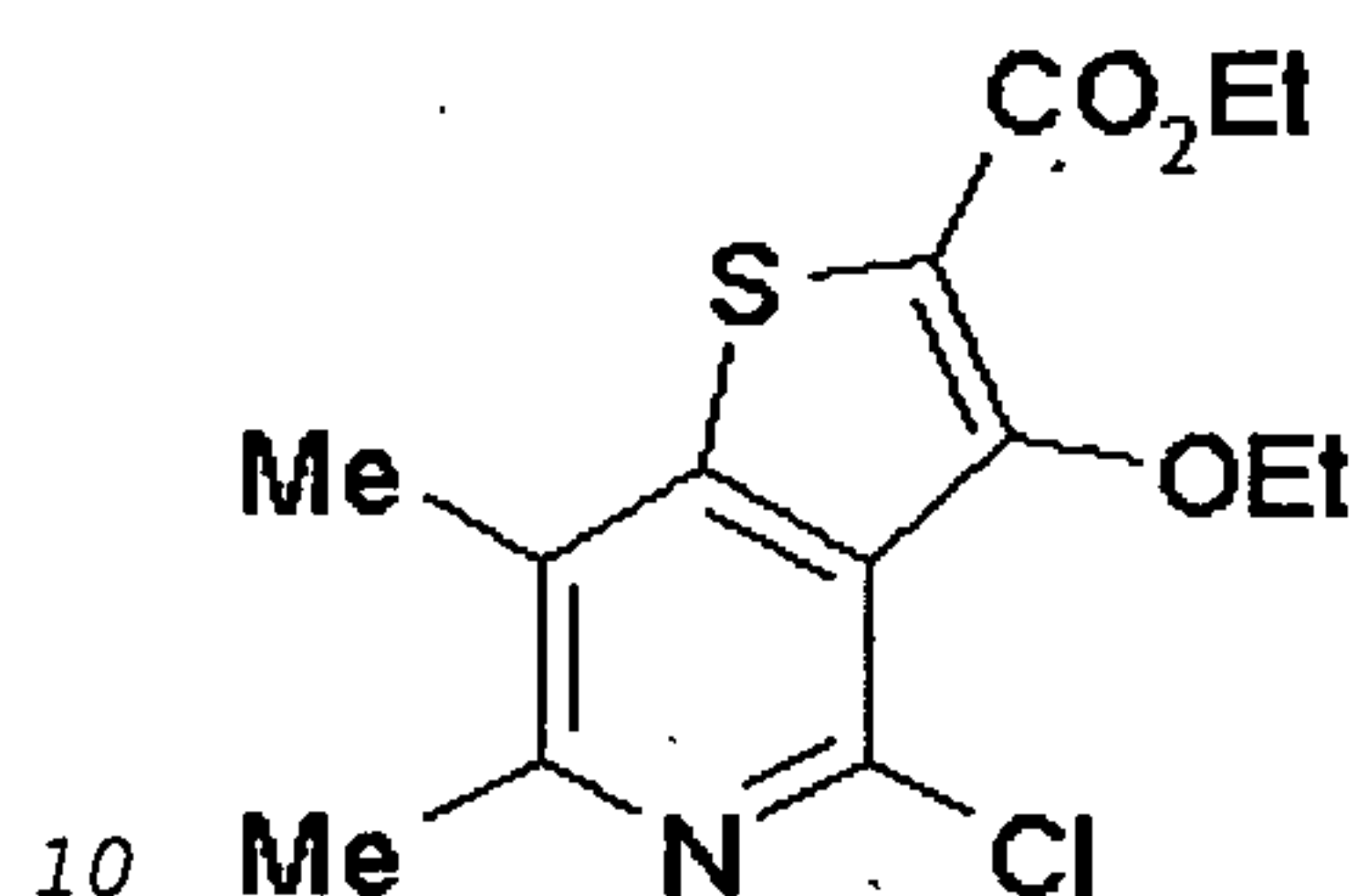
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 1.43 (3H, t, $J = 7.2$ Hz), 2.40 (3H, s), 2.61 (3H, s), 4.44 (2H, q, $J = 7.2$ Hz), 10.63 (1H, s).

5 [0422]

Reference Example 72

Production of ethyl 4-chloro-3-ethoxy-6,7-dimethylthieno[3,2-c]pyridine-2-carboxylate

[0423]



[0424]

In the same manner as in Reference Example 6, the title compound (350 mg, 91%) was obtained as a white solid from the compound of Reference Example 71 (350 mg, 1.22 mmol), DBU (380 mg, 2.02 mmol) and iodoethane (315 mg, 2.02 mmol).

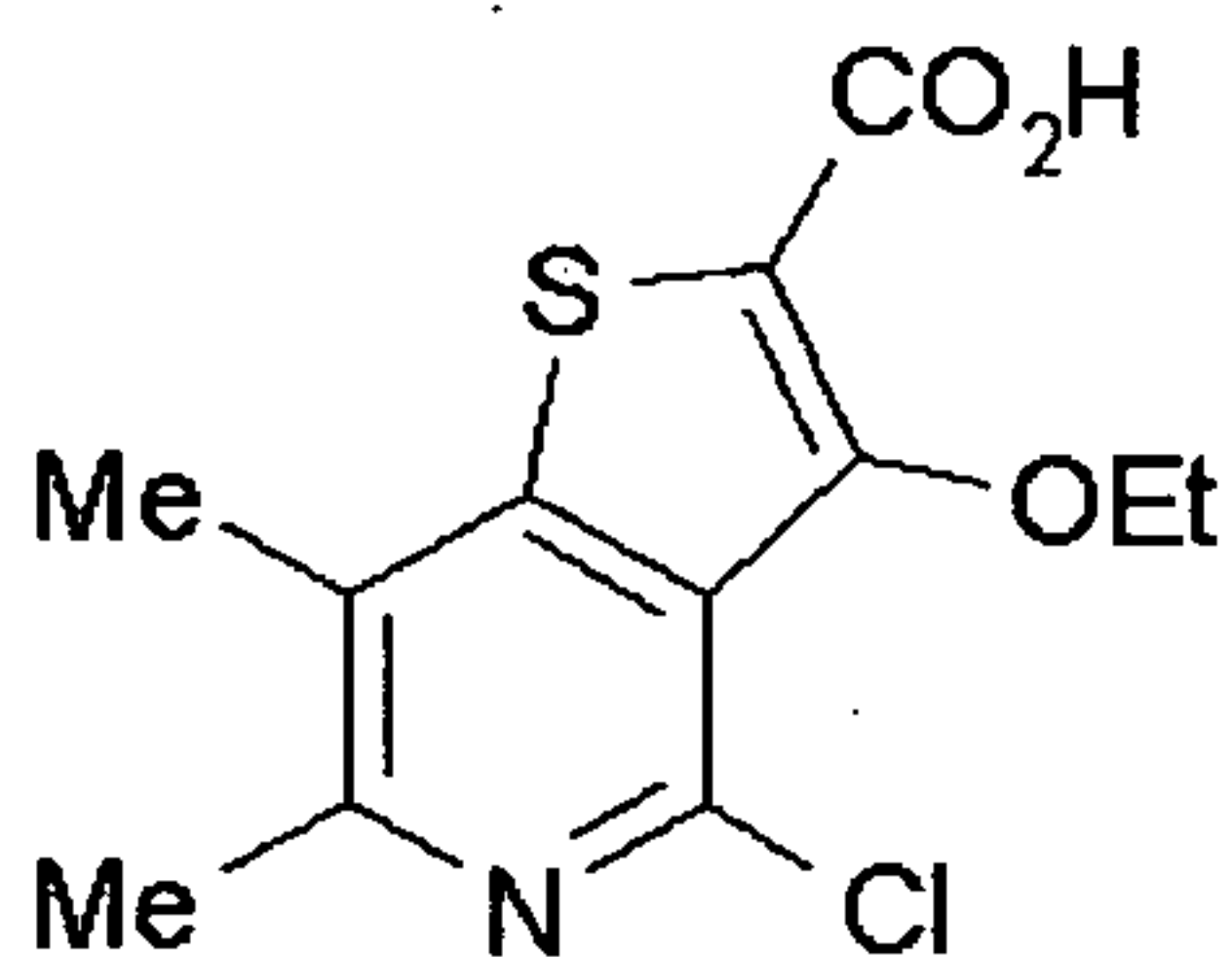
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 1.43 (3H, t, $J = 7.2$ Hz), 1.54 (3H, t, $J = 7.2$ Hz), 2.42 (3H, s), 2.60 (3H, s), 4.31 (2H, q, $J = 7.2$ Hz), 4.41 (2H, q, $J = 7.2$ Hz).

[0425]

20 Reference Example 73

Production of 4-chloro-3-ethoxy-6,7-dimethylthieno[3,2-c]pyridine-2-carboxylic acid

[0426]



[0427]

A mixed solution of the compound of Reference Example 72 (250 mg, 0.80 mmol) and 4N aqueous sodium hydroxide solution

(2 mL) in THF (2 mL)-ethanol (1 mL) was stirred at room temperature for 18 hr. The reaction mixture was partitioned between 1N hydrochloric acid and ethyl acetate, and the organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give the title compound (210 mg, 92%) as a white solid.

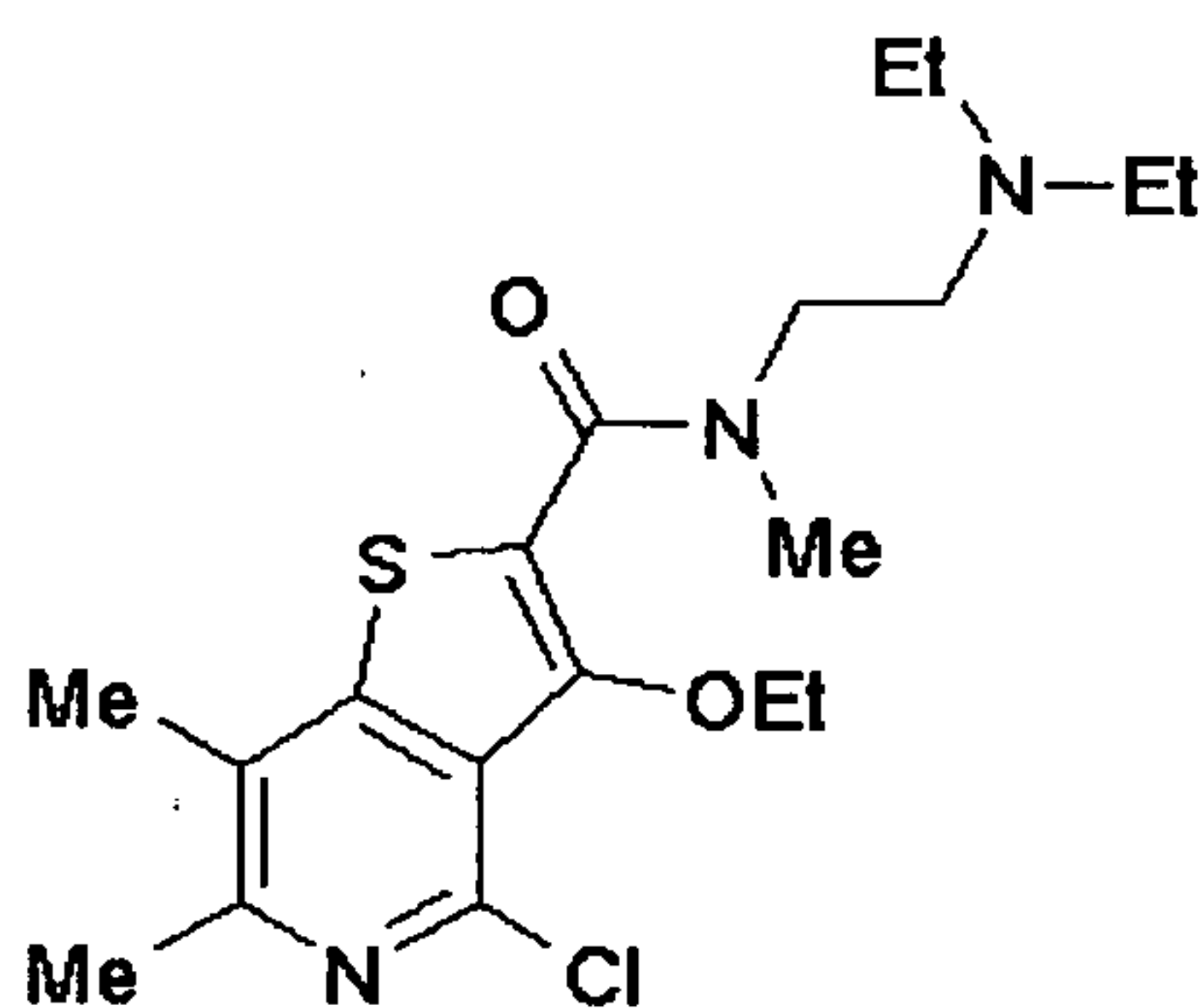
¹H-NMR (300 MHz, DMSO-d₆) δ:1.40 (3H, t, J= 7.1 Hz), 2.40 (3H, s), 2.53 (3H, s), 4.25 (2H, q, J = 7.0 Hz).

[0428]

10 Reference Example 74

Production of 4-chloro-N-[2-(diethylamino)ethyl]-3-ethoxy-N,6,7-trimethylthieno[3,2-c]pyridine-2-carboxamide

[0429]



15 [0430]

In the same manner as in Example 25, the title compound (230 mg, 79%) was obtained as a colorless oil from the compound of Reference Example 73 (210 mg, 0.73 mmol) and N,N-diethyl-N'-methylethane-1,2-diamine (144 mg, 1.10 mmol).

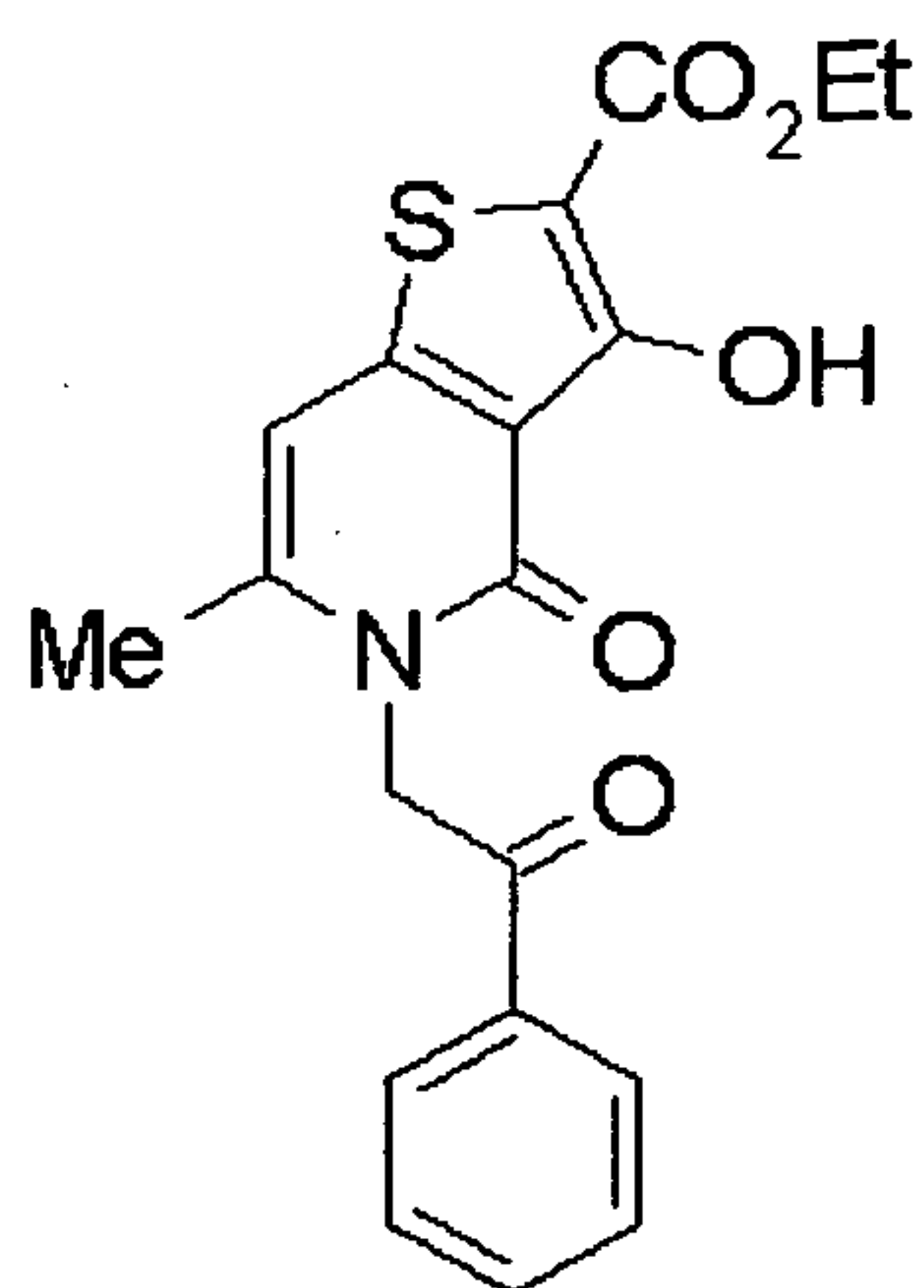
20 ¹H-NMR (300 MHz, CDCl₃) δ:0.80-1.10 (6H, m), 1.42 (3H, t, J = 6.9 Hz), 2.30-2.50 (5H, m), 2.60-2.80 (7H, m), 3.19 (3H, s), 3.45-3.70 (2H, m), 4.18 (2H, q, J = 7.0 Hz).

[0431]

Reference Example 75

25 Production of ethyl 3-hydroxy-6-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate

[0432]



[0433]

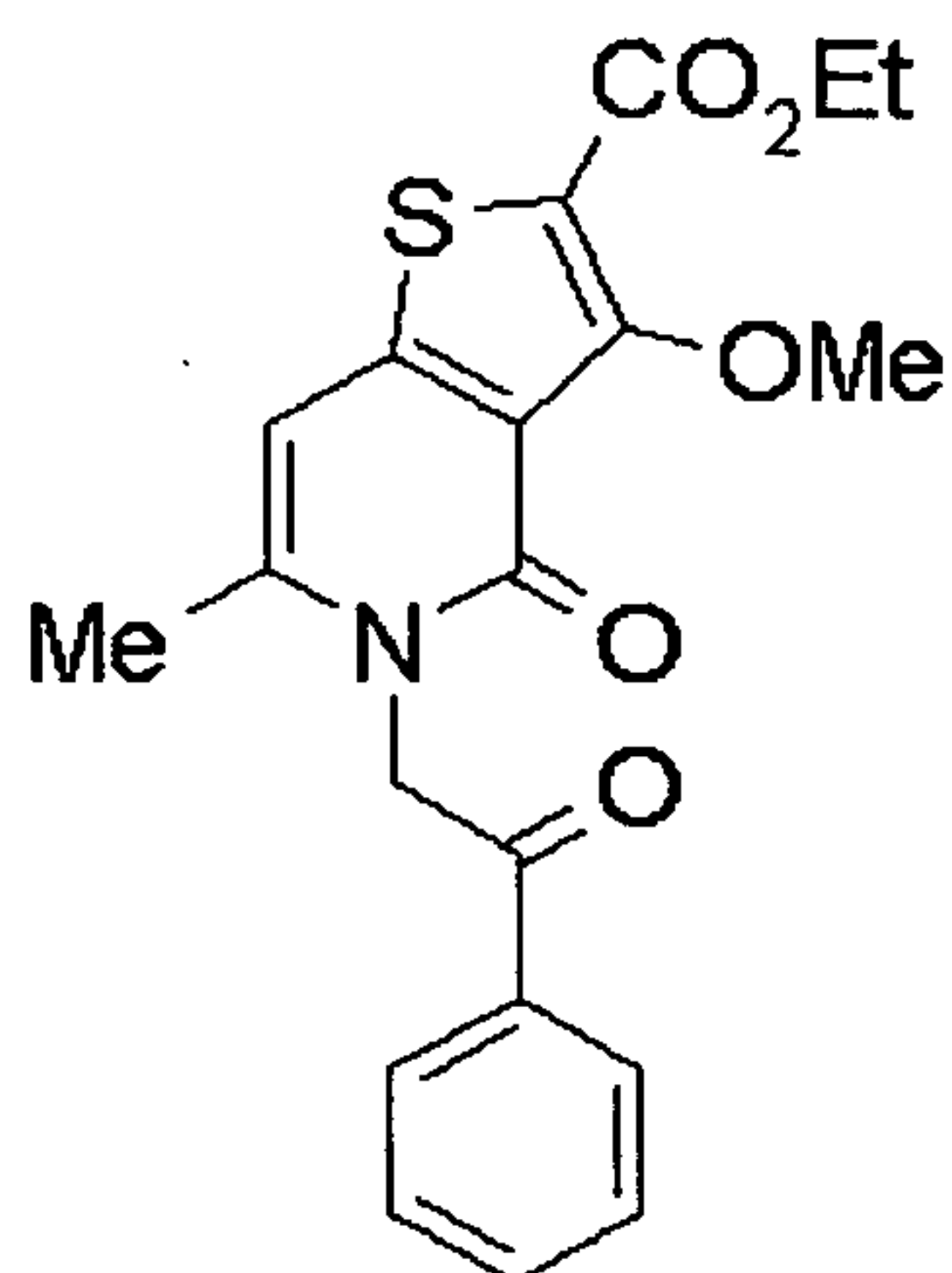
In the same manner as in Reference Example 5, the title compound (8.31 g, 88%) was obtained as a white powder from the compound of Reference Example 32 (8.50 g, 25.5 mmol), ethyl thioglycolate (6.70 mL, 61.1 mmol), a 20% solution (17.4 g, 51.0 mmol) of sodium ethoxide in ethanol and ethanol (100 mL). ¹H-NMR (300 MHz, DMSO-d₆) δ: 1.28 (3H, t, J=7.2 Hz), 2.33 (3H, s), 4.27 (2H, q, J=7.1 Hz), 5.71 (2H, s), 6.93 (1H, d, J=0.9 Hz), 7.62 (2H, t, J=7.5 Hz), 7.69-7.83 (1H, m), 8.01-8.21 (2H, m), 10.34 (1H, s).

[0434]

Reference Example 76

Production of ethyl 3-methoxy-6-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate

[0435]



[0436]

A mixture of the compound of Reference Example 75 (3.00 g, 8.08 mmol), dimethyl sulfate (4.58 mL, 48.4 mmol), potassium carbonate (3.35 g, 24.2 mmol) and acetone (60 mL) was stirred

for 3 days under refluxing conditions. Water (120 mL) was added to the mixture, and the precipitated solid was collected by filtration, and washed with water, ethanol and ethyl acetate to give the title compound (2.45 g, 79%) as a white solid.

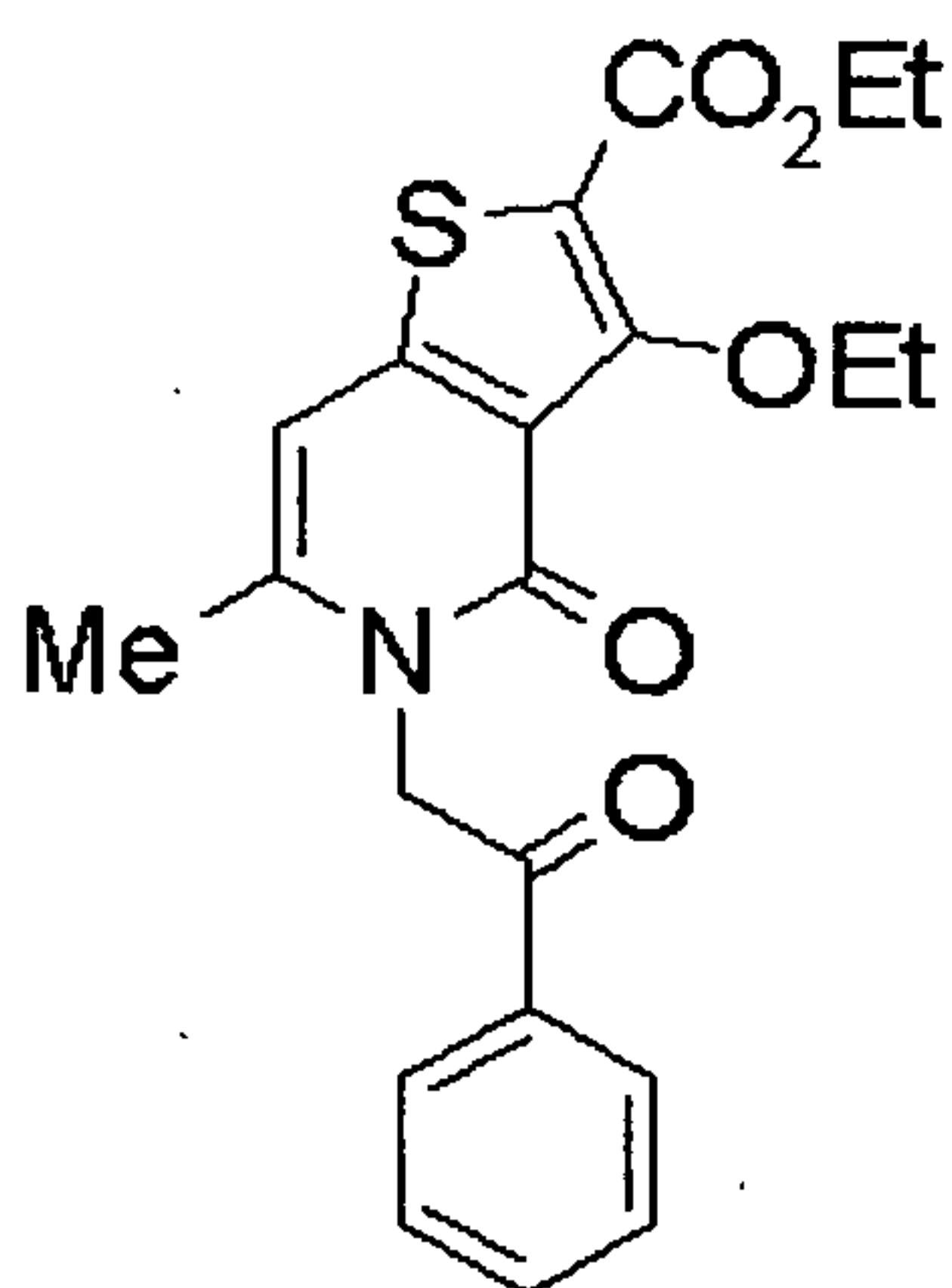
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.30 (3H, t, J=7.1 Hz), 2.31 (3H, s), 3.88 (3H, s), 4.28 (2H, q, J=7.2 Hz), 5.66 (2H, s), 6.85 (1H, d, J=0.8 Hz), 7.58-7.67 (2H, m), 7.70-7.80 (1H, m), 8.06-8.15 (2H, m).

10 [0437]

Reference Example 77

Production of ethyl 3-ethoxy-6-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate

[0438]



15

[0439]

In the same manner as in Reference Example 6, the title compound (585 mg, 54%) was obtained as a white powder from the compound of Reference Example 75 (1.00 g, 2.69 mmol), DBU (604 μL, 4.04 mmol) and iodoethane (323 μL, 4.04 mmol).

¹H-NMR (300 MHz, DMSO-d₆) δ: 1.23-1.35 (6H, m), 2.31 (3H, s), 4.14 (2H, q, J=7.0 Hz), 4.27 (2H, q, J=7.1 Hz), 5.67 (2H, s), 6.84 (1H, d, J=0.8 Hz), 7.57-7.67 (2H, m), 7.71-7.79 (1H, m), 8.07-8.15 (2H, m).

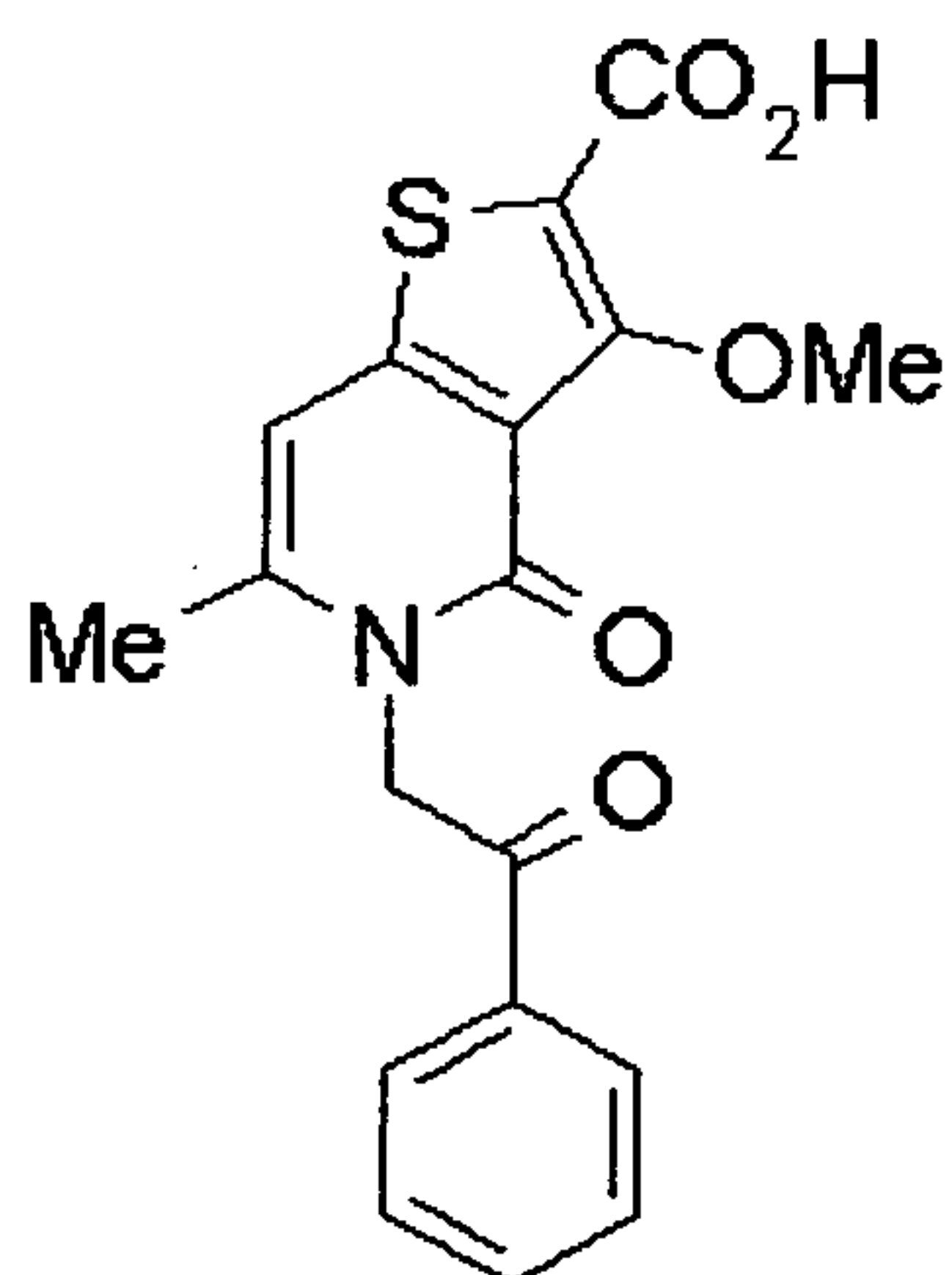
25 [0440]

Reference Example 78

Production of 3-methoxy-6-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylic

acid

[0441]



[0442]

5 In the same manner as in Reference Example 7, the title compound (1.25 g, 67%) was obtained as a white powder from the compound of Reference Example 76 (2.00 g, 5.19 mmol), 8N aqueous sodium hydroxide solution (3 mL) and ethanol (21 mL). ¹H-NMR (300 MHz, DMSO-d₆) δ: 2.31 (3H, m), 3.86 (3H, s), 5.66 (2H, s), 6.83 (1H, d, J=0.8 Hz), 7.58-7.68 (2H, m), 7.71-7.80 (1H, m), 8.08-8.17 (2H, m), 13.07 (1H, br s).

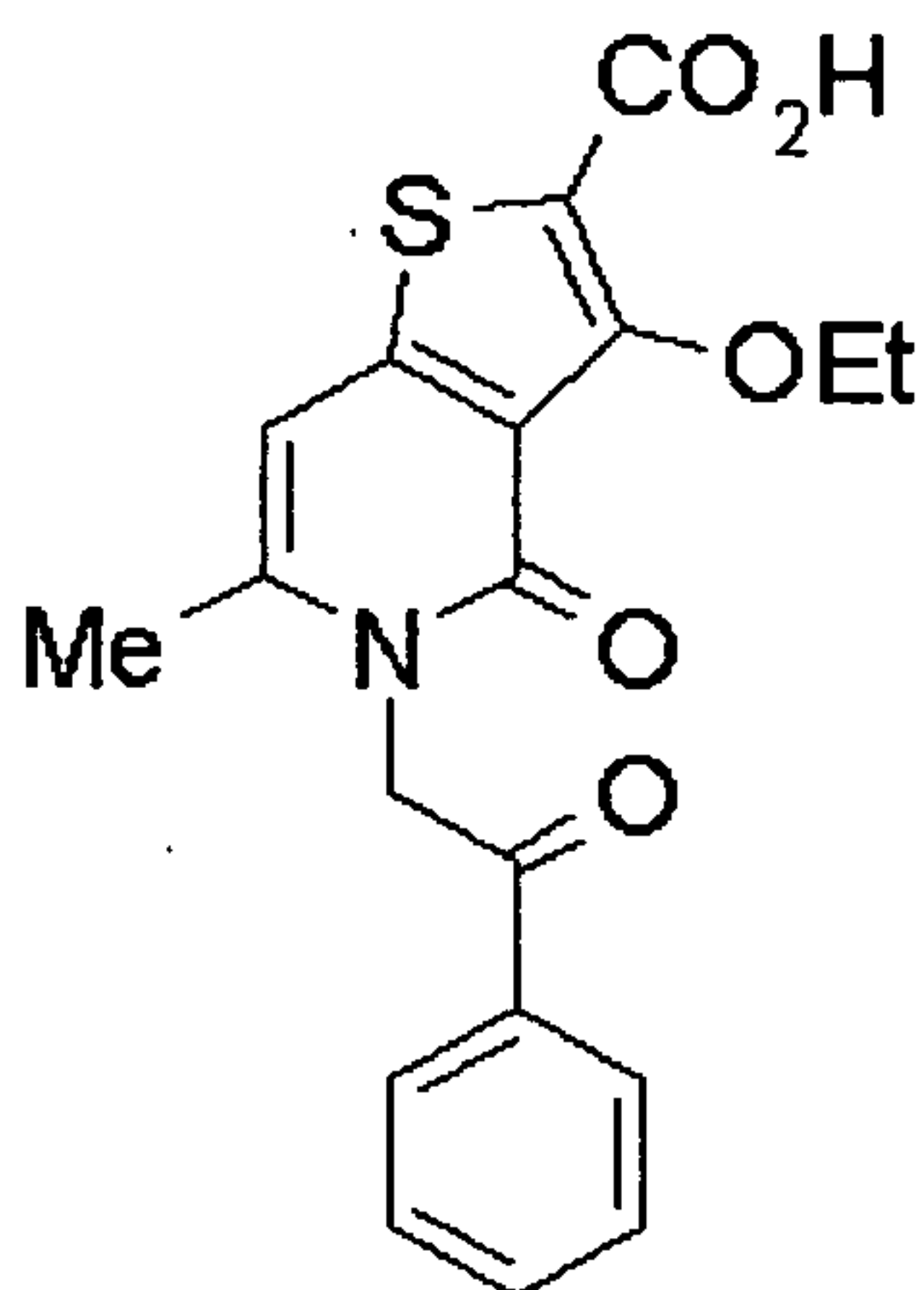
10

[0443]

Reference Example 79

Production of 3-ethoxy-6-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-
 15 4,5-dihydrothieno[3,2-c]pyridine-2-carboxylic acid

[0444]



[0445]

In the same manner as in Reference Example 7, the title
 20 compound (311 mg, 67%) was obtained as a white powder from the compound of Reference Example 77 (500 mg, 1.25 mmol), 8N

aqueous sodium hydroxide solution (1 mL) and ethanol (7 mL).

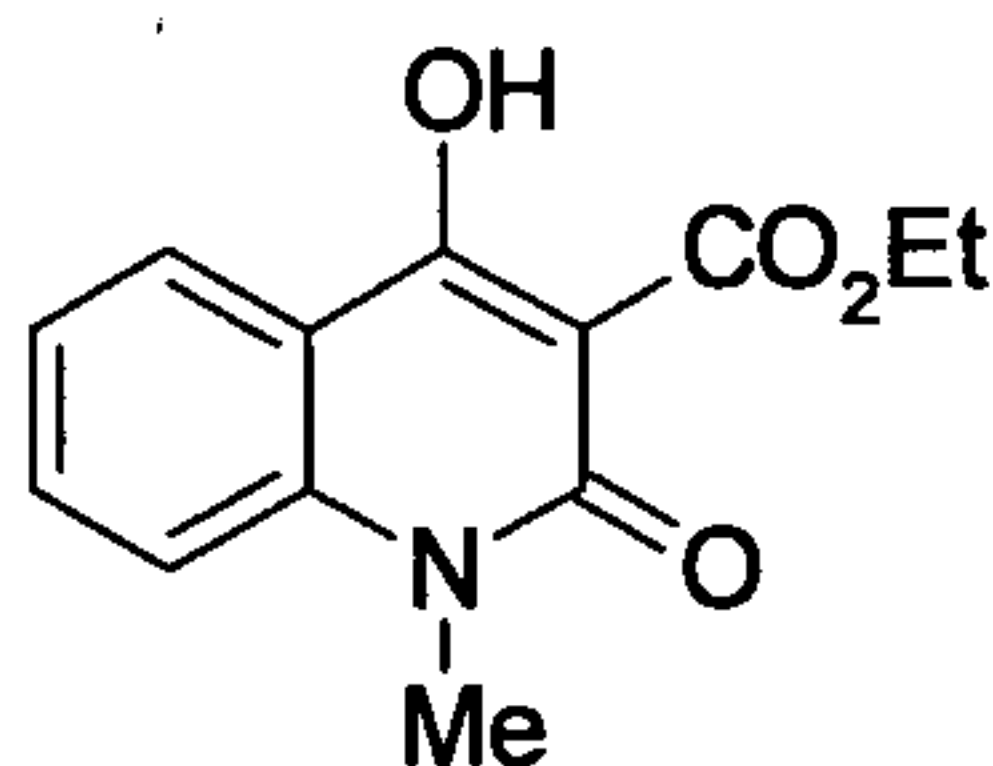
¹H-NMR (300 MHz, DMSO-d₆) δ:1.27 (3H, t, J=7.0 Hz), 2.30 (3H, s), 4.14 (2H, q, J=7.0 Hz), 5.66 (2H, s), 6.82 (1H, s), 7.58-7.66 (2H, m), 7.71-7.79 (1H, m), 8.08-8.17 (2H, m), 13.05 (1H, br s).

[0446]

Reference Example 80

Production of ethyl 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate

10 [0447]



[0448]

To a solution of diethyl malonate (68.0 g, 0.425 mol) in DMF (400 mL) was added sodium hydride (66% in oil, 10.8 g, 0.30 mol) under ice-cooling, and the mixture was stirred at the same temperature for 5 min and at room temperature for 15 min. N-Methylisatoic anhydride (50.8 g, 0.287 mol) was added to the obtained mixture by small portions, and the mixture was stirred at 120°C for 3 hr. Diisopropyl ether (500 mL) was added to the reaction mixture, and the precipitated solid was collected by filtration and washed with diisopropyl ether. The obtained solid was suspended in a mixture of methanol (250 mL) and water (500 mL), 5N hydrochloric acid (60 mL) was added dropwise, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with water, and concentrated under reduced pressure. The residue was washed with diisopropyl ether to give the title compound (41.4 g, 58%).

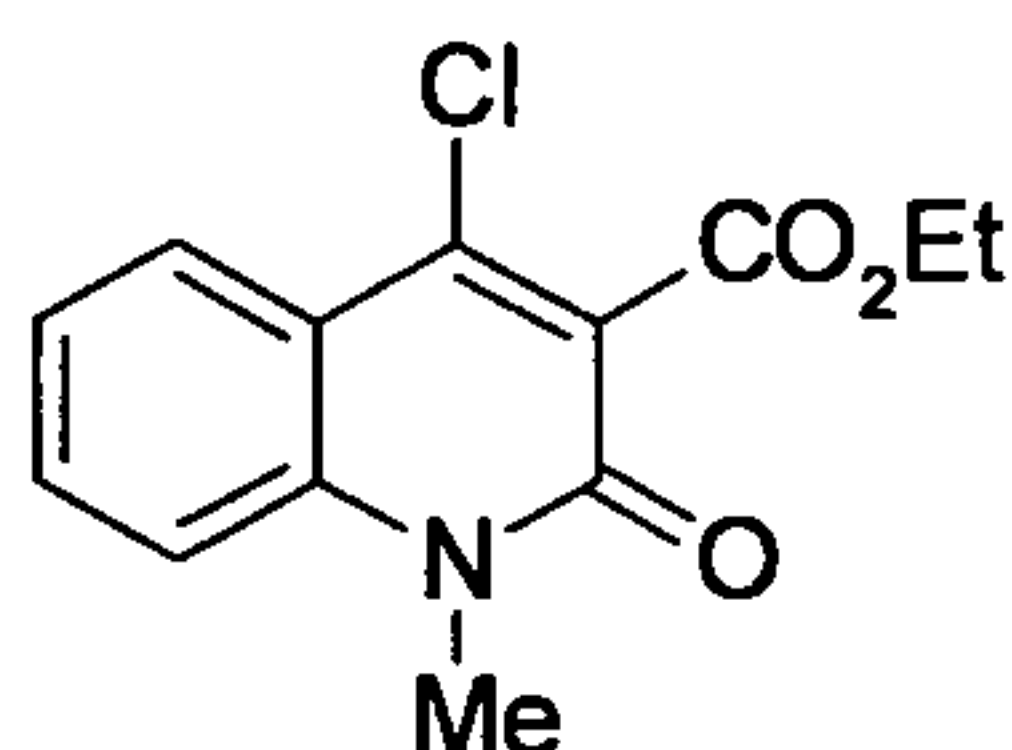
¹H-NMR (300 MHz, CDCl₃) δ:1.49 (3H, t, J = 7.1 Hz), 3.66 (3H, s), 4.51 (2H, q, J = 7.1 Hz), 7.23-7.30 (1H, m), 7.32 (1H, d, J = 8.7 Hz), 7.69 (1H, ddd, J = 8.7, 7.1, 1.6 Hz), 8.19 (1H, dd, J = 8.0, 1.6 Hz), 14.21 (1H, s).

[0449]

Reference Example 81

Production of ethyl 4-chloro-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate

5 [0450]



[0451]

A mixture of the compound of Reference Example 80 (58.0 g, 0.235 mol) and phosphorus oxychloride (33 mL, 0.35 mol) was stirred at 110°C for 30 min. The reaction mixture was concentrated under reduced pressure, and ice water and ethyl acetate were added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, 1N sodium hydroxide solution (3 times) and water, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (47.7 g, 76%).

¹H-NMR (300 MHz, CDCl₃) δ: 1.42 (3H, t, J = 7.1 Hz), 3.73 (3H, s), 4.48 (2H, q, J = 7.1 Hz), 7.35 (1H, ddd, J = 8.7, 7.1, 1.0 Hz), 7.40 (1H, d, J = 8.7 Hz), 7.68 (1H, ddd, J = 8.7, 7.1, 1.4 Hz), 8.07 (1H, dd, J = 8.0, 1.4 Hz).

10 15 20

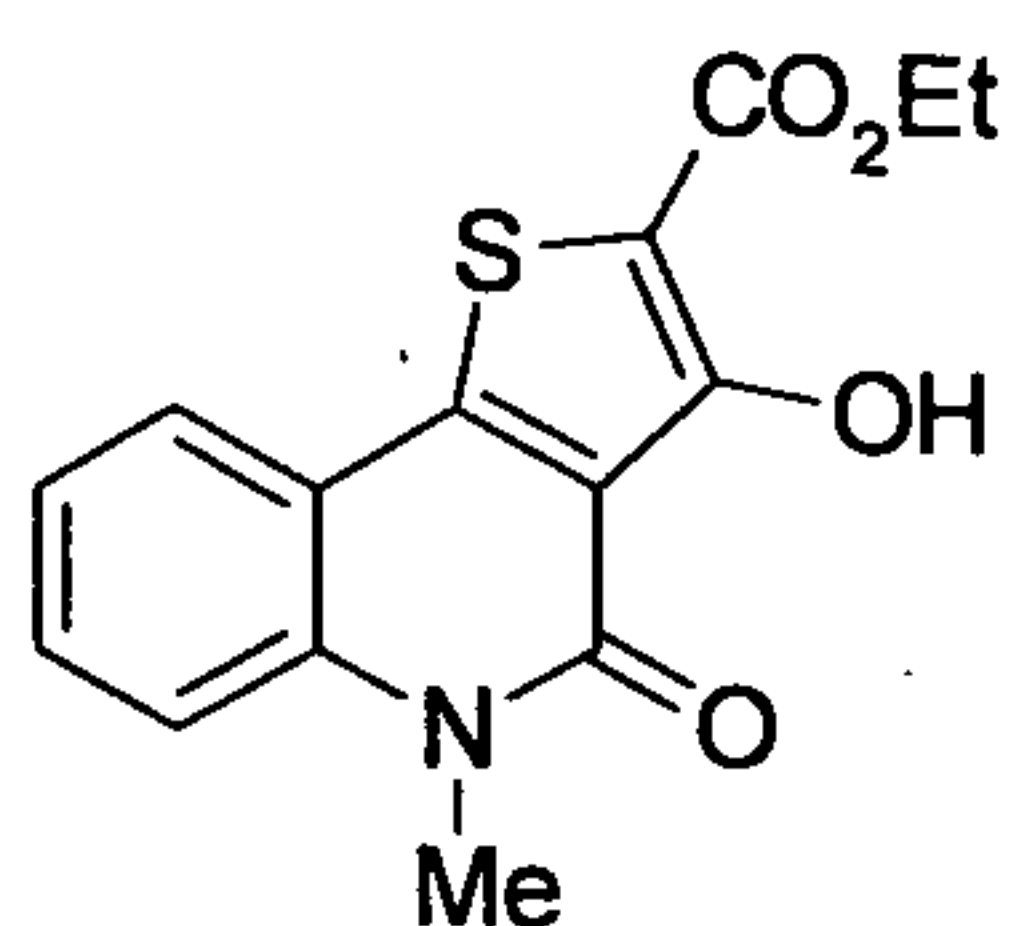
[0452]

Reference Example 82

Production of ethyl 3-hydroxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

25

[0453]



[0454]

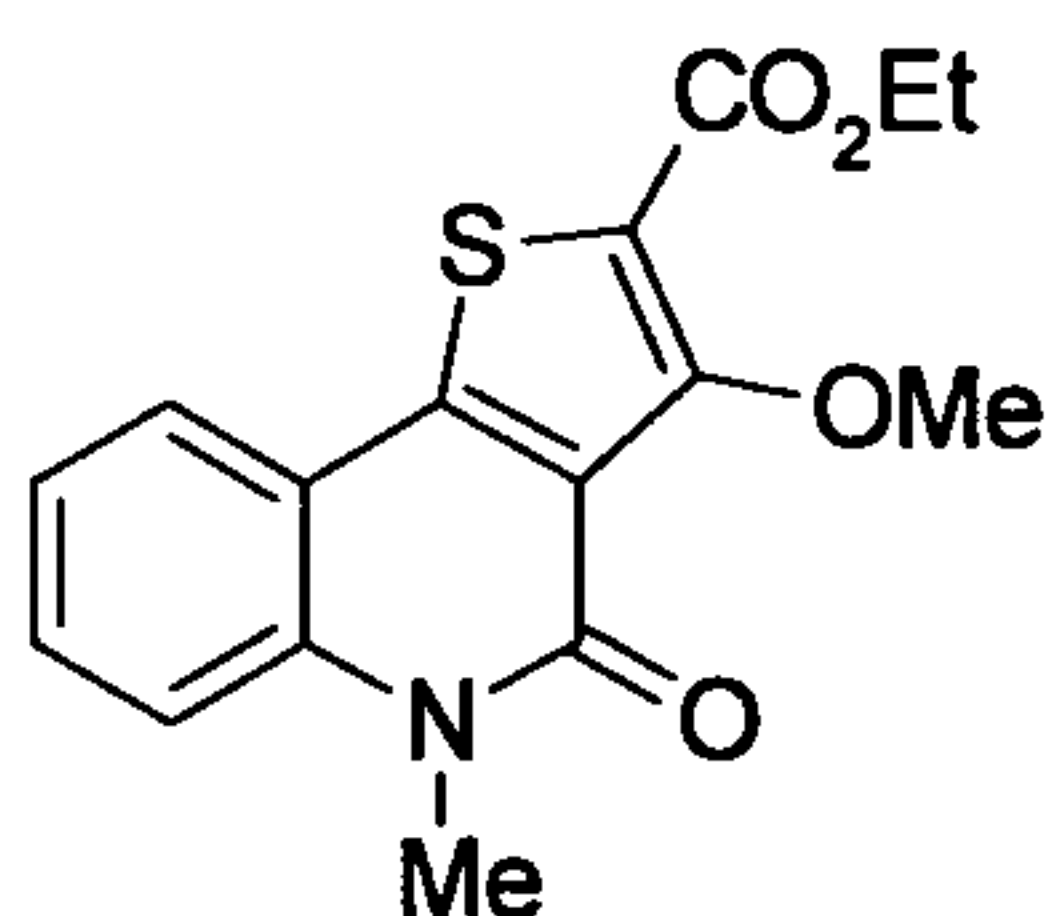
A 20% solution (23.2 g, 68 mmol) of sodium ethoxide in ethanol was diluted with ethanol (70 mL), ethyl thioglycolate (9.0 mL, 82 mmol) was added to the obtained solution, and the mixture was stirred at room temperature for 10 min. The compound of Reference Example 81 (9.04 g, 34.0 mmol) was added to this mixture, and the mixture was stirred at room temperature for 4 hr. The reaction mixture was neutralized with ice water and 2N hydrochloric acid (40 mL) under ice-cooling, and the mixture was extracted twice with chloroform. The combined organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was recrystallized from THF-diisopropyl ether to give the title compound (9.12 g, 88%).
¹H-NMR (300 MHz, CDCl₃) δ: 1.42 (3H, t, J = 7.2 Hz), 3.76 (3H, s), 4.41 (2H, q, J = 7.2 Hz), 7.34 (1H, ddd, J = 7.9, 7.2, 0.8 Hz), 7.44-7.49 (1H, m), 7.63 (1H, ddd, J = 8.6, 7.2, 1.4 Hz), 7.83 (1H, dd, J = 7.9, 1.4 Hz), 10.76 (1H, s).

[0455]

Reference Example 83

Production of ethyl 3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0456]



[0457]

To a suspension of the compound of Reference Example 82 (3.04 g, 10.0 mmol) in DMF (30 mL) was added DBU (1.65 mL, 11 mmol), and iodomethane (0.81 mL, 13 mmol) was added to the obtained solution under ice-cooling. The obtained mixture was stirred at room temperature for 21 hr, water was added and the precipitated solid was collected by filtration. This was dissolved in ethanol by heating, treated with activated carbon,

filtered, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, and the mixture was washed with water and 0.5N sodium hydroxide solution, filtered through Celite (trade name), further washed twice with water, and concentrated under reduced pressure. The residue was recrystallized from ethanol-diisopropyl ether to give the title compound (1.51 g, 48%).

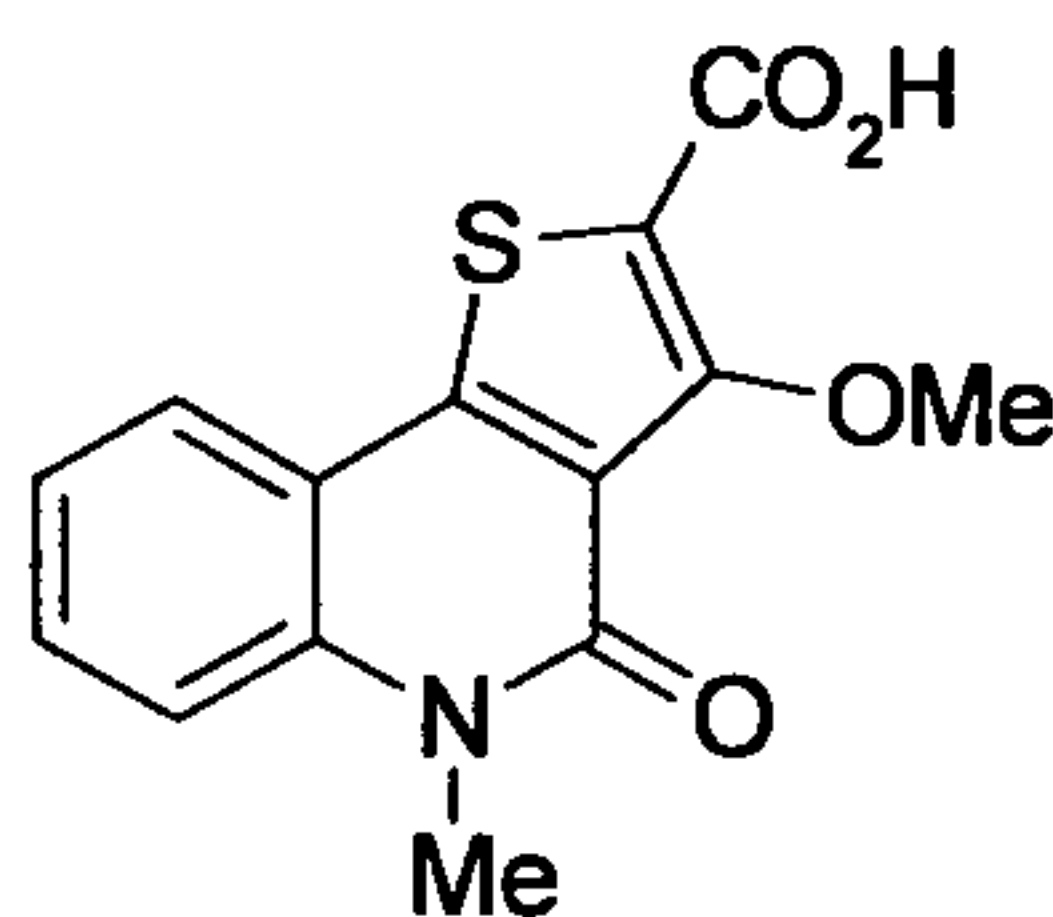
¹H-NMR (300 MHz, CDCl₃) δ: 1.42 (3H, t, J = 7.2 Hz), 3.76 (3H, s), 4.14 (3H, s), 4.40 (2H, q, J = 7.2 Hz), 7.24-7.31 (1H, m), 7.41 (1H, d, J = 8.7 Hz), 7.59 (1H, ddd, J = 8.7, 7.3, 1.5 Hz), 7.84 (1H, dd, J = 8.1, 1.5 Hz).

[0458]

Reference Example 84

Production of 3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0459]



[0460]

To a suspension of the compound of Reference Example 83 (1.90 g, 5.99 mmol) in THF (20 mL) and ethanol (20 mL) was added 5N sodium hydroxide solution (2.4 mL, 12 mmol). The obtained mixture was stirred at room temperature for 1.5 hr. 1N Hydrochloric acid (13 mL) was added to the reaction mixture, and the precipitated solid was collected by filtration, and recrystallized from methanol to give the title compound (1.14 g, 66%).

¹H-NMR (300 MHz, DMSO-d₆) δ: 3.66 (3H, d, J = 1.1 Hz), 3.95 (3H, s), 7.30-7.37 (1H, m), 7.58-7.71 (2H, m), 7.94-8.00 (1H, m).

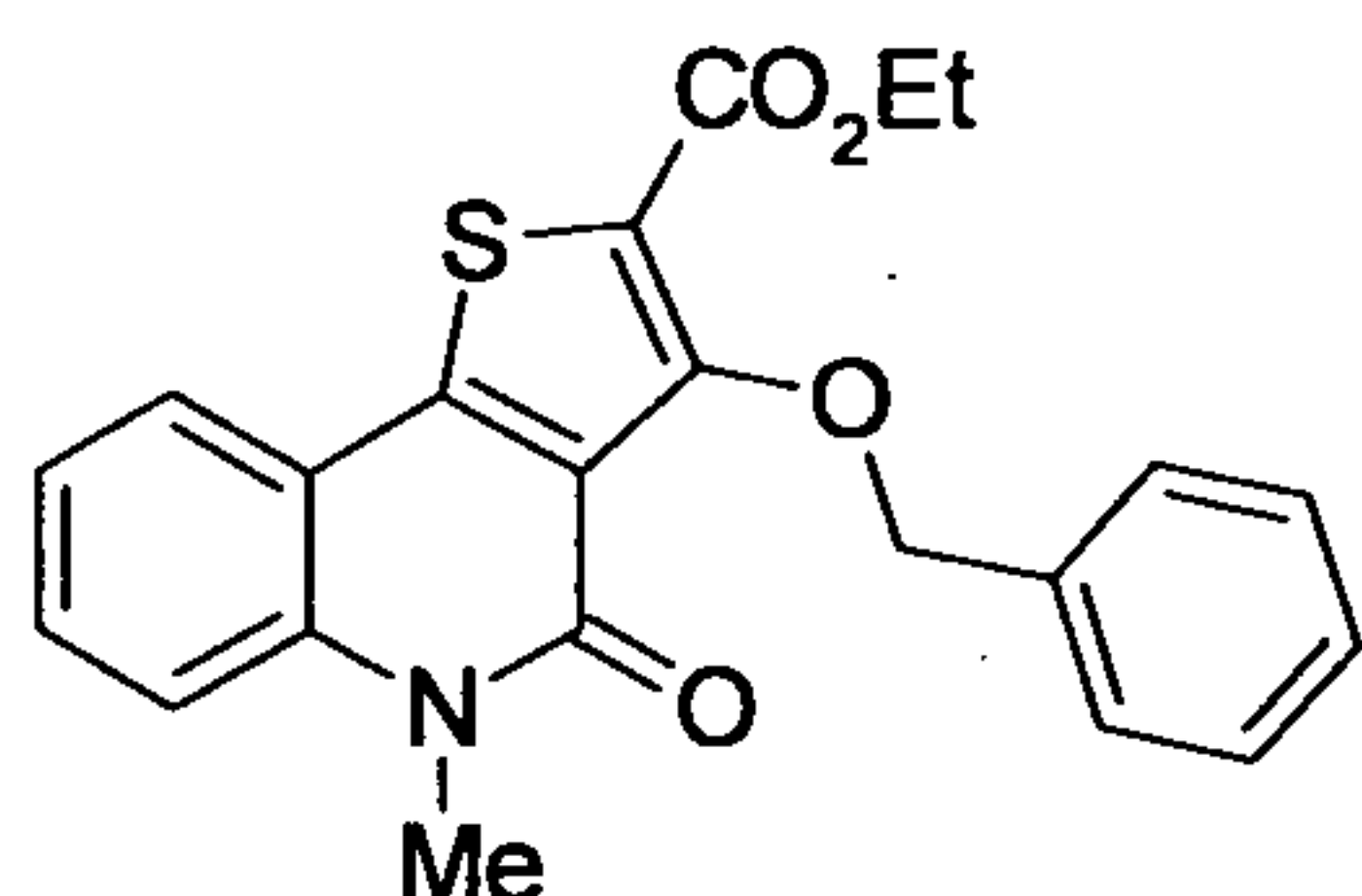
[0461]

Reference Example 85

Production of ethyl 3-(benzyloxy)-5-methyl-4-oxo-4,5-

dihydrothieno[3,2-c]quinoline-2-carboxylate

[0462]



[0463]

5 To a suspension of the compound of Reference Example 82 (1.00 g, 3.30 mmol) in DMF (10 mL) was added DBU (0.592 mL, 3.96 mmol), and benzylbromide (0.510 mL, 4.29 mmol) was added to the obtained solution. The obtained mixture was stirred at room temperature for 15 hr. Ethyl acetate and water were added
10 to the reaction mixture and the organic layer was separated. The aqueous layer was extracted twice with ethyl acetate. The combined organic layer was washed with water and 0.5N sodium hydroxide solution, filtered through Celite (trade name), further washed with water, and concentrated under reduced
15 pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=1/4 - 1/2 - 2/1) to give the title compound (980 mg, 75%).

