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(54) Title: PROCESS FOR PREPARING SUBSTITUTED BENZOPYRAN COMPOUNDS

(57) Abstract: The present invention relates to a novel method of synthesizing substituted benzopyran compounds, their novel intermediates and a method of their preparation thereof.

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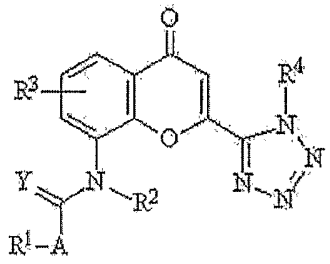
PROCESS FOR PREPARING SUBSTITUTED BENZOPYRAN COMPOUNDS

Field of Invention

The present invention relates to a novel method of preparing substituted benzopyran compounds of the following formula 1, their corresponding novel intermediates and a method of their preparation thereof.

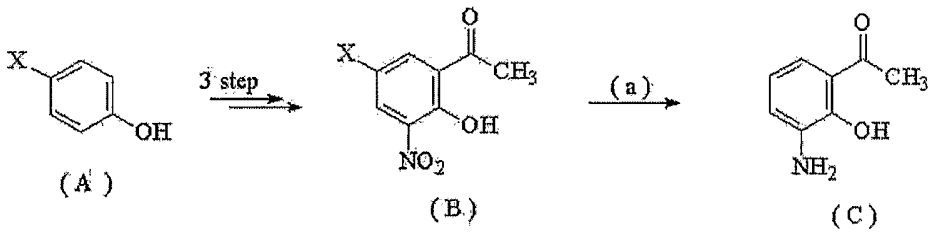


(1)

In the above formula 1, R^1, R^2, R^3, R^4, A and Yare the same as defined in the detailed description of the invention.

Background of Invention

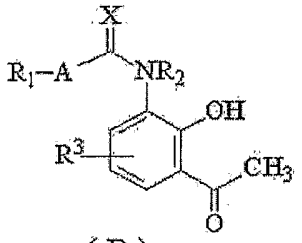
A benzopyran compound is a leukotriene-receptor antagonist already disclosed in EP 0173516 and others, which is also known as a therapeutic agent for treating diseases induced by leukotriene and 5-α-reductase. For example, JP Hei 3-95144 discloses a method of preparing 3-amino-2-hydroxyacetophenone from the phenol compound of the following formula (A) via a four step process. However, this method is not considered efficient due to its rather long process and also it lacks industrial applicability due to the risk of explosion during a hydrogenation reaction using Pd/C in the reduction step (a) for introducing an amino group.



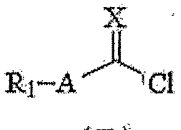
(A) (B) (C)

In the above reaction, X indicates a halogen atom.

Meanwhile, in USP 5,675,036, and 5,597,929 and WO94/124923, their methods of synthesis are not suitable in terms of safety and environmental aspects because not only they employ an acetophenone compound (D) as an intermediate which is rather difficult to be synthesized, but also they use highly explosive and corrosive reagent, $SOCl_2$, for prepariing acyl chloride (E) required for introducing an amide group from amine moiety. Further, the acyl chloride thus produced is in general not very stable and is very difficult to adjust during the commercial production.



(D)



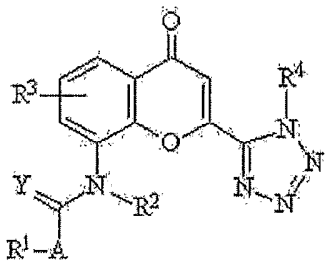
(E)

This invention relates to a method of synthesizing a few novel benzopyran compounds disclosed in EP 0173516. The method of the present invention is industrially more applicable since it provides an added safety and efficiency with a fewer number of steps in process as compared to the conventional methods. In particular, the method of this invention follows the convergent pathway, a more

efficient process than the conventional linear process. Further, the method of the present invention does not employ a risky process such as hydrogenation reaction and the intermediate materials produced during the reaction are so stable that their separation and purification are quite easy.

Detailed Description of Invention

This invention relates to a method of preparing substituted benzopyran compounds having the chemical structure of the following formula 1, a novel intermediate compound used for the process thereof, and a method of preparing the intermediate compound.



