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(54) Titre : DERIVES DE PURINE SUBSTITUEE PAR UN GROUPE N2-QUINOLEYLE OU ISOQUINOLEYLE, LEURS PREPARATIONS ET UTILISATIONS

(54) Title: N²-QUINOLYL OR ISOQUINOLYL SUBSTITUTED PURINE DERIVATIVES, THE PREPARATION AND USES THEREOF

(57) Abrégé/Abstract:
The present invention discloses N²-quinolyl or isoquinolyl substituted purine derivatives, and pharmaceutical compositions containing them. The compounds of the invention have the characteristic of lower toxicity, broad anticancer spectrum, higher anticancer activity, good stability and the like. The compounds are useful for the manufacture of an antitumor medicament. The present invention also discloses a process for preparing these compounds.
N\textsuperscript{2}QUINOLINE- OR ISOQUINOLINE-SUBSTITUTED PURINE DERIVATIVES AND METHOD OF PREPARATION AND USES THEREOF

ABSTRACT

Disclosed is a novel compound having the following formula:

\[ \text{(A)} \]

wherein \( W \) represents a hydrogen, an optionally substituted \( C_{1-6} \) alkyl, an optionally substituted \( C_{3-6} \) cycloalkyl, or an optionally substituted \( C_{1-6} \) haloalkyl; \( Y \) represents a hydrogen, or a saccharide, \( Q \) represents a quinoline or an isoquinoline. Also disclosed is a pharmaceutical composition comprising the same, methods for treating cancer using the same, and methods for the synthesis of the same.
DESCRIPTION

[0001] The present invention relates to pharmaceutical chemistry, and particularly to N²-quinoline- or isoquinoline-substituted purine derivatives, processes for their production, pharmaceutical compositions comprising the same, and methods for using these derivatives in the treatment of cancer.

[0002] Cancer remains a major threat to human health. Most human cancers are caused by environment factors, and not fewer than 5 million people die of cancer per year worldwide. Although many methods of treatment, such as surgery, radiation therapy, chemotherapy, etc., are available, curative ratio is generally low. Presently, the use of pharmaceuticals remains one of the most effective cancer prevention and therapy method.

[0003] Purine or pyridine derivatives are known to have anti-viral or anti-cancer activities. See, e.g., EP 173624, EP 253412, EP 353955, WO 9201698, and EP 481214, etc.

[0004] In natural or synthetic nucleotide derivatives, the pyridine, purine or other heterocyclic substituent is located on the 1 position of the saccharide ring (corresponding to the 2 position of a hydroxyl-substituted tetrahydrofuran derivative). These compounds have recently been reported to have anti-cancer or antiviral activities.

[0005] Another group of derivatives, O⁶-alkyl purine derivatives, are known for their ability to inhibit the activity of O⁶-alkylguanine-DNA alkyltransferase (AGT), thereby enhancing the effectiveness of alkylating agents as tumor chemotherapeutics.

[0006] Although the cancer cell killing mechanism of the O⁶-methyl guanine in the ATase defect cell is not clear, it is generally understood that the mechanism of the O⁶- chloroethyl guanine includes a cycloethidene guanine intermediate, which cross links the DNA double strand in the cytidine residue.
This linkage can be eliminated or prevented via an ATase mediated de-
chloroethylation or a complex formal. Methods for antagonizing O^6-
alkylguanine-DNA alkyl transferase in tumor cells have been reported, e.g., in
U.S. Patent No. 5,091,430 and WO 9113898.

[0007] N^2-substituted purine derivatives are known. For example, N^6-
disubstituted purine derivatives which can be used to treat allergies are
described in U.S. Patent No. 4,853,386. 6-cyclopropylamino-9H purine
derivatives are described in JP 2003-55377A and JP 2003-119197A, which
have antiviral properties. Glycosylated purine derivatives which have anti-
N^2-butyphenyl-2'-desoxypurine derivatives are described in J. Med. Chem
(1984, 27:175-181), which have the activity of inhibiting eukaryotic DNA α
polymerase. 2, 6, 9-substituted purine derivatives are described in
compounds have partially the same or similar structure with the compounds of
this invention, but none of the above mentioned compounds, however, have
been shown to have anti-cancer activities or the ability to inhibit abnormal cell
growth. Accordingly, there is a need for discovery of anti-tumor drugs that
may be used as anti-cancer agents, with low toxicity, wide anti-cancer
spectrum, high anti-cancer activity, and high stability.

[0008] The present invention relates to highly stable N^2-substituted purine
derivatives with low toxicity wide anti-cancer spectrum and high anti-cancer
activities.

[0009] The present invention relates to compounds having the following
formula A of N^2-quinoline- or isoquinoline-substituted purine compounds, their
salts, or hydrates.

[0010] The invention features a compound having the following formula A, its
salts, or hydrates:
wherein

W represents a hydrogen, an optionally substituted C_{1-6} straight or branched alkyl, an optionally substituted C_{3-6} cycloalkyl, or an optionally substituted C_{1-6} haloalkyl;

Y represents a hydrogen, or a pharmaceutically-acceptable saccharide of any one of the following formulas:

Z represents a hydrogen or a substituent having any one of the following formulas:
Q represents a substituent having any one of the following formulas:

B, E, G, R, T, and M each independently represent a hydrogen, a straight or branched C<sub>1-6</sub> alkyl or haloalkyl, a C<sub>3-6</sub> cycloalkyl, a halogen, a cyano, or an amino.
[0011] Preferably, in the compound of the present invention having formula A, W represent a hydrogen or a substituent having any one of the following formulas:

[0012] More preferably, W is one of:

[0013] Still more preferably, W represents:

[0014] In one preferred embodiment, in the compound of the present invention having Formula A, Q represents:
[0015] More preferably, Q represents the following group:

[0016] In one preferred embodiment, in the compound of the present invention having Formula A, the substituent B, E, G, R, T, or M each independently represents a hydrogen, a fluorine, a methyl, a trifluoromethyl, a cyano, or an amino, especially a hydrogen.

[0017] In one preferred embodiment, in the compound of the present invention having Formula A, Y is a hydrogen.

[0018] The following specific compounds are particularly preferred:

I

II
[0019] Compound (I) is especially preferred:
[0020] The another propose of this invention is to provide with a pharmaceutical composition of compounds of formula I to XVIII, the composition being composed by one of any compound or its salts or hydrates in formula I to XVIII with pharmaceutical adjuvants. The described composition is suitable for intestinal, local or parenteral administration, or a pharmaceutical composition for the administration of mammalian animals via inhalation. The compositions can be tablets, capsules, pills, oral liquid preparations, granules, powders, injections, implants or preparations for external use.