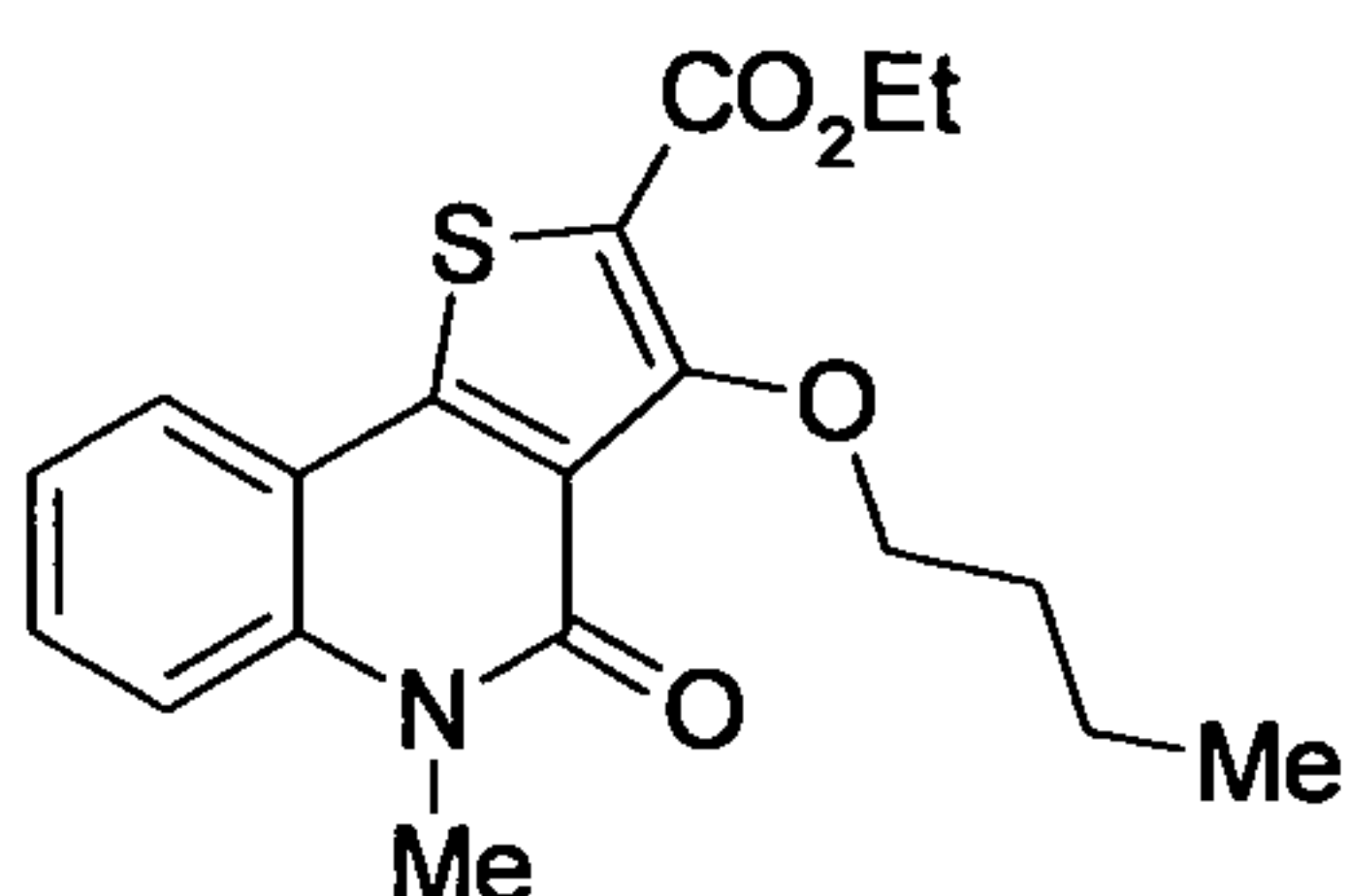
¹H-NMR (300 MHz, CDCl₃) δ: 1.36 (3H, t, J = 7.2 Hz), 3.78 (3H, s), 4.36 (2H, q, J = 7.2 Hz), 5.34 (2H, s), 7.24-7.44 (5H, m),
20 7.59 (1H, ddd, J = 8.6, 7.1, 1.4 Hz), 7.63-7.69 (2H, m), 7.85 (1H, dd, J = 7.8, 1.4 Hz).

[0464]

Reference Example 86

Production of ethyl 3-butoxy-5-methyl-4-oxo-4,5-
25 dihydrothieno[3,2-c]quinoline-2-carboxylate

[0465]



[0466]

To a suspension of the compound of Reference Example 82 (1.00 g, 3.30 mmol) in DMF (10 mL) was added DBU (0.592 mL, 3.96 mmol), and 1-iodobutane (0.488 mL, 4.29 mmol) was added to the obtained solution. The obtained mixture was stirred at room temperature for 15 hr. Ethyl acetate and water were added to the reaction mixture, the organic layer was separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layer was washed with water and 0.5N aqueous sodium hydroxide solution, filtered through Celite (trade name), further washed with water, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=1/4 - 1/2 - 2/1) to give the title compound (1.05 g, 89%).

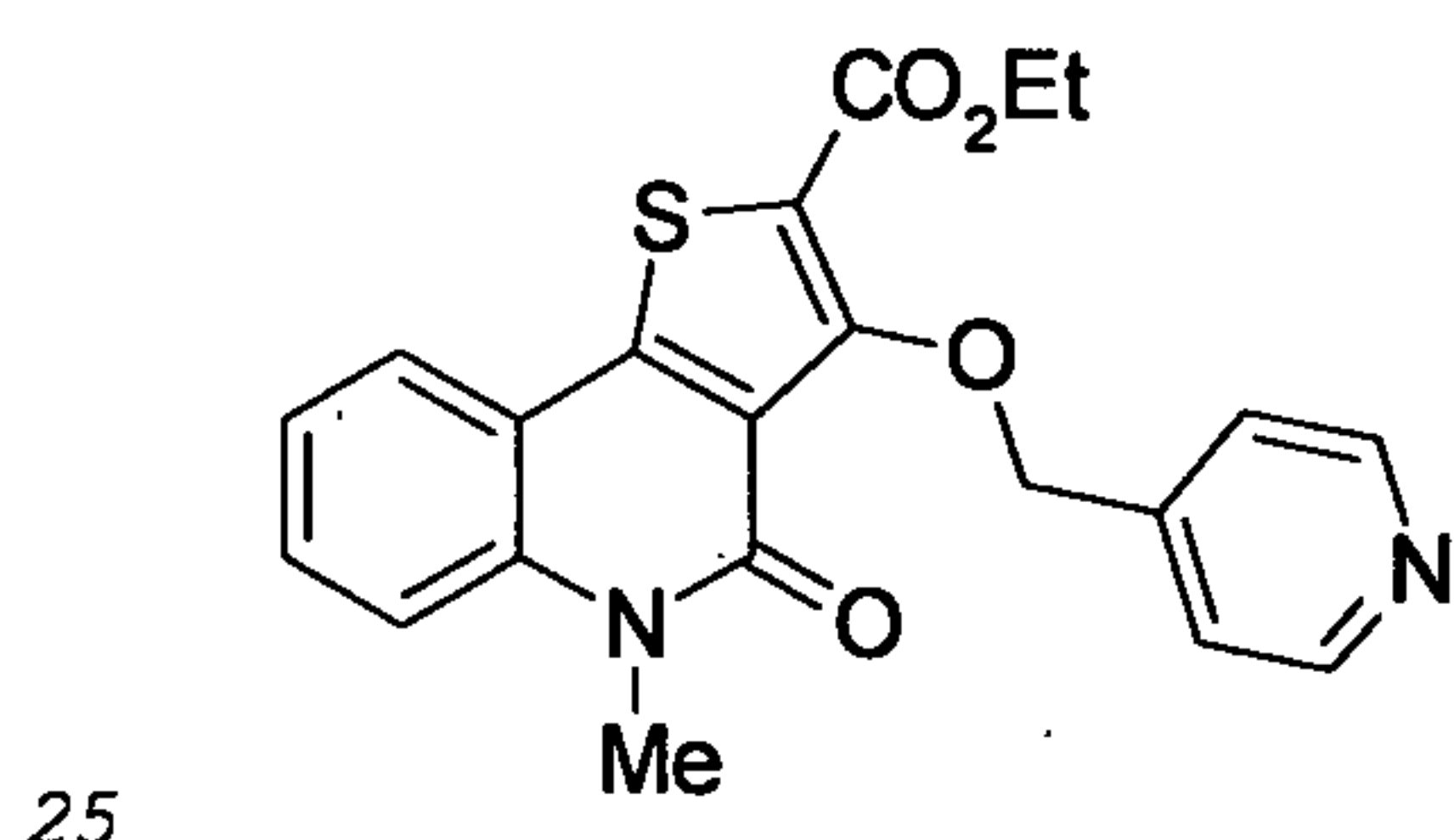
¹H-NMR (300 MHz, CDCl₃) δ: 1.01 (3H, t, J = 7.5 Hz), 1.42 (3H, t, J = 7.2 Hz), 1.50-1.66 (2H, m), 1.87-1.99 (2H, m), 3.74 (3H, s), 4.28 (2H, t, J = 6.6 Hz), 4.39 (2H, q, J = 7.2 Hz), 7.27 (1H, ddd, J = 8.0, 7.1, 0.9 Hz), 7.40 (1H, d, J = 8.1 Hz), 7.58 (1H, ddd, J = 8.6, 7.1, 1.4 Hz), 7.81-7.86 (1H, m).

[0467]

Reference Example 87

Production of ethyl 5-methyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0468]



[0469]

To a suspension of the compound of Reference Example 82 (1.00 g, 3.30 mmol) in DMF (20 mL) was added DBU (1.18 mL, 7.89 mmol), and 4-(chloromethyl)pyridine hydrochloride (704 mg, 4.29 mmol) was added to the obtained solution. The obtained mixture was stirred at room temperature for 18 hr, at 45°C for

2 hr, and at 60°C for 18 hr. DBU (1.18 mL, 7.89 mmol) and 4-(chloromethyl)pyridine hydrochloride (704 mg, 4.29 mmol) were added, and the mixture was stirred at 60°C for 10 hr.

Chloroform and water were added to the reaction mixture, the organic layer was separated, and the aqueous layer was extracted with chloroform. The combined organic layer was washed with water, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (678 mg, 53%).

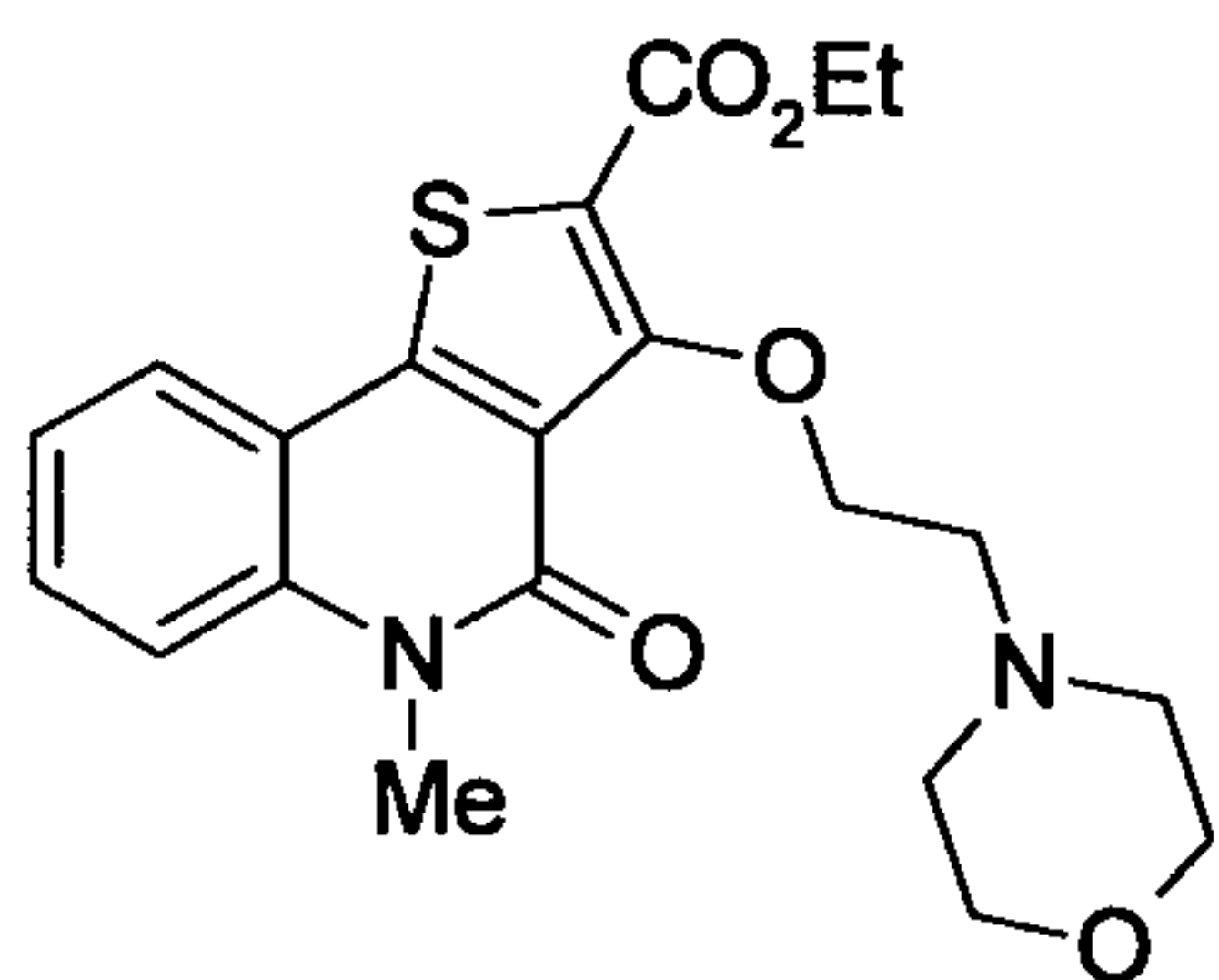
¹H-NMR (300 MHz, CDCl₃) δ: 1.35 (3H, t, J = 7.2 Hz), 3.77 (3H, s), 4.37 (2H, q, J = 7.2 Hz), 5.36 (2H, s), 7.27-7.34 (1H, m), 7.43 (1H, d, J = 8.4 Hz), 7.58-7.65 (3H, m), 7.86 (1H, dd, J = 7.8, 1.2 Hz), 8.61-8.65 (2H, m).

[0470]

15 Reference Example 88

Production of ethyl 5-methyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0471]



20 [0472]

To a suspension of the compound of Reference Example 82 (1.00 g, 3.30 mmol) in DMF (20 mL) was added DBU (1.18 mL, 7.89 mmol), and 4-(2-chloroethyl)morpholine hydrochloride (798 mg, 4.29 mmol) was added to the obtained solution. The obtained mixture was stirred at room temperature for 17 hr. Chloroform and water were added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with chloroform. The combined organic layer was washed with water, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropyl

ether to give the title compound (2.16 g, 85%).

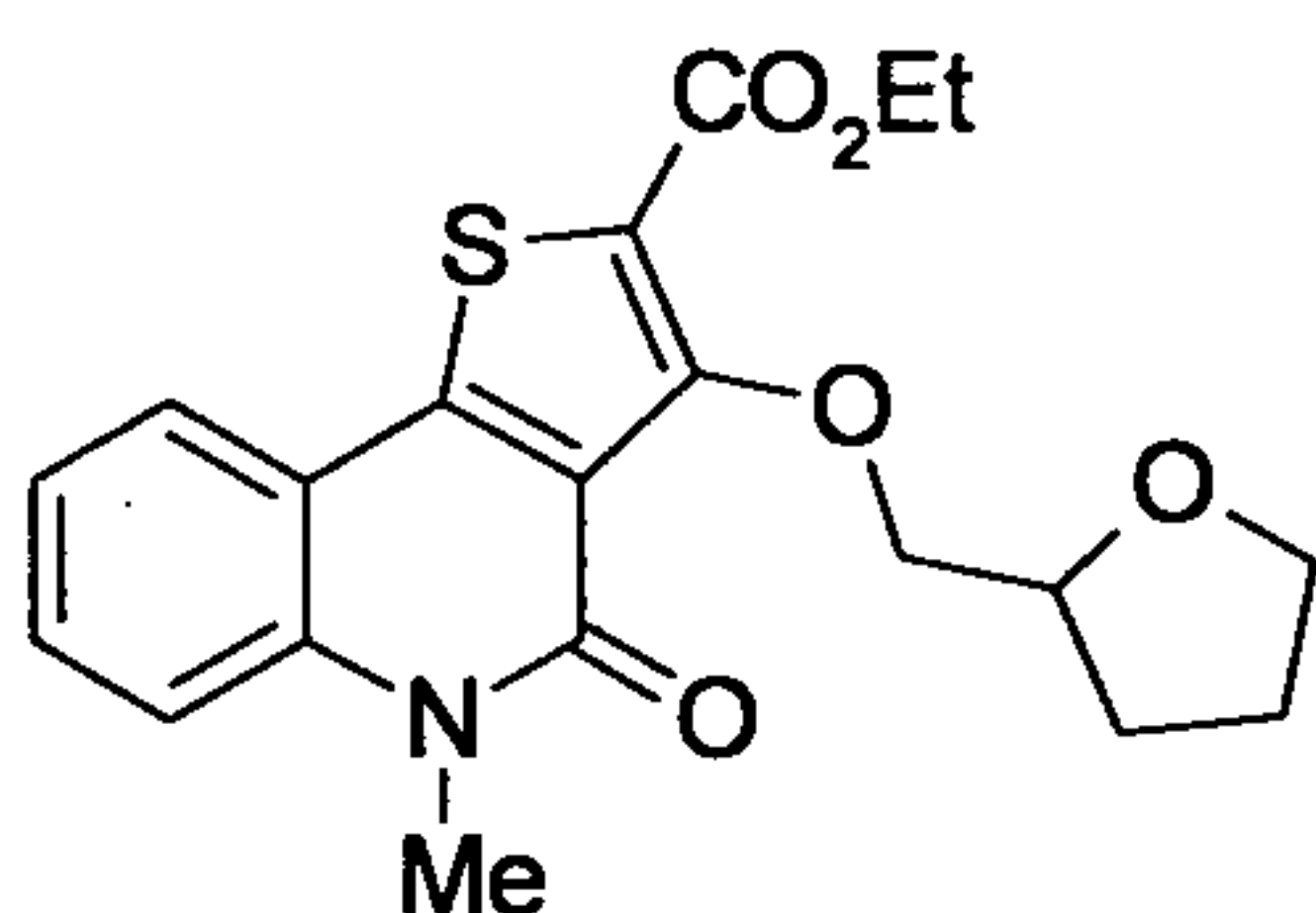
¹H-NMR (300 MHz, CDCl₃) δ: 1.41 (3H, t, J = 7.1 Hz), 2.63 (4H, br t, J = 4.7 Hz), 2.96 (2H, t, J = 5.7 Hz), 3.72 (4H, br t, J = 4.7 Hz), 3.74 (3H, s), 4.38 (2H, q, J = 7.1 Hz), 4.43 (2H, t, J = 5.7 Hz), 7.24-7.31 (1H, m), 7.40 (1H, d, J = 8.5 Hz), 7.58 (1H, ddd, J = 8.5, 7.2, 1.5 Hz), 7.81-7.86 (1H, m).

[0473]

Reference Example 89

Production of ethyl 5-methyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0474]



[0475]

To a suspension of the compound of Reference Example 82 (1.00 g, 3.30 mmol) in DMF (20 mL) was added DBU (0.740 mL, 4.95 mmol), and 2-(bromomethyl)tetrahydrofuran (90% containing) (0.617 mL, 4.9 mmol) was added to the obtained solution. The obtained mixture was stirred at 40°C for 19 hr and at 80°C for 23 hr, DBU (0.740 mL, 4.95 mmol) and 2-(bromomethyl)tetrahydrofuran (90% containing) (0.617 mL, 4.9 mmol) were added, and the mixture was stirred at 80°C for 66 hr. Ethyl acetate and water were added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with 0.5N aqueous sodium hydroxide solution, filtered through Celite (trade name), washed with water, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=3/17 - 2/1) and crystallized from ethyl acetate-diisopropyl ether to give the title compound (821 mg, 64%).

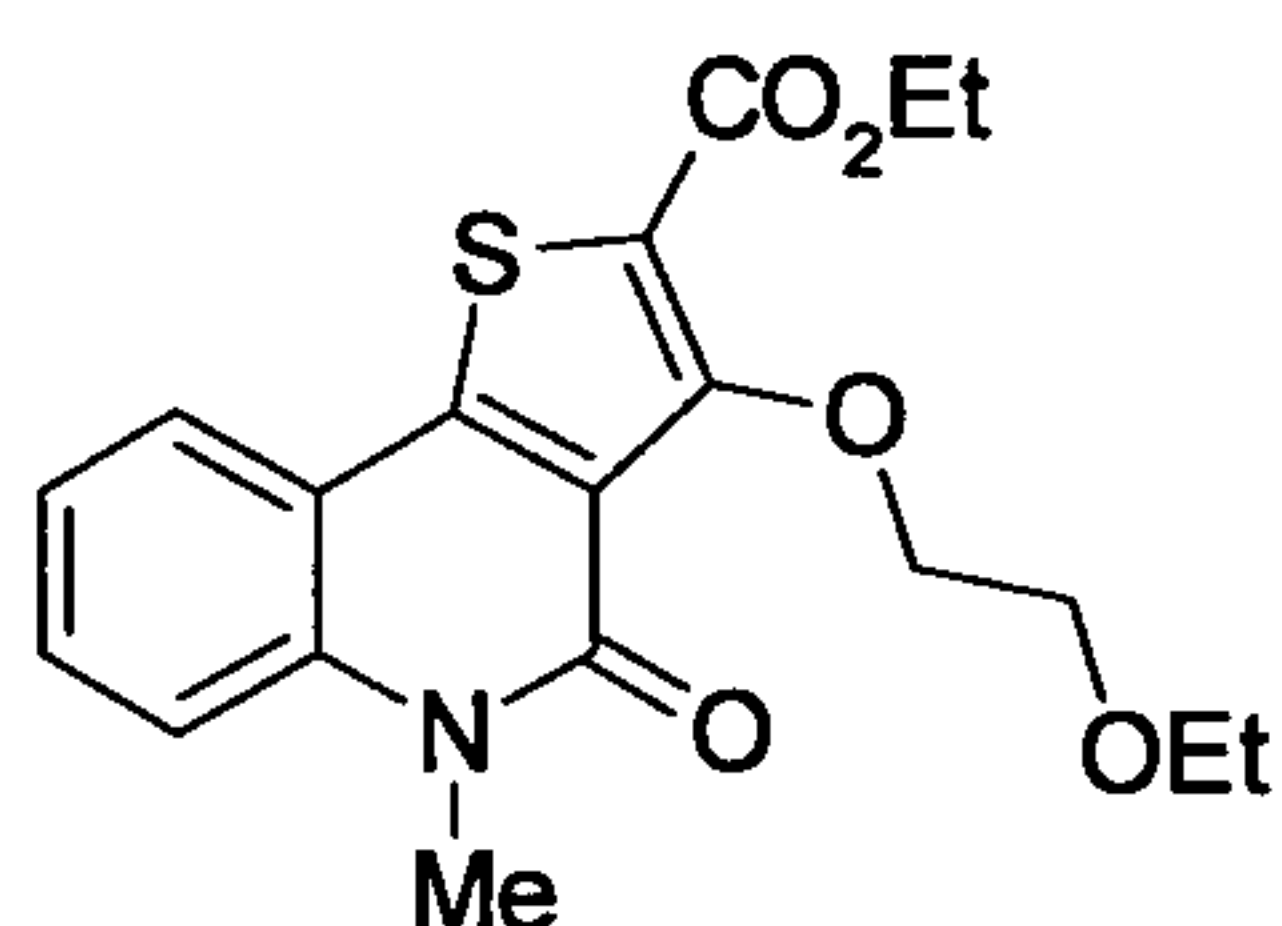
¹H-NMR (300 MHz, CDCl₃) δ:1.42 (3H, t, J = 7.2 Hz), 1.84-2.19 (4H, m), 3.74 (3H, s), 3.76-3.85 (1H, m), 3.89-3.98 (1H, m), 4.22-4.49 (5H, m), 7.27 (1H, ddd, J = 8.0, 7.1, 1.0 Hz), 7.39 (1H, d, J = 8.1 Hz), 7.58 (1H, ddd, J = 8.6, 7.1, 1.4 Hz),
 5 7.81-7.86 (1H, m).

[0476]

Reference Example 90

Production of ethyl 3-(2-ethoxyethoxy)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

10 [0477]



[0478]

To a suspension of the compound of Reference Example 82 (1.00 g, 3.30 mmol) in DMF (20 mL) was added DBU (1.48 mL, 9.90 mmol), and 1-bromo-2-ethoxyethane (1.12 mL, 9.93 mmol)
 15 was added to the obtained solution. The obtained mixture was stirred at 60°C for 24 hr. Ethyl acetate and water were added to the reaction mixture, the organic layer was separated, and aqueous layer was extracted with ethyl acetate. The combined
 20 organic layer was washed with 0.5N aqueous sodium hydroxide solution, filtered through Celite (trade name), further washed with water, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=1/4 - 1/1) and crystallized from
 25 ethyl acetate-hexane to give the title compound (986 mg, 80%).

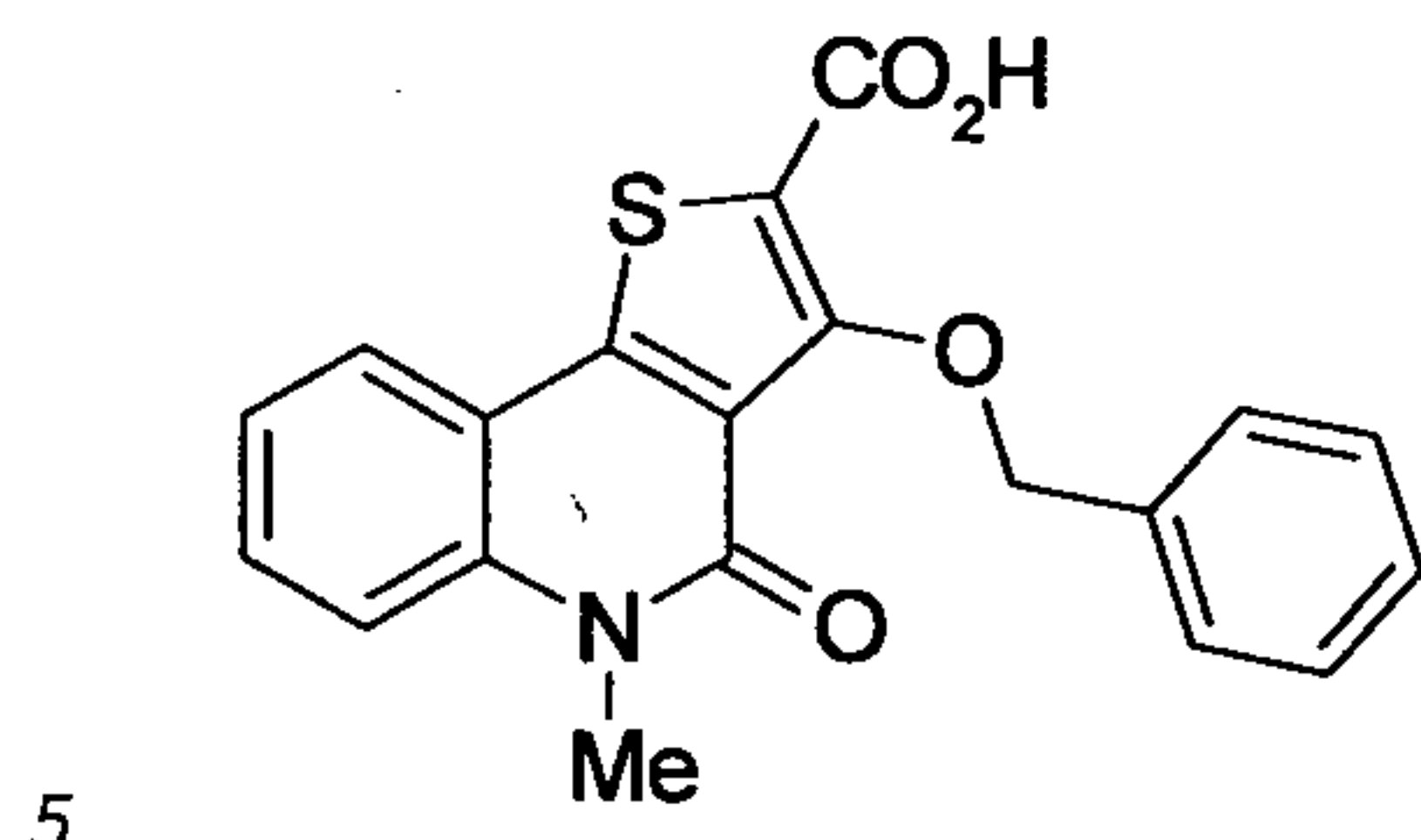
¹H-NMR (300 MHz, CDCl₃) δ:1.19 (3H, t, J = 7.0 Hz), 1.43 (3H, t, J = 7.1 Hz), 3.59 (2H, q, J = 7.0 Hz), 3.74 (3H, s), 3.93 (2H, t, J = 5.0 Hz), 4.40 (2H, q, J = 7.1 Hz), 4.46 (2H, t, J = 5.0 Hz), 7.26-7.31 (1H, m), 7.40 (1H, d, J = 8.5 Hz), 7.58 (1H, ddd, J = 8.5, 7.2, 1.4 Hz), 7.84 (1H, dd, J = 8.0, 1.4 Hz).
 30

[0479]

Reference Example 91

Production of 3-(benzyloxy)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0480]



[0481]

To a solution of the compound of Reference Example 85 (867 mg, 2.20 mmol) in THF (7 mL) and ethanol (7 mL) was added 5N aqueous sodium hydroxide solution (0.88 mL, 4.4 mmol). The
 10 obtained mixture was stirred at room temperature for 3 hr. 1N Hydrochloric acid (5.0 mL) was added to the reaction mixture, and the precipitated solid was collected by filtration, washed with water, and air dried to give the title compound (665 mg, 83%).

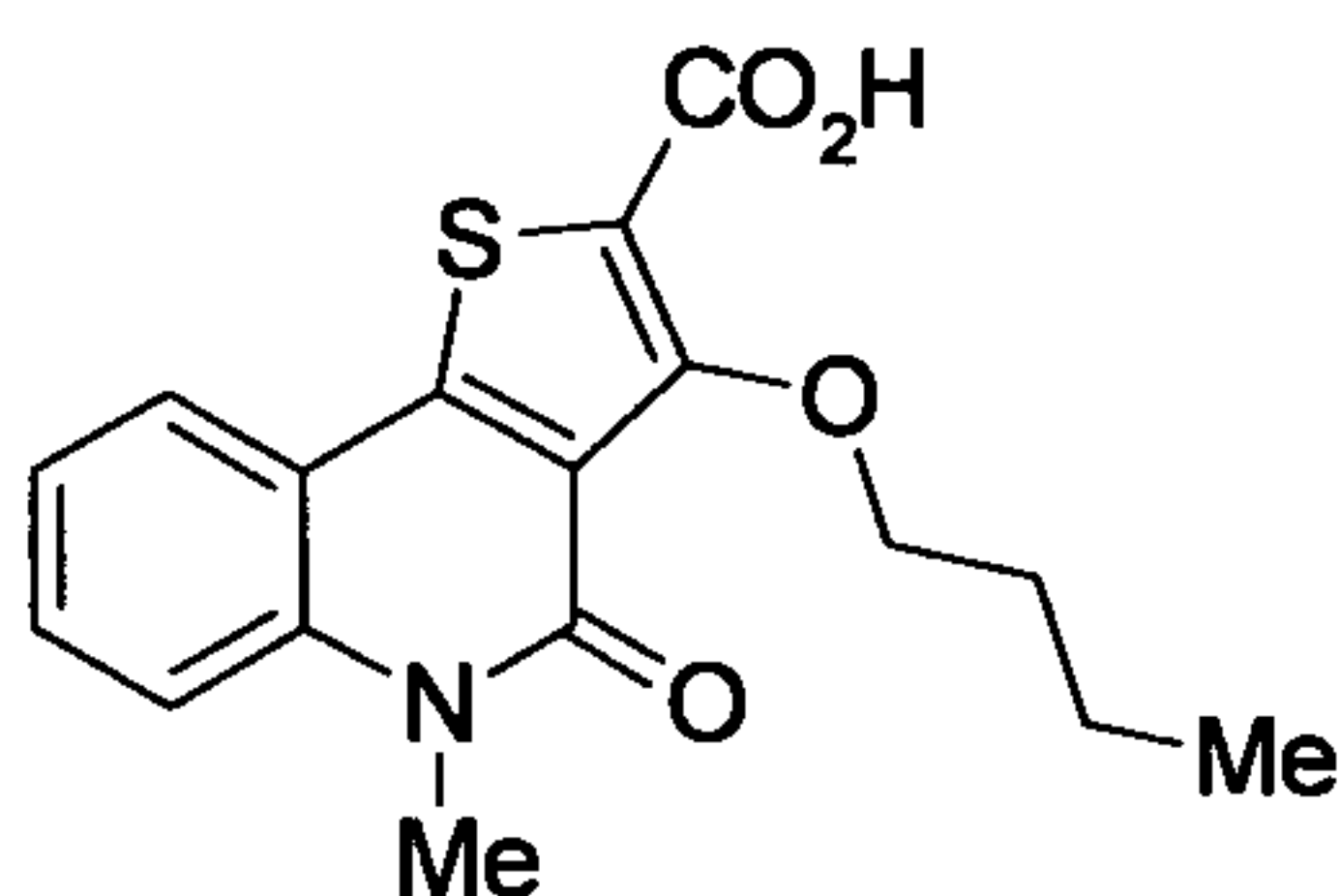
15 $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ : 3.69 (3H, s), 5.22 (2H, s), 7.30-7.41 (4H, m), 7.57-7.72 (4H, m), 7.98 (1H, d, $J = 8.1$ Hz), 13.31 (1H, br s).

[0482]

Reference Example 92

20 Production of 3-butoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0483]



[0484]

25 To a solution of the compound of Reference Example 86 (923 mg, 2.57 mmol) in THF (7 mL) and ethanol (7 mL) was added 5N aqueous sodium hydroxide solution (1.0 mL, 5.0 mmol). The

obtained mixture was stirred at room temperature for 3 hr. 1N Hydrochloric acid (6.0 mL) was added to the reaction mixture, and the precipitated solid was collected by filtration, washed with water, and air dried to give the title compound (872 mg, 5 quantitative).

¹H-NMR (300 MHz, DMSO-d₆) δ: 0.94 (3H, t, J = 7.5 Hz), 1.41-1.55 (2H, m), 1.71-1.82 (2H, m), 3.65 (3H, s), 4.16 (2H, t, J = 6.6 Hz), 7.32 (1H, t, J = 7.2 Hz), 7.54-7.70 (2H, m), 7.91-7.98 (1H, m), 13.21 (1H, br s).

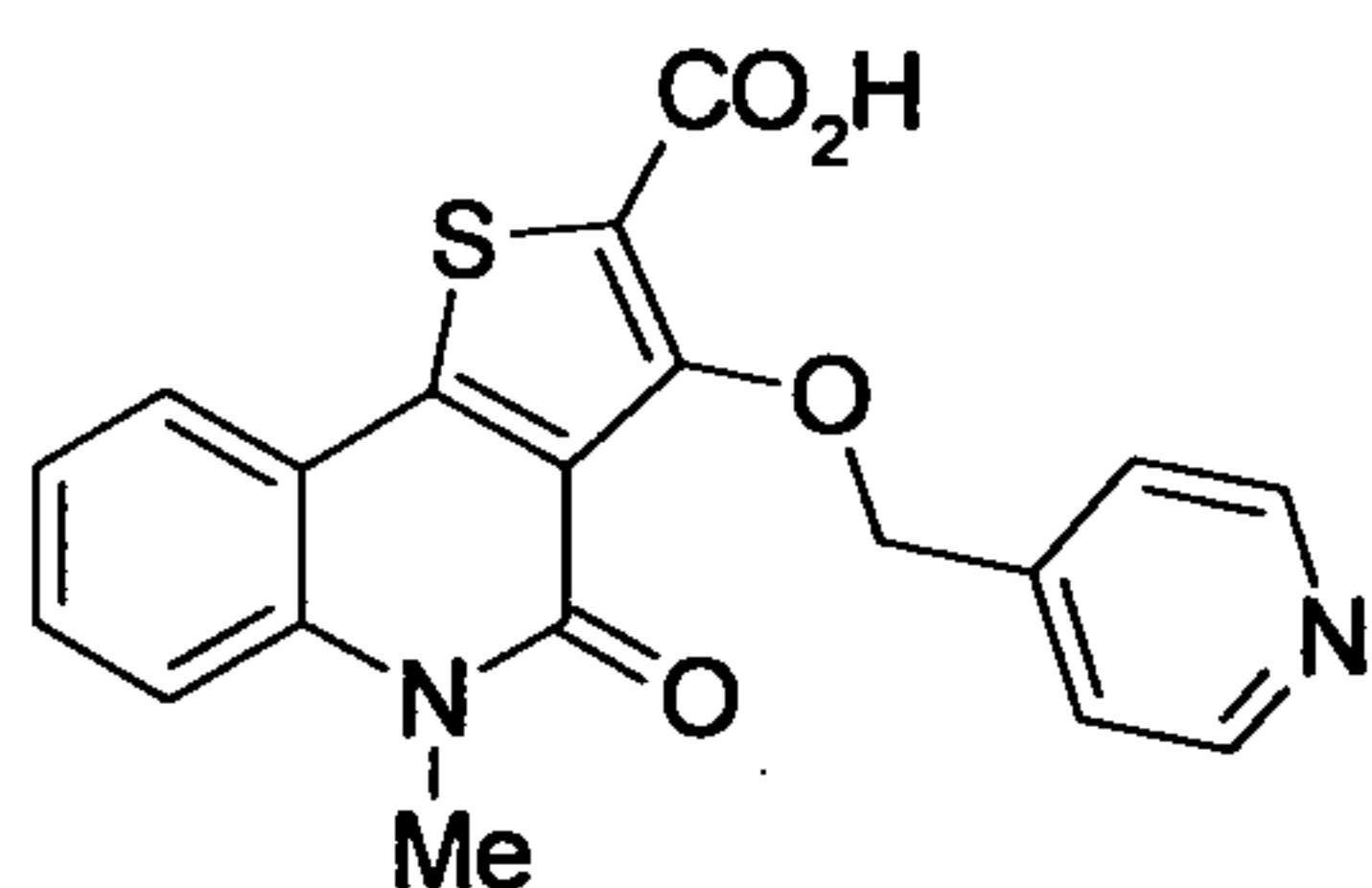
10 [0485]

Reference Example 93

Production of 5-methyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0486]

15



[0487]

To a suspension of the compound of Reference Example 87 (723 mg, 1.83 mmol) in THF (6 mL) and ethanol (6 mL) was added 5N aqueous sodium hydroxide solution (0.74 mL, 3.7 mmol). The 20 obtained mixture was stirred at room temperature for 4 hr. 1N Hydrochloric acid (3.7 mL) was added to the reaction mixture and the mixture was diluted with water. The precipitated solid was collected by filtration, washed with water, and air dried to give the title compound (424 mg, 63%).

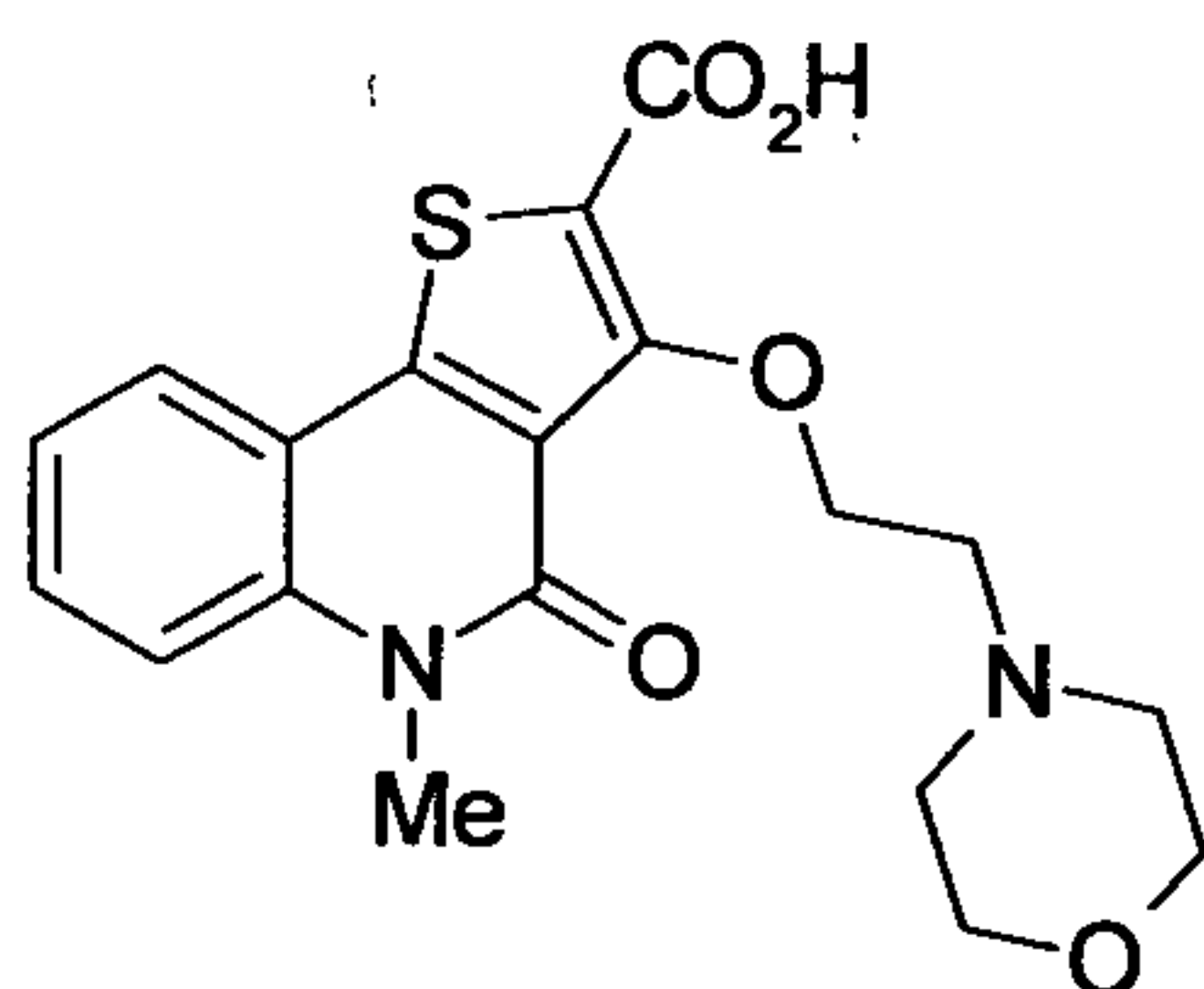
25 ¹H-NMR (300 MHz, DMSO-d₆) δ: 3.67 (3H, s), 5.28 (2H, s), 7.32-7.38 (1H, m), 7.59-7.72 (4H, m), 7.98 (1H, dd, J = 7.8, 1.2 Hz), 8.59 (2H, dd, J = 4.5, 1.5 Hz).

[0488]

Reference Example 94

30 Production of 5-methyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0489]



[0490]

To a suspension of the compound of Reference Example 88
 5 (832 mg, 2.00 mmol) in THF (7 mL) and ethanol (7 mL) was added
 5N aqueous sodium hydroxide solution (0.80 mL, 4.0 mmol). The
 obtained mixture was stirred at room temperature for 4 hr. 1N
 Hydrochloric acid (4.0 mL) was added to the reaction mixture
 and the mixture was diluted with water, and concentrated under
 10 reduced pressure. Methanol was added to the residue and the
 mixture was concentrated under reduced pressure, and
 crystallized from water-methanol to give the title compound
 (477 mg, 61%).

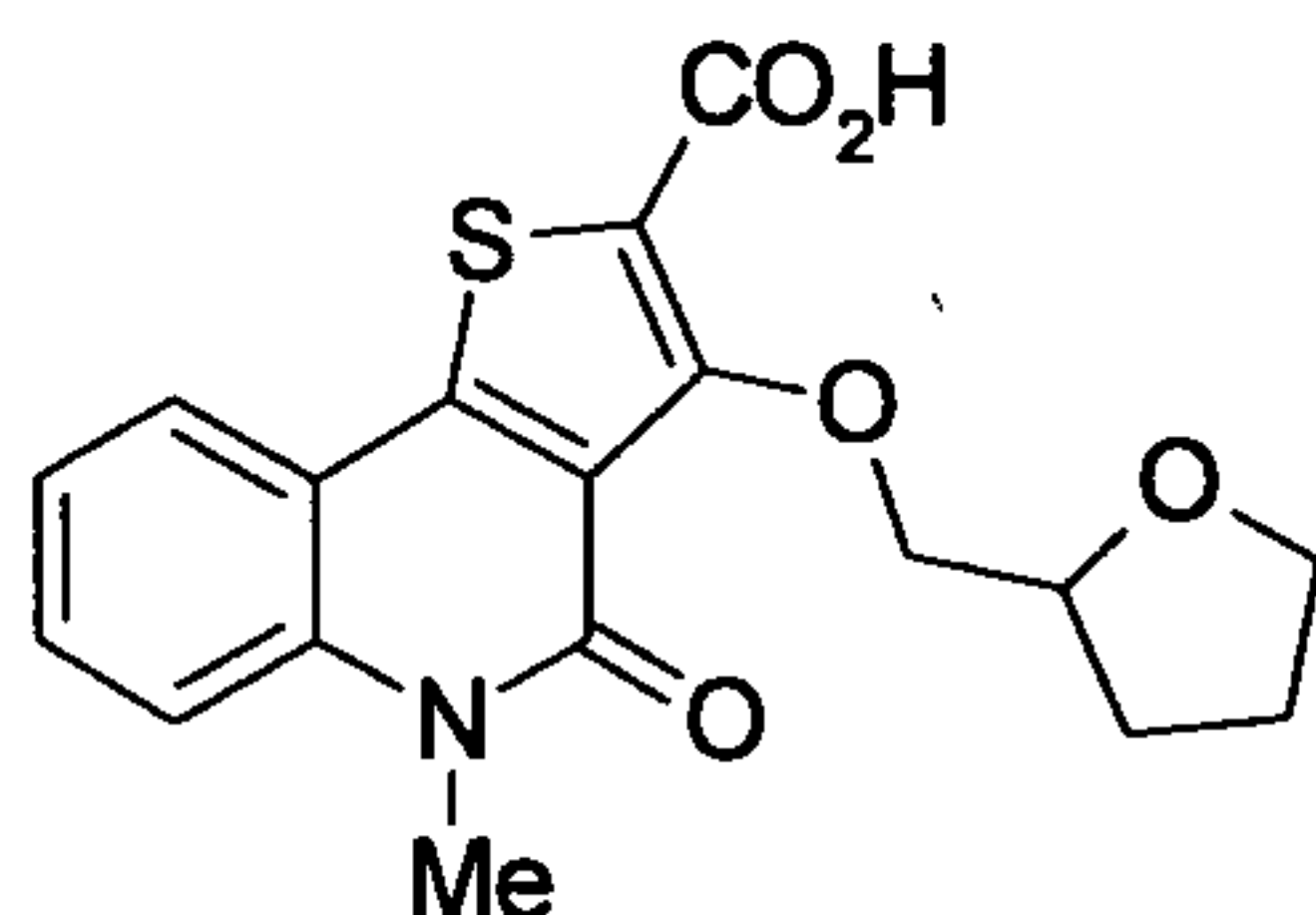
¹H-NMR (300 MHz, DMSO-d₆) δ: 3.00–3.20 (6H, m), 3.67 (3H, s),
 15 3.84 (4H, br t, J = 4.4 Hz), 4.53 (2H, br t, J = 5.0 Hz), 7.31
 (1H, ddd, J = 8.0, 6.3, 1.8 Hz), 7.55–7.67 (2H, m), 7.88–7.91
 (1H, m).

[0491]

Reference Example 95

20 Production of 5-methyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-
 4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0492]



[0493]

25 To a suspension of the compound of Reference Example 89
 (728 mg, 1.88 mmol) in THF (6 mL) and ethanol (6 mL) was added

5N aqueous sodium hydroxide solution (0.76 mL, 3.8 mmol). The obtained mixture was stirred at room temperature for 4 hr. 1N Hydrochloric acid (3.8 mL) was added to the reaction mixture and the mixture was diluted with water and the mixture was
5 extracted 3 times with chloroform. The combined organic layer was washed with aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The obtained solid was washed with diisopropyl ether to give the title compound (659 mg, 97%).

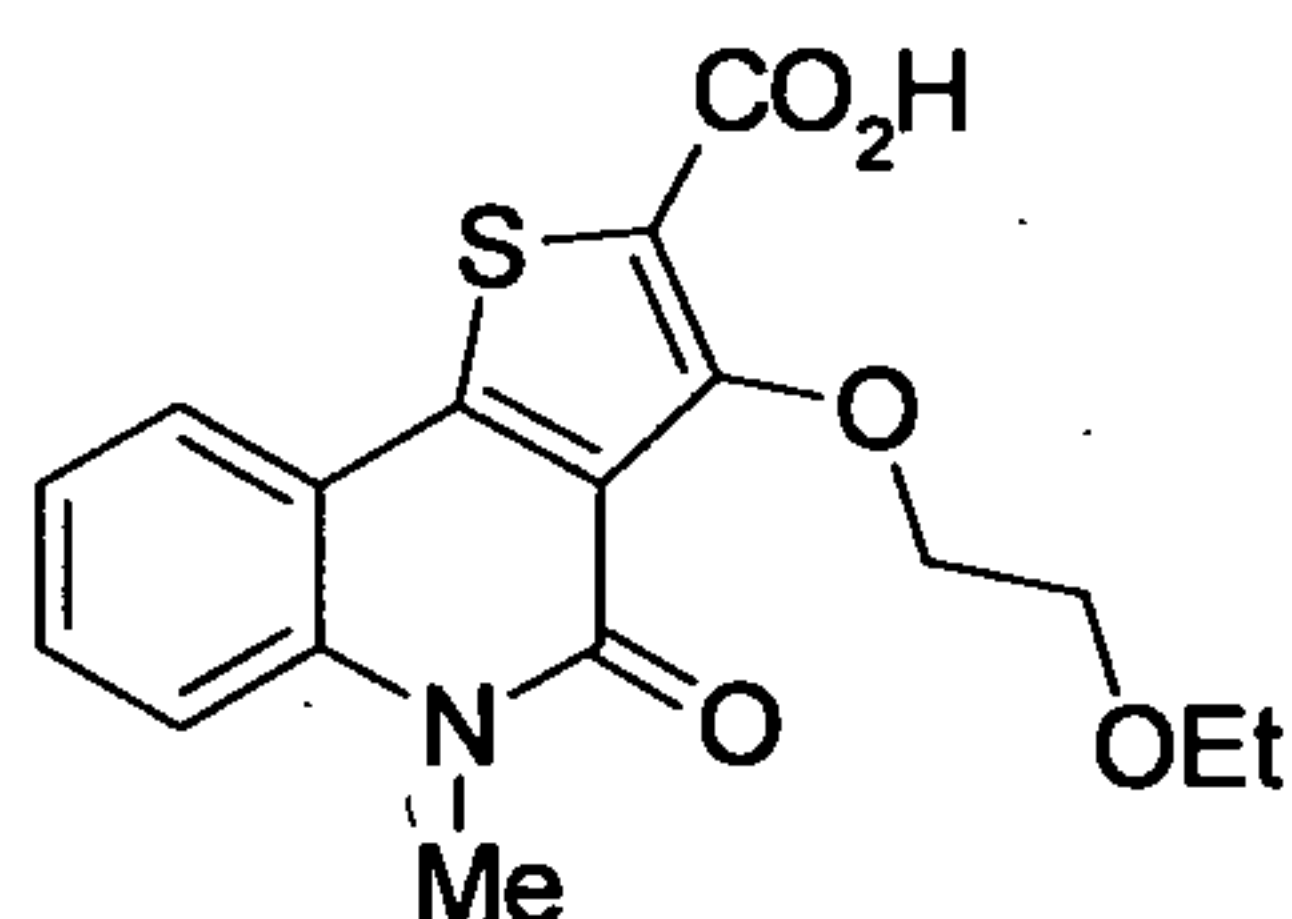
10 ¹H-NMR (300 MHz, DMSO-d₆) δ:1.73-2.04 (4H, m), 3.56-3.78 (2H, m), 3.65 (3H, s), 4.02-4.10 (1H, m), 4.19-4.30 (2H, m), 7.29-7.37 (1H, m), 7.57-7.71 (2H, m), 7.92-7.99 (1H, m), 13.20 (1H, br s).

[0494]

15 Reference Example 96

Production of 3-(2-ethoxyethoxy)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0495]



20 [0496]

To a suspension of the compound of Reference Example 90 (826 mg, 2.20 mmol) in THF (7 mL) and ethanol (7 mL) was added 5N aqueous sodium hydroxide solution (0.88 mL, 4.4 mmol). The obtained mixture was stirred at room temperature for 2.5 hr,
25 5N aqueous sodium hydroxide solution (4.4 mL, 22 mmol) was added, and the mixture was stirred at 50°C for 3.5 hr. The reaction mixture was acidified with 1N hydrochloric acid and diluted with water, and the precipitated solid was collected by filtration, washed with water, and air dried to give the
30 title compound (719 mg, 94%).

¹H-NMR (300 MHz, DMSO-d₆) δ:1.03 (3H, t, J = 6.9 Hz), 3.44 (2H,

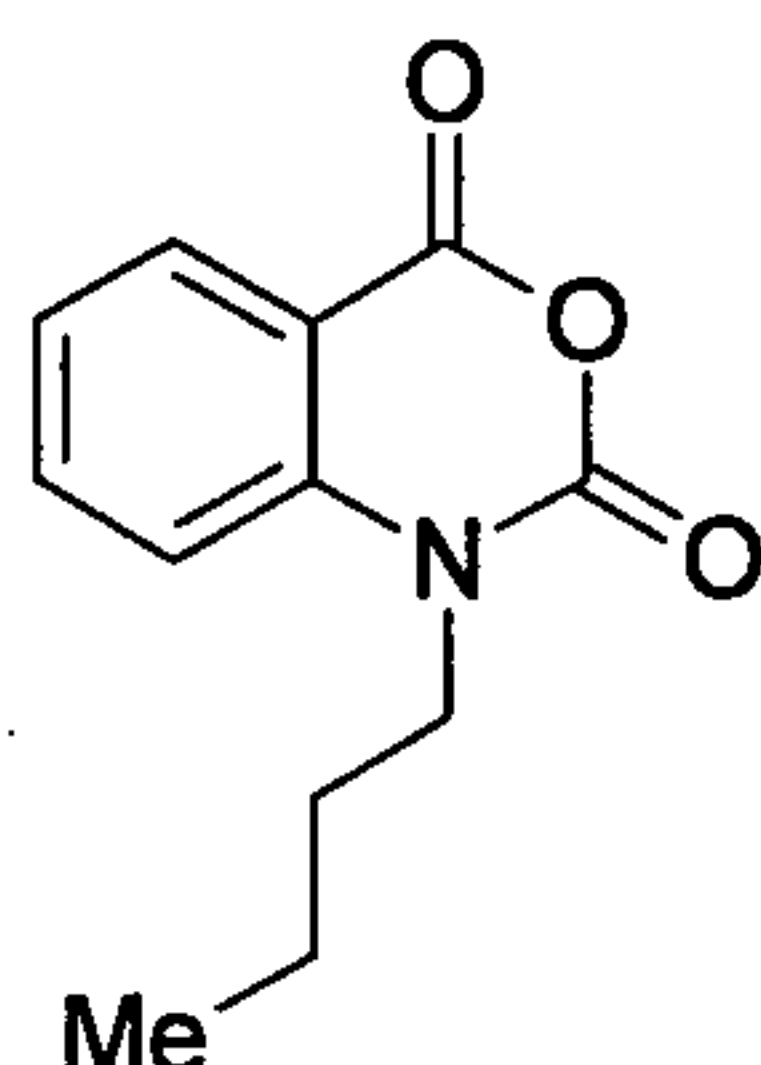
q, $J = 6.9$ Hz), 3.66 (3H, s), 3.75 (2H, t, $J = 5.0$ Hz), 4.33 (2H, t, $J = 5.0$ Hz), 7.33 (1H, t, $J = 7.4$ Hz), 7.58-7.71 (2H, m), 7.96 (1H, d, $J = 8.1$ Hz), 13.21 (1H, br s).

[0497]

5 Reference Example 97

Production of 1-butyl-2H-3,1-benzoxazine-2,4(1H)-dione

[0498]



[0499]

10 To a solution of isatoic anhydride (8.16 g, 50.0 mmol) in DMF (100 mL) was added sodium hydride (66% in oil, 2.00 g, 55 mmol) under ice-cooling, and the mixture was stirred at the same temperature for 10 min. 1-Iodobutane (8.5 mL, 75 mmol) was added to the obtained mixture and the mixture was stirred
15 at room temperature for 64 hr. Ice water was added to the reaction mixture and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed twice with water and concentrated under reduced pressure to give the title compound (10.5 g), which was used for the next reaction
20 without purification.

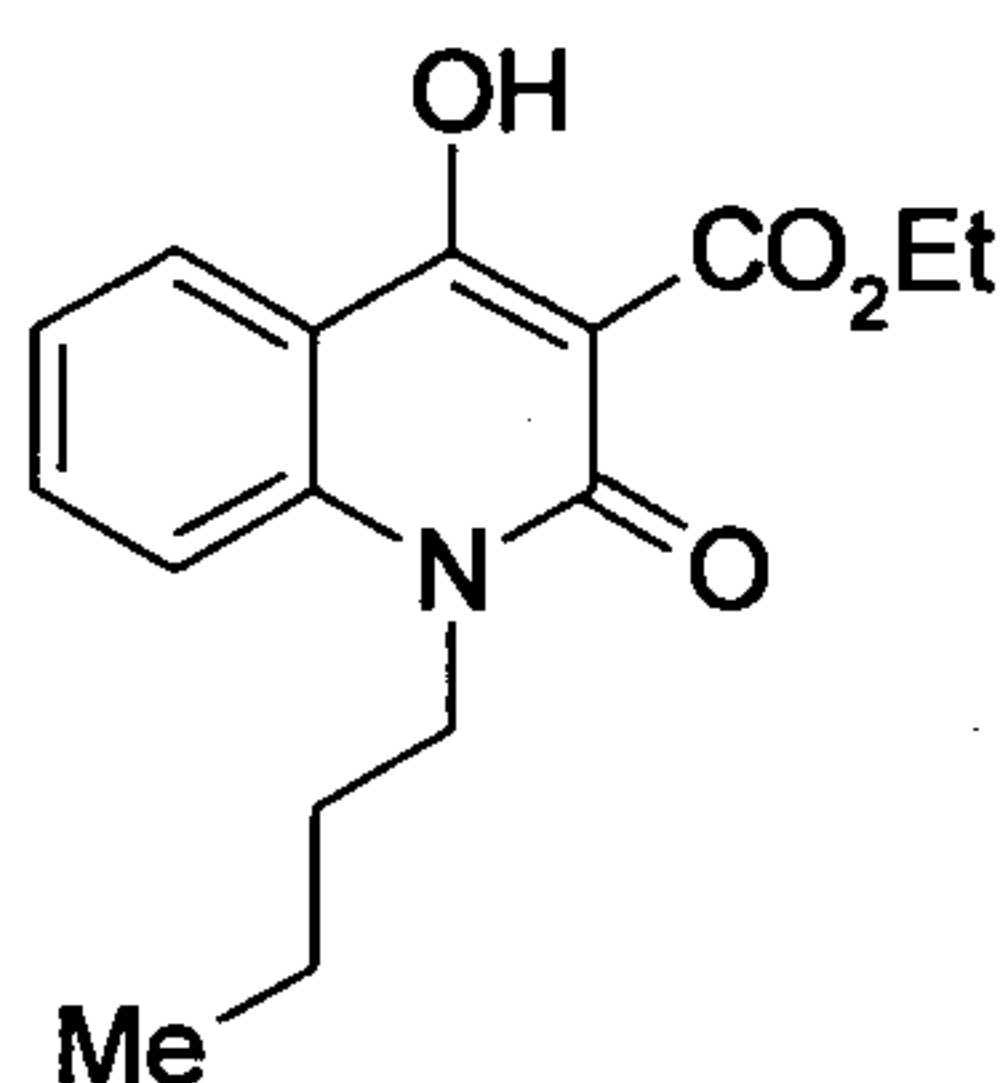
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 1.01 (3H, t, $J = 7.4$ Hz), 1.48 (2H, sext, $J = 7.4$ Hz), 1.69-1.81 (2H, m), 4.02-4.10 (2H, m), 7.17 (1H, d, $J = 8.6$ Hz), 7.25-7.32 (1H, m), 7.75 (1H, ddd, $J = 8.6, 7.4, 1.7$ Hz), 8.16 (1H, dd, $J = 7.8, 1.7$ Hz).

25 [0500]

Reference Example 98

Production of ethyl 1-butyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate

[0501]



[0502]

To a solution of diethyl malonate (12.0 g, 74.9 mmol) in DMF (70 mL) was added sodium hydride (66% in oil, 2.00 g, 55 mmol) under ice-cooling, and the mixture was stirred at the same temperature for 10 min. A solution of the compound of Reference Example 97 (10.5 g) in DMF (20 mL) was added dropwise to the obtained mixture, and the mixture was stirred at 120°C for 6 hr. The reaction mixture was concentrated under reduced pressure, ice water was added to the residue and the obtained aqueous layer was washed with diethyl ether. The aqueous layer was weakly acidified with 5N hydrochloric acid (12 mL) under ice-cooling, and extracted twice with ethyl acetate. The combined organic layer was washed with water, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=1/9 - 1/2) to give the title compound (9.96 g, 69%, 2 steps) as a solid.

