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Notice Of Entitlement

I, John David O'Connor, of 31 Market Street, Sydney, New South Wales, 2000, Australia, Patent Attorney for the Applicant/Nominated Person in respect of Application No. 55163/96, state the following:-

The Applicant/Nominated Person has entitlement from the actual inventors as follows:

The Applicant/Nominated Person is the assignee of the actual inventors.

The Applicant/Nominated Person is the applicant of the application listed in the Declaration under Article 8 of the PCT.

The basic application listed on the Declaration under Article 8 of the PCT is the first application made in a Convention country in respect of the invention.

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John David O'Connor

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PROPENONE DERIVATIVES

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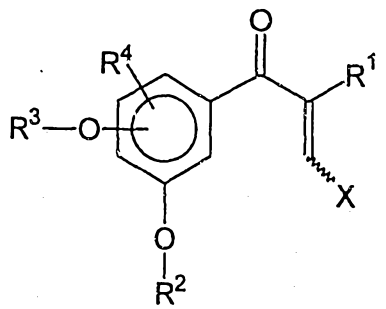
(56) Prior Art Documents
US 4904697

(57) Claim

1. A propenone derivative represented by the following formula (I):



wherein R^1 represents hydrogen or lower alkyl; R^2 and R^3 independently represent hydrogen, lower alkyl, or substituted or unsubstituted aralkyl, or alternatively R^2 and R^3 are combined to form substituted or unsubstituted methylene or ethylene; R^4 represents hydrogen, hydroxy, lower alkyl, substituted or unsubstituted aralkyl, lower alkoxy, substituted or unsubstituted aralkyloxy, or halogen; and X represents substituted or unsubstituted indolyl, with the proviso that when OR^3 is on the position 2 or position 6 of the benzene ring, R^3 is not hydrogen that when R^4 is on the position 2 or position 6 of the benene ring, R^4 is not hydroxy; and that the combination of OR^2, OR^3, and R^4 is not 3,4-dimethoxy or 3,4,5-trimethoxy; or pharmaceutically acceptable salts thereof.

33. A method for the treatment or prophylaxis of a tumour in a mammal, which method comprises administering to said mammal an effective amount of at least one compound according to any one of claims 1 to 30, or of a composition according to claim

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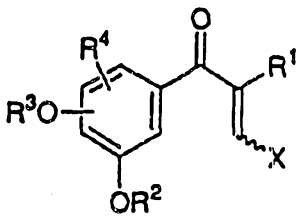
(54) Title : PROPENONE DERIVATIVES

(54) 発明の名称 プロペノン誘導体



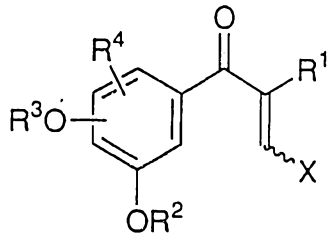
(I)

(57) Abstract

Propenone derivatives represented by general formula (I) or pharmacologically acceptable salts thereof, wherein R^1 represents hydrogen or lower alkyl; R^2 and R^3 are the same or different and each represents hydrogen, lower alkyl or optionally susbtituted aralkyl, or R^2 and R^3 form together optionally substituted methylene or ethylene; R^4 represents hydrogen, hydroxy, lower alkyl, optionally substituted aralkyl, lower alkoxy, optionally substituted aralkyloxy or halogeno; and X represents optionally substituted indolyl, provided that when OR^3 is located at the 2- or 6-position of the benzene ring, then R^3 is not hydrogen, while when R^4 is located at the 2- or 6-position of the benzene ring, then R^4 is not hydroxy, and the case where OR^2, OR^3 and R^4 represent together 3,4-dimethoxy or 3,4,5-trimethoxy is excepted.

（５７）要約

本発明は、一般式（Ｉ）



(I)

（式中、R^1 は水素または低級アルキルを表し、R^2 およびR^3 は同一または異なって水素、低級アルキルまたは置換もしくは非置換のアラルキルを表すか、あるいはR^2 とR^3 が一緒になって置換もしくは非置換のメチレンまたはエチレンを表し、R^4 は水素、ヒドロキシ、低級アルキル、置換もしくは非置換のアラルキル、低級アルコキシ、置換もしくは非置換のアラルキルオキシまたはハロゲンを表し、Ｘは置換もしくは非置換のインドリル基を表す。ただし、OR^3 がベンゼン環の２位または６位上にあるときR^3 は水素でなく、R^4 がベンゼン環の２位または６位上にあるときR^4 はヒドロキシでなく、OR^2 、OR^3 およびR^4 で３，４－ジメトキシまたは３，４，５－トリメトキシを表す場合を除く）で表されるプロペノン誘導体またはその薬理上許容される塩に関する。

SPECIFICATION
PROPENONE DERIVATIVES

Technical Field

The present invention relates to propenone derivatives having an antitumor activity.

Background Art

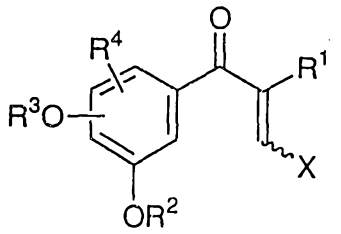
Typical examples of compounds having an antitumor activity include mitomycin C, adriamycin, vincristine, and the like, all of which are clinically used as useful anticancer agents. However, since each of the compounds also has adverse effects such as myelotoxicity, cardiotoxicity, nerve damage, etc., a novel anticancer agent having less adverse effects is demanded.

Chalcone derivatives are known as having the activity to inhibit polymerization of tubulin [Journal of the Medicinal Chemistry (J. Med. Chem.), 33, 1948 (1990) and Journal of Natural Products (J. Nat. Prod.), 56, 1718 (1993)]. Chalcone derivatives are also known as having an anticancer activity (U. S. Patent No. 4904697). 3-Indolyl-1-phenyl-2-propen-1-one derivatives are known as inhibiting the tyrosine-phospholylation of cell growth factor receptor [Cancer Research (Cancer Res.), 54, 6106 (1994) and WO 91/16305], being useful as an organic nonlinear optical material (Japanese Published Unexamined Patent Application No. 255426/91), and having an antiallergic activity [Khim.-Farm. Zh., 25, 18 (1991)].

Further, 3-(indol-3-yl)-1-phenyl-2-propen-1-one derivatives are disclosed in French Patent No. 2230349, Khim. Geterotsikl. Soedin, 1066 (1970), Khim. Geterotsikl. Soedin, 268 (1969), Khim. Geterotsikl. Soedin, 399 (1970), Farmaco Ed. Sci., 26, 591 (1971), etc.

Disclosure of the Invention

The present invention relates to propenone derivatives represented by the following formula (I):



(I)

wherein R^1 represents hydrogen or lower alkyl; R^2 and R^3 independently represent hydrogen, lower alkyl, or substituted or unsubstituted aralkyl, or alternatively R^2 and R^3 are combined to form substituted or unsubstituted methylene or ethylene; R^4 represents hydrogen, hydroxy, lower alkyl, substituted or unsubstituted aralkyl, lower alkoxy, substituted or unsubstituted aralkyloxy, or halogen; and X represents substituted or unsubstituted indolyl, with the proviso that when OR^3 is on the position 2 or position 6 of the benzene ring, R^3 is not hydrogen; that when R^4 is on the position 2 or position 6 of the benzene ring, R^4 is not hydroxy; and that the combination of OR^2, OR^3, and R^4 is not 3,4-dimethoxy or 3,4,5-trimethoxy; or pharmaceutically acceptable salts thereof.

Compounds represented by the formula (I) are hereinafter referred to as Compounds (I). Compounds (Ia) and the like are included in Compounds (I).

In the definitions of the groups of Compounds (I), the lower alkyl and the lower alkyl moiety of the lower alkoxy mean a straight-chain or branched alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, 2-butyl, isobutyl, tert-butyl, 1-pentyl, 2-pentyl, 3-pentyl, isoamyl, neopentyl, and hexyl. The aralkyl and the aralkyl moiety of the aralkyloxy mean an aralkyl group having 7 to 15 carbon atoms, such as benzyl, naphthylmethyl, and benzhydryl. The halogen includes fluorine, chorine, bromide, and iodine.

The substituted aralkyl and substituted aralkyloxy each has the same or different 1 to 3 substituents such as lower alkyl, hydroxy, lower alkoxy, amino, lower alkylamino, di(lower alkyl)amino, lower alkanoylamino, lower

alkoxycarbonylamino, halogen, nitro, carboxy, lower alkanoyl, and lower alkoxycarbonyl. In the definitions of the substituents, the lower alkyl moiety of the lower alkylamino, di(lower alkyl)amino, lower alkanoylamino, lower alkoxycarbonylamino, lower alkanoyl, and lower alkoxycarbonyl has the same meaning as the lower alkyl defined above, and the lower alkyl, lower alkoxy, and halogen have the same meanings as defined above.

The substituted methylene or ethylene has the same or different 1 to 3 substituents such as lower alkyl, and the lower alkyl has the same meaning as defined above.

Examples of the substituent on the nitrogen atom at position 1 of the substituted indolyl group are lower alkyl, lower alkanoyl, lower alkoxycarbonyl, and aralkyl, and examples of the substituents on the carbon atoms at positions 2 to 7 of the substituted indolyl group are lower alkyl, lower alkoxy, amino, lower alkylamino, di(lower alkyl)amino, lower alkanoylamino, lower alkoxycarbonylamino, halogen, nitro, carboxy, lower alkanoyl, lower alkoxycarbonyl, and aralkyl. In the definitions of the substituents, the lower alkyl, lower alkoxy, lower alkylamino, di(lower alkyl)amino, lower alkanoylamino, lower alkoxycarbonylamino, halogen, lower alkanoyl, lower alkoxycarbonyl, and aralkyl have the same meanings as defined above.

The pharmaceutically acceptable salts of Compounds (I) include inorganic acid addition salts such as hydrochloride, sulfate, and phosphate, organic acid addition salts such as acetate, maleate, fumarate, succinate, tartrate, citrate, oxalate, and methanesulfonate, alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, metal salts such as aluminium salt and zinc salt, and ammonium salt.

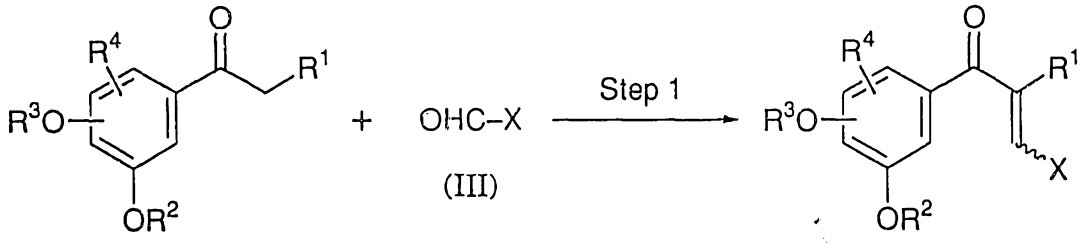
The present invention is described in detail below.

In the processes shown below, if the defined

groups are converted into undesired groups under the conditions of the processes or are not suitable for carrying out the processes, the processes can be readily carried out by applying thereto means conventionally used in organic synthetic chemistry, for example, a means such as protection or deprotection of functional groups, or a method such as oxidation, reduction, or hydrolysis.

Process for Producing Compound (I) - 1

Compound (I) can be prepared according to the following reaction step.



(II) (I)

(In the formulae, R^1, R^2, R^3, R^4, and X have the same meanings as defined above.)

