AWT - F. 38083

AUSTRALIA

Patents Act 1952

Form 1.
Regulation 9

APPLICATION FOR A STANDARD PATENT

I/We MECT CORPORATION, a Japanese corporation whose registered office is situate at 2-1-1, Nishi-Shinjyuku, Shinjyuku-ku, Tokyo, JAPAN

~~I/~~

hereby apply for the grant of a ~~Patent~~ Standard Patent for an invention entitled

"Indoloquinoline system compounds, process for their preparation, and carcinostative composition containing them".

which is described in the accompanying ~~provisional~~ complete specification.

For a Convention application – details of basic application(s) –

NUMBER	COUNTRY	DATE OF APPLICATION
56883/1988	JAPAN	10th March, 1988

~~For an application made by virtue of section 51~~

~~Original Application No.~~ ~~by~~

~~I request that the Patent may be granted as a Patent of Addition~~

~~the Patent applied for on Application No.~~

~~to~~

~~Patent No.~~ ~~in the name of~~

~~I request that the term of the Patent of Addition be the same as that for the main invention or so much of the term of the patent for the main invention as is unexpired.~~

117

Our ~~My~~ address for service is COLLISON & CO., Patent Attorneys, ~~Savings Bank Building,~~ 117 King William Street, Adelaide, South Australia, 5000.

Dated this 21st day of February , 1989

MECT CORPORATION

001198 08/03/89

Yasunori Kondo
(Signature)

Yasunori KONDO, President

~~(To be completed where application is made by a person other than the applicant for, or the patentee under, the patent for the main invention.)~~

~~I,~~

~~applicant for Application No.~~

~~the~~

~~patentee of Patent No.~~

~~hereby consent to this application.~~

~~Dated this~~ ~~day of~~ ~~19~~

~~(Signature)~~

To:

THE COMMISSIONER OF PATENTS

*o/4374

This form must be accompanied by either a provisional specification (Form 9 and true copy) or by a complete specification (Form 10 and true copy).

AWT - F. 38083

AUSTRALIA

Form 8

Patents Act 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

in support of the Convention application made for a patent for an invention entitled: "CONDENSED QUINOLINE SYSTEM COMPOUND, CONDENSED ACRIDINE SYSTEM COMPOUND, PROCESS FOR PREPARING THE SAME, AND CARCINOSTATIC COMPOSITION CONTAINING THE SAME"

I, Yasunori KONDO, President of MECT CORPORATION, of 2-1-1, Nishi-Shinjyuku, Shinjyuku-ku, Tokyo, JAPAN

~~We~~

do solemnly and sincerely declare as follows:

~~1. I am the applicant for the patent~~

(or, in the case of an application by a body corporate)

1. I am authorized by MECT CORPORATION , the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by section 141 of the Act was made in JAPAN on the 10th day of March , 19 88 , by MECT CORPORATION

~~day of , 19 , by~~

3. ~~I am the actual inventor of the invention referred to in the basic application.~~

(or, where a person other than the inventor is the applicant)

3. Masatoshi YAMATO, of 1507-204, Tsudaka, Okayama-shi, Okayama-ken, JAPAN

~~We~~

is the actual inventor of the invention and the facts upon which ~~I am~~ the applicant company is entitled to make the application are as follows:

The applicant company is the assignee of the actual inventor.

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

~~*(or where a request is made under section 142AA of the Patents Act 1952, for an earlier application made in a Convention country to be disregarded)*~~

~~4.—(1.) The basic application referred to in paragraph 2 of this Declaration was not the first application made in a Convention country in respect of the invention the subject of the application.~~

~~(2.) An earlier application in respect of the invention the subject of the application was made in on—~~

~~(3.) A request has been made to you under section 142AA of the *Patents Act* 1952 to disregard that earlier application.—~~

~~*—(Here set out in succeeding sub-paragraphs the facts that show that section 142AA is applicable)*~~

~~Except as stated in this paragraph, the basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.~~

Declared at Tokyo, Japan this 21st day of February , 19 89

MECT CORPORATION

Yasunori Kondo

(Signature of Declarant)

Yasunori KONDO, President

TO:

THE COMMISSIONER OF PATENTS.

(IMPORTANT – Cross out inapplicable words in above Form.)