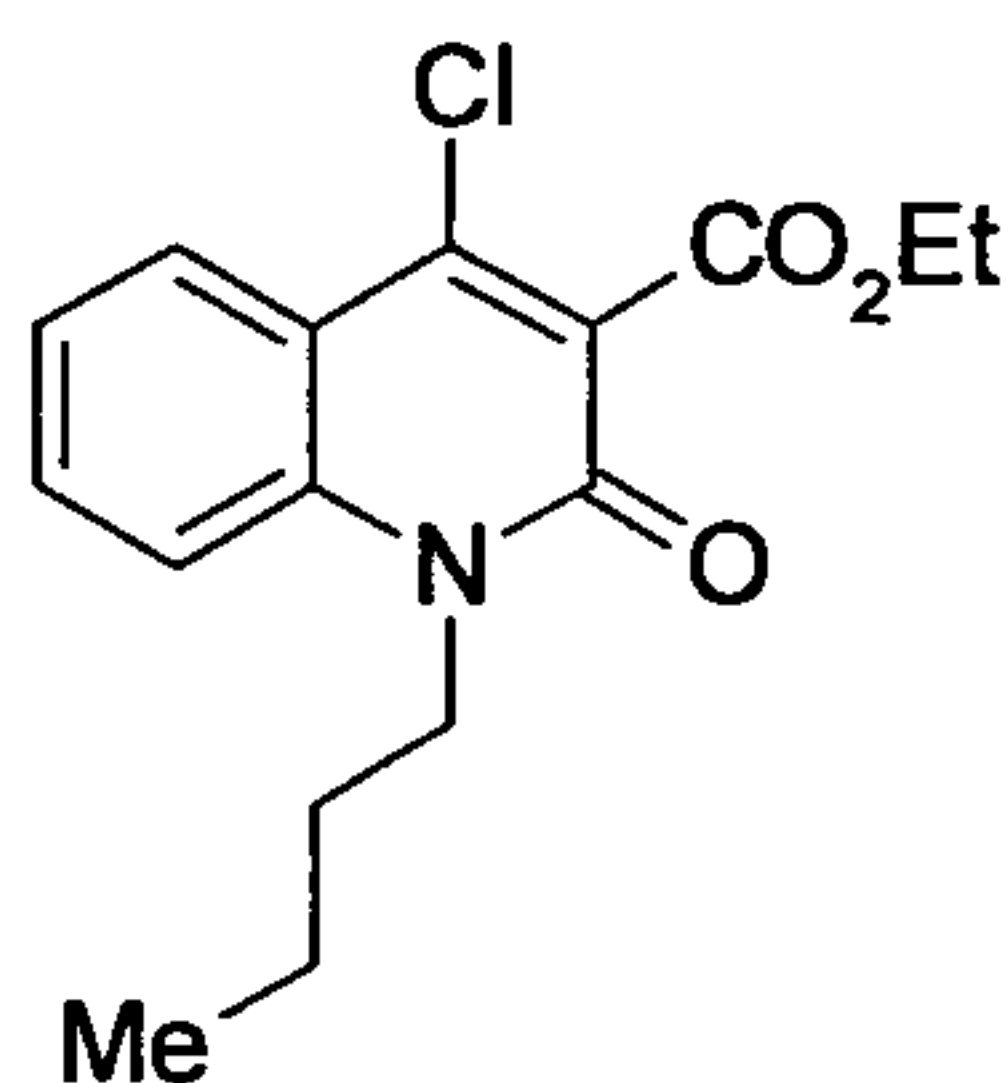
¹H-NMR (300 MHz, CDCl₃) δ: 0.99 (3H, t, J = 7.4 Hz), 1.482 (2H, sext, J = 7.4 Hz), 1.485 (3H, t, J = 7.1 Hz), 1.64-1.76 (2H, m), 4.17-4.26 (2H, m), 4.50 (2H, q, J = 7.1 Hz), 7.20-7.26 (1H, m), 7.29 (1H, d, J = 8.4 Hz), 7.66 (1H, ddd, J = 8.6, 7.4, 1.6 Hz), 8.18 (1H, dd, J = 8.3, 1.6 Hz), 14.20 (1H, s).

[0503]

Reference Example 99

Production of ethyl 1-butyl-4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate

[0504]



[0505]

A mixture of the compound of Reference Example 98 (9.73 g, 33.6 mmol) and phosphorus oxychloride (4.7 mL, 50 mmol) was stirred at 110°C for 30 min. The reaction mixture was concentrated under reduced pressure, and ice water and ethyl acetate were added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, saturated sodium hydrogen carbonate solution and water (twice), and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (eluate; ethyl acetate/hexane=1/9 - 1/3), and the fractions containing the desired product were combined, and washed with 1N sodium hydroxide solution and water (twice). The insoluble material was filtered off and the filtrate was concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (6.07 g, 59%).

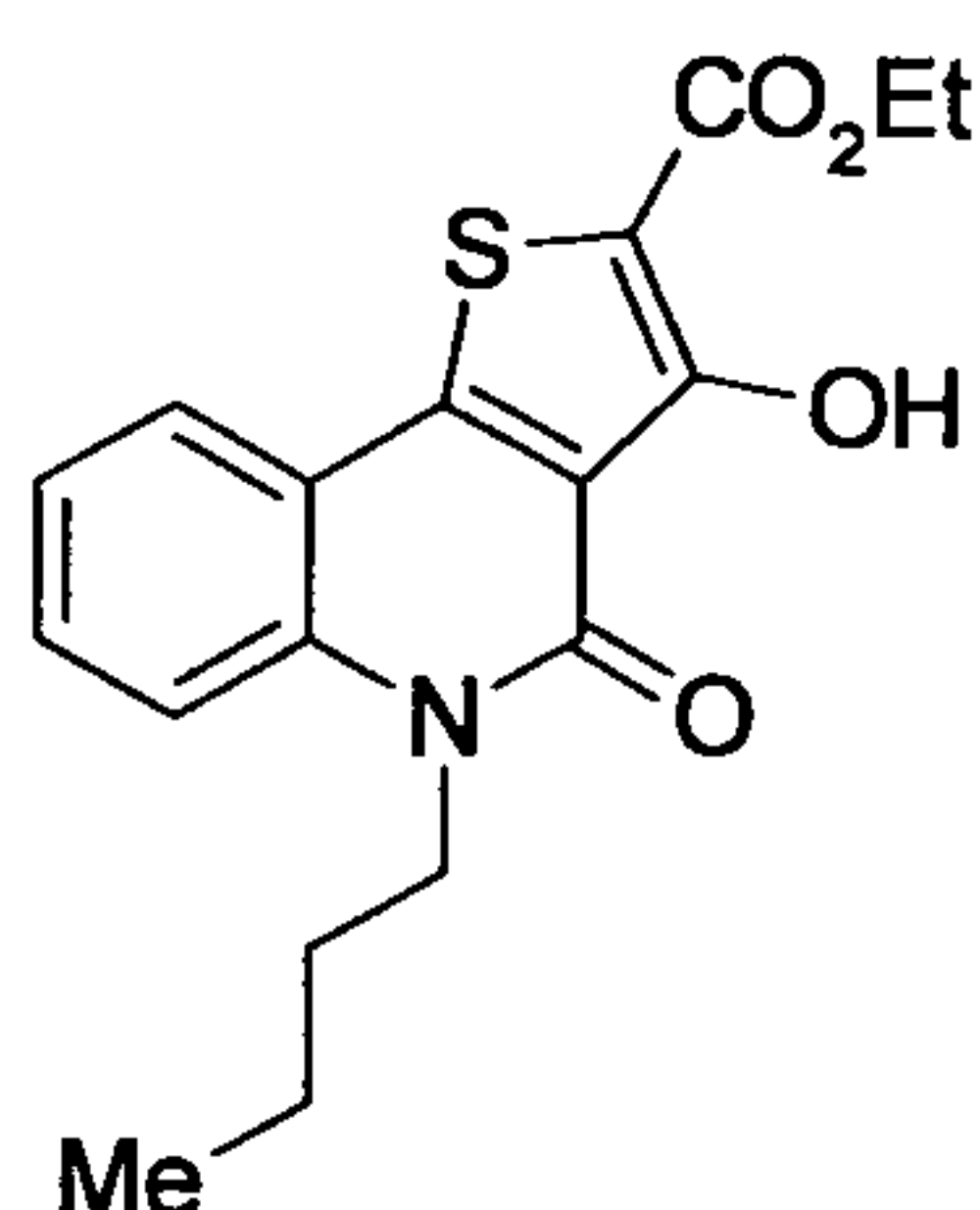
¹H-NMR (300 MHz, CDCl₃) δ: 1.00 (3H, t, J = 7.4 Hz), 1.42 (3H, t, J = 7.2 Hz), 1.42-1.56 (2H, m), 1.67-1.79 (2H, m), 4.23-4.31 (2H, m), 4.47 (2H, q, J = 7.2 Hz), 7.33 (1H, ddd, J = 8.1, 7.2, 0.9 Hz), 7.37-7.41 (1H, m), 7.66 (1H, ddd, J = 8.7, 7.2, 1.4 Hz), 8.07 (1H, dd, J = 8.1, 1.4 Hz).

[0506]

Reference Example 100

Production of ethyl 5-butyl-3-hydroxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0507]



[0508]

A 20% solution (16.0 g, 47 mmol) of sodium ethoxide in ethanol was diluted with ethanol (45 mL), ethyl thioglycolate (6.2 mL, 55 mmol) was added to the obtained solution, and the mixture was stirred at room temperature for 10 min. The compound of Reference Example 99 (7.21 g, 23.4 mmol) was added to this mixture, and the mixture was stirred at room temperature for 5 hr. The reaction mixture was neutralized with ice water and 2N hydrochloric acid (25 mL) under ice-cooling, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed twice with water, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (6.44 g, 80%).

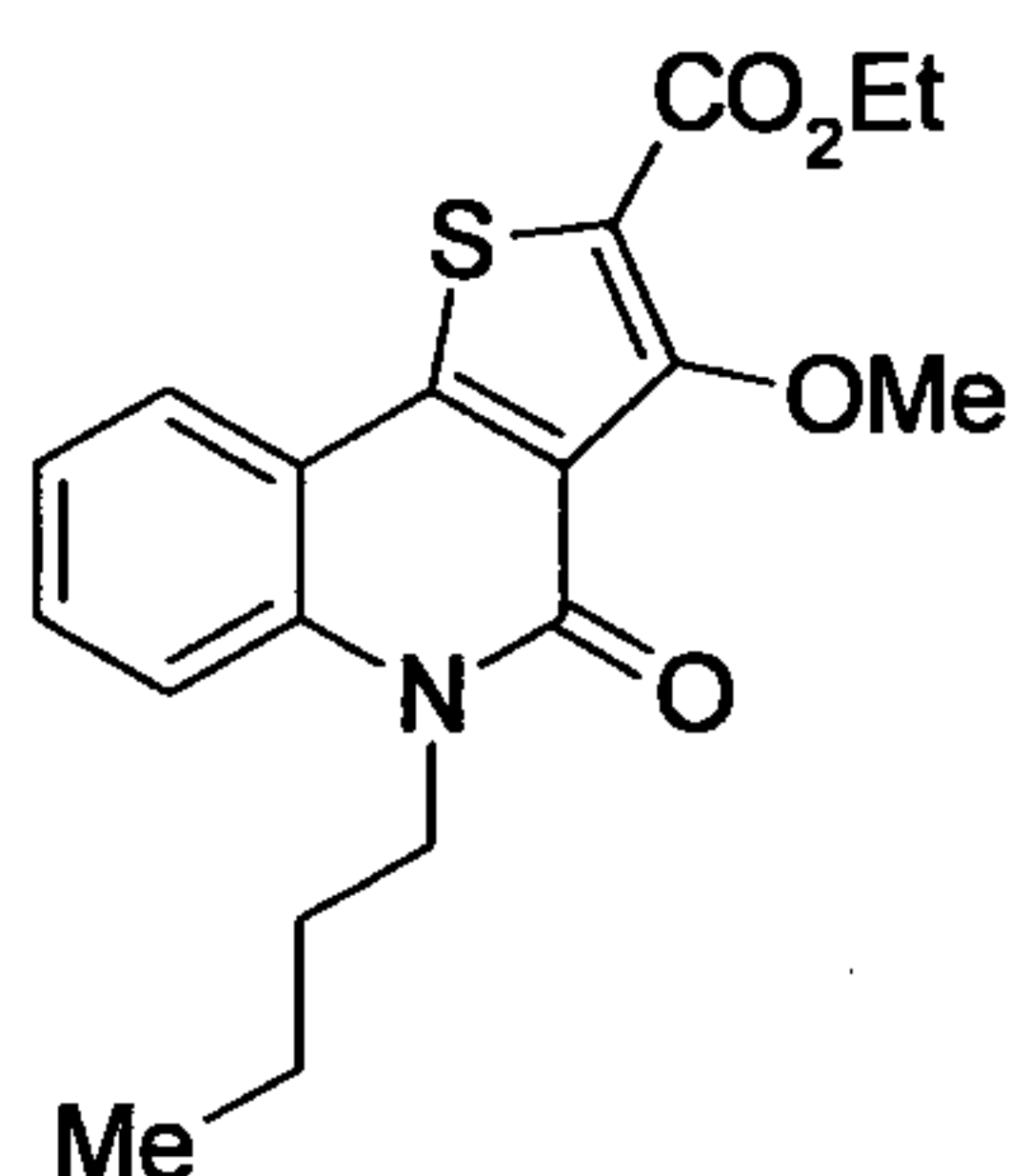
¹H-NMR (300 MHz, CDCl₃) δ: 1.02 (3H, t, J = 7.4 Hz), 1.42 (3H, t, J = 7.2 Hz), 1.44-1.58 (2H, m), 1.71-1.83 (2H, m), 4.29-4.36 (2H, m), 4.41 (2H, q, J = 7.2 Hz), 7.32 (1H, ddd, J = 8.0, 7.2, 0.9 Hz), 7.43-7.48 (1H, m), 7.61 (1H, ddd, J = 8.6, 7.3, 1.6 Hz), 7.81-7.86 (1H, m), 10.81 (1H, s).

[0509]

Reference Example 101

Production of ethyl 5-butyl-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

25 [0510]



[0511]

To a suspension of the compound of Reference Example 100 (3.11 g, 9.00 mmol) in DMF (30 mL) was added DBU (1.62 mL, 10.8 mmol), and iodomethane (1.12 mL, 18.0 mmol) was added to the obtained solution. The obtained mixture was stirred at room temperature for 14 hr, water was added and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with water and 0.5N aqueous sodium hydroxide solution, filtered through Celite (trade name), further washed twice with water, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=1/4 - 1/1) and recrystallized from ethyl acetate-hexane to give the title compound (1.03 g, 32%).

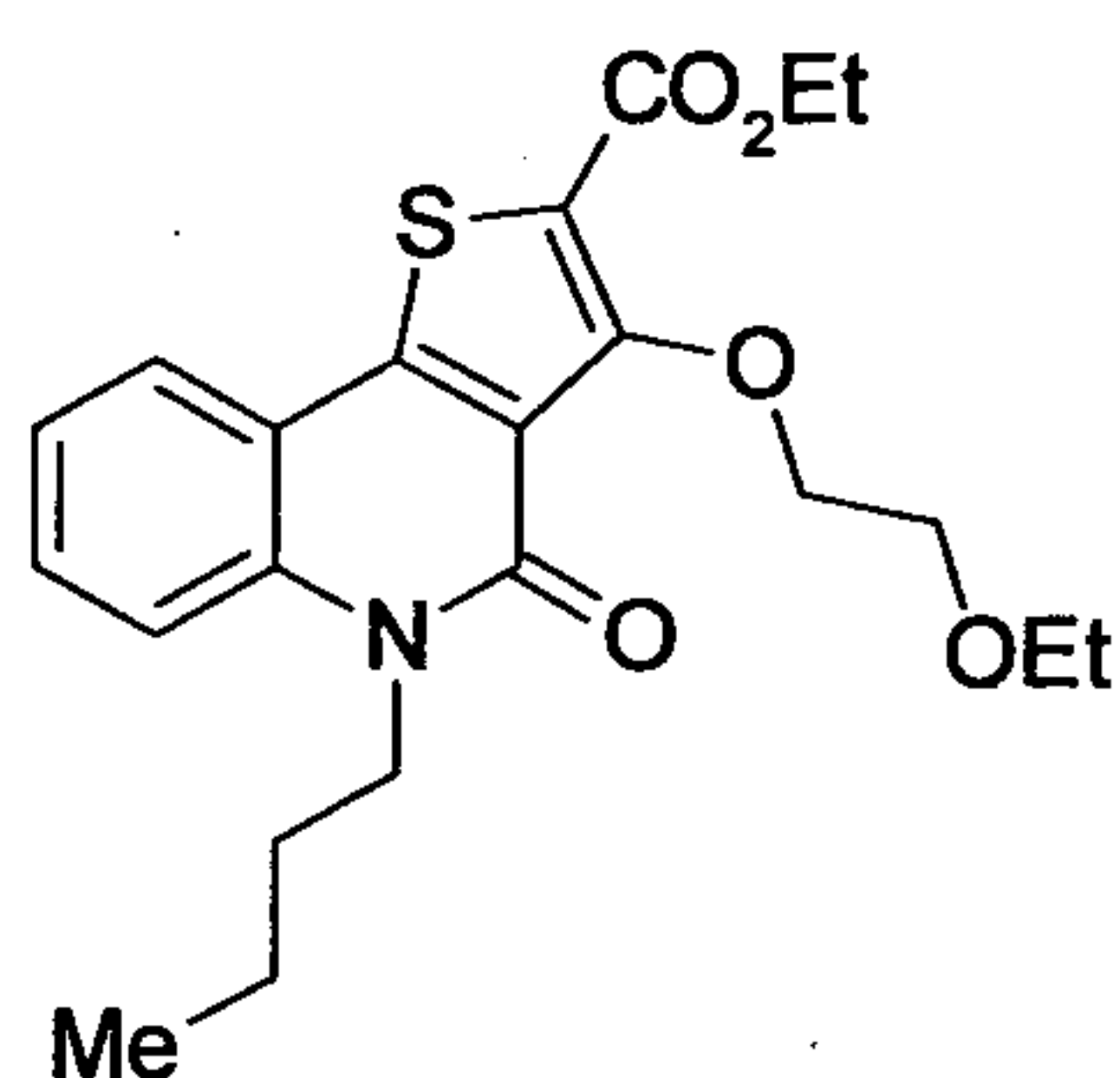
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 1.01 (3H, t, $J = 7.4$ Hz), 1.40-1.60 (2H, m), 1.42 (3H, t, $J = 7.2$ Hz), 1.69-1.81 (2H, m), 4.14 (3H, s), 4.28-4.36 (2H, m), 4.40 (2H, q, $J = 7.2$ Hz), 7.22-7.29 (1H, m), 7.39 (1H, d, $J = 8.5$ Hz), 7.57 (1H, ddd, $J = 8.5, 7.1, 1.4$ Hz), 7.84 (1H, dd, $J = 8.0, 1.4$ Hz).

[0512]

Reference Example 102

Production of ethyl 5-butyl-3-(2-ethoxyethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

25 [0513]



[0514]

To a suspension of the compound of Reference Example 100 (1.14 g, 3.30 mmol) in DMF (20 mL) was added DBU (1.48 mL, 9.90 mmol), and 1-bromo-2-ethoxyethane (1.12 mL, 9.93 mmol) was added to the obtained solution. The obtained mixture was stirred at 60°C for 30 hr and ethyl acetate and water were added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with 0.5N aqueous sodium hydroxide solution and water, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=1/4 - 1/2) to give the title compound (1.28 g, 93%) as a solid.

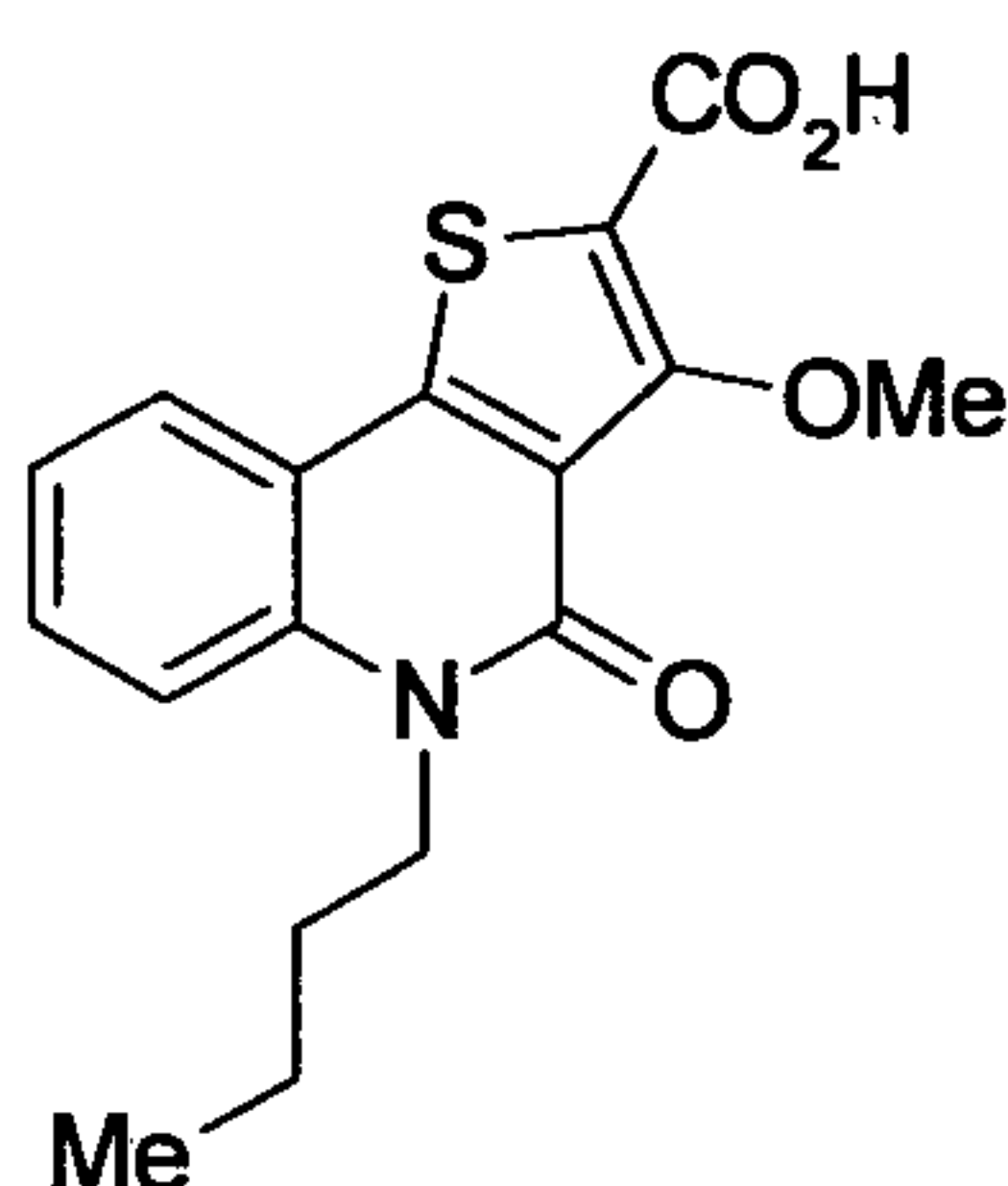
¹H-NMR (300 MHz, CDCl₃) δ: 1.01 (3H, t, J = 7.4 Hz), 1.18 (3H, t, J = 7.0 Hz), 1.42 (3H, t, J = 7.2 Hz), 1.43-1.57 (2H, m), 1.65-1.79 (2H, m), 3.58 (2H, q, J = 7.0 Hz), 3.92 (2H, dd, J = 5.6, 4.7 Hz), 4.30 (2H, br t, J = 7.8 Hz), 4.39 (2H, q, J = 7.2 Hz), 4.47 (2H, t, J = 5.1 Hz), 7.21-7.28 (1H, m), 7.37 (1H, d, J = 8.5 Hz), 7.56 (1H, ddd, J = 8.5, 7.1, 1.4 Hz), 7.83 (1H, dd, J = 8.1, 1.4 Hz).

[0515]

Reference Example 103

Production of 5-butyl-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0516]



[0517]

To a suspension of the compound of Reference Example 101 (1.81 g, 5.04 mmol) in THF (15 mL) and ethanol (15 mL) was added 5N aqueous sodium hydroxide solution (2.0 mL, 10 mmol). The obtained mixture was stirred at room temperature for 1.5 hr. The reaction mixture was ice-cooled, 1N hydrochloric acid (15 mL) and ethyl acetate were added, and the precipitated solid was collected by filtration, and washed with water and ethyl acetate to give a solid. The filtrate was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, and concentrated under reduced pressure. The residue and the solid obtained earlier were combined, and the mixture was recrystallized from methanol-diisopropyl ether to give the title compound (1.43 g, 86%).

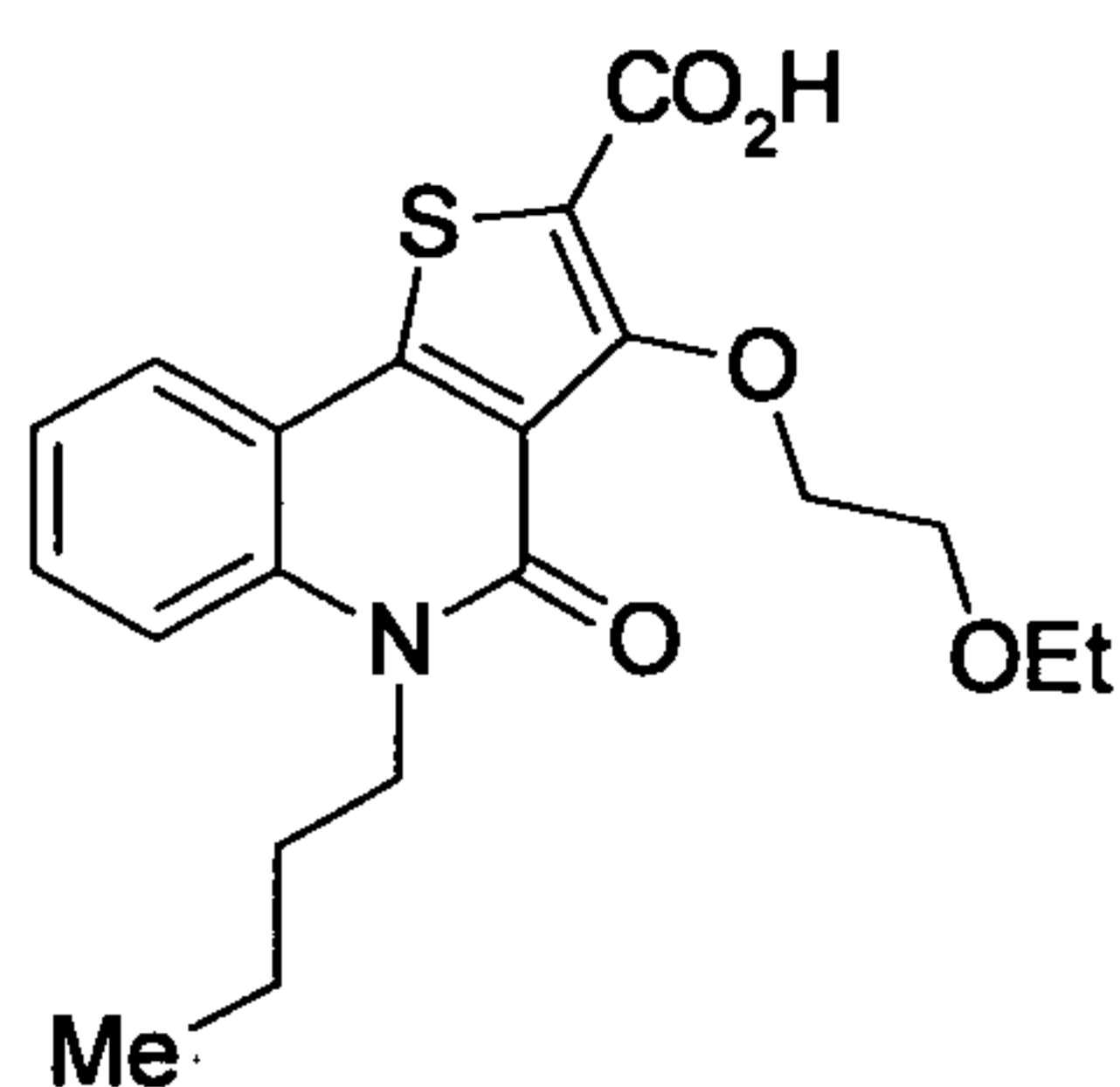
$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ : 0.95 (3H, t, $J = 7.3$ Hz), 1.43 (2H, sext, $J = 7.3$ Hz), 1.56-1.68 (2H, m), 3.95 (3H, s), 4.29 (2H, t, $J = 7.5$ Hz), 7.29-7.36 (1H, m), 7.60-7.71 (2H, m), 7.95-8.00 (1H, m).

[0518]

Reference Example 104

Production of 5-butyl-3-(2-ethoxyethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

25 [0519]



[0520]

To a solution of the compound of Reference Example 102 (1.16 g, 2.78 mmol) in THF (9 mL) and ethanol (9 mL) was added 5 5N aqueous sodium hydroxide solution (1.12 mL, 5.6 mmol). The obtained mixture was stirred at room temperature for 2.5 hr, 5N aqueous sodium hydroxide solution (4.48 mL, 22 mmol) was added, and the mixture was stirred at 50°C for 3 hr. The reaction mixture was acidified with 1N hydrochloric acid, and 10 extracted twice with chloroform. The combined organic layer was washed with water, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (965 mg, 89%).

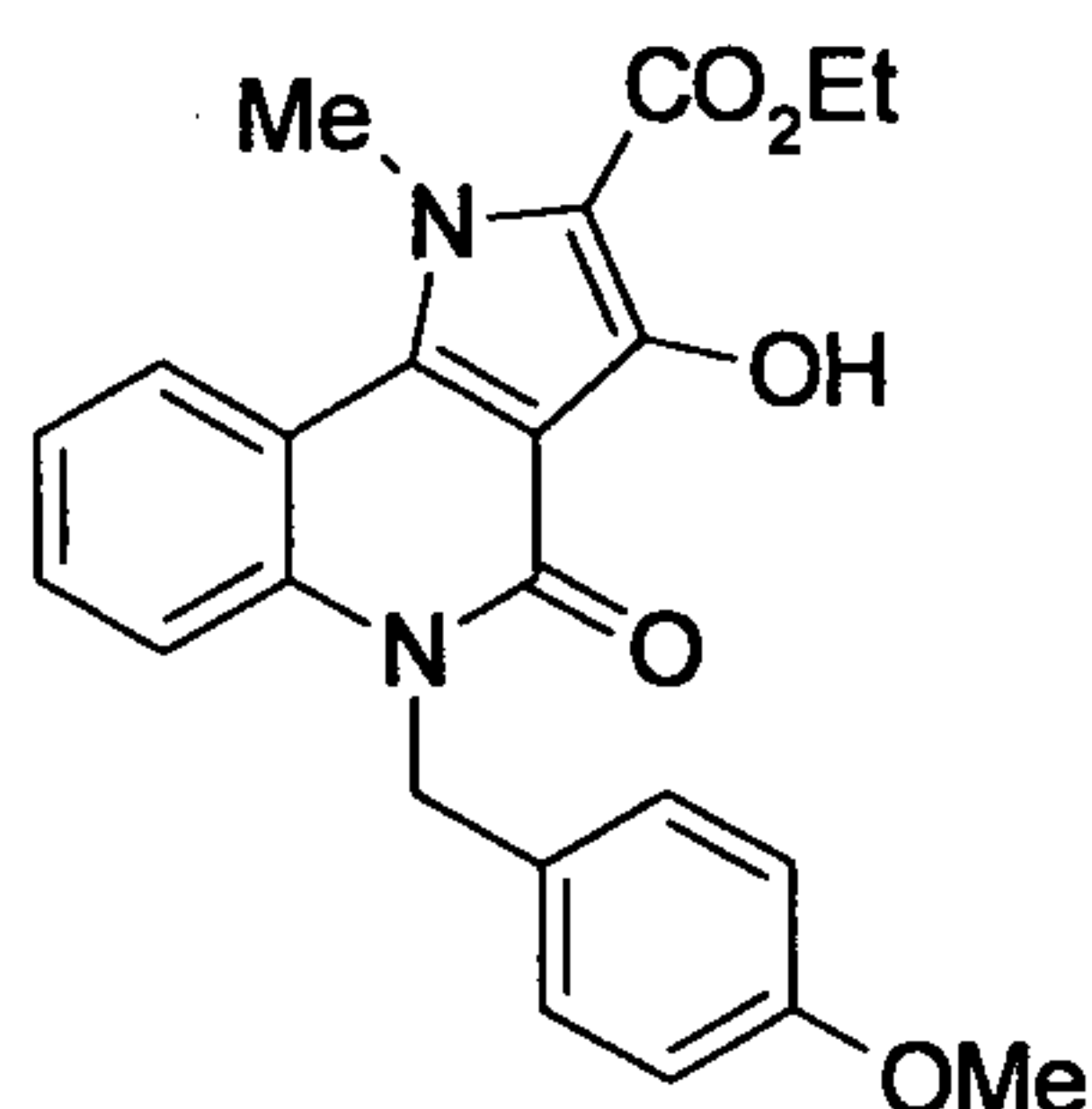
¹H-NMR (300 MHz, DMSO-d₆) δ: 0.95 (3H, t, J = 7.3 Hz), 1.02 (3H, 15 t, J = 7.0 Hz), 1.43 (2H, sext, J = 7.3 Hz), 1.56-1.68 (2H, m), 3.43 (2H, q, J = 7.0 Hz), 3.74 (2H, t, J = 5.0 Hz), 4.24-4.40 (2H, m), 4.30 (2H, t, J = 5.0 Hz), 7.32 (1H, t, J = 7.4 Hz), 7.59-7.71 (2H, m), 7.97 (1H, d, J = 7.5 Hz), 13.20 (1H, br s).

[0521]

20 Reference Example 105

Production of ethyl 3-hydroxy-5-(4-methoxybenzyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate

[0522]



25 [0523]

In the same manner as in Reference Example 25, ethyl 4-[(2-ethoxy-2-oxoethyl)(methyl)amino]-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxylate (14.7 g, 63%) was obtained as a white powder from the compound of Reference
 5 Example 10 (19.2 g, 51.6 mmol).

In the same manner as in Reference Example 26, the title compound (10.35 g, 49%) was obtained as a white solid from the ethyl 4-[(2-ethoxy-2-oxoethyl)(methyl)amino]-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxylate (14.73
 10 g).

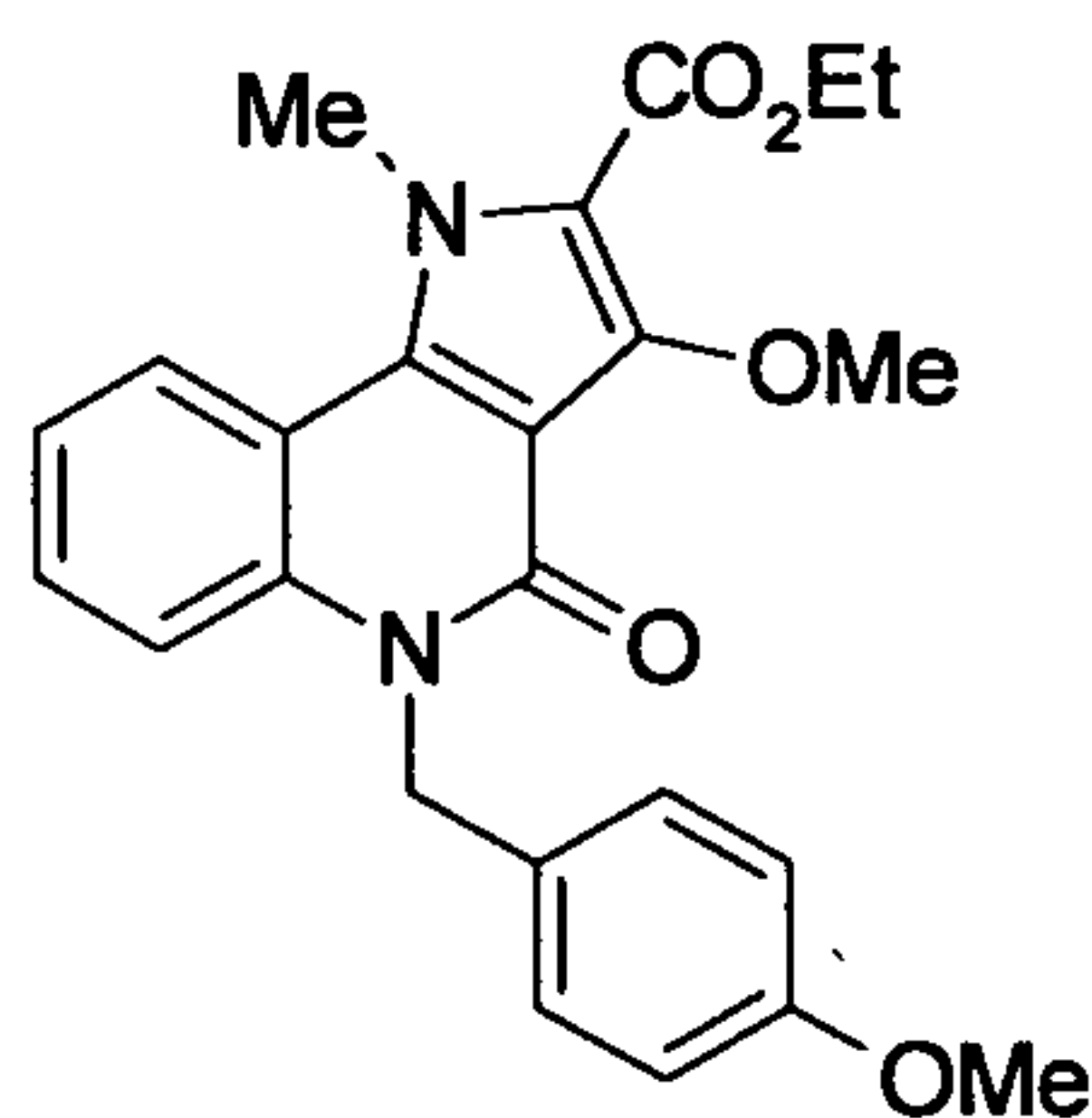
¹H-NMR (300 MHz, CDCl₃) δ: 1.33 (3H, t, J = 7.1 Hz), 3.69 (3H, s), 4.27 (3H, s), 4.34 (2H, q, J = 7.1 Hz), 5.47 (2H, s), 6.86 (2H, d, J = 8.7 Hz), 7.16 (2H, d, J = 8.7 Hz), 7.27-7.30 (1H, m), 7.48 (2H, d, J = 3.3 Hz), 8.32 (1H, d, J = 8.1 Hz), 9.10
 15 (1H, s).

[0524]

Reference Example 106

Production of ethyl 3-methoxy-5-(4-methoxybenzyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate

20 [0525]



[0526]

In the same manner as in Reference Example 6, the title compound (6.51 g, 61%) was obtained as a pale-yellow solid
 25 from the compound of Reference Example 105 (10.4 g, 25.5 mmol).

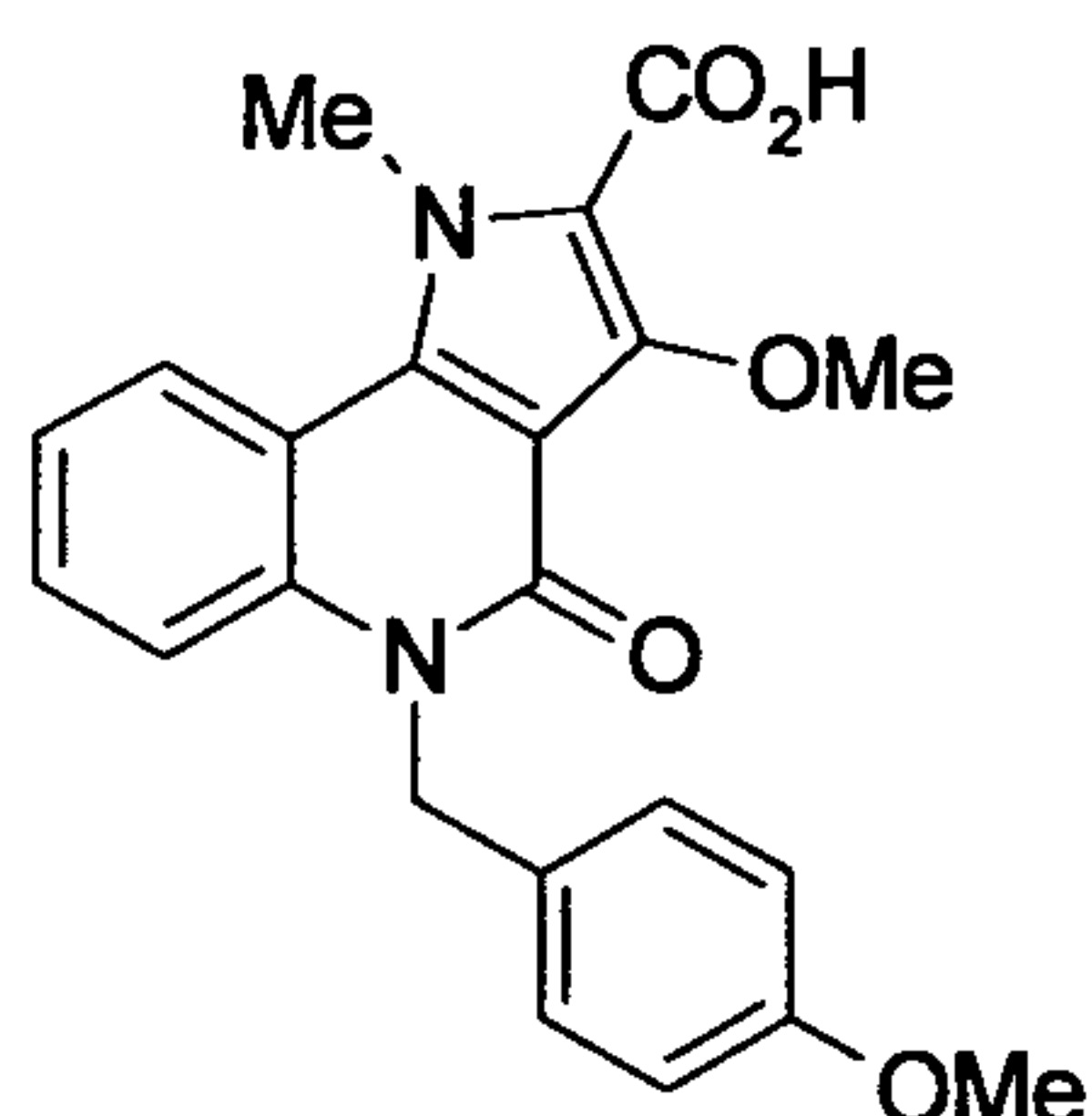
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.35 (3H, t, J = 7.1 Hz), 3.69 (3H, s), 3.94 (3H, s), 4.26 (3H, s), 4.34 (2H, q, J = 7.1 Hz), 5.51 (2H, br s), 6.86 (2H, d, J = 8.7 Hz), 7.15 (1H, d, J = 8.4 Hz), 7.25-7.31 (1H, m), 7.47 (2H, d, J = 3.6 Hz), 8.34 (1H, d, J =
 30 8.1 Hz).

[0527]

Reference Example 107

Production of 3-methoxy-5-(4-methoxybenzyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylic acid

5 [0528]



[0529]

In the same manner as in Reference Example 28, the title compound (5.67 g, 96%) was obtained as a pale-yellow solid from the compound of Reference Example 106 (6.50 g, 15.5 mmol).

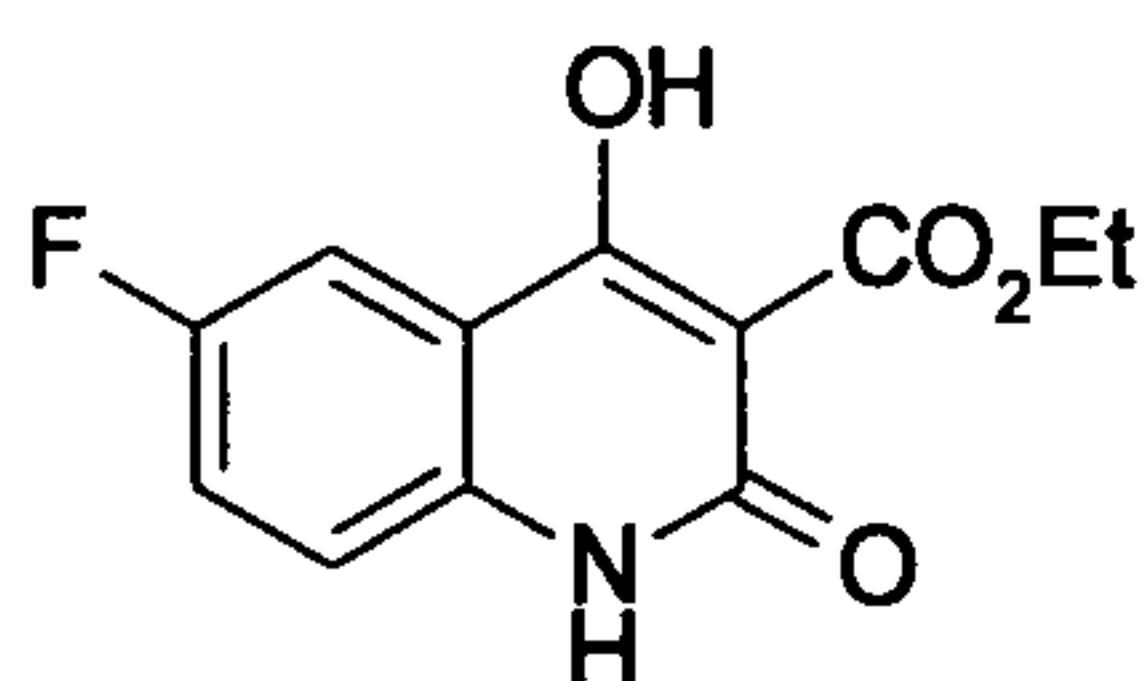
¹H-NMR (300 MHz, DMSO-d₆) δ: 3.70 (3H, s), 3.94 (3H, s), 4.28 (3H, s), 5.51 (2H, br s), 6.86 (2H, d, J = 8.7 Hz), 7.15 (1H, d, J = 8.4 Hz), 7.25-7.30 (1H, m), 7.46 (2H, d, J = 3.9 Hz), 8.34 (1H, d, J = 8.4 Hz), 12.90 (1H, br s).

15 [0530]

Reference Example 110

Production of ethyl 6-fluoro-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate

[0531]



20

[0532]

In the same manner as in Reference Example 1, the title compound (8.60 g, 56%) was obtained as a pale-yellow solid from ethyl 2-amino-5-fluorobenzoate (10.3 g, 61.0 mmol), diethyl malonate (9.2 mL, 61.0 mmol), a 20% solution (21.0 g, 61.0 mmol) of sodium ethoxide in ethanol and ethanol (70 mL).

¹H-NMR (300 MHz, CDCl₃) δ: 1.52 (3H, t, J = 7.2 Hz), 4.54 (2H, q,

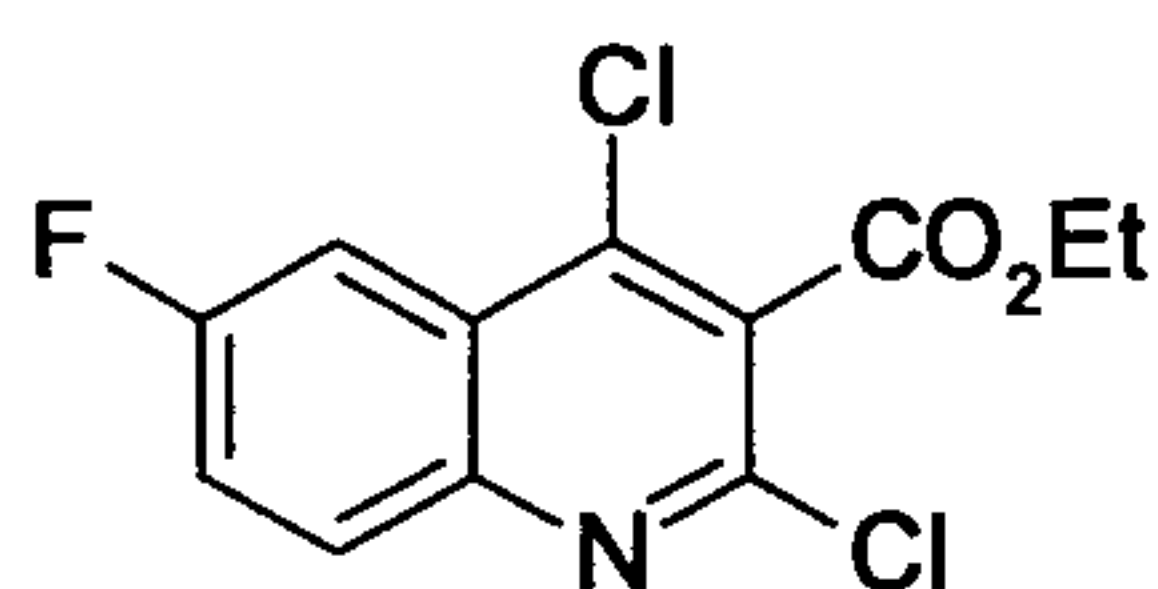
J = 7.1 Hz), 7.20-7.29 (1H, m), 7.31-7.42 (1H, m), 7.75 (1H, dd, J = 8.6, 2.7 Hz), 11.02 (1H, br s), 14.31 (1H, s).

[0533]

Reference Example 111

5 Production of ethyl 2,4-dichloro-6-fluoroquinoline-3-carboxylate

[0534]



[0535]

10 In the same manner as in Reference Example 2, the title compound (2.2 g, 96%) was obtained as a white solid from the compound of Reference Example 110 (2.0 g, 7.8 mmol) and phosphorus oxychloride (9.0 mL).

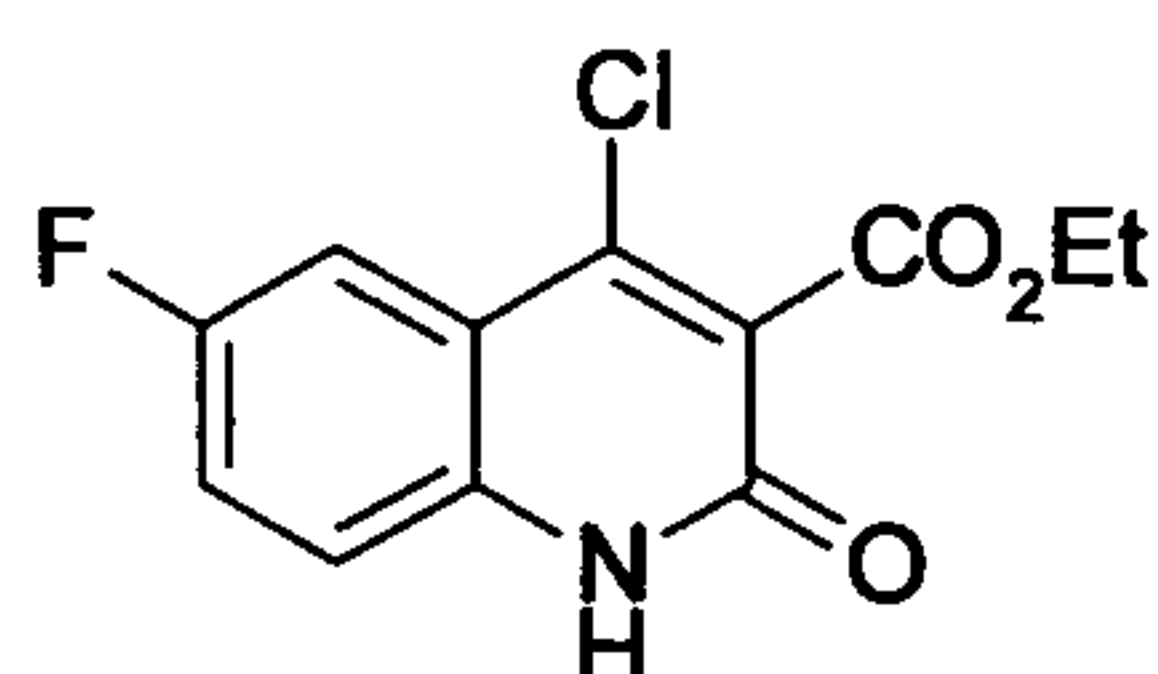
¹H-NMR (300 MHz, CDCl₃) δ: 1.46 (3H, t, J = 7.1 Hz), 4.54 (2H, q, J = 7.2 Hz), 7.54-7.68 (1H, m), 7.86 (1H, dd, J = 9.1, 2.8 Hz), 8.07 (1H, dd, J = 9.2, 5.2 Hz).

[0536]

Reference Example 112

Production of ethyl 4-chloro-6-fluoro-2-oxo-1,2-dihydroquinoline-3-carboxylate

[0537]



[0538]

25 In the same manner as in Reference Example 3, the title compound (1.6 g, 79%) was obtained as a white solid from the compound of Reference Example 111 (2.2 g, 7.5 mmol), sodium acetate (615 mg, 7.5 mmol) and acetic acid (20 mL).

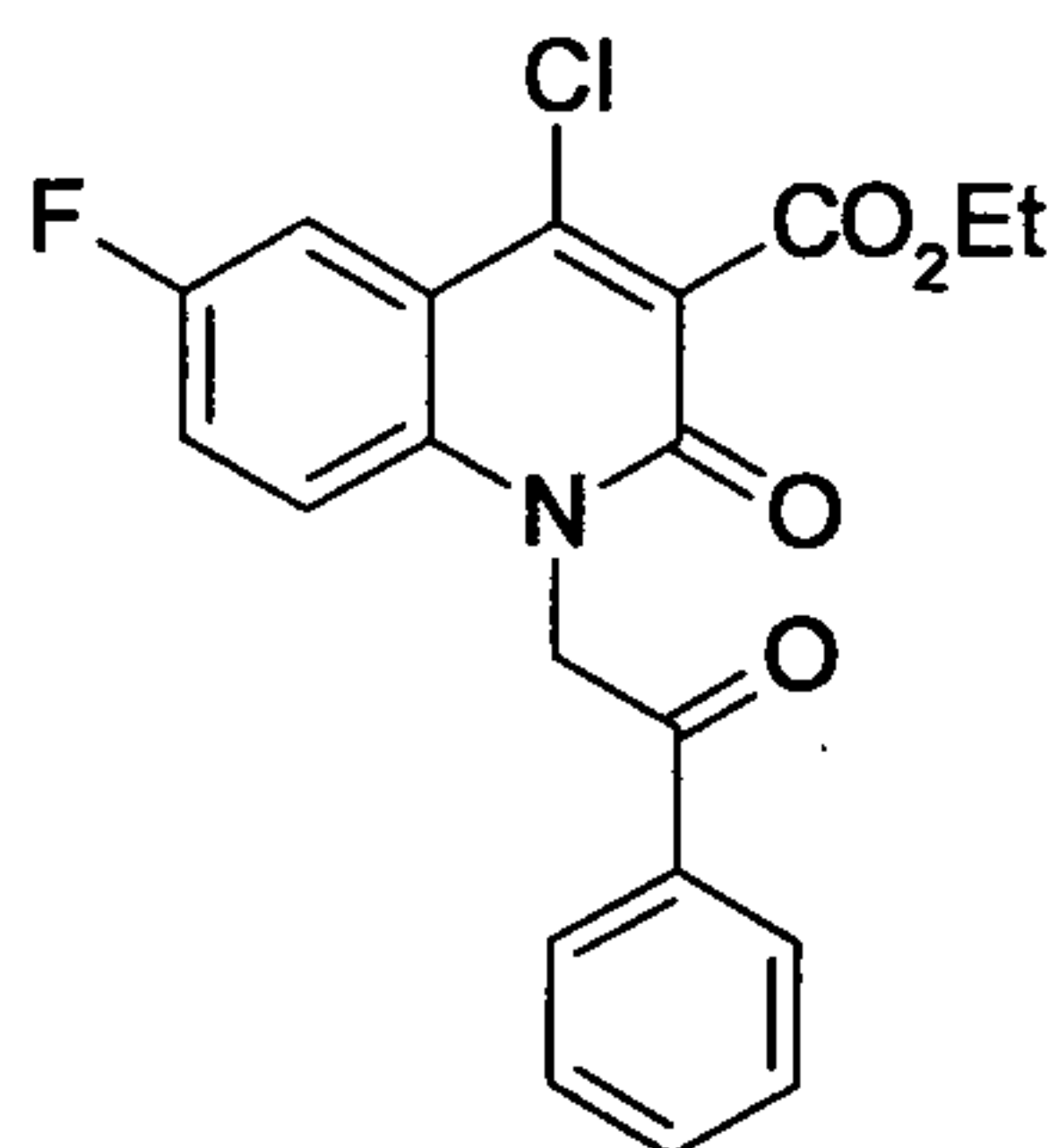
¹H-NMR (300 MHz, CDCl₃) δ: 1.40-1.51 (3H, m), 4.46-4.57 (2H, m), 7.36-7.46 (2H, m), 7.69 (1H, dd, J = 9.1, 1.9 Hz), 12.36 (1H, br s).

[0539]

Reference Example 113

Production of ethyl 4-chloro-6-fluoro-2-oxo-1-(2-oxo-2-phenylethyl)-1,2-dihydroquinoline-3-carboxylate

5 [0540]



[0541]

In the same manner as in Reference Example 4, the title compound (1.3 g, 57%) was obtained as a pale-yellow solid from
 10 the compound of Reference Example 112 (1.6 g, 5.9 mmol), sodium hydride (60% in oil, 248 mg, 6.2 mmol), phenacyl bromide (1.3 g, 6.5 mmol) and DMF (20 mL).

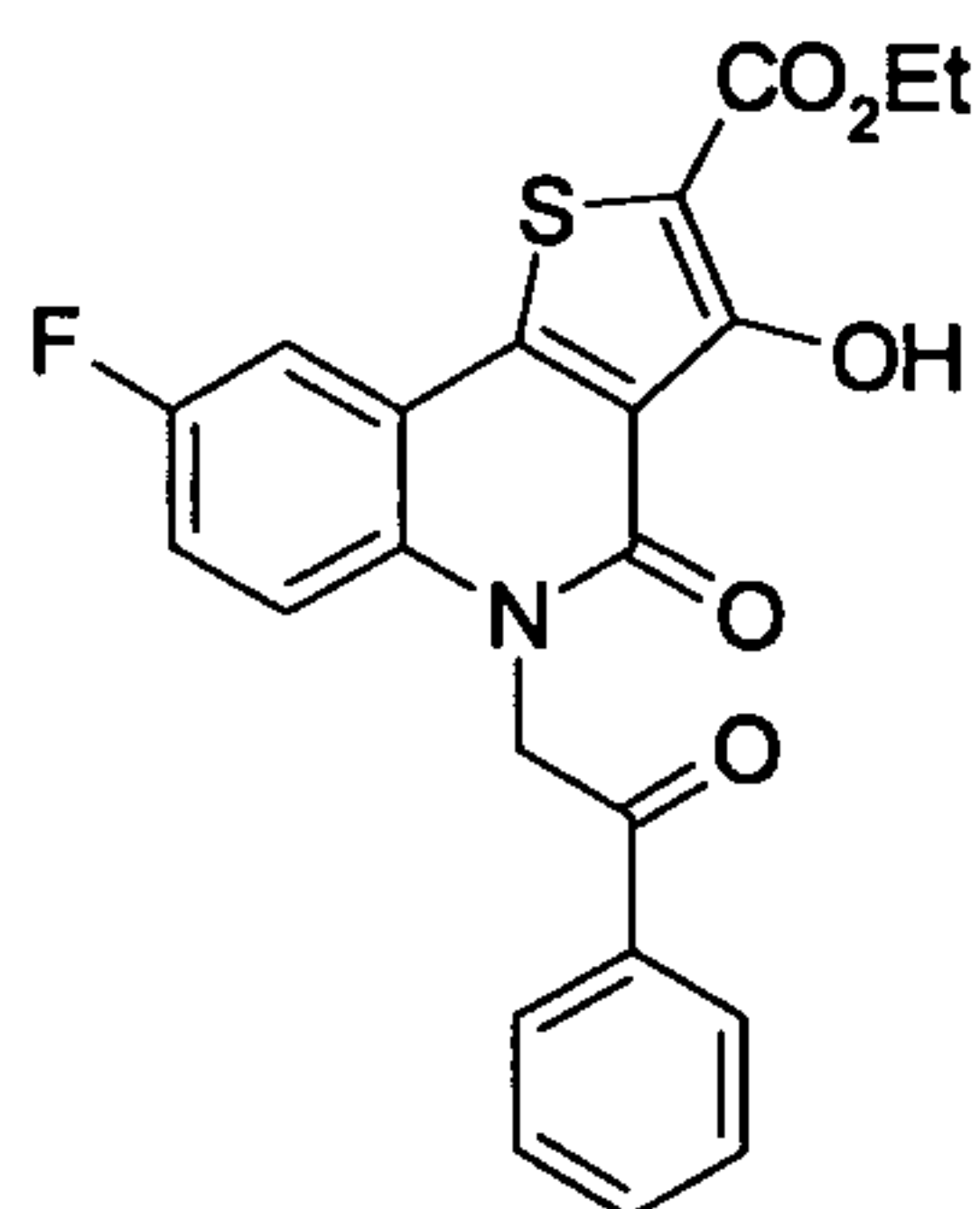
¹H-NMR (300 MHz, CDCl₃) δ: 1.42 (3H, t, J = 7.1 Hz), 4.47 (2H, q, J = 7.1 Hz), 5.79 (2H, s), 7.00 (1H, dd, J = 9.3, 4.2 Hz),
 15 7.27-7.38 (1H, m), 7.49-7.61 (2H, m), 7.63-7.73 (1H, m), 7.80 (1H, dd, J = 9.1, 2.8 Hz), 8.02-8.12 (2H, m).