In the above formula 1,

R^1 is selected from the group consisting of a C_{1-20} alkyl group, a C_{2-20} alkenyl group, a C_{2-20} alkynyl group, a phenyl group, a naphthalenyl group and an indanyl group, wherein the groups can be independently substituted by 1 or 2 substituents selected from a C_{1-20} alkyl group, a C_{2-20} alkenyl group and a C_{2-20} alkynyl group, wherein up to 5 carbon atoms of the substitution groups can be selectively substituted by O, S, N, a halogen atom, a benzene ring, a thiophene ring, a naphthalene ring, a C_{4-7} carbocyclic ring, a carbonyl group, a carbonyloxy group, a hydroxyl group, a carboxy group, an azido group or a nitro group;

R^2 and R^4 are independently H, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{1-6} alkyl group substituted with from 1 to 3 aryl groups, a C_{1-6} alkoxycarbonyl group, a C_{1-6} alkoxycarbonyl group substituted with an aryl group, an aryloxycarbonyl group, a C_{1-6} alkoxy C_{1-6} alkyl group, a C_{3-9} trialkyltin group, a triaryltin group, or a C_{3-9} trialkylsylyl group, wherein the aryl group or said aryl is a phenyl group substituted with from 1 to 3 substituents which are selected from the group consisting of a phenyl group, a halogen atom, a C_{1-6} alkyl group and a C_{1-6} alkoxy group;

R^3 is H, a halogen atom, a hydroxy group, a nitro group, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkylthio group, or -$COOR^5$ (wherein R^5 is H or a C_{1-6} alkyl group);

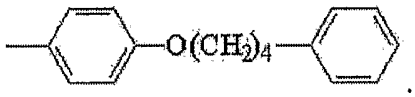
A is a single bond; or a C_{1-10} alkylene group, a C_{2-10} alkenylene group, or a C_{2-10} alkynylene group either substituted or unsubstituted with from 1 to 3 substituents selected from a C_{1-10} alkyl group and a phenyl group;

X is a halogen atom; and

Y is O or S.

In preparing the substituted benzopyran compounds of the above formula 1, R^1 is a phenyl group or a substituted phenyl group, wherein the above substituted phenyl group can be substituted with 1 or 2 substituents selected from a C_{1-20} alkyl group, a C_{2-20} alkenyl group and a C_{2-20} alkynyl group, wherein up to 5 carbon atoms of the substitution groups can be selectively substituted by O, S, N, a halogen atom, a benzene ring, a thiophene ring, a naphthalene ring, a C_{4-7} carbocyclic ring, a carbonyl group, a carbonyloxy group, a hydroxyl group, a carboxy group, an azido

group or a nitro group. Preferably, R^1 is a phenyl group substituted at *p*-position with a substituent from those exemplified above, and more preferably



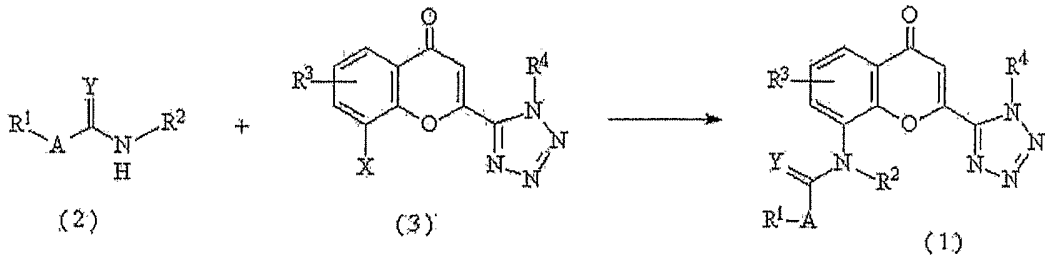
In preparing the substituted benzopyran compounds of the above formula 1, R^2 and R^4 are independently H, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{1-6} alkyl group substituted with from 1 to 3 aryl groups, or a C_{1-6} alkoxycarbonyl group. More preferably, R^2 and R^4 are independently H.

In preparing the substituted benzopyran compounds of the above formula 1, R^3 is H.

In preparing the substituted benzopyran compounds of the above formula 1, A is a single bond; or a methylene, ethylene, trimethylene, tetramethylene, vinylene, propenylene, butenylene, butadienylene or ethynylene group either substituted or unsubstituted with from 1 to 3 substituents selected from a C_{1-10} alkyl group and a phenyl group. More preferably, A is a single bond.

The substituted benzopyran compounds of the above formula 1 according to the present invention can be prepared by reacting a compound of the following formula 2 with a compound of the following formula 3 as shown in the following reaction scheme 1.

[Reaction Scheme 1]



(2) (3) (1)

In the above reaction scheme 1, R^1, R^2, R^3, R^4, A, X and Y are the same as defined in the above formula 1.

The above preparation method according to the reaction scheme 1 is performed at reflux temperature using an organic solvent in the presence of a Pd or Cu catalyst, a ligand and a base.