*0/4524

(12) PATENT ABRIDGMENT (11) Document No. AU-B-31120/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 618991

(54) Title
INDOLOQUINOLINE SYSTEM COMPOUNDS, PROCESS FOR THEIR PREPARATION, AND CARCINOSTATIVE COMPOSITIONS CONTAINING THEM

International Patent Classification(s)
(51)[4] C07D 471/04 A61K 031/44 C07D 221/18

(21) Application No. : 31120/89 (22) Application Date : 08.03.89

(30) Priority Data

(31) Number (32) Date (33) Country
63-56883 10.03.88 JP JAPAN

(43) Publication Date : 14.09.89

(44) Publication Date of Accepted Application : 16.01.92

(71) Applicant(s)
MECT CORPORATION

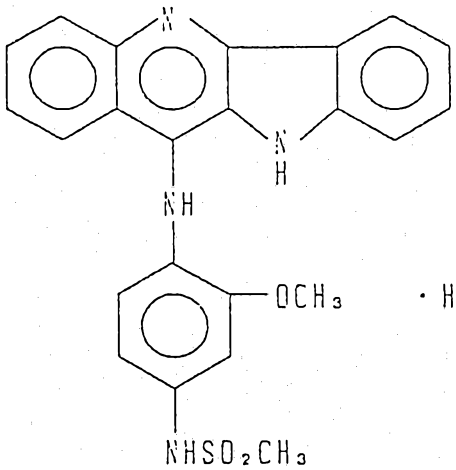
(72) Inventor(s)
MASATOSHI YAMATO

(74) Attorney or Agent
COLLISON & CO , 117 King William Street, ADELAIDE SA 5000

(57) Indoloquinoline system as carcinostatic agents.

CLAIM

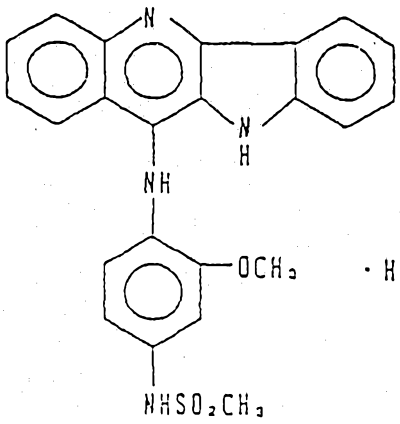
1. An indoloquinoline system compound represented by the following formula (1):



· HCℓ · · · (1)

3. A carcinostatic composition containing, as an efficacious ingredient, an effective amount of a compound represented by the following formula (1):

. . ./2



· HCℓ · · · (1)

in a pharmacologically acceptable carrier.

COMMONWEALTH OF AUSTRALIA

Form 10

Patents Act 1952-1969

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE:

Class Int. Class

Application Number :
Lodged :

Complete Application No. ;
Specification Lodged :
Published :

618961

Priority:

Related art:

TO BE COMPLETED BY APPLICANT

Name of Applicant: MECT CORPORATION

Address of Applicant: 2-1-1, Nishi-Shinjyuku, Shinjyuku-ku, Tokyo, JAPAN

Actual Inventor: Masatoshi YAMATO

Address for Service: COLLISON & CO., Patent Attorneys, of 117 King William Street, Adelaide, South Australia, 5000.

Complete Specification for the invention entitled:

"Indoloquinoline system compounds, process for their preparation, and carcinostative composition containing them".

The following statement is a full description of this invention, including the best method of performing it known to ~~me~~ us:

MTS

TITLE OF THE INVENTION:

Condensed Quinoline System Compound, Condensed Acridine System Compound, Process for Preparing the same, and Carcinostatic Composition containing the Same

BACKGROUND OF THE INVENTION:

Field of the Invention:

The present invention relates to novel quinoline system compounds (more particularly, indoloquinoline system compounds) and novel acridine system compounds (more particularly, benzo(b)acridine system compounds and benzo(c)acridine system compounds) which have carcinostatic activities. The present invention further relates to processes for preparing the aforementioned compounds and carcinostatic compositions containing the same.

Prior Art Statement:

B. F. Cain, G. J. Atwell and R. N. Sealye synthesized various acridine system compounds each having an alkylamino group at 9-position, and found that they have antileukemia activities (see J. Med. Chem., vol 15, 611 (1972)).

Cain, Atwell and Sealy further replaced the alkylamino group at the 9-position of acridine with another molecule or group and found that N-(4-(9-acridylamino)-3-methoxyphenyl)methanesulfonamide (Amsacrine) has the highest carcinostatiac function. (Refer to J. Med. Chem., vol. 17, 922 (1974).)

On the other hand, G. W. Rewcastle, B. C. Baguley, G. J. Atwell and W. A. Denny modified Amsacrine molecule to synthesize derivatives each having acridine ring introduced with methyl group or N-methylcarbamoyl group, and found that the derivatives have strong carcinostatic activities. (Refer to J. Med. Chem., vol. 30, 1576 (1987).)

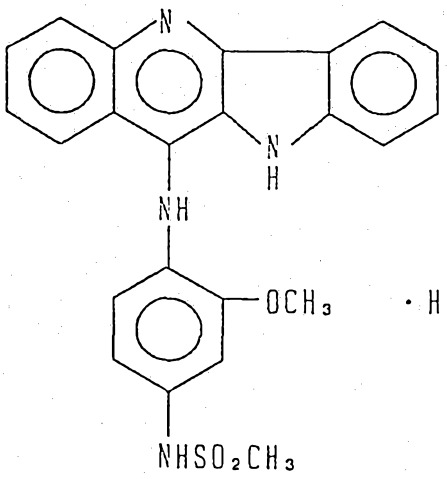
We previously synthesized indenoquinoline system compounds having high carcinostatic activities, and filed Patent Application relating them. (See Japanese Patent Appln. No. 246776/1986.)