[0542]

Reference Example 114

Production of ethyl 8-fluoro-3-hydroxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate
 20

[0543]



[0544]

In the same manner as in Reference Example 5, the title compound (1.3 g, 94%) was obtained as a yellow solid from the compound of Reference Example 113 (1.3 g, 3.3 mmol), a 20% solution (2.3 g, 6.7 mmol) of sodium ethoxide in ethanol, ethyl thioglycolate (0.97 g, 8.0 mmol) and ethanol (14 mL).

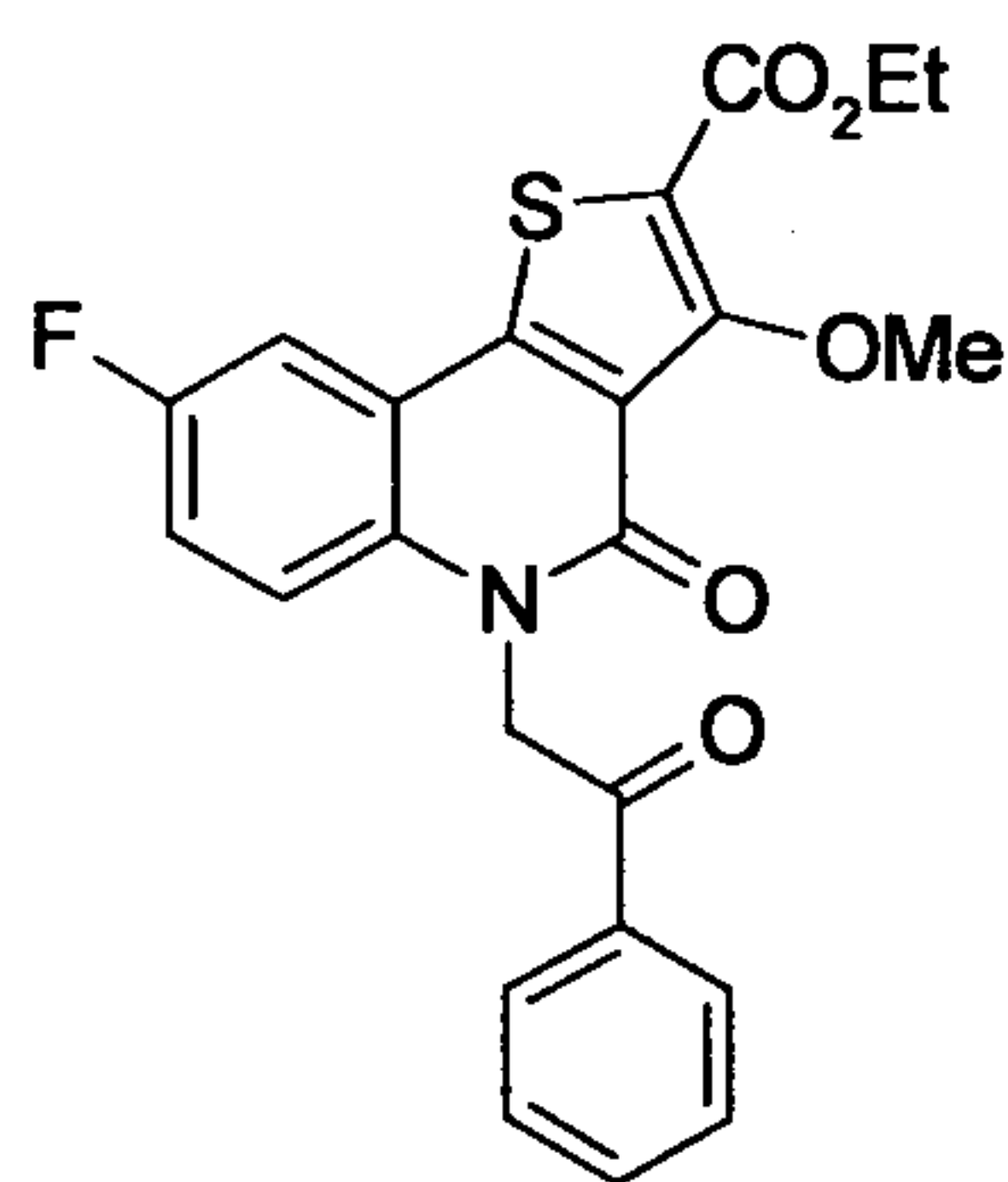
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.32 (3H, t, J = 7.1 Hz), 4.32 (2H, q, J = 7.2 Hz), 6.02 (2H, s), 7.47-7.58 (1H, m), 7.59-7.70 (3H, m), 7.72-7.82 (1H, m), 8.00 (1H, dd, J = 8.7, 2.8 Hz), 8.11-8.21 (2H, m), 10.52 (1H, br s).

10 [0545]

Reference Example 115

Production of ethyl 8-fluoro-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0546]



15

[0547]

In the same manner as in Reference Example 6, the title compound (880 mg, 65%) was obtained as a yellow solid from the compound of Reference Example 114 (1.3 g, 3.1 mmol), iodomethane (0.31 mL, 5.0 mmol), DBU (0.75 mL, 5.0 mmol) and DMF (40 mL).

¹H-NMR (300 MHz, CDCl₃) δ: 1.43 (3H, t, J = 7.5 Hz), 4.12 (3H, s), 4.42 (2H, q, J = 7.2 Hz), 5.84 (2H, s), 6.98 (1H, dd, J = 9.3, 4.2 Hz), 7.16-7.25 (1H, m), 7.49-7.60 (3H, m), 7.64-7.72 (1H, m), 8.03-8.15 (2H, m).

25

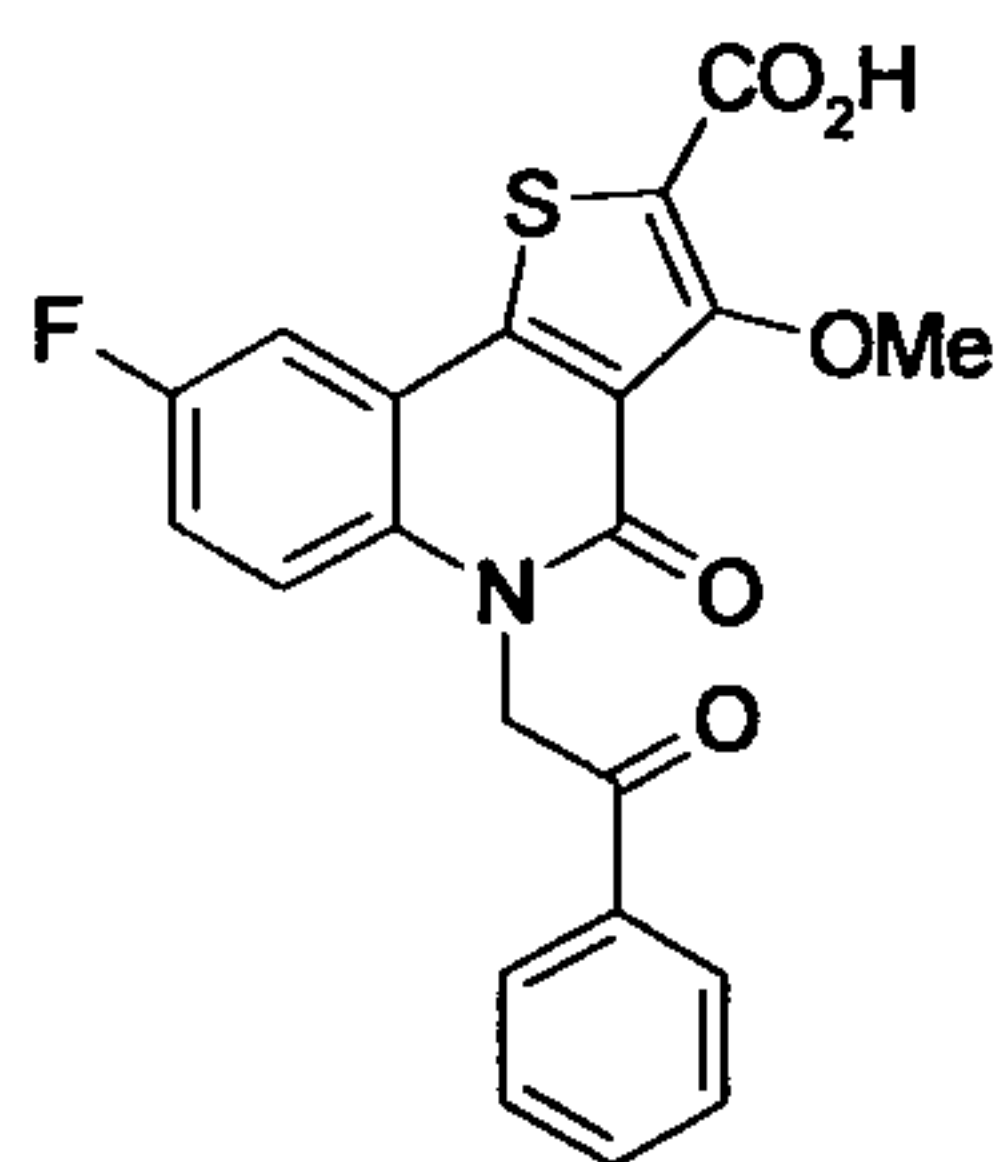
[0548]

Reference Example 116

Production of 8-fluoro-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic

acid

[0549]



[0550]

5 In the same manner as in Reference Example 7, the title compound (602 mg, 73%) was obtained as a pale-brown solid from the compound of Reference Example 115 (880 mg, 2.0 mmol), 8N aqueous sodium hydroxide solution (5.7 mL), ethanol (32 mL) and THF (9.1 mL).

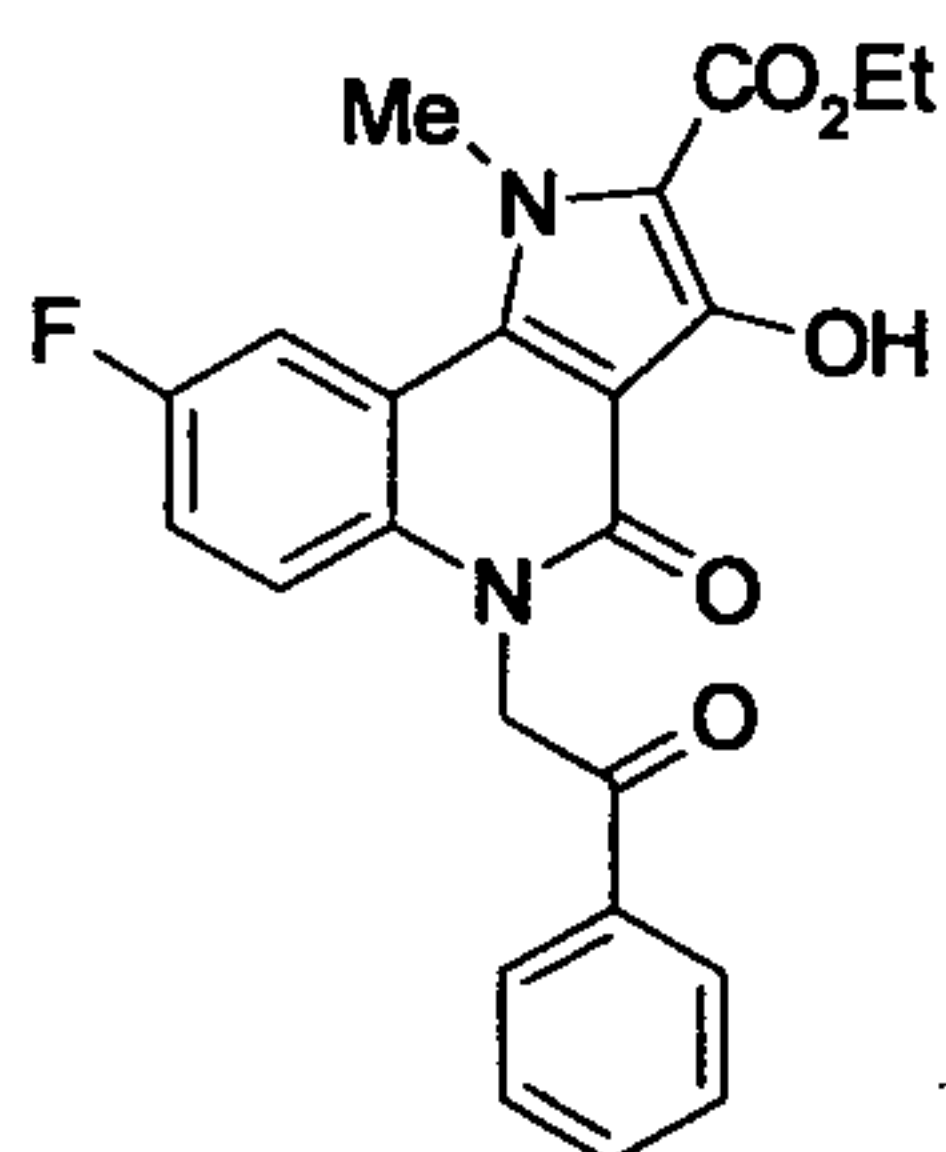
10 ¹H-NMR (300 MHz, DMSO-d₆) δ: 3.92 (3H, s), 5.98 (2H, s), 7.39-7.60 (2H, m), 7.60-7.69 (2H, m), 7.72-7.81 (1H, m), 7.91-8.01 (1H, m), 8.12-8.23 (2H, m).

[0551]

Reference Example 117

15 Production of ethyl 8-fluoro-3-hydroxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate

[0552]



20 [0553]

In the same manner as in Reference Example 25, the title compound (4.1 g, 83%) was obtained as a pale-brown solid from the compound of Reference Example 113 (4.6 g, 12 mmol), sarcosine ethyl ester hydrochloride (4.5 g, 30 mmol),
25 triethylamine (6.0 mL, 43 mmol), ethanol (35 mL), a 20%

solution (3.4 g, 9.9 mmol) of sodium ethoxide in ethanol and ethanol (35 mL).

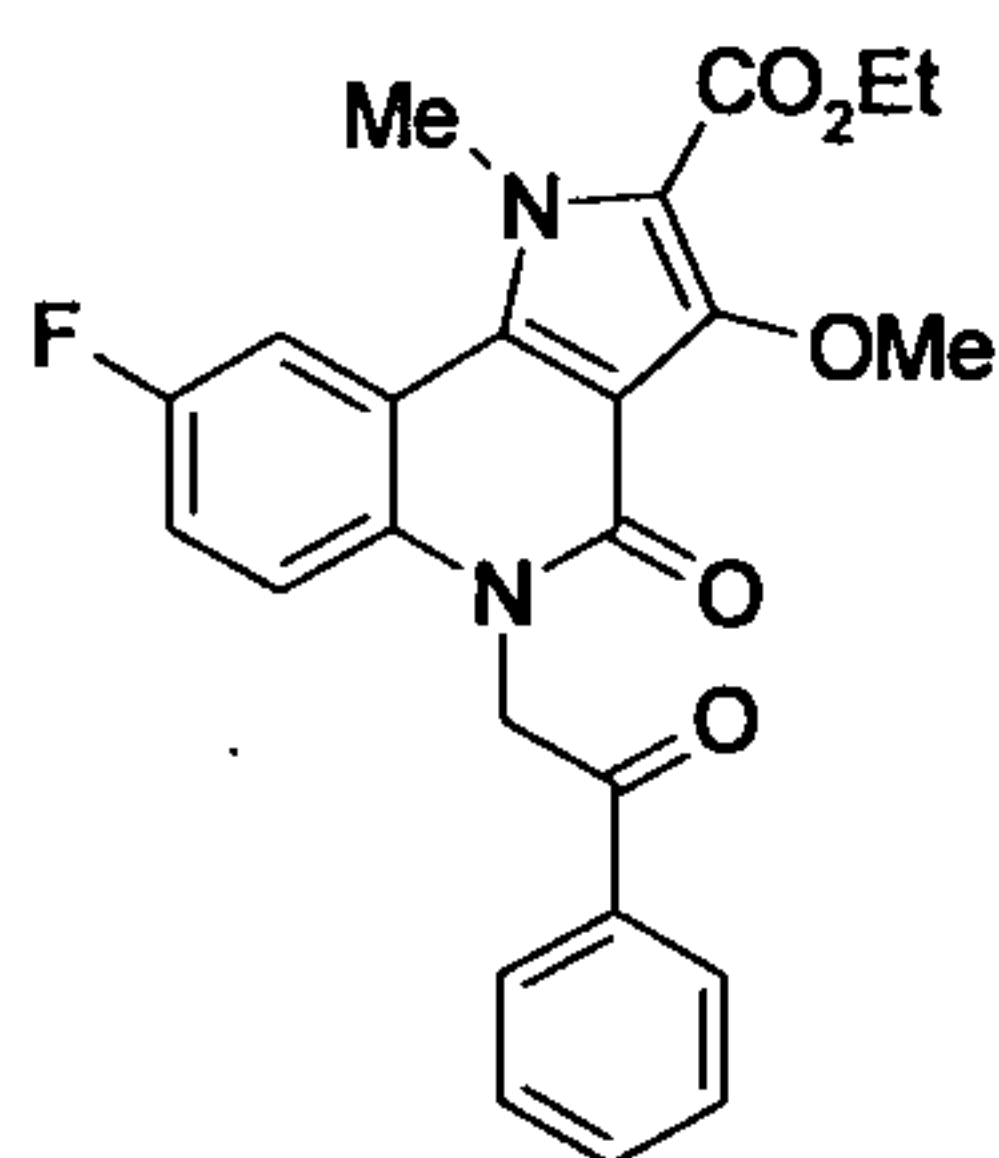
¹H-NMR (300 MHz, DMSO-*d*₆) δ:1.33 (3H, t, J = 8.9 Hz), 4.26-4.42 (5H, m), 5.94 (2H, s), 7.33-7.50 (2H, m), 7.58-7.69 (2H, m),
5 7.71-7.80 (1H, m), 8.03-8.23 (3H, m), 9.01 (1H, br s).

[0554]

Reference Example 118

Production of ethyl 8-fluoro-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-
10 carboxylate

[0555]



[0556]

A solution of the compound of Reference Example 117 (3.4
15 g, 8.0 mmol), dimethylsulfuric acid (1.1 mL, 12 mmol) and DBU (2.4 mL, 16 mmol) in DMF (100 mL) was stirred at room temperature for 2.5 hr. Dimethylsulfuric acid (1.1 mL, 12 mmol) and DBU (2.4 mL, 16 mmol) were added to the reaction mixture, and the mixture was stirred at room temperature for 1
20 day. Dimethylsulfuric acid (0.75 mL, 8.0 mmol) and DBU (1.8 mL, 11 mmol) were further added, and the mixture was stirred at room temperature for 21 hr and diluted with water, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure
25 to give the title compound (2.8 g, 80%) as a white solid.

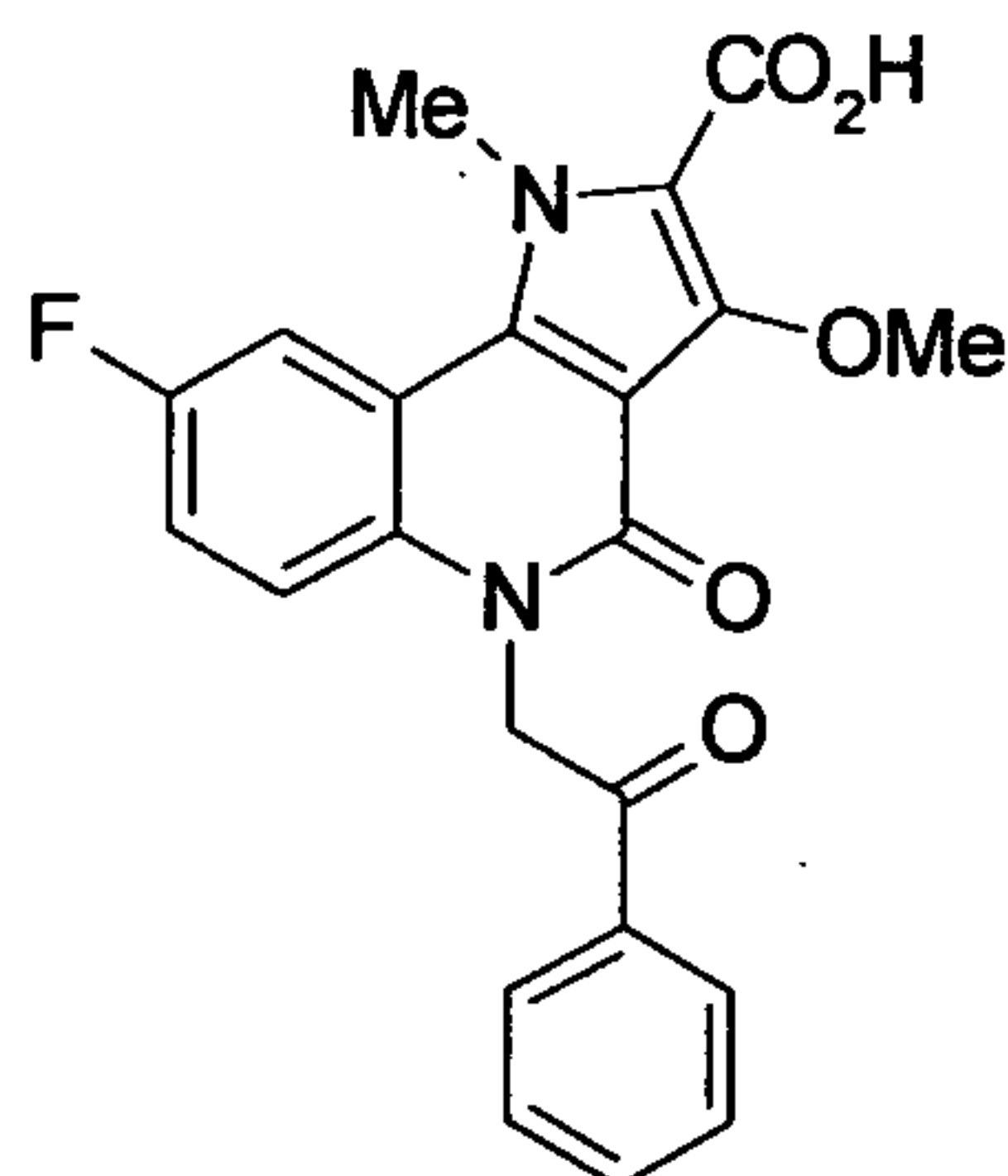
¹H-NMR (300 MHz, DMSO-*d*₆) δ:1.35 (3H, t, J = 7.1 Hz), 3.88 (3H, s), 4.21-4.42 (5H, m), 5.96 (2H, s), 7.28-7.51 (2H, m), 7.55-7.69 (2H, m), 7.71-7.81 (1H, m), 7.98-8.39 (3H, m).

[0557]

30 Reference Example 119

Production of 8-fluoro-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylic acid

[0558]



5

[0559]

In the same manner as in Reference Example 7, the title compound (2.4 g, 90%) was obtained as a pale-yellow solid from the compound of Reference Example 118 (2.8 g, 6.4 mmol).

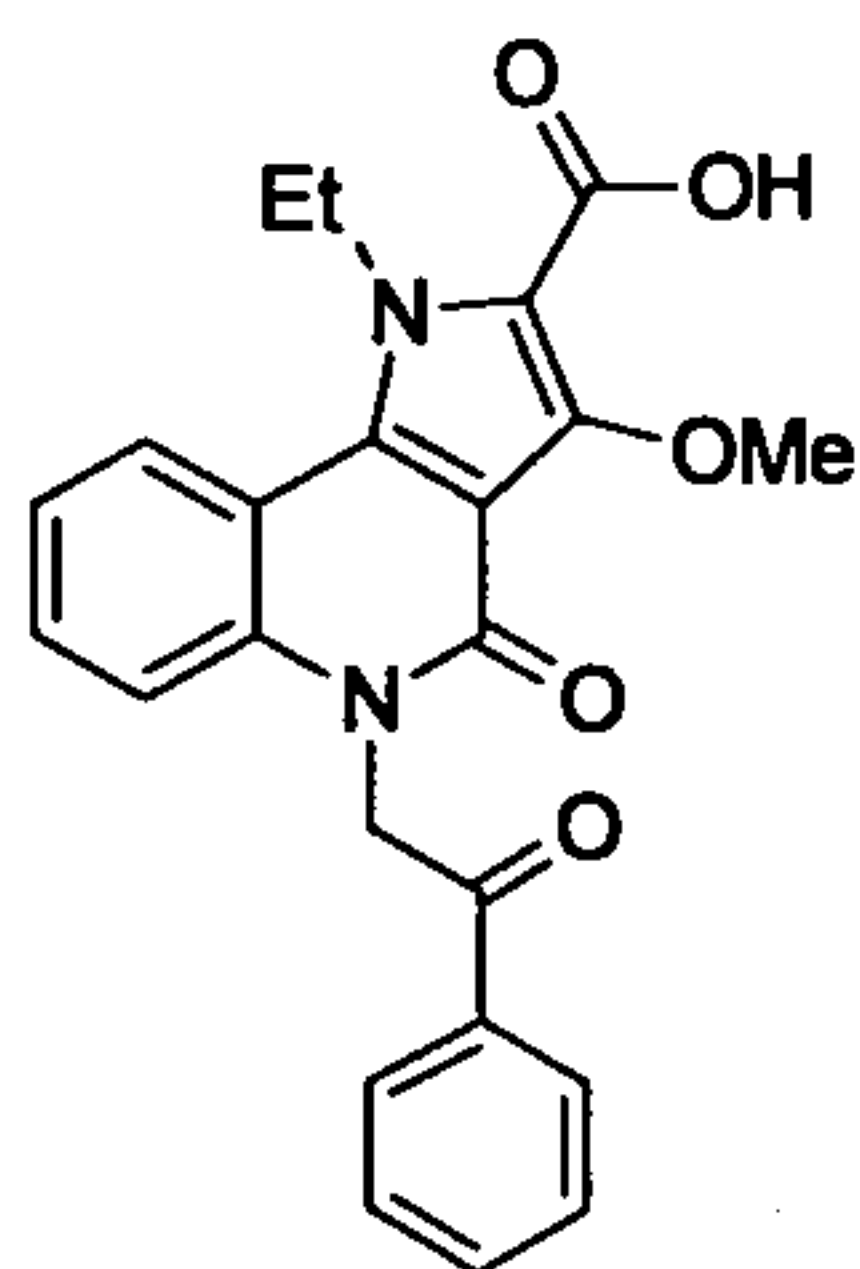
10 $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ : 3.85 (3H, s), 4.30 (3H, s), 5.95 (2H, s), 7.19–7.49 (2H, m), 7.53–7.69 (2H, m), 7.70–7.82 (1H, m), 7.97–8.26 (3H, m).

[0560]

Reference Example 120

15 Production of 1-ethyl-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylic acid

[0561]



[0562]

20 A solution of the compound of Reference Example 4 (1.0 g, 2.7 mmol), N-ethylglycine ethyl ester hydrochloride (499 mg, 3.0 mmol) and triethylamine (3.8 mL, 27 mmol) in 1-butanol (10 mL) was heated under reflux for 6 hr. N-Ethylglycine ethyl ester hydrochloride (499 mg, 3.0 mmol) was added and the

mixture was heated under reflux for 17 hr. N-Ethylglycine ethyl ester hydrochloride (499 mg, 3.0 mmol) and triethylamine (0.41 mL, 3.0 mmol) were added, and the mixture was heated under reflux for 6 hr, and N-ethylglycine ethyl ester hydrochloride (499 mg, 3.0 mmol) and triethylamine (0.41 mL, 3.0 mmol) were added, and the mixture was heated under reflux for 6 hr. Water was added to the reaction mixture, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure.

10 A mixture of the obtained solid, a 20% solution (777 mg, 2.3 mmol) of sodium ethoxide in ethanol and ethanol (150 mL) was stirred at room temperature for 5 hr. A 20% solution (777 mg, 2.3 mmol) of sodium ethoxide in ethanol was added, and the reaction mixture was stirred at room temperature for 1 hr. The

15 reaction mixture was diluted with water, neutralized with 5N hydrochloric acid, and the mixture was stirred for 30 min. The precipitated solid was collected by filtration, washed with water, dried under reduced pressure, and recrystallized from DMF-diethyl ether. To a solution of the obtained solid and DBU

20 (0.19 mL, 1.3 mmol) in DMF (8.0 mL) was added dimethylsulfuric acid (0.092 mL, 0.97 mmol) under ice-cooling, and the mixture was stirred at room temperature for 14 hr. DBU (0.19 mL, 1.3 mmol) and dimethylsulfuric acid (0.092 mL, 0.97 mmol) were further added under ice-cooling, and the mixture was stirred

25 at room temperature for 4 hr, and diluted with water. The precipitated solid was collected by filtration, the obtained solid was washed with water, and dried under reduced pressure. A mixed solution of the obtained solid and 8N sodium hydroxide solution (1.4 mL) in THF (2.3 mL)-ethanol (8.0 mL) was stirred

30 at room temperature for 15 hr. 8N Sodium hydroxide solution (0.70 mL) was added, and the mixture was stirred at room temperature for 3.5 hr. 8N Sodium hydroxide solution (0.14 mL) was further added, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was neutralized

35 with 1N hydrochloric acid and concentrated under reduced

pressure, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (180 mg, 16%) as a white solid.

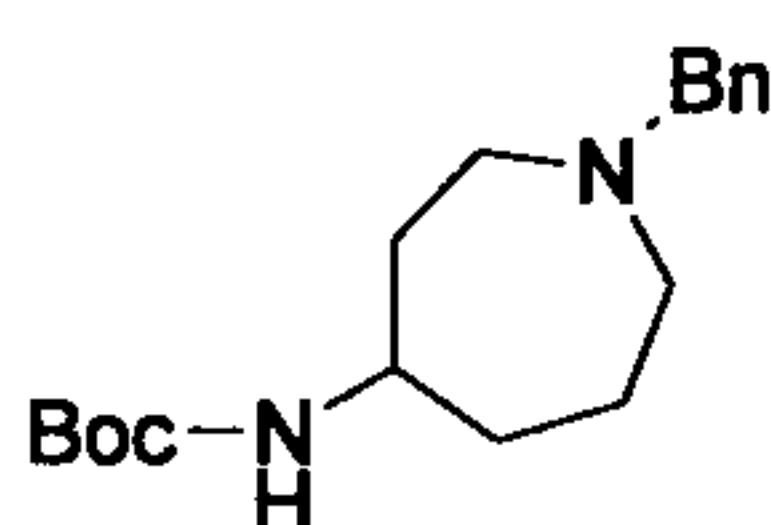
5 ¹H-NMR (300 MHz, DMSO-*d*₆) δ:1.51 (3H, t, J = 6.5 Hz), 3.86 (3H, s), 4.85 (2H, q, J = 7.0 Hz), 5.97 (2H, s), 7.27-7.43 (2H, m), 7.44-7.54 (1H, m), 7.58-7.69 (2H, m), 7.71-7.83 (1H, m), 8.01-8.45 (3H, m), 12.89 (1H, br s).

[0563]

10 Reference Example 121

Production of tert-butyl (1-benzylazepan-4-yl)carbamate

[0564]



[0565]

15 To a solution of 1-benzylazepan-4-amine (400 mg, 2.0 mmol) and triethylamine (0.82 mL, 5.9 mmol) in THF (5.0 mL) was added di-tert-butyl dicarbonate (591 mg, 2.7 mmol) under ice-cooling, and the mixture was stirred at room temperature for 4 hr. The reaction mixture was diluted with saturated
20 sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=10/90 - 100/0) to
25 give the title compound (447 mg, quant.) as a colorless oil.

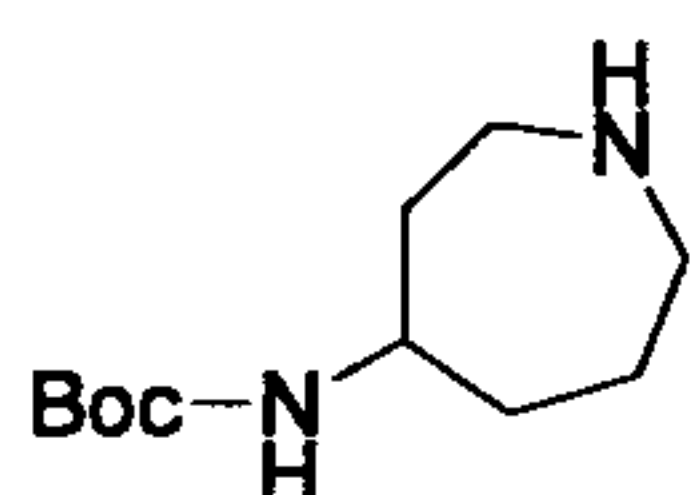
¹H-NMR (300 MHz, CDCl₃) δ:1.45 (9H, s), 1.53-1.77 (5H, m), 1.78-1.93 (1H, m), 2.37-2.58 (2H, m), 2.61-2.83 (2H, m), 3.61 (2H, s), 3.73-4.00 (1H, m), 4.92-5.27 (1H, m), 7.07-7.44 (5H, m).

30 [0566]

Reference Example 122

Production of tert-butyl azepan-4-ylcarbamate

[0567]



[0568]

A solution of the compound of Reference Example 121 (447 mg, 1.5 mmol) and palladium-carbon (65 mg) in ethanol (10 mL) was stirred at room temperature for 4.5 hr under a hydrogen atmosphere. Palladium-carbon was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in methanol (10 mL), palladium-carbon (120 mg) was added, and the mixture was stirred at room temperature for 4.5 hr under a hydrogen atmosphere. Palladium-carbon was filtered off, and the filtrate was concentrated under reduced pressure to give the title compound (315 mg, quant.) as a colorless oil.

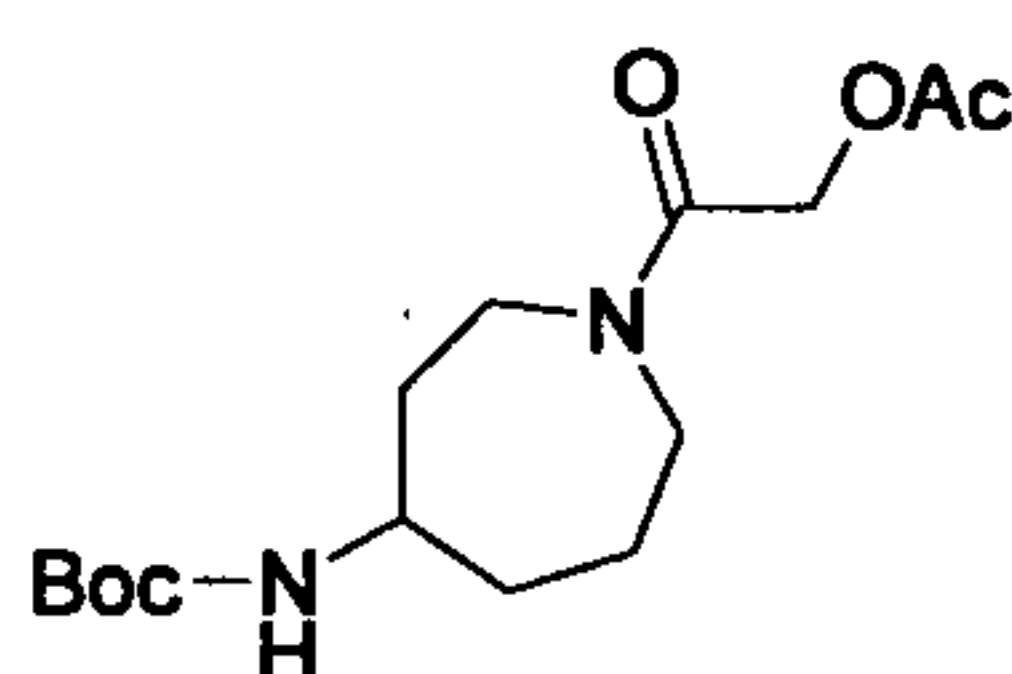
¹H-NMR (300 MHz, CDCl₃) δ: 1.34-1.76 (13H, m), 1.78-2.07 (2H, m), 2.39-2.70 (1H, m), 2.71-3.04 (4H, m), 3.66-3.94 (1H, m), 4.60-5.01 (1H, m).

[0569]

Reference Example 123

Production of 2-{4-[(tert-butoxycarbonyl)amino]azepan-1-yl}-2-oxoethyl acetate

[0570]



[0571]

In the same manner as in Example 544, the title compound (220 mg, 96%) was obtained as a white solid from the compound of Reference Example 122 (157 mg, 0.73 mmol).

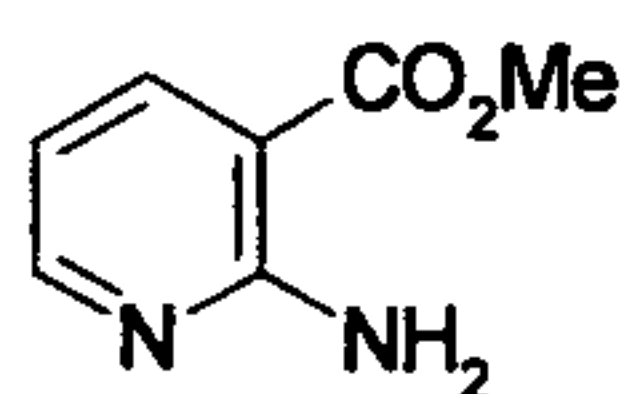
¹H-NMR (300 MHz, CDCl₃) δ: 1.37-1.55 (11H, m), 1.61-2.00 (4H, m), 2.07-2.23 (4H, m), 3.21-3.77 (4H, m), 4.35-4.59 (1H, m), 4.59-4.81 (2H, m).

[0572]

Reference Example 124

Production of methyl 2-aminopyridine-3-carboxylate

[0573]



5 [0574]

To a solution of 2-aminopyridine-3-carboxylic acid (4.3 g, 31 mmol) in methanol (62 mL) was added dropwise sulfuric acid (31 mL) under ice-cooling, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture
10 was stirred at 70°C for 15 hr, and neutralized with sodium bicarbonate under ice-cooling. The reaction mixture was extracted twice with ethyl acetate, and the extracts were combined, and washed with brine. The extract was dried over magnesium sulfate, and concentrated under reduced pressure to
15 give the title compound (4.3 g, 90%) as a white solid.

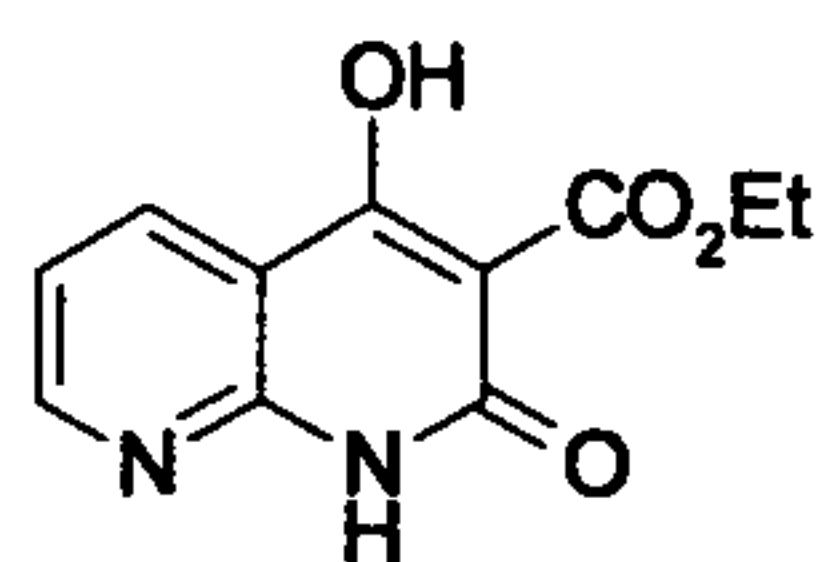
¹H-NMR (300 MHz, CDCl₃) δ: 3.89 (3H, s), 6.38 (2H, br s), 6.63 (1H, dd, J = 7.8, 4.8 Hz), 8.13 (1H, dd, J = 7.7, 1.9 Hz), 8.22 (1H, dd, J = 4.7, 1.9 Hz).

[0575]

20 Reference Example 125

Production of ethyl 4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate

[0576]



25 [0577]

In the same manner as in Reference Example 1, the title compound (2.6 g, 53%) was obtained as a pale-red solid from the compound of Reference Example 124 (3.1 g, 21 mmol).

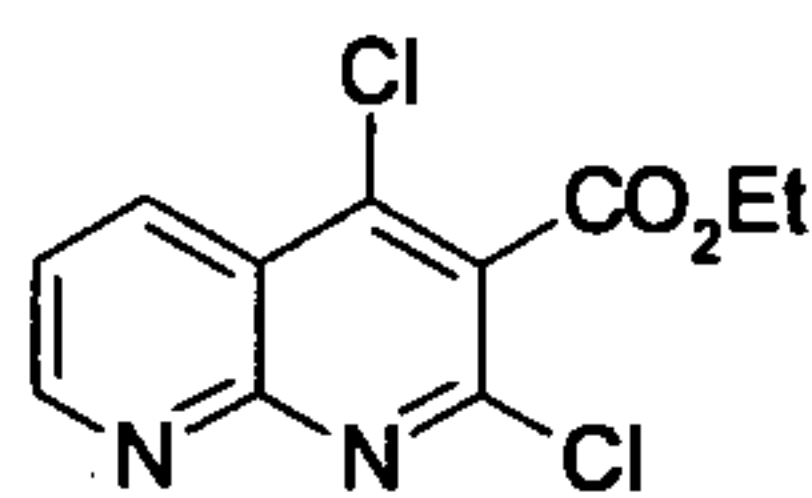
¹H-NMR (300 MHz, DMSO-*d*₆) δ: 1.30 (3H, t, J = 7.1 Hz), 4.32 (2H, q, J = 7.1 Hz), 7.27 (1H, dd, J = 7.9, 4.7 Hz), 8.22-8.38 (1H, m), 8.60 (1H, dd, J = 4.6, 1.8 Hz), 11.86 (1H, s), 13.29 (1H, br s).

[0578]

Reference Example 126

Production of ethyl 2,4-dichloro-1,8-naphthyridine-3-carboxylate

5 [0579]



[0580]

In the same manner as in Reference Example 2, the title compound (2.3 g, 77%) was obtained as a pale-yellow solid from
10 the compound of Reference Example 125 (2.6 g, 11 mmol).

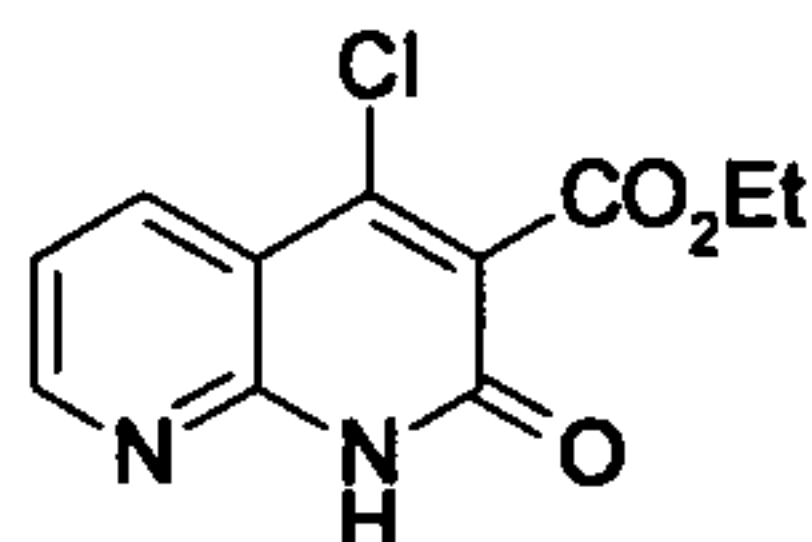
¹H-NMR (300 MHz, CDCl₃) δ: 1.47 (3H, t, J = 7.2 Hz), 4.56 (2H, q, J = 7.2 Hz), 7.67 (1H, dd, J = 8.4, 4.2 Hz), 8.62 (1H, dd, J = 8.3, 1.9 Hz), 9.21 (1H, dd, J = 4.2, 1.9 Hz).

[0581]

15 Reference Example 127

Production of ethyl 4-chloro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate

[0582]



20 [0583]

In the same manner as in Reference Example 3, the title compound (1.5 g, 71%) was obtained as a white solid from the compound of Reference Example 126 (2.2 g, 8.3 mmol).

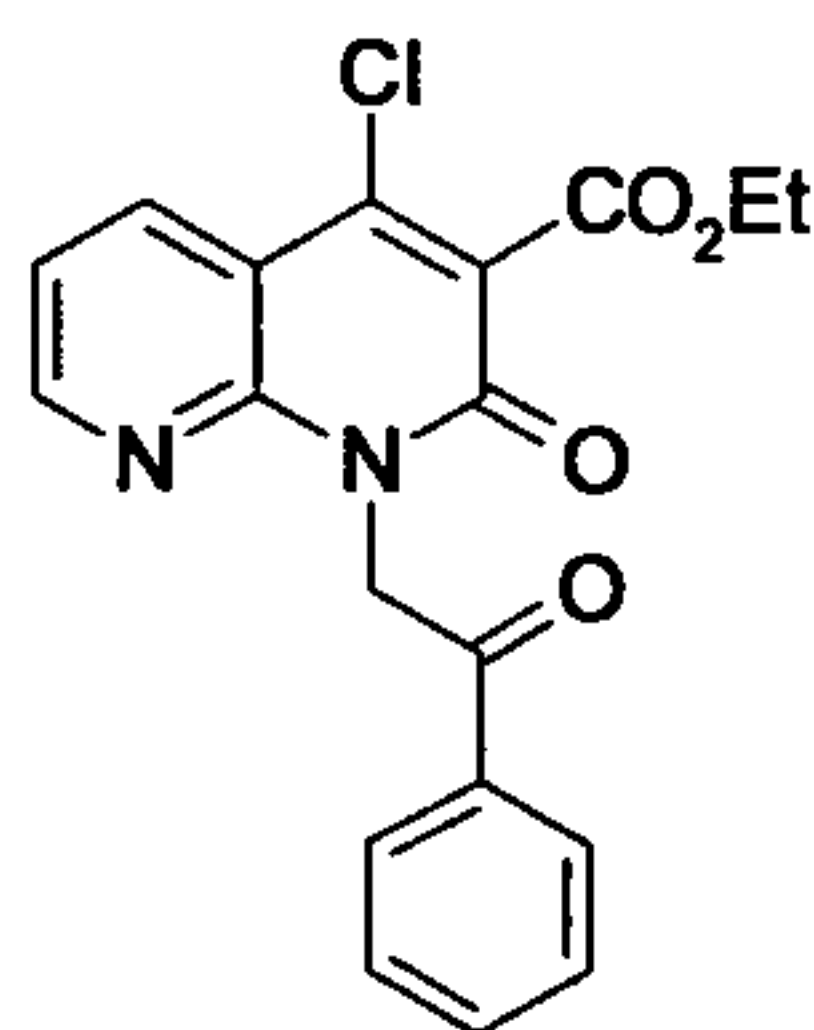
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.31 (3H, t, J = 7.1 Hz), 4.37 (2H, q, J = 7.1 Hz), 7.43 (1H, dd, J = 8.1, 4.7 Hz), 8.33 (1H, dd, J = 8.1, 1.7 Hz), 8.69 (1H, dd, J = 4.7, 1.7 Hz), 12.88 (1H, br s).

[0584]

Reference Example 128

30 Production of ethyl 4-chloro-2-oxo-1-(2-oxo-2-phenylethyl)-1,2-dihydro-1,8-naphthyridine-3-carboxylate

[0585]



[0586]

In the same manner as in Reference Example 4, the title
 5 compound (1.1 g, 51%) was obtained as a pale-yellow oil from
 the compound of Reference Example 127 (1.5 g, 5.7 mmol).

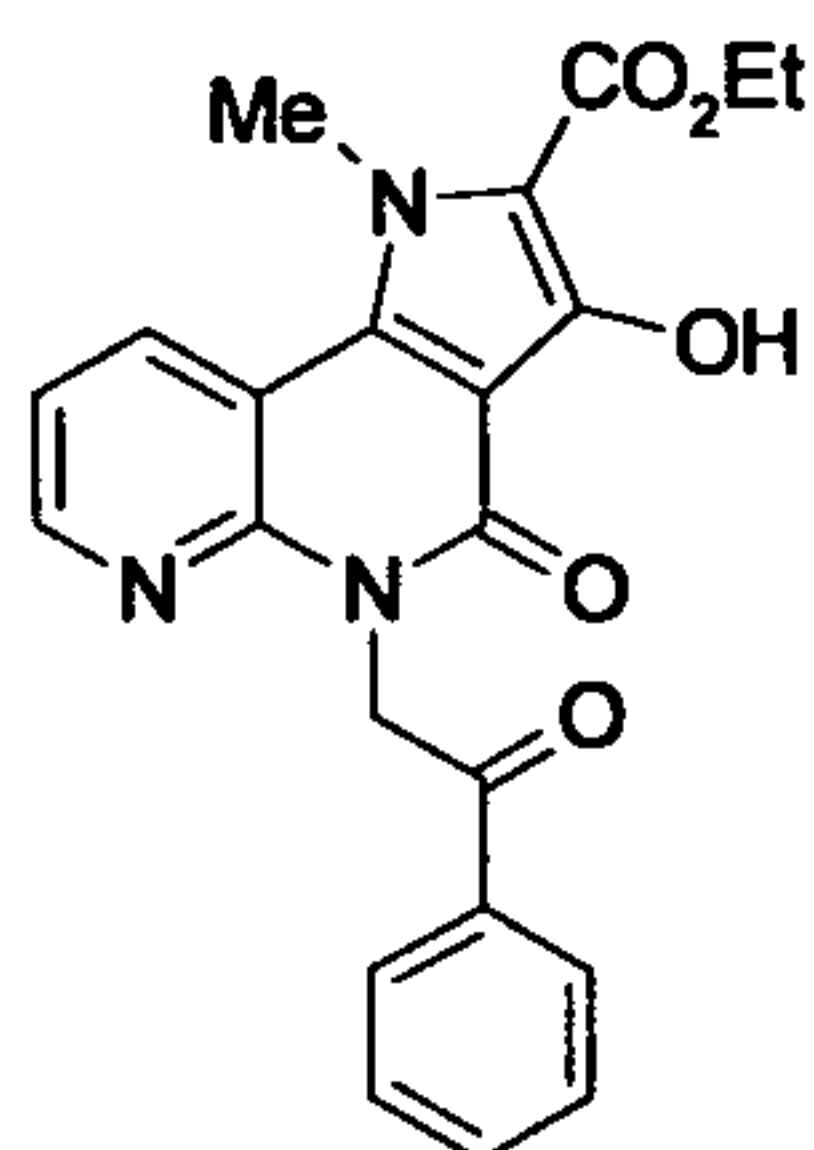
¹H-NMR (300 MHz, CDCl₃) δ: 1.42 (3H, t, J = 7.1 Hz), 4.48 (2H, q,
 J = 7.1 Hz), 5.98 (2H, s), 7.27-7.33 (1H, m), 7.48-7.58 (2H,
 m), 7.59-7.69 (1H, m), 8.02-8.12 (2H, m), 8.36 (1H, dd, J =
 10 8.0, 1.8 Hz), 8.54 (1H, dd, J = 4.7, 1.7 Hz).

[0587]

Reference Example 129

Production of ethyl 3-hydroxy-1-methyl-4-oxo-5-(2-oxo-2-
 phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c][1,8]naphthyridine-
 15 2-carboxylate

[0588]



[0589]

In the same manner as in Reference Example 33, the title
 20 compound (653 mg, 55%) was obtained as a pale-yellow solid
 from the compound of Reference Example 128 (1.1 g, 2.9 mmol).

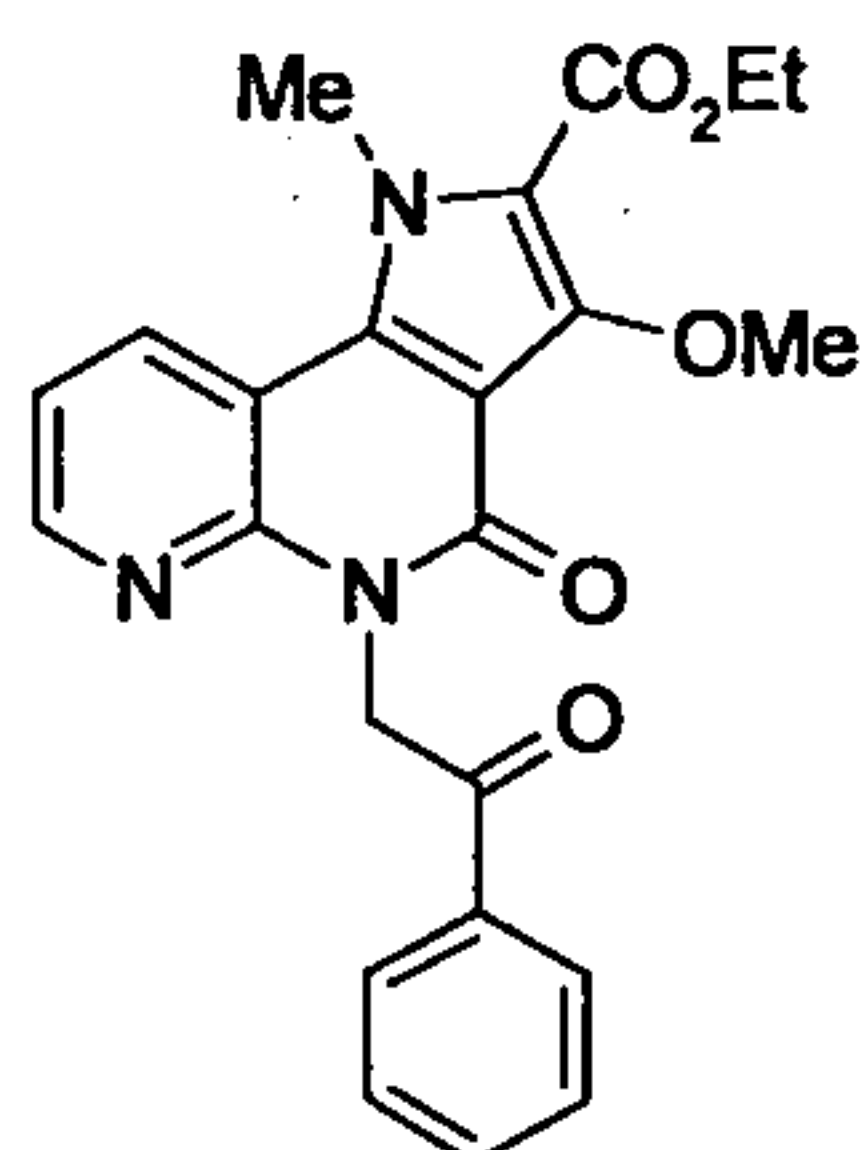
¹H-NMR (300 MHz, CDCl₃) δ: 1.45 (3H, t, J = 7.1 Hz), 4.36 (3H,
 s), 4.46 (2H, q, J = 7.2 Hz), 6.00 (2H, s), 7.20 (1H, dd, J =
 7.9, 4.7 Hz), 7.45-7.58 (2H, m), 7.58-7.69 (1H, m), 8.02-8.15
 25 (2H, m), 8.33-8.51 (2H, m), 8.70 (1H, s).

[0590]

Reference Example 130

Production of ethyl 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c][1,8]naphthyridine-2-carboxylate

5 [0591]



[0592]

In the same manner as in Reference Example 115, the title compound (420 mg, 79%) was obtained as a white solid from the
10 compound of Reference Example 129 (512 mg, 1.3 mmol).

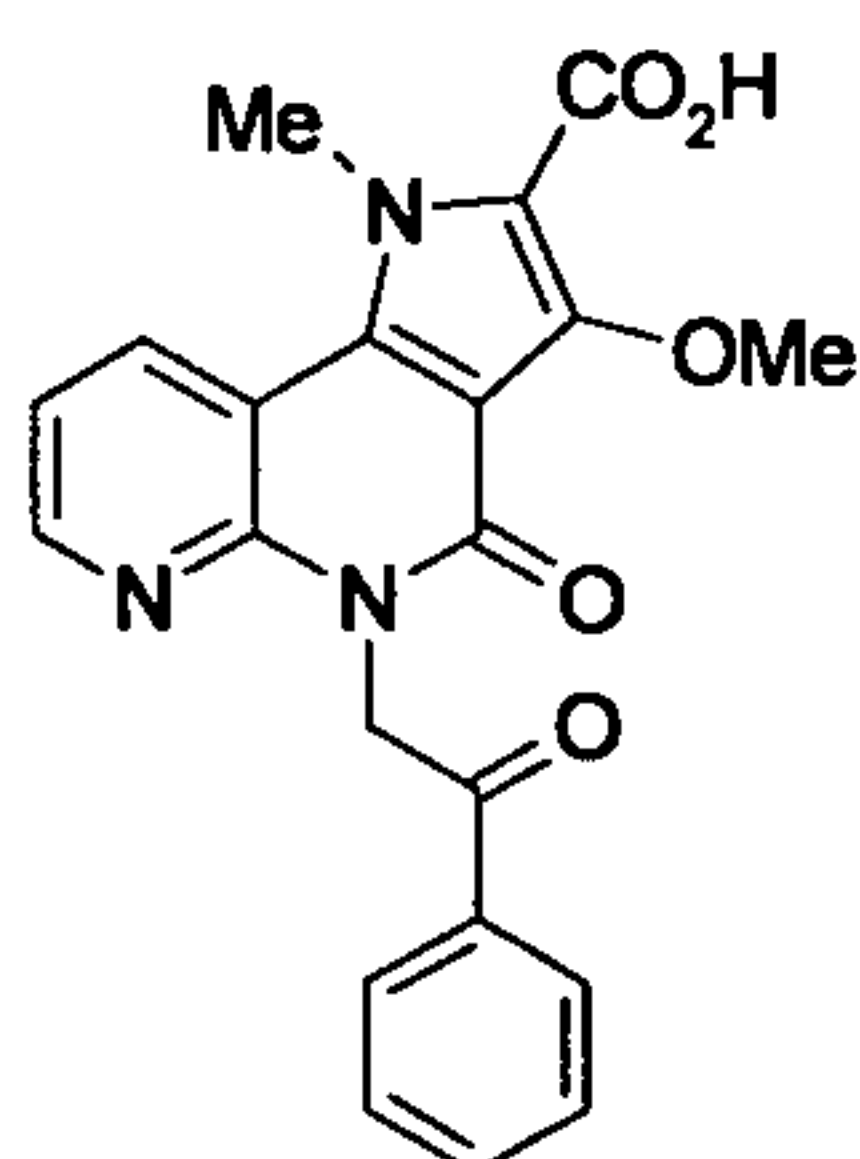
¹H-NMR (300 MHz, DMSO-*d*₆) δ: 1.35 (3H, t, J = 7.1 Hz), 3.91 (3H, s), 4.24-4.44 (5H, m), 5.97 (2H, s), 7.36 (1H, dd, J = 8.1, 4.5 Hz), 7.55-7.69 (2H, m), 7.68-7.82 (1H, m), 8.06-8.24 (2H, m), 8.46 (1H, dd, J = 4.6, 1.4 Hz), 8.75 (1H, dd, J = 8.1, 1.5
15 Hz).

[0593]

Reference Example 131

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c][1,8]naphthyridine-2-carboxylic acid
20

[0594]



[0595]

In the same manner as in Reference Example 7, the title
25 compound (264 mg, 75%) was obtained as a white solid from the

compound of Reference Example 130 (380 mg, 0.91 mmol).

