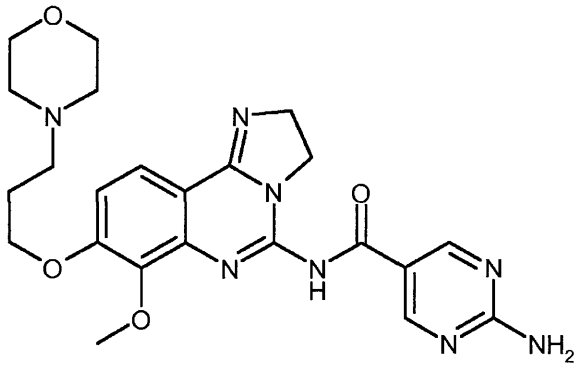
CLAIMS

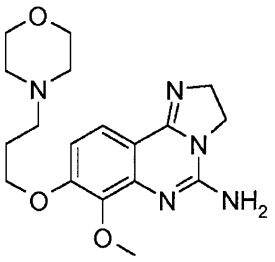
1. A method of preparing copanlisib (10) :



(10),

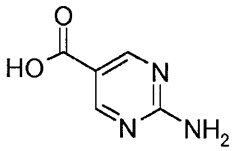
comprising the following step A9 :

wherein a compound of formula (9) :



(9)

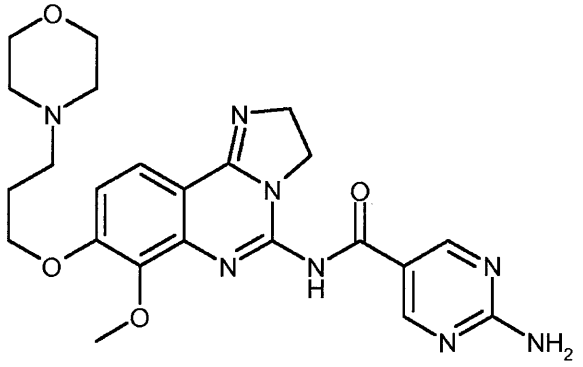
is allowed to react with a compound of formula (9b) :



(9b)

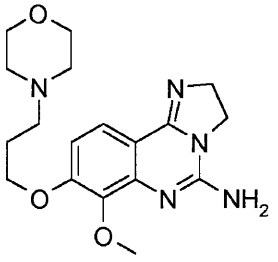
optionally in the presence of a catalyst, such as N,N-dimethyl-4-aminopyridine for example, optionally in the presence of a coupling agent, such as N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride for example, optionally in a solvent, such as N,N-dimethylformamide for example,

thereby providing copanlisib (10) :



(10) ;

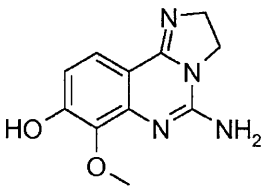
said compound of formula (9) :



(9)

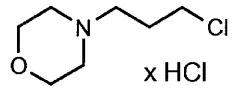
being prepared by the following step A8 :

wherein a compound of formula (8) :



(8),

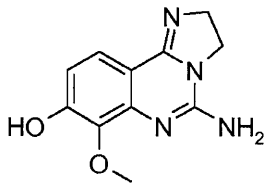
is allowed to react with a compound of formula (8a) :



(8a)

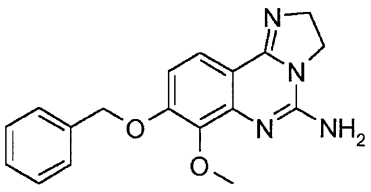
optionally in the presence of a base, such as potassium carbonate for example, in a solvent, such as n-butanol for example, optionally with heating, such as under reflux for example,
thereby providing a compound of formula (9) ;

said compound of formula (8) :



(8)

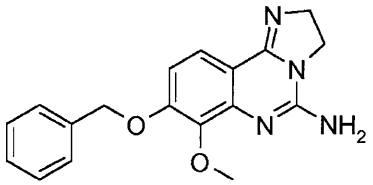
being prepared by the following step A7 :
wherein a compound of formula (7) :