We further synthesized novel benzofuroquinoline and benzothienoquinoline system compounds having similar high carcinostatic activities, and filed another Patent Application relating them. (See Japanese Patent Appln. No. 69766/1987.)

OBJECTS AND SUMMARY OF THE INVENTION:

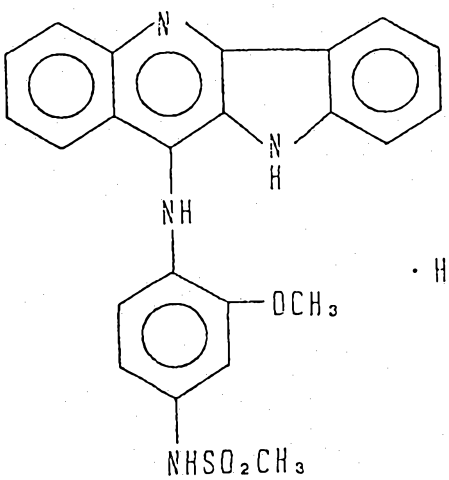
The present invention is based on our further investigations, and relates to indoloquinoline and benzoacridine system compounds, processes for preparing the same and uses thereof as carcinostatic agents.

According to a first aspect of this invention, there is provided an indoloquinoline system compound represented by the following formula (1):



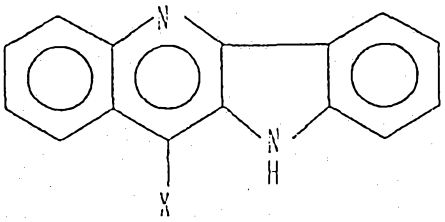
· HCℓ · · · (1)

Further provided by the invention is a process for preparing a condensed quinoline system compound represented by the following formula (1):



· HCℓ · · · (1)

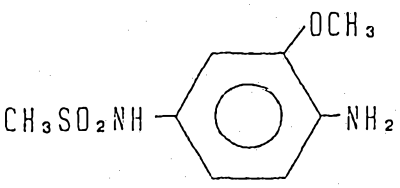
characterized in that a compound represented by the following formula (4):



. . . (4)

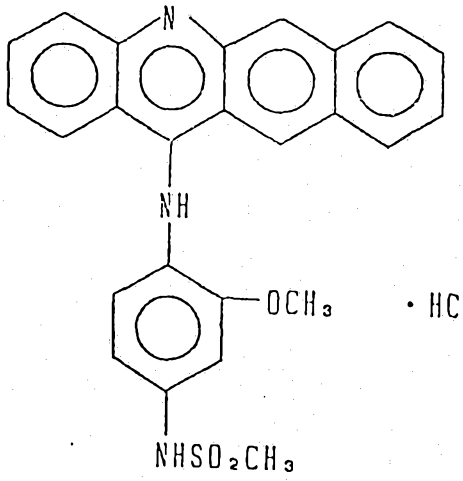
wherein X stands for a halogen atom;

is allowed to react with a compound represented by the following formula (5):



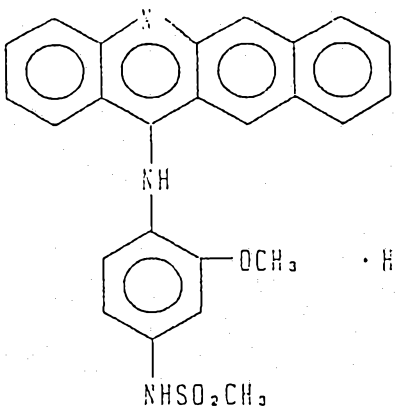
. . . (5)

According to a second aspect of this invention, there is provided a benzo(b)acridine system compound represented by the following formula (2):



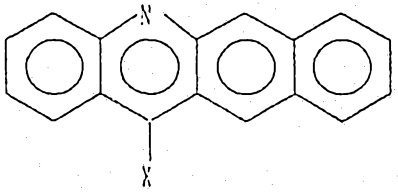
. . . (2)

Further provided by the invention is a process for preparing a condensed acridine system compound represented by the following formula (2):



· HCℓ · · · (2)

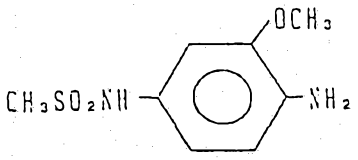
characterized in that a compound represented by the following formula (6):



· · · (6)