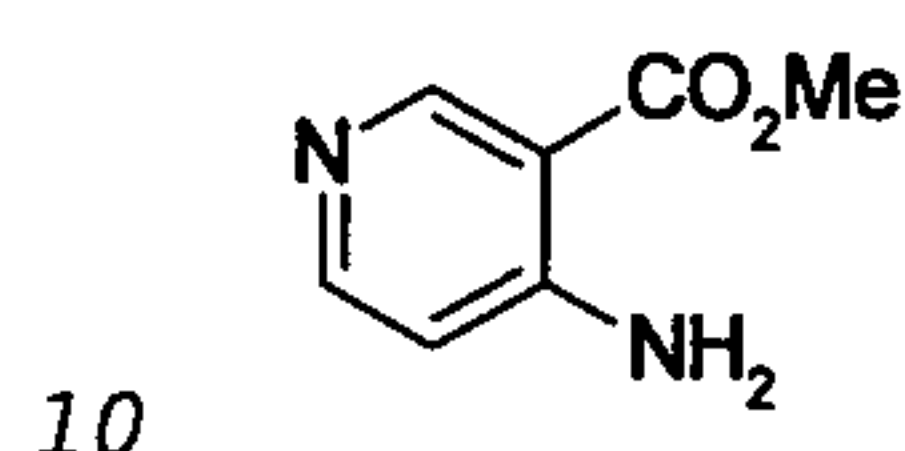
¹H-NMR (300 MHz, DMSO-*d*₆) δ: 3.90 (3H, s), 4.32 (3H, s), 5.97 (2H, s), 7.35 (1H, dd, *J* = 8.1, 4.7 Hz), 7.54–7.68 (2H, m), 7.69–7.81 (1H, m), 8.03–8.27 (2H, m), 8.33–8.56 (1H, m), 8.75 (1H, d, *J* = 7.2 Hz), 13.04 (1H, br s).

[0596]

Reference Example 132

Production of methyl 4-aminopyridine-3-carboxylate

[0597]



[0598]

In the same manner as in Reference Example 124, the title compound (4.9 g, 89%) was obtained as a pale-yellow solid from 4-aminopyridine-3-carboxylic acid (5.0 g, 36 mmol), sulfuric acid (36 mL) and methanol (72 mL).

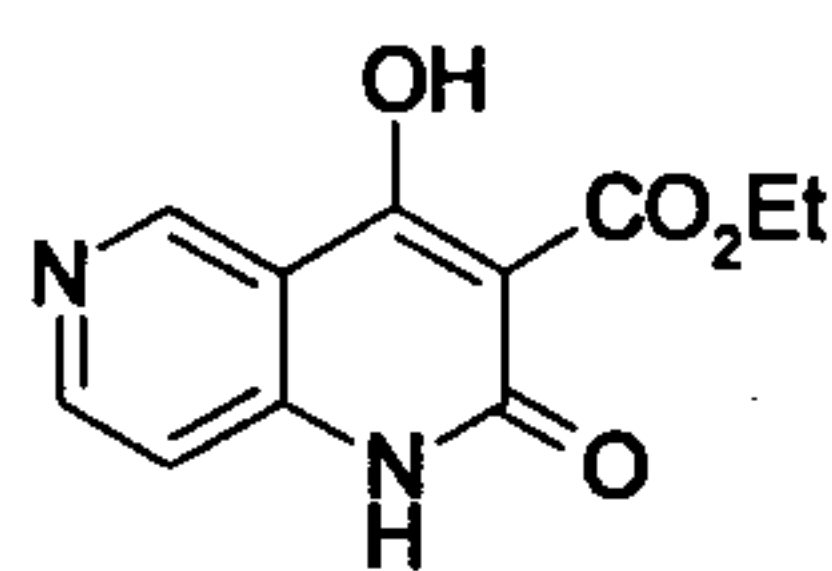
¹H-NMR (300 MHz, CDCl₃) δ: 3.91 (3H, s), 6.20 (2H, br s), 6.51 (1H, d, *J* = 5.9 Hz), 8.20 (1H, d, *J* = 6.0 Hz), 8.90 (1H, s).

[0599]

Reference Example 133

20 Production of ethyl 4-hydroxy-2-oxo-1,2-dihydro-1,6-naphthyridine-3-carboxylate

[0600]



[0601]

25 In the same manner as in Reference Example 1, the title compound (3.5 g, 49%) was obtained as a pale-yellow powder from the compound of Reference Example 132 (4.7 g, 31 mmol).

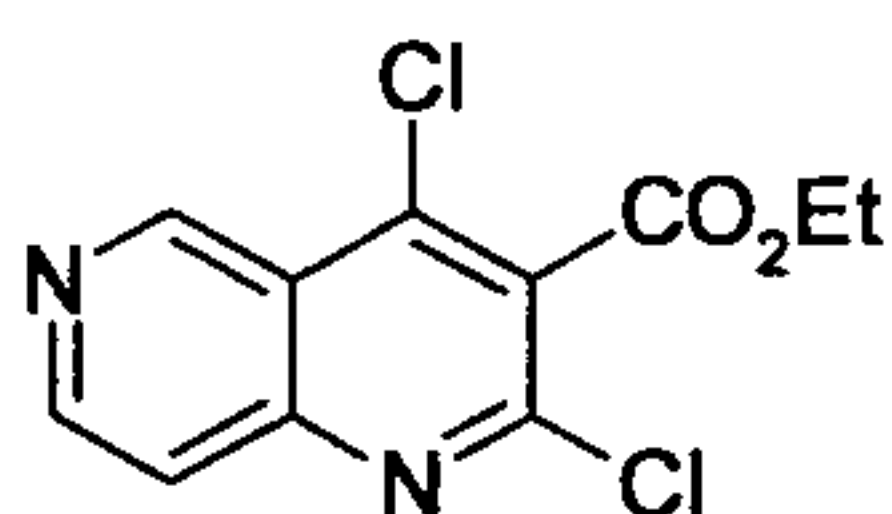
¹H-NMR (300 MHz, DMSO-*d*₆) δ: 1.28 (3H, t, *J* = 7.1 Hz), 4.26 (2H, q, *J* = 7.0 Hz), 7.20 (1H, d, *J* = 6.0 Hz), 8.50 (1H, d, *J* = 6.0 Hz), 8.92–9.09 (1H, m), 11.66 (1H, br s).

[0602]

Reference Example 134

Production of ethyl 2,4-dichloro-1,6-naphthyridine-3-carboxylate

[0603]



5 [0604]

In the same manner as in Reference Example 2, the title compound (2.7 g, 66%) was obtained as a pale-yellow solid from the compound of Reference Example 133 (3.5 g, 15 mmol).

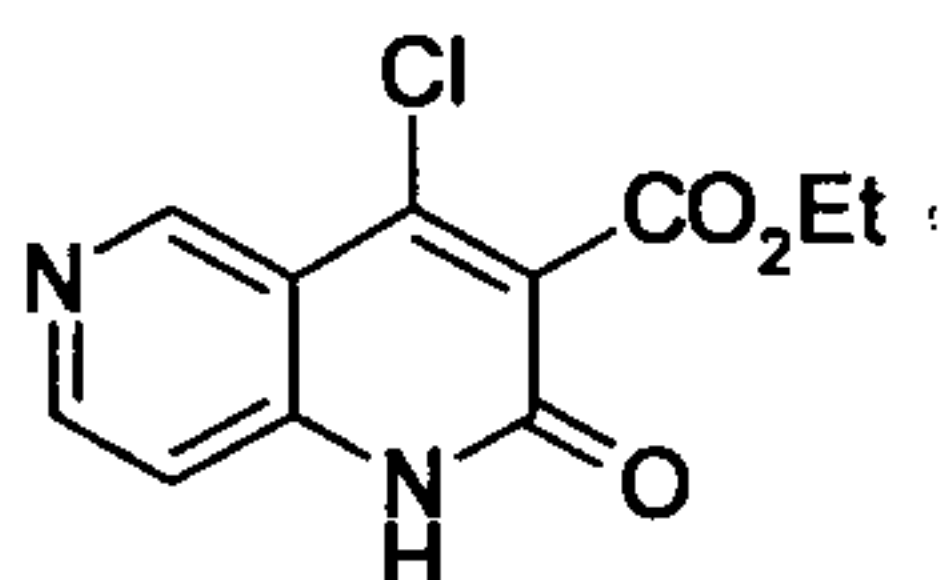
¹H-NMR (300 MHz, CDCl₃) δ: 1.47 (3H, t, J = 7.2 Hz), 4.56 (2H, q, J = 7.1 Hz), 7.87 (1H, dd, J = 5.9, 0.8 Hz), 8.92 (1H, d, J = 5.9 Hz), 9.66 (1H, d, J = 0.9 Hz).

[0605]

Reference Example 135

Production of ethyl 4-chloro-2-oxo-1,2-dihydro-1,6-naphthyridine-3-carboxylate

[0606]



[0607]

In the same manner as in Reference Example 3, the title compound (733 mg, 30%) was obtained as a pale-brown solid from the compound of Reference Example 134 (2.6 g, 9.7 mmol).

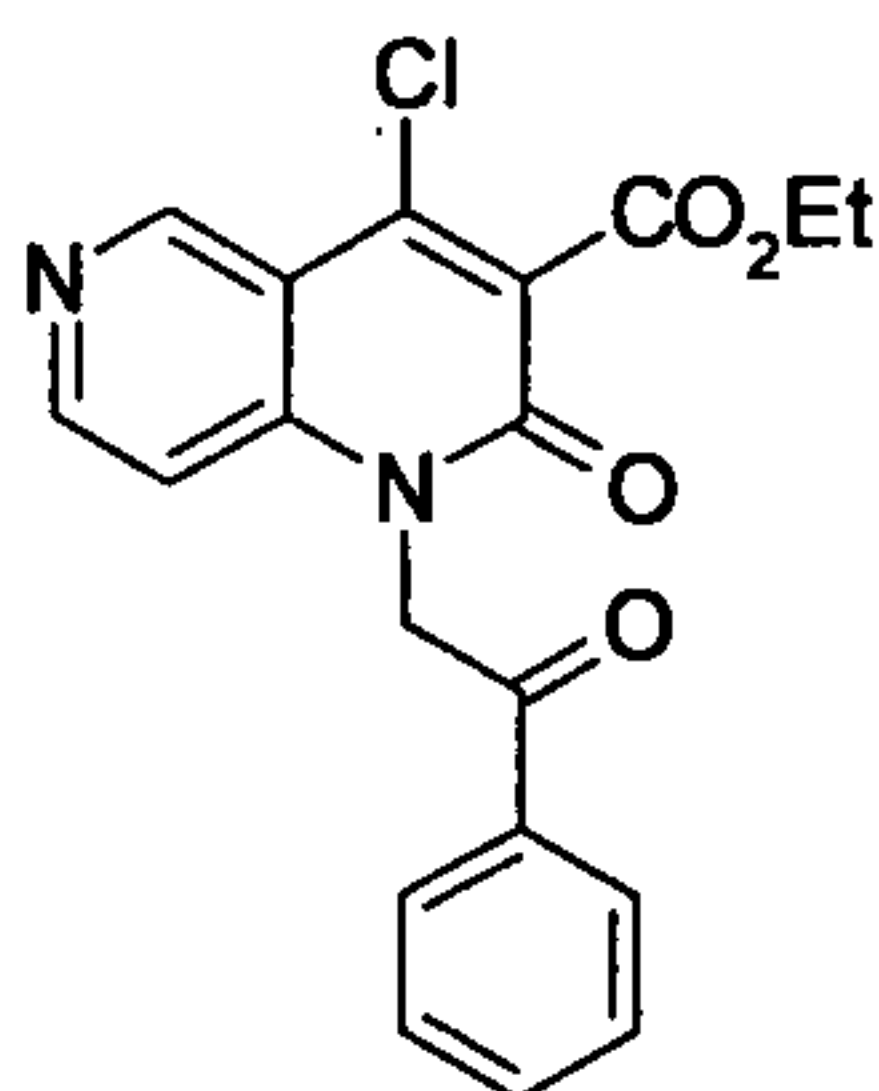
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.31 (3H, t, J = 7.1 Hz), 4.36 (2H, q, J = 7.1 Hz), 7.29 (1H, d, J = 5.7 Hz), 8.63 (1H, d, J = 5.7 Hz), 9.06 (1H, s), 12.72 (1H, br s).

25 [0608]

Reference Example 136

Production of ethyl 4-chloro-2-oxo-1-(2-oxo-2-phenylethyl)-1,2-dihydro-1,6-naphthyridine-3-carboxylate

[0609]



[0610]

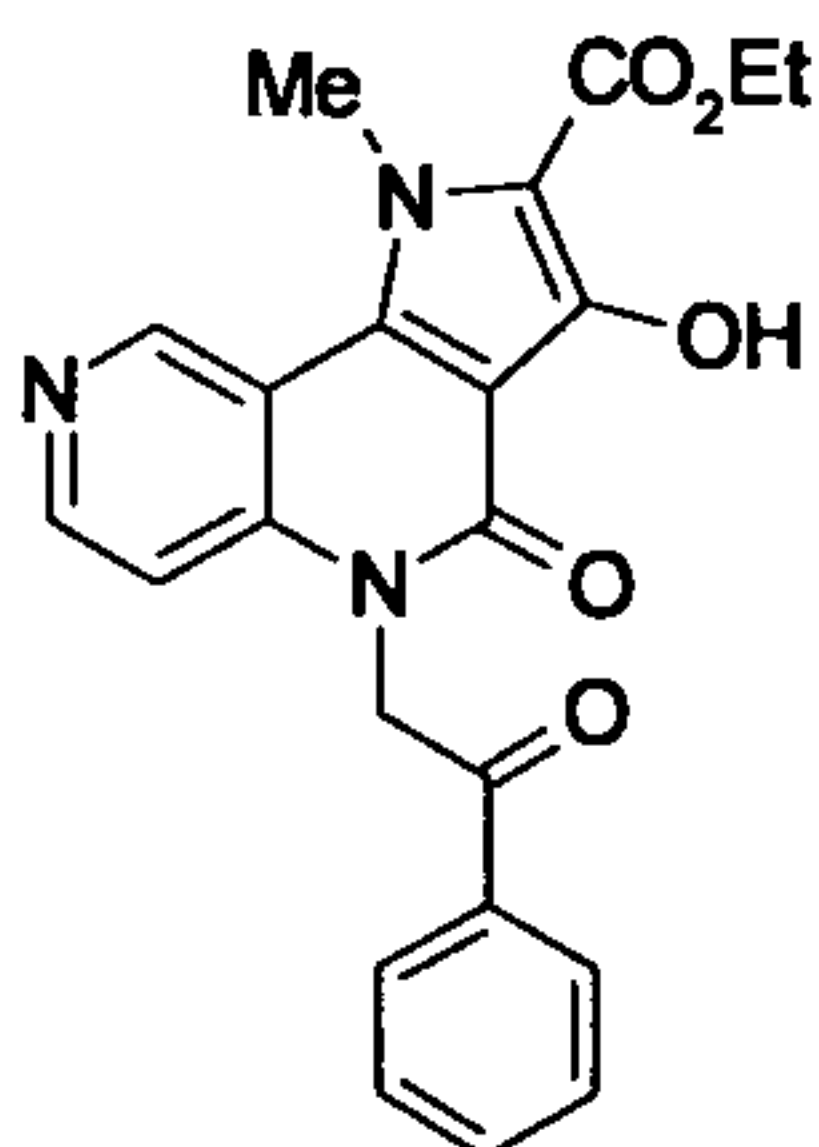
In the same manner as in Reference Example 4, the title compound (344 mg, 33%) was obtained as a pale-yellow solid
 5 from the compound of Reference Example 135 (710 mg, 2.8 mmol).
¹H-NMR (300 MHz, CDCl₃) δ: 1.42 (3H, t, J = 7.2 Hz), 4.48 (2H, q, J = 7.2 Hz), 5.73 (2H, s), 6.86 (1H, d, J = 5.9 Hz), 7.49–7.63 (2H, m), 7.64–7.79 (1H, m), 7.95–8.19 (2H, m), 8.64 (1H, br s), 9.30 (1H, br s).

10 [0611]

Reference Example 137

Production of ethyl 3-hydroxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c][1,6]naphthyridine-2-carboxylate

15 [0612]



[0613]

A mixture of the compound of Reference Example 136 (574 mg, 1.6 mmol), sarcosine ethyl ester hydrochloride (286 mg, 1.9 mmol), triethylamine (0.65 mL, 4.7 mmol), and ethanol (29
 20 mL) was heated under reflux for 2.5 hr. Sarcosine ethyl ester hydrochloride (286 mg, 1.9 mmol) and triethylamine (0.43 mL, 3.1 mmol) were further added and the mixture was heated under reflux for 5.5 hr. Sarcosine ethyl ester hydrochloride (286 mg,
 25 1.9 mmol) and triethylamine (0.65 mL, 4.7 mmol) were added and

the mixture was heated under reflux for 46 hr. Triethylamine (0.65 mL, 4.7 mmol) was added, and the mixture was heated under reflux for 3 hr. Triethylamine (0.65 mL, 4.7 mmol) was added and the mixture was heated under reflux for 64 hr.

5 Triethylamine (0.65 mL, 4.7 mmol) was further added and the mixture was heated under reflux for 3 hr. Triethylamine (0.65 mL, 4.7 mmol) was further added and the mixture was heated under reflux for 3 hr. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and

10 the mixture was acidified with 20% aqueous citric acid solution and stirred for 30 min under ice-cooling. The precipitated solid was collected by filtration, the obtained solid was washed with water, and dried under reduced pressure. The solid was washed with ethyl acetate-hexane mixed solvent

15 and hexane to give the title compound (485 mg, 77%) as a pale-brown powder.

$^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ : 1.34 (3H, t, $J = 7.1$ Hz), 4.27-4.43 (5H, m), 5.91 (2H, s), 7.42 (1H, d, $J = 6.0$ Hz), 7.58-7.69 (2H, m), 7.71-7.82 (1H, m), 8.08-8.23 (2H, m), 8.50 (1H, d, $J = 5.9$

20 Hz), 9.07 (1H, br s), 9.49 (1H, s).

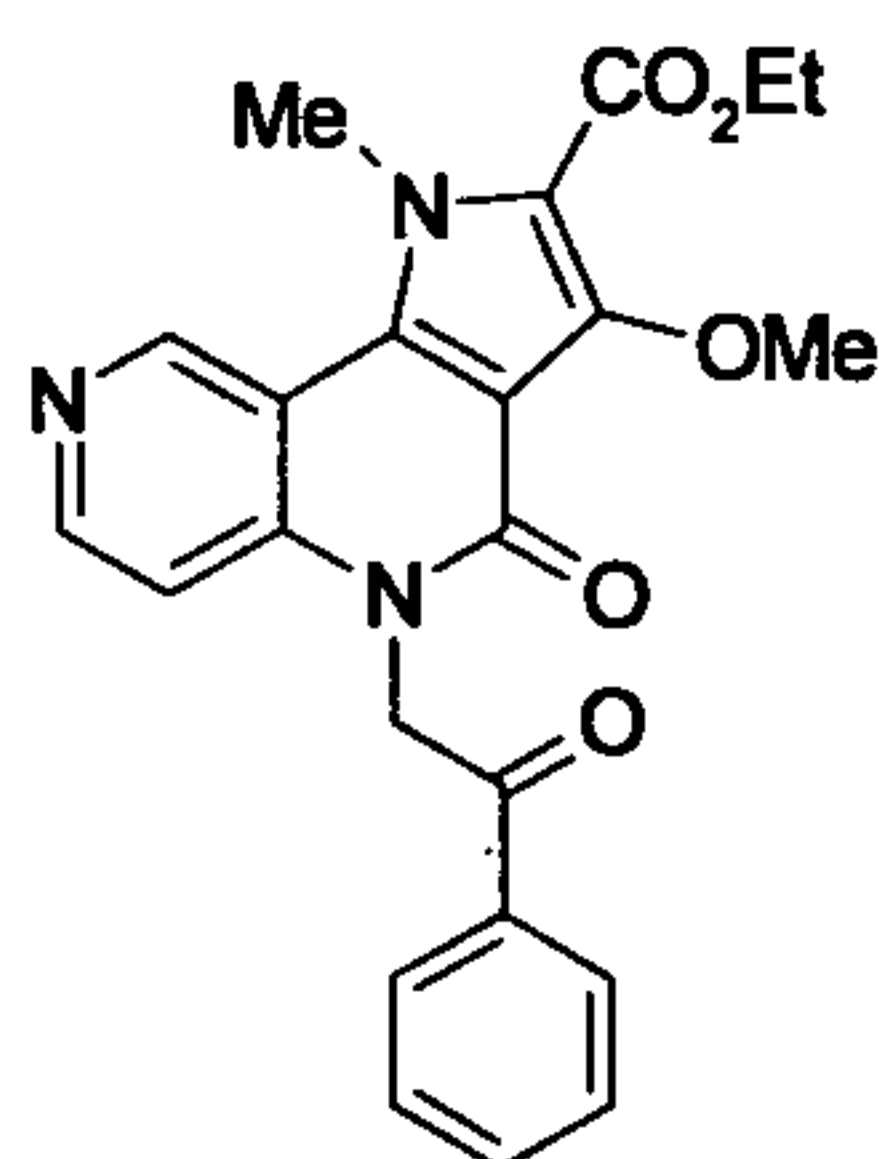
[0614]

Reference Example 138

Production of ethyl 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c][1,6]naphthyridine-2-carboxylate

25

[0615]



[0616]

In the same manner as in Reference Example 115, the title

30 compound (313 mg, 64%) was obtained as a white solid from the

compound of Reference Example 137 (471 mg, 1.2 mmol).

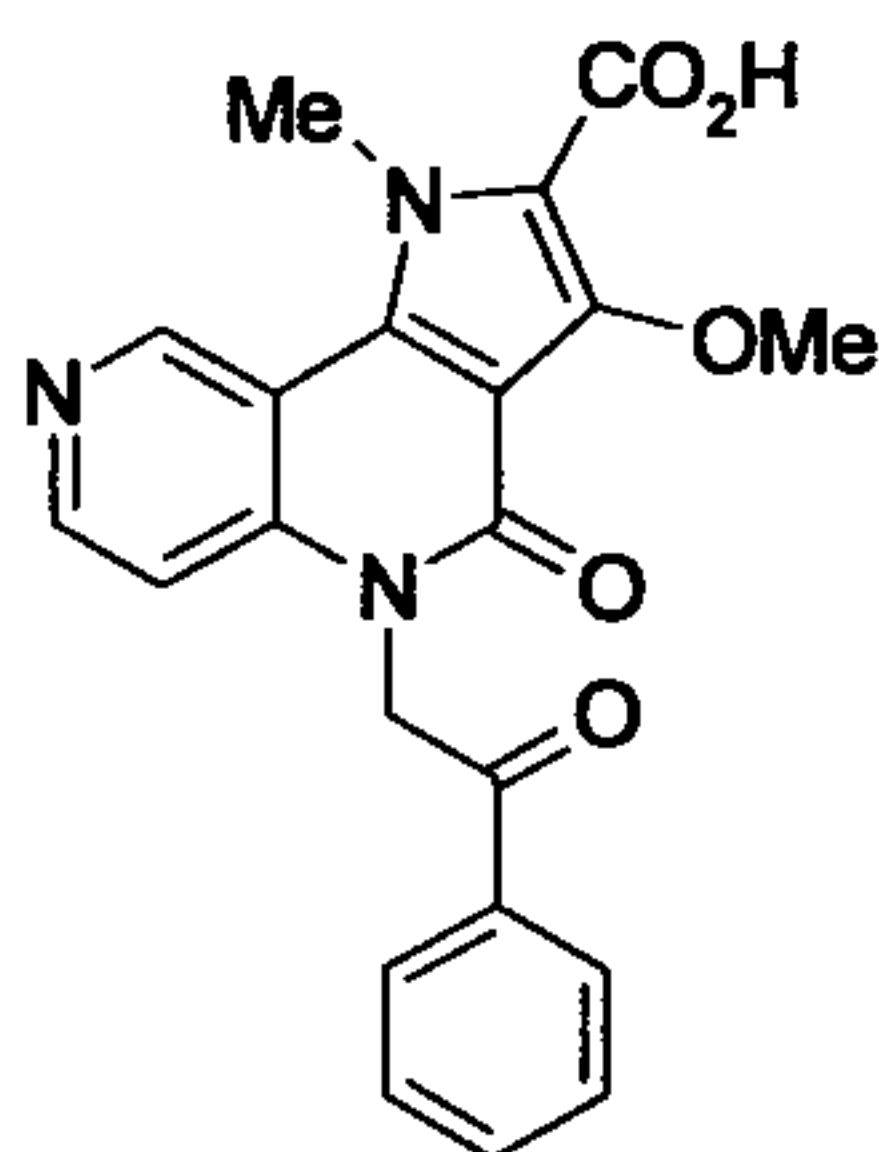
¹H-NMR (300 MHz, DMSO-*d*₆) δ: 1.35 (3H, t, J = 6.0 Hz), 3.88 (3H, s), 4.28-4.40 (5H, m), 5.94 (2H, s), 7.43 (1H, d, J = 6.0 Hz), 7.59-7.69 (2H, m), 7.72-7.82 (1H, m), 8.11-8.22 (2H, m), 8.51
5 (1H, d, J = 6.0 Hz), 9.52 (1H, s).

[0617]

Reference Example 139

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c][1,6]naphthyridine-
10 2-carboxylic acid

[0618]



[0619]

In the same manner as in Reference Example 7, the title
15 compound (259 mg, 92%) was obtained as a white solid from the compound of Reference Example 138 (301 mg, 0.72 mmol).

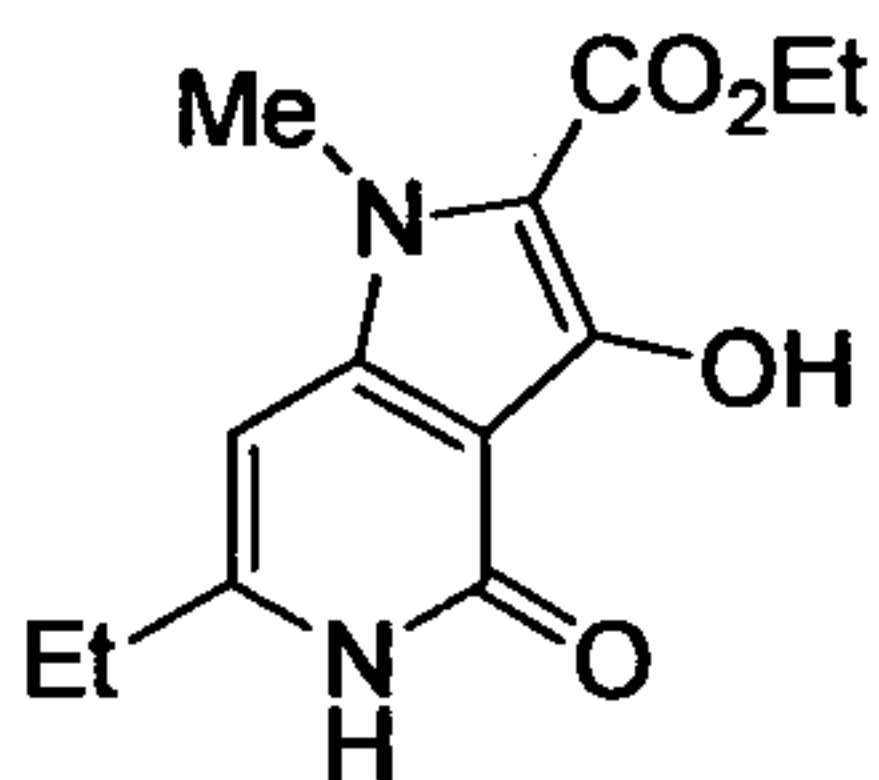
¹H-NMR (300 MHz, DMSO-*d*₆) δ: 3.87 (3H, s), 4.36 (3H, s), 5.94 (2H, s), 7.42 (1H, d, J = 6.0 Hz), 7.57-7.70 (2H, m), 7.71-7.83 (1H, m), 8.07-8.26 (2H, m), 8.49 (1H, d, J = 5.9 Hz),
20 9.51 (1H, s), 13.01 (1H, br s).

[0620]

Reference Example 140

Production of ethyl 6-ethyl-3-hydroxy-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

25 [0621]



[0622]

In the same manner as in Reference Example 40, the title compound (4.87 g, 85%) was obtained as a brown powder from the compound of Reference Example 38 (5.00 g, 21.8 mmol).

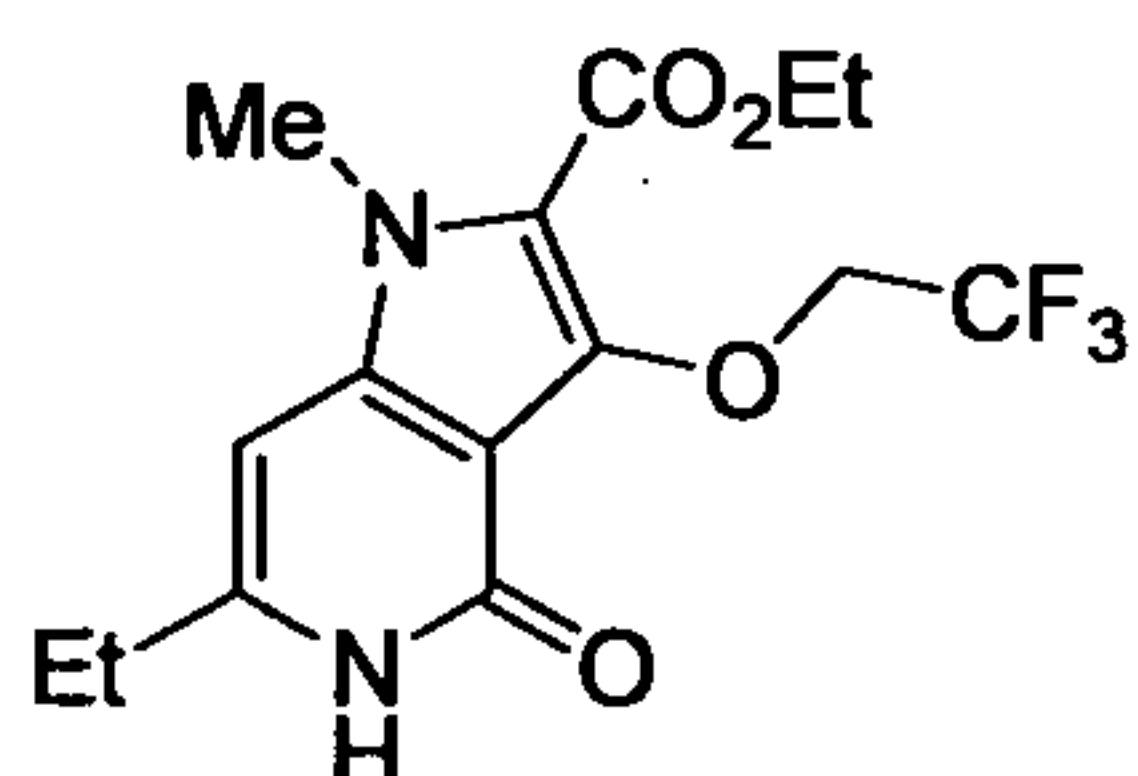
¹H-NMR (300 MHz, DMSO-d₆) δ:1.18 (3H, t, J = 7.6 Hz), 1.30 (3H, t, J = 7.1 Hz), 2.39-2.49 (2H, m), 3.73 (3H, s), 4.29 (2H, q, J = 7.1 Hz), 6.25 (1H, s), 8.87 (1H, br s), 10.81 (1H, br s).

[0623]

Reference Example 141

Production of ethyl 6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0624]



[0625]

A mixture of the compound of Reference Example 140 (200 mg, 0.757 mmol), cesium carbonate (271 mg, 0.832 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.109 mL, 0.757 mmol), dimethyl sulfoxide (2.0 mL) and DMF (2.0 mL) was stirred at 60°C for 2 hr. The reaction mixture was diluted with water, and the precipitated solid was collected by filtration. The obtained solid was washed with water and diisopropyl ether, and dried under reduced pressure to give the title compound (161 mg, 61%) as a white solid.

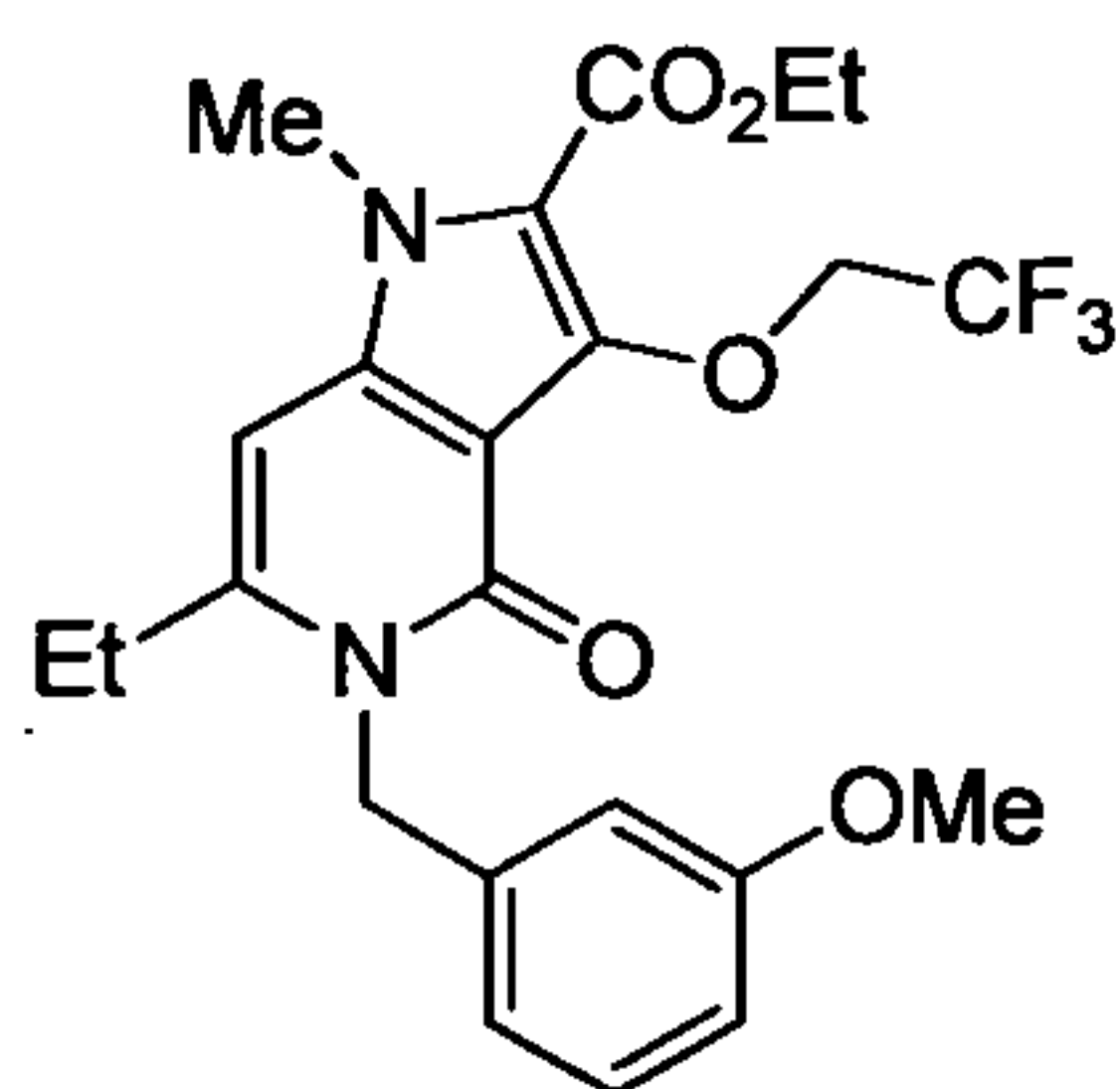
¹H-NMR (300 MHz, DMSO-d₆) δ:1.19 (3H, t, J = 7.5 Hz), 1.27 (3H, t, J = 7.0 Hz), 2.51-2.56 (2H, m), 3.79 (3H, s), 4.24 (2H, q, J = 7.0 Hz), 4.97 (2H, q, J = 9.3 Hz), 6.38 (1H, s), 11.06 (1H, br s).

[0626]

Reference Example 142

Production of ethyl 6-ethyl-5-(3-methoxybenzyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0627]



[0628]

A mixture of the compound of Reference Example 141 (500
 5 mg, 1.44 mmol), sodium tert-butoxide (180 mg, 1.87 mmol),
 lithium bromide (250 mg, 2.88 mmol), 1-(chloromethyl)-3-
 methoxybenzene (0.313 mL, 2.16 mmol), DME (8.0 mL) and DMF
 (2.0 mL) was stirred at 60°C for 13 hr. Water (50 mL) was
 added to the reaction mixture, and the mixture was extracted
 10 with ethyl acetate. The extract was washed with brine, dried
 over sodium sulfate, and concentrated under reduced pressure.
 The residue was purified by silica gel chromatography (eluate;
 ethyl acetate/hexane=3/97 - 70/30) to give the title compound
 (508 mg, 76%) as a yellow oil.

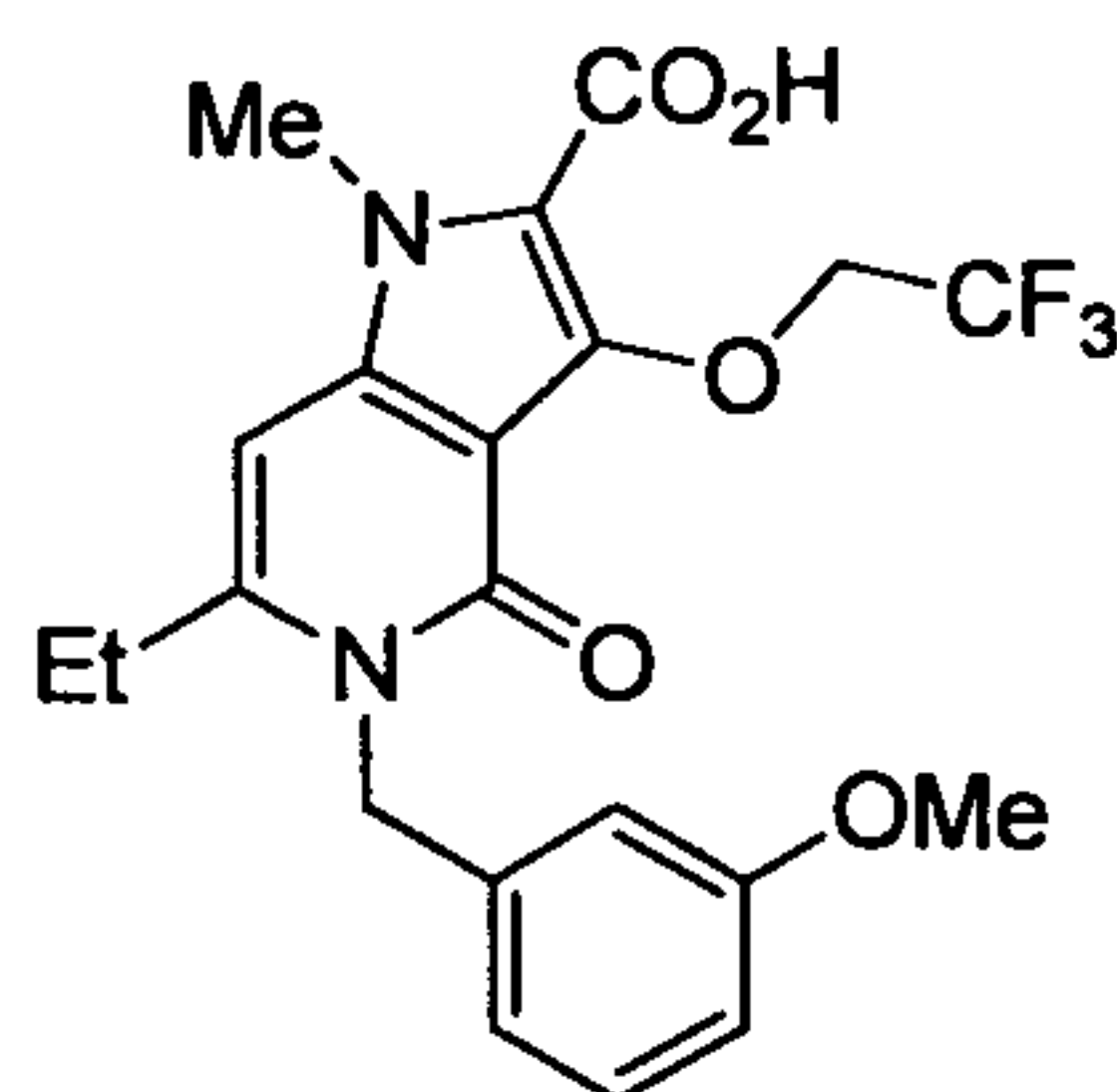
15 ¹H-NMR (300 MHz, DMSO-d₆) δ:1.14-1.36 (6H, m), 2.60 (2H, q, J =
 7.2 Hz), 3.70 (3H, s), 3.85 (3H, s), 4.26 (2H, q, J = 7.2 Hz),
 4.89 (2H, q, J = 9.3 Hz), 5.28 (2H, br s), 6.44-6.67 (3H, m),
 6.74-6.95 (1H, m), 7.22 (1H, t, J = 7.9 Hz).

[0629]

20 Reference Example 143

Production of 6-ethyl-5-(3-methoxybenzyl)-1-methyl-4-oxo-3-
 (2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-
 2-carboxylic acid

[0630]



25

[0631]

In the same manner as in Reference Example 49, the title

compound (333 mg, 66%) was obtained as a white powder from the compound of Reference Example 142 (508 mg, 1.09 mmol).

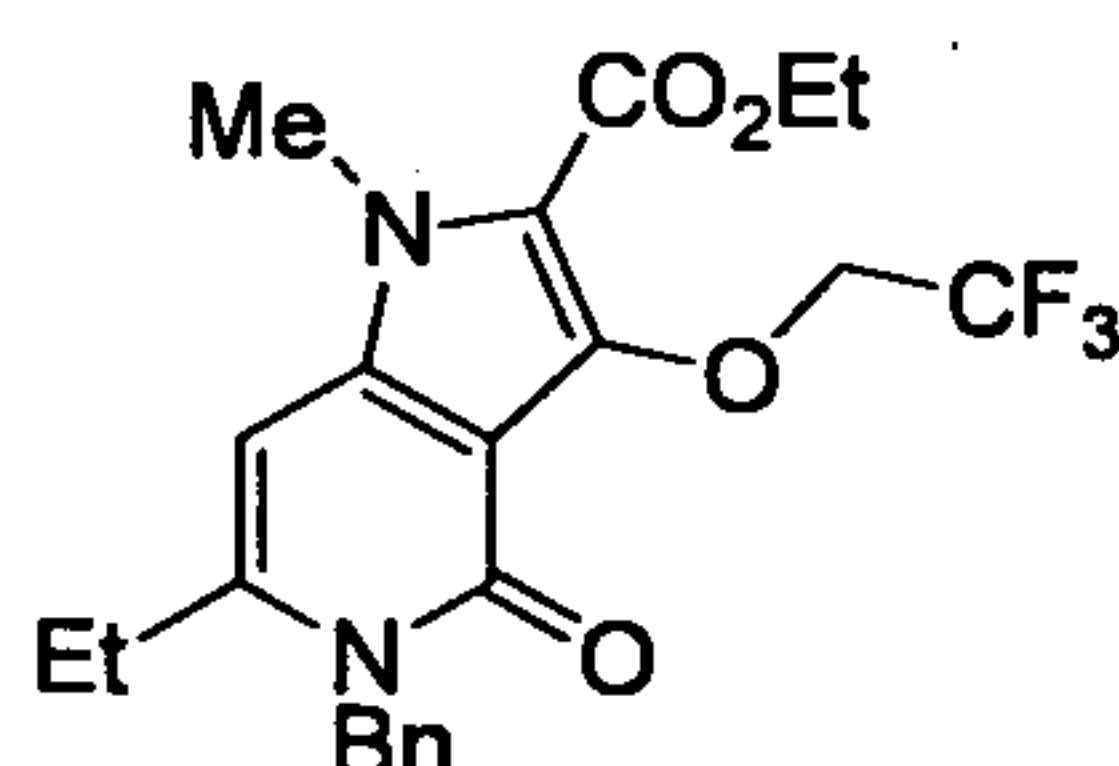
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.17 (3H, t, J = 7.3 Hz), 2.60 (2H, q, J = 7.3 Hz), 3.70 (3H, s), 3.85 (3H, s), 4.87 (2H, q, J = 9.4 Hz), 5.30 (2H, br s), 6.43-6.67 (3H, m), 6.81 (1H, dd, J = 7.9, 2.3 Hz), 7.22 (1H, t, J = 7.9 Hz), 12.70 (1H, br s).

[0632]

Reference Example 144

Production of ethyl 5-benzyl-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0633]



[0634]

In the same manner as in Reference Example 142, the title compound (312 mg, 62%) was obtained as a yellow oil from the compound of Reference Example 141 (400 mg, 1.16 mmol) and benzyl bromide (0.207 mL, 1.74 mmol).

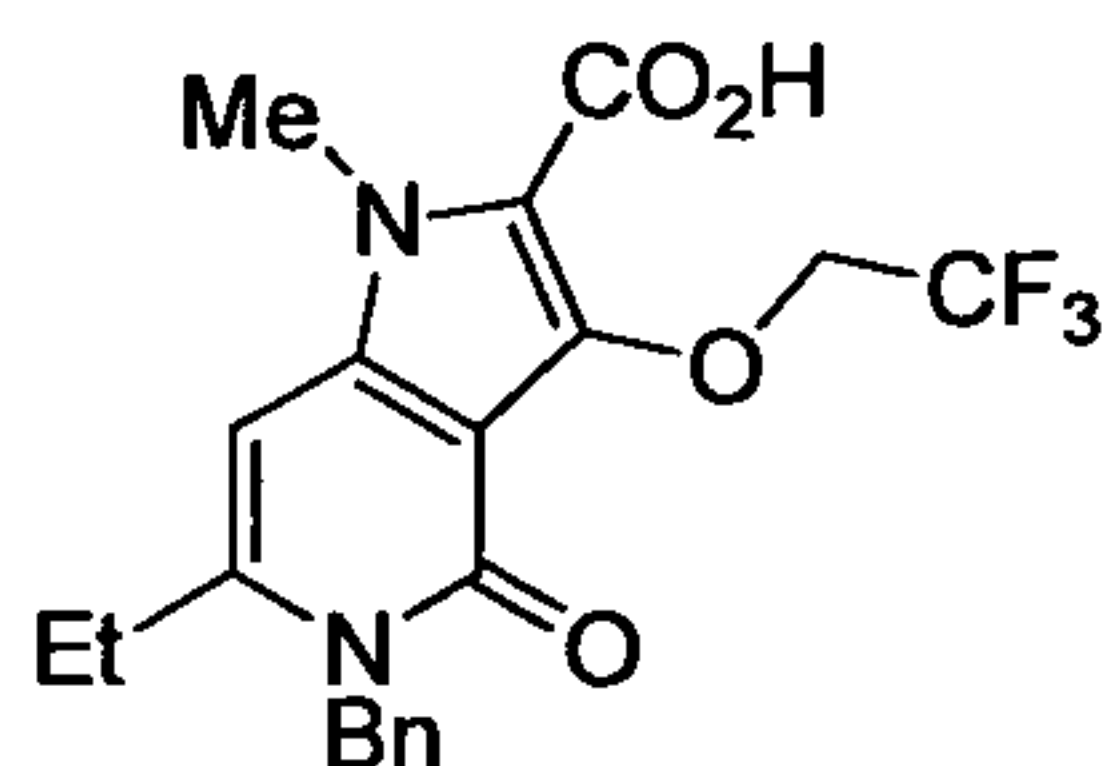
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.16 (3H, t, J = 7.3 Hz), 1.29 (3H, t, J = 7.1 Hz), 2.61 (2H, q, J = 7.3 Hz), 3.85 (3H, s), 4.26 (2H, q, J = 7.1 Hz), 4.89 (2H, q, J = 9.3 Hz), 5.34 (2H, br s), 6.54 (1H, s), 7.03-7.09 (2H, m), 7.20-7.27 (1H, m), 7.28-7.36 (2H, m).

[0635]

Reference Example 145

Production of 5-benzyl-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0636]



[0637]

In the same manner as in Reference Example 49, the title compound (213 mg, 73%) was obtained as a white powder from the compound of Reference Example 144 (312 mg, 0.715 mmol).

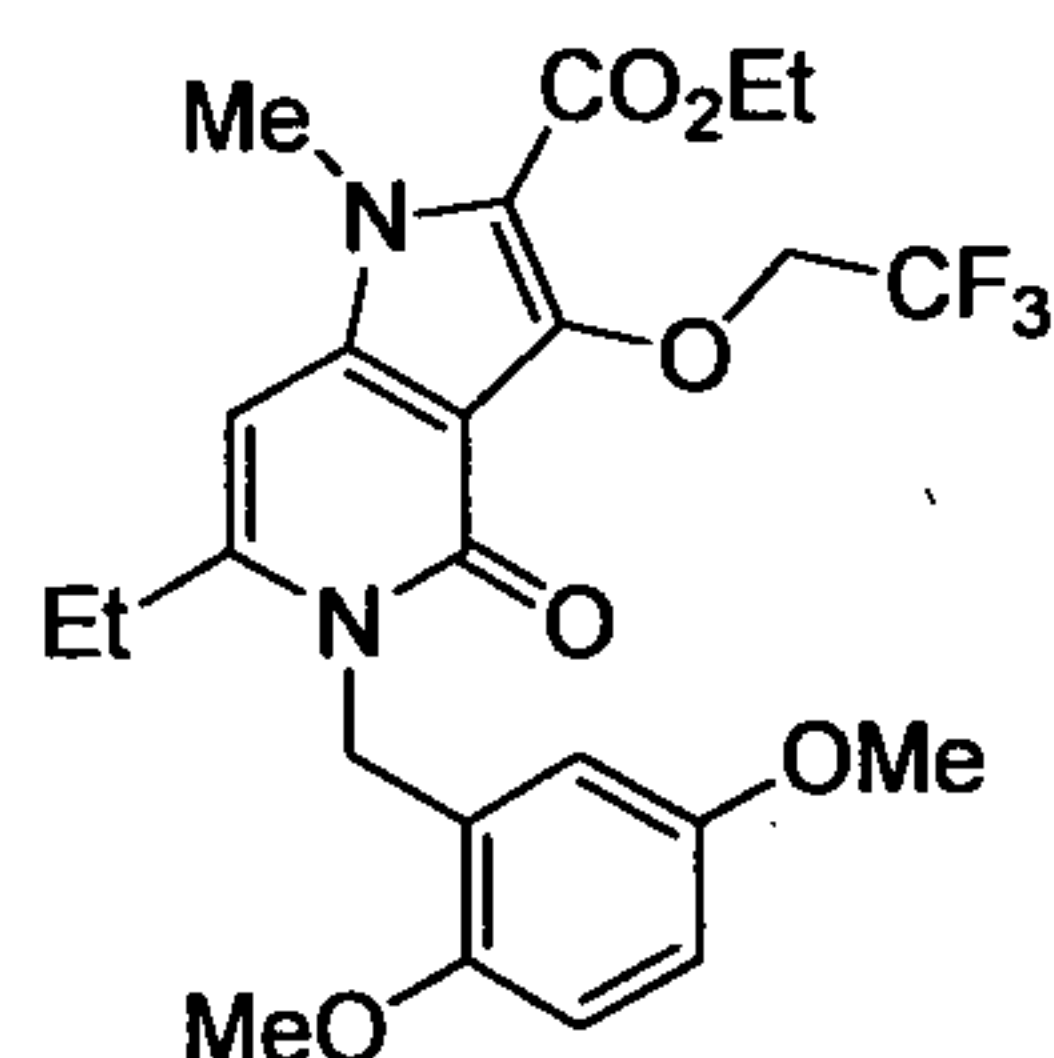
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.16 (3H, t, J = 7.3 Hz), 2.60 (2H, q, J = 7.3 Hz), 3.85 (3H, s), 4.87 (2H, q, J = 9.3 Hz), 5.34 (2H, br s), 6.52 (1H, s), 7.01-7.10 (2H, m), 7.17-7.39 (3H, m), 12.73 (1H, br s).

10 [0638]

Reference Example 146

Production of ethyl 5-(2,5-dimethoxybenzyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

15 [0639]



[0640]

In the same manner as in Reference Example 142, the title compound (121 mg, 21%) was obtained as a white powder from the compound of Reference Example 141 (400 mg, 1.16 mmol) and 2-(chloromethyl)-1,4-dimethoxybenzene (325 mg, 1.74 mmol).

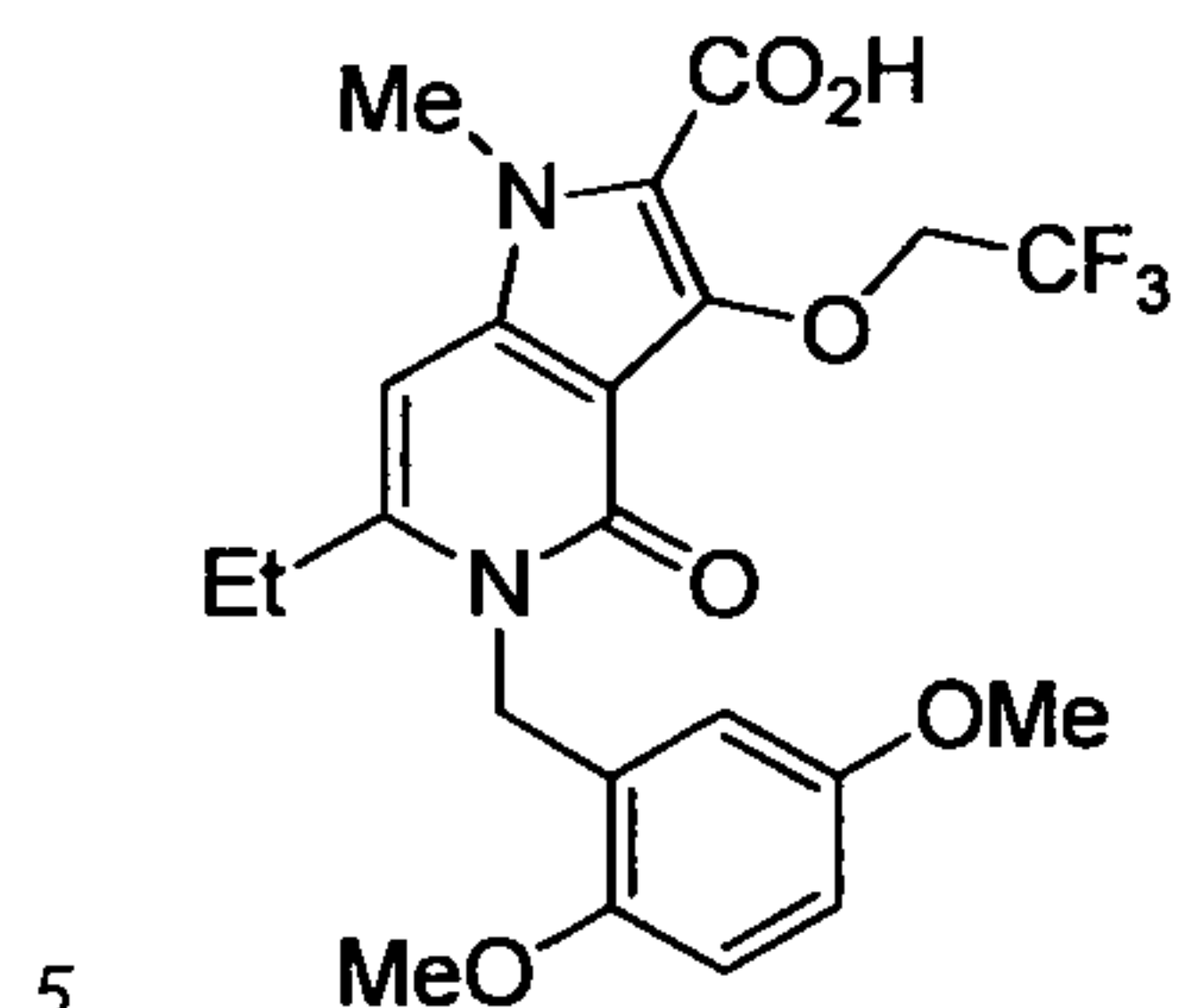
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.17 (3H, t, J = 7.3 Hz), 1.29 (3H, t, J = 7.2 Hz), 2.53-2.61 (2H, m), 3.56 (3H, s), 3.83 (3H, s), 3.86 (3H, s), 4.26 (2H, q, J = 7.2 Hz), 4.87 (2H, q, J = 9.3 Hz), 5.19 (2H, br s), 5.93 (1H, d, J = 3.0 Hz), 6.58 (1H, s), 6.79 (1H, dd, J = 8.9, 3.0 Hz), 6.97 (1H, d, J = 8.9 Hz).

[0641]

Reference Example 147

Production of 5-(2,5-dimethoxybenzyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0642]



[0643]

In the same manner as in Reference Example 49, the title compound (82.7 mg, 72%) was obtained as a white powder from the compound of Reference Example 146 (121 mg, 0.244 mmol).

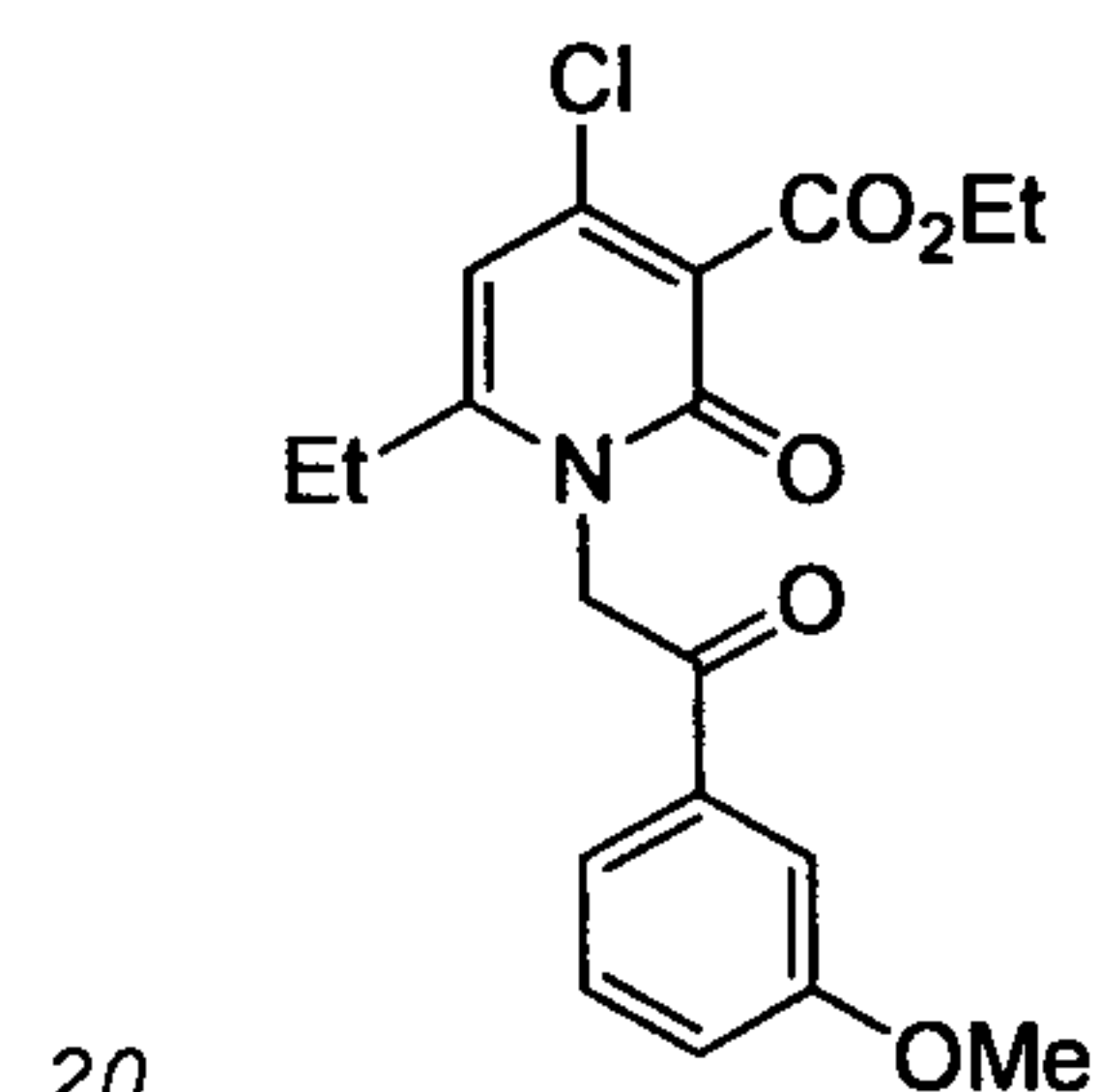
10 ¹H-NMR (300 MHz, DMSO-d₆) δ:1.17 (3H, t, J = 7.3 Hz), 2.52-2.60 (2H, m), 3.56 (3H, s), 3.83 (3H, s), 3.86 (3H, s), 4.85 (2H, q, J = 9.3 Hz), 5.19 (2H, br s), 5.92 (1H, d, J = 3.0 Hz), 6.56 (1H, s), 6.79 (1H, dd, J = 9.0, 3.0 Hz), 6.97 (1H, d, J = 9.0 Hz), 12.74 (1H, br s).

15 [0644]

Reference Example 148

Production of ethyl 4-chloro-6-ethyl-1-[2-(3-methoxyphenyl)-2-oxoethyl]-2-oxo-1,2-dihydropyridine-3-carboxylate

[0645]



[0646]

In the same manner as in Reference Example 142, the title compound (879 mg, 53%) was obtained as a yellow oil from the compound of Reference Example 38 (1.00 g, 4.35 mmol) and 2-bromo-1-(3-methoxyphenyl)ethanone (1.99 g, 8.71 mmol).

