ingredient of pharmaceutical products, and a method for manufacturing the compound (WO2013/157540A and WO2015/056683A).

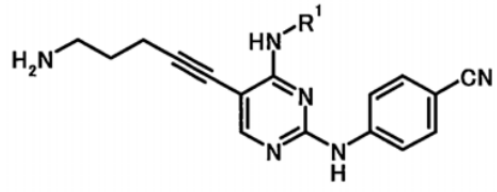
SUMMARY

[0004] There is a demand for a method for industrially manufacturing a nitrogen-containing heterocyclic compound which shows excellent FLT3 inhibitory activity and is useful as an active pharmaceutical ingredient of pharmaceutical products.

An object of the present disclosure is to provide a method for industrially manufacturing a nitrogen-containing heterocyclic compound, which shows excellent FLT3 inhibitory activity and is useful as an active pharmaceutical ingredient of pharmaceutical products, and an intermediate of the method.

[0005] Under the circumstances described above, the inventors of the present disclosure conducted an intensive study. As a result, the inventors obtained knowledge that a nitrogen-containing heterocyclic compound which shows excellent FLT3 inhibitory activity and is useful as an active pharmaceutical ingredient of pharmaceutical products can be industrially manufactured by the manufacturing method shown below. Furthermore, the inventors of the present disclosure obtained knowledge that a compound represented by General Formula [14] is a useful intermediate. Based on the knowledge, the inventors accomplished the present disclosure.

[0005a] In one aspect of the present disclosure, there is provided a method for manufacturing a compound represented by General Formula [5] or a salt thereof

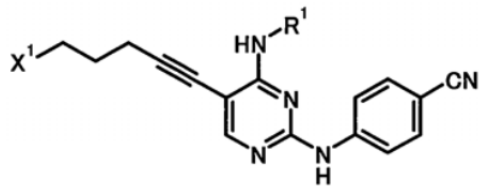


[5]

(in the formula, R^1 represents a C_{1-6} alkyl group which may be substituted),

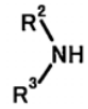
the method comprising:

a step of reacting a compound represented by General Formula [1] or a salt thereof



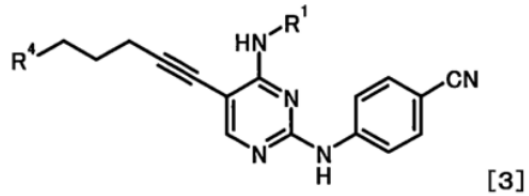
[1]

(in the formula, R^1 has the same definition as described above; and X^1 represents a chlorine atom) with a compound represented by General Formula [2] or a salt thereof



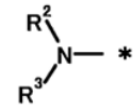
[2]

(in the formula, R^2 represents a hydrogen atom or an amino-protecting group; R^3 represents a hydrogen atom or an amino-protecting group; and R^2 and R^3 represent a phthaloyl group, which may be substituted, by being combined together), or with hexamethylenetetramine, thereby manufacturing a compound represented by General Formula [3] or a salt thereof



[3]

[in the formula, R^4 represents a group represented by General Formula [4]

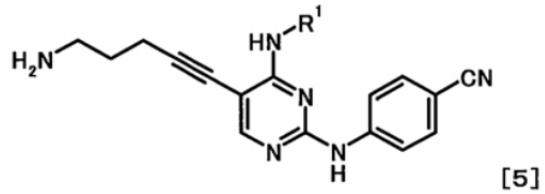


[4]

(in the formula, * represents a binding position; R^2 has the same definition as described above; R^3 has the same definition as described above) or a hexamethylenetetraminium group; and R^1 has the same definition as described above],

and then, if necessary, subjecting the obtained compound or a salt thereof to a deprotection reaction or a hydrolysis reaction.