The solvent used in the above reaction can be selected from those having high polarity such as *N,N'*-dimethylformamide, *N*-methylpyrolidone, pyridine, 1,4-dioxane, C_{1-6} alkanol(methanol, ethanol, *t*-butanol) or a mixture thereof, and preferably *N,N'*-dimethylformamide.

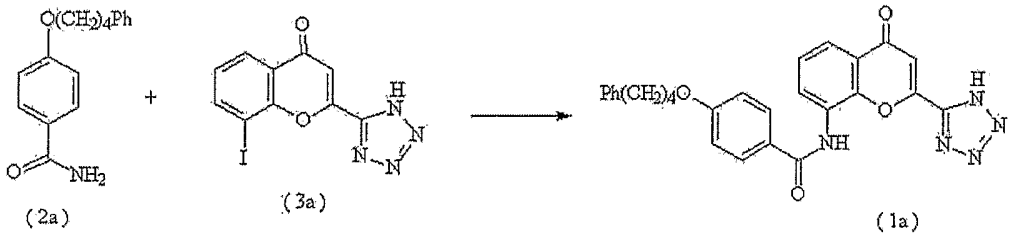
The catalyst used in the above reaction is a Pd- or Cu-containing compound and is used in the range of about 0.1 to 100 mol% with reference to the amount of reactants. Preferably, the catalyst is selected from the group consisting of CuI, CuCl, and Cu_2O, and more preferably CuI.

The ligand in the above reaction is used in the range of about 0.5 to 3 equivalents with reference to the amount of the catalyst being used. The ligand used is diamines or phosphines, preferably the one selected from the group consisting of *N,N'*-dimethylethylenediamine, trans-*N,N'*-1,2-cyclohexanediamine and trans-*N,N'*-dimethyl-1,2-cyclohexanediamine, and more preferably *N,N'*-dimethylethylenediamine.

The base in the above reaction is used in the range of about 1 to 10 equivalents with reference to the substrate material. The base can be selected from the group consisting of alkali metal alkoxide such as potassium *t*-butoxide, potassium methoxide, and sodium methoxide; hydrides such as sodium hydride and potassium hydride; alkali metal carbonate such as potassium carbonate, cesium carbonate, and sodium carbonate; or an alkali metal phosphate such as potassium phosphate and sodium phosphate; and preferably an alkali metal phosphate.

In a preferred embodiment of the preparation method according to the reaction scheme 1, as shown in the following reaction scheme 1a, the substituted benzopyran compounds of the following formula 1a, its salts or its solvates (e.g., hydrates) are synthesized by reacting a compound of the following formula 2a with a compound of the following formula 3a, its salts or its solvates (e.g., hydrates).

[Reaction Scheme 1a]



(2a) (3a) (1a)

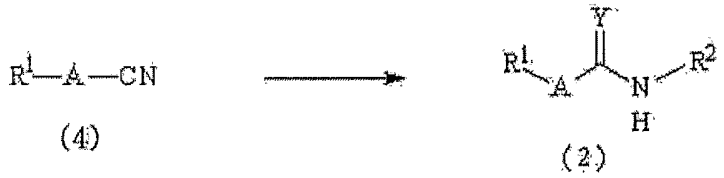
In the above reaction scheme 1a, the reaction is performed while stirring at about 70 to about 100°C for more than a day using *N,N'*-dimethylformamide as a solvent in the presence of CuI as a catalyst, *N,N'*-dimethylethylenediamine as a ligand, and potassium phosphate as a base.

Meanwhile, in performing the synthesis according to the above reaction scheme 1, the reactants, i.e., the compound of the above formula 2 (especially the

compound of the above formula 2a) and the compound of the above formula 3 (especially the compound of the above formula 3a), are novel intermediate compounds used in synthesizing the compound of the above formula 1. Therefore, the compounds of the above formulas 2 and 3 also belong to the scope of the present invention.

The compound of the above formula 2, being a novel intermediate compound according to the present invention, can be synthesized by hydrolysis of the compound of the following formula 4 as shown in the following reaction scheme 2.

[Reaction Scheme 2]



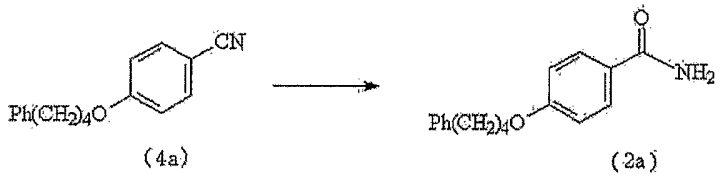
In the above reaction scheme 2, R^1, R^2, A and Y are the same as defined in the above formula 1.