[0021] The present invention further provides with a process for the production of the above described compounds or its salts or hydrates. In one embodiment, the compounds of this invention can be prepared in accordance with the following schemes:

1). The reaction is carried out in the presence of formula (j) compound and Q-NH₂,

\[ \text{O} \]
\[ \text{HN} \]
\[ \text{N} \]
\[ \text{X} \]
\[ \text{N} \]
\[ \text{HN} \]
\[ \text{H} \]

resulting in formula (b) compound
The above reaction is carried out in an organic solvent, in the presence of formula (j) compound and 0.8-1.5 mol/ml Q-NH$_2$, the mixture was heated at 50-150 °C to react for 1-72 hours, then water was added to the reaction mixture, and the reaction mixture was allowed to cool to room temperature.

2). Preparation of formula (c) compound with formula (b) compound

The reaction is carried out in an organic solvent, in the presence of formula (b) compound and a halogenating agent, the mixture was heated at 50-150 °C to react for 1-72 hours, cooled. Water was added and the pH of the mixture pH was adjusted to 2-5 with an acid, and was allowed to cool at room temperature.

3). Preparation of formula (f) compound by react formula (c) compound with W-N H$_2$
The reaction is carried out in an organic solvent, in the presence of formula (c) compound, 0.8-1.5 mol/mol W-NH₂ and an acid acceptor, the mixture was heated at 50-150°C to react for 1-72 hours. The solvent was then distilled off.

X represents Br, X' represents Cl, W is as defined above.

[0022] According to another embodiment, the present invention also provides a process for the production of the above mentioned compound or its salts, the compounds of this invention can be prepared in accordance with the following schemes:

1) The reaction is carried out in the presence of to formula (k) compound and W-NH₂,

resulting in formula (e) compound:
The reaction is carried out in an organic solvent, in the presence of formula (k) compound, 0.8-1.5mol/mol W-NH₂ and an acid acceptor, the mixture was heated at 30-120°C to react for 1-72 hours. The solvent was then distilled off.

2) Preparation of formula (f) compound by react formula (e) compound with Q-NH₂

The reaction is carried out in an organic solvent, in the presence of formula (e) compound, 0.8-1.5mol/mol Q-NH₂, and an acid acceptor. The mixture was heated at 70-170 °C to react for 1-72 hours. The solvent was then distilled off.

X and X’ represent Cl, and W is as defined above.

[0023] The salt of the compound of Formula A can be any pharmaceutically acceptable salt, known to those skilled in the art. The addition salt of the compound can be synthesized by inorganic acid or organic acid, preferably as hydrochloride, hydrobromide, hydroiodide, p-toluenesulfonate, phosphate, sulfate, perchloride, acetate, trifluoroacetate, propionate, citrate, malonate,
succinate, lactate, oxalate, tartrate, benzoate. The salt also can be formed by a base, including an inorganic or organic base, alkali earth metal salts such as magnesium salts, calcium salts, organic amines such as morpholine, piperidine, dimethylamine, diethylamine, etc.

[0024] In a preferred embodiment, the compounds of this invention are prepared in accordance with the following routines A and B:

Route A:

\[ \text{2-bromohyoxanthine} \xrightarrow{Q-NH_2} \text{b} \xrightarrow{W} \text{c} \xrightarrow{Q} \text{d} \]

Route B:

\[ \text{4} \xrightarrow{WNH_2} \text{e} \xrightarrow{Q-NH_2} \text{f} \]

[0025] The pharmaceutical composition of the present invention may be administered to mammals (include humans) internally (such as orally or via rectal administration), local, or parenterally or by inhalation spray, such as oral, injection, implantation, or external form. Suitable formulations for oral include tablets (such as conventional tablets, buccal tablets, sublingual tablet, oral cavity patch, chewable tablet, dispersible tablet, soluble tablet, effervescent
tablet, vaginal tablet, vaginal effervescent tablet, sustained-release tablet, controlled release tablet, enteric coated tablet, buccal rapid-release tablet), capsules (hard capsules, soft capsules, sustained-release capsules, controlled-release capsules, enteric-coated capsules, etc), pills (dripping pills, sugar coated pills, pellets), oral liquid preparation (syrups oral solution, oral suspension, oral emulsion, etc), granules (suspension granules, effervescent granules, enteric coated granules, sustained-release granules, controlled-release granules, etc), and powders. Injections including injectable solution, sterile, powder for injection, or sterile solids (including preparation produced by solvent crystallization, spray dry or lyophilization technologies etc.) concentrated solution for injection; implants; etc, and other external medicament forms such as suppositories, aerosol, aerosol powder, spray, pellicles, gel, patches, etc.

[0026] Pharmaceutical composition of the present invention may be prepared according to any public known dosage form preparation method in the field of pharmaceutical composition. It is suitable for treating cancers and the related diseases, and may be used alone or in combination with other one or more anti-cancer drugs. The quantity of active ingredient composited with carrier substance to prepare single dosage form can be varied according to the treated hosts and types of administration.

[0027] The compounds of this invention can be used to prevent or treat abnormal cell proliferation, especially those found in tumors or cancers, including lung cancer, liver cancer, leukemia, osteocarcinoma, pancreas cancer, skin cancer, melanoma, metrocarcinoma, oophoroma, rectal carcinoma, gastric carcinoma, colon cancer, breast carcinoma, salpingo-carcinoma, endometrium carcinoma, cervix carcinoma, vagina carcinoma, carcinoma of vulva, esophagus carcinoma, small intestine carcinoma, endocrinium carcinoma, soft tissue sarcoma, urethra carcinoma, prostatic cancer, lymphocyтомa, bladder cancer, kidney on ureter cancer, tumors of vertebral column, tumors in the neuroglia of the brain, and pituitary adenoma, especially lung cancer, liver cancer, leucocythaemia, pancreas cancer and breast cancer.
[0028] It was discovered from the determination of compounds in this invention in the experiments for inhibition the growth of tumor cell in vitro, that this compound shows remarkable inhibition action to the growth of human cells of lung cancer, liver cancer and leukemia incubated in vitro, and also showed dose-response effect relationship. The better formula I compound shows IC$_{50} = 11.22 \mu g/ml$ to human liver cancer, IC$_{50} = 12.8 \mu g/ml$ to human leukemia cells (blood cancer) and IC$_{50} = 10.24 \mu g/ml$ of human lung cancer cells. When administered the pharmaceutical composition of the invention by intraperitoneal injection to mouse, the LD$_{50}$ of mouse is 160mg/kg.

[0029] In the tumor inhibition experiment to liver cancer of H$_{22}$ mouse 80mg/kg, the inhibition rate of this drugs is 69%.

[0030] The compound can be applied to treat tumor in association with chemotherapy, radiotherapy and biochemical therapy to enhance effect and lowering pharmaceutical side effects.

[0031] Pharmacological Experiments

[0032] The activity of compounds has been determined with compound I as example:

[0033] Compound I:

![Chemical Structure]

1. Determination of IC$_{50}$ (Lewis lung cancer).
   (a) Incubated the Lewis lung cancer cells in DMEM nutrition solution containing 15% bovine serum, inoculate into 96-holer inoculation plate with $1 \times 10^4$ cells/hole, placed the plate in a 37°C 5% CO$_2$ incubator. Diluted the compound to suitable concentration with DMEM incubation solution which containing 15% bovine serum. Added the diluted solution into each hole of 96 holes plate, 3 holes for each concentration and 6 holes for blank control, lucubrated for 72 hours,
MTT solution was added and allowed to stand for 1 hour, added DMSO to develop the color, the OD value was determined with Enzyme Label instrument. Calculated the killing rate of each concentration, and calculated IC$_{50}$ value according to coordinate method.

