

Process for preparing the anti-tumor agent 6-(7-((1-aminocyclopropyl)methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide and its crystalline

This application claims the benefit of U.S. Provisional Applications 61/754,516 filed on January 18, 2013

FIELD OF THE INVENTION

The present invention relates a new process to synthesize 6-(7-((1-aminocyclo-propyl)-methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide (AL3810) by deprotection of substituted benzyl 1-((6-methoxy-4-(5-(methylcarbamoyl)naphthalen-2-yloxy)quinolin-7-yloxy)-methyl)cyclopropylcarbamate (Formula I) under a diluted or weak acidic condition. A stable crystalline form of 6-(7-((1-aminocyclo-propyl)-methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide has also been prepared.

BACKGROUND OF THE INVENTION

6-(7-((1-Aminocyclopropyl)-methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide (AL3810), or a pharmaceutically acceptable salt (such as hydrochloride salt) thereof, has been developed as an anti-tumor agent also named as E3810 and lucitanib, see “*Journal of Cellular and Molecular Medicine* vol. 16 issue 10 October 2012. p. 2321-2330”, “*Cancer Res* February 15, 2011 vol. 71 no.4 1396-1405”.

This compound has been structurally disclosed in WO2008112408 as an angiogenesis inhibitor with few preparation methods. A new process has been disclosed in WO2010105761 with the removal of use of sodium azide. Both above disclosed processes have involved a deprotection of benzyl carbamate protected precursor by HBr/Acetic acid solution that is a strong, fuming and high corrosive acidic condition. No crystalline form has been disclosed.

SUMMARY OF THE INVENTION

Abbreviations

The following abbreviations are used and have the meaning below for ease of reference. EtOH: ethanol, MeOH: methanol, IPA: isopropanol, EtOAc: ethyl acetate, RT: room temperature, DIPEA: diisopropylethylamine, DCM: Dichloromethane, DMF: *N,N*-dimethylformamide, NMP: 1-Methyl-2-pyrrolidinone, ACN: acetonitrile, DEAD: Diethyl azodicarboxylate, DIAD: Diisopropyl azodicarboxylate, CDI: 1,1'-Carbonyldiimidazole, MeNH₂.HCl: methylamine hydrochloride, TSA.H₂O: 4-toluensulfonic acid monohydrate, DMAP: 4-*N,N*-dimethylaminopyridine, MsCl: methanesulfonyl chloride, THF: tetrahydrofuran, TFA: trifluoroacetic acid, TEA: triethylamine, DPPA: diphenyl phosphoryl azide,

eq: equivalent, g: gram, mg: milligram, ml: milliliter, min: minutes

Definitions

The term “halogen”, as used herein, unless otherwise indicated, includes fluoro, chloro, bromo or iodo. such as fluoro and chloro.

The term “halogeno-C₁-C₆alkyl”, as used herein, unless otherwise indicated, includes 1 to 6 halogen substituted alkyl, such as trifluoromethyl.

The term “C₁-C₆alkyl”, as used herein, unless otherwise indicated, includes 1 to 6 saturated monovalent hydrocarbon radicals having straight or branched moieties, including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, and the like.

The term “C₁-C₆alkoxy”, as used herein, unless otherwise indicated, includes –OC₁-C₆alkyl groups wherein C₁-C₆alkyl is as defined above, such as methoxy and ethoxy.

The term “cyano”, as used herein, unless otherwise indicated, includes –C≡N.

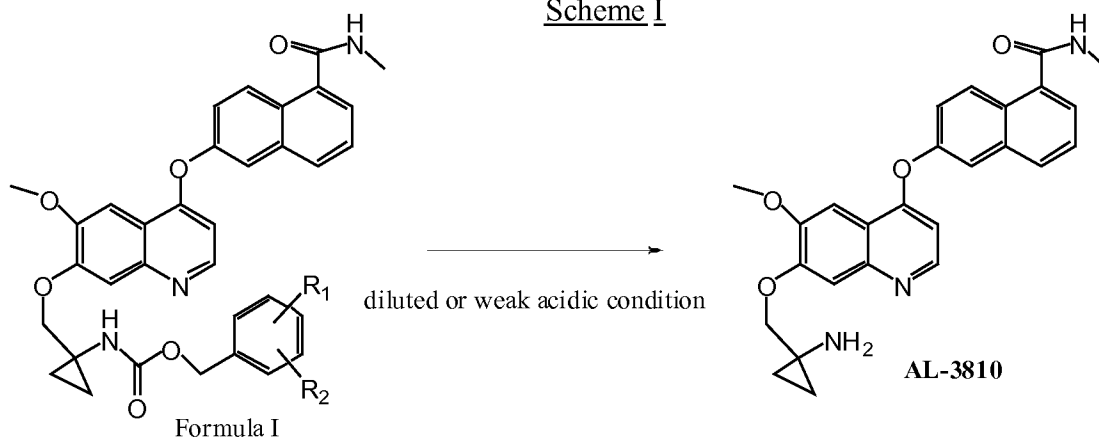
The term “nitro”, as used herein, unless otherwise indicated, includes –NO₂.

Methods of Preparation

The present invention relates to a process for preparing 6-(7-((1-aminocyclopropyl)-methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide (AL3810) by deprotection of substituted benzyl 1-((6-methoxy-4-(5-(methylcarbamoyl)naphthalen-2-yloxy)quinolin-7-yloxy)-methyl)cyclopropylcarbamate Formula I under a diluted or weak acidic condition according to Process A.

Process A

Scheme I



Wherein

R₁ is selected from H, halogen, halogeno-C₁-C₆alkyl, C₁-C₆alkyl, C₁-C₆alkoxy, cyano or nitro;

R₂ is selected from C₁-C₆alkoxy, or nitro.

The present invention relates to the compound of Formula I.

The present invention relates to the methods of preparing a compound having the Formula I.

The present invention also relates to various intermediates useful in the preparation of a compound having the Formula I, and the present invention further relates to the methods of preparing such intermediates.

The present invention relates to the methods of preparing a crystalline form of 6-(7-((1-aminocyclopropyl)-methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide.

DESCRIPTION OF DRAWINGS

Fig 1 provides a ¹H nuclear magnetic resonance (NMR) graph of a crystalline form of 6-(7-((1-aminocyclopropyl)-methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide.

Fig 2 provides a differential scanning calorimetric (DSC) graph of a crystalline form of 6-(7-((1-aminocyclopropyl)-methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide.

Fig 3 provides a thermogravimetric analysis (TGA) graph of a crystalline form of 6-(7-((1-aminocyclopropyl)-methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide.

Fig 4 provides an X-ray powder diffraction (XRPD) graph of a crystalline form of 6-(7-((1-aminocyclopropyl)-methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for preparing 6-(7-((1-aminocyclo-propyl)-methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide (AL3810) by deprotection of substituted benzyl 1-((6-methoxy-4-(5-(methylcarbamoyl)naphthalen-2-yloxy)quinolin-7-yloxy)-methyl)cyclopropylcarbamate Formula I under a diluted or weak acidic condition according to above Process A.

Wherein

R₁ is selected from H, halogen, halogeno-C₁-C₆alkyl, C₁-C₆alkyl, C₁-C₆alkoxy, cyano or nitro; preferably selected from H, C₁-C₆alkoxy, or nitro;

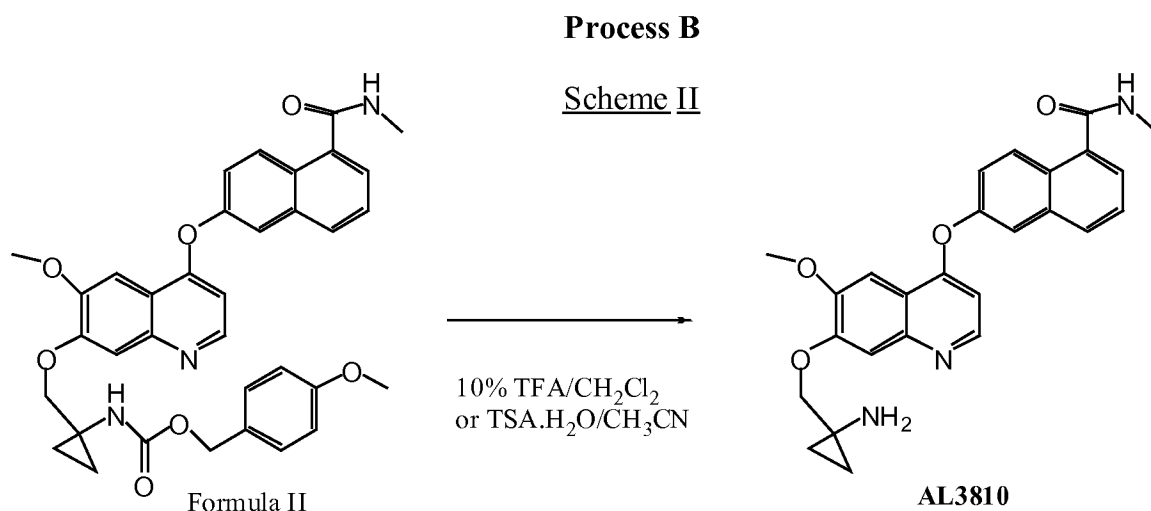
R₂ is selected from C₁-C₆alkoxy, or nitro; preferably R₂ is methoxy.

A diluted or weak acidic condition is selected from 5-50% TFA in CH₂Cl₂ or CH₃CN, 10% HCl in ethanol, 4NHCl in dioxane, HCOOH in CH₃CN or p-toluenesulfonic acid monohydrate in CH₃CN; preferably the acid is 10% TFA in CH₂Cl₂.

The total volume ratio of solvent to reactant is from 2 to 20 folds by weight. The reaction temperature is selected from 0 to 80°C and the reaction time is selected from 0.5 to 24 hours.

A preferred procedure is shown in Scheme I.