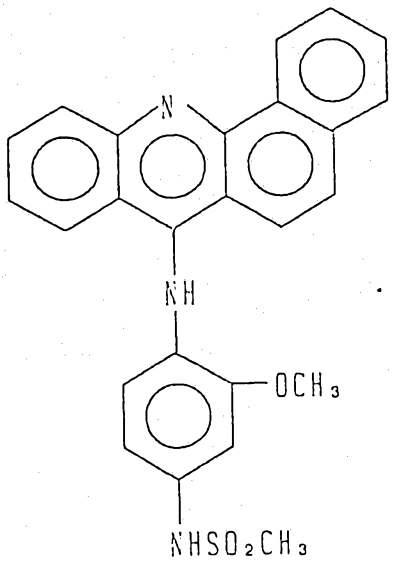
wherein X stands for a halogen atom;

is allowed to react with a compound represented by the following formula (5):



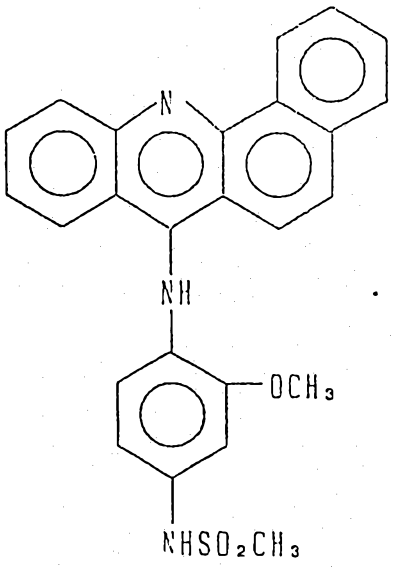
· · · (5)

According to a third aspect of this invention, there is provided a benzo(c)acridine system compound represented by the following formula (3):



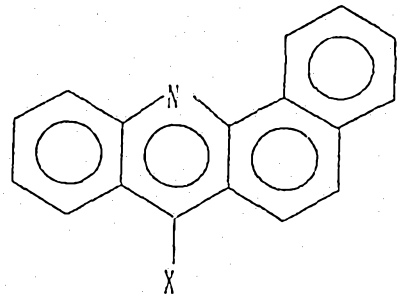
$\cdot HC\ell$ ... (3)

Further provided by the invention is a process for preparing a benzo(c)acridine system compound represented by the following formula (3):



$\cdot HC\ell$ ... (3)

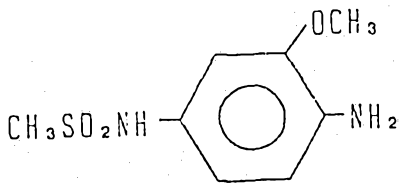
characterized in that a compound represented by the following formula (7):



. . . (7)

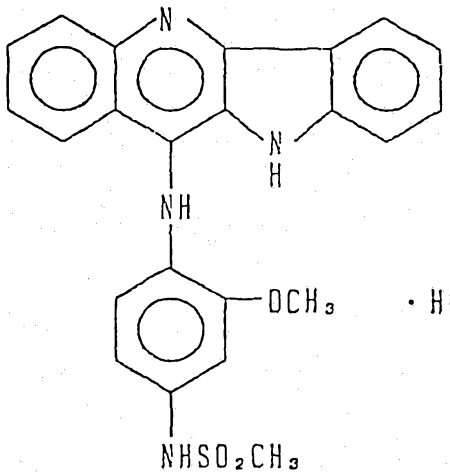
wherein X stands for a halogen atom;

is allowed to react with a compound represented by the following formula (5):

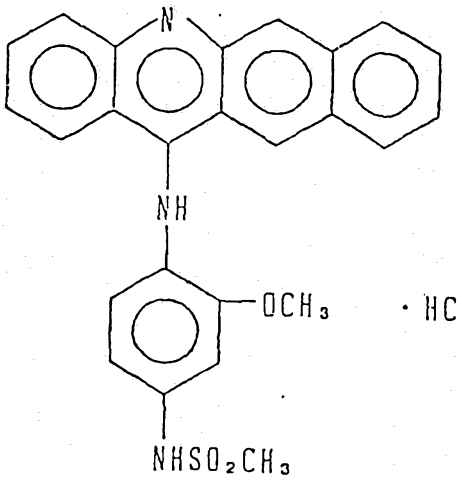


. . . (5)

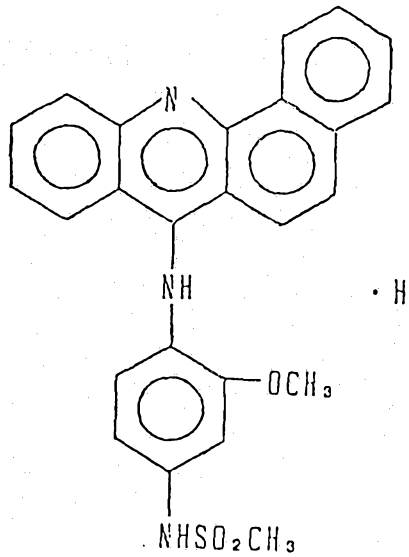
According to a further aspect of this invention, there is provided a carcinostatic composition containing, as an efficacious ingredient, at least one of the compounds represented by any one of the following formulae (1), (2) and (3):