[0005b] In another aspect of the present disclosure, there is provided a method for manufacturing a compound represented by General Formula [5] or a salt thereof

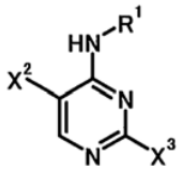


[5]

(in the formula, R^1 represents a $C_{1\text{-}6}$ alkyl group which may be substituted),

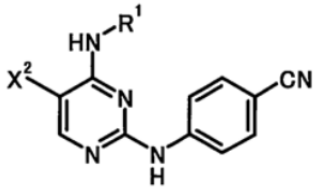
the method comprising:

(1) step of reacting a compound represented by General Formula [6] or a salt thereof



[6]

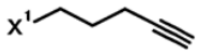
(in the formula, R^1 has the same definition as described above; X^2 represents a leaving group; and X^3 represents a leaving group) with 4-aminobenzonitrile or a salt thereof in the presence of hydrochloric acid, thereby manufacturing a hydrochloride of a compound represented by General Formula [7]



[7]

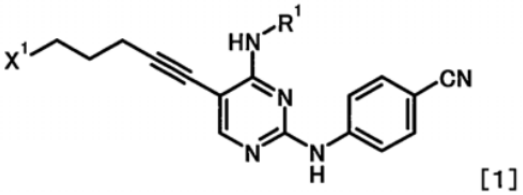
(in the formula, R^1 has the same definition as described above; and X^2 has the same definition as described above);

(2) step of reacting the hydrochloride of the compound represented by General Formula [7] with a compound represented by General Formula [8]



[8]

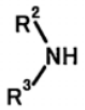
(in the formula, X^1 represents a chlorine atom), thereby manufacturing a compound represented by General Formula [1] or a salt thereof



[1]

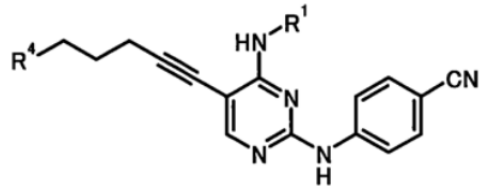
(in the formula, R^1 and X^1 have the same definition as described above) ; and

(3) step of reacting the compound represented by General Formula [1] or a salt thereof with a compound represented by General Formula [2] or a salt thereof



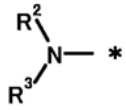
[2]

(in the formula, R^2 represents a hydrogen atom or an amino-protecting group; R^3 represents a hydrogen atom or an amino-protecting group; and R^2 and R^3 represent a phthaloyl group, which may be substituted, by being combined together), or with hexamethylenetetramine, thereby manufacturing a compound represented by General Formula [3] or a salt thereof



[3]

(in the formula, R^4 represents a group represented by General Formula [4] or a hexamethylenetetraminium group; and R^1 has the same definition as described above)

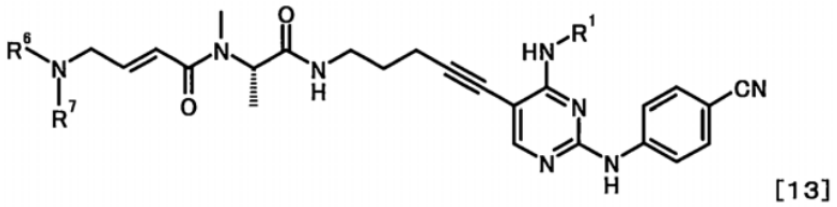


[4]

(in the formula, * represents a binding position; R^2 and R^3 have the same definition as described above),

and then, if necessary, subjecting the obtained compound or a salt thereof to a deprotection reaction or a hydrolysis reaction.

[0005c] In a further aspect of the present disclosure, there is provided a method for manufacturing a compound represented by General Formula [13] or a salt thereof

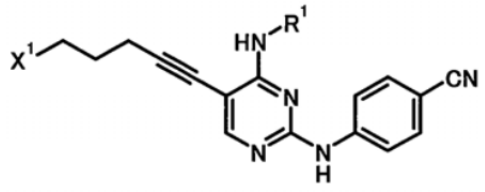


[13]

(in the formula, R^1 represents a C_{1-6} alkyl group which may be substituted; R^6 represents a hydrogen atom or a C_{1-6} alkyl group which may be substituted; and R^7 represents a C_{1-6} alkyl group which may be substituted),

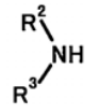
the method comprising:

(1) step of reacting a compound represented by General Formula [1] or a salt thereof



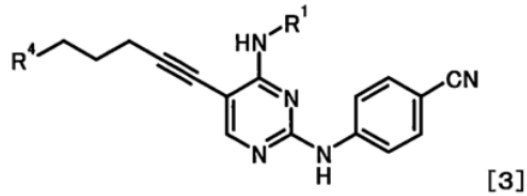
[1]

(in the formula, R^1 has the same definition as described above; and X^1 represents a chlorine atom) with a compound represented by General Formula [2] or a salt thereof



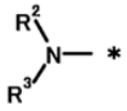
[2]