Lewis lung cancer: IC$_{50}$=10.24µg/ml.

(b) Determined the IC$_{50}$=11.22µg/ml of compound I for human liver cancer cells with the same of above mentioned testing method.

(c) Determined the IC$_{50}$=12.8µg/ml of compound I for human leukemia cells (blood cancer) with the same of above mentioned testing method. It showed that this compound has the ability to inhibit the growth of non solid tumor cells.

2. Remarkable antitumor activity

(a) Divided randomly 30 mice (Kunming special) of a equal numbers of male and female of 21-22g body weight into 3 groups, each group consisted 10 mice. Inoculated liver cancer H$_{22}$ cells suspension 0.2ml for each mouse subcutaneous by at the right side of abdomen. The next day, intraperitoneally injected separately 80mg and 40mg/kg of this compound into 2 groups of mice once a day, continuously for 7days. Injected the control group IP with DMSO + normal saline. Killed the mice at the following day after stopping the administration, weighed the body weigh and tumor weigh, and calculated the tumor inhibition rate. The compound possessed obvious antitumor activity to H$_{22}$, with tumor inhibition rate of 69% and 40% with dosage of 80 mg and 40 mg/kg respectively.

<table>
<thead>
<tr>
<th>Class</th>
<th>body weight(g)</th>
<th>tumor weight(g)</th>
<th>inhibition rate(%)</th>
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<td>Before</td>
<td>after</td>
<td></td>
<td></td>
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<td>21.4</td>
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<tr>
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<td>29.7</td>
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</tbody>
</table>
(b) Inhibition of cancer cells in vitro

Treated human lung cancer cells (Lewis) and leukemia cells with 8μg/m, 16μg/ml of compound I, observed the dynamic growth of cells for 4 days. The difference between medicated and control groups is small within two days, at beginning of third day, the cells number of medicated group dropped rapidly, and the cancer cells in control group were continuously growing logarithmically The difference between groups were increasing with time prolongation.

[0034] The above pharmacological experiments show that the compound mentioned in this invention possesses obvious growth inhibition effect to the liver cancer cells, leukemic cells (solid tumor and non-solid tumor), and with dose-response relationship.

[0035] Specific embodiments of the invention

[0036] The following will illustrate the present invention in cooperate with examples, the examples are only used to illustrate the technical scheme for the invention but not limited to the present invention.

[0037] EXAMPLE 1-3:

[0038] The preparation of compounds I, II and III.

[0039] Route A:
[0040] Example 1. Preparation of Title Compound I

1). In 200ml water, 20g (93mmol) of 2-bromo-hypoxanthine, 13g (90mmol) of 6-aminoquinoline, 60ml ethylene glycol monomethyl ether were mixed and the mixture was refluxed for 48 hours checked the completion of reaction with TLC analysis. The reaction mixture was then poured into ice-water, the solid was isolated by filtration, washed with 200 ml concentrate ammonia water and 3×50 ml methanol, and dried. The crude product obtained was purified by column chromatography on silica gel to afford 14.2 g of compound 2. (yield 57%)

2). 12g (43mmol) of quinoline compound 2, 150ml phosphorus oxychloride, and 15 ml of N,N-xylidine were mixed and the mixture was refluxed for 30 minutes. The mixture was then cooled to room temperature. The reaction mixture was then poured into 2000 ml ice-water. After 2 hours, the pH of mixture was adjusted to 3 with acetic acid. The yellow solid was isolated by filtration. The crude product obtained was purified by column chromatography on silica gel to afford 11.5g of chloride 3. (yield 90%)
3). 10g (34mmol) of chloride 3, 10 ml (145mmol) of cyclopropylamine, 28 ml (200 mmol) of triethylamine, and 100 ml of DMF were mixed. The mixture was stirred at 100°C for to react 3 hours. Checked the completion of reaction with TLC analysis. The solvent was then distilled off and the residue was dissolved with ethylene glycol dimethyl ether. The mixture was filtered, and the solvent of filtrate was distilled off and the residue obtained was purified by column chromatography on silica gel to afford 7g (22mmol) target compound I (mp>250°C). (yield 65%)

[0041] Compound I: 1H NMR (DMSO-d6,δ): 0.640-0.642 (2H, s), 0.845-0.860(2H, m), 3.045 (1H, s), 7.0411-7.432 (1H, m), 7.632(1H, s, peak disappeared after added the heavy water), 7.865-7.888 (2H, m), 7.997-8.018 (1H, m), 8.116-8.136(1H, m), 8.623-8.682 (2H, m), 9.242 (1H, s, peak disappeared after added the heavy water), 12.400 (1H, s, peak disappeared after added the heavy water). MS (ESI): 318 (M+H⁺) 340 (M+Na⁺).

[0042] Example 2. Preparation of Title compound II

[0043] 10ml of anhydrous acetonitrile, 4.76 g (15mmol) of compound I obtained from example 1, and 6.3 ml (25mmol) of N,O-Bis(trimethylsilyl) acetamide (BSA) were mixed. The mixture was stirred at room temperature for 1 hour. A solution of 1.27g (4mmol) of tetraacetyl ribofuranose dissolved in 10 ml of acetonitrile, and 1.10 ml(16mmol) of TMSTF was then added to the mixture and was refluxed for 5 hours. 1.25 ml (5mmol) of N,O-Bis(trimethylsilyl)acetamide was added to the mixture, and then stirred for 24 hours. Monitored the completion of reaction with TLC analysis. The solvent was distilled off under reduced pressure and the residue was dissolved with 20 ml of methanol. The reaction mixture was passed ammonia gas for 2 hours. The solvent was distilled off under reduced pressure. The residue obtained was purified by column chromatography on silica gel to afford 4.65g of compound II. (yield 72%)

[0044] Compound II: MS (ESI): 450 (M+H⁺), 472 (M+Na⁺).