・HCℓ　　・・・(1)



・HCℓ　　・・・(2)

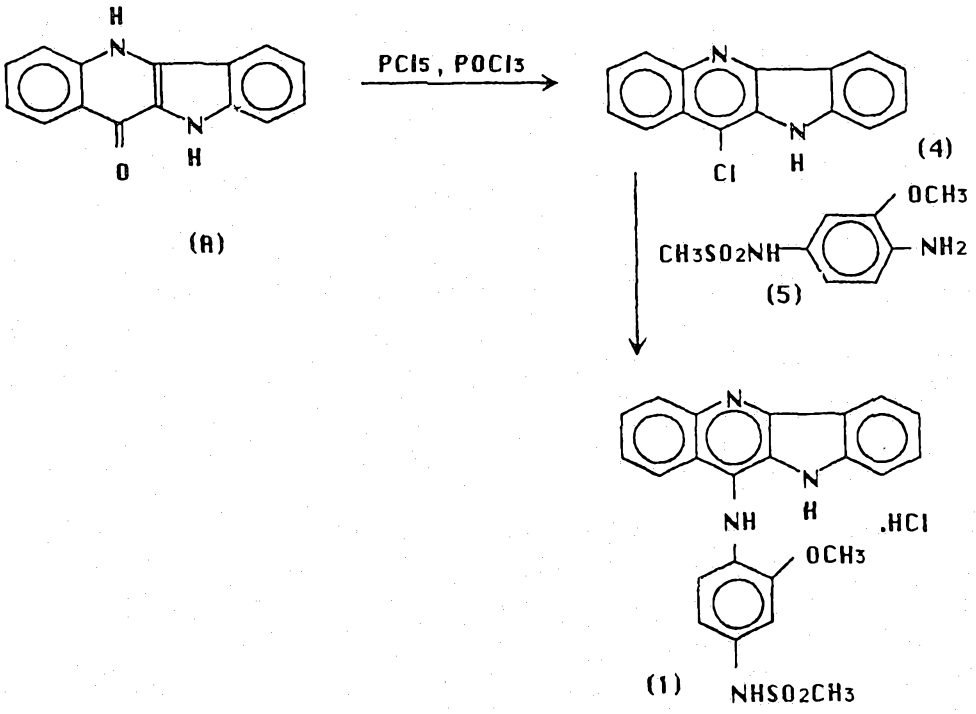


・HCℓ　　・・・(3)

EXAMPLES OF THE INVENTION:

The present invention will be described in detail with referring to some presently preferred embodiments thereof. However, it should be noted that the invention is not limited to the following specific examples but may be modified or altered within the scope of the invention clearly defined by the appended claims.

Example 1: Preparation of N-(4-((indolo(3,2-b) quinoline-10-yl)-amino)-3-methoxyphenyl)methanesulfonamide--Compound (1)



The step of preparing the Compound (4) from the starting material (A) has been reported by Klaus Gorlitzer and Josef Weber in Arch. Pharm. vol. 341, 852 (1981).

505 mg of the Compound (4) prepared by the method of Gorlitzer and Weber was dissolved in 8 ml of ethoxyethanol, pyridine dioxane or dimethylformamide together with 432 mg of the Compound (5), and heated to reflux for 6 hours while being added with a few drops of conc. hydrochloric acid if necessary. The separated crystal was filtered and recrystallized from ethanol to obtain 600 mg of the compound (1). The yield was 72%.

Melting Point: 280 to 282°C (Decomposition Point)

NMR(DMSO-d_6)

δ: 3.08 (3H, s. SO_2CH_3)

3.52 (3H, s, OCH_3)