The present invention relates to a process for preparing 6-(7-((1-aminocyclo-propyl)-methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide (AL3810) by deprotection of 4-methoxybenzyl 1-((6-methoxy-4-(5-(methylcarbamoyl)naphthalen-2-yloxy)-quinolin-7-yloxy)-methyl)cyclopropylcarbamate Formula II according to Process B.



The present invention relates to the compound of Formula II.

The present invention relates to the methods of preparing a compound having the Formula II.

The present invention also relates to various intermediates useful in the preparation of a compound having the Formula II, and the present invention further relates to the methods of preparing such intermediates.

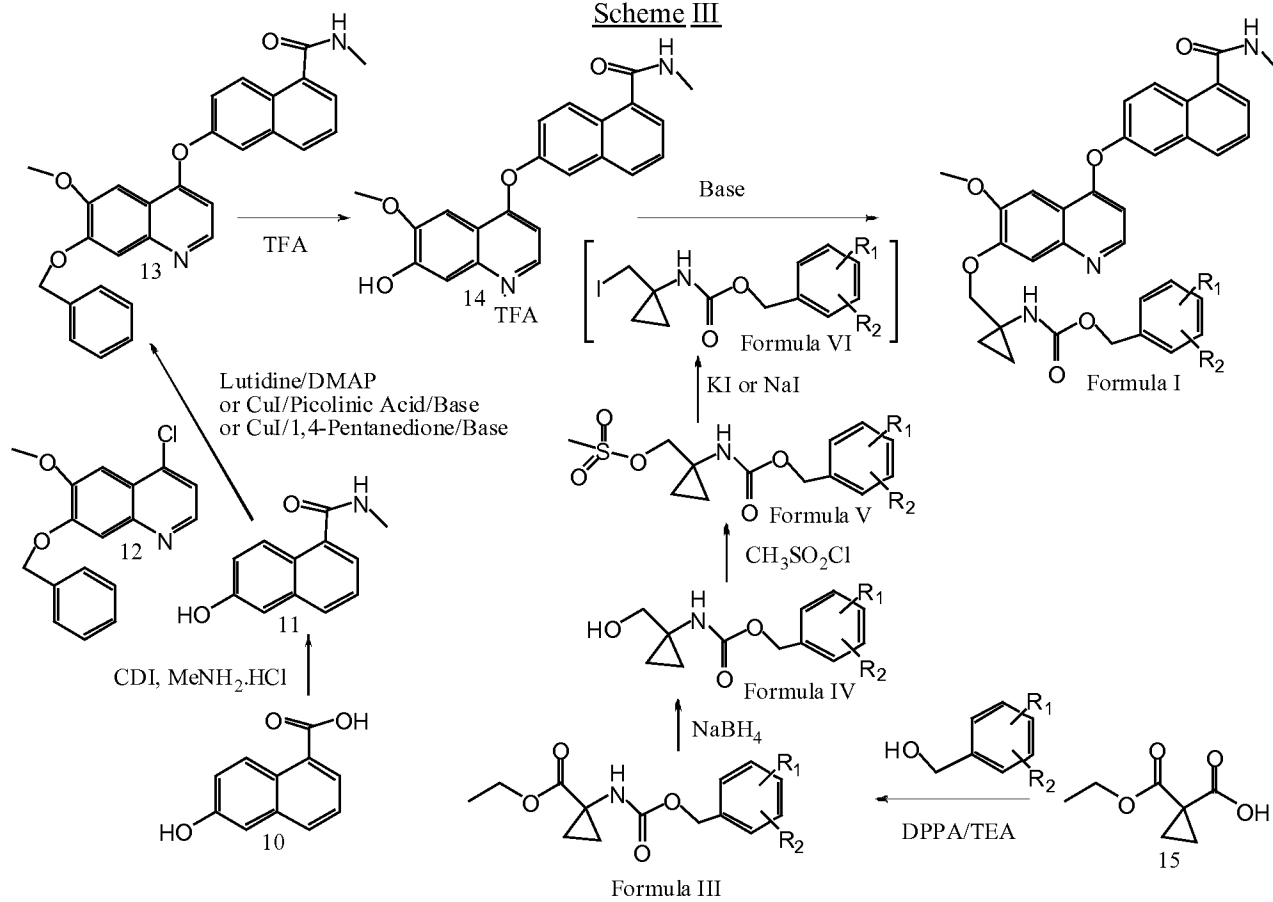
Process B of the invention comprises preparing AL3810, a preferred procedure is shown in Scheme II via:

- (a) under a condition of 10% TFA in CH_2Cl_2 , preferably at 0°C to 50°C for 3-10 hours with 5-20 folds volume of 10% TFA in CH_2Cl_2 as the solvent, or
- (b) under a condition of 2-4 eq $\text{TSA.H}_2\text{O}$, preferably at room temperature to 80°C for 10-24 hours with CH_3CN as the solvent.

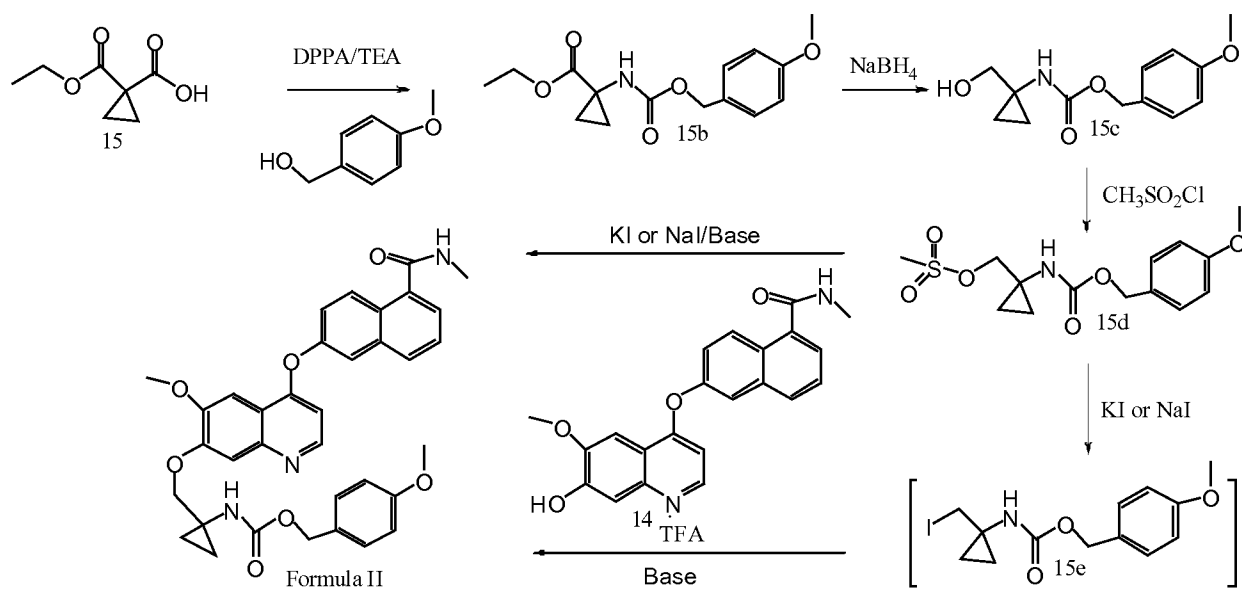
The present invention relates to a compound of Formula I or Formula II and the method preparing Formula I or Formula II according to Process C.

Process C

Scheme III



Scheme IV



Wherein

R₁ is selected from H, halogen, halogeno-C₁-C₆alkyl, C₁-C₆alkyl, C₁-C₆alkoxy, cyano or nitro;

R₂ is selected from C₁-C₆alkoxy, or nitro.

Process C of the invention comprises preparing Formula I, a preferred procedure is shown in Scheme III via the reaction between formula 14 and Formula VI using a base, such as: Na₂CO₃, Cs₂CO₃ or K₂CO₃, or between formula 14 and Formula V using a base, such as: Na₂CO₃, Cs₂CO₃ or K₂CO₃, and KI or NaI to give Formula I, preferably the reaction is at a heated condition, such as 60-120 °C in acetone, DMF or NMP.

Formula 14 can be prepared by following steps:

(a) A direct acylation of formula 10 without any protection by methylamine hydrochloride with heat pre-activation of formula 10 at the presence of CDI gives formula 11, preferably the reaction is carried out in DMF or dioxane for 2-8 hours with 1.5-4 eq CDI at a heated condition, such as at 50-120 °C,

(b) (i) Coupling formula 11 with formula 12 (WO2008112408) at 100-160 °C in lutidine, such as 1,6-lutidine, or pyridine with 1.5-3 eq DMAP for 2-24 hours gives formula 13, or

(ii) Coupling formula 11 with formula 12 under similar Ullmann reaction conditions, such as: a base, CuI and 2-picolinic acid gives formula 13, preferably a base is one of Na₂CO₃, Cs₂CO₃ and K₂CO₃, CuI amount is catalytic amount at 1-50% eq and 2-piclinic acid is at 1-50% eq. The reaction is at 100-160 °C in DMF or NMP for 10-36 hours, or

(iii) Coupling formula 11 with formula 12 under similar Ullmann reaction conditions, such as: a base, CuI and pentanedione gives formula 13, preferably a base is one of Na₂CO₃, Cs₂CO₃ and K₂CO₃, CuI amount is catalytic amount at 1-50% eq and pentanedione is 1,4-pentanedione. The reaction is at 100-160 °C in DMF or NMP for 10-36 hours.

(c) Deprotecting formula 13 with TFA gives formula 14 as a TFA salt, preferably at 60-100 °C for 0.5-8 hours.

Formula VI or Formula V can be prepared by following steps:

(d) Reacting formula 15 with R₁, R₂ substituted benzyl alcohol with DPPA and triethylamine gives Formula III, preferably using 2-4 eq DPPA and 2-4 eq TEA in toluene or dioxane at a heated condition for 10-28 hours through Curtis rearrangement.