Step 1

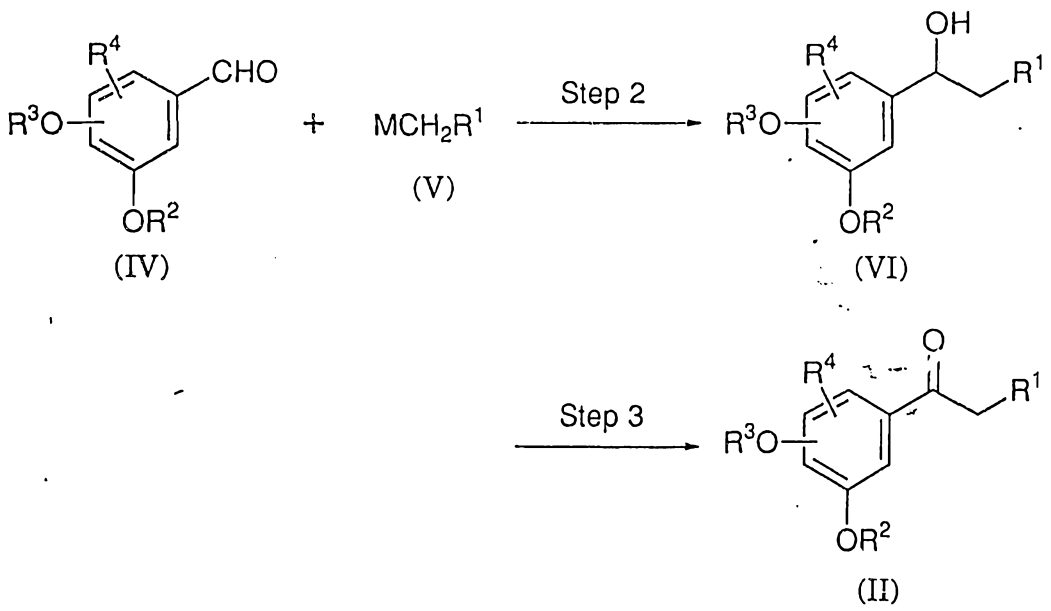
Compound (I) can be obtained by reacting Compound (II) with Compound (III) in the presence of a base in an inert solvent. As the base, inorganic bases such as potassium carbonate, sodium carbonate, and cesium fluoride, quaternary ammonium fluorides such as tetra-n-butylammonium fluoride, secondary amines such as piperidine, pyrrolidine, and morpholine, metal alkoxides such as potassium tert-butoxide, metal amides such as lithium diisopropylamide, metal hydrides such as sodium hydride, and the like may be used in an amount of 0.01 to 10 equivalents. As the solvent, aprotic solvents (for example, ethyl acetate and tetrahydrofuran), aromatic hydrocarbons (for example, toluene), halogenated hydrocarbons (for example, chloroform), alcohols (for example, methanol and ethanol), and the like may be used alone or in combination. The

reaction is carried out at the temperature between -78°C and the boiling point of the solvent employed in the reaction, and is completed in 0.1 hour to 10 days.

The starting Compound (II) is commercially available, is reported in a literature, or can be prepared according to the following reaction steps.

Process for Producing Compound (II) - 1

Compound (II) can be prepared according to the following reaction steps.



(In the formulae, M represents alkali metal, alkaline earth metal halide, or cerium dichloride; and R^1, R^2, R^3, and R^4 have the same meanings as defined above.)

In the definition of M, the alkali metal means lithium, sodium, potassium, cesium, or the like, and the alkaline earth metal halide means magnesium chloride, magnesium bromide, magnesium iodide, or the like.

Step 2

Compound (VI) can be obtained by reacting Compound (IV) with 1 to 2 equivalents of Compound (V) in an inert solvent. As the solvent, aprotic solvents (for example,

diethyl ether, tetrahydrofuran, and ethyl acetate), aromatic hydrocarbons (for example, toluene), and the like may be used alone or in combination. The reaction is carried out at the temperature between -100°C and the boiling point of the solvent employed in the reaction, and is completed in 0.1 to 24 hours.

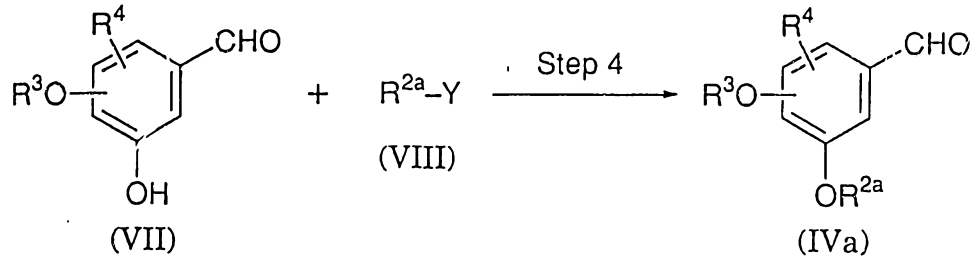
Step 3

Compound (II) can be obtained by treating Compound (VI) in the presence of an oxidizing agent in an inert solvent. As the oxidizing agent, 1 to 50 equivalents of chromium trioxide, a pyridine complex or hydrochloric acid complex thereof, potassium dichromate, manganese dioxide, 2,3-dichloro-5,6-dicyanobenzoquinone, and the like may be used. As the solvent, aprotic solvents (for example, acetone and N,N-dimethylformamide), halogenated hydrocarbons (for example, dichloromethane and chloroform), acetic acid, sulfuric acid, water, and the like may be used alone or in combination. The reaction is carried out at the temperature between -10°C and the boiling point of the solvent employed in the reaction, and is completed in 0.1 to 150 hours.

Compound (IV) is commercially available, is reported in a literature, or can be prepared according to the following reaction steps.

Process for Producing Compound (IV) - 1

Compound (IVa) which is Compound (IV) in which R^2 is lower alkyl or substituted or unsubstituted aralkyl can be prepared according to the following reaction step from the aldehyde which is commercially available or known in the literature.



(VII) (VIII) (IVa)

(In the formulae, R^{2a} represents lower alkyl or substituted or unsubstituted aralkyl; Y represents halogen; and R^3 and R^4 have the same meanings as defined above.)

In the definition of R^{2a}, the lower alkyl and substituted or unsubstituted aralkyl have the same meanings as defined above. In the definition of Y, the halogen has the same meaning as defined above.

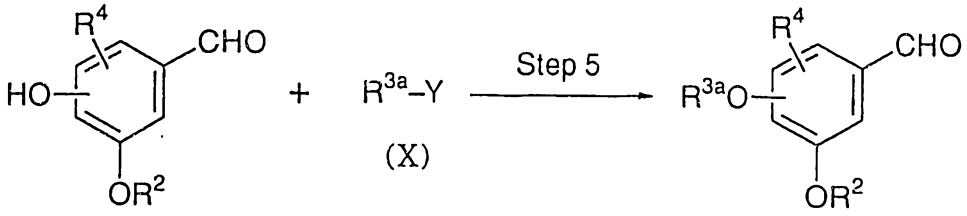
Step 4

Compound (IVa) can be obtained by reacting Compound (VII) with Compound (VIII) in the presence of a base in an inert solvent. As the base, inorganic bases such as sodium hydroxide, potassium carbonate, sodium carbonate, and cesium fluoride, quaternary ammonium fluorides such as tetra-n-butylammonium fluoride, metal alkoxides such as potassium tert-butoxide, metal amides such as lithium diisopropylamide, metal hydrides such as sodium hydride, and the like may be used in an amount of 1 to 100 equivalents. As the solvent, aprotic solvents (for example, ethyl acetate, tetrahydrofuran, acetone, and N,N-dimethylformamide), aromatic hydrocarbons (for example, toluene), halogenated hydrocarbons (for example, chloroform), alcohols (for example, methanol and ethanol), water, and the like may be used alone or in combination. The reaction is carried out at the temperature between -78°C and the boiling point of the solvent employed in the reaction, and is completed in 0.1 hour to 3 days.

Process for Producing Compound (IV) - 2

Compound (IVb) which is Compound (IV) in which R^3 is lower alkyl or substituted or unsubstituted aralkyl can

be prepared according to the following reaction step from the aldehyde which is commercially available or known in the literature.



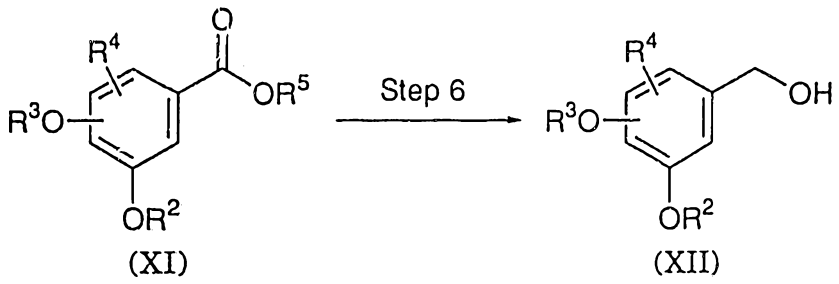
(In the formulae, R^{3a} represents lower alkyl or substituted or unsubstituted aralkyl; and R^2, R^4, and Y have the same meanings as defined above.)

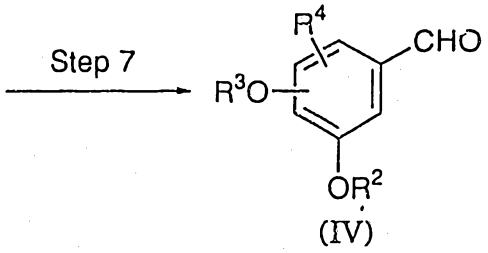
Step 5

Compound (IVb) can be obtained by reacting Compound (IX) with Compound (X) according to the same method in Step 4.

Process for Producing Compound (IV) - 3

Compound (IV) can be prepared according to the following reaction steps from the carboxylic acid or ester which is commercially available or known in the literature.





(In the formulae, R^5 represents hydrogen, lower alkyl, or aralkyl; and R^2, R^3, and R^4 have the same meanings as defined above.)

In the definition of R^5, the lower alkyl and aralkyl have the same meanings as defined above.

Step 6

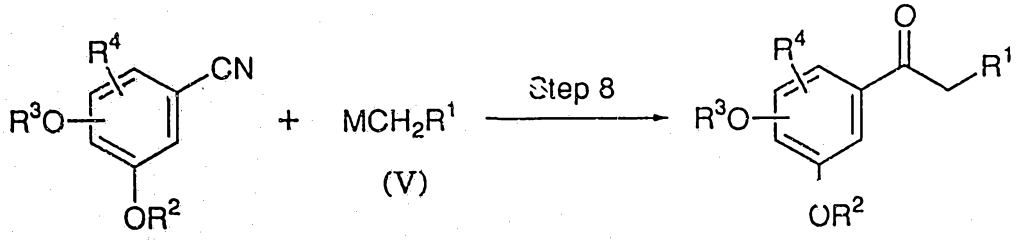
Compound (XII) can be obtained by treating Compound (XI) with a hydride reagent in an inert solvent. As the hydride reagent, 1 to 100 equivalents of sodium borohydride, lithium aluminum hydride, alane, borane, diisopropyl aluminium hydride, and the like may be used. As the solvent, aprotic solvents (for example, diethyl ether and tetrahydrofuran), aromatic hydrocarbons (for example, toluene), alcohols (for example, methanol and ethanol), and the like may be used alone or in combination. The reaction is carried out at the temperature between -78°C and the boiling point of the solvent employed in the reaction, and is completed in 0.1 hour to 3 days.

Step 7

Compound (IV) can be obtained by reacting Compound (XII) according to the same method in Step 3.

Process for Producing Compound (II) - 2

Compound (II) can be prepared according to the following reaction step from the nitrile which is commercially available or known in the literature.