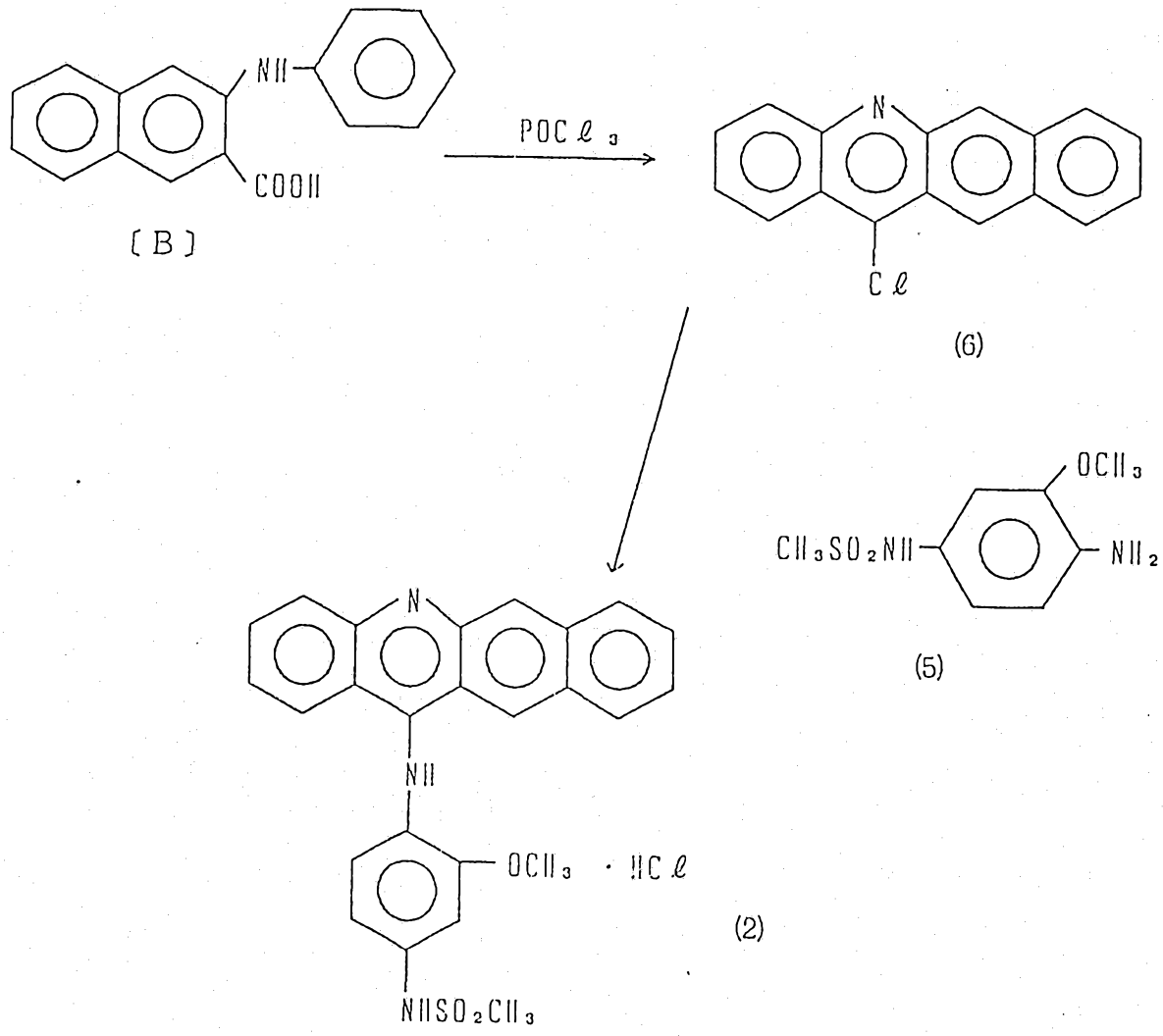
6.70 to 7.16 (3H, m, Ar-H)

7.32 to 7.82 (7H, m, Ar-H and NH x 2)

8.12 to 8.64 (3H, m, Ar-H)

11.03 to 11.20 (1H, b, NH)

Example 2: Preparation of N-(4-((benzo(b)acridine-12-yl) amino)-3-methoxyphenyl)methanesulfonamide ---- Compound (2)



The step for preparing the Compound (6) from the starting material (B) is the same as reported by A. Albert, D. J. Brown and H. Duewell in J. Am. Chem. Soc., vol. 70, 1284 (1948). 825 mg of the Compound (6) and 678 mg of the Compound (5) were dissolved in 10 ml of ethoxyethanolpyridinedioxane or dimethylformamide, and heated to reflux for an hour while being added with a few drops of conc. hydrochloric acid if necessary. The separated precipitate was filtered and recrystallized from dimethylformamide to obtain 800 mg of the Compound (2). The yield was 61%.

Melting Point: above 300°C (Decomposition Point)

NMR ($DMSO-d_6$)

δ : 2.92 (3H, s, SO_2CH_3)

3.48 (3H, s, OCH_3)

6.82 to 7.20 (3H, m, Ar-H)