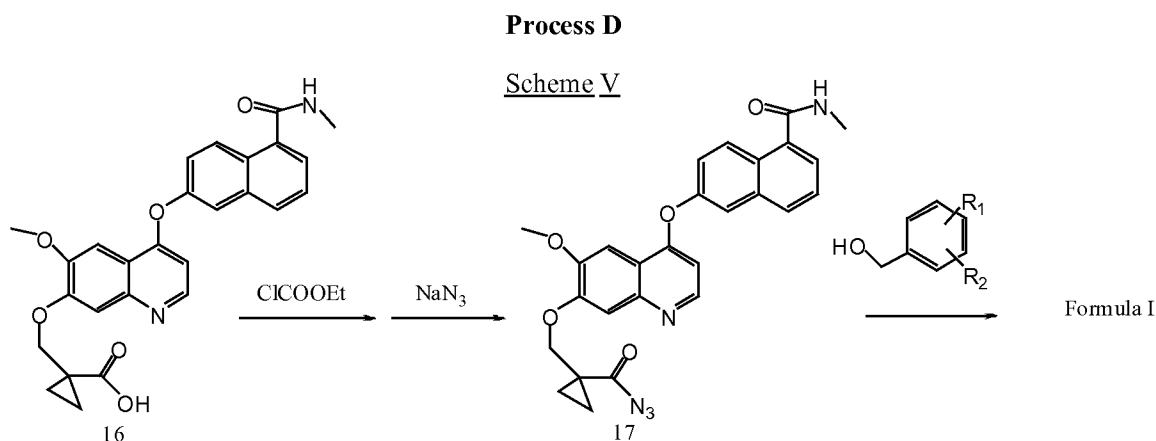
(e) Reducting Formula III by NaBH₄ gives Formula IV, preferably at reflux condition in THF with addition of methanol.

(f) Reacting Formula IV with CH₃SO₂Cl gives Formula V, preferably in a basic condition at -10 °C -25°C.

(g) Reacting Formula V with KI or NaI gives Formula VI, preferably refluxing in acetone or acetonitrile. This step can be modified as one pot reaction without isolation as Scheme III described.

Process C of the invention comprises preparing Formula II, a preferred procedure is shown in Scheme IV via the reaction between formula 14 and formula 15f using a base, such as: Na_2CO_3 , Cs_2CO_3 or K_2CO_3 , or between formula 14 and formula 15d using a base, such as: Na_2CO_3 , Cs_2CO_3 or K_2CO_3 , and KI or NaI at a heated condition, such as at 60-120 °C of one pot reaction in acetone, DMF or NMP to give Formula II.

The present invention relates to the compound of Formula I and the method preparing Formula I according to Process D.



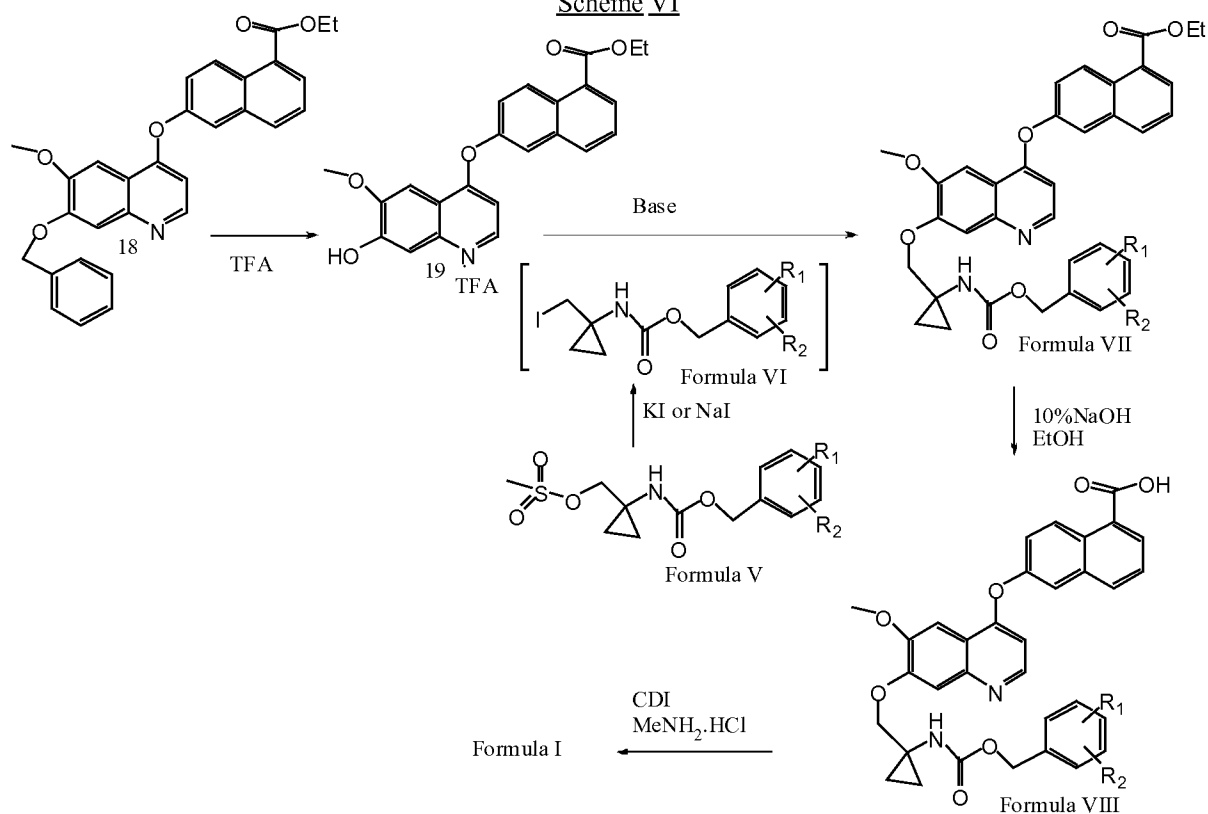
Process D of the invention comprises preparing Formula I, a preferred procedure is shown in Scheme V via acylazide formula 17 reacting with R_1 , R_2 substituted benzyl alcohol in a heated condition, preferably toluene or dioxane refluxing condition.

Formula 17 can be prepared by reacting formula 16 with ethyl chloroformate at 0°C in DMF or THF at the presence of TEA or DIPEA to form a mixed anhydride that can be reacted with NaN_3 /DMF solution at similar temperature. Formula 16 can be prepared according to WO2008112408.

The present invention relates to the compound of Formula I and the method preparing Formula I according to Process E.

Process E

Scheme VI



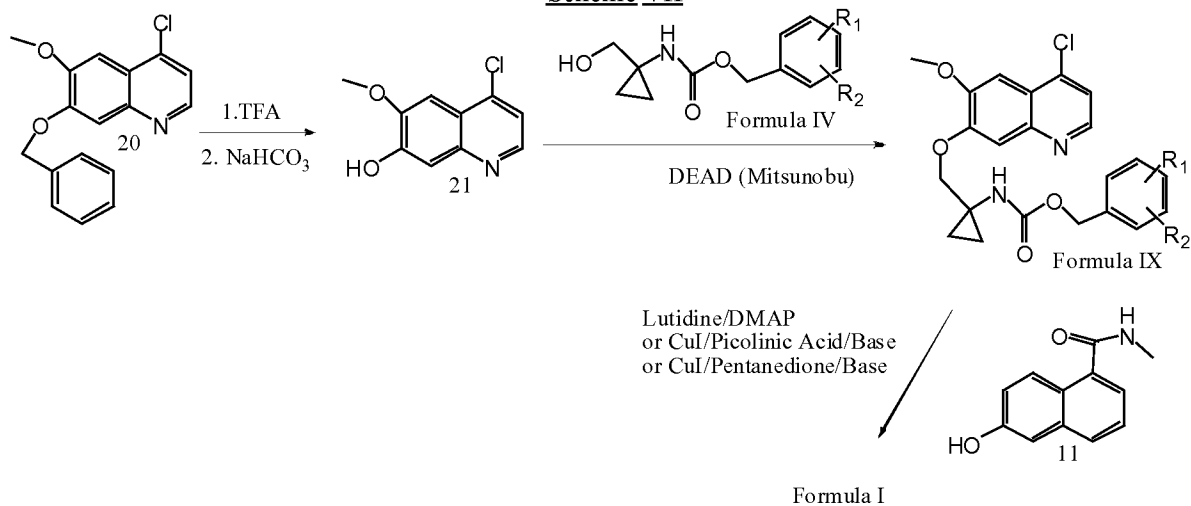
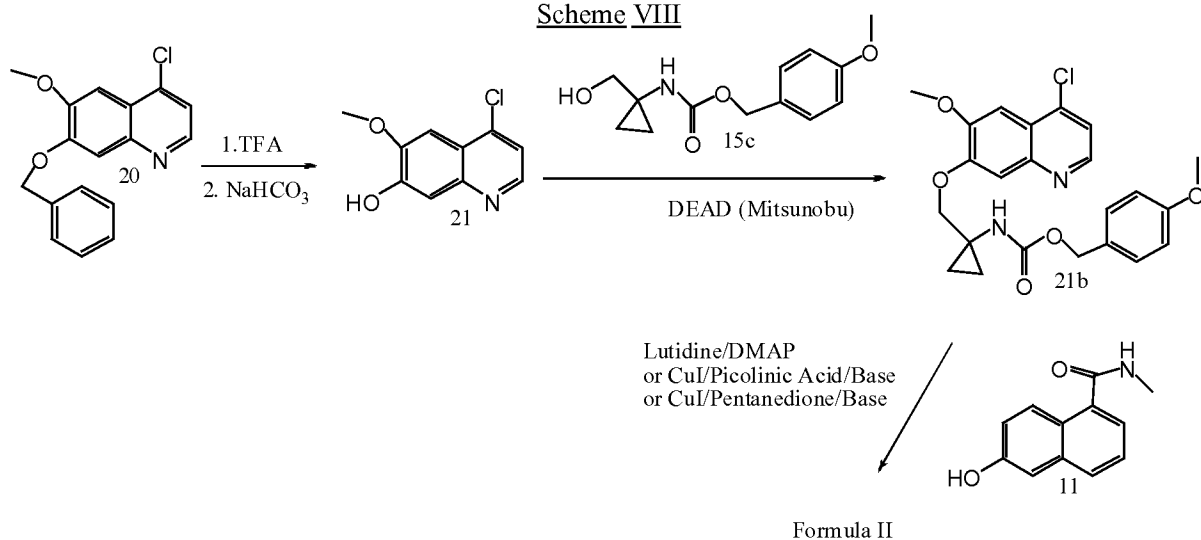
Wherein

R₁ is selected from H, halogen, halogeno-C₁-C₆alkyl, C₁-C₆alkyl, C₁-C₆alkoxy, cyano or nitro;

R₂ is selected from C₁-C₆alkoxy, or nitro.