(XIII) (II)

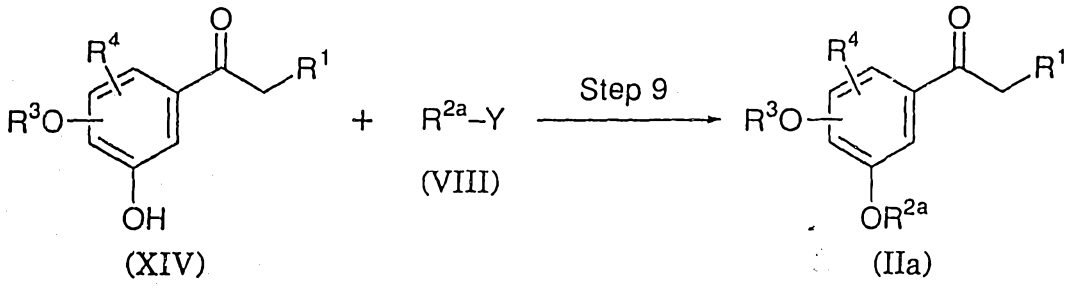
(In the formulae, R^1, R^2, R^3, R^4, and M have the same meanings as defined above.)

Step 8

Compound (II) can be obtained by reacting Compound (XIII) with Compound (V) according to the same method in Step 2.

Process for Producing Compound (II) - 3

Compound (IIa) which is Compound (II) in which R^2 is lower alkyl or substituted or unsubstituted aralkyl can be prepared according to the following reaction step from the ketone which is commercially available or known in the literature.



(XIV) (IIa)

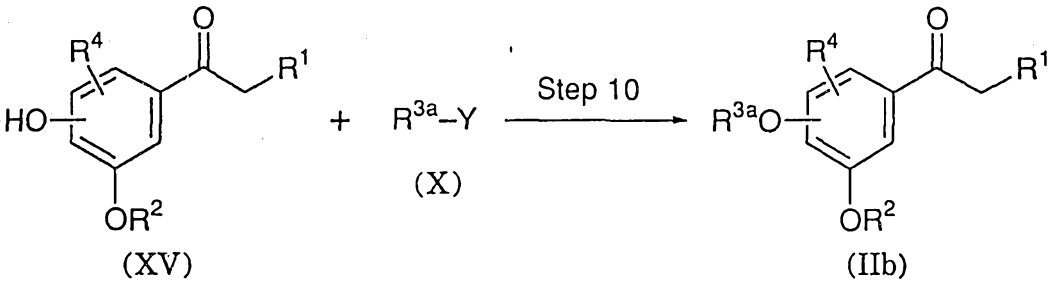
(In the formulae, R^1, R^{2a}, R^3, R^4, and Y have the same meanings as defined above.)

Step 9

Compound (IIa) can be obtained by reacting Compound (XIV) with Compound (VIII) according to the same method in Step 4.

Process for Producing Compound (II) - 4

Compound (IIb) which is Compound (II) in which R^3 is lower alkyl or substituted or unsubstituted aralkyl can be prepared according to the following reaction step from the ketone which is commercially available or known in the literature.



(XV) (X) (IIb)

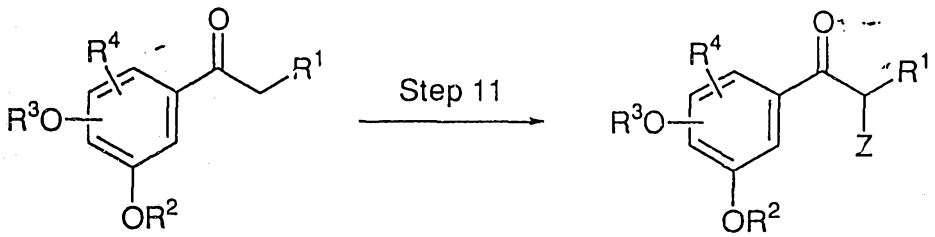
(In the formulae, R^1, R^2, R^{3a}, R^4, and Y have the same meanings as defined above.)

Step 10

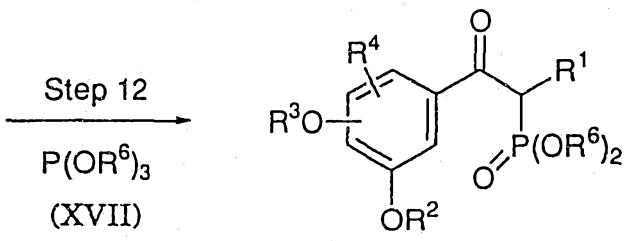
Compound (IIb) can be obtained by reacting Compound (XV) with Compound (X) according to the same method in Step 4.

Process for Producing Compound (I) - 2

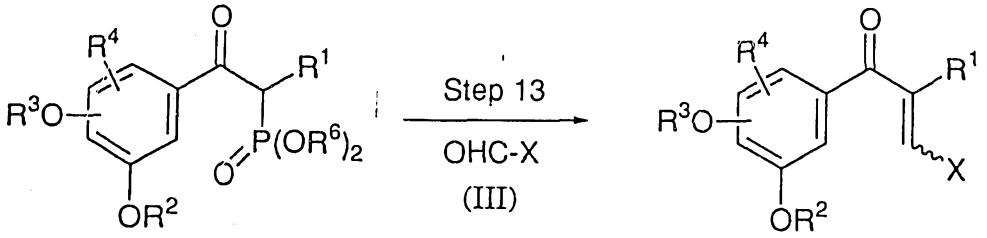
Compound (I) can be prepared according to the following reaction steps.



(II) (XVI)



(XVII) (XVIII)



(XVIII) (I)

(In the formulae, R^6 represents lower alkyl; Z represents halogen; and R^1, R^2, R^3, R^4, and X have the same meanings as defined above.)

In the definition of R^6, the lower alkyl has the same meaning as defined above. In the definition of Z, the halogen has the same meaning as defined above.

Step 11

Compound (XVI) can be obtained by treating Compound (II) with a halogenating agent in an inert solvent. As the halogenating agent, 1 to 5 equivalents of pyrrolidone hydrotribromide, tetra-n-butylammonium tribromide, bromine, and the like may be used. As the solvent, aprotic solvents (for example, ethyl acetate and tetrahydrofuran), acetic acid, water, and the like may be used alone or in combination. The reaction is carried out at the temperature between 0°C and the boiling point of the solvent employed in the reaction, and is completed in 0.1 to 24 hours.

Step 12

Compound (XVIII) can be obtained by reacting Compound (XVI) with 1 to 10 equivalents of Compound (XVII) in an inert solvent or without a solvent. As the solvent, aprotic solvents (for example, ethyl acetate, tetrahydrofuran, and N,N-dimethylformamide), aromatic hydrocarbons (for example, toluene), and the like may be used alone or in combination. The reaction is carried out at the temperature between 0°C and 200°C, and is completed in 0.5 to 100 hours.

Step 13

Compound (I) can be obtained by reacting Compound (XVIII) with Compound (III) according to the same method in Step 1.

The starting Compound (III) is commercially available, is known in the literature, or can be prepared according to the reaction steps which is known in the literature.

The intermediates and the desired compounds in the processes described above can be isolated and purified by purification methods conventionally used in organic synthetic chemistry, for example, filtration, extraction, washing, drying, concentration, recrystallization, and various kinds of chromatography. The intermediates may also be subjected to the subsequent reaction without isolation.

In the case where a salt of Compound (I) is desired and it is produced in the form of the desired salt, it can be subjected to purification as such. In the case where Compound (I) is produced in the free form and its salt is desired, Compound (I) is dissolved or suspended in a suitable solvent, followed by addition of an acid or base to form a salt by a conventional method.

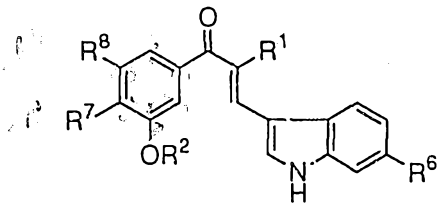
Compounds (I) can exist in the form of E/Z geometrical isomers, and the present invention covers all isomers including these geometrical isomers and mixtures thereof. In the case where Compound (I) is obtained in a E/Z mixture, and separation of E/Z isomers is desired, they can be isolated and purified by fractionation methods, for example, fractional crystallization, fractional precipitation, fractional dissolution, or the like.

Compounds (I) and pharmaceutically acceptable salts thereof may be in the form of adducts with water or various solvents, which are also within the scope of the present invention.

Examples of Compounds (I) obtained in the

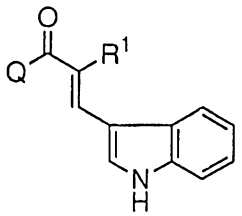
processes described above are shown in Table 1.

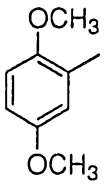
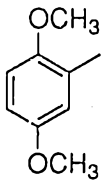
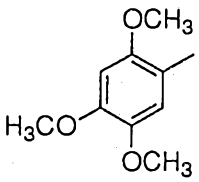
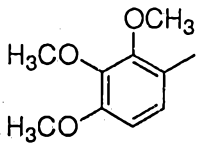
Table 1-1



Compd. No.	R^8	R^7	OR^2	R^1	R^6
1	OCH_3	H	OCH_3	H	H
2	OCH_3	OH	OCH_3	H	H
3	OCH_3	$OCH_2C_6H_5$	OCH_3	H	H
4	OCH_2CH_3	OCH_2CH_3	OCH_2CH_3	CH_3	H
5	OCH_3	OCH_2CH_3	OCH_3	CH_3	H
6	OCH_3	$OCH_2CH(CH_3)_2$	OCH_3	CH_3	H
7	OCH_3	CH_2CH_3	OCH_3	CH_3	H
8	OCH_3	- O CH_2 O -		CH_3	H
9	OCH_2CH_3	OCH_3	OCH_3	CH_3	H
10	Br	OCH_3	OCH_3	CH_3	H
11	OCH_3	OCH_2CH_3	OCH_3	CH_3	CH_3
12	OCH_3	- O CH_2 O -		CH_3	CH_3
13	Br	$OCH_2CH(CH_3)_2$	OCH_3	CH_3	H
14	Br	$OCH_2CH(CH_3)_2$	OCH_3	CH_3	CH_3
15	OCH_3	$OCH_2CH(CH_3)_2$	OCH_3	CH_3	CH_3
16	OCH_3	OCH_2CH_3	OCH_3	CH_3	CH_2CH_3
17	OCH_3	OCH_2CH_3	OCH_3	CH_3	$CH(CH_3)_2$
18	OCH_3	OCH_2CH_3	OCH_3	CH_3	Cl
19	OCH_3	$OCH_2CH_2CH_3$	OCH_3	CH_3	CH_3
20	OCH_3	$O(CH_2)_3CH_3$	OCH_3	CH_3	CH_3

Table 1–2



Compd. No.	Q	R^1
21		H
22		CH_3
23		CH_3
24		CH_3

The antitumor activities of Compounds (I) are shown in detail below by test examples.

Test Example 1: HeLa S_3 Cell Growth Inhibition Test

Each 0.1 ml of HeLa S_3 cells which had been prepared to 3 x 10^4 cells/ml using a medium consisted of MEM medium, 10% fetal bovine serum and 2 mM glutamine was distributed in each well of 96 well-microtiter plate. HeLa S_3 was cultured at 37°C in a CO_2 incubator for one night, each 0.05 ml of test compounds which had been appropriately diluted with the culture solution was added thereto and the mixture was cultured at 37°C for 72 hours in a CO_2 incubator. Supernatant was removed, each 0.1 ml of the culture solution containing 0.02% neutral red was added to the residue, the mixture was incubated at 37°C for one hour in a CO_2 incubator and the cells were stained. Supernatant was removed and the residue was washed once with physiological saline. Then, the pigment was extracted with 0.001 N hydrochloric acid/30% ethanol and the absorbance at 550 nm was measured by a microplatereader. A concentration of the test compound (IC_{50}) at which the growth of cell is inhibited by 50% was calculated by comparing the absorbance of non-treated cells and that of cells treated with a predetermined concentration of the test compound.