(7),

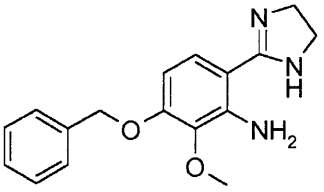
is allowed to react with a reducing agent, such as hydrogen for example, optionally in the presence of a catalyst, such as a metallic catalyst such as palladium on charcoal for example, particularly 5% palladium on charcoal which is water-wetted, optionally dissolved in a solvent or in suspension in a solvent, such as N,N-dimethylformamide for example, optionally in presence of an acid, such as trifluoroacetic acid for example, thereby providing a compound of formula (8) ;

said compound of formula (7) :



(7)

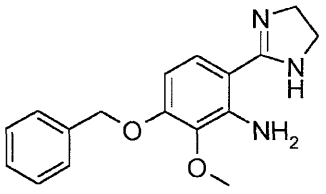
being prepared by the following step A6 :
wherein a compound of formula (6) :



(6)

is allowed to react, optionally in the presence of a base, such as triethylamine for example, with an annelating agent, such as cyanogen bromide (also known as bromocyanide) for example, optionally in a solvent, such as acetonitrile or dichloromethane for example,
thereby providing a compound of formula (7) ;

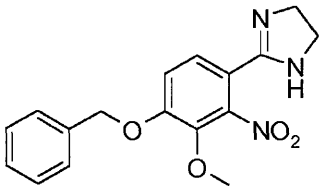
said compound of formula (6) :



(6)

being prepared by the following step A5 :

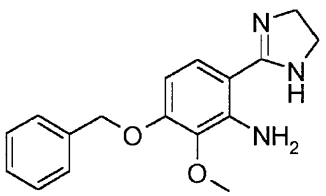
wherein a compound of formula (5) :



(5)

is allowed to react with a reducing agent, such as hydrogen for example, optionally in the presence of a catalyst, such as a bimetallic catalyst such as platinum/iron on charcoal for example, particularly 1% Pt/0.2% Fe/C, which is water-wetted, optionally dissolved in a solvent or in suspension in a solvent, such as tetrahydrofuran for example, thereby providing a compound of formula (6).

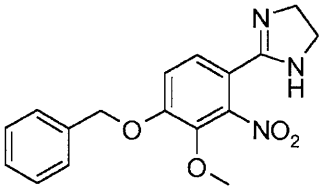
2. The method according to claim 1, wherein said compound of formula (6) :



(6)

is prepared by the following step A5 :

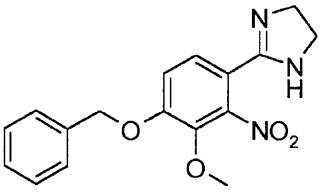
wherein a compound of formula (5) :



(5)

is allowed to react with hydrogen in the presence of a bimetallic catalyst, which is 1% Pt/0.2% Fe/C which is water-wetted in suspension in tetrahydrofuran, thereby providing a compound of formula (6).

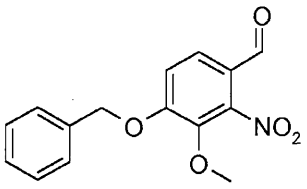
3. The method according to claim 1 or 2, wherein said compound of formula (5) :



(5)

is prepared by the following step A4 :

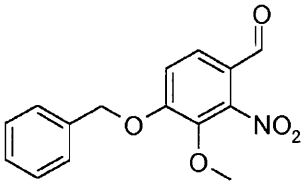
wherein a compound of formula (4) :



(4)

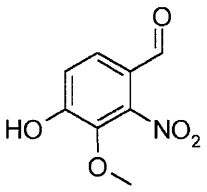
is allowed to react with ethylenediamine, optionally in the presence of N-bromosuccinimide, optionally in a solvent mixture, such as methanol and acetonitrile for example,
thereby providing a compound of formula (5).

4. The method according to any one of claims 1 to 3, wherein said compound of formula (4) :



(4),

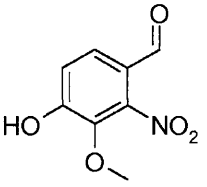
is prepared by the following step A3,
wherein a compound of formula (3) :



(3),

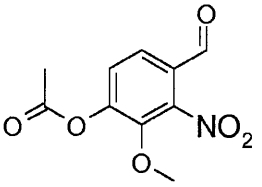
optionally in a solvent, such as N,N-dimethylformamide for example, optionally in the presence of a base, such as potassium carbonate for example,
is allowed to react with benzyl bromide, optionally with heating, such as under reflux for example,
thereby providing a compound of formula (4).