Process E of the invention comprises preparing Formula I, a preferred procedure is shown in Scheme VI via acylation of Formula VIII with methylamine hydrochloride with heat pre-activation of formula VIII at the presence of CDI gives Formula I, preferably the reaction is carried out in DMF or dioxane for 2-8 hours with 1.5-4 eq CDI at 50-120 °C. Formula VII can be similarly prepared by reacting formula 19 with Formula VI with a base, such as: Na₂CO₃, Cs₂CO₃ or K₂CO₃, or with Formula V in one pot KI or NaI with a base, such as: Na₂CO₃, Cs₂CO₃ or K₂CO₃, as described in Scheme III. Formula VIII can be prepared by hydrolysis of Formula VII under a strong basic condition, such as a mixture of an aqueous NaOH solution and EtOH. Formula 19 can be prepared according to WO2008112408 from formula 18.

The present invention relates to the compound of Formula I or Formula II and the method preparing Formula I or Formula II according to Process F.

Process FScheme VIIScheme VIII

Wherein

R₁ is selected from H, halogen, halogeno-C₁-C₆alkyl, C₁-C₆alkyl, C₁-C₆alkoxy, cyano or nitro;

R₂ is selected from C₁-C₆alkoxy, or nitro.

Process F of the invention comprises preparing Formula I, a preferred procedure is shown in Scheme VII via:

(a) Coupling formula 11 with Formula IX at 100-160 °C in lutidine, such as 1,6-lutidine, or pyridine with 1.5-3 eq DMAP for 2-24 hours gives Formula I, or

(b) coupling formula 11 with Formula IX under similar Ullmann reaction conditions, such as: a base of Na_2CO_3 , Cs_2CO_3 and K_2CO_3 with catalytic amount of CuI (1-50% eq) and 2-piclinic acid (1-50% eq) at 100-160 °C in DMF or NMP for 10-36 hours gives Formula I, or

(c) coupling formula 11 with Formula IX under similar Ullmann reaction conditions, such as: a base of Na_2CO_3 , Cs_2CO_3 and K_2CO_3 with catalytic amount of CuI (1-50% eq) and pentanedione (1-50% eq), such as 1,4-pentanedione, at 100-160 °C in DMF or NMP for 10-36 hours gives Formula I.

Formula IX can be prepared by reacting Formula IV with formula 21 under Mitsunobu reaction condition in THF at 0-40°C for 2-24 hours by use of Mitsunobu reagents, such as: DEAD or DIAD at the presence of a Mitsunobu ligand, such as triphenylphosphine. Formula 21 can be prepared by deprotection of formula 20 with TFA at 60-100 °C for 0.5-8 hours to give a TFA salt that can be neutralized by aqueous NaHCO_3 solution, and then filtered off.

Process F of the invention comprises preparing Formula II, a preferred procedure is shown in Scheme VIII via:

(a) Coupling formula 11 with formula 21b at 100-160°C in lutidine, such as 1,6-lutidine, or pyridine with 1.5-3 eq DMAP for 2-24 hours gives Formula II, or

(b) coupling formula 11 with formula 21b under similar Ullmann reaction conditions, such as: a base of Na_2CO_3 , Cs_2CO_3 and K_2CO_3 with catalytic amount of CuI (1-50% eq) and 2-picolinic acid (1-50% eq) at 100-160 °C in DMF or NMP for 10-36 hours gives Formula II, or

(c) coupling formula 11 with formula 21b under similar Ullmann reaction conditions, such as: a base of Na_2CO_3 , Cs_2CO_3 and K_2CO_3 with catalytic amount of CuI (1-50% eq) and pentanedione (1-50% eq), such as 1,4-pentanedione, at 100-160°C in DMF or NMP for 10-36 hours gives Formula II.

Formula 21b can be prepared by reacting formula 15c with formula 21 under Mitsunobu reaction condition in THF at 0-40°C for 2-24 hours with use of Mitsunobu reagents, such as: DEAD or DIAD, at the presence of a Mitsunobu ligand, such as triphenylphosphine.

The present invention relates to the methods of preparing a crystalline form of 6-(7-((1-aminocyclopropyl)-methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide (AL3810) by recrystallizing the crude product from isopropanol to give a stable crystalline form. The crude product was dissolved at refluxing condition for 15 minutes to 3 hours in isopropanol with certain amount of active carbon. The reaction was filtered at hot condition and cooled to room temperature (optionally cooled at 4°C) for 4 to 48 hours. The precipitate was filtered and dried under high vacuum at 25°C-80°C to give a stable crystalline form with melting point at 185°C-

205°C. The crystalline form has no observable endotherm from about 40°C to about 185°C as determined by DSC. It has observable endotherm from about 185°C to about 210°C as determined by DSC. The crystalline form has a TGA thermogram that doesn't exhibit significant weight loss until at 210°C to 250°C to indicate that it is an unsolvated material. The crystalline form has 20-40 characteristic peaks on XRPD graph.

The following examples further illustrate the present invention, but should not be construed as in any way to limit its scope.

Example 1

Representation of Process A and Process B

Process for preparation of 6-(7-((1-aminocyclopropyl)methoxy)-6-methoxy-quinolin-4-yloxy)-N-methyl-1-naphthamide (AL3810)

To a stirred mixture of 4-methoxybenzyl 1-((6-methoxy-4-(5-(methylcarbamoyl)-naphthalen-2-yloxy)-quinolin-7-yloxy)methyl)cyclopropylcarbamate Formula II (150 g) in DCM (1.5 L) was added TFA (150 ml) through an additional funnel for about 30 min at RT. The reaction was stirred at 30°C for 4 hours and added into water (3 L). The aqueous layer was extracted with DCM twice (1.5L X 2) and basified with 3N NaOH (620 ml) to adjust pH 11-12 with a fine white solid precipitation. The solid was filtered and washed with water, further suction dry. The solid was dissolved into a mixture of chloroform/methanol (5 L, 3.5L/1.5L) and further washed with brine (2 L). It was dried with MgSO₄ and filtered. The solution was evaporated with EtOAc (2 L) three times to a slurry solution and cooled to RT. It was filtered and the filter cake was washed with ether, further air dried to give the crude titled compound 105g, yield: 95.9%. MS: (M+1) 444.

Example 2

Representation of Process A and Process B

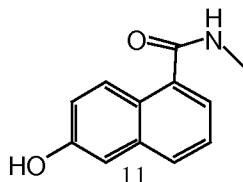
Process for preparation of 6-(7-((1-aminocyclopropyl)methoxy)-6-methoxy-quinolin-4-yloxy)-N-methyl-1-naphthamide (AL3810)

To a stirred mixture of 4-methoxybenzyl 1-((6-methoxy-4-(5-(methylcarbamoyl)naphthalen-2-yloxy)-quinolin-7-yloxy)methyl)cyclopropylcarbamate Formula II (1 g) in ACN (15 ml) was added TSA.H₂O (3 eq). The reaction was stirred at RT for 24 hours and it was basified with 3N NaOH. The solution was extracted with DCM three times, washed with brine and dried with MgSO₄. The solution then was filtered and evaporated, further recrystallized from IPA to give pure titled compound 550 mg, yield: 75%. MS: (M+1) 444.

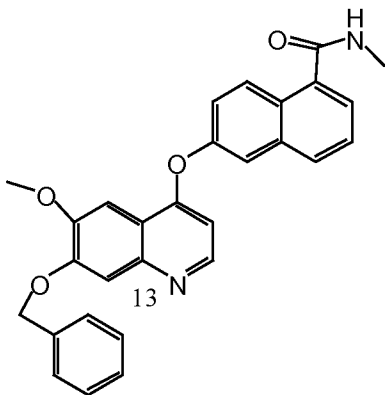
Example 3

Representation of Process C

Process for preparation of 4-methoxybenzyl 1-(((6-methoxy-4-(5-(methylcarbamoyl)-naphthalen-2-yloxy)-quinolin-7-yloxy)methyl)cyclopropylcarbamate Formula II



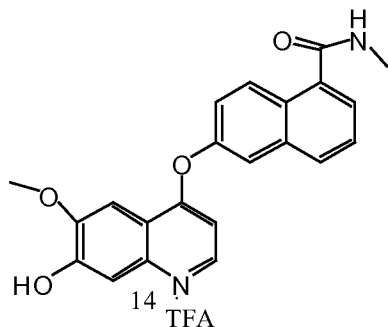
To a stirred mixture of 6-hydroxy-1-naphthoic acid (19 g, formula 10) in DMF (150 ml) was added CDI (22 g). The reaction was heated at 80°C for 30 min and CH₃NH₂.HCl (40 g) was added into the reaction. The reaction was heated for 3 hours at 80°C and cooled to RT and further diluted with water (300 ml). It was acidified with 1N HCl to pH 2-3 and extracted three times with EtOAc (150 ml). The combined organic layer was washed with saturated NaHCO₃ solution followed by water and brine. The solution was dried with Na₂SO₄ and evaporated to give the 4-hydroxy-N-methyl-naphthamide formula 11 compound 12 g.