(in the formula, R^2 represents a hydrogen atom or an amino-protecting group; R^3 represents a hydrogen atom or an amino-protecting group; and R^2 and R^3 represent a phthaloyl group, which may be substituted, by being combined together), or with hexamethylenetetramine, thereby manufacturing a compound represented by General Formula [3] or a salt thereof



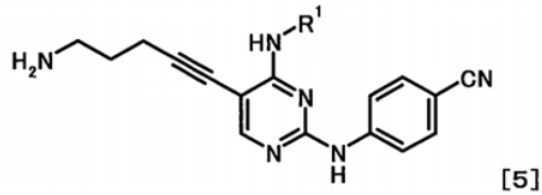
[3]

(in the formula, R^4 represents a group represented by General Formula [4] or a hexamethylenetetraminium group; and R^1 has the same definition as described above)



[4]

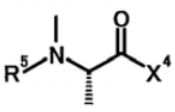
(in the formula, * represents a binding position; R^2 and R^3 have the same definition as described above; and R^2 and R^3 represent a phthaloyl group, which may be substituted, by being combined together) and then, if necessary, subjecting the obtained compound or a salt thereof to a deprotection reaction or a hydrolysis reaction, to obtain a compound represented by General Formula [5] or a salt thereof



[5]

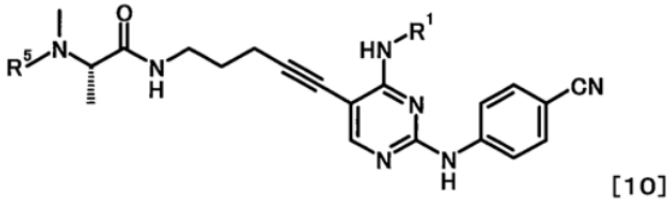
(in the formula, R^1 has the same definition as described above) ;

(2) step of reacting the compound represented by General Formula [5] or a salt thereof with a compound represented by General Formula [9] or a salt thereof



[9]

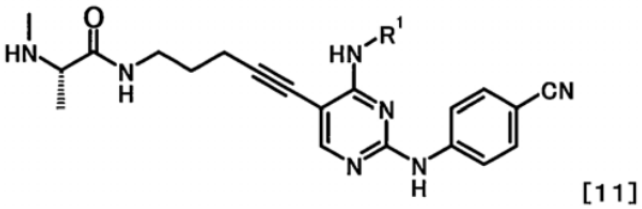
(in the formula, R^5 represents an amino-protecting group, and X^4 represents a hydroxyl group or a leaving group), thereby manufacturing a compound represented by General Formula [10] or a salt thereof



[10]

(in the formula, R^1 has the same definition as described above; and R^5 has the same definition as described above);

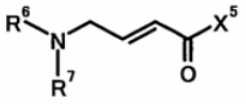
(3) step of subjecting the compound represented by General Formula [10] or a salt thereof to a deprotection, thereby manufacturing a compound represented by General Formula [11] or a salt thereof



[11]

(in the formula, R^1 has the same definition as described above); and

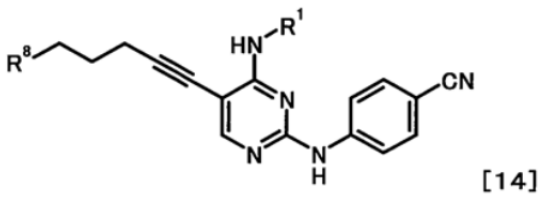
(4) step of reacting the compound represented by General Formula [11] or a salt thereof with a compound represented by General Formula [12] or a salt thereof



[12]

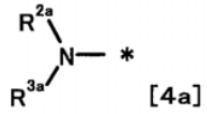
(in the formula, R^6 and R^7 have the same definition as described above; and X^5 represents a hydroxyl group or a leaving group).

[0005d] In another aspect of the present disclosure, there is provided a compound represented by General Formula [14] or a salt thereof



[14]

[in the formula, R^1 represents a C_{1-6} alkyl group which may be substituted; and R^8 represents a chlorine atom, a group represented by General Formula [4a]

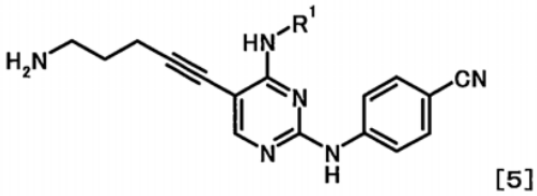


[4a]

(in the formula, R^{2a} represents a C_{1-6} alkoxycarbonyl group; R^{3a} represents a C_{1-6} alkoxycarbonyl group; and * represents a binding position), or a hexamethylenetetraminium group].