¹H-NMR (300 MHz, DMSO-d₆) δ:1.13 (3H, t, J = 7.4 Hz), 1.24 (3H,

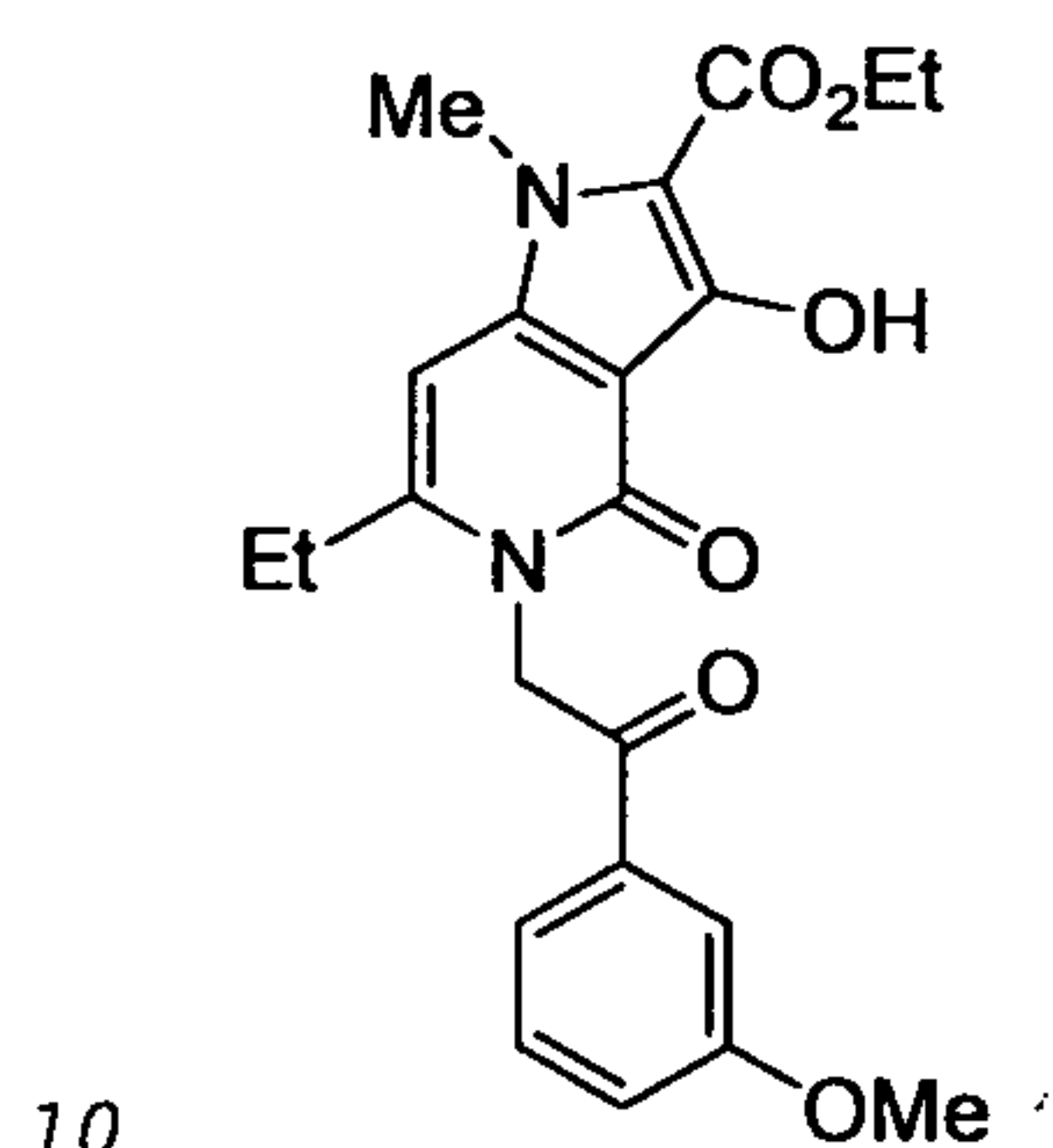
t, J = 7.1 Hz), 2.61 (2H, q, J = 7.4 Hz), 3.85 (3H, s), 4.25 (2H, q, J = 7.1 Hz), 5.60 (2H, s), 6.44 (1H, s), 7.28-7.35 (1H, m), 7.48-7.59 (2H, m), 7.66-7.74 (1H, m).

[0647]

5 Reference Example 149

Production of ethyl 6-ethyl-3-hydroxy-5-[2-(3-methoxyphenyl)-2-oxoethyl]-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0648]



[0649]

In the same manner as in Reference Example 40, the title compound (526 mg, 55%) was obtained as a green powder from the compound of Reference Example 148 (879 mg, 2.33 mmol).

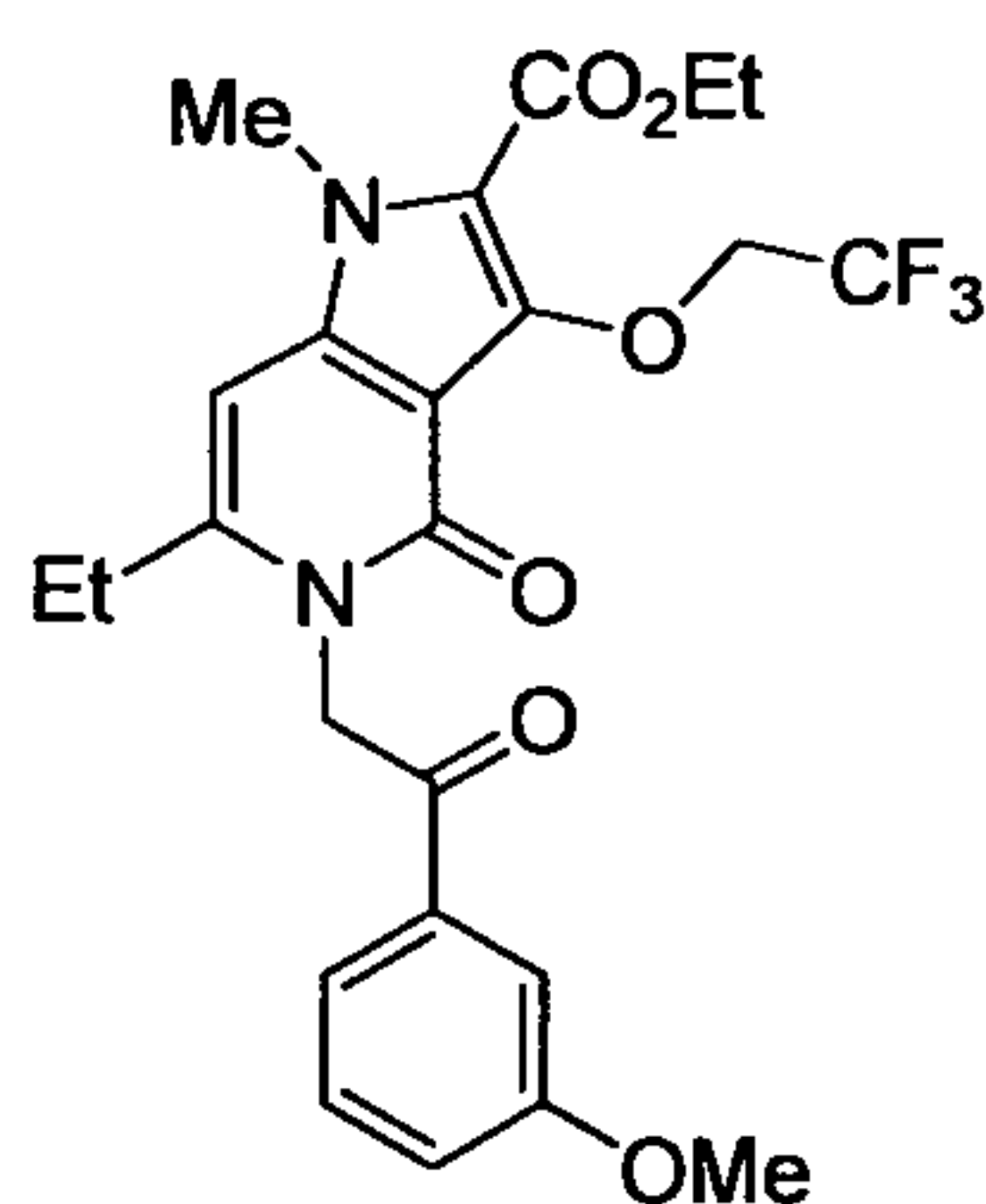
15 ¹H-NMR (300 MHz, DMSO-d₆) δ: 1.18 (3H, t, J = 7.4 Hz), 1.31 (3H, t, J = 7.1 Hz), 2.52-2.61 (2H, m), 3.80 (3H, s), 3.85 (3H, s), 4.30 (2H, q, J = 7.1 Hz), 5.54 (2H, s), 6.43 (1H, s), 7.26-7.36 (1H, m), 7.48-7.60 (2H, m), 7.68-7.76 (1H, m), 8.89 (1H, br s).

20 [0650]

Reference Example 150

Production of ethyl 6-ethyl-5-[2-(3-methoxyphenyl)-2-oxoethyl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

25 [0651]



[0652]

A mixture of the compound of Reference Example 149 (470 mg, 1.14 mmol), cesium carbonate (446 mg, 1.37 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.197 mL, 1.37 mmol) and DMF (4.7 mL) was stirred at room temperature for 1 hr. The reaction mixture was diluted with water, and the precipitated solid was collected by filtration. The obtained solid was washed with water, diisopropyl ether and ethanol, and dried under reduced pressure to give the title compound (423 mg, 75%) as a green powder.

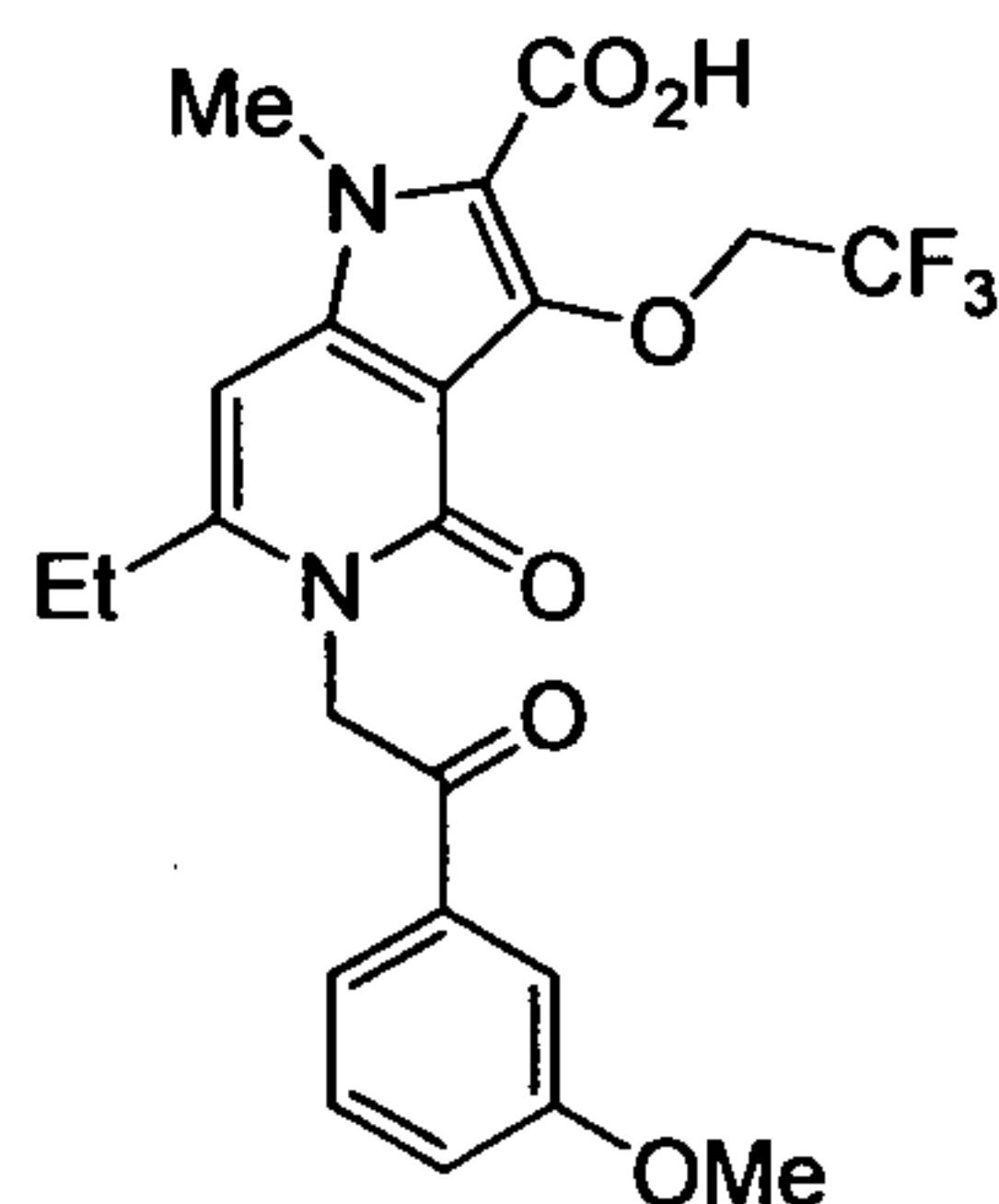
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.19 (3H, t, J = 7.3 Hz), 1.28 (3H, t, J = 7.2 Hz), 2.59 (2H, q, J = 7.3 Hz), 3.83-3.90 (6H, m), 4.26 (2H, q, J = 7.2 Hz), 4.83 (2H, q, J = 9.3 Hz), 5.61 (2H, s), 6.55 (1H, s), 7.27-7.34 (1H, m), 7.48-7.61 (2H, m), 7.68-7.76 (1H, m).

[0653]

Reference Example 151

Production of 6-ethyl-5-[2-(3-methoxyphenyl)-2-oxoethyl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0654]



[0655]

In the same manner as in Reference Example 49, the title

compound (300 mg, 86%) was obtained as a brown powder from the compound of Reference Example 150 (370 mg, 0.748 mmol).

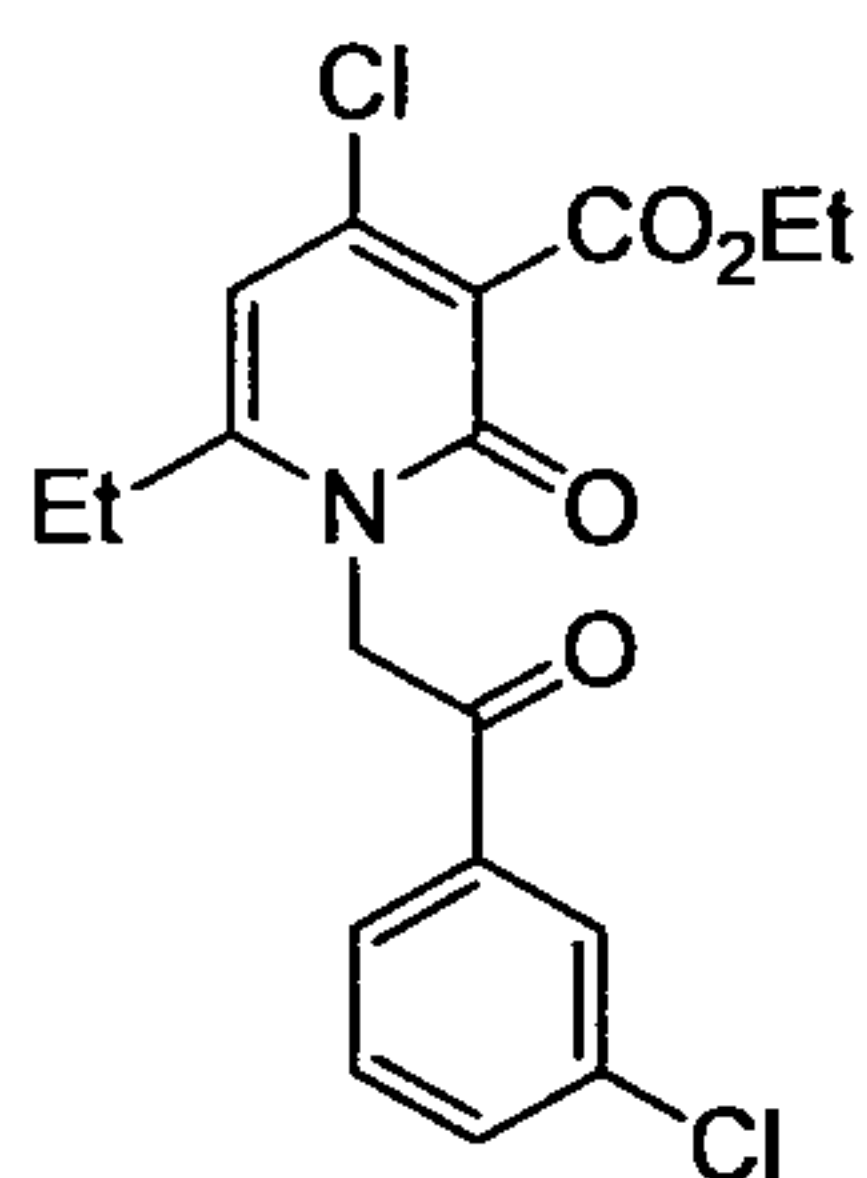
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.19 (3H, t, J = 7.3 Hz), 2.58 (2H, q, J = 7.3 Hz), 3.83-3.91 (6H, m), 4.82 (2H, q, J = 9.3 Hz),
5 5.60 (2H, s), 6.54 (1H, s), 7.26-7.37 (1H, m), 7.47-7.62 (2H, m), 7.67-7.83 (1H, m), 12.70 (1H, br s).

[0656]

Reference Example 152

Production of ethyl 4-chloro-1-[2-(3-chlorophenyl)-2-oxoethyl]-6-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylate
10

[0657]



[0658]

In the same manner as in Reference Example 142, the title
15 compound (486 mg, 29%) was obtained as a white powder from the compound of Reference Example 38 (1.50 g, 6.53 mmol) and 2-bromo-1-(3-chlorophenyl)ethanone (2.02 g, 8.65 mmol).

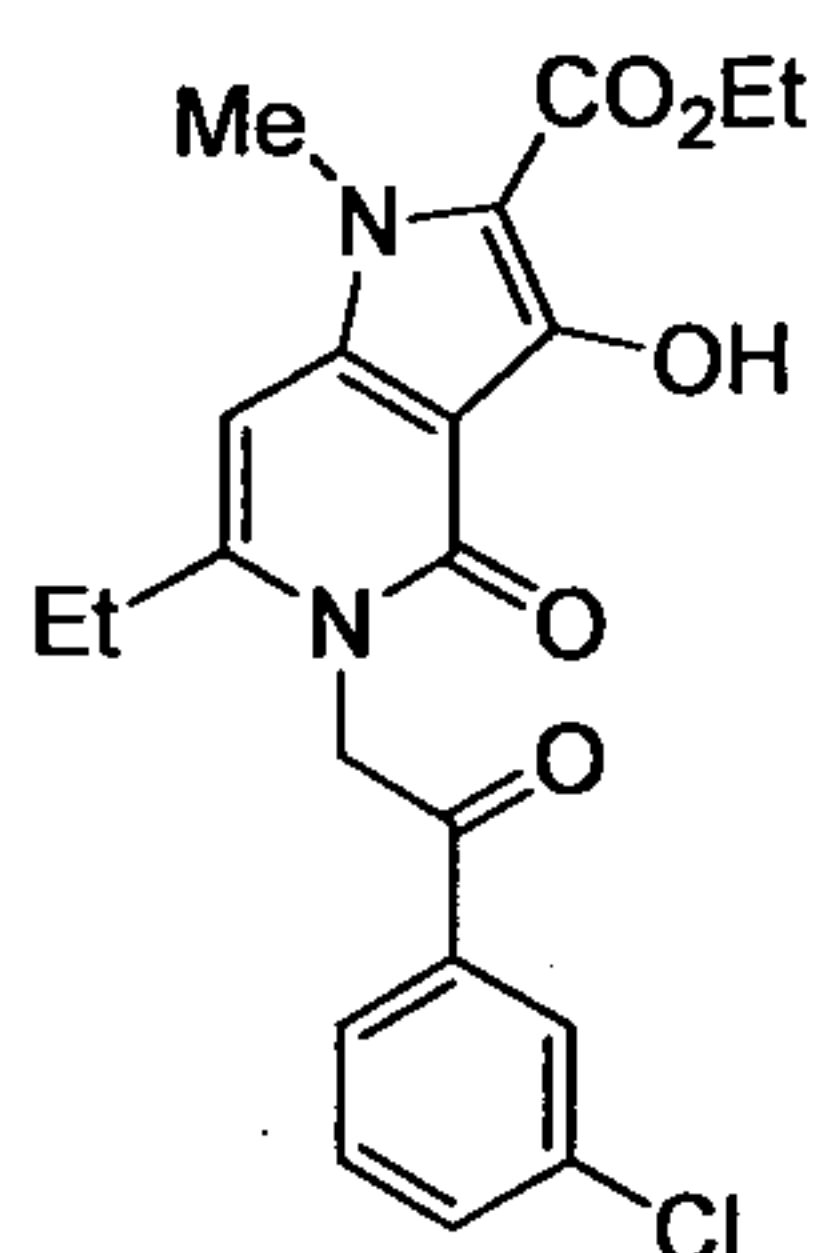
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.14 (3H, t, J = 7.4 Hz), 1.24 (3H, t, J = 7.1 Hz), 2.63 (2H, q, J = 7.4 Hz), 4.25 (2H, q, J = 7.1
20 Hz), 5.61 (2H, s), 6.45 (1H, s), 7.59-7.70 (1H, m), 7.77-7.86 (1H, m), 8.00-8.07 (1H, m), 8.08-8.17 (1 H, m).

[0659]

Reference Example 153

Production of ethyl 5-[2-(3-chlorophenyl)-2-oxoethyl]-6-ethyl-3-hydroxy-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate
25

[0660]



[0661]

In the same manner as in Reference Example 40, the title compound (460 mg, 87%) was obtained as a green powder from the compound of Reference Example 152 (486 mg, 1.27 mmol).

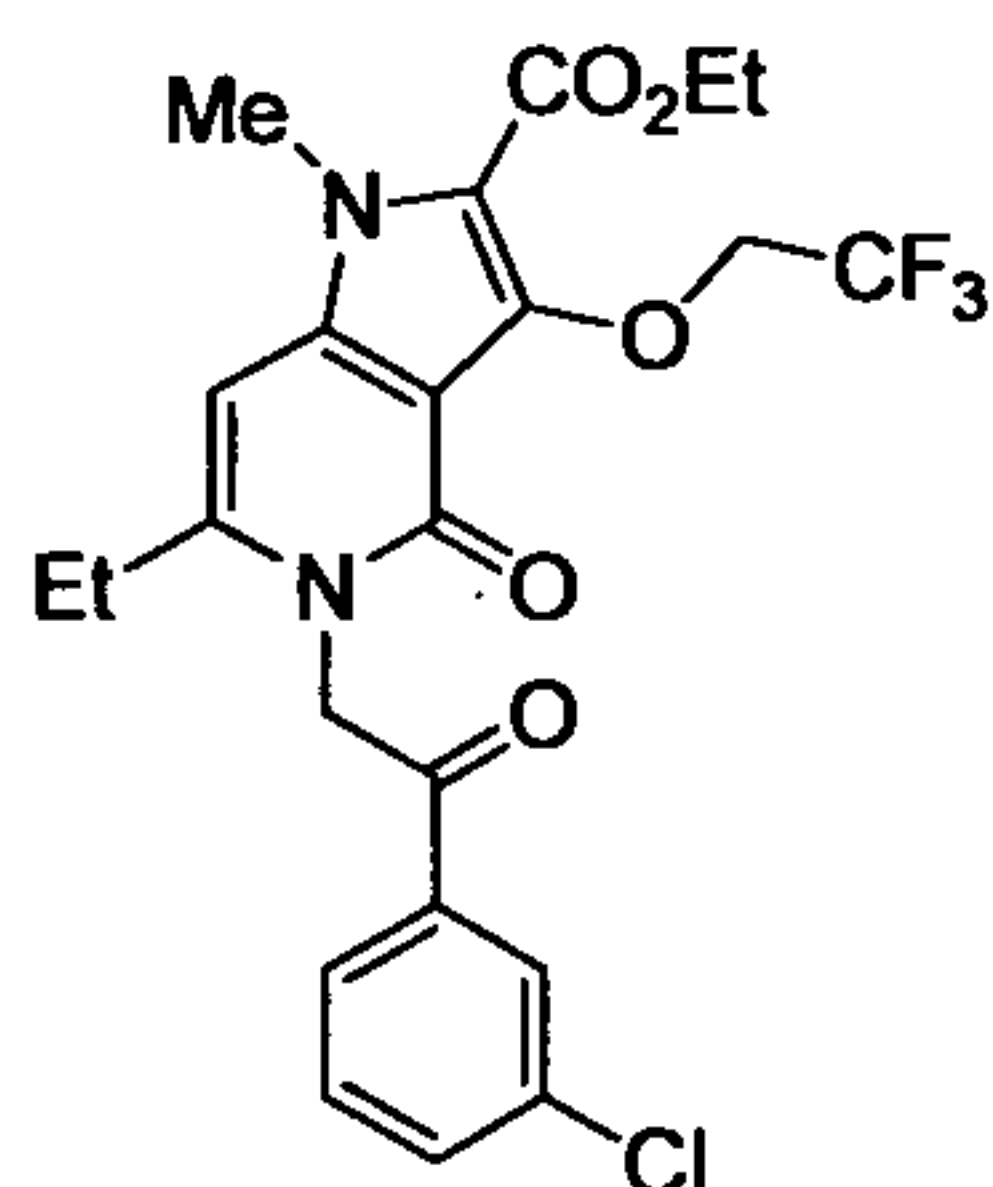
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.18 (3H, t, J = 7.4 Hz), 1.31 (3H, t, J = 7.0 Hz), 2.57 (2H, q, J = 7.4 Hz), 3.80 (3H, s), 4.30 (2H, q, J = 7.0 Hz), 5.53 (2H, s), 6.44 (1H, s), 7.61–7.68 (1H, m), 7.80 (1H, ddd, J = 7.8, 2.0, 0.9 Hz), 8.05 (1H, dt, J = 7.8, 0.9 Hz), 8.13 (1H, t, J = 2.0 Hz), 8.90 (1H, s).

[0662]

Reference Example 154

Production of ethyl 5-[2-(3-chlorophenyl)-2-oxoethyl]-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0663]



[0664]

In the same manner as in Reference Example 150, the title compound (348 mg, 63%) was obtained as a green powder from the compound of Reference Example 153 (460 mg, 1.10 mmol).

¹H-NMR (300 MHz, DMSO-d₆) δ: 1.19 (3H, t, J = 7.3 Hz), 1.28 (3H, t, J = 7.1 Hz), 2.60 (2H, q, J = 7.3 Hz), 3.86 (3H, s), 4.26 (2H, q, J = 7.1 Hz), 4.83 (2H, q, J = 9.3 Hz), 5.61 (2H, s), 6.56 (1H, s), 7.61–7.69 (1H, m), 7.78–7.84 (1H, m), 8.03–8.09

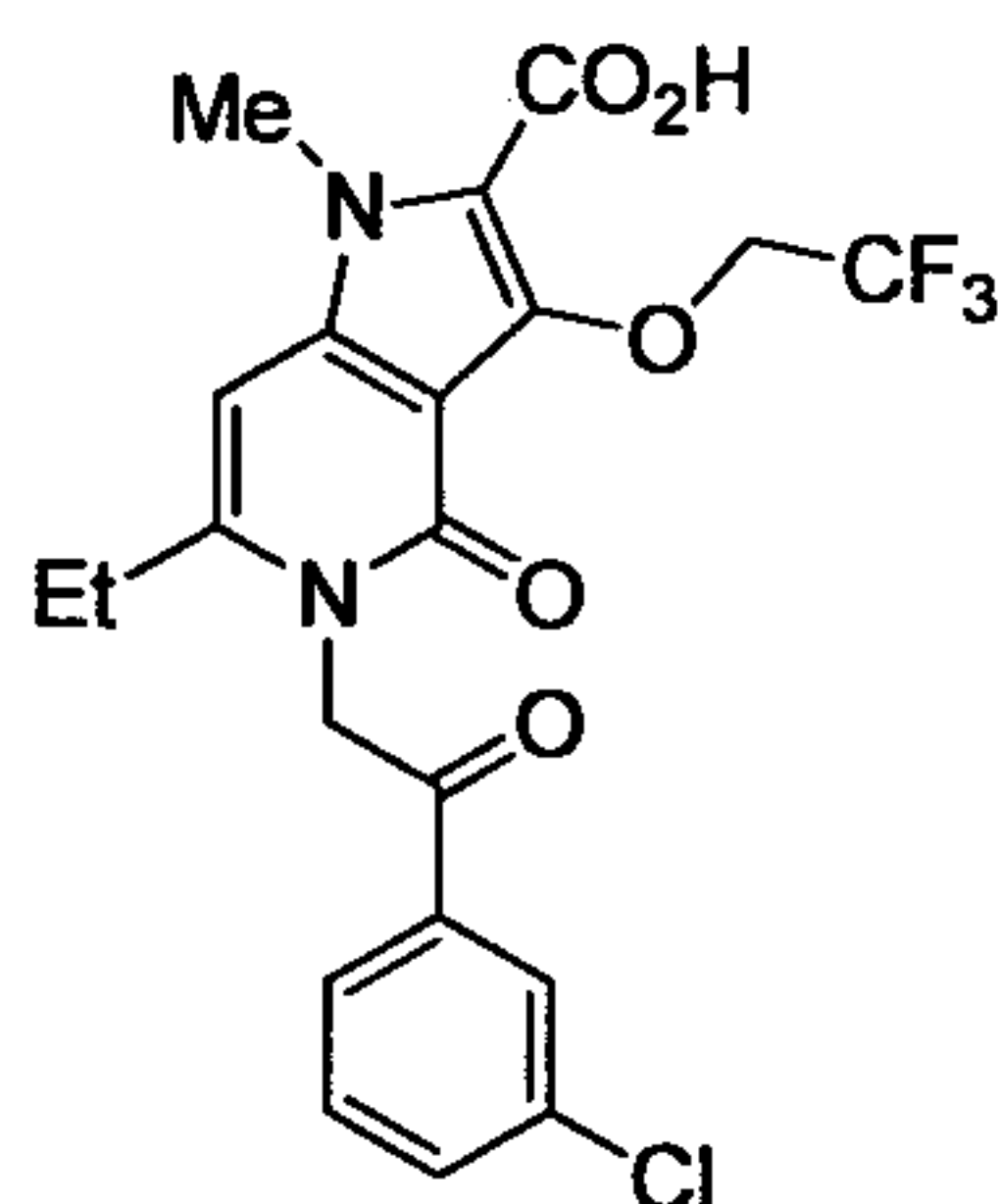
(1H, m), 8.14 (1H, t, J = 1.7 Hz).

[0665]

Reference Example 155

Production of 5-[2-(3-chlorophenyl)-2-oxoethyl]-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0666]



[0667]

10 In the same manner as in Reference Example 49, the title compound (192 mg, 59%) was obtained as a brown powder from the compound of Reference Example 154 (348 mg, 0.698 mmol).

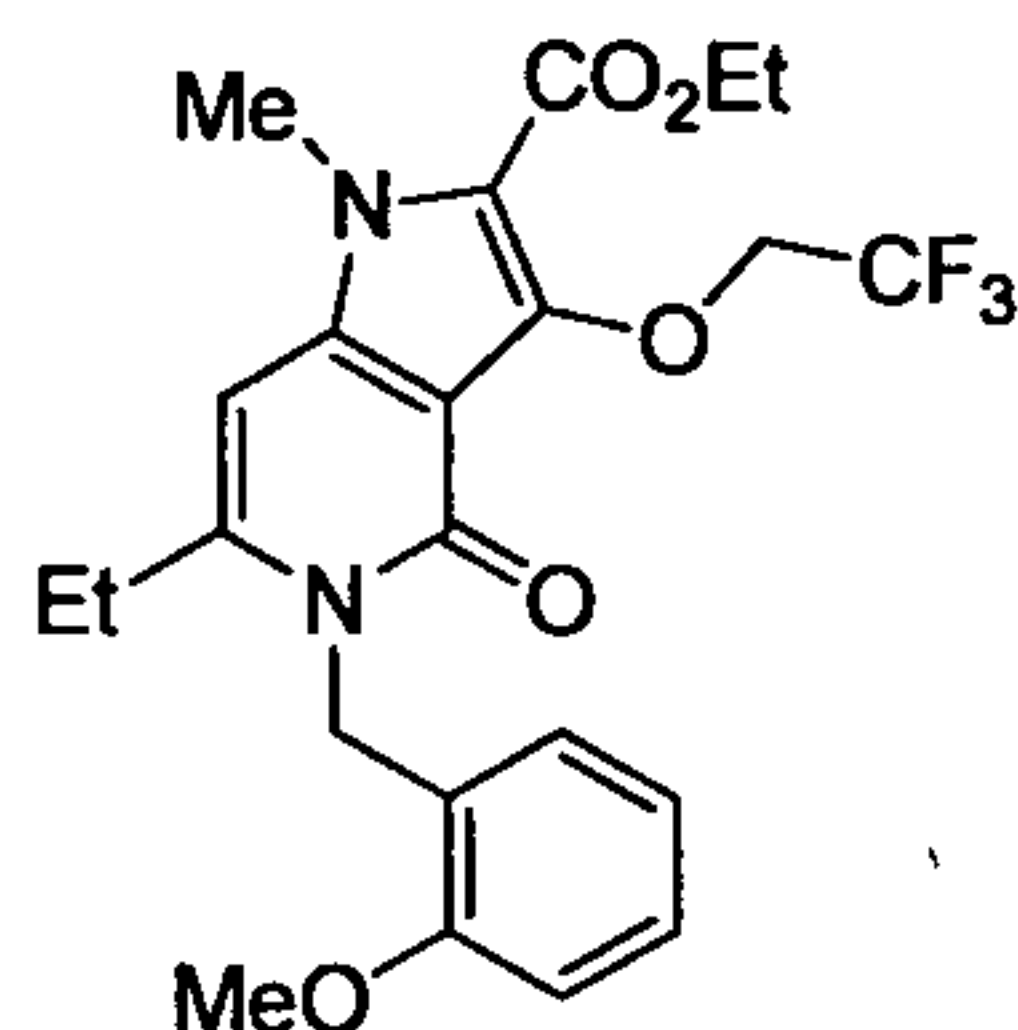
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.19 (3H, t, J = 7.3 Hz), 2.60 (2H, q, J = 7.3 Hz), 3.86 (3H, s), 4.81 (2H, q, J = 9.2 Hz), 5.60
15 (2H, s), 6.55 (1H, s), 7.58-7.71 (1H, m), 7.76-7.86 (1H, m), 8.00-8.10 (1H, m), 8.14 (1H, t, J = 1.7 Hz), 12.72 (1H, br s).

[0668]

Reference Example 156

Production of ethyl 6-ethyl-5-(2-methoxybenzyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0669]



[0670]

25 In the same manner as in Reference Example 142, the title compound (138 mg, 26%) was obtained as a white powder from the

compound of Reference Example 141 (400 mg, 1.16 mmol) and 1-(chloromethyl)-2-methoxybenzene (272 mg, 1.74 mmol).

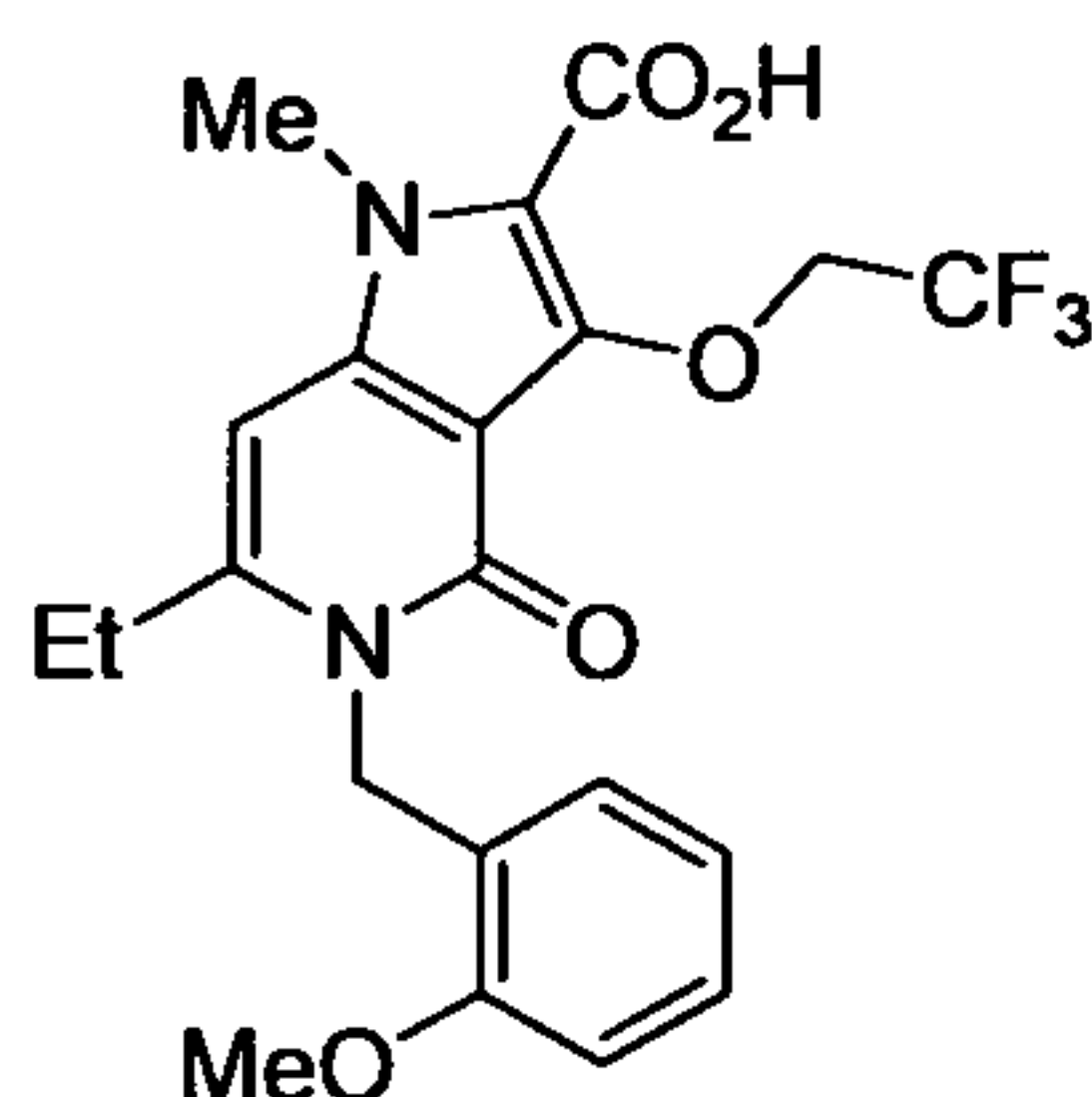
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.17 (3H, t, J = 7.4 Hz), 1.29 (3H, t, J = 7.1 Hz), 2.53-2.61 (2H, m), 3.86 (3H, s), 3.88 (3H, s),
 5 4.26 (2H, q, J = 7.1 Hz), 4.86 (2H, q, J = 9.3 Hz), 5.22 (2H, br s), 6.41 (1H, dd, J = 7.5, 1.2 Hz), 6.57 (1H, s), 6.82 (1H, td, J = 7.5, 0.9 Hz), 7.01-7.09 (1H, m), 7.18-7.28 (1H, m).

[0671]

Reference Example 157

10 Production of 6-ethyl-5-(2-methoxybenzyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0672]



15 [0673]

In the same manner as in Reference Example 49, the title compound (104 mg, 80%) was obtained as a white powder from the compound of Reference Example 156 (138 mg, 0.296 mmol).

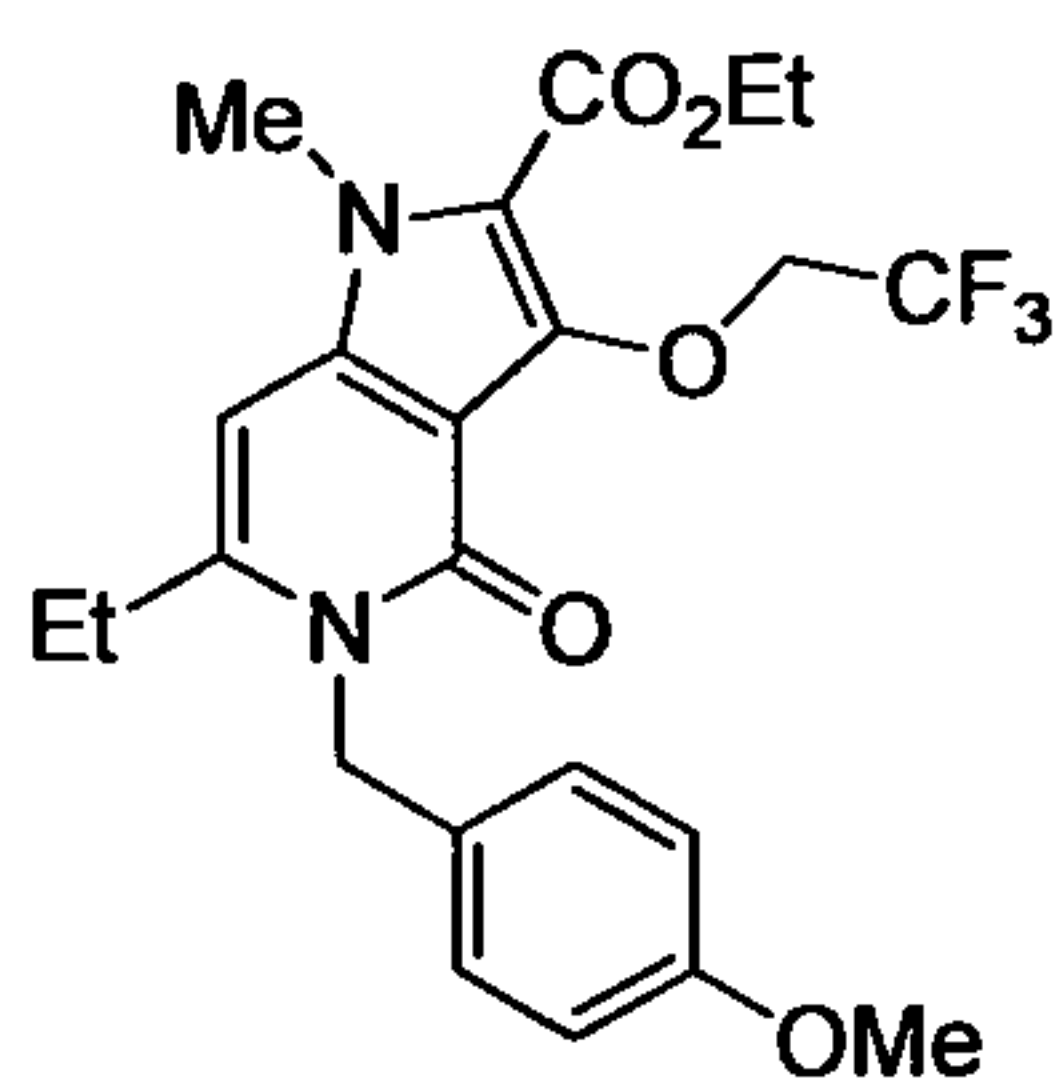
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.17 (3H, t, J = 7.3 Hz), 2.53-2.60
 20 (2H, m), 3.86 (3H, s), 3.88 (3H, s), 4.84 (2H, q, J = 9.3 Hz), 5.22 (2H, br s), 6.40 (1H, dd, J = 7.5, 1.3 Hz), 6.55 (1H, s), 6.82 (1H, td, J = 7.5, 0.9 Hz), 7.00-7.11 (1H, m), 7.16-7.31 (1H, m), 12.72 (1H, br s).

[0674]

25 Reference Example 158

Production of ethyl 6-ethyl-5-(4-methoxybenzyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0675]



[0676]

In the same manner as in Reference Example 142, the title compound (175 mg, 43%) was obtained as a white powder from the compound of Reference Example 141 (300 mg, 0.866 mmol) and 1-(chloromethyl)-4-methoxybenzene (0.175 mL, 1.30 mmol).

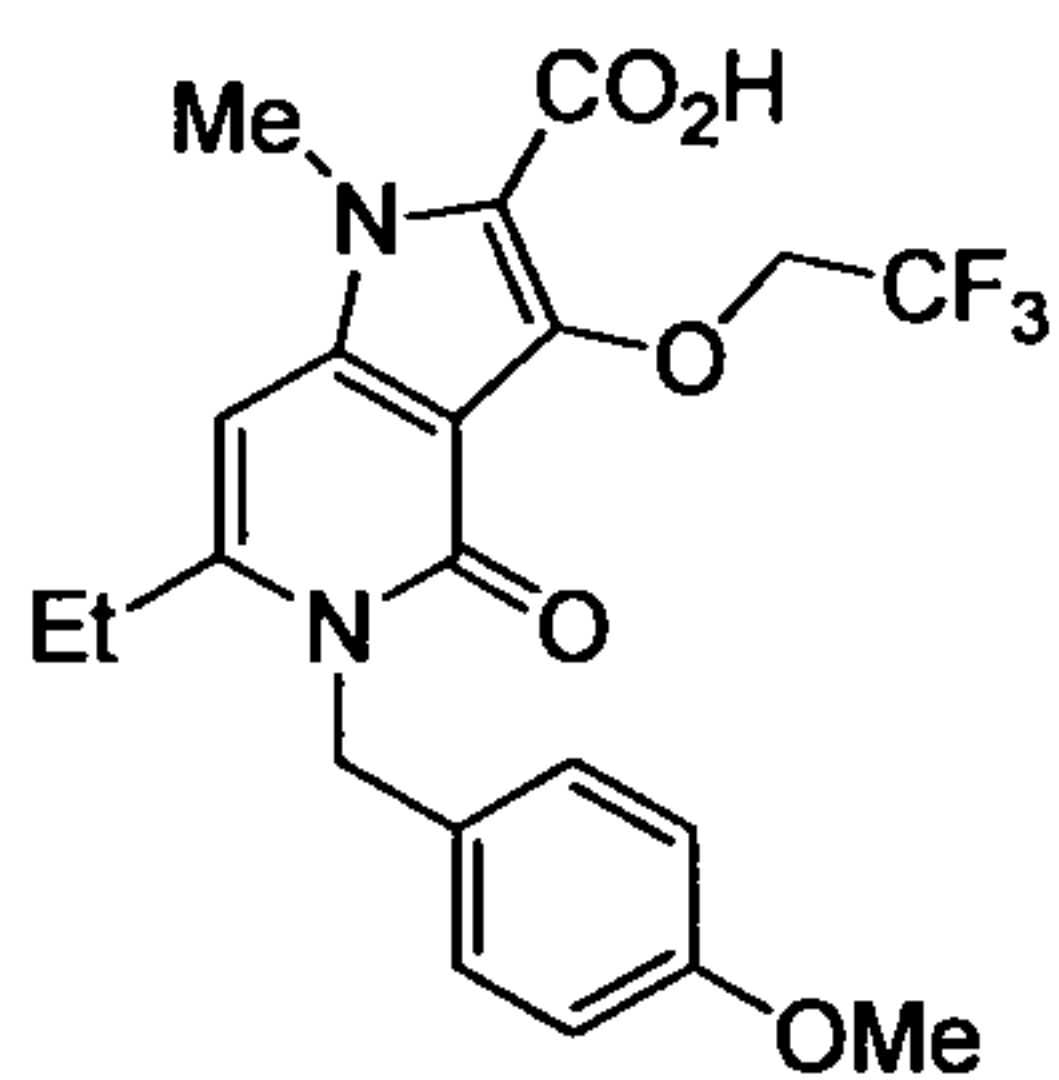
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.16 (3H, t, J = 7.2 Hz), 1.29 (3H, t, J = 7.2 Hz), 2.62 (2H, q, J = 7.2 Hz), 3.71 (3H, s), 3.84 (3H, s), 4.26 (2H, q, J = 7.2 Hz), 4.90 (2H, q, J = 9.3 Hz), 5.26 (2H, br s), 6.51 (1H, s), 6.82-6.92 (2H, m), 6.97-7.08 (2H, m).

[0677]

Reference Example 159

Production of 6-ethyl-5-(4-methoxybenzyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0678]



[0679]

In the same manner as in Reference Example 49, the title compound (157 mg, 96%) was obtained as a white powder from the compound of Reference Example 158 (175 mg, 0.375 mmol).

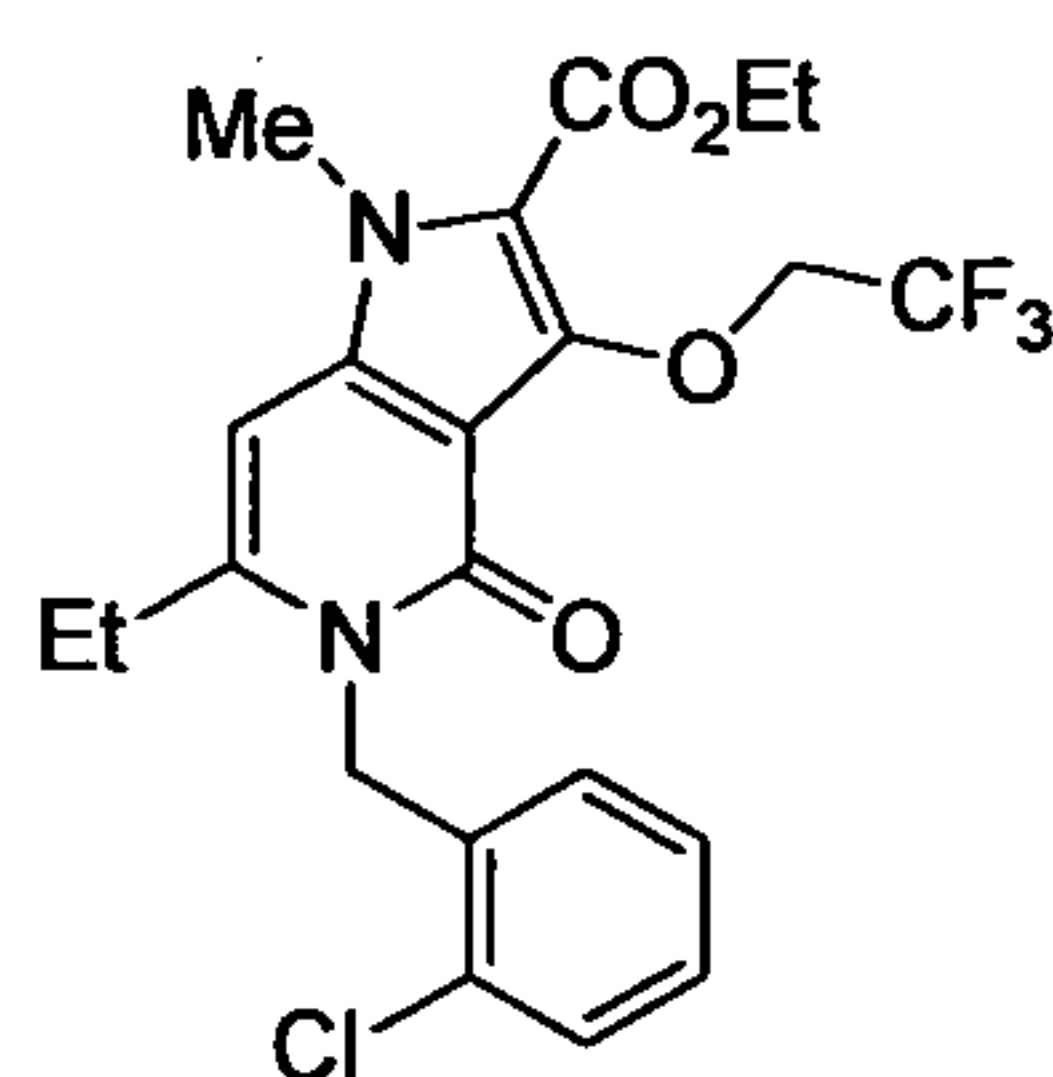
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.16 (3H, t, J = 7.3 Hz), 2.62 (2H, q, J = 7.3 Hz), 3.71 (3H, s), 3.84 (3H, s), 4.88 (2H, q, J = 9.3 Hz), 5.26 (2H, br s), 6.49 (1H, s), 6.81-6.92 (2H, m), 6.96-7.09 (2H, m), 12.70 (1H, br s).

[0680]

Reference Example 160

Production of ethyl 5-(2-chlorobenzyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

5 [0681]



[0682]

In the same manner as in Reference Example 142, the title compound (163 mg, 30%) was obtained as a white powder from the
10 compound of Reference Example 141 (400 mg, 1.16 mmol) and 1-chloro-2-(chloromethyl)benzene (0.226 mL, 1.74 mmol).

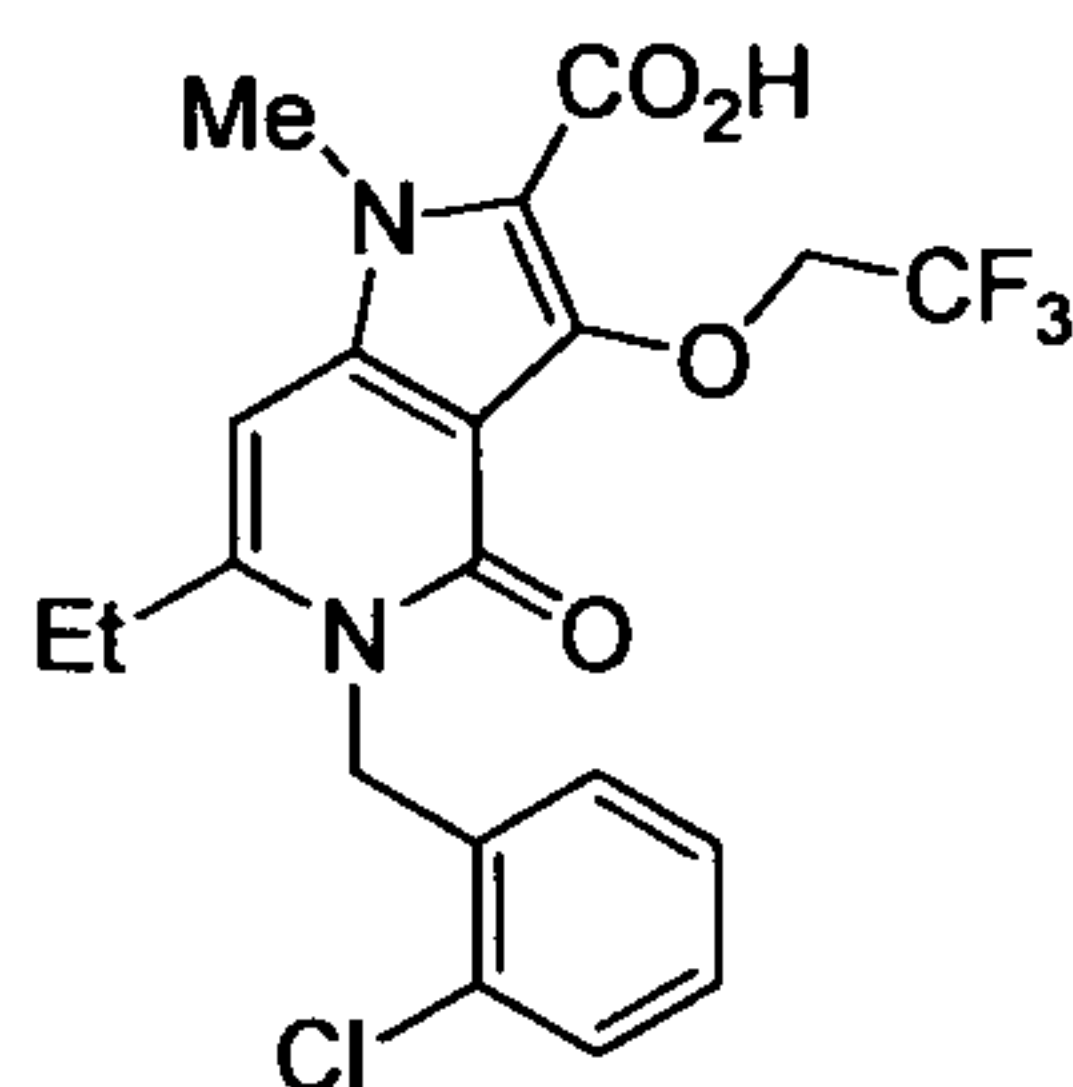
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.18 (3H, t, J = 7.4 Hz), 1.29 (3H, t, J = 7.1 Hz), 2.53-2.62 (2H, m), 3.87 (3H, s), 4.27 (2H, q, J = 7.1 Hz), 4.86 (2H, q, J = 9.3 Hz), 5.32 (2H, s), 6.55 (1H, dd, J = 7.6, 1.5 Hz), 6.62 (1H, s), 7.21-7.33 (2H, m), 7.52
15 (1H, dd, J = 7.7, 1.3 Hz).

[0683]

Reference Example 161

Production of 5-(2-chlorobenzyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid
20

[0684]



[0685]

In the same manner as in Reference Example 49, the title compound (138 mg, 90%) was obtained as a white powder from the
25 compound of Reference Example 160 (163 mg, 0.346 mmol).

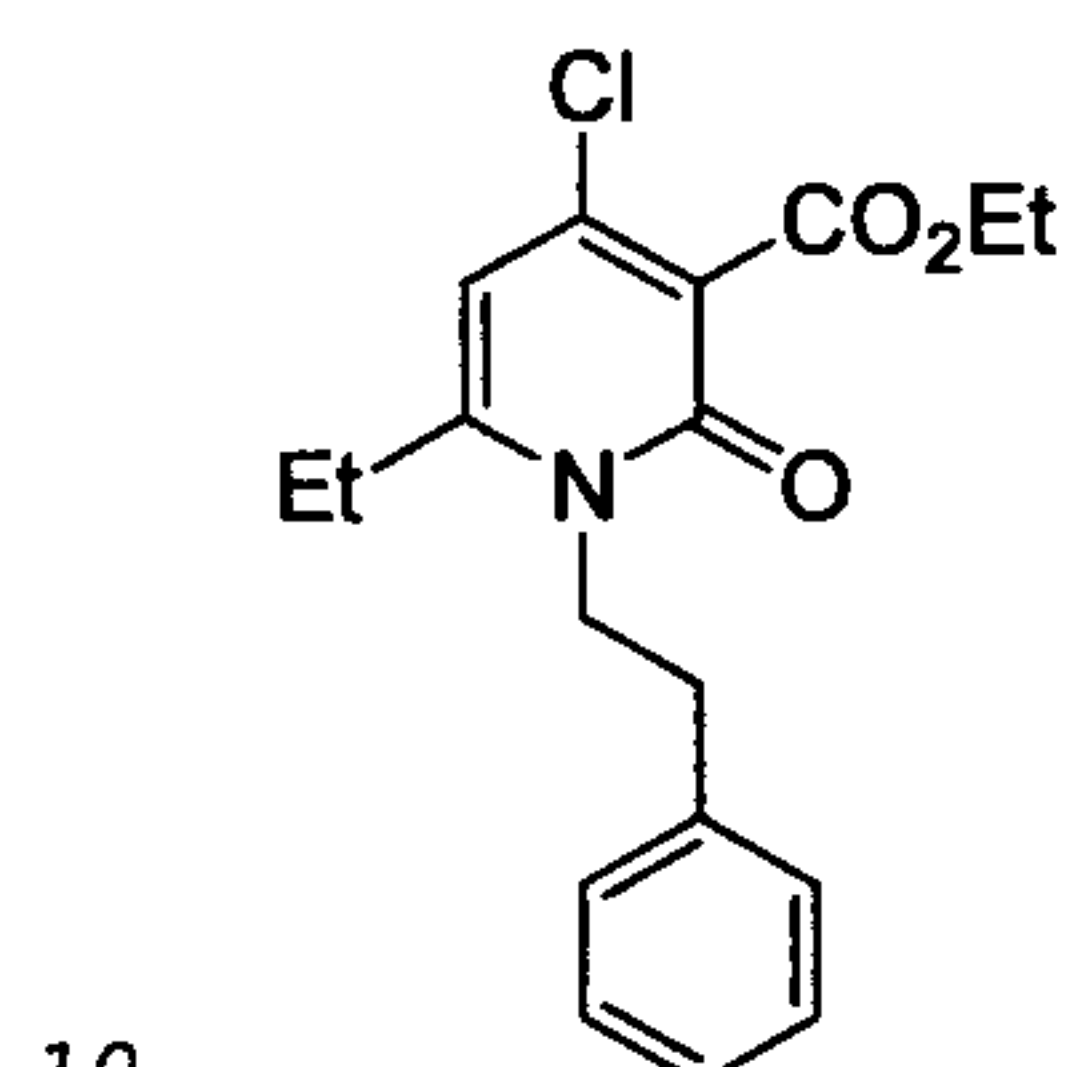
^1H -NMR (300 MHz, DMSO- d_6) δ : 1.18 (3H, t, $J = 7.4$ Hz), 2.52-2.62 (2H, m), 3.87 (3H, s), 4.83 (2H, q, $J = 9.3$ Hz), 5.32 (2H, s), 6.50 (1H, dd, $J = 7.7, 1.6$ Hz), 6.60 (1H, s), 7.22-7.33 (2H, m), 7.52 (1H, dd, $J = 7.7, 1.3$ Hz), 12.76 (1H, br s).