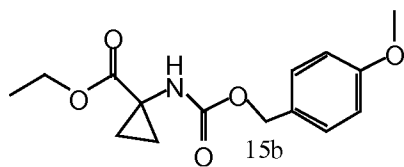
(i) To a mixture of formula 11 (6.5 g), formula 12 (6.5 g) and DMAP (5.5 g) was added 1,6-lutidine (20 ml). The reaction was stirred and heated at 135°C for 5 hours from heterogeneous to homogeneous. The reaction was cooled and IPA (35 ml) was added into the reaction under slow stirring for 2 hours at RT. The solid was filtered and further washed with IPA, dried to give the formula 13 compound 5.8 g as a gray solid, yield 57%, or

(ii) To a mixture of formula 11 (500 mg), formula 12 (500 mg), CuI (80 mg), Cs₂CO₃ (1 g) and 1-picolinic acid (150 mg) was added DMF (0.5 ml). The reaction was stirred and heated at 120°C for 24 hours. It was directed loaded on silica gel column to purify to give the formula 13 compound 370 mg, yield 48%, or

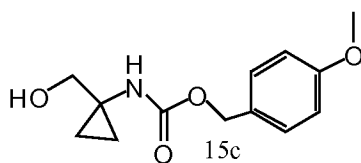
(iii) To a mixture of formula 11 (500 mg), formula 12 (500 mg), CuI (80 mg), Cs₂CO₃ (1 g) and 2,4-pentanedione (10 mg) was added DMF (0.5 ml). The reaction was stirred and heated at 120 °C for 24 hours. It was directed loaded on silica gel column to purify to give the formula 13 compound 450 mg, yield 58%.



A mixture of formula 13 (5.8 g) and TFA (12 ml) was heated at 90 °C for one hour. The reaction was evaporated under reduced pressure and triturated with EtOAc. The solid was filtered and washed with EtOAc twice to give formula 14 as a TFA salt 5.5 g, yield 95%.

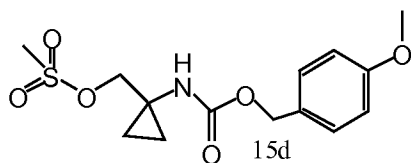


To a mixture of acid-ester (8.2 g, formula 15) and 4-methoxybenzyl alcohol (9.5 g) in toluene (50 ml) was added DPPA (15 g), the reaction was stirred and TEA was added into the reaction through an additional funnel at RT. The reaction then was refluxed for 20 hours and cooled to RT. To the reaction was added 2N NaOH (30 ml) and followed by extraction with EtOAc three times. The combined organic layer was washed with water to neutral and dried with Na₂SO₄. The solution was filtered and evaporated followed by addition of EtOAc/PE (petroleum ether) and stored in a refrigerator overnight. The crystals were filtered and washed with cold EtOAc/PE to give an off white powder. The product formula 15b was vacuum oven dried at 30 °C to give 8.0 g as ethyl 1-((4-methoxybenzyloxy)carbonylamino)cyclopropanecarboxylate (formula 15b), yield: 53%. MS: (M+1) 294.

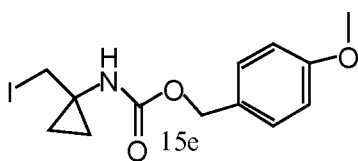


To a mixture of formula 15b (8.0 g) and THF (50 ml) was added NaBH₄ (8 g). The reaction was refluxed for 12 hours. Methanol (15 ml) was slowly added to the reaction and refluxed for 4 hour. The solvent was evaporated and cooled. NH₄Cl (6.3 g) and water (60 ml)

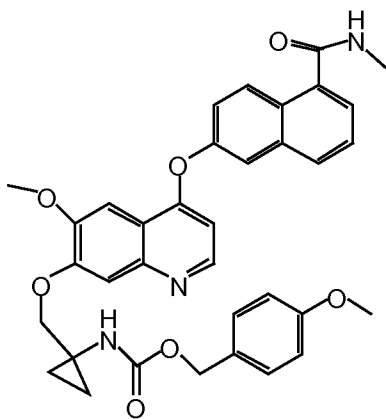
were added and stirred. The mixture was extracted with DCM three times and dried with Na_2SO_4 . The solution was filtered and evaporated followed by addition of ethanol to recrystallize overnight. The crystal was filtered to give an off white powder and further dried in oven to give the product 4.0 g as 4-methoxybenzyl 1-(hydroxymethyl)cyclopropylcarbamate (formula 15c), yield: 58%. MS: (M+1) 252.



To a stirred mixture of formula 15c (100 g) and DCM (400 ml) was added DIPEA (78g). The result solution was cooled to 0-5°C with ice/water and further stirred under this temperature for 15 min. MsCl (60g) was added via an addition funnel dropwise keeping temperature below 5°C for about 1.5 hours. After completion of addition, the reaction mixture was allowed stirring at 0-5°C for 30 min and quenched with saturated NaHCO_3 (300 ml). The solution was extracted with 200 ml DCM twice. The combined DCM layer was washed with 0.1 N HCl (400 ml) followed by brine. It was dried over Na_2SO_4 and concentrated to obtain an off-white solid 123 g of formula 15d, MS: (M+1) 330.



To a stirred mixture of formula 15d (3.3 g) and KI (3.3 g) was added acetone (30 ml), the reaction was refluxed for 2 hours and cooled. The reaction was evaporated and extracted with EtOAc (30 ml) twice and washed with brine, further evaporated under reduced pressure to give the crude product 2.3 g of formula 15e, MS: (M+1) 362.



Formula II

Method A:

To a stirred mixture of formula 14 (500 mg), formula 15d (450 mg), K₂CO₃ (400 mg) and NaI (180 mg) was added acetone (10 ml), the reaction suspension was heated to reflux for 20 hours as one pot reaction. The reaction was evaporated and purified on silica gel column to give the product 510 mg of Formula II. MS: (M+1) 608. ¹H NMR (DMSO-d₆): δ: 8.53-8.54 (m, 2H), 8.37-8.39 (d, 1H), 8.00-8.02 (d, 1H), 7.83-7.88 (m, 2H), 7.53-7.61 (m, 4H), 7.42 (s, 1H), 7.22-7.24 (d, 2H), 6.83-6.85 (d, 2H), 6.61-6.62 (d, 1H), 4.91 (s, 2H), 4.23 (s, 2H), 3.95 (s, 3H), 3.70 (s, 3H), 2.86-2.87 (d, 3H), 0.83-0.93 (d, 4H).

Method B:

To a stirred mixture of formula 14 (500 mg), formula 15e (500 mg) and K₂CO₃ (400 mg) was added acetone (10 ml), the reaction suspension was heated to reflux for 20 hours. The reaction was evaporated and purified on silica gel column to give the product 560 mg of Formula II. MS: (M+1) 608. ¹H NMR conforms to Formula II from above Method A.

Method C:

To a stirred mixture of formula 14 (33 g), formula 15d (43 g), K₂CO₃ (41 g) and KI (16.6 g) was added acetone (400 ml). The reaction suspension was heated to reflux for about 30 hr. The reaction was concentrated and to the residue was added water (700 ml). The result suspension was stirred for 1 hour slowly to get a brown solid. The solid was filtered and rinsed with water twice further rinsed with ethanol. The crude product was dried in oven at 40⁰C for 2-3 hours. The product was purified with IPA by recrystallization to give 29 g of Formula II. MS: (M+1) 608. ¹H NMR conforms to Formula II from above Method A.

Example 4

Representation of Process D

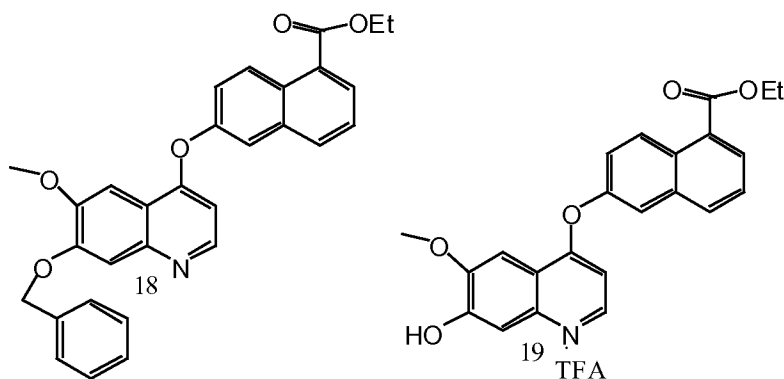
Process for preparation of 4-methoxybenzyl 1-((6-methoxy-4-(5-(methylcarbamoyl)naphthalen-2-yloxy)-quinolin-7-yloxy)methyl)cyclopropyl-carbamate Formula II

A mixture of 2-(1-((6-methoxy-4-(5-(methylcarbamoyl)naphthalen-2-yloxy)quinolin-7-yloxy)methyl)cyclopropyl)acetyl azide formula 17 (WO2008112408, 150 mg) and 4-methoxybenzyl alcohol (0.15 ml) in toluene (10 ml) was refluxed for 1.5 hour. The reaction was evaporated and purified with silica gel column to give the titled product. Mass: (M + 1), 608

Example 5

Representation of Process E

Process for preparation of 4-methoxybenzyl 1-((6-methoxy-4-(5-(methylcarbamoyl)naphthalen-2-yloxy)-quinolin-7-yloxy)methyl)cyclopropylcarbamate Formula II



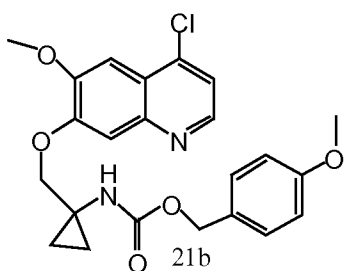
A mixture of 6-Hydroxy-1-naphthoic acid (1 g) and H_2SO_4 (0.2ml) in EtOH (25 ml) was refluxed overnight and evaporated, followed by dissolving into EtOAc. The solution was washed with water, 1N NaHCO_3 solution and brine, further dried by Na_2SO_4 . The solution was evaporated to give crude ethyl 6-hydroxy-1-naphthoate 0.9 g which was reacted with formula 12 at similar preparation conditions to formula 13 of Example 3 to give the above product of formula 18. Formula 19 was similarly prepared to formula 14 of Example 3.