The results are shown in Table 2.

Table 2

Compd. No.	IC_{50} (72 hours, nM)
4	22
5	2.5
6	9.4
7	64
8	6.1
9	3.2
10	6.6
11	6.7
12	2.3
15	18
16	6.2
18	6.3
19	5.2
20	6.1
24	22

Test Example 2: Effect upon P388 Ascites Tumor

The experiment was carried out by using groups of 6-weeks-old male CDF_1 mice, each group consisting of five mice. 10^6 cells of P388 mouse leukemia were implanted into the abdominal cavities of the mice. A test compound was sufficiently wetted by adding 10 µl of Tween 80 relative to 1 mg of a sample, and 0.3% CMC (sodium carboxymethyl

cellulose) solution was then added to the test compound to form a suspension. The resultant suspension was administered once 24 hours after implantation of the tumor, or repeatedly for consecutive 5 days from 24 hours after implantation of the tumor. The average survival day (T) in a group was calculated from the survival days of the respective mice in the group administered with the test compound at each dose. On the other hand, the average survival day (C) of a group which was not administered was measured, and the increased life span [ILS (%)] was calculated according to the following equation:

$$[(T - C)/C] \times 100 \ (\%)$$

The results are shown in Table 3.

Table 3

Compd. No.	ILS (%) [Dose (mg/kg)] five consec. admin.	single admin.
4	NT	21 (50)
5	41 (3.1)	59 (25)
6	43 (3.1)	32 (6.3)
7	40 (25)	43 (100)
8	50 (6.3)	36 (50)
9	NT	51 (25)
10	NT	30 (25)
11	NT	36 (13)
12	NT	45 (6.3)

NT; not tested

The compounds of the present invention are useful as antitumor agents, and can be used as they are or in various administration forms. For example, when Compounds (I) are used as injections, Compounds (I) may be dissolved in a diluting agent conventionally used in this field such

as physiological saline, glucose injections, lactose injections, mannitol injections or the like, freeze-dried on the basis of the Japanese Pharmacopoeia, or mixed with sodium chloride to form powder injections. Compounds (I) can also be used as lipid emulsions. These injections may contain an adjuvant such as polyethylene glycol, HCO-60 (surfactant: produced by Nikko Chemical Co., Ltd.) or the like; and a carrier such as ethanol and/or liposome, cyclodextrin or the like. Although the injections are generally subjected to intravenous administration, they can also be subjected to arterial administration, intra-abdominal administration or intrathoracic administration.

When Compounds (I) are mixed with appropriate excipients, disintegrators, binders, lubricants and the like and formed to tablets, granules, powders, syrups or the like by a conventional method, the compounds can also be used as oral agents. Compounds (I) may be mixed with carriers conventionally used and formed, by a conventional method, to suppositories which can be administered to the rectum.

The dose varies depending upon the mode of administration, the type of Compound (I), the age and conditions of a patient, etc., and the administration schedule can be changed according to the conditions of a patient or the dose. For example, intravenous administration can be made at a dose of 0.01 to 1000 mg/60 kg once a week or once every three weeks.

Examples are described below.

Best Mode for Carrying Out the Invention

The physicochemical data of each compound were measured by the following apparatus.

^{1}H-NMR: Nihon Denshi JNM-GX270 (270 MHz)
Hitachi R-90H (90 MHz)

MS: Nihon Denshi JSM-D300

Elemental Analysis: Perkin Elmer 2400 CHN Analyzer

Example 1

(E)-1-(3,5-Dimethoxyphenyl)-3-(indol-3-yl)-2-propen-1-one (Compound 1)

3',5'-Dimethoxyacetophenone (1.10 g) and indole-3-carboxaldehyde (1.45 g) were dissolved in ethanol (20 ml), and piperidine (0.85 g) was added thereto, followed by heating under reflux for 32 hours. The reaction solution was cooled to room temperature, and the precipitated crystals were collected by filtration, followed by recrystallization from ethanol to give Compound 1 (1.79 g).

^{1}H-NMR (270 MHz, DMSO-d_6) δ 3.85 (s, 6H), 6.70 (t, J = 2.5 Hz, 1H), 7.19 (t, J = 2.5 Hz, 2H), 7.21-7.27 (m, 2H), 7.50 (m, 1H) 7.56 (d, J = 15.6 Hz, 1H), 8.04 (m, 1H), 8.05 (d, J = 15.6 Hz, 1H), 8.14 (d, J = 2.5 Hz, 1H), 11.91 (s, 1H)

EI-MS m/z = 307 (M^+)

Elemental analysis: $C_{19}H_{17}NO_3$

Calcd.(%): C, 74.25; H, 5.58; N, 4.56

Found (%): C, 74.15; H, 5.79; N, 4.24

Example 2

(E)-1-(4-Hydroxy-3,5-dimethoxyphenyl)-3-(indol-3-yl)-2-propen-1-one (Compound 2)

4'-Hydroxy-3',5'-dimethoxyacetophenone (1.96 g) and indole-3-carboxaldehyde (1.45 g) were dissolved in ethanol (20 ml), and piperidine (0.85 g) was added thereto, followed by heating under reflux for 32 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography. The obtained crude crystals were recrystallized from ethyl acetate to give Compound 2 (0.62 g).

^{1}H-NMR (270 MHz, DMSO-d_6) δ 3.91 (s, 6H), 7.19-7.26 (m, 2H), 7.40 (s, 2H), 7.48 (m, 1H), 7.65 (d, J = 15.6 Hz, 1H), 8.02 (d, J = 15.6 Hz, 1H), 8.05 (m, 1H), 8.11 (d, J = 2.5 Hz, 1H), 9.26 (s, 1H), 11.91 (s,

1H)

EI-MS m/z = 323 (M^+)

Elemental analysis: $C_{19}H_{17}NO_4$

Calcd.(%): C, 70.57; H, 5.30; N, 4.33

Found (%): C, 70.56; H, 5.34; N, 4.38

Example 3

(E)-1-(4-Benzyloxy-3,5-dimethoxyphenyl)-3-(indol-3-yl)-2-propen-1-one (Compound 3)

4'-Hydroxy-3',5'-dimethoxyacetophenone (1.57 g) and benzyl bromide (1.35 g) were dissolved in acetone (50 ml), and potassium carbonate (1.70 g) was added thereto, followed by heating under reflux for 24 hours. Insoluble matters were filtered off, and the filtrate was concentrated under reduced pressure. The residue was washed with hexane and collected by filtration. The obtained crystals (1.96 g) and indole-3-carboxaldehyde (0.99 g) were dissolved in ethanol (10 ml), and piperidine (0.85 g) was added thereto, followed by heating under reflux for 32 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography. The obtained crude crystals were recrystallized from a mixed solvent of ethyl acetate and hexane to give Compound 3 (0.17 g).

^{1}H-NMR (270 MHz, DMSO-d_6) δ 3.92 (s, 6H), 5.03 (s, 2H), 7.21-7.25 (m, 2H), 7.31-7.41 (m, 5H), 7.45-7.52 (m, 3H), 7.63 (d, J = 15.3 Hz, 1H), 8.05 (m, 1H), 8.06 (d, J = 15.3 Hz, 1H), 8.15 (d, J = 3.0Hz, 1H), 11.91 (s, 1H)

EI-MS m/z = 413 (M^+)

Elemental analysis: $C_{26}H_{23}NO_4$

Calcd.(%): C, 75.53; H, 5.61; N, 3.39

Found (%): C, 75.41; H, 5.45; N, 3.38

Example 4

3-(Indol-3-yl)-2-methyl-1-(3,4,5-triethoxyphenyl)-2-propen-1-one (Compound 4)

Process 1

3,4,5-Triethoxybenzoic acid (2.54 g) was dissolved in tetrahydrofuran (250 ml), and lithium aluminum hydride (1.20 g) was added thereto, followed by heating under reflux for 24 hours. Ethyl acetate and then a 2N aqueous solution of sodium hydroxide were added to the reaction solution, insoluble matters were filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (100 ml), and manganese dioxide (5.10 g) was added thereto, followed by stirring for 120 hours. Insoluble matters were filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (100 ml), and ethylmagnesium bromide (1M tetrahydrofuran solution, 15 ml) was added thereto, followed by stirring at room temperature for 30 minutes. 1N Hydrochloric acid was added to the reaction solution and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in acetone (100 ml), and Jones' reagent (2 ml) was added thereto under ice-cooling, followed by stirring at the same temperature for 30 minutes. 2-Propanol (10 ml) was added to the reaction solution and the mixture was concentrated under reduced pressure. The residue was subjected to partitioning between ethyl acetate and water. The organic layer was washed with a saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 3',4',5'-triethoxypropiophenone (0.76 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.21 (t, J = 7.2 Hz, 3H), 1.37 (t, J = 6.9 Hz, 3H), 1.45 (t, J = 6.9 Hz,

6H), 2.95 (q, J = 7.2 Hz, 2H), 4.12(q, J = 6.9 Hz,4H), 4.14 (q, J = 6.9 Hz, 2H), 7.21 (s, 2H)

EI-MS m/z = 266 (M^+)

Process 2

3',4',5'-Triethoxypropiophenone (0.67 g) obtained in the above Process 1 and indole-3-carboxaldehyde (0.37 g) were dissolved in ethanol (5 ml), and piperidine (0.43 g) was added thereto, followed by heating under reflux for 32 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography. The obtained crude crystals were recrystallized from ethanol to give Compound 4 (0.25 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.41 (t, J = 7.0 Hz, 3H), 1.42 (t, J = 7.0 Hz, 6H), 2.31 (d, J = 1.0 Hz, 3H), 4.10 (q, J = 7.0 Hz, 4H), 4.18(q, J = 7.0 Hz, 2H), 7.00 (s, 2H), 7.18 (m, 1H), 7.28 (m, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.66 (brs, 1H), 8.71 (brs, 1H)

EI-MS m/z = 393 (M^+)

Elemental analysis: $C_{24}H_{27}NO_4$

Calcd.(%): C, 73.26; H, 6.92; N, 3.56

Found (%): C, 73.43; H, 7.32; N, 3.54

Example 5

1-(4-Ethoxy-3,5-dimethoxyphenyl)-3-(indol-3-yl)-2-methyl-2-propen-1-one (Compound 5)

Process 1

4-Hydroxy-3,5-dimethoxybenzaldehyde (3.64 g) and ethyl iodide (6.24 g) were dissolved in N,N-dimethylformamide (30 ml), and sodium hydride (60% oil dispersion, 1.00 g) was added thereto, followed by stirring at 80°C for 24 hours. The reaction solution was subjected to partitioning between ethyl acetate and 1N hydrochloric acid. The organic layer was washed successively with a 5%

saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue (3.71 g) was dissolved in tetrahydrofuran (88 ml), and ethylmagnesium bromide (1M tetrahydrofuran solution, 26.5 ml) was added thereto, followed by stirring at room temperature for 30 minutes. 1N Hydrochloric acid was added to the reaction solution and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in acetone (100 ml), and Jones' reagent (5.3 ml) was added thereto under ice-cooling, followed by stirring at the same temperature for 30 minutes. 2-Propanol (5.3 ml) was added to the reaction solution and the mixture was concentrated under reduced pressure. The residue was subjected to partitioning between ethyl acetate and water. The organic layer was washed with a saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 4'-ethoxy-3',5'-dimethoxypropiophenone (3.37 g).