5 [0686]

Reference Example 162

Production of ethyl 4-chloro-6-ethyl-2-oxo-1-(2-phenylethyl)-1,2-dihydropyridine-3-carboxylate

[0687]



[0688]

In the same manner as in Reference Example 142, the title compound (480 mg, 16%) was obtained as a white powder from the compound of Reference Example 38 (2.00 g, 8.71 mmol) and (2-bromoethyl)benzene (1.77 mL, 11.3 mmol).

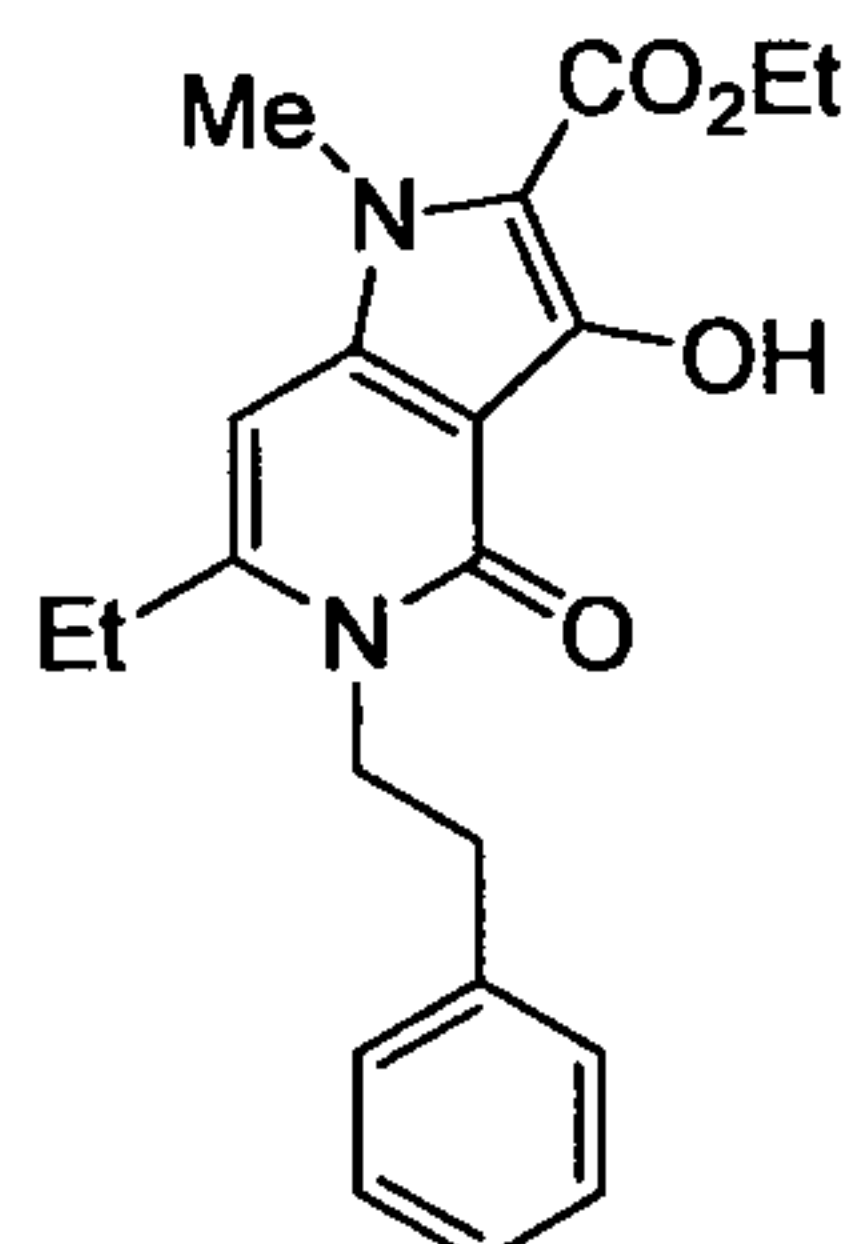
^1H -NMR (300 MHz, DMSO- d_6) δ : 1.14 (3H, t, $J = 7.4$ Hz), 1.28 (3H, t, $J = 7.1$ Hz), 2.63 (2H, q, $J = 7.4$ Hz), 2.85-2.93 (2H, m), 4.07-4.15 (2H, m), 4.29 (2H, q, $J = 7.1$ Hz), 6.30 (1H, s), 7.19-7.28 (3H, m), 7.28-7.38 (2H, m).

20 [0689]

Reference Example 163

Production of ethyl 6-ethyl-3-hydroxy-1-methyl-4-oxo-5-(2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

25 [0690]



[0691]

In the same manner as in Reference Example 40, the title compound (481 mg, 80%) was obtained as a white powder from the compound of Reference Example 162 (480 mg, 1.44 mmol).

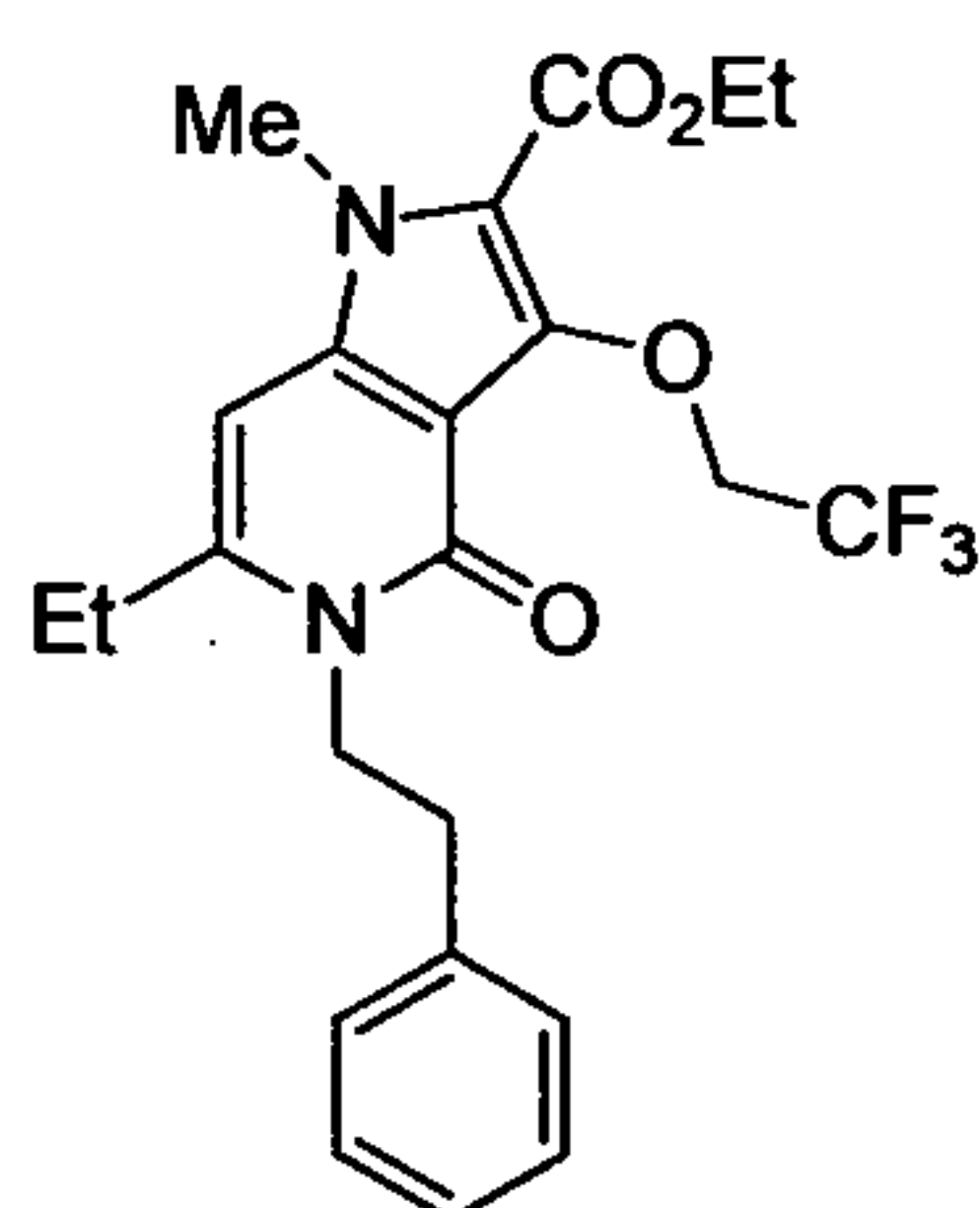
5 $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ : 1.20 (3H, t, $J = 7.3$ Hz), 1.31 (3H, t, $J = 7.1$ Hz), 2.63 (2H, q, $J = 7.3$ Hz), 2.80-2.94 (2H, m), 3.75 (3H, s), 4.01-4.16 (2H, m), 4.30 (2H, q, $J = 7.1$ Hz), 6.34 (1H, s), 7.11-7.41 (5H, m), 8.94 (1H, br s).

[0692]

10 Reference Example 164

Production of ethyl 6-ethyl-1-methyl-4-oxo-5-(2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0693]



15

[0694]

In the same manner as in Reference Example 150, the title compound (185 mg, 31%) was obtained as a white powder from the compound of Reference Example 163 (482 mg, 1.31 mmol).

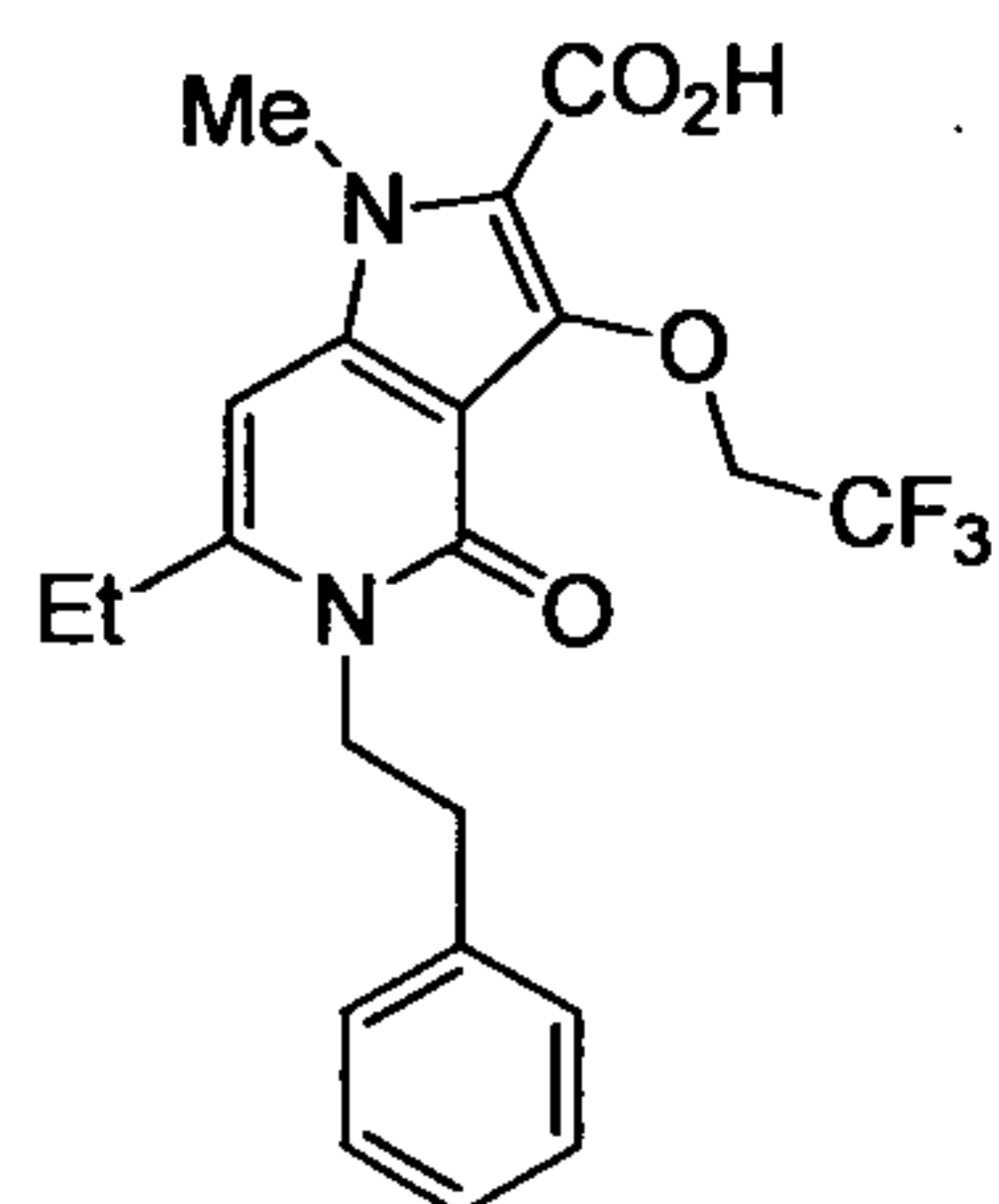
20 $^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ : 1.22 (3H, t, $J = 7.3$ Hz), 1.29 (3H, t, $J = 7.2$ Hz), 2.67 (2H, q, $J = 7.3$ Hz), 2.82-2.94 (2H, m), 3.82 (3H, s), 4.10-4.20 (2H, m), 4.26 (2H, q, $J = 7.2$ Hz), 4.90 (2H, q, $J = 9.3$ Hz), 6.46 (1H, s), 7.15-7.38 (5H, m).

[0695]

25 Reference Example 165

Production of 6-ethyl-1-methyl-4-oxo-5-(2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0696]



[0697]

In the same manner as in Reference Example 49, the title compound (143 mg, 83%) was obtained as a brown powder from the compound of Reference Example 164 (185 mg, 0.411 mmol).

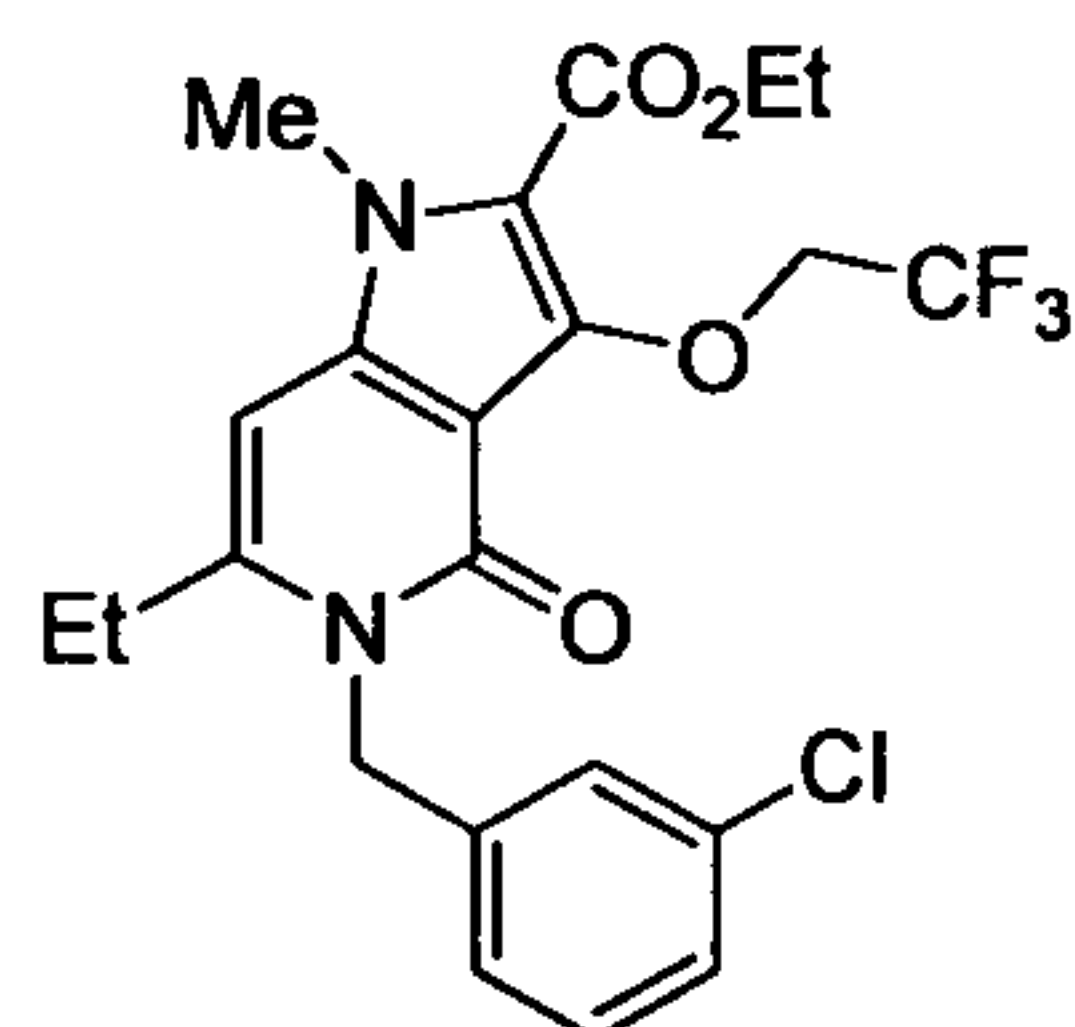
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.21 (3H, t, J = 7.2 Hz), 2.66 (2H, q, J = 7.2 Hz), 2.81-2.94 (2H, m), 3.81 (3H, s), 4.05-4.30 (2H, m), 4.89 (2H, q, J = 9.3 Hz), 6.44 (1H, s), 7.09-7.48 (5H, m), 12.67 (1H, br s).

10 [0698]

Reference Example 166

Production of ethyl 5-(3-chlorobenzyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

15 [0699]



[0700]

In the same manner as in Reference Example 142, the title compound (325 mg, 60%) was obtained as a white powder from the compound of Reference Example 141 (400 mg, 1.16 mmol) and 1-chloro-3-(chloromethyl)benzene (357 mg, 1.74 mmol).

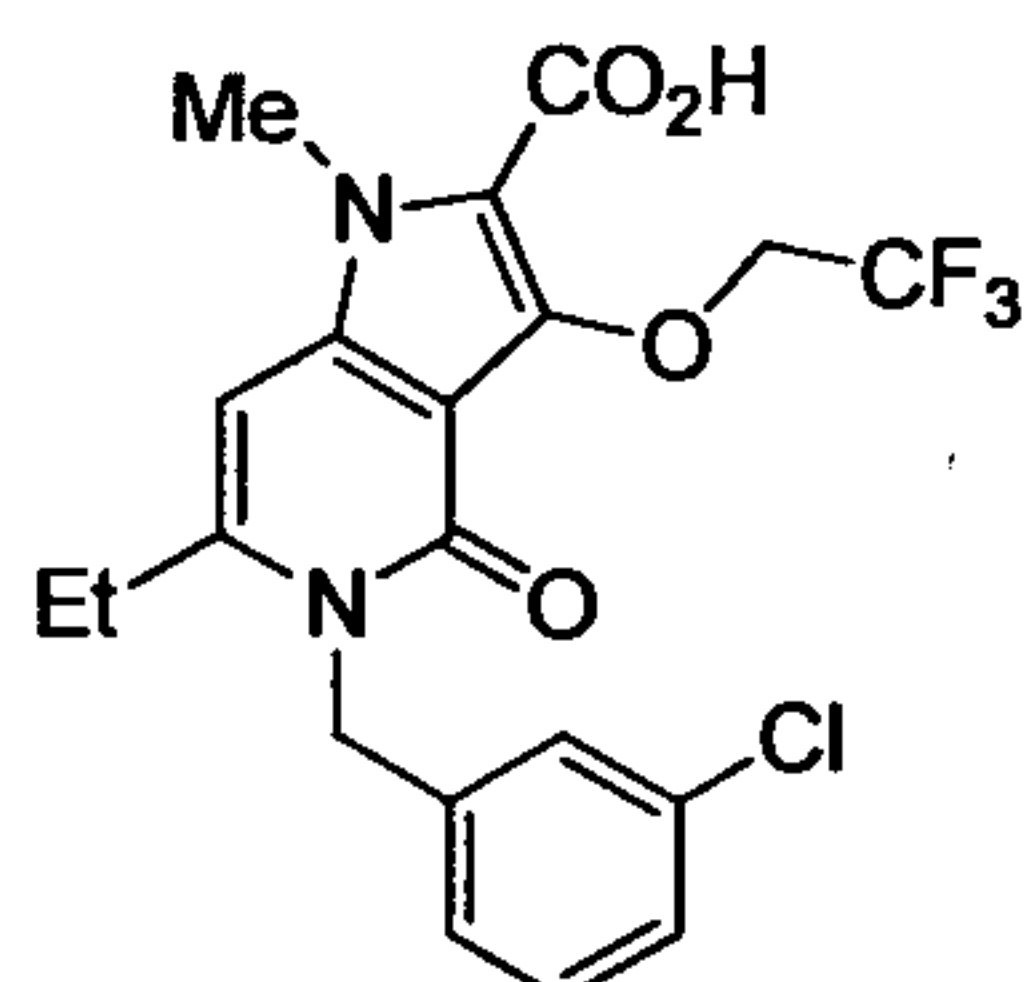
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.17 (3H, t, J = 7.4 Hz), 1.29 (3H, t, J = 7.1 Hz), 2.60 (2H, q, J = 7.1 Hz), 3.85 (3H, s), 4.26 (2H, q, J = 7.4 Hz), 4.88 (2H, q, J = 9.3 Hz), 5.33 (2H, br s), 6.56 (1H, s), 6.96-7.05 (1H, m), 7.10-7.18 (1H, m), 7.27-7.43 (2H, m).

[0701]

Reference Example 167

Production of 5-(3-chlorobenzyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0702]



[0703]

In the same manner as in Reference Example 49, the title compound (281 mg, 92%) was obtained as a white powder from the compound of Reference Example 166 (325 mg, 0.690 mmol).

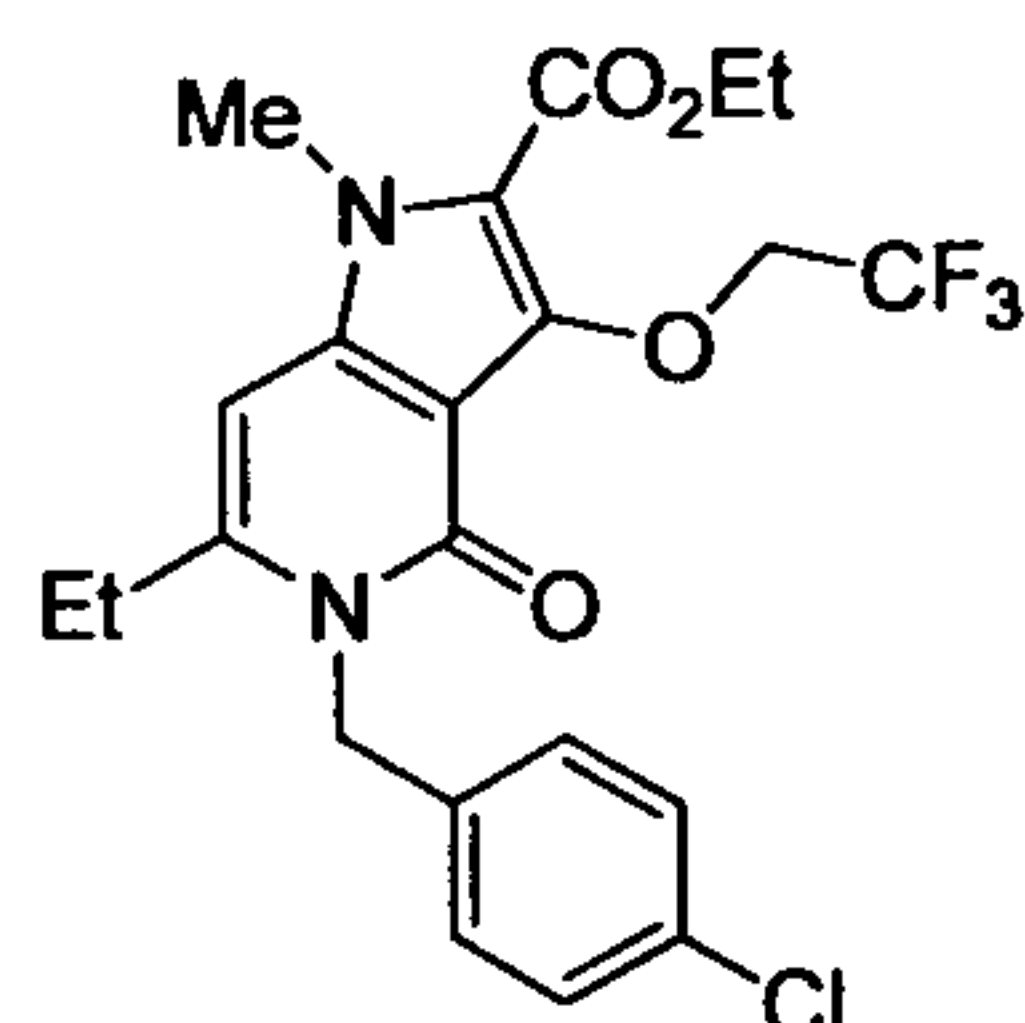
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.17 (3H, t, J = 7.2 Hz), 2.60 (2H, q, J = 7.2 Hz), 3.85 (3H, s), 4.86 (2H, q, J = 9.3 Hz), 5.34 (2H, br s), 6.54 (1H, s), 6.95-7.05 (1H, m), 7.10-7.18 (1H, m), 7.26-7.43 (2H, m), 12.74 (1H, s).

[0704]

Reference Example 168

Production of ethyl 5-(4-chlorobenzyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0705]



[0706]

In the same manner as in Reference Example 142, the title compound (213 mg, 39%) was obtained as a white powder from the compound of Reference Example 141 (400 mg, 1.16 mmol) and 1-chloro-4-(chloromethyl)benzene (357 mg, 1.74 mmol).

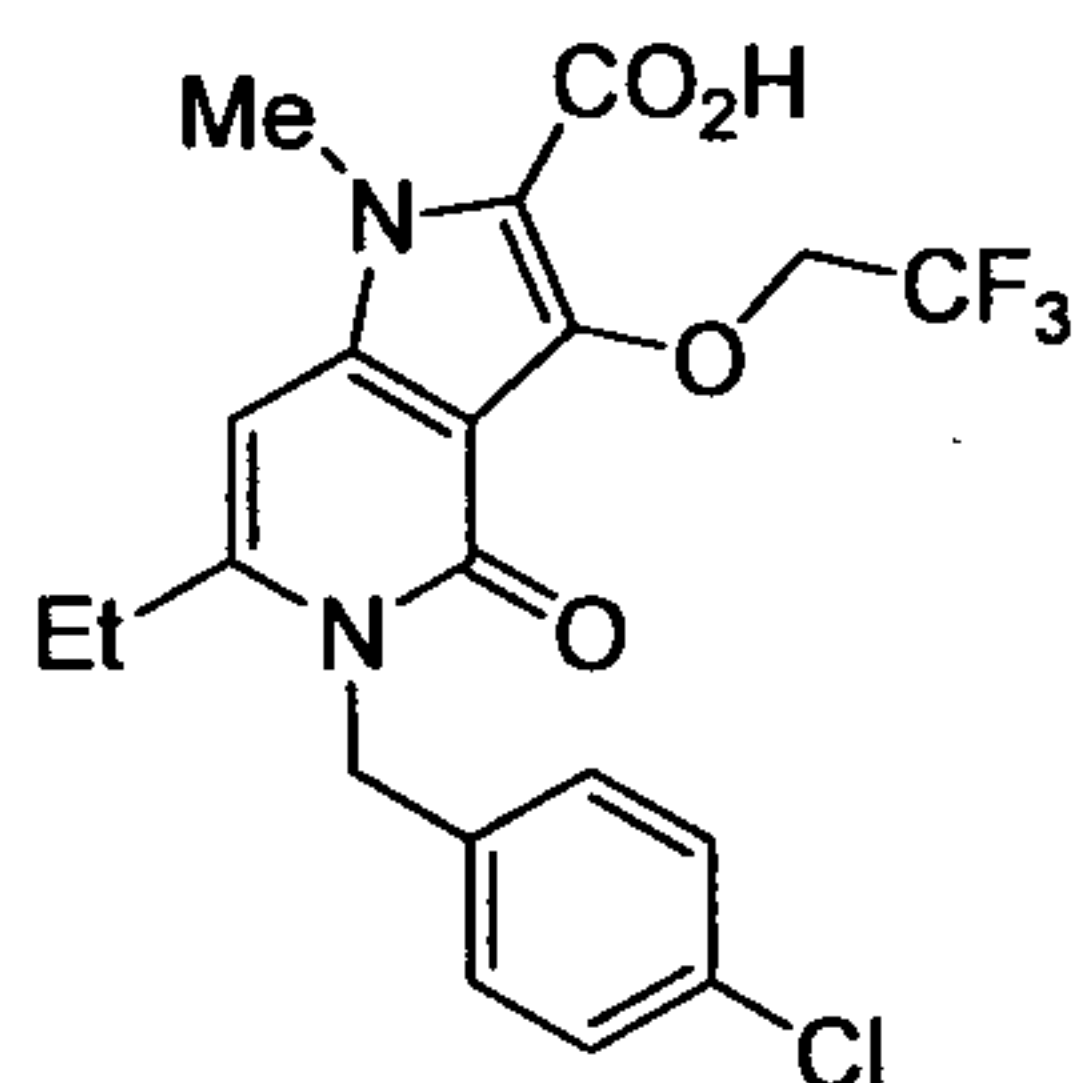
^1H -NMR (300 MHz, DMSO- d_6) δ : 1.16 (3H, t, $J = 7.3$ Hz), 1.29 (3H, t, $J = 7.1$ Hz), 2.60 (2H, q, $J = 7.1$ Hz), 3.85 (3H, s), 4.26 (2H, q, $J = 7.3$ Hz), 4.88 (2H, q, $J = 9.3$ Hz), 5.32 (2H, br s), 6.55 (1H, s), 7.03-7.16 (2H, m), 7.66-7.43 (2H, m).

5 [0707]

Reference Example 169

Production of 5-(4-chlorobenzyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

10 [0708]



[0709]

In the same manner as in Reference Example 49, the title compound (188 mg, 94%) was obtained as a white powder from the compound of Reference Example 168 (213 mg, 0.452 mmol).

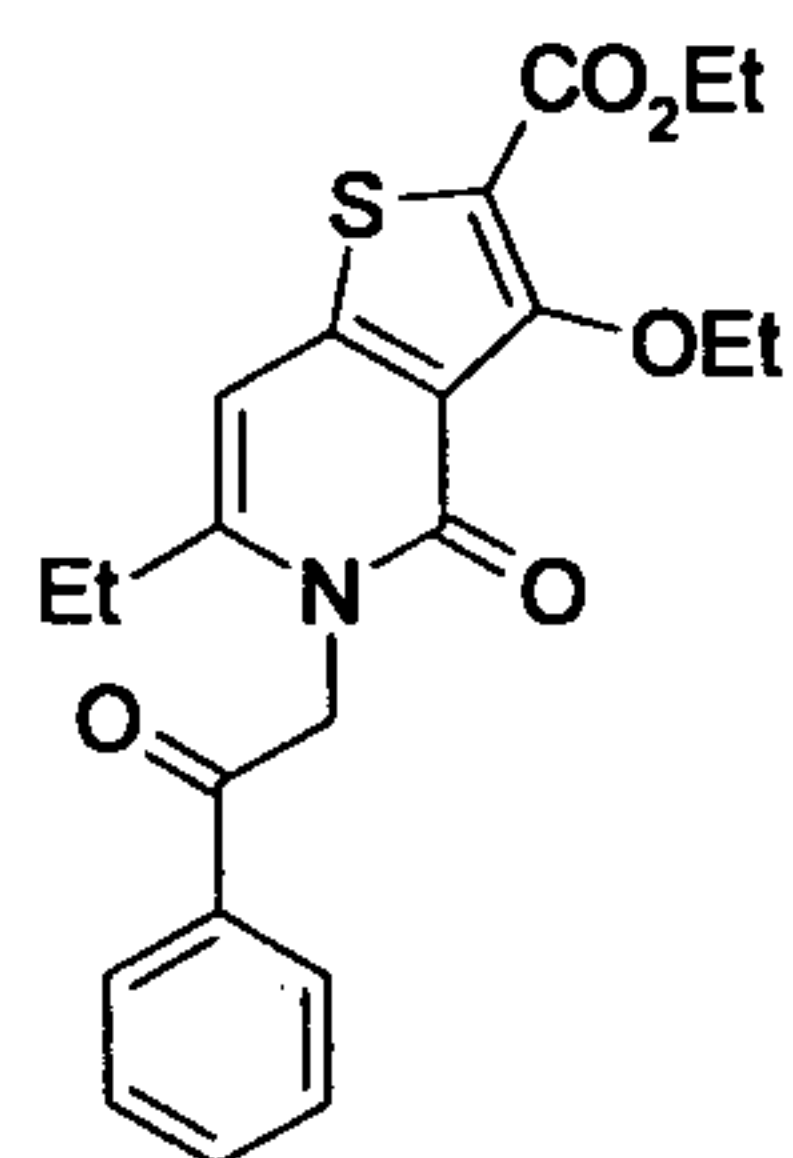
^1H -NMR (300 MHz, DMSO- d_6) δ : 1.16 (3H, t, $J = 7.3$ Hz), 2.59 (2H, q, $J = 7.3$ Hz), 3.84 (3H, s), 4.86 (2H, q, $J = 9.3$ Hz), 5.32 (2H, br s), 6.53 (1H, s), 7.01-7.20 (2H, m), 7.28-7.49 (2H, m), 12.75 (1H, br s).

20 [0710]

Reference Example 170

Production of ethyl 3-ethoxy-6-ethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate

[0711]



25

[0712]

In the same manner as in Reference Example 5, ethyl 6-ethyl-3-hydroxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate was obtained from the compound of Reference Example 39 (3.6 g, 10.3 mmol), ethyl thioglycolate (14.4 mL, 103 mmol) and triethylamine (2.3 mL, 20.6 mmol). The title compound (900 mg, 47%) was obtained as a white solid from the thus-obtained ethyl 6-ethyl-3-hydroxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate (1.8 g, 4.7 mmol) by a method similar to that in Reference Example 43.

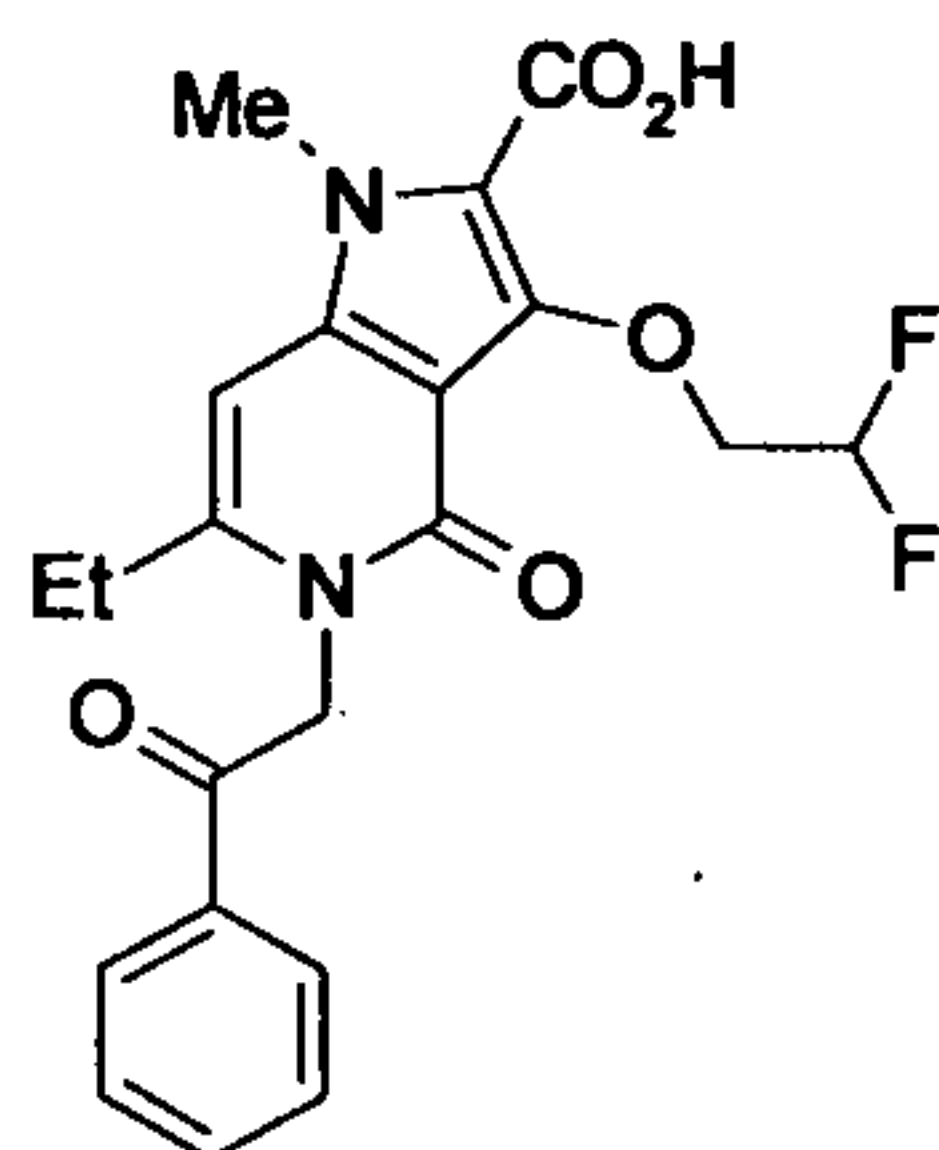
¹H-NMR (300 MHz, DMSO-d₆) δ: 1.17 (3H, t, J = 7.4 Hz), 1.23-1.36 (6H, m), 2.61 (2H, q, J = 7.4 Hz), 4.14 (2H, q, J = 7.1 Hz), 4.28 (2H, q, J = 7.0 Hz), 5.65 (2H, s), 6.83 (1H, s), 7.62 (2H, t, J = 7.6 Hz), 7.70-7.79 (1H, m), 8.12 (2H, d, J = 7.2 Hz).

[0713]

Reference Example 171

Production of 3-(2,2-difluoroethoxy)-6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0714]



[0715]

In the same manner as in Reference Example 56, ethyl 3-(2,2-difluoroethoxy)-6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate was obtained from the compound of Reference Example 40 (500 mg, 1.31 mmol), 2,2-difluoroethyl trifluoromethanesulfonate (336 mg, 1.57 mmol) and cesium carbonate (554 mg, 1.70 mmol). The title compound (314 mg, 83%) was obtained as a white powder from the thus-obtained

ethyl 3-(2,2-difluoroethoxy)-6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (400 mg, 0.90 mmol) by a method similar to that in Reference Example 59.

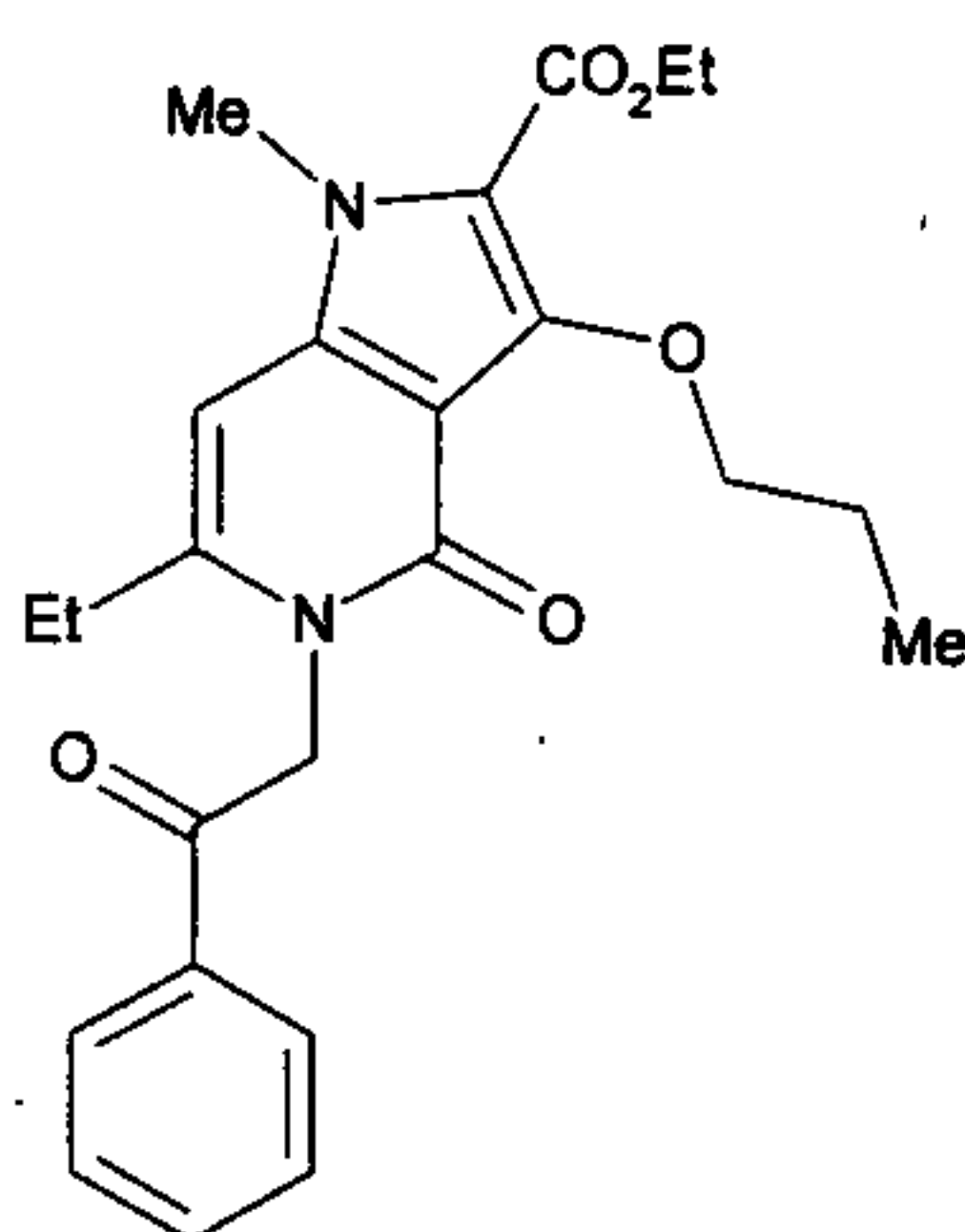
5 ¹H-NMR (300 MHz, DMSO-d₆) δ:1.19 (3H, t, J = 7.2 Hz), 2.58 (2H, q, J = 7.3 Hz), 3.85 (3H, s), 4.40 (2H, td, J = 14.6, 1.2 Hz), 5.60 (2H, s), 6.26 (1H, tt, J = 55.0, 3.9 Hz), 6.77 (1H, s), 7.58-7.76 (3H, m), 8.12 (2H, d, J = 7.5 Hz), 12.50-12.70 (1H, br).

10 [0716]

Reference Example 172

Production of ethyl 6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-propoxy-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

15 [0717]



[0718]

In the same manner as in Reference Example 56, the title compound (177 mg, 83%) was obtained as a brown powder from the compound of Reference Example 40 (191 mg, 0.50 mmol), dipropyl sulfate (364 mg, 2.0 mmol), potassium carbonate (414 mg, 3.0 mmol) and acetone (20 mL).

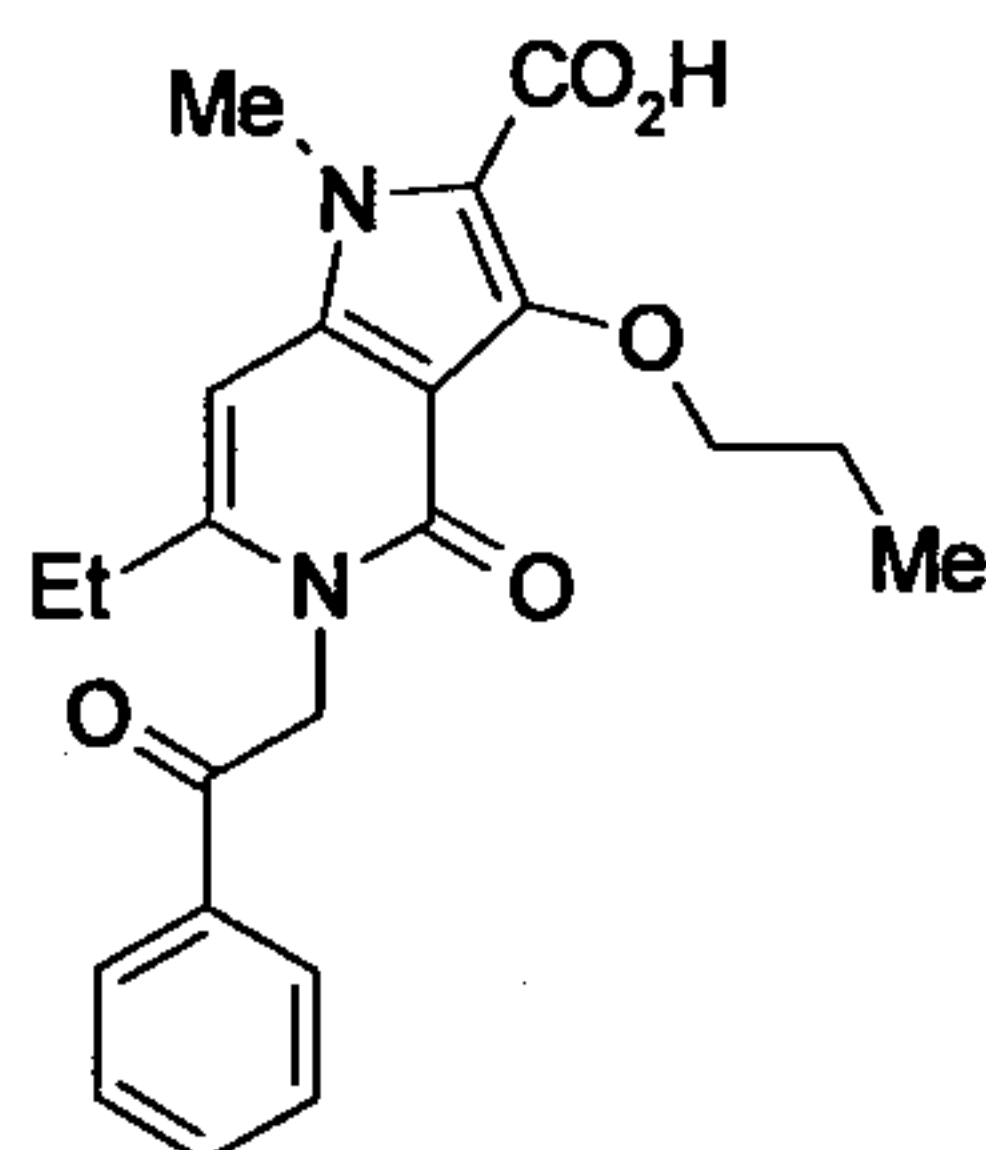
¹H-NMR (300 MHz, CDCl₃) δ:1.01 (3 H, t, J = 7.5 Hz), 1.28 (3H, t, J = 7.3 Hz), 1.40 (3H, t, J = 7.5 Hz), 1.75-1.89 (2H, m), 2.51 (2 H, q, J = 7.2 Hz), 3.88 (3 H, s), 4.21 (2 H, t, J = 6.7 Hz), 4.36 (2H, q, J = 7.2 Hz), 5.59 (2 H, s), 6.19 (1 H, s), 7.47-7.56 (2 H, m), 7.59-7.67 (1 H, m), 8.02-8.09 (2H, m).

Reference Example 173

Production of 6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-propoxy-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic

acid

[0719]



[0720]

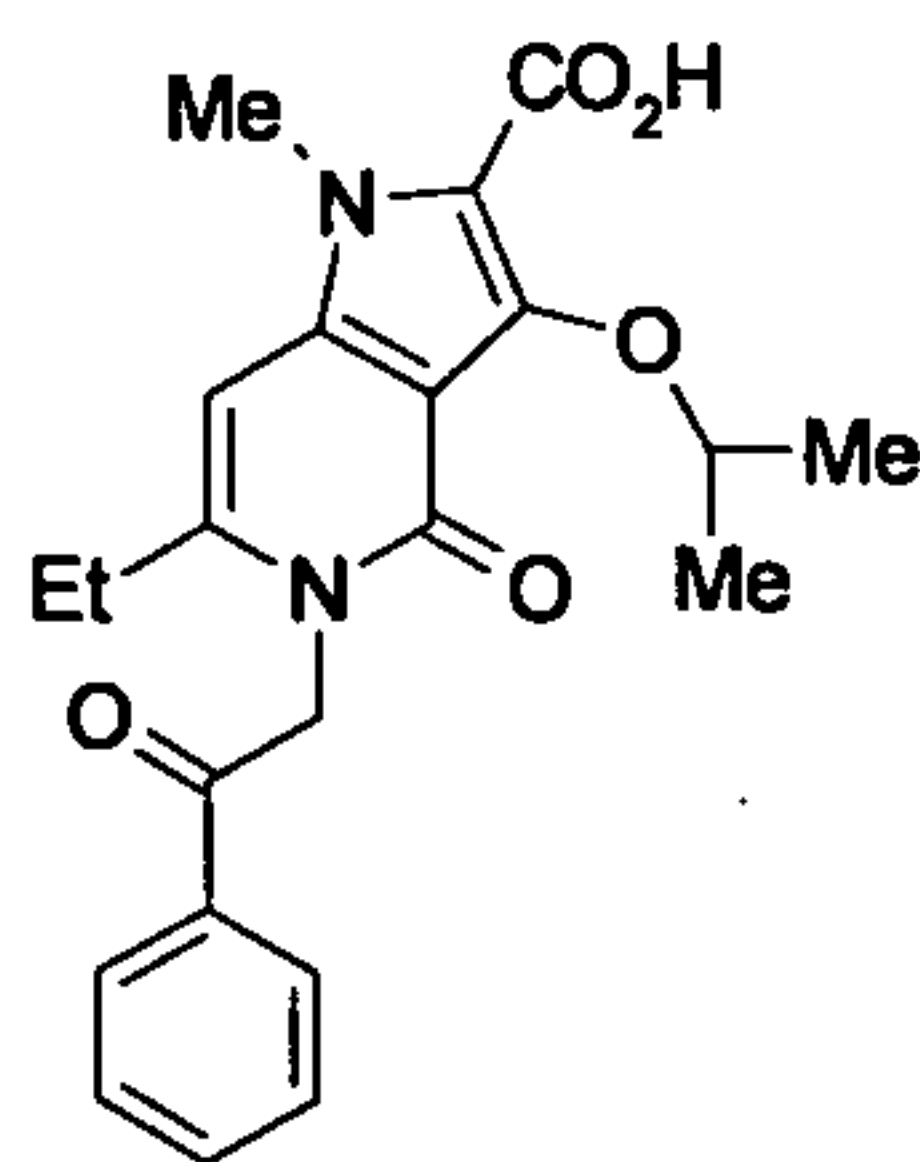
5 In the same manner as in Reference Example 59, the title compound (237 mg, 93%) was obtained as a pale-yellow powder from the compound of Reference Example 172 (274 mg, 0.65 mmol). ¹H-NMR (300 MHz, DMSO-d₆) δ: 0.91 (3 H, t, J = 7.5 Hz), 1.18 (3H, t, J = 7.3 Hz), 1.55-1.70 (2H, m), 2.57 (2 H, q, J = 7.4 Hz),
10 3.84 (3 H, s), 4.07 (2 H, t, J = 6.5 Hz), 5.58 (2 H, s), 6.47 (1 H, s), 7.56-7.66 (2 H, m), 7.69-7.78 (1 H, m), 8.07-8.16 (2H, m), 12.42 (1 H, s).

[0721]

Reference Example 174

15 Production of 6-ethyl-1-methyl-3-(1-methylethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0722]



20 [0723]

In the same manner as in Reference Example 56, ethyl 6-ethyl-1-methyl-3-(1-methylethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (291 mg, 46%) was obtained as a pale-purple powder
25 from the compound of Reference Example 40 (574 mg, 1.50 mmol),

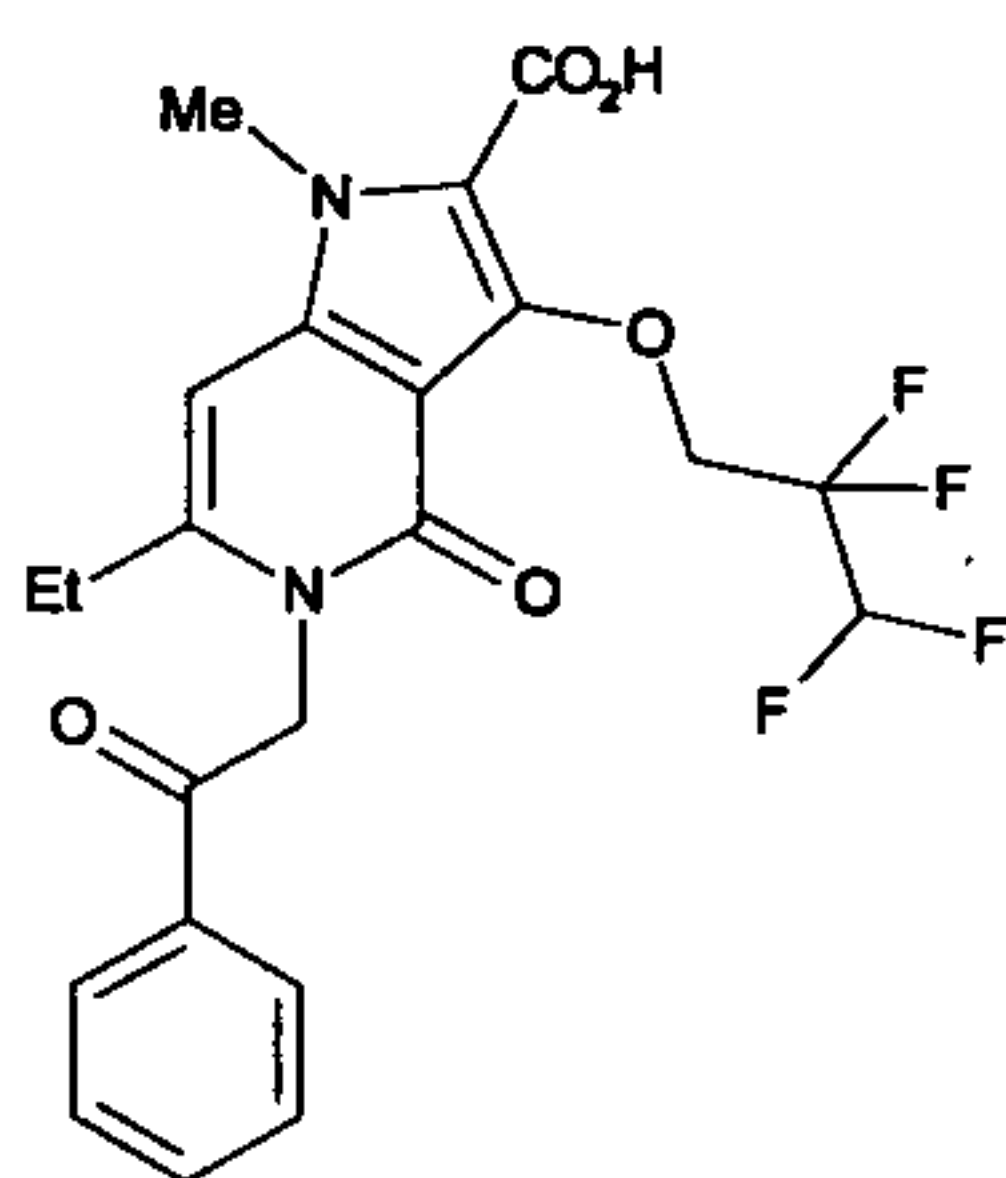
potassium carbonate (1.04 g, 7.5 mmol) and diisopropyl sulfate (1.37 g, 7.5 mmol). The title compound (242 mg, 97%) was obtained as a colorless powder from the thus-obtained ethyl 6-ethyl-1-methyl-3-(1-methylethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (267 mg, 0.63 mmol) by a method similar to that in Reference Example 59.

¹H-NMR (300 MHz, DMSO-d₆) δ: 1.13-1.23 (9 H, m), 2.57 (2 H, q, J = 7.5 Hz), 3.84 (3 H, s), 4.65-4.80 (1H, m), 5.58 (2 H, s), 6.47 (1 H, s), 7.56-7.66 (2 H, m), 7.69-7.78 (1 H, m), 8.07-8.16 (2H, m), 12.29 (1 H, s).

Reference Example 175

Production of 6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,3,3-tetrafluoropropoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0724]



[0725]

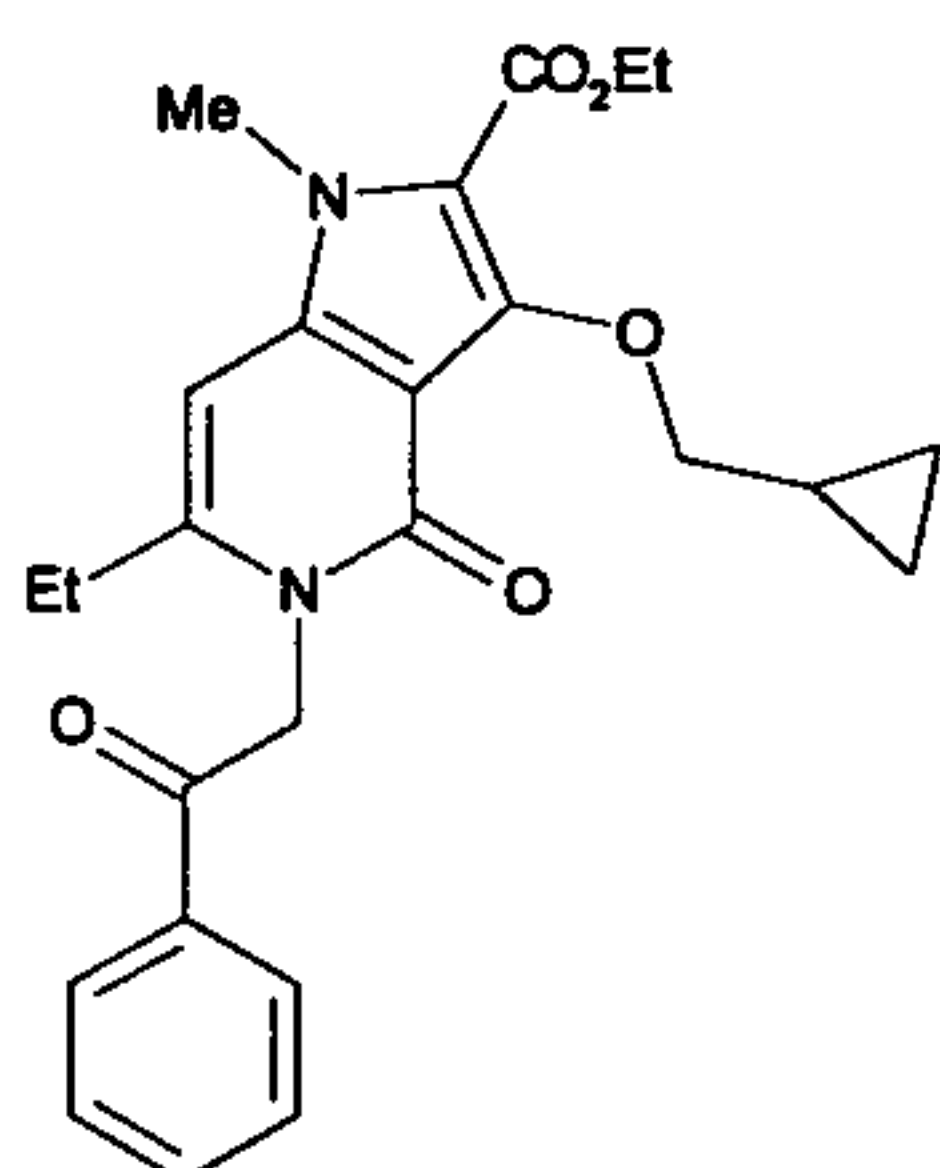
In the same manner as in Reference Example 150, ethyl 6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,3,3-tetrafluoropropoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (460 mg, 93%) was obtained as a gray powder from the compound of Reference Example 40 (382 mg, 1.00 mmol), 2,2,3,3-tetrafluoropropyl trifluoromethanesulfonate (913 mg, 3.46 mmol), cesium carbonate (391 mg, 1.20 mmol) and DMF (10 mL). The title compound (310 mg, 95%) was obtained as a gray powder from the thus-obtained ethyl 6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,3,3-tetrafluoropropoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (348 mg, 0.70 mmol) by a method similar to that in Reference Example 59.