A reaction between formula 19 and formula 15d similarly to the preparation of Formula II of Method A gave ethyl 6-(6-methoxy-7-((1-((4-methoxybenzyloxy)carbonylamino)cyclopropyl)methoxy)quinolin-4-yloxy)-1-naphthoate which was hydrolyzed with 10% NaOH in EtOH at RT to give 6-(6-methoxy-7-((1-((4-methoxybenzyloxy)carbonylamino)cyclopropyl)methoxy)-quinolin-4-yloxy)-1-naphthoic acid. The resulting acid was acylated similarly to the preparation of formula 11 of Example 3 with $\text{CH}_3\text{NH}_2 \cdot \text{HCl}$ under the heat pre-activation at the presence of CDI to give the titled product.

Example 6

Representation of Process F

Process for preparation of 4-methoxybenzyl 1-((6-methoxy-4-(5-(methylcarbamoyl)naphthalen-2-yloxy)-quinolin-7-yloxy)methyl)cyclopropylcarbamate Formula II



To a mixture of 4-chloro-6-methoxyquinolin-7-ol (formula 21, 5.2g), 1-((4-methoxybenzyloxy)carbonylamino)cyclopropanecarboxylate (formula 15b, 8.3g) and triphenylphosphine (9.8 g) in THF (250 ml) was added DEAD (6.5 g) dropwise at RT in 1.5 hours, the reaction was further stirred for 20 hours at RT and evaporated. The residue was purified with silica gel column to give the 4-methoxybenzyl 1-((4-chloro-6-methoxy-quinolin-7-yloxy)methyl)cyclopropylcarbamate formula 21b product 6.5 g.

The titled compound of Formula II was then similarly prepared by using formula 21b to react with 4-hydroxy-N-methyl-naphthamide formula 11 according to formula 13 of Example 3.

Example 7

Preparation of the crystalline form of 6-(7-((1-aminocyclopropyl)methoxy)-6-methoxy-quinolin-4-yloxy)-N-methyl-1-naphthamide (AL3810)

The crude product from Example 1 (105 g) was mixed with isopropanol (2.5 L) and active carbon (5 g), the mixture was heated to reflux for 0.5 hour to dissolve all crude product followed by filtration while it was hot, then the filtrate was refluxed again for 10 minutes and it was cooled to room temperature overnight under a slow stirring condition. The precipitate was filtered and washed with ethyl ether (500 ml x 2), further dried under high vacuum at 80°C to give the pure product (85 g) with melting point at 192°C-196°C.

H1 NMR shown in Fig 1.

DSC shown in Fig 2 having observable endotherm from about 193°C-202°C

TGA shown in Fig 3 demonstrating as an unsolvated material with weight loss at about 230°C

XRPD shown in Fig 4 having pattern comprising thirty three characteristic peaks with all intensity and intensity% expressed in d values and angles as follows:

NO.	Angle	d value	NO.	Angle	d value	NO.	Angle	d value
1	10.429	8.476	14	20.545	4.320	27	29.137	3.062
2	11.811	7.487	15	21.214	4.185	28	30.331	2.944
3	12.287	7.198	16	21.843	4.066	29	31.172	2.867
4	13.293	6.655	17	22.058	4.026	30	31.803	2.811
5	13.658	6.478	18	22.682	3.917	31	32.613	2.743
6	15.778	5.612	19	23.453	3.790	32	37.959	2.369
7	16.186	5.472	20	24.065	3.695	33	39.470	2.281
8	16.682	5.310	21	24.708	3.600			
9	17.102	5.181	22	25.072	3.549			
10	17.907	4.949	23	25.435	3.499			
11	18.631	4.759	24	25.886	3.439			
12	19.027	4.661	25	27.929	3.192			
13	19.847	4.470	26	28.420	3.138			

And

H1 NMR shown in Fig 1.

DSC shown in Fig 2 having observable endotherm from about 193⁰C-202⁰C

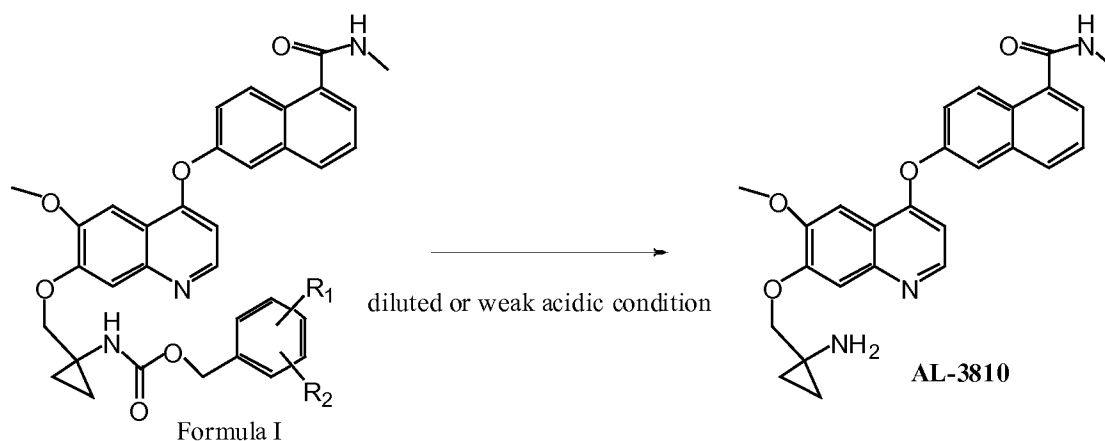
TGA shown in Fig 3 demonstrating as an unsolvated material with weight loss at about 230⁰C

XRPD shown in Fig 4 having pattern compromising characteristic peaks with intensity% greater than 10% expressed in d values and angles as follows:

NO.	Angle	d value	NO.	Angle	d value	NO.	Angle	d value
1	10.429	8.476	15	21.214	4.185			
			16	21.843	4.066			
4	13.293	6.655	17	22.058	4.026			
			18	22.682	3.917	31	32.613	2.743
6	15.778	5.612	19	23.453	3.790			
7	16.186	5.472	20	24.065	3.695	33	39.470	2.281
			21	24.708	3.600			
			22	25.072	3.549			
10	17.907	4.949	23	25.435	3.499			
12	19.027	4.661	25	27.929	3.192			
13	19.847	4.470						

What is claimed is:

1. A process for preparing 6-(7-((1-aminocyclopropyl)methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide (AL3810), or a pharmaceutically acceptable salt thereof, by deprotection of substituted benzyl 1-((6-methoxy-4-(5-(methylcarbamoyl)naphthalen-2-yloxy)quinolin-7-yloxy)methyl)cyclopropylcarbamate Formula I under a diluted or weak acidic condition according to following chemistry scheme:



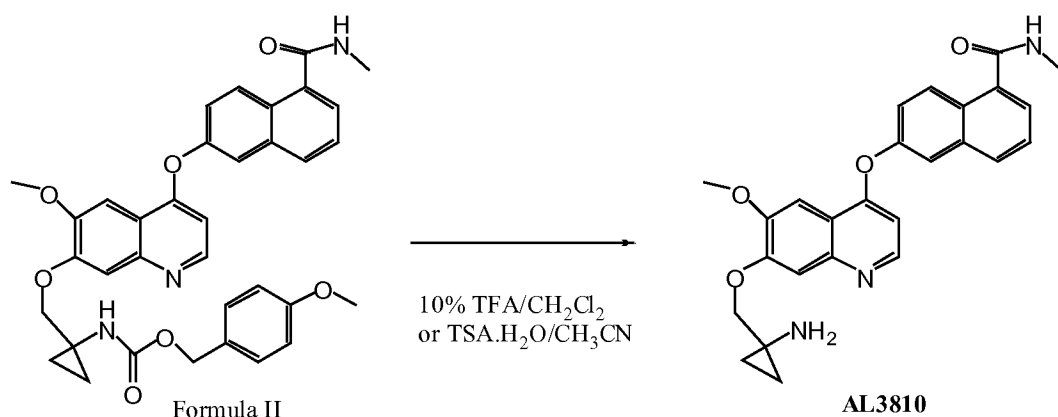
Wherein

R₁ is selected from H, halogen, halogeno-C₁-C₆alkyl, C₁-C₆alkyl, C₁-C₆alkoxy, cyano or nitro; preferably selected from H, C₁-C₆alkoxy, or nitro;

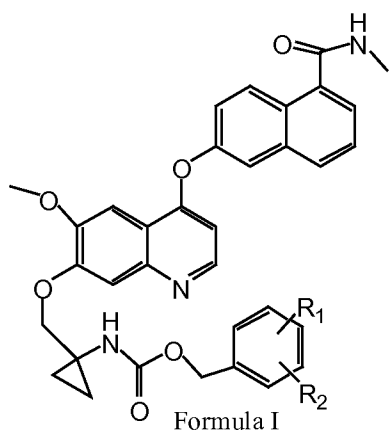
R₂ is selected from C₁-C₆alkoxy, or nitro; preferably R₂ is methoxy.

A diluted or weak acidic condition is selected from 5-50% TFA in CH₂Cl₂ or CH₃CN, 10% HCl in ethanol, 4N HCl in dioxane, HCOOH in CH₃CN or p-toluenesulfonic acid monohydrate in CH₃CN.