[0045] Example 3. Preparation of Title compound III
[0046] 10 g (31.5 mmol) of 2-(6-aminoquinolyl)-6-cyclopropyl purine i.e. compound I obtained from example 1, 1.5 g (37.8 mmol) of 60% NaH, and 150 ml of anhydrous acetonitrile were mixed. The mixture was stirred for 30 minutes in an atmosphere of nitrogen. 12 g (31.5mmol) of 3,5-diparatoluensulfonyl-2-deoxy-β-D- ribofuranose-1-chloride was added batchwise to the mixture in 20 minutes. The mixture was reacted at room temperature for 2 hours. The mixture was filtered, and the solvent of the filtrate was distilled off. The oil residue was purified by column chromatography on silica gel to afford 9.8g of 2-(6-aminoquinolyl)-6-cyclopropyl amino-9-(3,5-diparatoluensulfonyl-2-deoxy-β-D- ribofuranose) purine. (yield 47%)

[0047] The above product was added to 25 mmol of sodium methoxide and 400 ml of methanol. The mixture was stirred at room temperature for to react 5 hours. The pH of the mixture was adjusted to 7 with acetic acid. The solvent was distilled off and the residue obtained was purified by column chromatography on silica gel to afford 5 g of 2-(6-aminoquinolyl)-6-cyclopropyl amino-9-(2-deoxy-β-D- ribofuranose) purine, i.e., compound III. (yield 80%)


[0049] Example 4: Preparation of compound I Preparation of compound I as described in example 1 according to following Routine B:

1) 3.78 g (20 mmol) of dichloropurine 4, was dissolved in 50 ml of DMF, 1.4 ml (20mmol) of cyclopropylamine, and 3.08 ml (22mmol) of triethylamine were added. The mixture was reacted at 80°C for 5 hours. The completion of reaction was checked with TLC. The solvent was
distilled off under reduced pressure and the residue obtained was purified by column chromatography on silica gel to afford 3.34g of cyclopropyl compound 5. (yield 80%)

2). 2.99 g (14.3 mmol) of cyclopropyl compound 5, 5.1 g (36.1 mmol) of 6-amino-quinoline, 50 ml of DMF, and 2.4ml (17.1 mmol) of triethylamine were mixed. The mixture was refluxed at 140°C for 72 hours. TLC analysis proved that the reaction was basically completed. The solvent was distilled off under reduced pressure. The residue obtained was purified by column chromatography on silica gel to afford 3.54 g of compound I. (yield 78%)

[0050] Examples 5-7 illustrate the preparation of compounds IV, V, and VI.

[0051] Example 5: Preparation of Compound IV

1). In 200 ml water, 20 g (93 mmol) of 2-bromo-hypoxanthine, 13g (90 mmol) of 5-aminoquinoline, and 60 ml ethylene glycol monomethyl
ether were mixed and the mixture was refluxed for 48 hours. Monitored the completion of reaction with TLC analysis. The reaction mixture was cooled to room temperature then poured into ice-water, and the solid was isolated by filtration, washed with 200 ml concentrate ammonia water and three times of 50 ml methanol, and dried. The residue obtained was purified by column chromatography on silica gel to afford 8g of product 6. (yield 32%)

2). 12 g (43 mmol) of quinoline product 6, 150ml phosphorus oxychloride, and 15ml of N,N-xylidine were mixed and the mixture was refluxed for 30 minutes. The mixture was then cooled at room temperature then poured into 2000 ml ice-water after 2 hours, the pH of mixture was adjusted to 3 with acetic acid. The yellow solid was isolated by filtration. The residue obtained was purified by column chromatography on silica gel to afford 12.0 g of chloride 7. (yield 94%)

3). 10g (34 mmol) of chloride 7, 10 ml (145 mmol) of cyclopropylamine, 28 ml (200 mmol) of triethylamine, and 100 ml of DMF were mixed. The mixture was reacted at 100°C for 3 hours. The completion of reaction was monitored with TLC analysis. The solvent was then distilled off and the residue was dissolved with ethylene glycol dimethyl ether. The mixture was filtered, and the solvent of filtrate was distilled off and the residue obtained was purified by column chromatography on silica gel to afford 9 g compound IV. (yield 84%)

[0052] Compound IV: MS (ESI): 318 (M+H+), 340(M+Na+)

[0053] Example 6: preparation of compound V

[0054] 10 ml of anhydrous acetonitrile, 4.76 g (15mmol) of compound IV obtained by example 5, and 6.3 ml (25 mmol) of N,O-Bis(trimethylsilyl) acetamide (BSA) were mixed. The mixture was stirred at room temperature for 1 hour. A solution of 1.27g (4mmol) of tetraacetyl ribofuranose dissolved in 10 ml of acetonitrile, and 1.10 ml (16mmol) of TMSTF was then added to the mixture and was refluxed for 5 hours. 1.25 ml (5mmol) of N,O-
Bis(trimethylsilyl) acetamide (BSA) was added to the mixture, and then stirred for 24 hours. Monitored the completion of reaction with TLC analysis. The solvent was distilled off in reduced pressure and the residue was dissolved in 20 ml of methanol. The reaction mixture was passed ammonia gas for 2 hours in reduced pressure. The solvent was distilled off. The residue obtained was purified by column chromatography on silica gel to afford 4.07 of compound V. (yield 63%)

[0055] Compound V: MS (ESI): 450 (M+H⁺), 472(M+Na⁺)

[0056] Example 7: Preparation of Compound VI

[0057] 10g (31.5mmol) of compound IV, i.e. 2-(5-aminoquinolyl)-6- cyclopropyl amino purine, obtained in example 5, 1.5 g(37.8mmol) of 60% NaH, and 150ml of anhydrous acetonitrile were mixed. The mixture was stirred for 30 minutes in an atmosphere of nitrogen. 12 g(31.5mmol) of 3,5-diparatoluensulfonyl-2-deoxy-β-D- ribofuranose-1- chloride was added batchwise to the mixture in 20 minutes. The mixture was reacted at room temperature for 2 hours. The mixture was filtered, and the solvent of the filtrate was distilled off. The oil residue was purified by column chromatography on silica gel to afford 8.0 g of 2-(5-aminoquinolyl)-6- cyclopropyl amino-9-(3,5-diparatoluensulfonyl-2-deoxy-β-D- ribofuranose) purine. (yield 38%)

[0058] The above product was added to 25 mmol of sodium methoxide and 400 ml of methanol. The mixture was stirred at room temperature for 5 hours. The pH of mixture was adjusted to 7 with acetic acid. The solvent was distilled off and the residue obtained was purified by column chromatography on silica gel to afford 5.75 g of 2-(5-aminoquinolyl)-6- cyclopropyl amino-9-(2-deoxy-β-D- ribofuranose) purine i.e. compound VI. (yield 92%)

[0059] Compound VI: MS (ESI): 434 (M+H⁺), 456 (M+Na⁺)

[0060] Example 8: Preparation of Compound IV, Alternative to Example 5

[0061] The process of preparation of Compound IV was as follows:
2.99 g (14.3 mmol) of cyclopropyl compound 5, 5.1 g (36.1 mmol) of 5-amino-quinoline, and 50ml of DMF, 2.4ml (17.1mmol) of triethylamine were mixed. The mixture was refluxed at 140 °C to react for 72 hours. The TLC analysis proved that the reaction was basically completed. The solvent was distilled off under reduced pressure. The residue obtained was purified by column chromatography on silica gel to afford 2.88 g of compound IV. (yield 63%)

[0062] Examples 9-11 illustrate the preparation of compounds VII, VIII and IX.
[0063] Example 9: Preparation of Compound VII