5. The method according to any one of claims 1 to 4, wherein said compound of formula (3) :



(3),

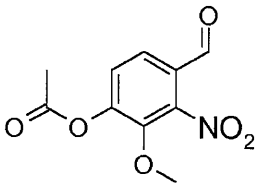
is prepared by the following step A2,
wherein a compound of formula (2) :



(2),

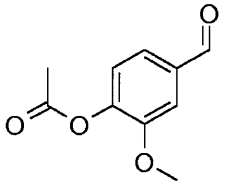
is allowed to react with a base, such as potassium carbonate for example, in a solvent, such as methanol for example,
thereby providing a compound of formula (3).

6. The method according to any one of claims 1 to 5, wherein said compound of formula (2) :



(2),

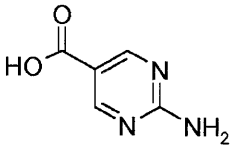
is prepared by the following step A1,
wherein a compound of formula (1) :



(1)

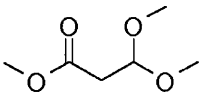
is allowed to react, in solution in a solvent, such as dichloromethane for example, with nitric acid and sulphuric acid,
thereby providing a compound of formula (2).

7. The method according to any one of claims 1 to 6, wherein said compound of formula (9b) :



(9b)

I
is prepared comprising the following step A10 :
wherein a compound of formula (9a) :



(9a)

is :

a) allowed to react with a base, such as sodium methoxide for example, optionally in a solvent, such as 1,4-dioxane for example, with heating, such as under reflux for example, then,

b) after cooling, such as to room temperature for example, adding methyl formate, then

c) adding guanidine hydrochloride, followed by heating, such as under reflux for example, then,

d) adding water and an aqueous solution of a base, such as sodium hydroxide for example, followed by heating, then,

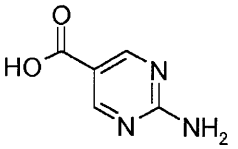
e) adding an aqueous solution of a mineral acid, such as hydrochloric acid for example,

f) adding an amine, such as dicyclohexylamine for example, and filter, then

g) adding an aqueous solution of a strong base, such as sodium hydroxide, then

h) adding an aqueous solution of a mineral acid, such as hydrochloric acid for example,

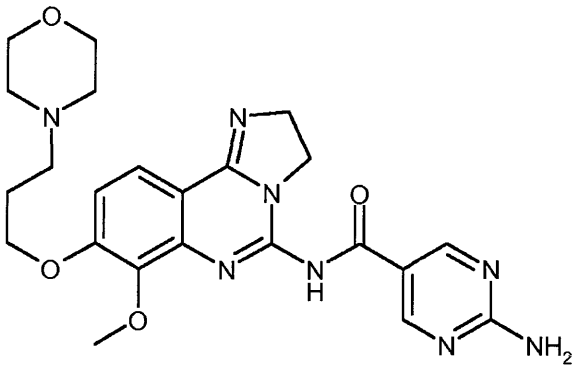
thereby providing a compound of formula (9b) :



(9b).

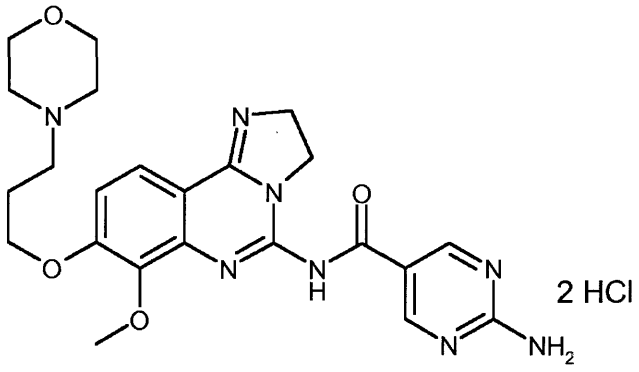
8. The method according to any one of claims 1 to 7, which further comprises the following step A11 :

wherein copanlisib, of formula (10) :



(10)