In the above reaction scheme 2, an amide group is introduced via hydrolysis using a base in the presence of water, an organic solvent or their mixture. The conditions for a base/solvent used in the above hydrolysis will be apparent to those skilled in the art. For example, the reaction is performed using a single C_{1-6} alkanol solvent such as methanol, ethanol, *t*-butanol or their mixture as a solvent while using alkali hydroxide such as sodium hydroxide or potassium hydroxide as a base.

In a preferred embodiment of the preparation method via the hydrolysis according to the reaction scheme 2, as shown in the following reaction scheme 2a, the compounds of the following formula 2a, its salts or its solvates (e.g., hydrates)

are synthesized by reacting the compound of the following formula 4a in the presence of NaOH/*t*-butanol.

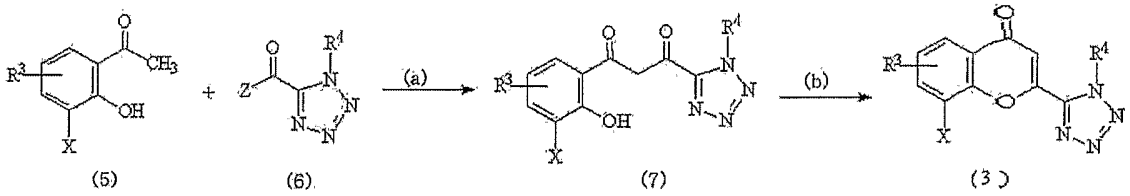
[Reaction Scheme 2a]



(4a) (2a)

Further, the compound of the following formula 3, being a novel intermediate compound of the present invention, can be prepared by (a) synthesizing the compound of the following formula 7 by reacting the compound of the following formula 5 with the compound of the following formula 6, and then (b) performing cyclization reaction of thus obtained compound of the following formula 7, as shown in the following reaction scheme 3.

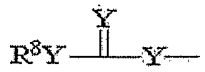
[Reaction Scheme 3]



(5) (6) (7) (3)

In the above reaction scheme 3, R^3, R^4 and X are the same as defined in the above formula 1 and Z indicates an activated leaving group.

Examples of the activated leaving group (Z) of the above reaction scheme 3 are, for example, a halogen atom, an activated amide group represented by -$N(R^6)(OR^6)$ (wherein R^6 is a C_{1-6} alkyl group), R^7O-, R^7S- or R^7SO_2O- (wherein R^7 is a C_{1-6} alkyl group, an arbitrarily substituted phenyl group or an arbitrarily substituted phenyl C_{1-6} alkyl group), or



(wherein R^8 is a C_{1-6} alkyl group, an arbitrarily substituted phenyl group or an arbitrarily substituted phenyl C_{1-6} alkyl group, Y's are independently O or S).

Preferably, the activated leaving group is R^7O-, wherein R^7 is a C_{1-6} alkyl group, an arbitrarily substituted phenyl group or an arbitrarily substituted phenyl C_{1-6} alkyl group, more preferably, R^7 is a C_{1-6} alkyl group, for example, a methyl group, an ethyl group, *i*--butyl group or *t*-butyl group, and most preferably R^7 is an ethyl group.

The step (a) of the synthesis according to the above reaction scheme 3 is performed in the presence of *N,N'*-dimethylformamide, an ether solvent such as tetrahydrofuran; an organic solvent such as toluene, benzene, hexane or a C_{1-6} alkanol (e.g., methanol, ethanol, *t*-butanol); and a base, wherein the base can be selected from the group consisting of alkali metal alkoxide such as potassium *t*-butoxide, potassium methoxide, and sodium methoxide; hydrides such as sodium hydride; and amides such as potassium amide and sodium amide.

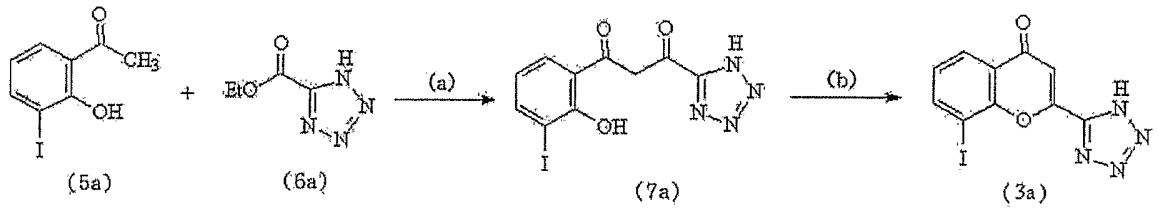
The cyclization in step (b) of the synthesis according to the above reaction scheme 3 is performed in the presence of an acid. For example, the cyclization can be performed in the presence of a sulfuric acid using a solvent such as C_{1-6} alkanol or acetic acid. Further, the cyclization can be performed in the presence of hydrochloric acid in the mixed solvent of C_{1-6} alkanol/tetrahydrofuran.