1). In 200 ml water, 20 g (93mmol) of 2-bromo- hypoxanthine, 13 g (90 mmol) of 8-aminoquinoline, and 60 ml ethylene glycol monomethyl ether were mixed and the mixture was refluxed for 48 hours. TLC test monitored the completion of reaction. The reaction mixture was then poured into ice-water, the solid was isolated by filtration, washed with 200 ml concentrate ammonia water and 3×50 ml methanol, and dried. The residue obtained was purified by column chromatography on silica gel to afford 11.4 g of product 8.(yield 46%)

2). 12 g (43 mmol) of quinoline product 8, 150 ml of phosphorus oxychloride, and 15 ml of N,N-xylidine were mixed and the mixture was refluxed for 30 minutes. The mixture was then cooled at room temperature then poured into 2000 ml ice-water after 2 hours the pH of
mixture was adjusted to 3 with acetic acid. The yellow solid was isolated by filtration. The residue obtained was purified by column chromatography on silica gel to afford 10.3g of chloride 9 (yield 81%)

3). 10 g (34 mmol) of chloride 9, 10 ml (145 mmol) of cyclopropylamine, 28 ml (200 mmol) of triethylamine, and 100 ml of DMF were mixed. The mixture was reacted at 100°C for 3 hours. TLC test monitored the completion of reaction. The solvent was then distilled off and the residue was dissolved with ethylene glycol dimethyl ether. The mixture was filtered, and the solvent of filtrate was distilled off and the residue obtained was purified by column chromatography on silica gel to afford 6 g compound VII (yield 56%)

[0064] Compound VII: MS (ESI): 318 (M+H+), 340 (M+Na+)

[0065] Example 10: Preparation of Compound VIII

[0066] 10 ml of anhydrous acetonitrile, 4.76 g (15 mmol) of compound VII, and 6.3 ml (25 mmol) of N,O-Bis(trimethylsilyl) acetamide (BSA) were mixed. The mixture was stirred at room temperature for 1 hour. A solution 1.27 g (4 mmol) of tetraacetyl ribofuranose dissolved in 10 ml of acetonitrile, and 1.10 ml (16 mmol) of TMSTF was then added to the mixture and was refluxed for 5 hours. 1.25 ml (5 mmol) of N,O-Bis(trimethylsilyl) acetamide was added to the mixture, and then stirred for 24 hours. TLC monitored the completion of reaction. The solvent was distilled off in reduced pressure and the residue was dissolved with 20 ml of methanol. The reaction mixture was in passed ammonia gas for 2 hours. The solvent was distilled off under reduced pressure. The residue obtained was purified by column chromatography on silica gel to afford 4.2 g of compound VIII (yield 65%)


[0068] Example 11: Preparation of Compound IX

[0069] 10 g (31.5 mmol) of compound VII i.e. 2-(8-aminooquinolyl)-6-cyclopropyl amino purine, 1.5 g (37.8 mmol) of 60% NaH, and 150 ml of anhydrous acetonitrile were mixed. The mixture was stirred for 30 minutes in
an atmosphere of nitrogen. 12 g (31.5 mmol) of 3,5-diparatoluensulfonly-2-deoxy-β-D- ribofuranose-1- chloride was added batchwise to the mixture in 20 minutes. The mixture was stirred at room temperature to react for 2 hours. The mixture was filtered, and the solvent of the filtrate was distilled off. The oil residue was purified by column chromatography on silica gel to afford 7.4 g of 2-(8-aminoquinolyl)-6- cyclopropyl amino-9-(3,5-diparatoluensulfonly-2-deoxy-β-D- ribofuranose) purine. (yield 35%)

[0070] The above product was added to 25 mmol of sodium methoxide and 400 ml of methanol. The mixture was stirred at room temperature to react for 5 hours. The pH of mixture was adjusted to 7 with acetic acid. The solvent was distilled off and the residue obtained was purified by column chromatography on silica gel to afford 3.2 g of 2-(8-aminoquinolyl)-6-cyclopropyl amino-9-(2-deoxy-β-D- ribofuranose) purine compound IX. (yield 51%)


[0072] Example 12: Preparation of Compound VII; Alternative to Example 9

[0073] The process of preparation of compound was as follows:

\[
\begin{align*}
&\text{NH} &\quad\quad &\text{NH} \\
&\text{N} &\quad\quad &\text{N} \\
&\text{Cl} &\quad\quad &\text{N} \\
&\text{N} &\quad\quad &\text{N} \\
&\text{N} &\quad\quad &\text{N} \\
&\text{N} &\quad\quad &\text{N}
\end{align*}
\]

2.99 (14.3 mmol) of cyclopropyl compound 5, 51 g (36.1 mmol) of 8-amino-quinoline, 50 ml of DMF, and 2.4 ml (17.1 mmol) of triethylamine were mixed. The mixture was refluxed at 140°C to react for 72 hours. Check the completion of reaction by TLC analysis. The solvent was distilled off under reduced pressure. The residue obtained was purified by column chromatography on silica gel to afford 4.10 g of compound VII. (yield 90%)
[0074] Examples 13-15 illustrate the preparation of compounds X, XI and XII.

2-bromohypoxanthine

[0075] Example 13: Preparation of Compound X

1). In 200 ml water, 20 g (93 mmol) of 2-bromo- hypoxanthine, 13 g (90 mmol) of 3-aminoquinoline, and 60 ml ethylene glycol monomethyl ether were mixed and the mixture was refluxed for 48 hours. Check the completion of reaction by TLC analysis. The reaction mixture was then poured into ice-water, the solid was isolated by filtration, washed with 200 ml concentrate ammonia water and 3×50 ml methanol, and dried. The residue obtained was purified by column chromatography on silica gel to afford 15.0 g of product 10. (yield 60%)

2). 12g (43 mmol) of compound quinoline product 10, 150 ml phosphorus oxychloride, and 15ml of N,N-xylidine were mixed and the mixture was refluxed for 30 minutes. The mixture was then cooled at room temperature. The reaction mixture was then poured slowly into 2,000 ml ice-water, after 2 hours the pH of mixture was adjusted to 3
with acetic acid. The yellow solid was isolated by filtration. The residue obtained was purified by column chromatography on silica gel to afford 10.9 g of chloride 11. (yield 85%)

3). 10 g (34 mmol) of chloride 11, 10 ml (145 mmol) of cyclopropylamine, 28 ml (200 mmol) of triethylamine, 100 ml of DMF were mixed. The mixture was stirred at 100°C to react for 3 hours, check the completion of reaction by TLC analysis. The solvent was then distilled off and the residue was dissolved with ethylene glycol dimethyl ether. The mixture was filtered, and the solvent of filtrate was distilled off and the residue obtained was purified by column chromatography on silica gel to afford 10.1g compound X (yield 94%).