¹H-NMR (300 MHz, DMSO-d₆) δ:1.19 (3 H, t, J = 7.3 Hz), 2.58 (2 H, q, J = 7.3 Hz), 3.86 (3 H, s), 4.70 (2H, t, J = 13.1 Hz), 5.62 (2 H, s), 6.54 (1 H, s), 6.73 (1H, tt, J = 52.6, 6.1 Hz), 7.56-7.66 (2H, m), 7.69-7.79 (1H, m), 8.07-8.17 (2H, m), 12.93
5 (1H, br s).

Reference Example 176

Production of ethyl 3-(cyclopropylmethoxy)-6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

10 [0726]



[0727]

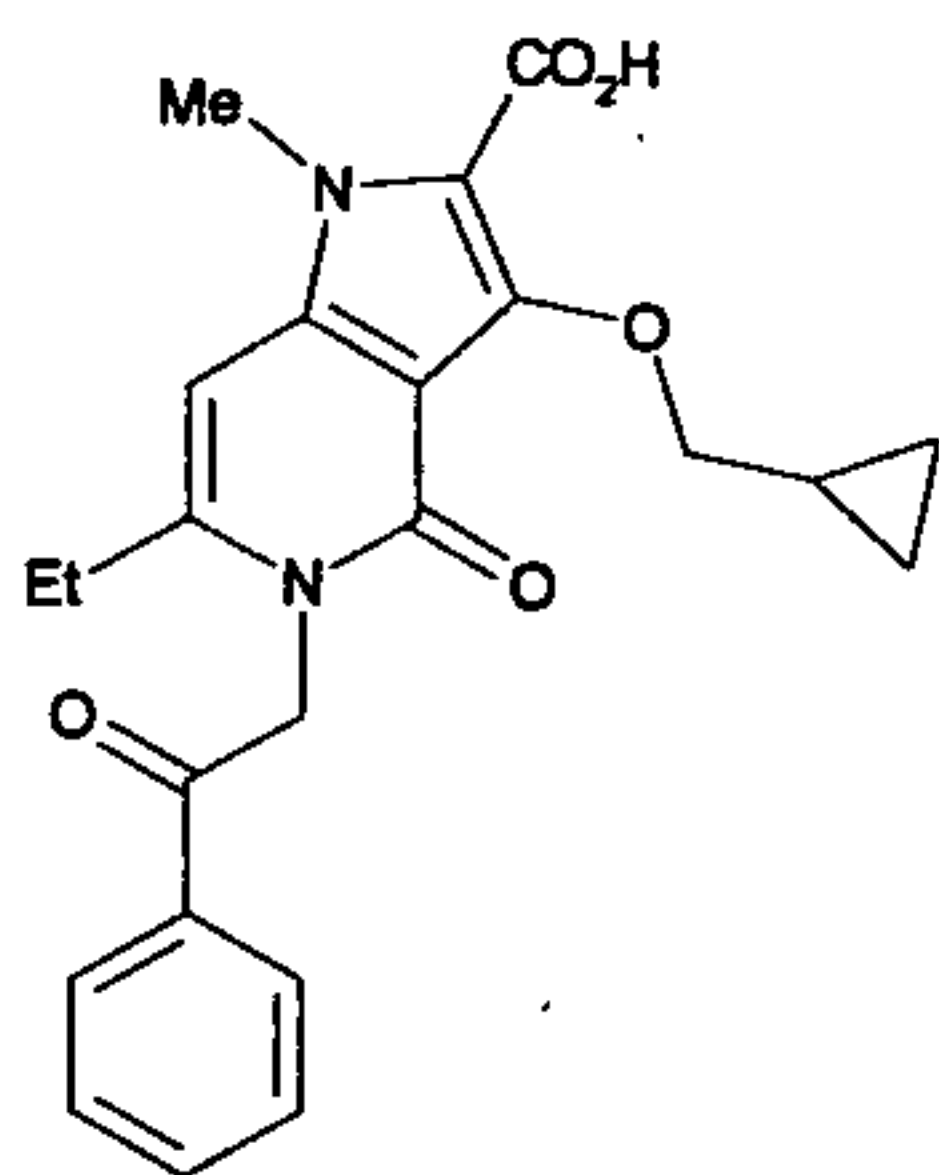
In the same manner as in Reference Example 150, the title compound (65 mg, 15%) was obtained as a yellow powder from the
15 compound of Reference Example 40 (382 mg, 1.00 mmol), cesium carbonate (358 mg, 1.10 mmol), cyclopropylmethyl methanesulfonate (750 mg, 5.00 mmol) and DMF (10 mL).

¹H-NMR (300 MHz, CDCl₃) δ:0.29-0.36 (2 H, m), 0.49-0.57 (2H, m), 1.24-1.37 (1H, m), 1.28 (3H, t, J = 7.3 Hz), 1.41 (3H, t, J =
20 7.1 Hz), 2.51 (2 H, q, J = 7.4 Hz), 3.88 (3 H, s), 4.10 (2 H, d, J = 7.2 Hz), 4.37 (2H, q, J = 7.1 Hz), 5.59 (2H, s), 6.19 (1H, s), 7.47-7.55 (2H, m), 7.59-7.67 (1H, m), 8.02-8.10 (2H, m).

Reference Example 177

25 Production of 3-(cyclopropylmethoxy)-6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0728]



[0729]

In the same manner as in Reference Example 59, the title compound (112 mg, 83%) was obtained as a colorless powder from the compound of Reference Example 176 (144 mg, 0.33 mmol).

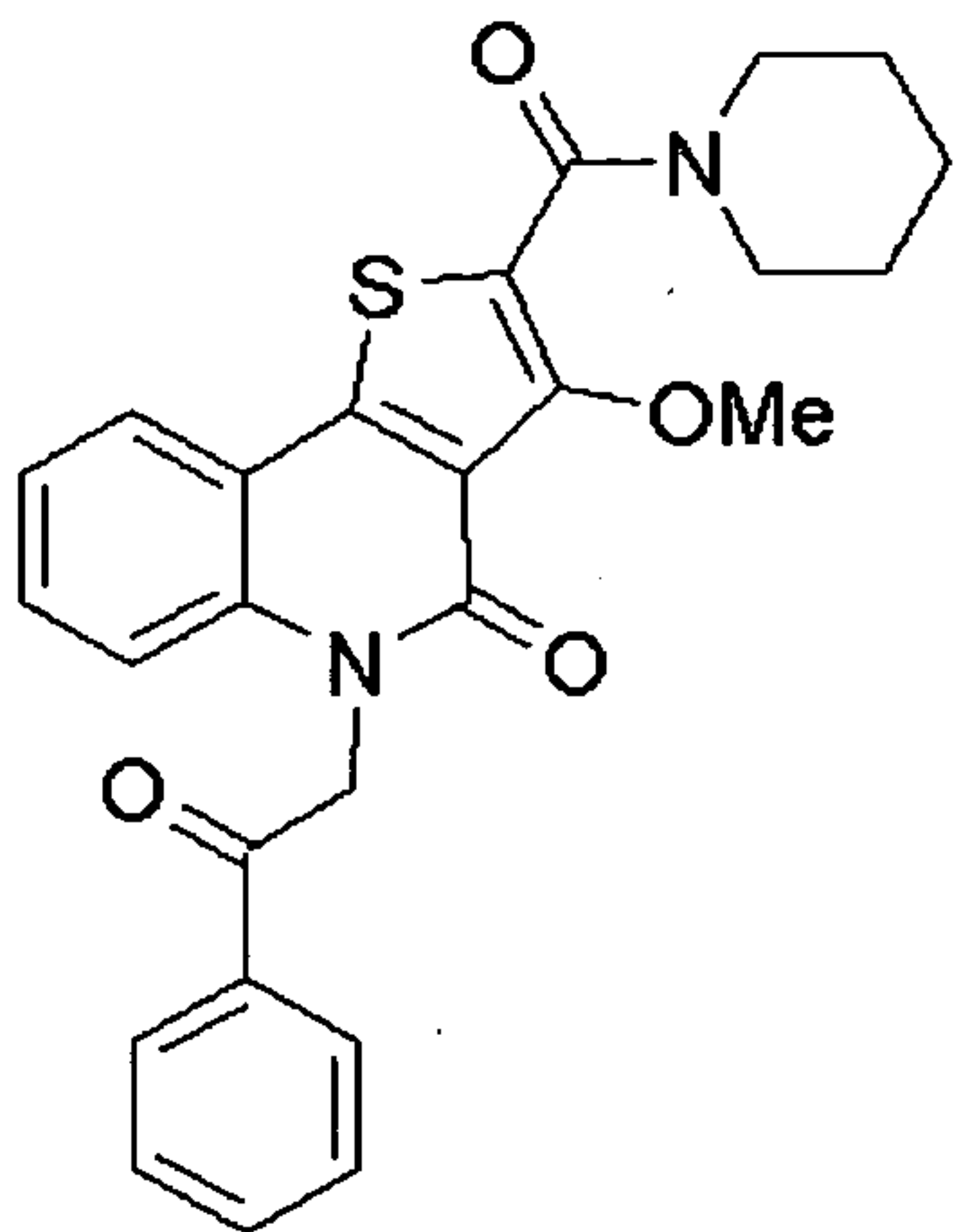
$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ : 0.17-0.27 (2H, m), 0.39-0.48 (2H, m), 1.03-1.22 (1H, m), 1.18 (3H, t, $J = 7.3$ Hz), 2.56 (2 H, q, $J = 7.3$ Hz), 3.84 (3 H, s), 3.94 (2H, d, $J = 7.0$ Hz), 5.58 (2 H, s), 6.46 (1H, s), 7.56-7.65 (2H, m), 7.69-7.77 (1H, m), 8.07-8.15 (2H, m), 12.43 (1H, br s).

[0730]

Example 1

Production of 3-methoxy-5-(2-oxo-2-phenylethyl)-2-(piperidin-1-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

15 [0731]



[0732]

A solution (0.10 M, 0.600 mL, 60 μmol) of the compound of Reference Example 7 in DMF was diluted with DMF (0.200 mL), and a solution (1.0 M, 0.063 mL, 63 μmol) of piperidine in DMF and a solution (0.50 M, 0.126 mL, 63 μmol) of HOBt and WSCD in 1:1 mixture in DMF were added. The obtained mixture was

agitated at room temperature for 13 hr. Dichloromethane (2 mL) and saturated aqueous sodium hydrogen carbonate solution (1 mL) were added to the reaction mixture, and the organic layer was filtered through a Teflon (registered trade mark) filter to separate from the aqueous layer, and concentrated under reduced pressure. The residue was purified by preparative HPLC to give the title compound (8.5 mg, 31%).

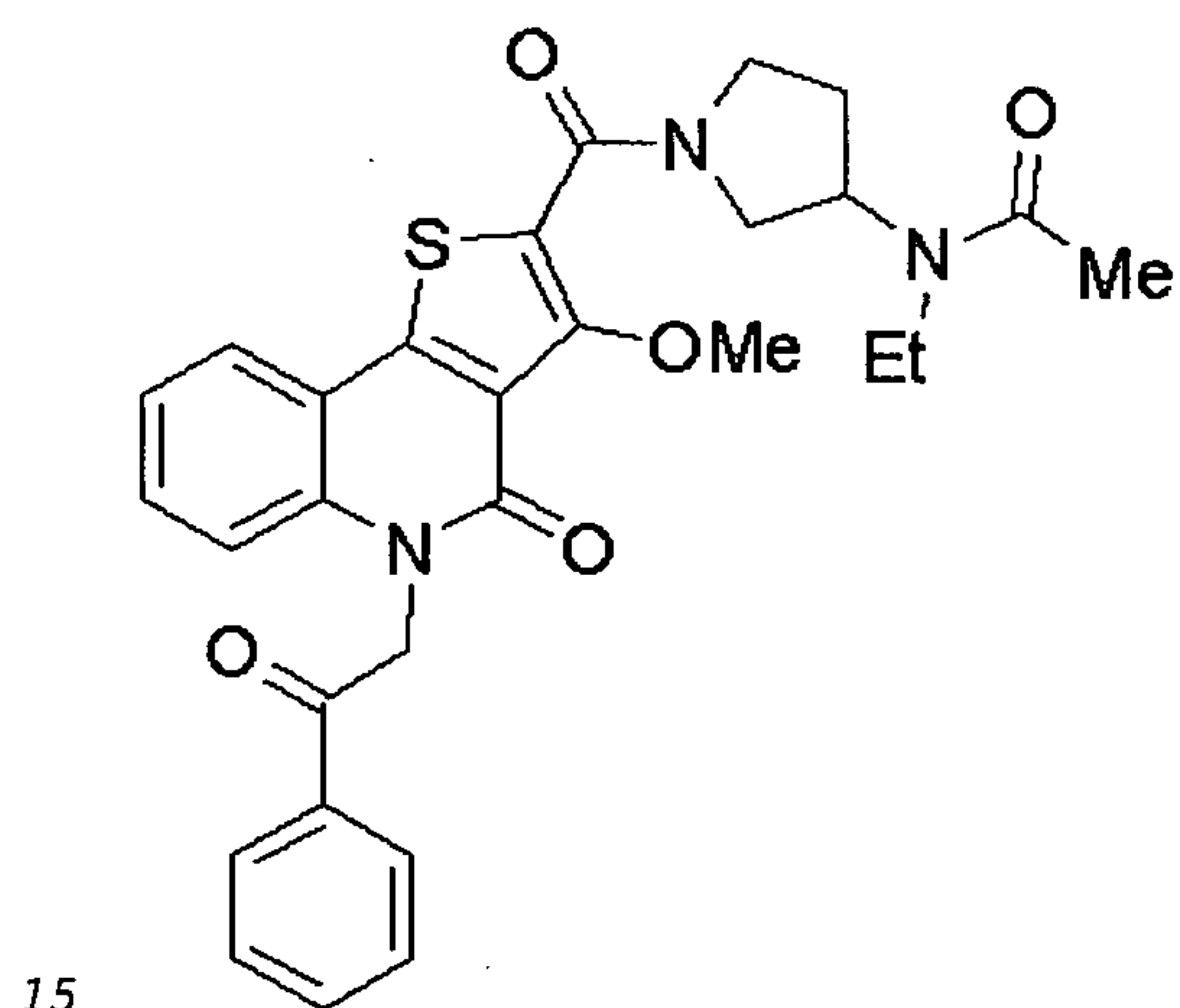
LC/MS 461 (M+H).

[0733]

10 Example 2

Production of N-ethyl-N-(1-{[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}pyrrolidin-3-yl)acetamide

[0734]



[0735]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and N-ethyl-N-pyrrolidin-3-ylacetamide.

20 LC/MS 532 (M+H).

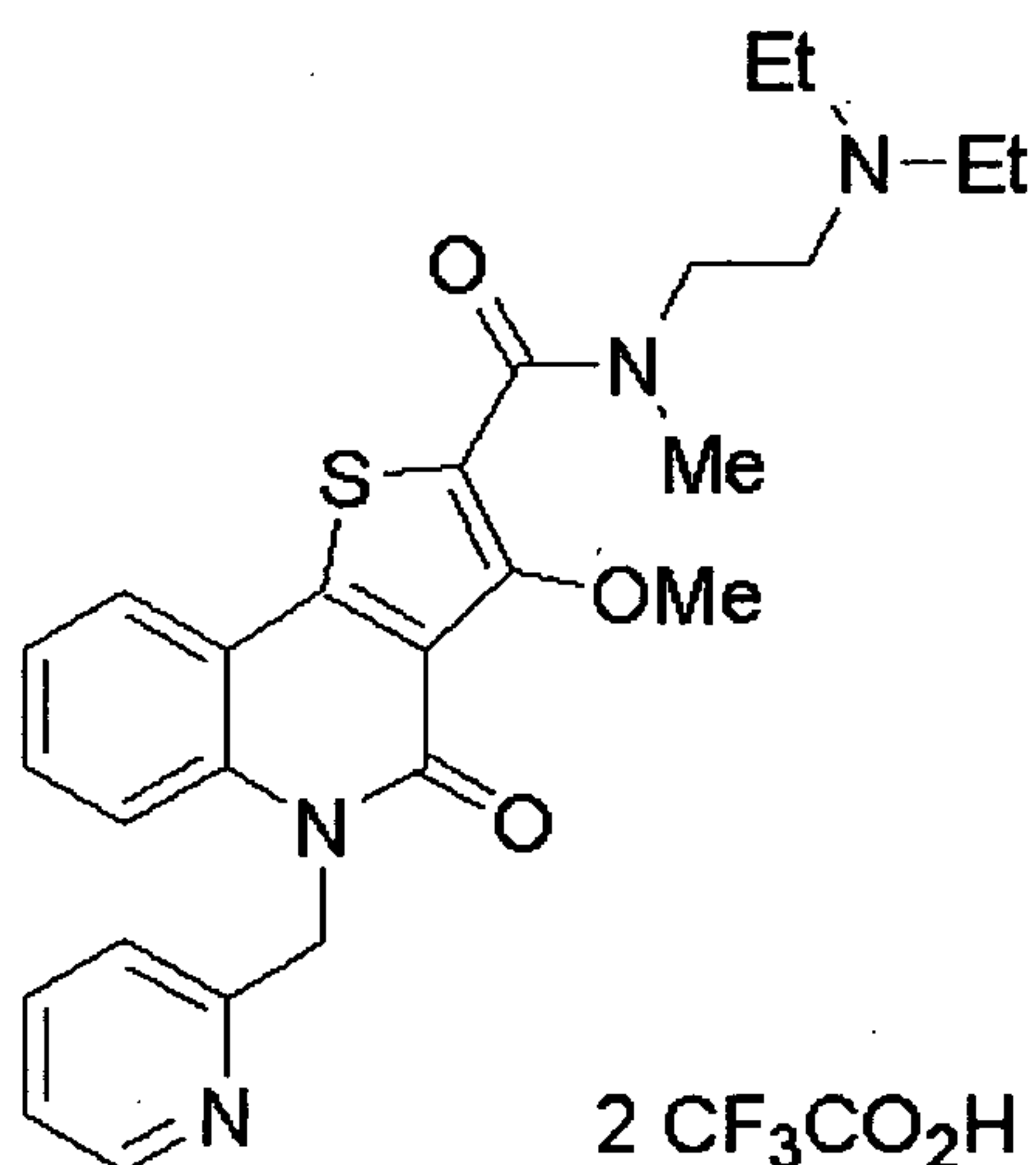
[0736]

Example 3

Production of N-[2-(diethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

25

[0737]



[0738]

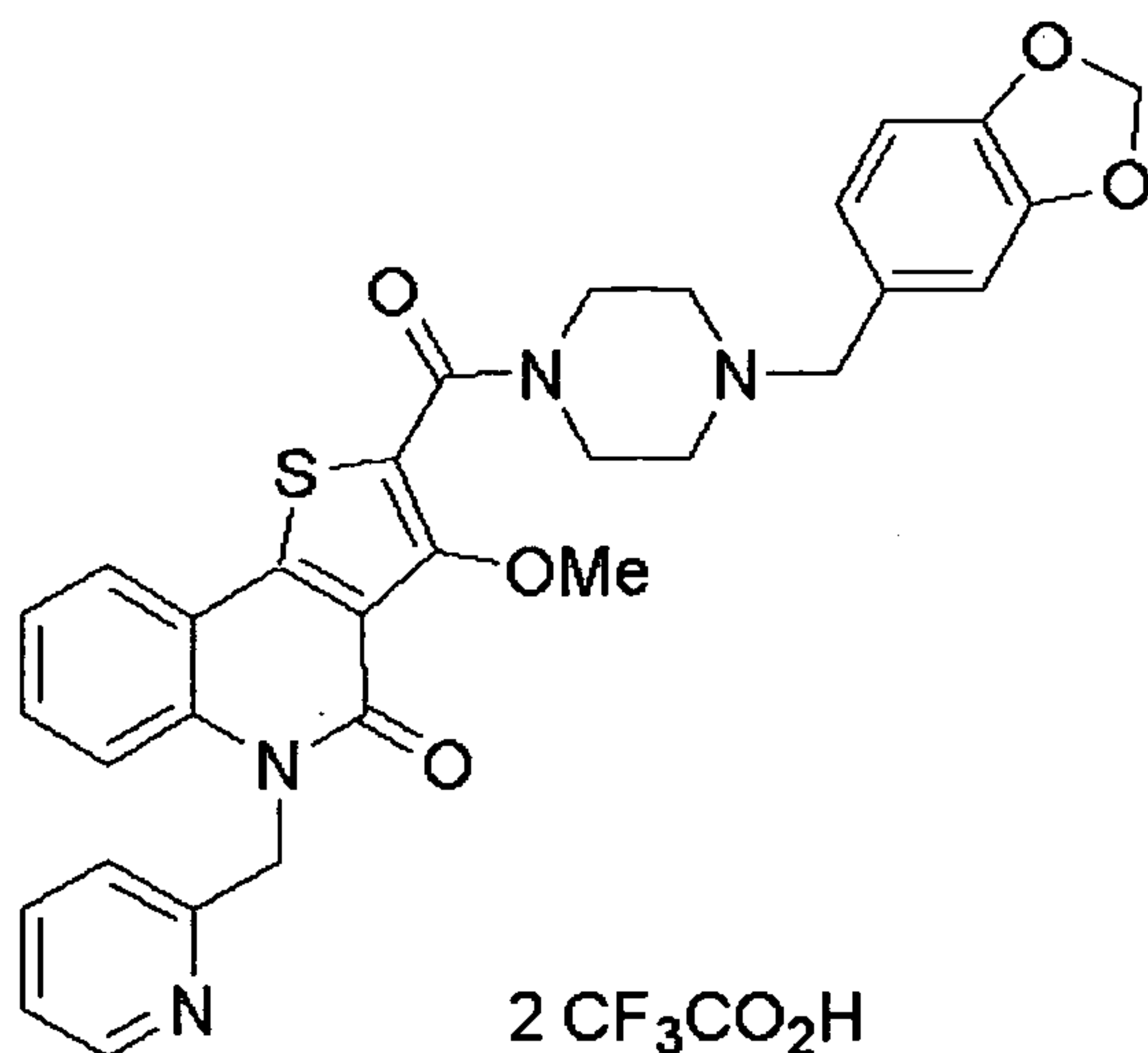
To a solution (0.12 M, 0.40 mL, 48 μ mol) of the compound of Reference Example 19 in DMF were added a solution (0.66 M, 5 0.10 mL, 63 μ mol) of N,N-diethyl-N'-methylethane-1,2-diamine in DMF and a solution (0.39 M, 0.20 mL, 78 μ mol) of HOBt and WSCD in 1:1 mixture in DMF. The obtained mixture was agitated at room temperature for 14 hr. Dichloromethane (2 mL) and saturated aqueous sodium hydrogen carbonate solution (1 mL) 10 were added to the reaction mixture, and the organic layer was filtered through a Teflon (registered trade mark) filter to separate from the aqueous layer, and the filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC to give the title compound (33.2 mg, 98%). 15 LC/MS 479 (M+H).

[0739]

Example 4

Production of 2-{[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]carbonyl}-3-methoxy-5-(pyridin-2-ylmethyl)thieno[3,2- 20 c]quinolin-4(5H)-one ditrifluoroacetate

[0740]



[0741]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 1-(1,3-benzodioxol-5-ylmethyl)piperazine.

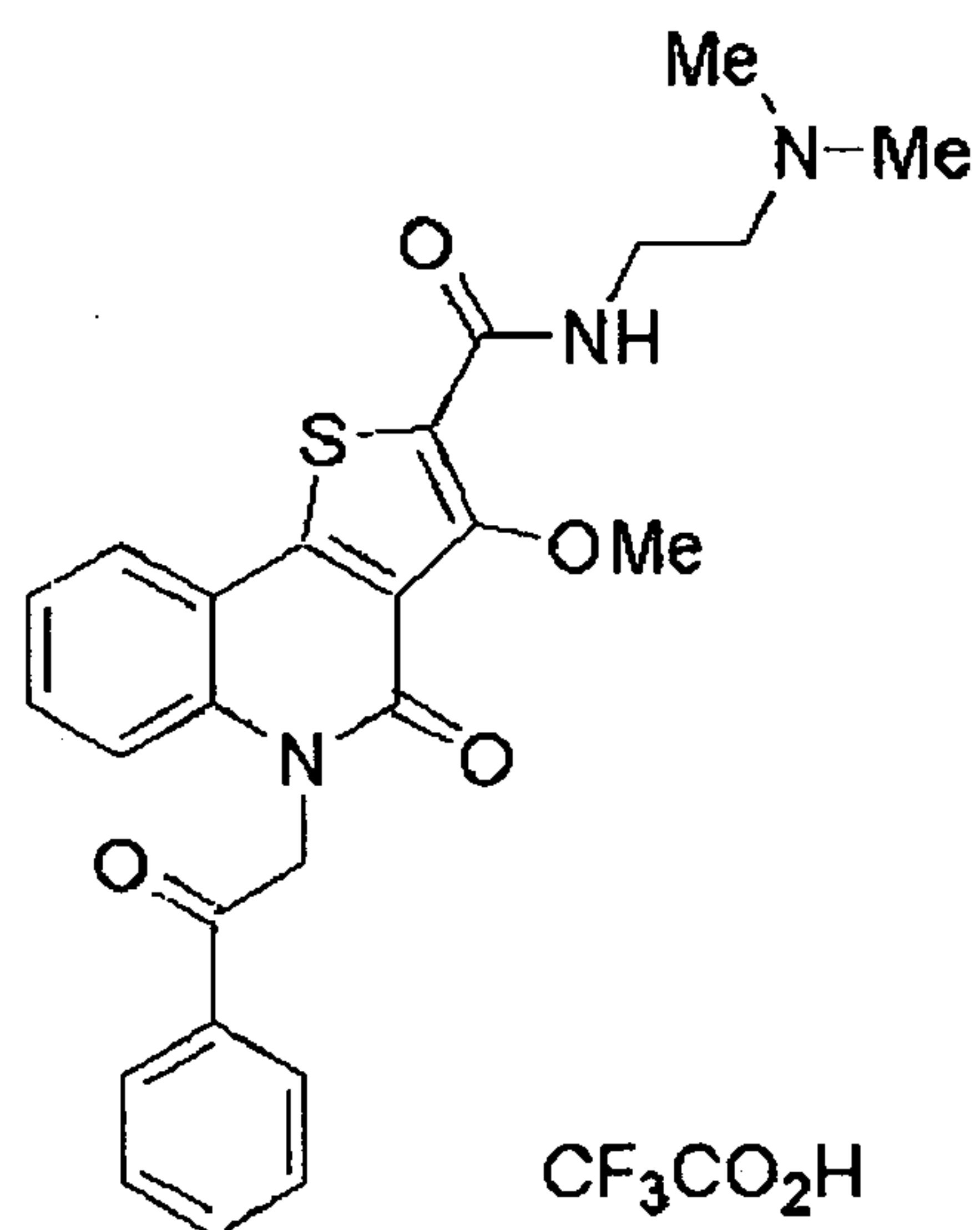
LC/MS 569 (M+H).

[0742]

Example 5

Production of N-[2-(dimethylamino)ethyl]-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0743]



[0744]

To a solution (0.15 M, 0.40 mL, 60 μmol) of the compound of Reference Example 7 in DMF were added a solution (0.66 M, 0.10 mL, 63 μmol) of N,N-dimethylethane-1,2-diamine in DMF and

a solution (0.39 M, 0.20 mL, 78 μ mol) of HOBt and WSCD in 1:1 mixture in DMF. The obtained mixture was agitated at room temperature for 14 hr. Dichloromethane (2 mL) and saturated aqueous sodium hydrogen carbonate solution (1 mL) were added to the reaction mixture, and the organic layer was filtered through a Teflon (registered trade mark) filter to separate from the aqueous layer, and the filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC to give the title compound (25.2 mg, 73%).

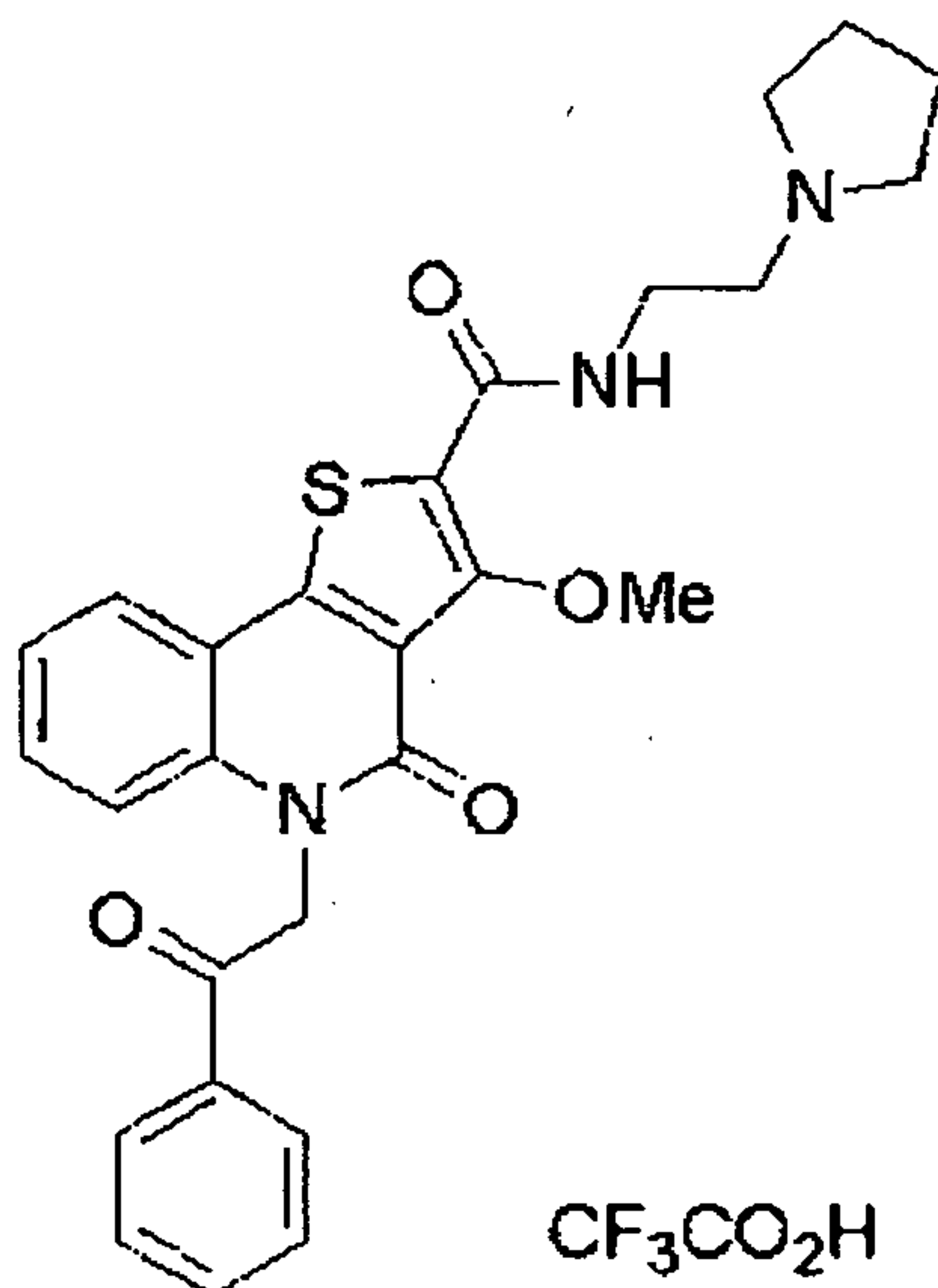
LC/MS 464 (M+H).

[0745]

Example 6

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0746]



[0747]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 2-pyrrolidin-1-ylethanamine.

LC/MS 490 (M+H).

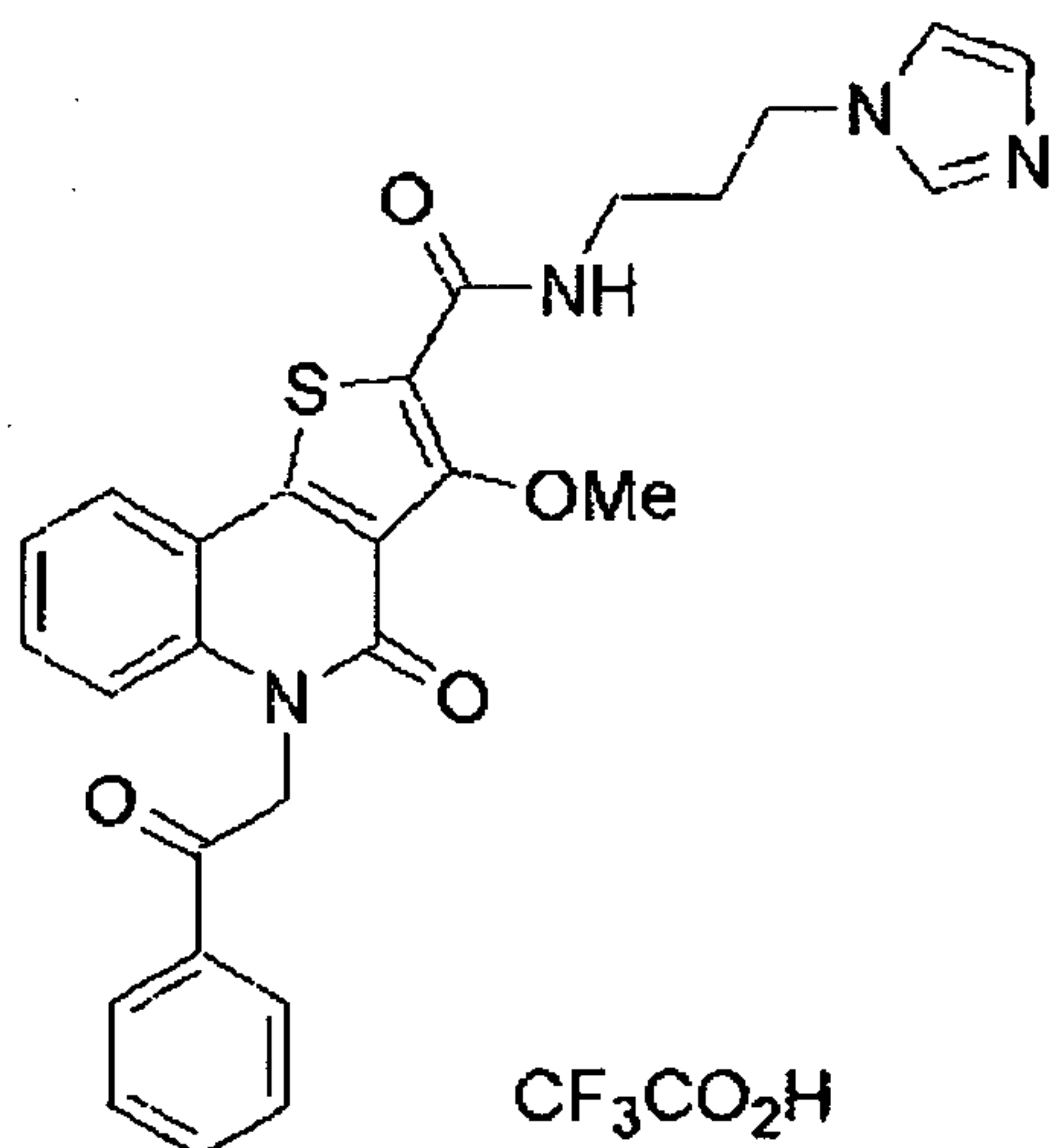
[0748]

Example 7

Production of N-[3-(1H-imidazol-1-yl)propyl]-3-methoxy-4-oxo-

5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0749]



5 [0750]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 3-(1H-imidazol-1-yl)propan-1-amine.

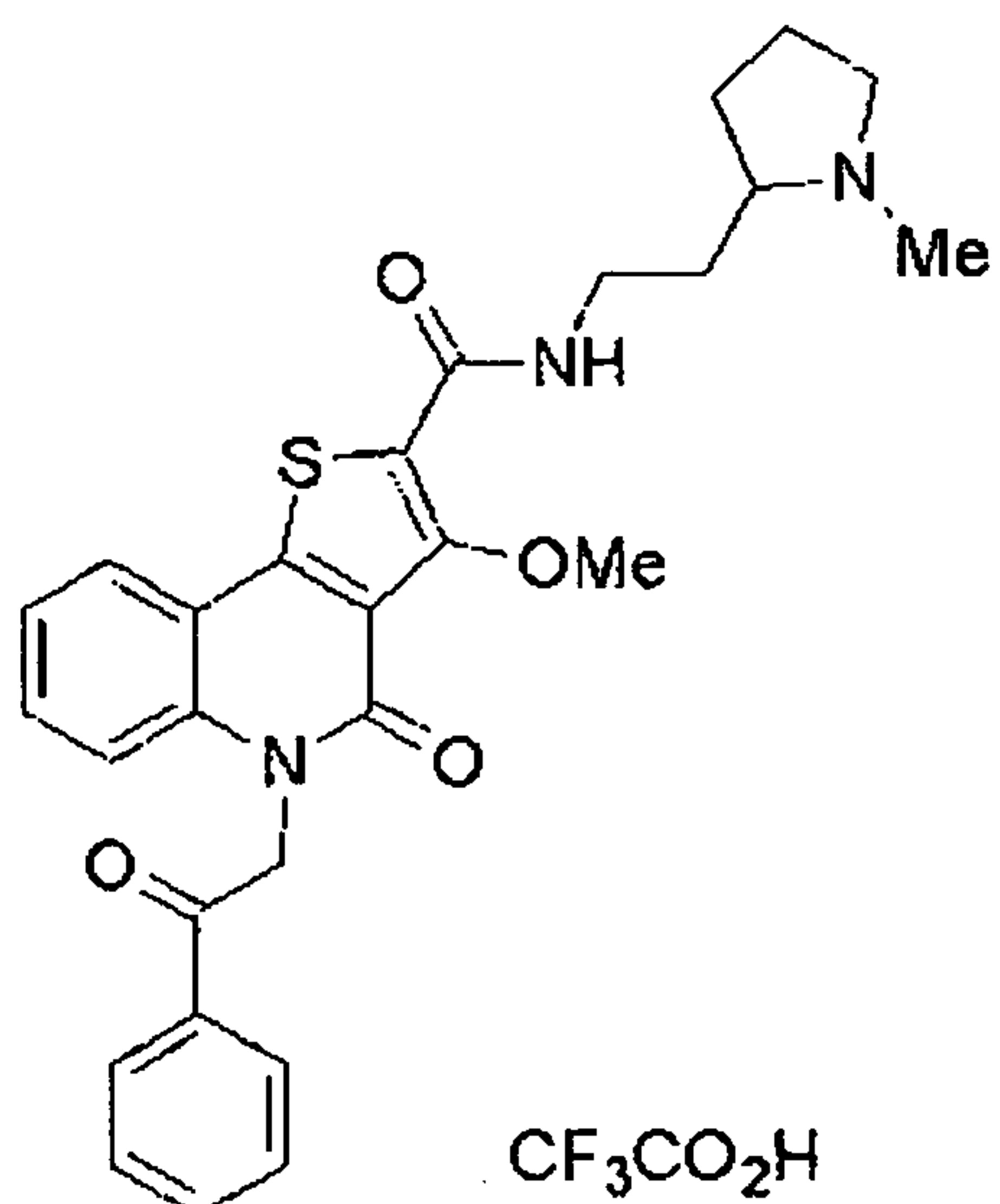
LC/MS 501 (M+H).

10 [0751]

Example 8

Production of 3-methoxy-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

15 [0752]



[0753]

In the same manner as in Example 5, the title compound

was obtained from the compound of Reference Example 7 and 2-(1-methylpyrrolidin-2-yl)ethanamine.

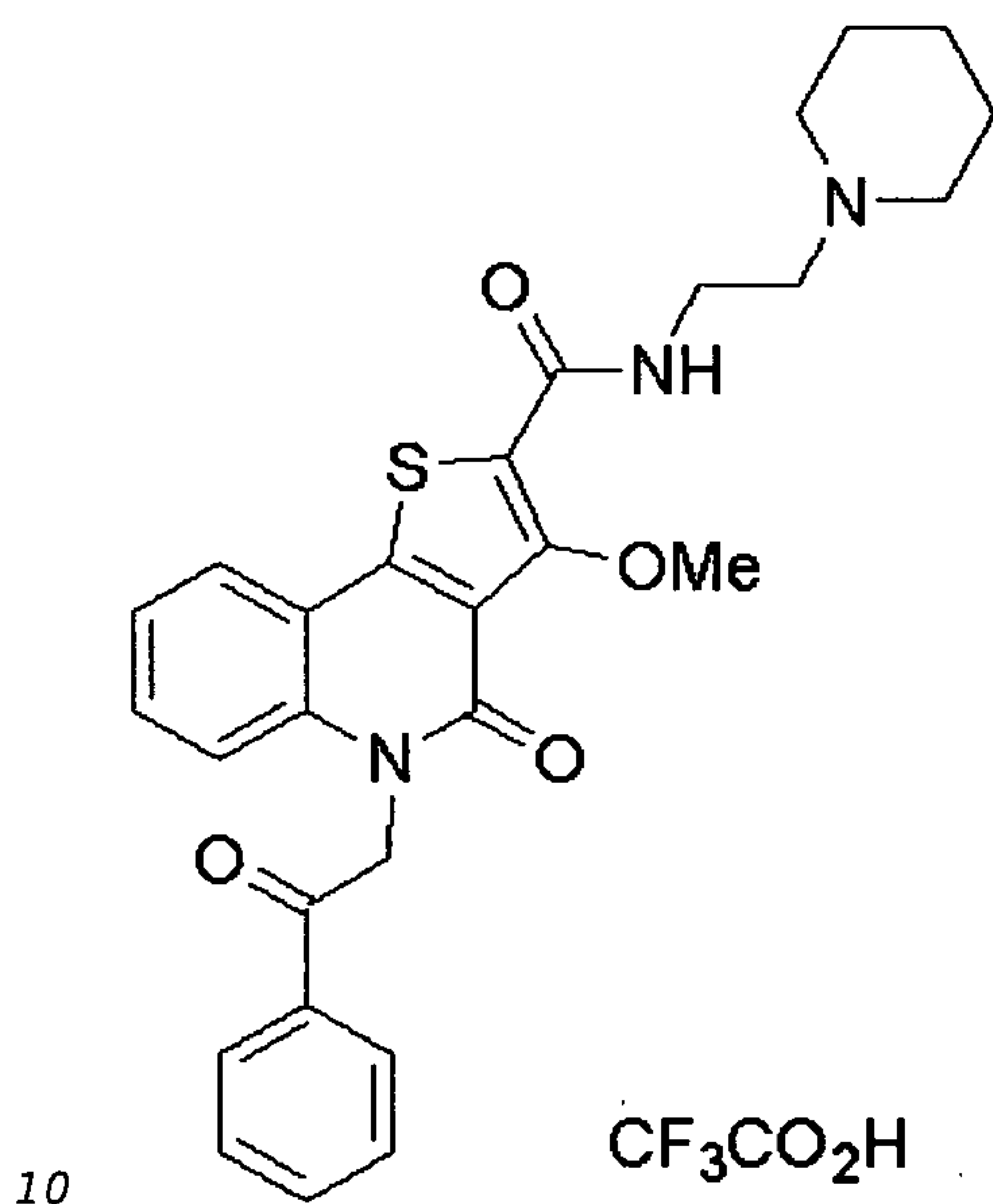
LC/MS 504 (M+H).

[0754]

5 Example 9

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-piperidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0755]



[0756]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 2-piperidin-1-ylethanamine.

15 LC/MS 504 (M+H).

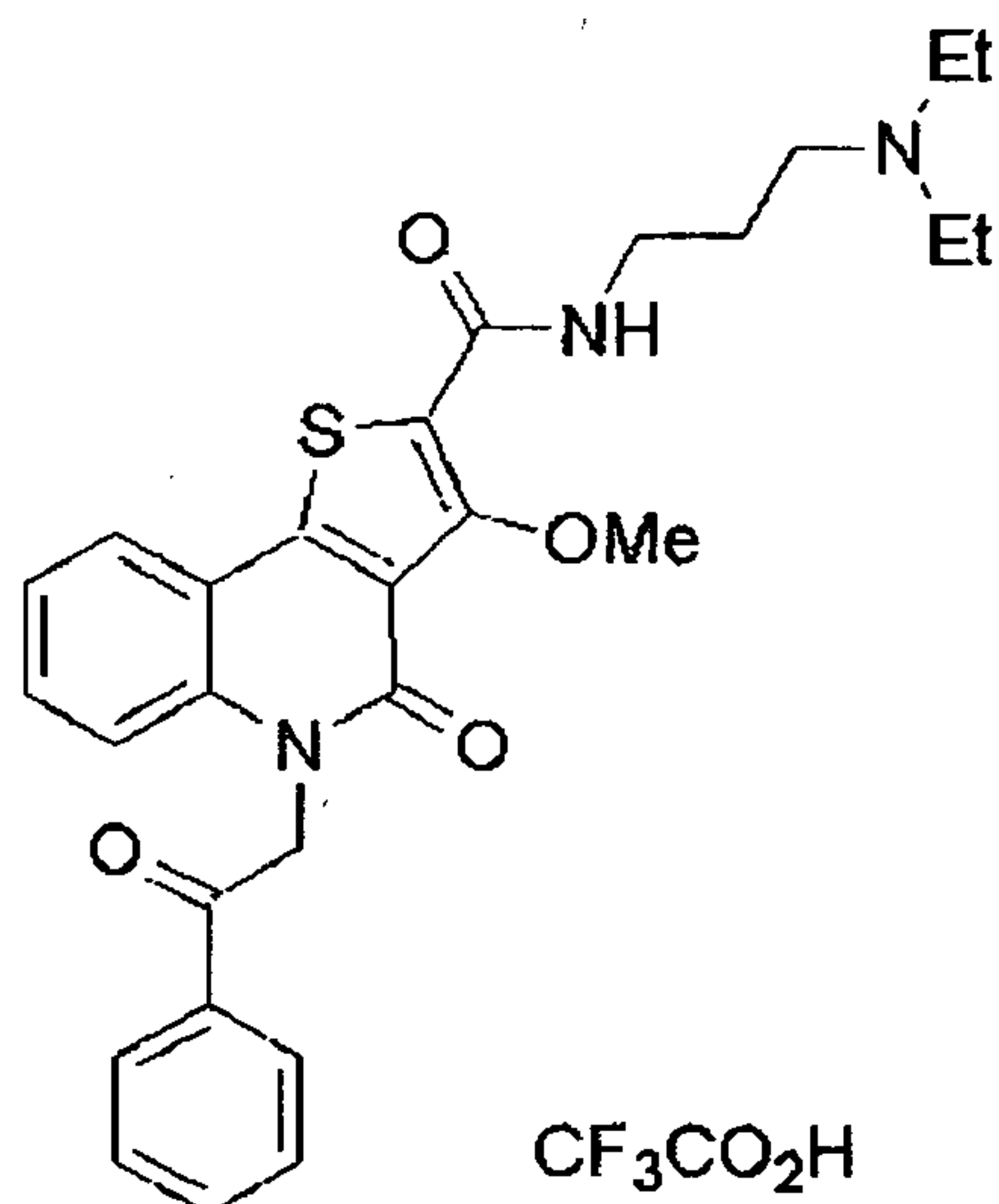
[0757]

Example 10

Production of N-[3-(diethylamino)propyl]-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-

20 carboxamide trifluoroacetate

[0758]



[0759]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and N,N-diethylpropane-1,3-diamine.

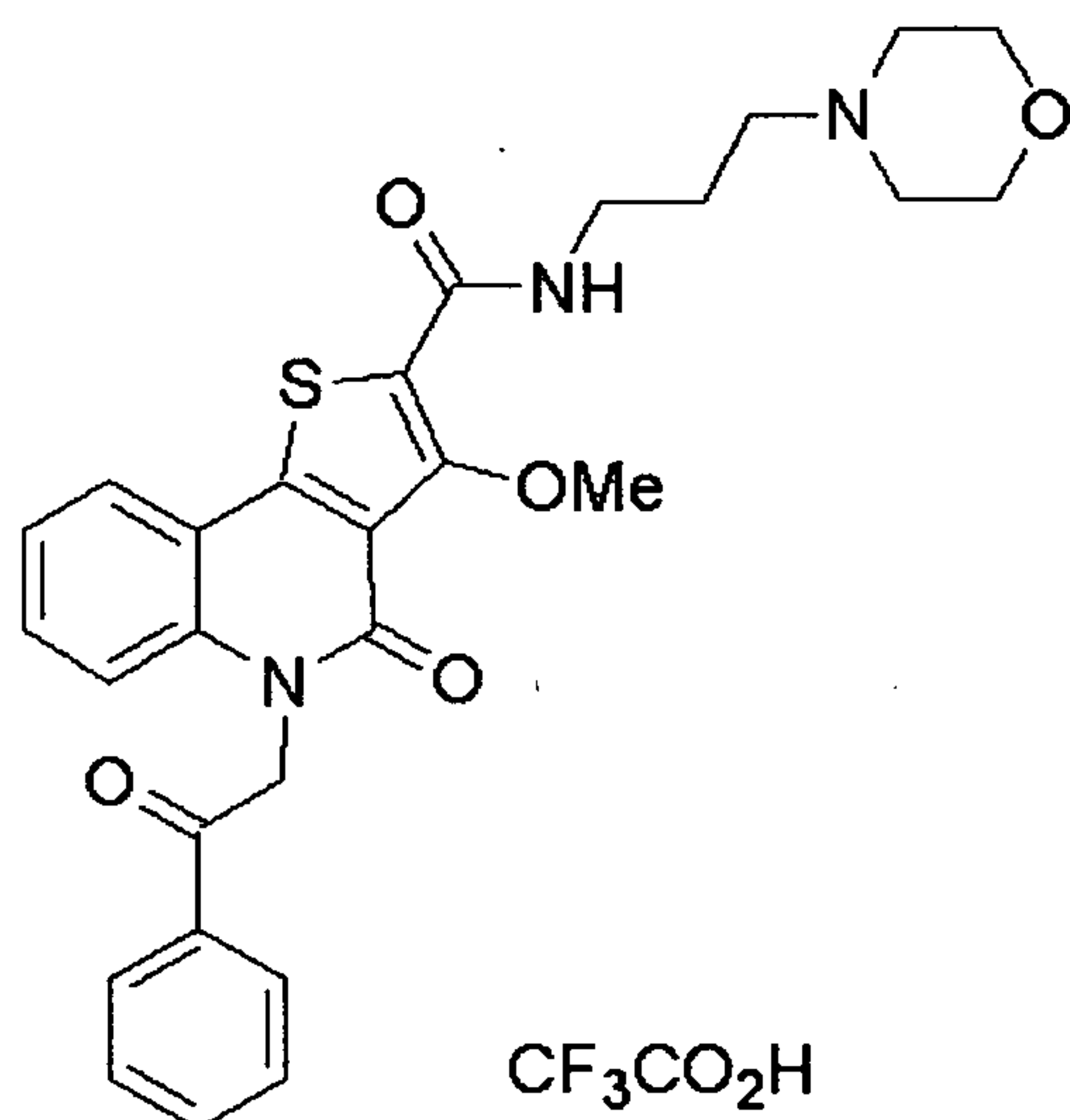
LC/MS 506 (M+H).

[0760]

Example 11

Production of 3-methoxy-N-(3-morpholin-4-ylpropyl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0761]



[0762]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 3-morpholin-4-ylpropan-1-amine.

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __3__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

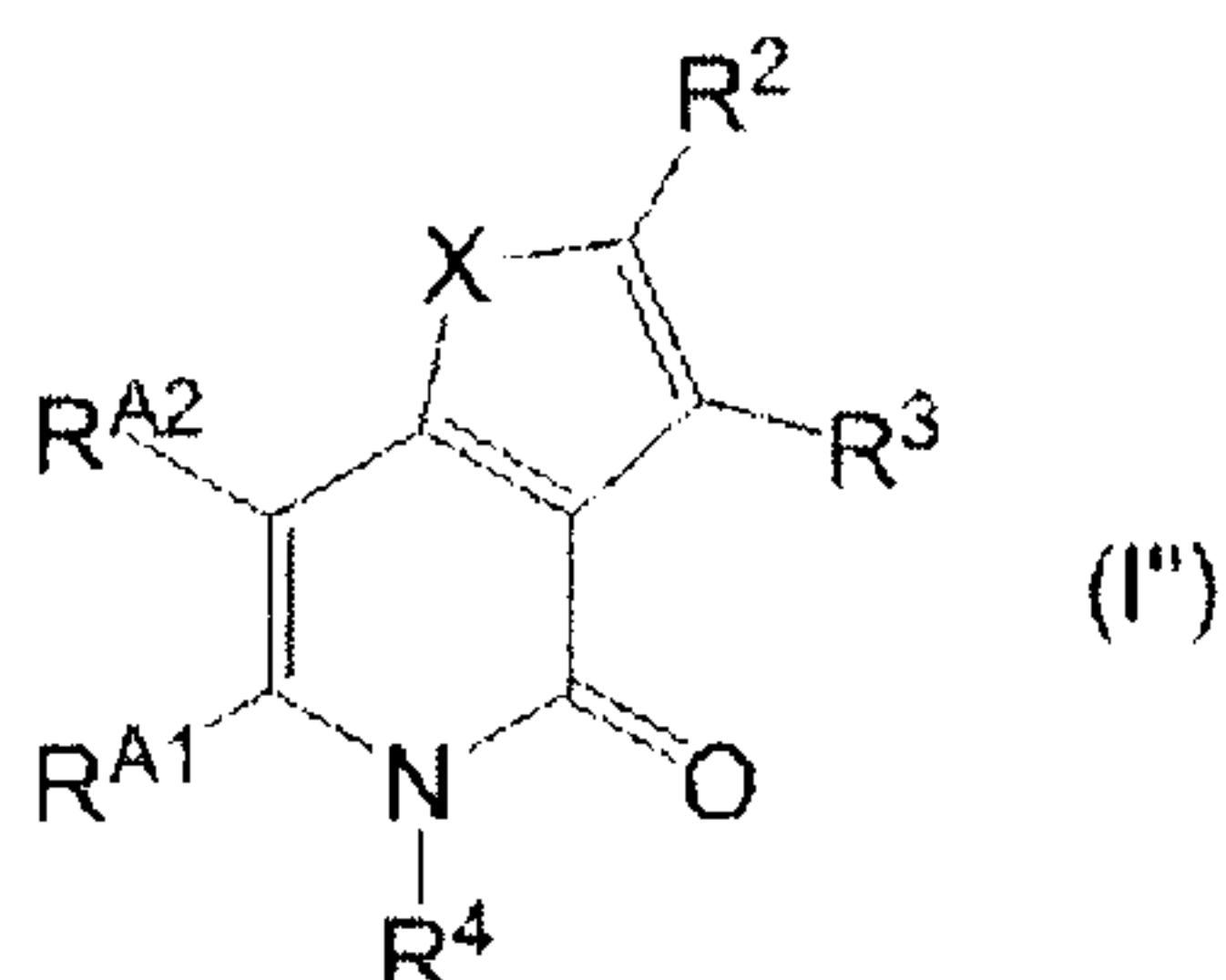
THIS IS VOLUME __1__ OF __3__

NOTE: For additional volumes please contact the Canadian Patent Office.

27103-668

CLAIMS:

1. A compound represented by the formula



wherein

- 5 X is S or N(C₁₋₆ alkyl);

R² is carbamoyl optionally having 1 or 2 substituents selected from

- (1) C₁₋₆ alkyl optionally having one substituent selected from

(1') di-C₁₋₆ alkylamino,

- 10 (2') hydroxy, and

(3') heterocyclic group,

- (2) C₃₋₆ cycloalkyl optionally substituted by hydroxy, and

- (3) heterocyclic group optionally having one substituent selected from

- 15 (1') C₁₋₆ alkyl optionally substituted by hydroxy,

- (2') C₁₋₆ alkyl-carbonyl optionally having one substituent selected from

(a) C₁₋₆ alkyl-carbonyloxy, and

27103-668

(b) hydroxy,

(3') C₁₋₆ alkoxy-carbonyl, and

(4') 6-membered aromatic heterocyclic group;

R³ is hydroxy optionally having C₁₋₆ alkyl optionally having 1
5 to 3 halogen atoms;

R⁴ is

(1) hydrogen atom, or

(2) C₁₋₆ alkyl optionally having one substituent selected from

(1') C₆₋₁₀ aryl optionally having (i) 1 or 2 C₁₋₆
10 alkoxy or (ii) one halogen atom,

(2') C₆₋₁₀ aryl-carbonyl optionally having one halogen
atom or C₁₋₆ alkoxy;

R^{A1} is a C₁₋₆ alkyl group; andR^{A2} is a hydrogen atom or a C₁₋₆ alkyl group;

15 or a salt thereof.

2. 3-Ethoxy-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-
1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-
pyrrolo[3,2-c]pyridine-2-carboxamide.

3. N-[1-(Hydroxyacetyl)piperidin-4-yl]-1,6-dimethyl-4-
20 oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-
dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide.

4. 6-Ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-

27103-668

4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide.

5. A salt of the compound of claim 2, 3 or 4.

6. A pharmaceutically acceptable salt of the compound of
5 claim 2, 3 or 4.

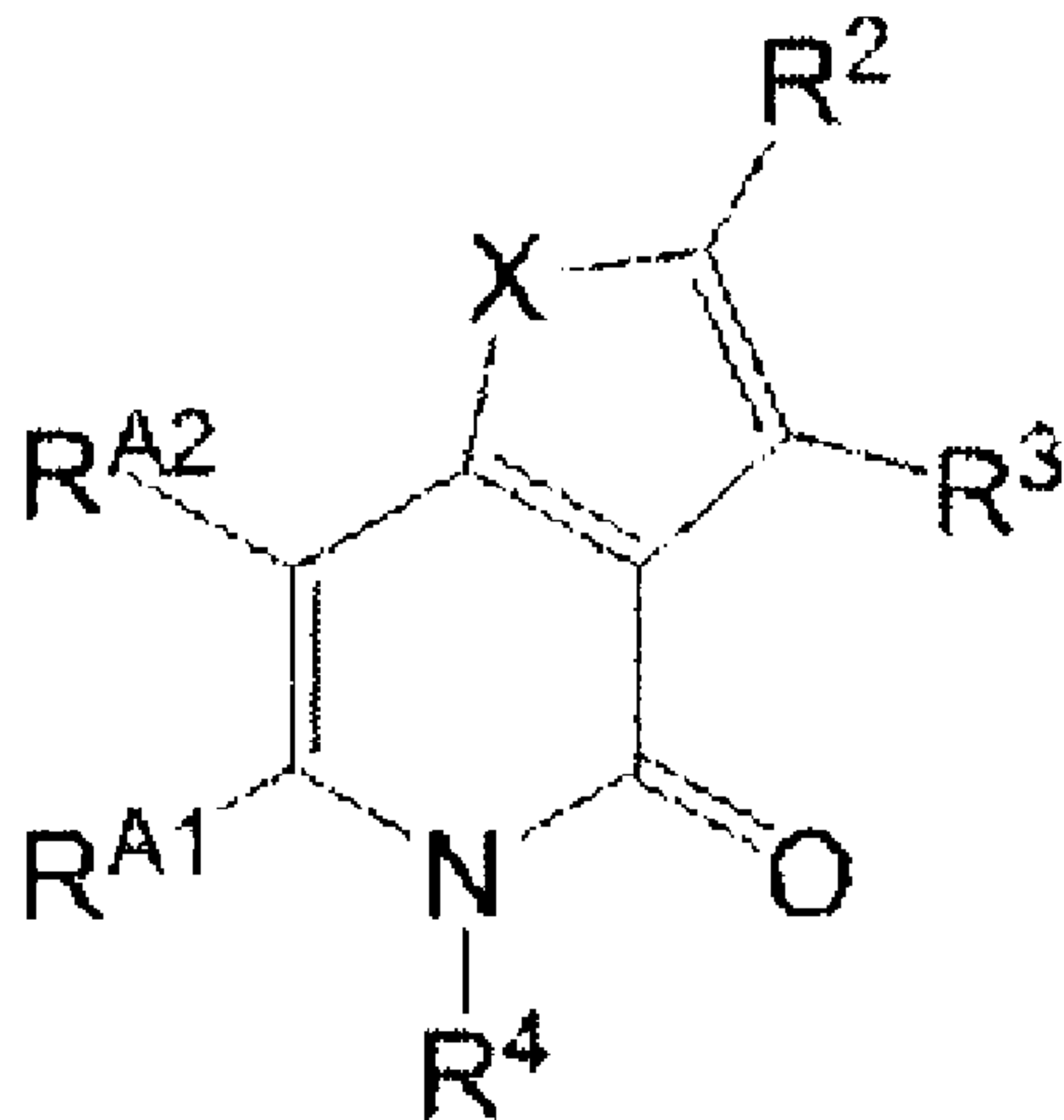
7. A pharmaceutical agent comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof and a pharmacologically acceptable carrier.

8. The pharmaceutical agent of claim 7, which is an Smo
10 inhibitor.

9. The pharmaceutical agent of claim 7, which is an agent for the prophylaxis or treatment of cancer.

10. Use of the compound of claim 1 or a pharmaceutically acceptable salt thereof for the production of an Smo inhibitor.

15 11. Use of the compound of claim 1 or a pharmaceutically acceptable salt thereof for the production of an agent for the prophylaxis or treatment of cancer.



(Iⁱⁱ)