[0006] That is, the present disclosure provides the following.

<1> A method for manufacturing a compound represented by General Formula [5] or a salt thereof

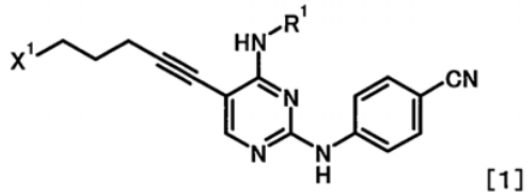


[5]

(in the formula, R^1 represents a C_{1-6} alkyl group which may be substituted),

the method comprising:

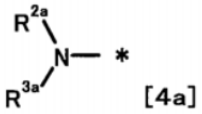
a step of reacting a compound represented by General Formula [1] or a salt thereof



[1]

(in the formula, R^1 has the same definition as described above; and X^1 represents a leaving group) with a compound represented by General Formula [2] or a salt thereof

[in the formula, R^1 represents a C_{1-6} alkyl group which may be substituted; and R^8 represents a leaving group, a group represented by General Formula [4a]



[4a]

(in the formula, R^{2a} represents a C_{1-6} alkoxycarbonyl group; R^{3a} represents a C_{1-6} alkoxycarbonyl group; and * represents a binding position), or a hexamethylenetetraminium group].

<11> The compound according to claim 10 or a salt thereof,

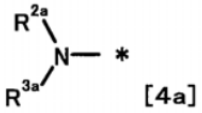
wherein R^1 is a C_{2-4} alkyl group, and

R^8 is a leaving group.

<12> The compound according to claim 10 or a salt thereof,

wherein R^1 represents C_{2-4} alkyl group; and

R^8 is a group represented by General Formula [4a]



[4a]

(in the formula, R^{2a} represents a C_{1-6} alkoxycarbonyl group; R^{3a} represents a C_{1-6} alkoxycarbonyl group; and * represents a binding position).

<13> A N^2-(4-cyanophenyl)-5-iodo-N^4-propylpyrimidine-2,4-diamine hydrochloride.

[0012] The manufacturing method of the present disclosure is useful as a method for industrially manufacturing a nitrogen-containing heterocyclic compound which shows excellent FLT3 inhibitory activity and is useful as an active pharmaceutical ingredient of pharmaceutical products.

The compound of the present disclosure is useful as an intermediate used in the method for industrially manufacturing a nitrogen-containing heterocyclic compound which shows excellent FLT3 inhibitory activity and is useful as an active pharmaceutical ingredient of pharmaceutical products.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0013] Hereinafter, the present invention will be specifically described.

In the present invention, unless otherwise specified, % means % by mass.

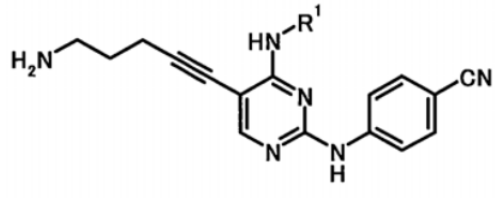
In the present invention, unless otherwise specified, each term has the following meaning.

The halogen atom means a chlorine atom, a bromine atom, or an iodine atom.

The C_{1-6} alkyl group means a linear or branched C_{1-6} alkyl group such as a methyl,

CLAIMS

1. A method for manufacturing a compound represented by General Formula [5] or a salt thereof

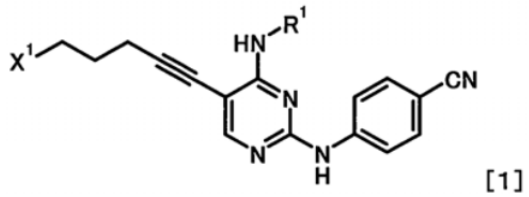


[5]

(in the formula, R^1 represents a $C_{1\text{-}6}$ alkyl group which may be substituted),

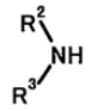
the method comprising:

a step of reacting a compound represented by General Formula [1] or a salt thereof