[0077] Example 14: Preparation of Compound XI

[0078] 10 ml of anhydrous acetonitrile, 4.76 g (15 mmol) of compound X, and 6.3 ml (25 mmol) of N,O-Bis(trimethylsilyl) acetamide (BSA) were mixed. The mixture was stirred at room temperature for 1 hour, a solution of 1.27 g(4mmol) of tetraacetyl ribofuranose dissolved in 10 ml of acetonitrile, and 1.10 ml(16mmol) of TMSTF was then added to the mixture and was refluxed for 5 hours. 1.25 ml (5 mmol) of N,O-Bis(trimethylsilyl) acetamide was added to the mixture, and then stirred for 24 hours, check the completion of reaction by TLC analysis. The solvent was distilled off under reduced pressure and the residue was dissolved with 20 ml of methanol. The reaction mixture was passed ammonia gas for 2 hours. The solvent was distilled off under reduced pressure. The residue obtained was purified by column chromatography on silica gel to afford 4.97g of compound XI.(yield 77%)


[0080] Example 15: Preparation of Compound XII

[0081] 10 g (31.5 mmol) of 2-(3-aminquinolyl)-6- cyclopropyl amino purine i.e. compound X, 1.5 g(37.8mmol) of 60 % NaH, and 150 ml of anhydrous acetonitrile were mixed. The mixture was stirred for 30 minutes in an
atmosphere of nitrogen. 12 g (31.5 mmol) of 3,5-diparatoluensulfonyl-2-deoxy-β-D- ribofuranose-1- chloride was added batchwise to the mixture in 20 minutes. The mixture was stirred at room temperature for 2 hours. The mixture was filtered, and the solvent of the filtrate was distilled off. The oil residue was purified by column chromatography on silica gel to afford 8.8 g of 2-(3-aminoquinolyl)-6- cyclopropyl amino-9-(3,5-diparatoluensulfonyl-2-deoxy-β-D- ribofuranose) purine. (yield 42%)

[0082] The above product was added to 25 mmol of sodium methoxide and 400 ml of methanol. The mixture was stirred at room temperature for 5 hours. The pH of mixture was adjusted to 7 with acetic acid. The solvent was distilled off and the residue obtained was purified by column chromatography on silica gel to afford 5.06 g of 2-(3-aminoquinolyl)-6- cyclopropyl amino-9-(2-deoxy-β-D- ribofuranose) purine i.e. compound XII. (yield 81%)


[0084] Example 16: Preparation of Compound X, Alternative to Example 9

[0085] The process of preparation of compound was as follows:

\[
\begin{align*}
\text{NH} & \quad \text{NH} \\
\text{Cl} & \quad \text{Cl} \\
\text{X} & \quad \text{X}
\end{align*}
\]

2.99 g (14.3 mmol) of cyclopropyl 5, 51 g (36.1 mmol) of 3-aminoquinoline, 50 ml of DMF, and 2.4 ml (17.1 mmol) of triethylamine were mixed. The mixture was refluxed at 140°C to react for 72 hours. The completion of reaction was monitored by TLC analysis. The solvent was distilled off. The residue obtained was purified by column chromatography on silica gel to afford 3.54 g of compound X. (yield 78%)

[0086] Examples 17-19 illustrate the preparation of compounds VII, XIV, and XV.
Example 17: Preparation of Compound XIII

1). In 200 ml water, 20 g (93 mmol) of 2-bromo-hypoxanthine, 13g (90 mmol) of 1-aminoisoquinoline, and 60 ml ethylene glycol monomethyl ether were mixed and the mixture was refluxed for 48 hours. The completion of reaction was monitored by TLC analysis. The reaction mixture was then poured into ice-water, the solid was isolated by filtration, washed with 200 ml concentrate ammonia water and 3×50 ml methanol, dried. The residue obtained was purified by column chromatography on silica gel to afford 14.2g of product 12.(yield 57%)

2). 12 g (43 mmol) of quinoline product 12, 150 ml phosphorus oxychloride, and 15 ml of N,N-xylidine were mixed and the mixture was refluxed for 30 minutes. The mixture was then cooled to room temperature. The reaction mixture was then poured into 2000 ml ice-
water after 2 hours the pH of mixture was adjusted to 3 with acetic acid. The yellow solid was isolated by filtration. The residue obtained was purified by column chromatography on silica gel to afford 11.5g of chloride 13. (yield 90%)

3). 10 g (34 mmol) of chloride 13, 10 ml (145 mmol) of cyclopropylamine, 28 ml (200 mmol) of triethylamine, and 100 ml of DMF were mixed. The mixture was stirred at 100°C for 3 hours. The completion of reaction was monitored with TLC analysis. The solvent was then distilled off and the residue was dissolved with ethylene glycol dimethyl ether. The mixture was filtered, and the solvent of filtrate was distilled off and the residue obtained was purified by column chromatography on silica gel to afford 4.2 g compound XIII.(yield 39%)


[0089] Example 18: Preparation of Compound XIV
10 ml of anhydrous acetonitrile, 4.76 g (15 mmol) of compound XIII, and 6.3 ml (25 mmol) of N,O-Bis(trimethylsilyl) acetamide (BSA) were mixed. The mixture was stirred at room temperature for 1 hour. A solution of 1.27 g(4mmol) of tetraacetyl ribofuranose dissolved in 10 ml of acetonitrile, and 1.10ml(16mmol) of TMSTF was then added to the mixture and was refluxed for 5 hours. 1.25 ml (5 mmol) of N,O-Bis(trimethylsilyl) acetamide was added to the mixture, and then stirred for 24 hours. The completion of reaction was monitored by TLC analysis. The solvent was distilled off under reduced pressure and the residue was dissolved with 20 ml of methanol. The reaction mixture passed ammonia gas for 2 hours. The solvent was distilled off under reduced pressure. The residue obtained was purified by column chromatography on silica gel to afford 4.2g of compound XIV. (yield 64%)


[0091] Example 19: Preparation of Compound XV
[0092] 10 g (31.5 mmol) of compound XIII i.e. 2-(1-aminoquinolyl)-6-cyclopropyl amino purine., 1.5 g (37.8mmol) of 60% NaH, and 150 ml of
anhydrous acetonitrile were mixed. The mixture was stirred for 30 minutes in an atmosphere of nitrogen. 12 g (31.5mmol) of 3,5-diparatoluensulfonyl-2-deoxy-β-D-ribofuranose-1-chloride was added batchwise to the mixture in 20 minutes. The mixture was stirred at room temperature to react for 2 hours. The mixture was filtered, and the solvent of the filtrate was distilled off. The oil residue was purified by column chromatography on silica gel to afford 7.09 g of 2-(1-aminoisoquinolyl)-6-cyclopropyl amino-9-(3,5-diparatoluensulfonyl-2-deoxy-β-D-ribofuranose) purine. (yield 34%)

[0093] The above product was added to 25mmol of sodium methoxide and 400 ml of methanol. The mixture was stirred at room temperature to react for 5 hours. The pH of mixture was adjusted to 7 with acetic acid. The solvent was distilled off and the residue obtained was purified by column chromatography on silica gel to afford 3.8 g of compound XV. (yield 60.8%)