Alternative acid/solvent conditions will be apparent to those skilled in the art. The reaction can be performed in a suitable solvent such as water or C_{1-6} alkanol, unsaturated carbocyclic hydrocarbon such as benzene or toluene, by using an acid

such as hydrobromic acid, hydroiodic acid, perchloric acid or *p*-toluenesulfonic acid; and a Lewis acid such as aluminum trichloride or titanium tetrachloride. Preferably, the above reaction is performed in methanol solvent in the presence of sulfuric acid.

In a preferred embodiment of the preparation method according to the reaction scheme 3, as shown in the following reaction scheme 3a, the compounds of the following formula 3a, its salts or its solvates (e.g., hydrides) are prepared by (a) synthesizing the compound of the following formula 7a, its salts and its solvates (e.g., hydrides) by reacting the compound of the following formula 5a with the compound of the following formula 6a, its salts and its solvates (e.g., hydrides) and then (b) performing the cyclization reaction of the compound of the following formula 7a, its salts and its solvates.

[Reaction Scheme 3a]



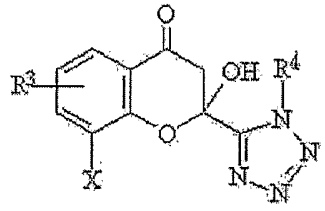
(5a) (6a) (7a) (3a)

Meanwhile, in performing the synthesis according to the above reaction scheme 3, the compound of the above formula 7 (especially the compound of the above formula 7a) is a novel intermediate compound synthesized during the reaction. Therefore, the compound of the above formula 7 also belongs to the scope of the present invention.

The compound of the above formula 7 is indicated as di-keto type in this invention for convenience, but it can be also present in the form of keto-enol and

cyclic hydroxy chromanone. Therefore, all of the tautomeric forms of the above formula 7 belong to the scope of this invention.

Cyclic hydroxy chromanone



Examples

A better understanding of the present invention may be obtained in light of the following examples which are set forth to illustrate, but are not to be construed to limit the present invention.

Example 1: Preparation of 4- (4-phenylbutoxy)benzamide

To a mixture of 4-(4-phenylbutoxy)benzonitrile (1.9 g, 7.5 mmol) and *t*-butanol (37 mL) was added NaOH (2.1 g, 38 mmol) and refluxed for 4 hours. The mixture was cooled to room temperature and then added to a mixed solution of water and methanol (4 : 1, 100 mL). The resulting precipitate was filtered, washed with water and then dried under vacuum to give the target compound as a white solid (1.9 g, 94%).

^{1}H NMR(300MHz, DMSO-d_6) δ 7.81-7.83(m, 3H), 7.15-7.30(m, 6H), 6.95(d, *J*=9.0Hz, 2H), 4.04(t, *J*=5.9Hz, 2H), 2.65(t, *J*=6.9Hz, 2H), 1.73(t, *J*=3.2Hz, 4H)

Example 2: Preparation of 2-iodo-6-[1,3-dioxo-3-(tetrazol-5-yl)propyl]phenol

Under the nitrogen atmosphere, anhydrous dimethylformamide (30 mL) was added to a mixture of 2-hydroxy-3-iodoacetophenone (1.5 g, 5.7 mmol), ethyl-1H-tetrazol-5-carboxylate (1.1 g, 7.5 mmol) and potassium *t*-butoxide (3.2 g, 28.7 mmol) and then stirred at 50 °C for 3 hours. The mixture was cooled to room temperature and then slowly added to cold 1*N* HCl (120 mL). The resulting orange precipitate was filtered, washed with water and then dried under vacuum to obtain the target compound. The target compound was dissolved in ethylacetate by applying heat, added with hexane and then placed at 0 °C for 2 hours. The resulting product was filtered, washed with hexane and then dried under vacuum to give the purified product as a yellow solid(1.7 g, 83%).