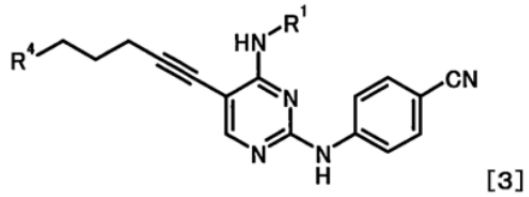
[1]

(in the formula, R^1 has the same definition as described above; and X^1 represents a chlorine atom) with a compound represented by General Formula [2] or a salt thereof



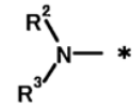
[2]

(in the formula, R^2 represents a hydrogen atom or an amino-protecting group; R^3 represents a hydrogen atom or an amino-protecting group; and R^2 and R^3 represent a phthaloyl group, which may be substituted, by being combined together), or with hexamethylenetetramine, thereby manufacturing a compound represented by General Formula [3] or a salt thereof



[3]

[in the formula, R^4 represents a group represented by General Formula [4]



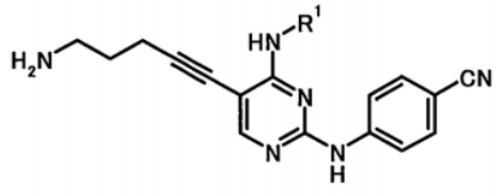
[4]

(in the formula, * represents a binding position; R^2 has the same definition as described above; R^3 has the same definition as described above) or a

hexamethylenetetraminium group; and R^1 has the same definition as described above],

and then, if necessary, subjecting the obtained compound or a salt thereof to a deprotection reaction or a hydrolysis reaction.

2. A method for manufacturing a compound represented by General Formula [5] or a salt thereof

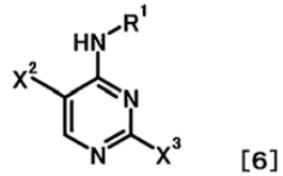


[5]

(in the formula, R^1 represents a $C_{1\text{-}6}$ alkyl group which may be substituted),

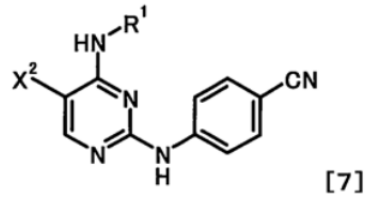
the method comprising:

(1) step of reacting a compound represented by General Formula [6] or a salt thereof



[6]

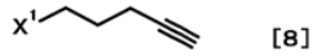
(in the formula, R^1 has the same definition as described above; X^2 represents a leaving group; and X^3 represents a leaving group) with 4-aminobenzonitrile or a salt thereof in the presence of hydrochloric acid, thereby manufacturing a hydrochloride of a compound represented by General Formula [7]



[7]

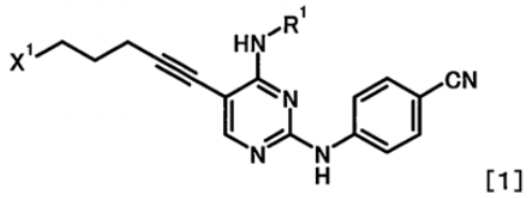
(in the formula, R^1 has the same definition as described above; and X^2 has the same definition as described above);

(2) step of reacting the hydrochloride of the compound represented by General Formula [7] with a compound represented by General Formula [8]



[8]

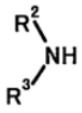
(in the formula, X^1 represents a chlorine atom), thereby manufacturing a compound represented by General Formula [1] or a salt thereof



[1]

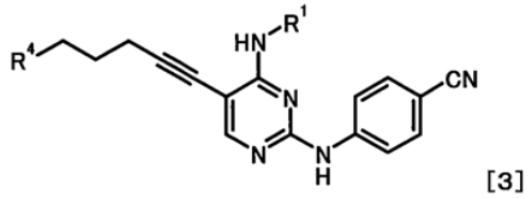
(in the formula, R^1 and X^1 have the same definition as described above) ; and

(3) step of reacting the compound represented by General Formula [1] or a salt thereof with a compound represented by General Formula [2] or a salt thereof



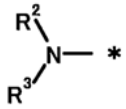
[2]

(in the formula, R^2 represents a hydrogen atom or an amino-protecting group; R^3 represents a hydrogen atom or an amino-protecting group; and R^2 and R^3 represent a phthaloyl group, which may be substituted, by being combined together), or with hexamethylenetetramine, thereby manufacturing a compound represented by General Formula [3] or a salt thereof



[3]

(in the formula, R^4 represents a group represented by General Formula [4] or a hexamethylenetetraminium group; and R^1 has the same definition as described above)



[4]

(in the formula, * represents a binding position; R^2 and R^3 have the same definition as described above),

and then, if necessary, subjecting the obtained compound or a salt thereof to a deprotection reaction or a hydrolysis reaction.