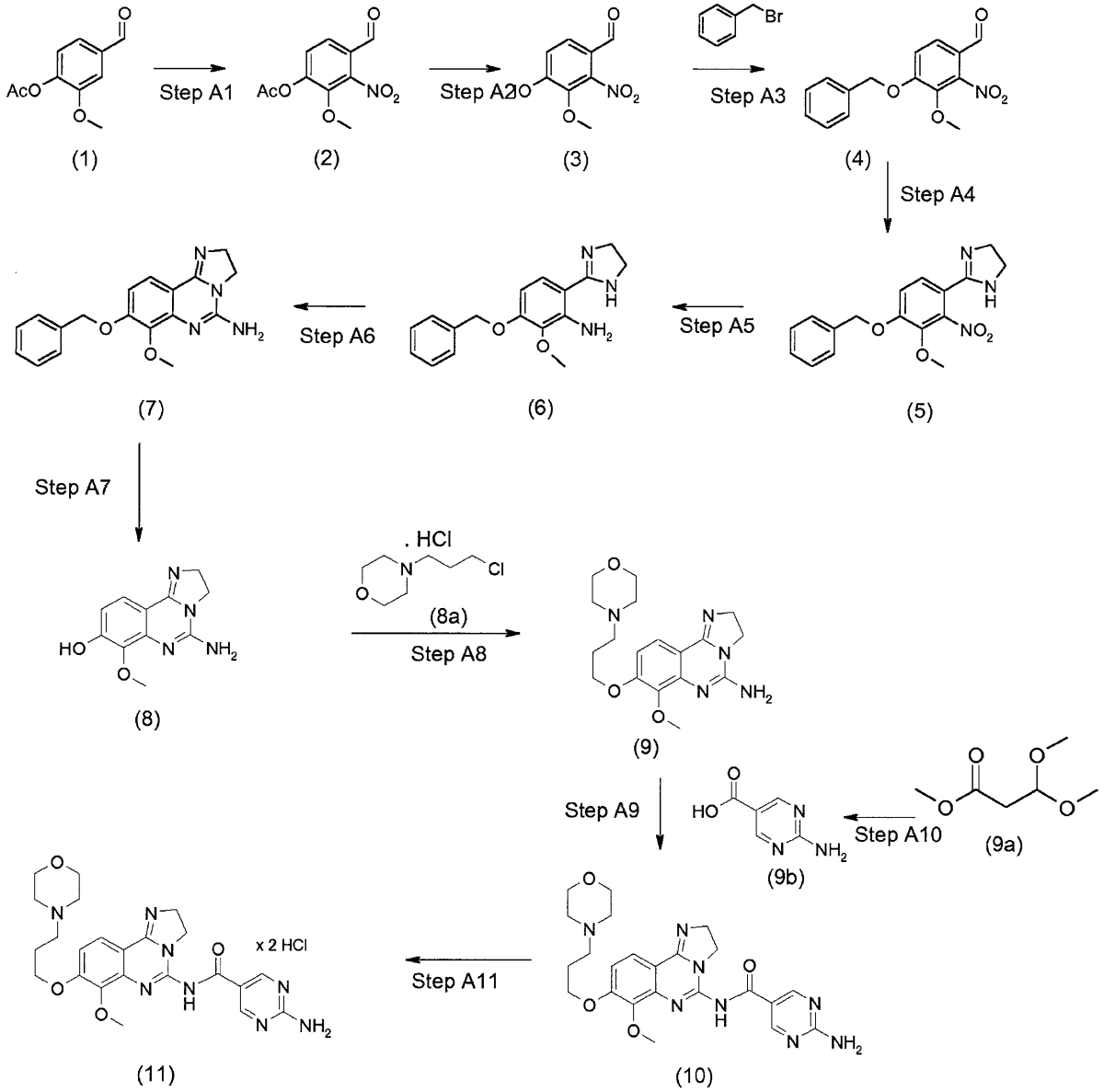
is allowed to react with hydrogen chloride, optionally hydrochloric acid, thereby providing copanlisib dihydrochloride (11) :



(11).

9. The method according to any one of claims 1 to 8, wherein copanlisib (10) or copanlisib dihydrochloride (11) is prepared via the following steps shown in Reaction Scheme 3, *infra* :

Reaction Scheme 3 :



10. The method according to claim 8 or 9, wherein said copanlisib dihydrochloride (11) is in the form of copanlisib dihydrochloride hydrate I.

11. The method according to claim 8 or 9, wherein said copanlisib dihydrochloride (11) is in the form of copanlisib dihydrochloride hydrate II.