^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.23 (t, J = 7.3 Hz, 3H), 1.34 (t, J = 7.0 Hz, 3H), 2.97 (q, J = 7.3 Hz, 2H), 3.90 (s, 6H), 4.13 (q, J = 7.0 Hz, 2H), 7.22 (s, 2H)

EI-MS m/z = 238 (M^+)

Process 2

4'-Ethoxy-3',5'-dimethoxypropiophenone (1.67 g) obtained in the above Process 1 and indole-3-carboxaldehyde (1.02 g) were dissolved in ethanol (14 ml), and piperidine (0.60 g) was added thereto, followed by heating under reflux for 144 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography. The obtained crude crystals were recrystallized from ethyl acetate to give Compound 5 (1.20

g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.41 (t, J = 7.1 Hz, 3H), 2.31 (d, J = 1.0 Hz, 3H), 3.87 (s, 6H), 4.16 (q, J = 7.1 Hz, 2H), 7.01 (s, 2H), 7.18 (m, 1H), 7.27 (m, 1H), 7.43 (brd, J = 7.9 Hz, 1H), 7.56 (brd, J = 7.6 Hz, 1H), 7.63 (d, J = 3.0 Hz, 1H). 7.68 (brs, 1H), 8.75 (brs, 1H)

EI-MS m/z = 365 (M^+)

Elemental analysis: $C_{22}H_{23}NO_4$

Calcd.(%): C, 72.31; H, 6.34; N, 3.83

Found (%): C, 72.44; H, 6.41; N, 3.75

Example 6

3-(Indol-3-yl)-1-(4-isobutyloxy-3,5-dimethoxyphenyl)-2-methyl-2-propen-1-one (Compound 6)

Process 1

Substantially the same procedure as in Process 1 of Example 5 was repeated using 4-hydroxy-3,5-dimethoxybenzaldehyde (3.64 g) and isobutyl bromide (5.48 g) to give 4'-isobutyloxy-3',5'-dimethoxypropiophenone (1.92 g).

^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.02 (d, J = 6.8 Hz, 6H), 1.22 (t, J = 7.2 Hz, 3H), 2.06 (m, 1H), 2.96 (q, J = 7.2 Hz, 2H), 3.81 (d, J = 6.6 Hz, 2H), 3.89 (s, 6H), 7.22 (s, 2H)

EI-MS m/z = 266 (M^+)

Process 2

4'-Isobutyloxy-3',5'-dimethoxypropiophenone (1.33 g) obtained in the above Process 1 and indole-3-carboxaldehyde (0.73 g) were dissolved in ethanol (10 ml), and piperidine (0.85 g) was added thereto, followed by heating under reflux for 48 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography. The obtained

crude crystals were recrystallized from a mixed solvent of ethyl acetate and hexane to give Compound 6 (0.90 g)

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.06 (d, J = 6.7 Hz, 6H), 2.11 (m, 1H), 2.31 (d, J = 1.0 Hz, 3H), 3.85 (d, J = 6.7 Hz, 2H), 3.87 (s, 6H), 7.02 (s, 2H), 7.19 (m, 1H), 7.28 (m, 1H), 7.44 (brd, J = 8.2 Hz, 1H), 7.57 (brd, J = 7.9 Hz, 1H), 7.64 (d, J = 2.6 Hz, 1H), 7.68 (brs, 1H), 8.73 (brs, 1H)

EI-MS m/z = 393 (M^+)

Elemental analysis: $C_{24}H_{27}NO_4$

Calcd.(%): C, 73.26; H, 6.92; N, 3.56

Found (%): C, 73.20; H, 7.31; N, 3.53

Example 7

1-(4-Ethyl-3,5-dimethoxyphenyl)-3-(indol-3-yl)-2-methyl-2-propen-1-one (Compound 7)

Process 1

3,4,5-Trimethoxybenznitrile (3.86 g) was dissolved in tetrahydrofuran (100 ml), and ethylmagnesium bromide (1M tetrahydrofuran solution, 60 ml) was added thereto, followed by heating under reflux for 12 hours. 1N Hydrochloric acid was added to the reaction solution, and the mixture was stirred at the same temperature for one hour and extracted with ethyl acetate. The organic layer was washed with a saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 4'-ethyl-3',5'-dimethoxypropiophenone (2.37 g).

^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.08 (t, J = 7.3 Hz, 3H), 1.23 (t, J = 7.3 Hz, 3H), 2.69 (q, J = 7.3 Hz, 2H), 2.97 (q, J = 7.3 Hz, 2H), 3.87(s, 6H), 7.15 (s, 2H)

EI-MS m/z = 222 (M^+)

Process 2

4'-Ethyl-3',5'-dimethoxypropiophenone (1.11 g) obtained in the above Process 1 and indole-3-carboxaldehyde (1.45 g) were dissolved in ethanol (10 ml), and piperidine (0.85 g) was added thereto, followed by heating under reflux for 27 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography. The obtained crude crystals were recrystallized from a mixed solvent of ethyl acetate and 2-propanol and then from a mixed solvent of ethyl acetate and hexane to give Compound 7 (0.45 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.14 (t, J = 7.4 Hz, 3H), 2.32 (d, J = 1.0 Hz, 3H), 2.74 (q, J = 7.4 Hz, 2H), 3.85 (s, 6H), 6.96 (s, 2H), 7.19 (m, 1H), 7.28 (m, 1H), 7.44 (brd, J = 8.4 Hz, 1H), 7.59 (brd, J = 7.9 Hz, 1H), 7.63 (d, J = 2.5 Hz, 1H), 7.72 (brs, 1H), 8.68 (brs, 1H)

EI-MS m/z = 365 (M^+)

Elemental analysis: $C_{22}H_{23}NO_3$

Calcd.(%): C, 75.62; H, 6.63; N, 4.01

Found (%): C, 75.78; H, 6.78; N, 3.98

Example 8

3-(Indol-3-yl)-1-(3-methoxy-4,5-methylenedioxyphenyl)-2-methyl-2-propen-1-one (Compound 8)

Process 1

3-Methoxy-4,5-methylenedioxybenzaldehyde (5.55 g) was dissolved in tetrahydrofuran (150 ml), and ethylmagnesium bromide (1M tetrahydrofuran solution, 46.2 ml) was added thereto, followed by stirring at room temperature for 30 minutes. 1N Hydrochloric acid was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water, a 5% aqueous solution of sodium bicarbonate and a saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was

dissolved in acetone (300 ml), and Jones' reagent (5.3 ml) was added thereto under ice-cooling, followed by stirring at the same temperature for 30 minutes. 2-Propanol (5.3 ml) was added to the reaction solution and the mixture was concentrated under reduced pressure. The residue was subjected to partitioning between ethyl acetate and water. The organic layer was washed successively with water and a saturated saline, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 3'-methoxy-4',5'-methylenedioxypropiophenone (5.27 g).

^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.21 (t, J = 7.3 Hz, 3H), 2.91 (q, J = 7.3 Hz, 2H), 3.94 (s, 3H), 6.05 (s, 2H), 7.13 (d, J = 1.5 Hz, 1H), 7.27 (d, J = 1.5 Hz, 1H)
EI-MS m/z = 208 (M^+)

Process 2

3'-Methoxy-4',5'-methylenedioxypropiophenone (1.46 g) obtained in the above Process 1 and indole-3-carboxaldehyde (1.02 g) were dissolved in ethanol (14 ml), and piperidine (0.69 g) was added thereto, followed by heating under reflux for 120 hours. The precipitated crystals were collected by filtration, and the obtained crude crystals were recrystallized from a mixed solvent of ethyl acetate and hexane to give Compound 8 (0.64 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.92 (s, 3H), 6.08 (s, 2H), 6.98 (d, J = 1.5 Hz, 1H), 7.06 (d, J = 1.5 Hz, 1H), 7.19 (m, 1H), 7.27 (m, 1H), 7.43 (brd, J = 7.9 Hz, 1H), 7.58-7.61 (m 3H), 8.68 (brs, 1H)
EI-MS m/z = 335 (M^+)
Elemental analysis: $C_{20}H_{17}NO_4$
Calcd.(%): C, 71.63; H, 5.11; N, 4.18
Found (%): C, 71.31; H, 5.14; N, 4.06

Example 9

1-(5-Ethoxy-3,4-dimethoxyphenyl)-3-(indol-3-yl)-2-methyl-2-propen-1-one (Compound 9)

Process 1

Substantially the same procedure as in Process 1 of Example 5 was repeated using 5-hydroxy-3,4-dimethoxybenzaldehyde (3.34 g) and ethyl iodide (5.72 g) to give 5'-ethoxy-3',4'-dimethoxypropiophenone (1.92 g).

^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.22 (t, J = 7.3 Hz, 3H), 1.46 (t, J = 7.0 Hz, 3H), 2.96 (q, J = 7.3 Hz, 2H), 3.91 (s, 6H), 4.14 (q, J = 7.0 Hz, 2H), 7.22 (s, 2H)

EI-MS m/z = 238 (M^+)

Process 2

5'-Ethoxy-3',4'-dimethoxypropiophenone (1.19 g) obtained in the above Process 1 and indole-3-carboxaldehyde (0.73 g) were dissolved in ethanol (10 ml), and piperidine (0.43 g) was added thereto, followed by heating under reflux for 72 hours. The precipitated crystals were collected by filtration, and the obtained crude crystals were recrystallized from a mixed solvent of acetone and hexane to give Compound 9 (0.75 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.44 (t, J = 7.1 Hz, 3H), 2.32 (d, J = 1.0 Hz, 3H), 3.89 (s, 3H), 3.96 (s, 3H), 4.12 (q, J = 7.1 Hz, 2H), 7.01 (s, 2H), 7.19 (m, 1H), 7.28 (m, 1H), 7.44 (brd, J = 7.9 Hz, 1H), 7.58 (brd, J = 7.9 Hz, 1H), 7.64 (d, J = 3.0 Hz, 1H), 7.67 (brs, 1H), 8.76 (brs, 1H)

EI-MS m/z = 365 (M^+)

Elemental analysis: $C_{22}H_{23}NO_4$

Calcd.(%): C, 72.31; H, 6.34; N, 3.83

Found (%): C, 72.36; H, 6.62; N, 3.80

Example 10

1-(3-Bromo-4,5-dimethoxyphenyl)-3-(indol-3-yl)-2-methyl-2-propen-1-one (Compound 10)

Process 1

Substantially the same procedure as in Process 1 of Example 5 was repeated using 5-bromovanillin (5.78 g) and methyl iodide (7.10 g) to give 3'-bromo-4',5'-dimethoxypropiophenone (5.45 g).