3. The manufacturing method according to claim 1 or 2,

wherein R^1 is a C_{2-4} alkyl group.

4. The manufacturing method according to any one of claims 1 to 3,

wherein R^2 is a C_{1-6} alkoxycarbonyl group, and

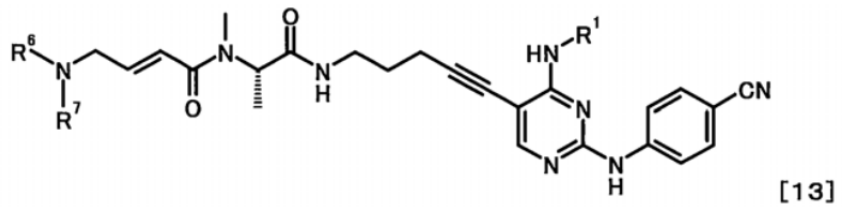
R^3 is a C_{1-6} alkoxycarbonyl group.

5. The manufacturing method according to any one of claims 2 to 4,

wherein X^2 is an iodine atom, and

X^3 is a chlorine atom.

6. A method for manufacturing a compound represented by General Formula [13] or a salt thereof

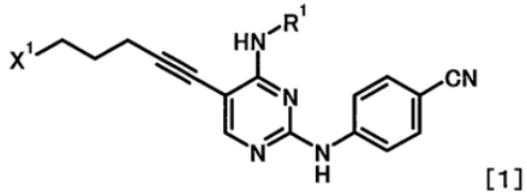


[13]

(in the formula, R^1 represents a $C_{1\text{-}6}$ alkyl group which may be substituted; R^6 represents a hydrogen atom or a $C_{1\text{-}6}$ alkyl group which may be substituted; and R^7 represents a $C_{1\text{-}6}$ alkyl group which may be substituted),

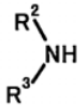
the method comprising:

(1) step of reacting a compound represented by General Formula [1] or a salt thereof



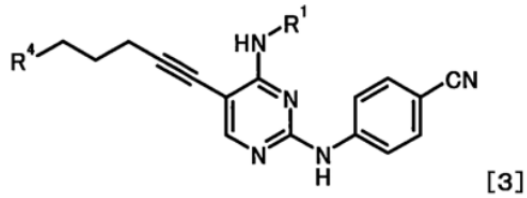
[1]

(in the formula, R^1 has the same definition as described above; and X^1 represents a chlorine atom) with a compound represented by General Formula [2] or a salt thereof



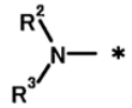
[2]

(in the formula, R^2 represents a hydrogen atom or an amino-protecting group; R^3 represents a hydrogen atom or an amino-protecting group; and R^2 and R^3 represent a phthaloyl group, which may be substituted, by being combined together), or with hexamethylenetetramine, thereby manufacturing a compound represented by General Formula [3] or a salt thereof



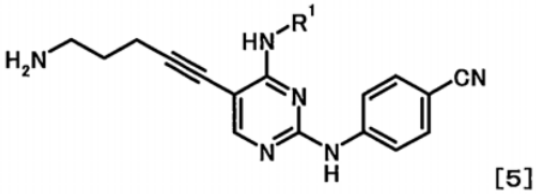
[3]

(in the formula, R^4 represents a group represented by General Formula [4] or a hexamethylenetetraminium group; and R^1 has the same definition as described above)



[4]

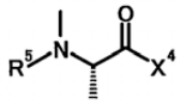
(in the formula, * represents a binding position; R^2 and R^3 have the same definition as described above; and R^2 and R^3 represent a phthaloyl group, which may be substituted, by being combined together) and then, if necessary, subjecting the obtained compound or a salt thereof to a deprotection reaction or a hydrolysis reaction, to obtain a compound represented by General Formula [5] or a salt thereof



[5]