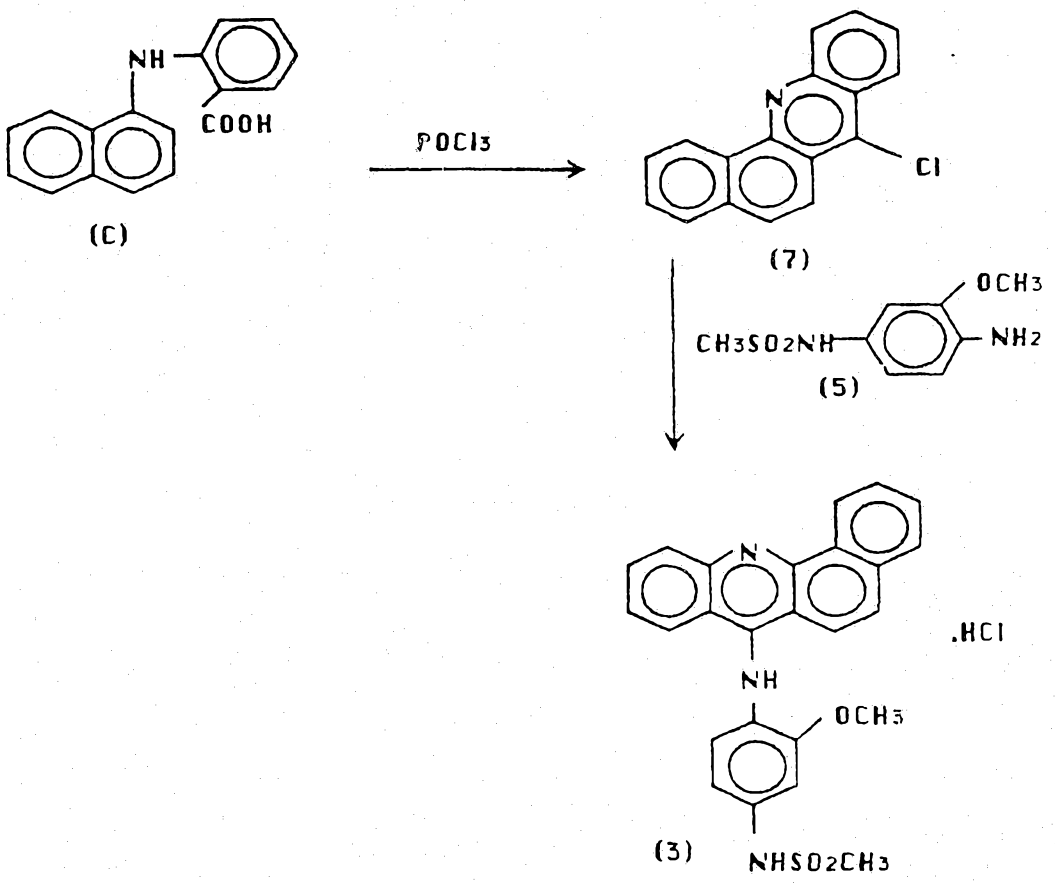
7.42 to 8.12 (9H, m, Ar-H and NH)

8.31 to 8.39 (1H, m, Ar-H)

9.13 to 9.20 (1H, m, Ar-H)

10.10 to 10.17 (1H, b, NH)

Example 3: Preparation of N-(4-((benzo(c)acridine-11-yl) amino)-3-methoxyphenyl)methanesulfonamide-- Compound (3)



The compound (7) was prepared from the starting material (C) through the step as reported by G. B. Bachman and G. M. Picha in J. Am. Chem. Soc., vol. 68, 1599 (1946).

825 mg of the thus prepared Compound (7) and 678 mg of the Compound (5) were dissolved in 8 ml of methoxyethanol, pyridinedioxane or dimethylformamide, being added with a few drops of conc. hydrochloric acid if necessary, and heated to reflux for 3 hours. The separated crystal was filtered and recrystallized from dimethylformamide to obtain 850 mg of the Compound (3). The yield was 61%.

Melting Point: above 300°C (Decomposition Point)

NMR (DMSO-d_6)

δ : 3.10 (3H, s, SO_2CH_3)
3.41 (3H, s, OCH_3)
7.15 to 7.32 (3H, m, Ar-H)
7.48 to 8.17 (9H, m, Ar-H and NH)
8.33 to 8.46 (1H, m, Ar-H)
8.93 to 9.23 (1H, m, Ar-H)
9.82 to 9.94 (1H, b, NH)

Ingredient Example 1 (Injection)

500 mg of each of the Compounds (1), (2) and (3) was separately dissolved in 19.6 ml of a 0.85% physical saline solution to prepare an intravenous injection. Each injection was administered intravenously at a dose of 20 ml a day.

Test Example 1: Test for Antitumorigenic Funciton:

1) Function for Inhibiting Multiplication of KB-1 Cell (in vitro test)

KB cells, carcinomatous cell tumors, were transferred to in vitro floatation incubator systems, and added respectively with the Compounds (1), (2) and (3). The results of cultivation added with the Compounds (1), (2) and (3) were compared with the result of the control which was not added with any compound.

Experimental System:

Cell used: KB Cell (Originating from Human Mouth Epidermal Cancer)

Culture medium: Eagles Minimal Essential Medium supplemented with 10% Calf Serum

Cultivation: 37°C Carbon dioxide Gas incubator (5% CO_2)

Method of Experiment:

Day 0: KB cells were diluted in the culture medium to adjust the KB cell density to 2×10^4/ml. Three ml of the cell suspension was inoculated in each of 60 mm plastic dishes. Two dishes per standard dosage were used.

Day 1: Test compound was added to the medium so that the final concentrations were set to 100, 30, 10, 3 and 1 µg/ml.

Day 4: Cells were scraped off from the dish using trypsin, and the cell number was countered using a Corter counter.

Criteria for Judgment:

In generally accordance with the stipulations set forth by the National Cancer Institute (NCI), U.S.A., the concentration of compound necessary for exerting 50% growth inhibition (ED_{50}) compared to the control was determined. A compound was judged as effective when ED_{50} was less than 4 µg/ml.