^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.21 (t, J = 7.3 Hz, 3H), 2.94 (q, J = 7.3 Hz, 2H), 3.92 (s, 6H), 7.49 (d, J = 1.9 Hz, 1H), 7.74 (d, J = 1.9 Hz, 1H)

EI-MS m/z = 272, 274 (M^+)

Process 2

3'-Bromo-4',5'-dimethoxypropiophenone (1.37 g) obtained in the above Process 1 and indole-3-carboxaldehyde (0.73 g) were dissolved in ethanol (10 ml), and piperidine (0.43 g) was added thereto, followed by heating under reflux for 72 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography. The obtained crude crystals were recrystallized from ethyl acetate to give Compound 10 (0.49 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.30 (d, J = 0.7 Hz, 3H), 3.92 (s, 3H), 3.96 (s, 3H), 7.21 (m, 1H), 7.23 (d, J = 2.1 Hz, 1H), 7.29 (m, 1H), 7.44 (brd, J = 7.8 Hz, 1H), 7.55 (d, J = 2.1 Hz, 1H), 7.61 (brd, J = 7.8 Hz, 1H), 7.64 (d, J = 2.1 Hz, 1H), 7.65 (brs, 1H), 8.71 (brs, 1H)

EI-MS m/z = 399, 401 (M^+)

Elemental analysis: $C_{20}H_{18}BrNO_3$

Calcd.(%): C, 60.01; H, 4.53; N, 3.50

Found (%): C, 60.18; H, 4.61; N, 3.40

Example 11

1-(4-Ethoxy-3,5-dimethoxyphenyl)-2-methyl-3-(6-methylindol-3-yl)-2-propen-1-one (Compound 11)

4'-Ethoxy-3',5'-dimethoxypropiophenone (1.19 g) obtained in Process 1 of Example 5 and 6-methylindole-3-carboxaldehyde [Journal of the Organic Chemistry (J. Org. Chem.), 44, 3741 (1979)] (0.80 g) were dissolved in ethanol (10 ml), and piperidine (0.49 g) was added thereto, followed by heating under reflux for 48 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography. The obtained crude crystals were recrystallized from ethyl acetate to give Compound 11 (1.20 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.41 (t, J = 7.1 Hz, 3H), 2.30 (d, J = 1.3 Hz, 3H), 2.47 (s, 3H), 3.87 (s, 6H), 4.17 (q, J = 7.1 Hz, 2H), 7.01 (dd, J = 7.6, 0.7 Hz, 1H), 7.02 (s, 2H), 7.22 (s, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.66 (s, 1H), 8.53 (brs, 1H)

FAB-MS m/z = 380 ($M^+ + 1$)

Elemental analysis: $C_{23}H_{25}NO_4$

Calcd.(%): C, 72.80; H, 6.64; N, 3.69

Found (%): C, 72.82; H, 6.78; N, 3.69

Example 12

1-(3-Methoxy-4,5-methylenedioxyphenyl)-2-methyl-3-(6-methylindol-3-yl)-2-propen-1-one (Compound 12)

3'-Methoxy-4',5'-methylenedioxypropiophenone (1.04 g) obtained in Process 1 of Example 8 and 6-methylindole-3-carboxaldehyde [Journal of the Organic Chemistry (J. Org. Chem.), 44, 3741 (1979)] (0.80 g) were dissolved in ethanol (10 ml), and piperidine (0.49 g) was added thereto, followed by heating under reflux for 48 hours. The precipitated crystals were collected by filtration, and the obtained crude crystals were recrystallized from a mixed solvent of ethyl acetate and hexane to give Compound 12 (0.64 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.29 (d, J = 1.0 Hz, 3H), 2.24 (s, 3H), 3.93 (s, 3H), 6.08 (s, 2H), 6.98 (d, J = 1.3 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 7.06 (d, J = 1.3 Hz, 1H), 7.22 (s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 2.6 Hz, 1H), 7.59 (brs, 1H), 8.51 (brs, 1H)

FAB-MS m/z = 350 (M^+ + 1)

Elemental analysis: $C_{21}H_{19}NO_4$

Calcd.(%): C, 72.19; H, 5.48; N, 4.01

Found (%): C, 72.41; H, 5.47; N, 3.99

Example 13

1-(3-Bromo-4-isobutyloxy-5-methoxyphenyl)-3-(indol-3-yl)-2-methyl-2-propen-1-one (Compound 13)

Process 1

Substantially the same procedure as in Process 1 of Example 5 was repeated using 5-bromovanillin (11.65 g) and isobutyl bromide (27.40 g) to give 3'-bromo-4'-isobutyloxy-5'-methoxypropiophenone (1.93 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.06 (d, J = 6.6 Hz, 6H), 1.21 (t, J = 7.0 Hz, 3H), 2.13 (m, 1H), 2.94 (q, J = 7.0 Hz, 2H), 3.84 (d, J = 6.6 Hz, 2H), 3.89 (s, 3H), 7.48 (d, J = 1.9 Hz, 1H), 7.74 (d, J = 1.9 Hz, 1H)

EI-MS m/z = 314, 316 (M^+)

Process 2

3'-Bromo-4'-isobutyloxy-5'-methoxypropiophenone (0.64 g) obtained in the above Process 1 and indole-3-carboxaldehyde (0.59 g) were dissolved in ethanol (1 ml), and piperidine (0.35 g) was added thereto, followed by heating under reflux for 25 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography. The obtained crude crystals were recrystallized from a mixed solvent of ethyl acetate and hexane to give Compound 13 (0.54 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.10 (d, J = 6.4 Hz, 6H), 2.17 (m, 1H), 2.30 (d, J = 0.7 Hz, 3H), 3.88 (d, J = 6.4 Hz, 2H), 3.89 (s, 3H), 7.22 (m, 1H), 7.27 (d, J = 1.7 Hz, 1H), 7.30 (m, 1H), 7.44 (m, 1H), 7.55 (d, J = 1.7 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.63 (s, 1H), 8.67 (s, 1H)

EI-MS m/z = 441, 443 (M^+)

Elemental analysis: $C_{23}H_{24}BrNO_3$

Calcd.(%): C, 62.45; H, 5.47; N, 3.17

Found (%): C, 62.65; H, 5.49; N, 3.15

Example 14

1-(3-Bromo-4-isobutyloxy-5-methoxyphenyl)-2-methyl-3-(6-methylindol-3-yl)-2-propen-1-one (Compound 14)

3'-Bromo-4'-isobutyloxy-5'-methoxypropiophenone (1.58 g) obtained in Process 1 of Example 13 and 6-methylindole-3-carboxaldehyde [Journal of the Organic Chemistry (J. Org. Chem.), 44, 3741 (1979)] (0.80 g) were dissolved in ethanol (2 ml), and piperidine (0.85 g) was added thereto, followed by heating under reflux for 48 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography. The obtained crude crystals were recrystallized from a mixed solvent of ethyl acetate and hexane to give Compound 14 (1.02 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.10 (d, J = 6.3 Hz, 6H), 2.17 (m, 1H), 2.29 (d, J = 1.0 Hz, 3H), 2.47 (s, 3H), 3.87 (d, J = 6.3 Hz, 2H), 3.88 (s, 3H), 7.04 (dd, J = 8.3, 1.0 Hz, 1H), 7.22 (s, 1H), 7.26 (d, J = 1.7 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 1.7 Hz, 1H), 7.56(d, J = 3.0 Hz, 1H), 7.62 (s, 1H), 8.57 (brs, 1H)

EI-MS m/z = 455, 457 (M^+)

Elemental analysis: $C_{24}H_{26}BrNO_3$

Calcd.(%): C, 63.28; H, 5.76; N, 3.08

Found (%): C, 63.66; H, 6.11; N, 2.88

Example 15

1-(4-Isobutyloxy-3,5-dimethoxyphenyl)-2-methyl-3-(6-methylindol-3-yl)-2-propen-1-one (Compound 15)

Process 1

4-Hydroxy-3,5-dimethoxybenzaldehyde (36.40 g) was dissolved in a mixed solvent of tetrahydrofuran (250 ml) and N,N-dimethylformamide (250 ml), and isobutyl bromide (54.80 g) and tetra-n-butylammonium fluoride (1M tetrahydrofuran solution, 400 ml) were added thereto, followed by heating under reflux for 15 hours. The reaction solution was cooled to room temperature, and subjected to partitioning between hexane and water. The organic layer was washed with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 4'-isobutyloxy-3',5'-dimethoxybenzaldehyde (41.17 g).

^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.30 (d, J = 6.6 Hz, 6H), 2.04 (m, 1H), 3.84 (d, J = 6.6 Hz, 2H), 3.91 (s, 6H), 7.12 (s, 2H), 9.86 (s, 1H)

EI-MS m/z = 238 (M^+)

Process 2

Substantially the same procedure as in Process 1 of Example 8 was repeated using 4'-isobutyloxy-3',5'-dimethoxybenzaldehyde (1.37 g) obtained in the above Process 1 to give 4'-isobutyloxy-3',5'-dimethoxypropiophenone (1.37 g).

Process 3

4'-Isobutyloxy-3',5'-dimethoxypropiophenone (1.33 g) obtained in the above Process 2 and 6-methylindole-3-carboxaldehyde [Journal of the Organic Chemistry (J. Org. Chem.), 44, 3741 (1979)] (0.80 g) were dissolved in ethanol

(2 ml), and piperidine (0.43 g) was added thereto, followed by heating under reflux for 80 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography. The obtained crude crystals were recrystallized from a mixed solvent of ethyl acetate and hexane to give Compound 15 (0.96 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.00 (d, J = 7.8 Hz, 6H), 2.05 (m, 1H), 2.25 (s, 3H), 2.41 (s, 3H), 3.79 (d, J = 7.8 Hz, 2H), 3.81 (s, 6H), 6.956 (d, J = 7.8 Hz, 1H), 6.957 (s, 2H), 7.16 (s, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 2.6 Hz, 1H), 7.60 (s, 1H), 8.53 (s, 1H)

EI-MS m/z = 407 (M^+)

Elemental analysis: $C_{25}H_{29}NO_4$

Calcd.(%): C, 73.69; H, 7.17; N, 3.44

Found (%): C, 74.13; H, 7.23; N, 3.40

Example 16

1-(4-Ethoxy-3,5-dimethoxyphenyl)-3-(6-ethylindol-3-yl)-2-methyl-2-propen-1-one (Compound 16)

Process 1

Phosphorus oxychloride (3.82 g) was added to N,N-dimethylformamide (20 ml), and the mixture was stirred at room temperature for 10 minutes. A solution of 6-ethylindole [Journal of the Chemical Society (J. Chem. Soc.), 7165 (1965)] in N,N-dimethylformamide (6 ml) was added to the reaction solution, and the mixture was stirred at room temperature for one hour. Ice (20 g) and then a 5N aqueous solution of sodium hydroxide (34 ml) were added to the reaction solution, and the mixture was heated under reflux for one hour. The reaction solution was ice-cooled, and the precipitated crystals were collected by filtration to give 6-ethylindole-3-carboxaldehyde (2.76 g).

^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.27 (t, J = 7.6 Hz, 3H), 2.76 (q, J = 7.6 Hz, 2H), 7.11-7.24 (m, 2H), 7.76 (s,

1H), 8.20 (d, J = 8.2 Hz, 1H), 8.99 (s, 1H), 10.01 (s, 1H)

EI-MS m/z = 173 (M^+)

Process 2

Substantially the same procedure as in Process 2 of Example 6 was repeated using 4'-ethoxy-3',5'-dimethoxypropiophenone (1.90 g) obtained in Process 1 of Example 5 and 6-ethylindole-3-carboxaldehyde (1.38 g) to give Compound 16 (0.84 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.30 (t, J = 7.4 Hz, 3H), 1.41 (t, J = 7.4 Hz, 3H), 2.30 (d, J = 1.0 Hz, 3H), 2.76 (q, J = 7.4 Hz, 2H), 3.87(s, 6H), 4.17 (q, J = 7.4 Hz, 2H), 7.02 (s, 2H), 7.05 (dd, J = 8.2, 1.5 Hz, 1H), 7.24 (s, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 2.5 Hz, 1H), 7.67 (s, 1H), 8.61 (s, 1H)

EI-MS m/z = 393 (M^+)

Elemental analysis: $C_{24}H_{27}NO_4$

Calcd.(%): C, 73.26; H, 6.92; N, 3.56

Found (%): C, 73.46; H, 7.02; N, 3.52

Example 17

1-(4-Ethoxy-3,5-dimethoxyphenyl)-3-(6-isopropylindol-3-yl)-2-methyl-2-propen-1-one (Compound 17)

Process 1

Substantially the same procedure as in Process 1 of Example 16 was repeated using 6-isopropylindole [Organic Synthesis (Org. Syn.), 63, 214 (1985)] (3.18 g) to give 6-isopropylindole-3-carboxaldehyde (3.56 g).