2. A process according to claim 1 for preparing 6-(7-((1-aminocyclo-propyl)methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide (AL3810) , or a pharmaceutically acceptable salt thereof, by deprotection of 4-methoxybenzyl 1-((6-methoxy-4-(5-(methylcarbamoyl)naphthalen-2-yloxy)-quinolin-7-yloxy)methyl)cyclo-propylcarbamate Formula II, under a condition of 10% TFA in CH₂Cl₂ or a condition of 2-4 eq TSA.H₂O in CH₃CN, according to following chemistry scheme:



3. A compound of Formula I



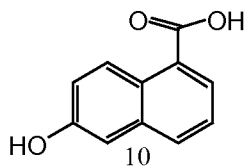
Wherein

R₁ is selected from H, halogen, halogeno-C₁-C₆alkyl, C₁-C₆alkyl, C₁-C₆alkoxy, cyano or nitro;

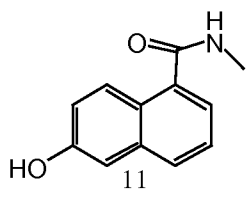
R₂ is selected from C₁-C₆alkoxy, or nitro.

4. A method of preparing a compound having Formula I of claim 3 comprising:

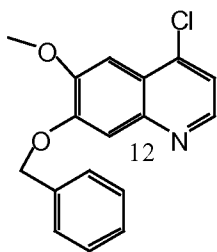
(a) treating formula 10



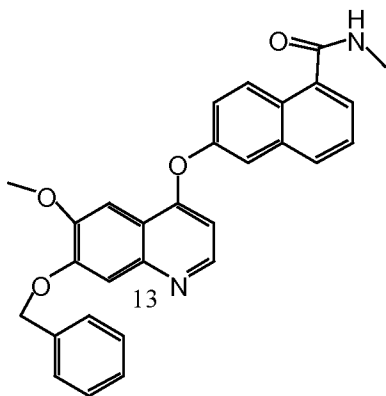
at 50-120°C with CDI and followed by reacting with CH₃NH₂.HCl to give formula 11



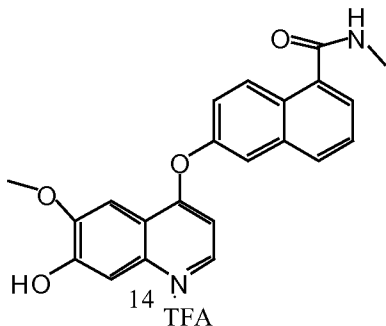
(b) treating formula 11 with formula 12



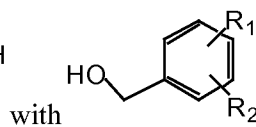
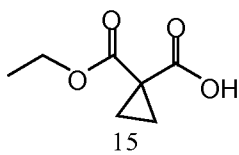
- i) at 100-160 °C in lutidine at the presence of DMAP to give formula 13, or;
 ii) at 100-160 °C in DMF or NMP with CuI and 2-picolinic acid at the presence of base to give formula 13, or;
 iii) at 100-160 °C in DMF or NMP with CuI and pentanedione at the presence of base to give formula 13



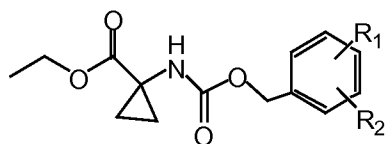
- (c) deprotecting benzyl group by TFA in a heated condition to give formula 14



- (d) treating formula 15

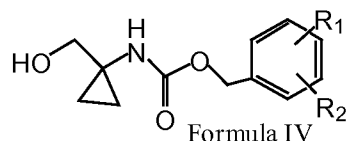


- and DPPA at a heated condition and the presence of triethylamine to give Formula III



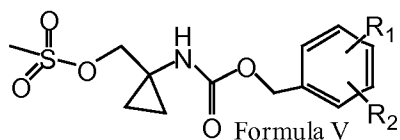
Formula III

(e) reducing Formula III by NaBH_4 to give Formula IV



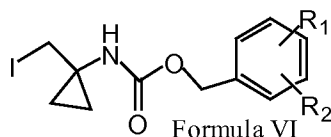
Formula IV

(f) treating Formula IV with $\text{CH}_3\text{SO}_2\text{Cl}$ to give Formula V



Formula V

(g) treating Formula V with KI or NaI to give Formula VI



Formula VI

(h)

i) treating formula 14 with Formula VI in acetone, DMF or NMP with Na_2CO_3 , Cs_2CO_3 or K_2CO_3 at a heated condition to give Formula I, or;

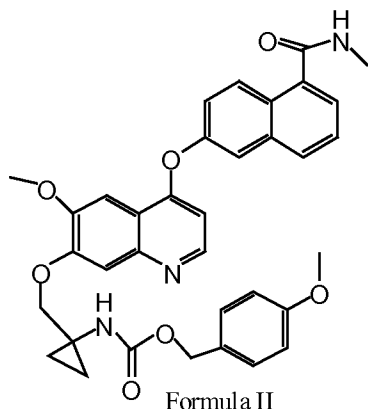
ii) treating formula 14 with Formula V in acetone, DMF or NMP with Na_2CO_3 , Cs_2CO_3 or K_2CO_3 , at the presence of KI or NaI at a heated condition to give Formula I

Wherein

R_1 is selected from H, halogen, halogeno- C_1 - C_6 alkyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, cyano or nitro;

R_2 is selected from C_1 - C_6 alkoxy, or nitro.

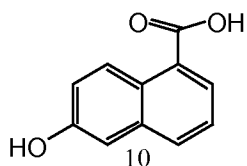
5. A compound of Formula II



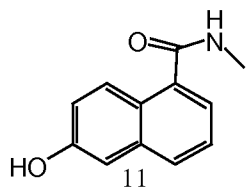
Formula II

6. A method of preparing a compound having Formula II of claim 5 comprising:

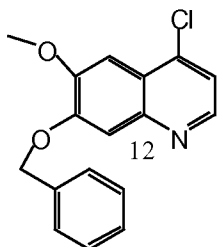
(a) treating formula 10



at 50-120°C with CDI and followed by reacting with $\text{CH}_3\text{NH}_2\cdot\text{HCl}$ to give formula 11



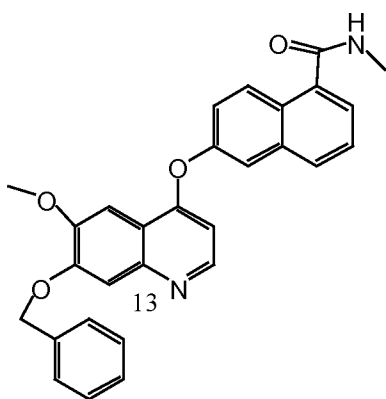
(b) treating formula 11 with formula 12



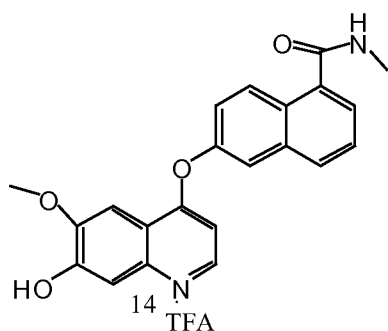
i) at 100-160 °C in lutidine at the presence of DMAP to give formula 13, or;

ii) at 100-160 °C in DMF or NMP with CuI and 2-picolinic acid at the presence of base to give formula 13, or;

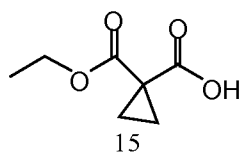
iii) at 100-160 °C in DMF or NMP with CuI and 2,4-pentanedione at the presence of base to give formula 13



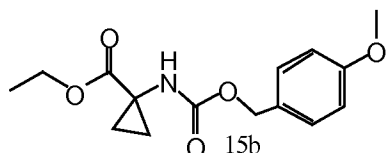
(c) deprotecting benzyl group by TFA in a heated condition to give formula 14



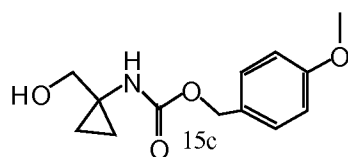
(d) treating formula 15



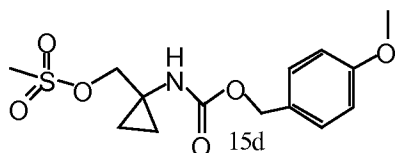
with 4-methoxybenzylalcohol and DPPA at a heated condition and the presence of triethylamine to give formula 15b



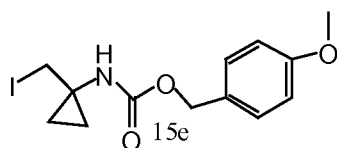
(e) reducing formula 15b by NaBH_4 to give formula 15c



(f) treating formula 15c with $\text{CH}_3\text{SO}_2\text{Cl}$ to give formula 15d



(g) treating formula 15d with KI or NaI to give formula 15e

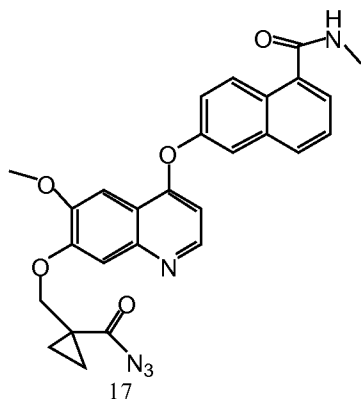


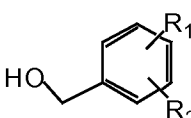
(h)

i) treating formula 14 with formula 15e in acetone, DMF or NMP with Na_2CO_3 , Cs_2CO_3 or K_2CO_3 at a heated condition to give Formula II, or;

ii) treating formula 14 with formula 15d in acetone, DMF or NMP with Na_2CO_3 , Cs_2CO_3 or K_2CO_3 at the presence of KI or NaI at a heated condition to give Formula II.

7. A method of preparing a compound having Formula I of claim 3 comprising to react formula 17



with  at a heated condition.