^{1}H NMR(300MHz, DMSO-d_6) δ 8.99(br s, 1H), 8.10(dd, *J*=7.7, 1.8Hz, 1H), 7.80(dd, *J*=8.0, 1.7Hz, 1H), 6.95(t, *J*=7.8Hz, 1H), 3.57(d, *J*=16.5Hz, 1H), 3.20(d, *J*=16.5Hz, 1H)

Example 3: Preparation of 8-iodo-4-oxo-2-tetrazol-5-yl-1H-1-benzopyran

The purified product obtained in Example 2(1.5 g, 4.2 mmol) was mixed in methanol(20 mL) and stirred to produce a slurry. The slurry was then added with a conc. sulfuric acid (265 μL, 5.0 mmol) and refluxed for 7 hours. The mixture was cooled to room temperature and then maintained at 0 °C for an hour. The resulting product was filtered, washed with cold methanol, water and cold methanol. The resulting product was dried under vacuum to afford the target compound as a pale yellow solid(1.3 g, 93%).

^{1}H NMR(300MHz, DMSO-d_6) δ8.35(dd, J=7.7, 1.7Hz, 1H), 8.07(dd J=7.8, 1.5Hz, 1H), 7.33(t, J=8.0, 1H), 7.11(s, 1H)

Example 4: Preparation of 4-oxo-8-[4-(4-phenylbutoxy)benzoylamino]-2-tetrazol-5-yl-4H-1-benzopyran

Under the nitrogen atmosphere, the purified product obtained in Example 1 (108 mg, 0.40 mmol), the purified product obtained in Example 3 (68 mg, 0.20 mmol), CuI (11.4 mg, 0.04 mmol), potassium phosphate (255 mg, 0.80 mmol) and *N,N'*-dimethylethylenediamine (13 μL, 0.08 mmol) were mixed together. The mixture was then added with anhydrous dimethylformamide (1 mL) and stirred at 100 °C for two days. The reaction solution was cooled to room temperature and added with water(15 mL). The resulting solution was acidified to pH1-2 by adding a saturated HCl solution. The precipitated solid was filtered and the resulting solid was suspended in methanol(10mL) and then filtered to remove the remaining purified product obtained in Example 1. The obtained solid was dissolved in methanol(7mL) by adding sodium acetate (32 mg, 0.40 mmol) and then filtered. The filtrate was added with saturated HCl solution. The precipitated solid was filtered, washed with cold methanol and then dried under vacuum to obtain the target compound as a pale yellow solid(77 mg, 81%).

Industrial Applicability

As stated above, the present invention relates to a manufacturing process suitable for industrial application, which provides a much improved and more efficient method with secured safety as compared to the conventional methods. In

particular, the compounds represented in the above formulas 2, 3 and 7 are novel intermediate compounds produced in the course of synthesizing substituted benzopyran compounds of the formula 1, and they will also be very useful in industrial application due to their great stability.

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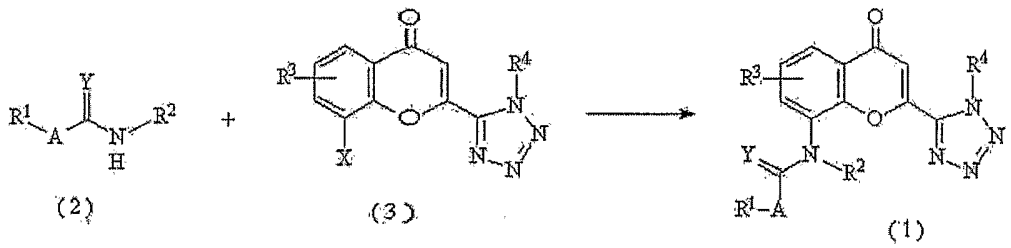
The invention has been described in detail with reference to preferred embodiments thereof. However, it will be appreciated that those skilled in the art, upon consideration of the disclosure, may make modifications and improvements within the scope and spirit of the invention.

Claims

1. A compound of the following formula 1, its salts or its solvates, prepared by reacting a compound of the following formula 2 with a compound of the following formula 3,



(2) (3) (1)

wherein R^1 is selected from the group consisting of a C_{1-20} alkyl group, a C_{2-20} alkenyl group, a C_{2-20} alkynyl group, a phenyl group, a naphthyl group and an indanyl group, wherein said groups can be independently substituted by 1 or 2 substituents selected from a C_{1-20} alkyl group, a C_{2-20} alkenyl group and a C_{2-20} alkynyl group, wherein up to 5 carbon atoms of said substitution groups can be optionally substituted by O, S, N, a halogen atom, a benzene ring, a thiophene ring, a naphthalene ring, a C_{4-7} carbocyclic ring, a carbonyl group, a carbonyloxy group, a hydroxy group, a carboxy group, an azido group or a nitro group;