^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.31 (d, J = 8.7 Hz, 6H), 2.70 (m, 1H), 7.08 (m, 1H), 7.24 (s, 1H), 7.74 (brs, 1H), 8.18 (d, J = 9.0 Hz, 1H), 9.28 (s, 1H), 9.97 (s, 1H)

EI-MS m/z = 187 (M^+)

Process 2

Substantially the same procedure as in Process 2 of Example 6 was repeated using 4'-ethoxy-3',5'-dimethoxypropiophenone (2.38 g) obtained in Process 1 of Example 5 and 6-isopropylindole-3-carboxaldehyde obtained in the above Process 1 (1.87 g) to give Compound 17 (1.80 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.30 (d, J = 6.9 Hz, 6H), 1.41 (t, J = 7.0 Hz, 3H), 2.30 (d, J = 1.0 Hz, 3H), 3.03 (m, 1H), 3.88 (s, 6H), 4.17 (q, J = 7.0 Hz, 2H), 7.02 (s, 2H), 7.08 (dd, J = 8.4, 1.5 Hz, 1H), 7.28 (s, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 2.5 Hz, 1H), 7.66 (s, 1H), 8.60 (s, 1H)

EI-MS m/z = 407 (M^+)

Elemental analysis: $C_{25}H_{29}NO_4$

Calcd.(%): C, 73.69; H, 7.17; N, 3.44

Found (%): C, 73.85; H, 7.27; N, 3.43

Example 18

3-(6-Chloroindol-3-yl)-1-(4-ethoxy-3,5-dimethoxyphenyl)-2-methyl-2-propen-1-one (Compound 18)

Process 1

Substantially the same procedure as in Process 1 of Example 16 was repeated using 6-chloroindole (4.11 g) to give 6-chloroindole-3-carboxaldehyde (4.78 g).

^{1}H-NMR (270 MHz, DMSO-d_6) δ 7.24 (dd, J = 8.5, 1.8 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 8.32 (s, 1H), 9.93 (s, 1H), 12.20 (s, 1H)

FAB-MS m/z = 180, 182 (M^+ + 1)

Process 2

Substantially the same procedure as in Process 2 of Example 6 was repeated using 4'-ethoxy-3',5'-dimethoxypropiophenone (2.38 g) obtained in Process 1 of Example 5 and 6-chloroindole-3-carboxaldehyde obtained in

the above Process 1 (1.80 g) to give Compound 18 (1.69 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.41 (t, J = 7.0 Hz, 3H), 2.31 (d, J = 0.9 Hz, 3H), 3.88 (s, 6H), 4.17 (q, J = 7.0 Hz, 2H), 7.01 (s, 2H), 7.15 (dd, J = 8.6, 1.8 Hz, 1H), 7.43 (d, J = 1.8 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.58 (s, 1H), 7.61 (d, J = 2.6 Hz, 1H), 8.72 (s, 1H)

EI-MS m/z = 399, 401 (M^+)

Elemental analysis: $C_{22}H_{22}ClNO_4$

Calcd.(%): C, 66.08; H, 5.55; N, 3.50

Found (%): C, 66.28; H, 5.64; N, 3.48

Example 19

1-(3,5-Dimethoxy-4-propoxyphenyl)-2-methyl-3-(6-methylindol-3-yl)-2-propen-1-one (Compound 19)

Process 1

Substantially the same procedure as in Process 1 of Example 5 was repeated using 4-hydroxy-3,5-dimethoxybenzaldehyde (9.10 g) and propyl iodide (12.75 g) to give 3',5'-dimethoxy-4'-propoxypropiophenone (4.85 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.00 (t, J = 7.0 Hz, 3H), 1.21 (t, J = 7.3 Hz, 3H), 1.76 (m, 2H), 2.96 (q, J = 7.3 Hz, 2H), 3.88 (s, 6H), 4.00 (t, J = 7.0 Hz, 2H), 7.21 (s, 2H)

EI-MS m/z = 252 (M^+)

Process 2

Substantially the same procedure as in Process 2 of Example 6 was repeated using 3',5'-dimethoxy-4'-propoxypropiophenone (2.48 g) obtained in the above Process 1 and 6-methylindole-3-carboxaldehyde [Journal of the Organic Chemistry (J. Org. Chem.), 44, 3741 (1979)] (1.59 g) to give Compound 19 (1.73 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.05 (t, J = 7.1 Hz, 3H), 1.83 (m, 2H), 2.31 (s, 3H), 2.48 (s, 3H), 3.88 (s, 6H), 4.05 (t, J = 7.1 Hz, 2H), 7.021 (s, 2H), 7.024 (m, 1H), 7.23 (s, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.57 (d, J = 2.6 Hz, 1H), 7.67 (s, 1H), 8.59 (s, 1H)

EI-MS m/z = 393 (M^+)

Elemental analysis: $C_{24}H_{27}NO_4$

Calcd.(%): C, 73.26; H, 6.92; N, 3.56

Found (%): C, 73.44; H, 7.02; N, 3.51

Example 20

1-(4-Buthoxy-3,5-dimethoxyphenyl)-2-methyl-3-(6-methylindol-3-yl)-2-propen-1-one (Compound 20)

Process 1

Substantially the same procedure as in Process 1 of Example 5 was repeated using 4-hydroxy-3,5-dimethoxybenzaldehyde (9.10 g) and butyl bromide (10.28 g) to give 4'-butoxy-3',5'-dimethoxypropiophenone (5.42 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3H), 1.20 (t, J = 7.3 Hz, 3H), 1.46 (m, 2H), 1.74 (m, 2H), 2.96 (q, J = 7.3 Hz, 2H), 3.90 (s, 6H), 4.02 (t, J = 7.3 Hz, 2H), 7.20 (s, 2H)

EI-MS m/z = 266 (M^+)

Process 2

Substantially the same procedure as in Process 2 of Example 6 was repeated using 4'-butoxy-3',5'-dimethoxypropiophenone (2.66 g) obtained in the above Process 1 and 6-methylindole-3-carboxaldehyde [Journal of the Organic Chemistry (J. Org. Chem.), 44, 3741 (1979)] (1.59 g) to give Compound 20 (1.43 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3H), 1.53 (m, 2H), 1.81 (m, 2H), 2.29 (s, 3H), 2.45 (s, 3H), 3.85 (s, 6H), 4.07 (t, J = 6.8 Hz, 2H), 6.996

(s, 2H), 6.999 (d, J = 7.6 Hz, 1H), 7.20 (s, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 2.6 Hz, 1H), 7.64 (s, 1H), 8.55 (s, 1H)

EI-MS m/z = 407 (M^+)

Elemental analysis: $C_{25}H_{29}NO_4$

Calcd.(%): C, 73.69; H, 7.17; N, 3.44

Found (%): C, 73.85; H, 7.29; N, 3.46

Example 21

1-(2,5-Dimethoxyphenyl)-3-(indol-3-yl)-2-propen-1-one (Compound 21)

2',5'-Dimethoxyacetophenone (1.80 g) and indole-3-carboxaldehyde (1.45 g) were dissolved in ethanol (20 ml), and piperidine (0.85 g) was added thereto, followed by heating under reflux for 72 hours. The precipitated crystals were collected by filtration, and the obtained crude crystals were recrystallized from ethanol to give Compound 21 (1.35 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.89 (s, 3H), 6.96 (d, J = 8.9 Hz, 1H), 7.04 (dd, J = 8.9, 3.0 Hz, 1H), 7.23 (d, J = 3.0 Hz, 1H), 7.28 (m, 2H), 7.43 (m, 1H), 7.51 (d, J = 15.8 Hz, 1H), 7.55 (d, J = 3.5 Hz, 1H), 7.92 (d, J = 15.8 Hz, 1H), 7.97 (m, 1H), 8.56(brs, 1H)

EI-MS m/z = 307 (M^+)

Elemental analysis: $C_{19}H_{17}NO_3$

Calcd.(%): C, 74.25; H, 5.58; N, 4.56

Found (%): C, 74.30; H, 5.60; N, 4.44

Example 22

1-(2,5-Dimethoxyphenyl)-3-(indol-3-yl)-2-methyl-2-propen-1-one (Compound 22)

Process 1

Substantially the same procedure as in Process 1 of Example 8 was repeated using 2,5-dimethoxybenzaldehyde

(11.62 g) to give 2′,5′-dimethoxypropiophenone (7.83 g).

^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.15 (t, J = 7.3 Hz, 3H), 2.99 (q, J = 7.3 Hz, 2H), 3.78 (s, 3H), 3.84 (s, 3H), 6.82-7.08 (m, 2H), 7.23 (d, J = 2.9 Hz, 1H)

EI-MS m/z = 194 (M^+)

Process 2

2′,5′-Dimethoxypropiophenone (1.94 g) obtained in the above Process 1 and indole-3-carboxaldehyde (1.45 g) were dissolved in ethanol (20 ml), and piperidine (0.85 g) was added thereto, followed by heating under reflux for 72 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography. The obtained crude crystals were recrystallized from a mixed solvent of ethyl acetate and hexane to give Compound 22 (0.64 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.28 (d, J = 1.0 Hz, 3H), 3.74 (s, 3H), 3.79 (s, 3H), 6.87 (d, J = 2.6 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.98 (dd, J = 8.8, 2.6 Hz, 1H), 7.15 (m, 1H), 7.24 (m, 1H), 7.37-7.46 (m, 2H), 7.607 (brs, 1H), 7.613 (d, J = 3.0 Hz, 1H), 8.76 (brs, 1H)

EI-MS m/z = 321 (M^+)

Elemental analysis: $C_{20}H_{19}NO_3$

Calcd.(%): C, 74.75; H, 5.96; N, 4.36

Found (%): C, 75.11; H, 6.12; N, 4.28

Example 23

3-(Indol-3-yl)-2-methyl-1-(2,4,5-trimethoxyphenyl)-2-propen-1-one (Compound 23)

Process 1

Substantially the same procedure as in Process 1 of Example 8 was repeated using 2,4,5-trimethoxybenzaldehyde (1.96 g) to give 2′,4′,5′-trimethoxypropiophenone (0.50 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.16 (t, J = 7.3 Hz, 3H), 2.99 (q, J = 7.3 Hz, 2H), 3.88 (s, 3H), 3.91 (s, 3H), 3.95 (s, 3H), 6.50 (s, 1H), 7.43 (s, 1H)

FAB-MS m/z = 225 (M^+ + 1)

Process 2

2',4',5'-Trimethoxypropiophenone (0.45 g) obtained in the above Process 1 and indole-3-carboxaldehyde (0.28 g) were dissolved in ethanol (5 ml), and piperidine (0.17 g) was added thereto, followed by heating under reflux for 144 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography. The obtained crude crystals were recrystallized from a mixed solvent of ethyl acetate and hexane to give Compound 23 (0.21 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.28 (d, J = 0.7 Hz, 3H), 3.77 (s, 3H), 3.85 (s, 3H), 3.98 (s, 3H), 6.62 (s, 1H), 6.92 (s, 1H), 7.16 (m, 1H), 7.23 (d, J = 2.1 Hz, 1H), 7.42 (brd, J = 8.2 Hz, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.62-7.65 (m, 2H), 8.74 (brs, 1H)

EI-MS m/z = 351 (M^+)

Elemental analysis: $C_{21}H_{21}NO_4 \cdot 0.2H_2O$

Calcd.(%): C, 71.05; H, 6.08; N, 3.95

Found (%): C, 71.05; H, 6.13; N, 3.83

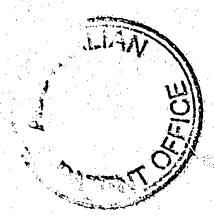
Example 24

3-(Indol-3-yl)-2-methyl-1-(2,3,4-trimethoxyphenyl)-2-propen-1-one (Compound 24)

Process 1

Substantially the same procedure as in Process 1 of Example 8 was repeated using 2,3,4-trimethoxybenzaldehyde (1.96 g) to give 2',3',4'-trimethoxypropiophenone (1.94 g).