The results are shown below.

Table I: Result of Test on Carcinostatic Effect (Effect of Inhibiting growth of KB-Cell)

Compound No. Tested	Concentration (µg/ml)	Inhibition Rate (%)
1	0.3	50
2	1.15	50
4	0.3	50
Control	0	0

Test Example 2: Effect on Prolongation of Life Span in Cancer implanted Mouse and Acute Toxicity

Pharmaccological effects of the compounds as used in Test Example 1 were tested in in vivo systems using P-388 implanted mice. The results were compared to that of a control which was ot added with any compound.

System Used in Experiment:

Animal Used: CDF Mouse (6 mice/group)

Tumor: P-388

Number of Inowlated Cells: 10^6 cells/mouse

Inowlated Site: i.p.

Day of Administration: Day 1 and Day 5

Dosage: LD_{50} or 400 mg/kg/day at the maximum

Criteria for Judgment:

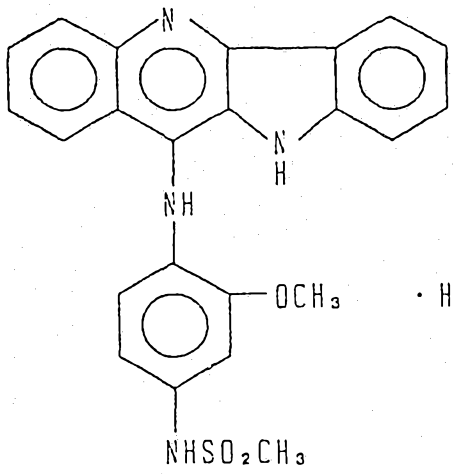
The treatment was judged as effective when the ratio of survival of the treated group to that of the control group (T/C %) was 120% or more. The survial period of the control group was generally about 10 days.

Table II: Effect on Prolongation of Life Span of Mouse implanted with P-388 Cancer Cells

Compound No. Tested	Dosage (mg/kg)	Ratio of Life Prolongation (%)
1	25	111
	12.5	203
	6.25	300
2	400	130
	200	130
	100	122
3	200	204
	100	163
	50	157

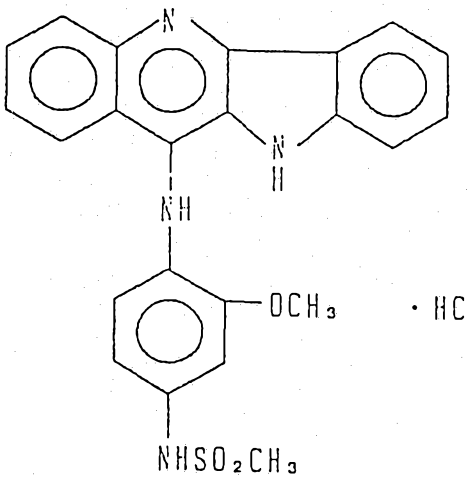
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An indoloquinoline system compound represented by the following formula (1):



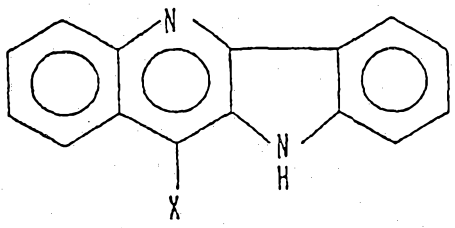
$\cdot HC\ell$ ... (1)

2. A process for preparing a condensed quinoline system compound represented by the following formula (1):



$\cdot HC\ell$ ... (1)

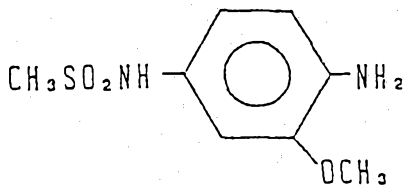
characterized in that a compound represented by the following formula (4):



. . . (4)

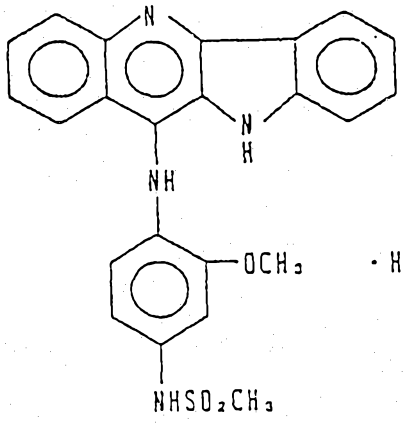
wherein X stands for halogen atom;

is allowed to react with a compound represented by the following formula (5):



. . . (5)

3. A carcinostatic composition containing, as an efficacious ingredient, an effective amount of a compound represented by the following formula (1):



. . . (1)

in a pharmacologically acceptable carrier.

Dated this 27th day of August 1991

MECT CORPORATION
By their Patent Attorneys
COLLISON & CO.