R^2 and R^4 are independently H, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{1-6} alkyl group substituted with from 1 to 3 aryl groups, a C_{1-6} alkoxycarbonyl group, a C_{1-6} alkoxycarbonyl group substituted with an aryl group, an aryloxycarbonyl group, a C_{1-6} alkoxy C_{1-6} alkyl group, a C_{3-9} trialkyltin group, a triaryltin group, or a C_{3-9} trialkylsilyl group, wherein said aryl group or said aryl is a phenyl group substituted with from 1 to 3 substituents which are selected from the group

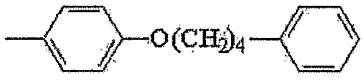
consisting of a phenyl group, a halogen atom, a C_{1-6} alkyl group and a C_{1-6} alkoxy group;

R^3 is H, a halogen atom, a hydroxy group, a nitro group, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkylthio group, or -$COOR^5$ (wherein R^5 is H or a C_{1-6} alkyl group);

A is a single bond; or a C_{1-10} alkylene group, a C_{2-10} alkenylene group, or a C_{2-10} alkynylene group either substituted or unsubstituted with from 1 to 3 substituents selected from a C_{1-10} alkyl group and a phenyl group;

X is a halogen atom; and

Y is O or S.

2. In claim 1, said R^1 is  , R^2, R^3 and R^4 are independently H, A is a single bond, X is I, Br or Cl; Y is O.

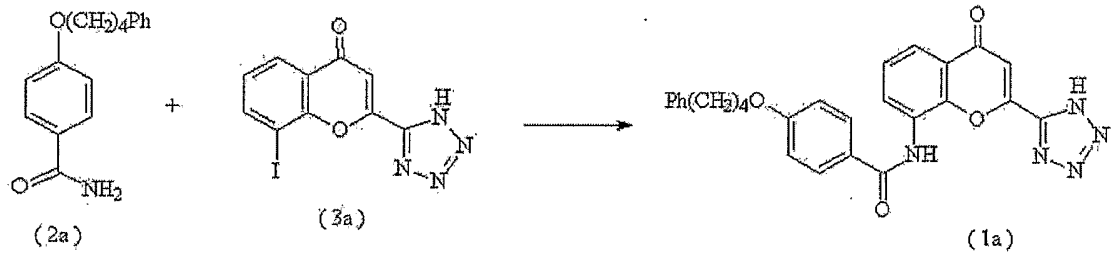
3. In claim 1, said reaction is performed in the presence of a palladium- or copper-containing compound as a catalyst, diamine as a ligand and a base.

4. In claim 3, said reaction is performed in the presence of a catalyst selected from the group consisting of CuI, CuCl, and Cu_2O; a ligand selected from the group consisting of *N,N'*-dimethylethylenediamine, trans-*N,N'*-1,2-cyclohexanediamine and trans-*N,N'*-dimethyl-1,2-cyclohexanediamine; and a base selected from the group consisting of cesium carbonate and potassium phosphate.

5. In claim 4, said reaction is performed in the presence of CuI as a catalyst, *N,N'*-dimethylethyleneamine as a ligand, and potassium phosphate as a base.

6. In any one of claims 3, 4 and 5, said reaction is performed by using dimethylformamide as a solvent.

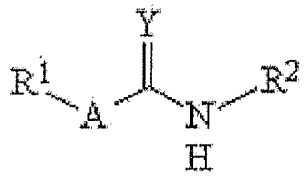
7. In claim 1, the compound of formula 1a, its salts and its solvates are prepared by reacting a compound of the formula 2a with a compound of the following formula 3a, its salts or its solvates



(2a) (3a) (1a)

8. In claim 7, said reaction is performed at about 70 to 100 °C in the presence of *N,N'*-dimethylformamide as a solvent, CuI as a catalyst, *N,N'*-dimethylethyleneamine as a ligand, and potassium phosphate as a base.

9. An intermediate compound represented by the following formula 2, its salts or its solvates,

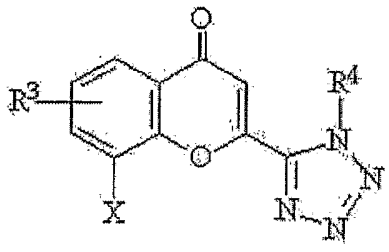


(2)

wherein R^1, R^2, A and Y are the same as defined in claim 1.