[0095] Example 20: Preparation of Compound XIII, Alternative to Example 17

[0096] The process of preparation of compound XIII was as follows:

![Diagram](image)

[0097] 2.99 g (14.3 mmol) of cyclopropyl 5, 51 g (36.1 mmol) of 3-aminoquinoline, 50 ml of DMF, and 2.4 ml (17.1 mmol) of triethylamine were mixed. The mixture was refluxed at 140°C to react for 72 hours. The completion of reaction was monitored by TLC analysis. The solvent was distilled off. The residue obtained was purified by column chromatography on silica gel to afford 4.16 g of compound XIII. (yield 92%)

[0098] Examples 21-22 illustrate the preparation of compound XVI, XVII, and XVIII.
[0099] Example 21: Preparation of Compound XVI

[0100] 10 g (34 mmol) of compound 3, 10.3 g (145 mmol) of cyclobutylamine, 28 ml (200 mmol) of triethylamine, and 100 ml of DMF were mixed. The mixture was reacted at 100°C for 3 hours. The completion of reaction was checked by TLC analysis. The solvent was then distilled off and the residue was dissolved with ethylene glycol dimethyl ether. The mixture was filtered, and the solvent of filtrate was distilled off and the residue obtained was purified by column chromatography on silica gel to afford 6.8 g compound XVI. (yield 60%)


[0102] Example 22: Preparation of Compound XVII

[0103] 10 ml of anhydrous acetonitrile, 4.97 g (15 mmol) of compound XVI, and 6.3 ml (25 mmol) of N,O-Bis(trimethylsilyl)acetamide (BSA) were mixed. The mixture was stirred at room temperature for 1 hour. A solution of 1.27 g (4 mmol) of tetraacetyl ribofuranose dissolved in 10 ml of acetonitrile, and 1.10 ml (16 mmol) of TMSTF were then added to the mixture and refluxed for 5
hours. 1.25 ml (5 mmol) of N,O-Bis(trimethylsilyl)acetamide was added to the mixture, and then stirred for 24 hours. Check the completion of reaction by TLC analysis. The solvent was distilled off under reduced pressure and the residue was dissolved in 20 ml of methanol. The reaction mixture passed ammonia gas for 2 hours. The solvent was distilled off under reduced pressure. The residue obtained was purified column chromatography on silica gel to afford 4.71 g of compound XVII. (yield 71%)


[0105] Example 23: Preparation of Compound XVIII

[0106] 10 g (31.5 mmol) of compound XVI, i.e. 2-(6-aminoquinolyl)-6-cyclobutyl amino purine. 1.5 g (37.8 mmol) of 60% NaH, and 150 ml of anhydrous acetonitrile were mixed. The mixture was stirred for 30 minutes in an atmosphere of nitrogen. 12 g (31.5 mmol) of 3,5-diparatholuensulfonyl-2-deoxy-β-D-ribofuranose-1-chloride was added batchwise to the mixture in 20 minutes. The mixture was stirred at room temperature to react for 2 hours. The mixture was filtered, and the solvent of the filtrate was distilled off. The oil residue was purified by column chromatography on silica gel to afford 2-(6-aminoquinolyl)-6-cyclobutyl amino-9-(3,5-diparatholuensulfonyl-2-deoxy-β-D-ribofuranose) purine.

[0107] The above product was added to 25 mmol of sodium methoxide and 400 ml of methanol. The mixture was stirred at room temperature to react for 5 hours. The pH of mixture was adjusted to 7 with acetic acid. The solvent was distilled off and the residue obtained was purified by column chromatography on silica gel to afford 7 g of compound XVIII, i.e. 2-(6-aminoquinolyl)-6-cyclobutyl amino-9-(2-deoxy-β-D-ribofuranose) purine. (yield 51.8%)


[0109] Example 24: Preparation of Compound XVI

[0110] The process of preparation of compound was as follows:
1). 3.78 g (20 mmol) of dichloropurine 4, was dissolved in 50 ml of DMF, 1.4 ml (20 mmol) of cyclobutylamine, and 3.08 ml (22 mmol) of triethylamine were mixed. The mixture was stirred at 80 °C to react for 5 hours. The completion of reaction was monitored by TLC analysis. The solvent was distilled off under reduced pressure and the residue obtained was purified by column chromatography on silica gel to afford 4.1 g of cyclobutyl compound 14. (yield 92%)

2). 3.19 g (14.3 mmol) of cyclobutyl compound 14, 5.1 g (36.1 mmol) of 6-amino-quinoline, 50 ml of DMF, and 2.4 ml (17.1 mmol) of triethylamine were mixed. The mixture was refluxed at 140 °C for 72 hours. The reaction was basically completed by TLC checking. The solvent was distilled off under reduced pressure. The residue obtained was purified by column chromatography on silica gel to afford 3.82 g of compound XVI. (yield 81%)

[0111] Example 25: Preparation of Hydrochloride and Lactate of Compound I

[0112] Preparation of the hydrochloride of compound I:

[0113] 10 g (31.54 mmol) of compound I, 210 ml of ethanol, and 25 ml of water were mixed. The mixture was heated to dissolve compound I. 0.7 ml (37.85 mmol) of 2 mol/L HCl was added dropwise to the mixture. The mixture was refluxed for 0.5 hour. The mixture was allowed to cool slowly at room temperature, and then was allowed to cool to below 5°C and stand for 5 hours. The pale yellow solid was isolated by filtration. The pale yellow solid was 10 g after dried. (yield 90%) The melting point of the pale yellow solid was above 270°C.
[0114] Preparation of the lactate of compound I:

[0115] 5g of compound I,(15.77mmol) 105 ml of 95% ethanol, and 12.5 ml of H₂O were mixed. The mixture was heated to dissolve compound I. 10% lactic acid in ethanol solution was added dropwise to the mixture. The mixture was then refluxed for 1 hour. The mixture was allowed to cool to room temperature, and then was allowed to cool to below 5°C for 5 hours. The pale yellow solid was isolated by filtration. The pale yellow solid was 5.6g after dried.(yield 87%) The melting point of the pale yellow solid was 239-248°C.

[0116] Example 26: Preparation of the Pharmaceutical Dosage Forms

[0117] Preparation of coated tablets:

[0118] Formula of the core of the tablets:

<table>
<thead>
<tr>
<th>Compound</th>
<th>g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 1</td>
<td>50</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>150</td>
</tr>
<tr>
<td>lactose</td>
<td>50</td>
</tr>
<tr>
<td>Sodium Carboxy Methyl Starch Soluble</td>
<td>25 g</td>
</tr>
<tr>
<td>Sodium Cros Carboxy Methyl Cellulose</td>
<td>15 g</td>
</tr>
<tr>
<td>Micro Powder Silica Gel</td>
<td>1.5</td>
</tr>
</tbody>
</table>

For 1000 Tablets

[0119] The process: the exact weight of compound I and lactose was mixed, then silica gel was added to the mixture in order to increase the fluidity. Other pharmaceutical adjuvants were added and mixed, followed by direct tabletting.