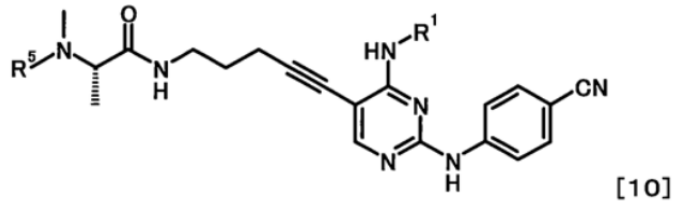
(in the formula, R^1 has the same definition as described above) ;

(2) step of reacting the compound represented by General Formula [5] or a salt thereof with a compound represented by General Formula [9] or a salt thereof



[9]

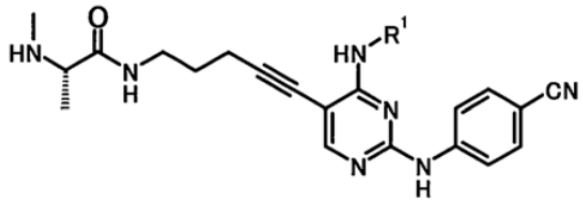
(in the formula, R^5 represents an amino-protecting group, and X^4 represents a hydroxyl group or a leaving group), thereby manufacturing a compound represented by General Formula [10] or a salt thereof



[10]

(in the formula, R^1 has the same definition as described above; and R^5 has the same definition as described above);

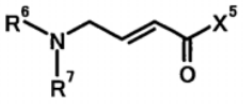
(3) step of subjecting the compound represented by General Formula [10] or a salt thereof to a deprotection, thereby manufacturing a compound represented by General Formula [11] or a salt thereof



[11]

(in the formula, R^1 has the same definition as described above); and

(4) step of reacting the compound represented by General Formula [11] or a salt thereof with a compound represented by General Formula [12] or a salt thereof



[12]

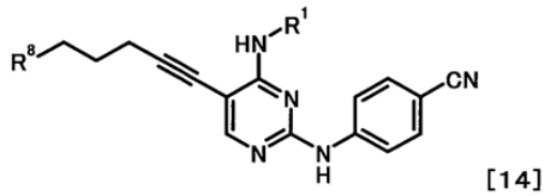
(in the formula, R^6 and R^7 have the same definition as described above; and X^5 represents a hydroxyl group or a leaving group).

7. The manufacturing method according to claim 6,
wherein R^1 is a C_{2-4} alkyl group.

8. The manufacturing method according to claim 6 or 7,
wherein R^2 is a C_{1-6} alkoxycarbonyl group, and
R^3 is a C_{1-6} alkoxycarbonyl group.

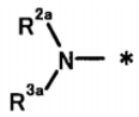
9. The manufacturing method according to any one of claims 6 to 8,
wherein R^6 is a C_{1-4} alkyl group, and
R^7 is a C_{1-4} alkyl group.

10. A compound represented by General Formula [14] or a salt thereof



[14]

[in the formula, R^1 represents a C_{1-6} alkyl group which may be substituted; and R^8 represents a chlorine atom, a group represented by General Formula [4a]



[4a]

(in the formula, R^{2a} represents a C_{1-6} alkoxycarbonyl group; R^{3a} represents a C_{1-6} alkoxycarbonyl group; and * represents a binding position), or a hexamethylenetetraminium group].

11. The compound according to claim 10 or a salt thereof,

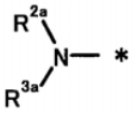
wherein R^1 is a C_{2-4} alkyl group, and

R^8 is a chlorine atom.

12. The compound according to claim 10 or a salt thereof,

wherein R^1 represents C_{2-4} alkyl group; and

R^8 is a group represented by General Formula [4a]

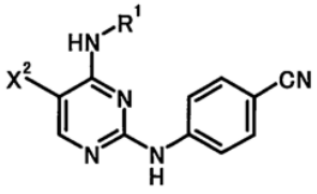


[4a]

(in the formula, R^{2a} represents a C_{1-6} alkoxycarbonyl group; R^{3a} represents a C_{1-6} alkoxycarbonyl group; and * represents a binding position).

13. The manufacturing method according to any one of claims 6 to 9,

the method further comprising a step of reacting a hydrochloride of a compound represented by General Formula [7]



[7]

(in the formula, R^1 has the same definition as described above; and X^2 has the same definition as described above) with a compound represented by General Formula [8]



[8]

(in the formula, X^1 represents a chlorine atom), thereby manufacturing the compound represented by General Formula [1] or a salt thereof.