10. In claim 9, said intermediate compound represented by the above formula 2 is 4-(4-phenylbutoxy)benzamide.

11. An intermediate compound represented by the following formula 3, its salts or its solvates,



(3)

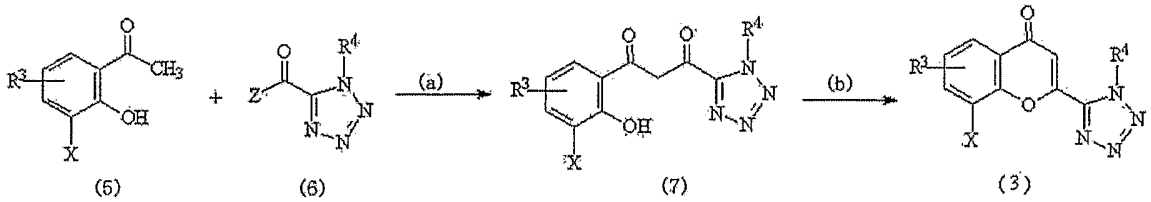
wherein R^3, R^4 and X are the same as defined in claim 1.

12. In claim 11, said intermediate compound represented by the above formula 3 is 8-iodo -4-oxo -2-tetrazol -5-yl -1H-1-benzopyran.

13. A method of preparing a compound of the following formula 3 comprising:

(a) preparing a compound of the following formula 7 by reacting a compound of the following formula 5 and a compound of the following formula 6; and

(b) performing a cyclization of the compound obtained in (a),



(5) (6) (7) (3)

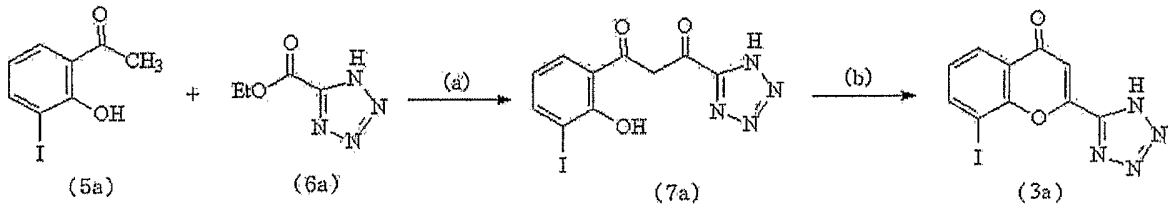
wherein R^3, R^4 and X are the same as defined in claim 1, and Z indicates an activated leaving group.

14. In claim 13, said cyclization is performed by using methanol as a solvent in the presence of sulfuric acid.

15. In claim 13, a compound of the following formula 3a, its salts or its solvates are prepared by:

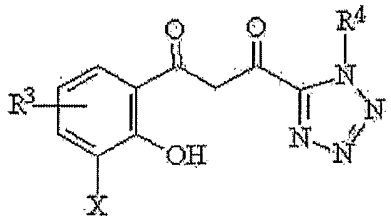
(a) preparing a compound of the following formula 7a by reacting a compound of the following formula 5a and a compound of the following formula 6a, its salts or its solvates; and,

(b) performing a cyclization of the compound obtained in (a).



(5a) (6a) (7a) (3a)

16. An intermediate compound represented by the following formula 7, its salts or its solvates,



(7)

wherein R^3, R^4 and X are the same as defined in claim 1.

17. In claim 16, said intermediate compound represented by the above formula 7 is 2-iodo-6-[1,3-dioxo-3-(tetrazol-5-yl)propyl]phenol.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2005/000365

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 405/04

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)
IPC7 as above

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean patents and applications for inventions since 1975

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3839339 (ALLEN & HANBURYS LIMITED) 1 Oct. 1974 See the compound of formula I.	11, 12
X	ELLIS et al., 'Benzopyrones. 7. Synthesis and antiallergic activity of some 2-(5-tetrazolyl) chromones', J. Med. Chem. 1972, Vol.15(8), pp.865-867 See the compound No. 9, 10.	11, 12
A	JP 60-246384 A (HOKURIKU SEIYAKU CO., LTD) 6 Dec. 1985 See the whole document.	1 - 17
A	US 4238495 (MILES LABORATORIES, INC.) 9 Dec. 1980 See the whole document.	1 - 17
A	US 4158663 (WARNER-LAMBERT COMPANY) 19 Jun. 1979 See the whole document.	1 - 17

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
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"P" document published prior to the international filing date but later than the priority date claimed
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"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
02 MAY 2005 (02.05.2005)	**04 MAY 2005 (04.05.2005)**

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2005/000365

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3839339	01.10.1974	JP 55011674 B4	26.03.1980
		DE 2105191 A1	26.08.1971
		DE 2105191 A	26.08.1971
JP 60-246384 A	06.12.1985	None	
US 4238495	09.12.1980	None	
US 4158663	19.06.1979	US 4179447	28.12.1979