^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.17 (t, J = 7.3 Hz, 3H), 2.97 (q, J = 7.3 Hz, 2H), 3.75 (s, 3H), 3.90 (s, 3H), .96 (s, 3H), 6.70 (d, J = 9.0 Hz, 1H), 7.43 (d, J



= 9.0 Hz, 1H)

FAB-MS m/z = 225 (M^+ + 1)

Process 2

2',3',4'-Trimethoxypropiophenone (1.12 g) obtained in the above Process 1 and indole-3-carboxaldehyde (0.73 g) were dissolved in ethanol (10 ml), and piperidine (0.43 g) was added thereto, followed by heating under reflux for 72 hours. The precipitated crystals were collected by filtration, and the obtained crude crystals were recrystallized from ethanol to give Compound 24 (0.49 g).

^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.29 (d, J = 1.0 Hz, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 6.74 (d, J = 8.6 Hz, 1H), 7.06 (d, J = 8.6 Hz, 1H), 7.15 (m, 1H), 7.25 (m, 1H), 7.41 (brd, J = 7.9 Hz, 1H), 7.48 (brd, J = 7.9 Hz, 1H), 7.58 (brs, 1H), 7.62 (d, J = 3.0 Hz, 1H), 8.74 (brs, 1H)

EI-MS m/z = 351 (M^+)

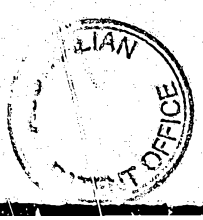
Elemental analysis: $C_{21}H_{21}NO_4$

Calcd.(%): C, 71.78; H, 6.02; N, 3.99

Found (%): C, 71.78; H, 6.19; N, 3.90

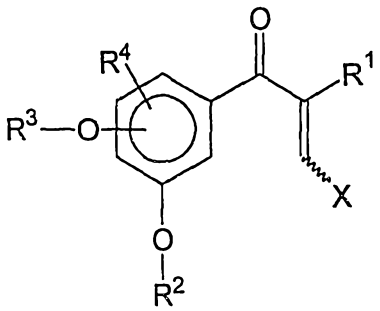
Industrial Applicability

According to the present invention, there can be provided propenone derivatives having an excellent antitumor activity.



The claims defining the invention are as follows:

1. A propenone derivative represented by the following formula (I):



wherein R^1 represents hydrogen or lower alkyl; R^2 and R^3 independently represent hydrogen, lower alkyl, or substituted or unsubstituted aralkyl, or alternatively R^2 and R^3 are combined to form substituted or unsubstituted methylene or ethylene; R^4 represents hydrogen, hydroxy, lower alkyl, substituted or unsubstituted aralkyl, lower alkoxy, substituted or unsubstituted aralkyloxy, or halogen; and X represents substituted or unsubstituted indolyl, with the proviso that when OR^3 is on the position 2 or position 6 of the benzene ring, R^3 is not hydrogen that when R^4 is on the position 2 or position 6 of the benene ring, R^4 is not hydroxy; and that the combination of OR^2, OR^3, and R^4 is not 3,4-dimethoxy or 3,4,5-trimethoxy; or pharmaceutically acceptable salts thereof.

2. A propenone derivative or a pharmaceutically acceptable salt thereof according to claim 1, wherein R^2 and R^3 are combined to form substituted or unsubstituted methylene or ethylene.

3. A propenone derivative or a pharmaceutically acceptable salt thereof according to claim 1, wherein OR^3 represents lower alkoxy, or substituted or unsubstituted aralkyloxy on the position 2 or position 6 of the benzene ring.

4. A propenone derivative or a pharmaceutically acceptable salt thereof according to claim 1, wherein OR^3 and R^4 are on the position 4 or position 5 of the benzene ring.

5. A propenone derivative or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein R4 represents lower alkyl, substituted or unsubstituted aralkyl, or halogen.

6. (E)-1-(3,5-dimethoxyphenyl)-3-(indol-3-yl)-2-propen-1-one

7. (E)-1-(4-hydroxy-3,5-dimethoxyphenyl)-3-(indol-3-yl)-2-propen-1-one

8. (E)-1-(4-benzyloxy-3,5-dimethoxyphenyl)-3-(indol-3-yl)-2-propen-1-one

9. 3-(indol-3-yl)-2-methyl-1-(3,4,5-triethoxyphenyl)-2-propen-1-one

10. 1-(4-ethoxy-3,5-dimethoxyphenyl)-3-(indol-3-yl)-2-methyl-2-propen-1-one

11. 3-(indol-3-yl)-1-(4-isobutyloxy-3,5-dimethoxyphenyl)-2-methyl-2-propen-1-one

12. 1-(4-ethyl-3,5-dimethoxyphenyl)-3-(indol-3-yl)-2-methyl-2-propen-1-one

13. 3-(indol-3-yl)-1-(3-methoxy-4,5-methylenedioxyphenyl)-2-methyl-2-propen-1-one

14 1-(5-ethoxy-3,4-dimethoxyphenyl)-3-(indol-3-yl)-2-methyl-2-propen-1-one

15. 1-(3-bromo-4,5-dimethoxyphenyl)-3-(indol-3-yl)-2-methyl-2-propen-1-one

16. 1-(4-ethoxy-3,5-dimethoxyphenyl)-2-methyl-3-(6-methylindol-3-yl)-2-propen-1-one

17. 1-(3-methoxy-4,5-methylenedioxyphenyl)-2-methyl-3-(6-methylindol-3-yl)-2-propen-1-one

18. 1-(3-bromo-4-isobutyloxy-5-methoxyphenyl)-3-(indol-3-yl)-2-methyl-2-propen-1-one

19. 1-(3-bromo-4-isobutyloxy-5-methoxyphenyl)-2-methyl-3-(6-methylindol-3-yl)-2-propen-1-one

20. 1-(4-isobutyloxy-3,5-dimethoxyphenyl)-2-methyl-3-(6-methylindol-3-yl)-2-methyl-2-propen-1-one

21. 1-(4-ethoxy-3,5-dimethoxyphenyl)-3-(6-ethylindol-3-yl)-2-methyl-2-propen-1-one

22. 1-(4-ethoxy-3,5-dimethoxyphenyl)-3-(6-isopropylindol-3-yl)-2-methyl-2-propen-1-one

23. 3-(6-chloroindol-3-yl)-1-(4-ethoxy-3,5-dimethoxyphenyl)-2-methyl-2-propen-1-one

24. 1-(3,5-dimethoxy-4-propoxyphenyl)-2-methyl-3-(6-methylindol-3-yl)-2-propen-1-one

25. 1-(4-butoxy-3,5-dimethoxyphenyl)-2-methyl-3-(6-methylindol-3-yl)-2-propen-1-one

26. 1-(2,5-dimethoxyphenyl)-3-(indol-3-yl)-2-propen-1-one

27. 1-(2,5-dimethoxyphenyl)-3-(indol-3-yl)-2-methyl-2-propen-1-one

28. 3-(indol-3-yl)-2-methyl-1-(2,4,5-trimethoxyphenyl)-2-propen-1-one

29. 3-(indol-3-yl)-2-methyl-1-(2,3,4-trimethoxyphenyl)-2-propen-1-one

30. A 1-phenyl-2-propen-1-one derivative, substantially as hereinbefore described with reference to any one of the examples.

31. A process for the preparation of a 1-phenyl-2-propen-1-one derivative, substantially as hereinbefore described with reference to any one of the examples.

32. A pharmaceutical composition comprising a propenone derivative or a pharmaceuticaliy acceptable salt thereof according to any one of claims 1 to 30.

33. A method for the treatment or prophylaxis of a tumour in a mammal, which method comprises administering to said mammal an effective amount of at least one compound according to any one of claims 1 to 30, or of a composition according to claim 32.

34. A propenone derivative according to any one of claims 1 to 30 or a pharmaceutical composition according to claim 32 when used for the treatment or prophylaxis of a tumour in a mammal.

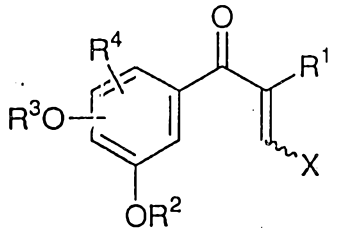
35. The use of a propenone derivative according to any one of claims 1 to 30 for the manufacture of a medicament for the prophylaxis or treatment of a tumour in a mammal.

Dated 19 August, 1998
Kyowa Hakko Kogyo Co., Ltd.

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

ABSTRACT

The present invention relates to propenone derivatives represented by the following formula (I):



(I)

wherein R^1 represents hydrogen or lower alkyl; R^2 and R^3 independently represent hydrogen, lower alkyl, or substituted or unsubstituted aralkyl, or alternatively R^2 and R^3 are combined to form substituted or unsubstituted methylene or ethylene; R^4 represents hydrogen, hydroxy, lower alkyl, substituted or unsubstituted aralkyl, lower alkoxy, substituted or unsubstituted aralkyloxy, or halogen; and X represents substituted or unsubstituted indolyl, with the proviso that when OR^3 is on the position 2 or position 6 of the benzene ring, R^3 is not hydrogen; that when R^4 is on the position 2 or position 6 of the benzene ring, R^4 is not hydroxy; and that the combination of OR^2, OR^3, and R^4 is not 3,4-dimethoxy or 3,4,5-trimethoxy; or pharmaceutically acceptable salts thereof.

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl^6 C07D209/12, 405/10, A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl^6 C07D209/12, 405/10, A61K31/40

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO, 95/19169, A2 (Sugen Inc. et al.), July 20, 1995 (20. 07. 95), Full descriptions & AU, 9515633, A	1 - 6
Y	Cancer Research, 54(23), (1994), p. 6106-14, Marina Kovalenko, et al., "Selective Platelet-derived Growth Factor Receptor Kinase Blockers Reverse sis-Transformation"	1 - 6
Y	US, 4904697, A (Merrell Dow Pharmaceuticals Inc.), February 27, 1990 (27. 02. 90), Full descriptions & EP, 288794, A & AU, 8814164, A & ZA, 8802391, A	1 - 6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
July 23, 1996 (23. 07. 96)	July 30, 1996 (30. 07. 96)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

国際調査報告	国際出願番号　PCT／JP96／01156

A.　発明の属する分野の分類（国際特許分類（IPC））
Int.Cl⁶　C07D209／12，405／10
　　A61K31／40

B.　調査を行った分野
調査を行った最小限資料（国際特許分類（IPC））
Int.Cl⁶　C07D209／12，405／10
　　A61K31／40

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）
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C.　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
P，A	WO，95／19169，A2（Sugen Inc. et al.），20．7月．1995（20．07．95），全文&AU，9515633，A	1－6
Y	Cancer Research，54（23），（1994），p.6106-14，Marina Kovalenko，et al.，"Selective Platelet-derived Growth Factor Receptor Kinase Blockers Reverse sis-Transformation"	1－6
Y	US，4904697，A（Merrell Dow Pharmaceuticals Inc.），27．2月．1990（27．02．90），全文&EP，288794，A&AU，8814164，A&ZA，8802391，A	1－6

☐ C欄の続きにも文献が列挙されている。　☐ パテントファミリーに関する別紙を参照。

＊　引用文献のカテゴリー
「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」先行文献ではあるが、国際出願日以後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

国際調査を完了した日　23．07．96	国際調査報告の発送日　30.07.96
国際調査機関の名称及びあて先 日本国特許庁（ISA／JP） 郵便番号100 東京都千代田区霞が関三丁目4番3号	特許庁審査官（権限のある職員） 冨永　保　4C　9159 電話番号　03－3581－1101　内線　3454

様式PCT／ISA／210（第2ページ）（1992年7月）