[0120] Formula of the coating liquid: Opadry 25 g, in a suitable amount of 80% ethanol, for coating.

[0121] Preparation of Injection:

[0122] Formula of the injection:

<table>
<thead>
<tr>
<th>Compound</th>
<th>g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound I</td>
<td>50</td>
</tr>
<tr>
<td>Tween-80</td>
<td>20</td>
</tr>
<tr>
<td>Ethyl alcohol for pharmaceutical use</td>
<td>30 g</td>
</tr>
<tr>
<td>Water for injection added to 10,000 mL</td>
<td></td>
</tr>
</tbody>
</table>

For 1000 vials
[0123] The process: the exact weight of compound I and Tween-80 was mixed and triturated, 0.3% ethyl alcohol was added to the mixture to dissolve compound I and Tween-80 with heating. The liquid was filtered with 0.22 μm filter membrane under aseptic conditions, and then filled 10 ml per vial, and steam sterilized at 100°C.
N^2-QUINOLINE- OR ISOQUINOLINE-SUBSTITUTED PURINE DERIVATIVES AND METHOD OF PREPARATION AND USES THEREOF

CLAIMS

1. A compound having the following formula A, its salts, or hydrates:

\[
\begin{align*}
\text{(A)}
\end{align*}
\]

wherein

W represents a hydrogen, an optionally substituted C\text{1-6} straight or branched alkyl, an optionally substituted C\text{3-6} cycloalkyl, or an optionally substituted C\text{1-6} haloalkyl;

Y represents a hydrogen, or a pharmaceutically-acceptable saccharide of any one of the following formulas:

\[
\begin{align*}
&\text{Z represents a hydrogen or a substituent having any one of the following formulas:} \\
\end{align*}
\]

\[
\begin{align*}
&\text{Z represents a hydrogen or a substituent having any one of the following formulas:} \\
\end{align*}
\]
Q represents a substituent having any one of the following formulas:

\[ \text{Diagram of structures} \]

, and

B, E, G, R, T, and M each independently represent a hydrogen, a straight or branched C\textsubscript{1-6} alkyl or haloalkyl, a C\textsubscript{3-6} cycloalkyl, a halogen, a cyano, or an amino.
2. The compound of formula (A), its salts, or hydrates according to Claim 1, wherein W represent a hydrogen or a substituent having any one of the following formulas:

3. The compound of formula (A), its salts, or hydrates according to Claim 1, wherein Y represents a hydrogen

4. The compound of formula (A), its salts, or hydrates according to Claim 1, wherein W represent a substituent having any one of the following formulas:

5. The compound of formula (A), its salts, or hydrates according to Claim 1 or Claim 3, wherein
W is or, 

Q a substituent having any one of the following formulas:

6. The compound of formula (A), its salts, or hydrates according to Claim 5, wherein Q represents

7. The compound of formula (A), its salts, or hydrates according to Claim 5, wherein the compound is represented by any one of the following formulas (I-XVIII):
8. The compound of formula (A), its salts, or hydrates according to Claim 5, wherein the compound is represented by the following formula (I):
9. A pharmaceutical composition comprising the compound of formula (A), its salts, or hydrates according to any one of claims 1 to 8, and a pharmaceutically acceptable excipient.

10. The pharmaceutical composition according to Claim 9, wherein the described pharmaceutical compositions is in the form of a tablet, a capsule, a pill, an oral liquid preparation, a granule, a powder, an injection, an implant, or a preparation for external use.

11. A method for producing the compound of formula (A), its salts, or hydrates according to any one of claims 1 to 8, the method comprising following steps:

   (1) reacting the compound (j) with 0.8-1.5 mol/mol Q-NH₂ in an organic solvent at a temperature of about 50 to about 150°C for 1-72 hours, to result in a first reaction mixture, followed by adding water to the first reaction mixture, and cooling the first reaction mixture at room temperature, to produce a compound of formula (b);
(2) reacting the compound of formula (b) with a halogenating agent in an organic solvent at about 50 to about 150 °C for 1-72 hours, cooling, followed by adding water to the reaction mixture and adjusting the pH of the reaction mixture to about 2-5 with an acid, and allowing the second reaction mixture to cool at a room temperature, to produce a compound of the formula (c):

![Diagram of compound (c)]

(c) , and

(3) reacting compound (c) in an organic solvent with 0.8-1.5 mol/mol of W-NH₂ in the presence of an acid acceptor at a temperature of about 50-150°C for 1-72 hours, followed by distilling off the solvent; to yield a compound of formula (f),

![Diagram of compound (f)]

(f) 

wherein X represents Br, X' represents Cl, and W and Q are as defined in claim1.
12. A method for producing the compound of formula (A), its salts, or hydrates according to any one of claims 1 to 8, the method comprising the following steps:

(1) reacting in an organic solvent, the compound of formula (k) with 0.8-1.5 mol/mol of W-NH₂, in the presence of an acid acceptor at a temperature of about 30-120°C for 1-72 hours, followed by distilling off the solvent, to produce a compound of formula (e):

![Chemical structure](k)

(2) reacting in an organic solvent the compound of formula (e) with 0.8-1.5 mol/mol of Q-NH₂, in the presence of an acid acceptor at a temperature of about 70-170°C for 1-72 hours, followed by distilling off the solvent to produce a compound of formula (f):

![Chemical structure](f)

wherein X represents Cl, X' represents Cl, and W and Q are as defined in Claim1.
13. The compound according to Claim 1, wherein the salts are pharmaceutically acceptable salts, which can be addition salts, produced by organic or inorganic acids, and are preferably hydrochloride salts, hydrobromide salts, hydroiodide salts, p-toluenesulfonate salts, phosphate salts, sulfate salts, perchloride salts, acetate salts, trifluoroacetate salts, propionate salts, citrate, malonate salts, succinate, lactate salts, oxalate, tartrate salts and benzoate salts, the salt also can be formed with a base, including an inorganic or organic base.

14. The use of any one of the compounds, their salts, or hydrates according to claims 1-8 in the preparation of pharmaceuticals for prevention and treatment of tumor diseases.

15. The use of any one of the compounds, their salts, or hydrates according to claims 1-8 in the preparation of pharmaceuticals for prevention and treatment of tumor diseases, wherein said tumor diseases are lung cancer, liver cancer, leukemia, osteosarcoma, pancreas cancer, skin cancer, melanoma, metaplastic carcinoma, oophoroma, rectal carcinoma, gastric carcinoma, colon cancer, breast carcinoma, salpingo-carcinoma, endometrium carcinoma, cervix carcinoma, vagina carcinoma, carcinoma of vulva, esophagus carcinoma, small intestine carcinoma, endocrinium carcinoma, soft tissue sarcoma, urethra carcinoma, prostatic cancer, lymphocytoma, bladder cancer, kidney or ureter cancer, tumors of vertebral column, tumors of the brain, and pituitary adenoma.