Wherein

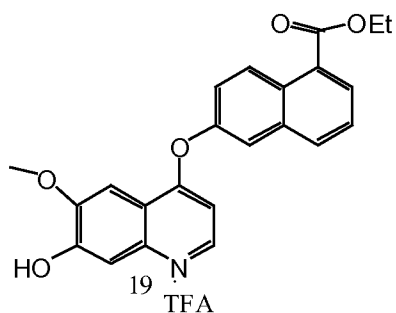
R_1 is selected from H, halogen, halogeno- C_1 - C_6 alkyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, cyano or nitro;

R_2 is selected from C_1 - C_6 alkoxy, or nitro.

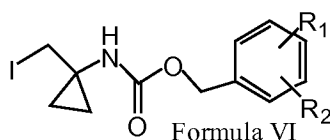
8. A method of preparing a compound having Formula II of claim 5 comprising to react formula 17 with 4-methoxybenzylalcohol in a refluxing toluene condition.

9. A method of preparing a compound having Formula I of claim 3 comprising:

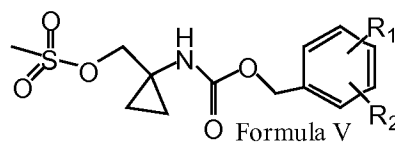
(a) treating formula 19



with Formula VI

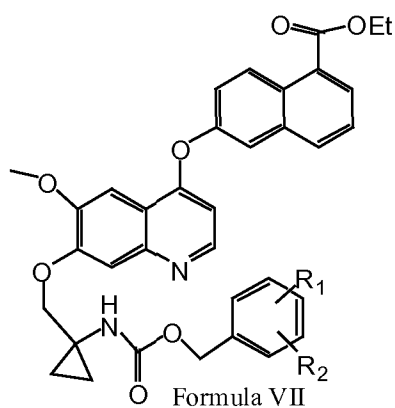


with a base at a heated condition to give Formula VII, or

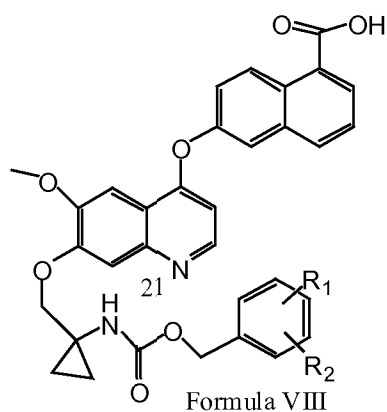


with Formula V

with a base and KI or NaI at a heated condition to give Formula VII



(b) hydrolyzing Formula VII under a strong basic condition to give Formula VIII



(c) acylating Formula VIII with $\text{CH}_3\text{NH}_2\cdot\text{HCl}$ under heat pre-activation reaction with CDI to give Formula I.

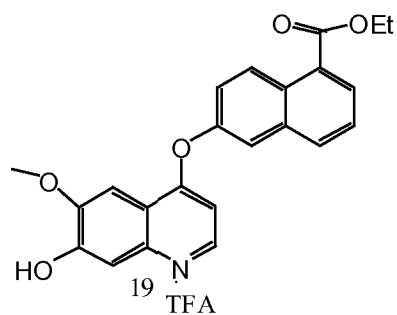
Wherein

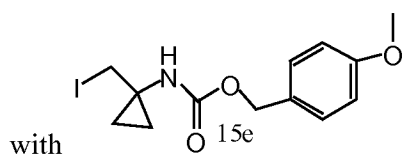
R_1 is selected from H, halogen, halogeno- $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, cyano or nitro;

R_2 is selected from $\text{C}_1\text{-C}_6$ alkoxy, or nitro.

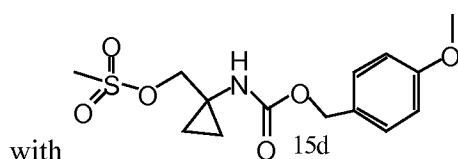
10. A method of preparing a compound having Formula II of claim 5 comprising:

(a) treating formula 19





with K_2CO_3 at a heated condition in acetone or,



with K_2CO_3 and KI at a heated condition in acetone to give

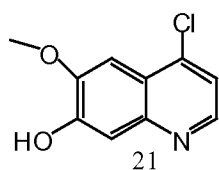
ethyl 6-(6-methoxy-7-((1-((4-methoxybenzyloxy)carbonylamino)-cyclopropyl)methoxy)quinolin-4-yloxy)-1-naphthoate

(b) hydrolyzing above ester with 10% NaOH in EtOH to give 6-(6-methoxy-7-((1-((4-methoxybenzyloxy)carbonylamino)cyclopropyl)methoxy)quinolin-4-yloxy)-1-naphthoic acid.

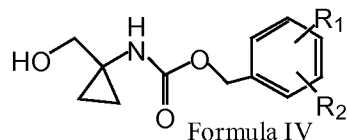
(c) acylating above naphthoic acid under heat pre-activation reaction with CDI followed by addition of $CH_3NH_2 \cdot HCl$ to give Formula II

11. A method of preparing a compound having Formula I of claim 3 comprising:

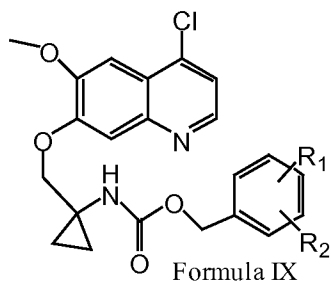
(a) treating formula 21



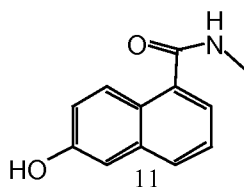
with Formula IV



by Mitsunobu reaction with DEAD or DIAD at the presence of a Mitsunobu ligand to give Formula IX



(b) treating formula IX with formula 11



- i) at 100-160 °C in lutidine at the presence of DMAP to give Formula I, or;
- ii) at 100-160 °C in DMF or NMP with CuI and 2-picolinic acid at the presence of base to give Formula I, or;
- iii) at 100-160 °C in DMF or NMP with CuI and pentanedione at the presence of base to give Formula I.

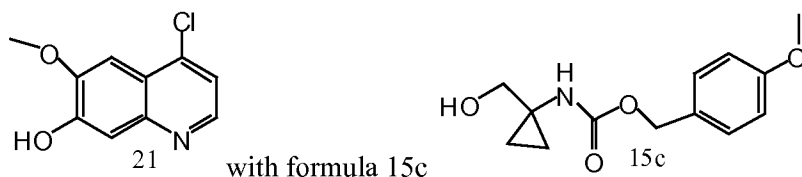
Wherein

R₁ is selected from H, halogen, halogeno-C₁-C₆alkyl, C₁-C₆alkyl, C₁-C₆ alkoxy, cyano or nitro;

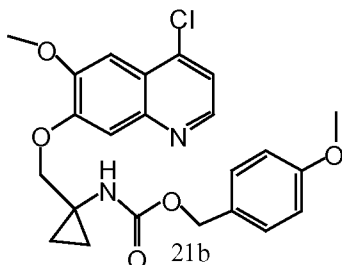
R₂ is selected from C₁-C₆ alkoxy, or nitro.

12. A method of preparing a compound having Formula II of claim 5 comprising:

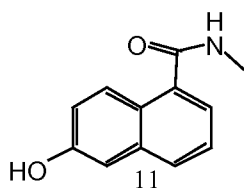
(a) treating formula 21



by Mitsunobu reaction with DEAD at the presence of triphenylphosphine to give formula 21b



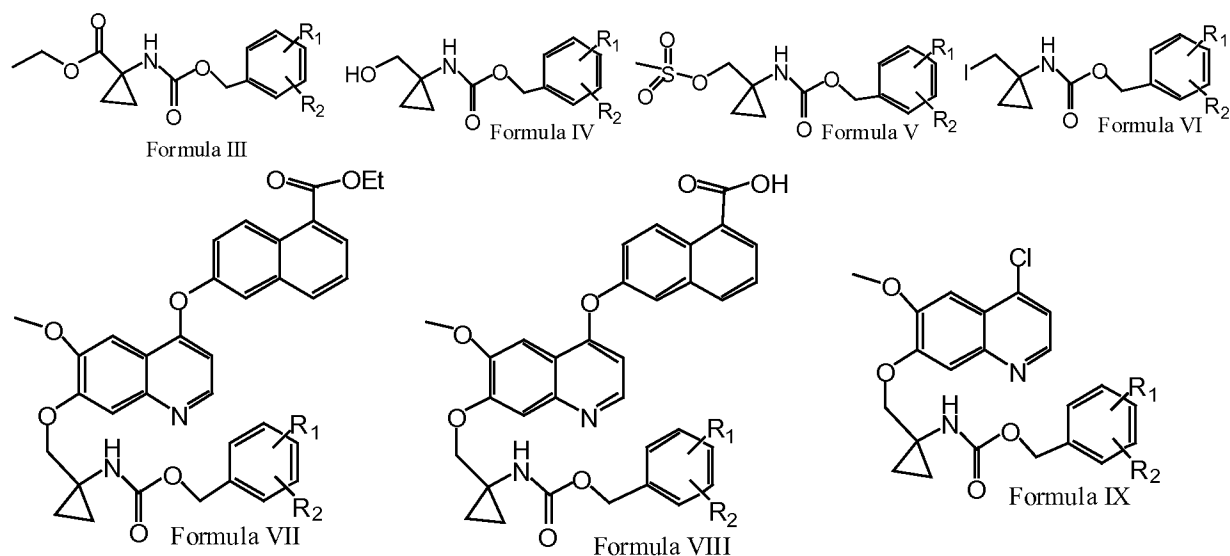
(b) treating formula 21b with formula 11



- i) at 120 °C in lutidine at the presence of DMAP to give Formula II, or;
- ii) at 120 °C in DMF or NMP with CuI and 2-picolinic acid at the presence of a base to give Formula II, or;

iii) at 120 °C in DMF or NMP with CuI and 2,4-pentanedione at the presence of a base to give Formula II.

13. An intermediate compound selected from the following compounds having Formula III, Formula IV, Formula V, Formula VI, Formula VII, Formula VIII or Formula IX:

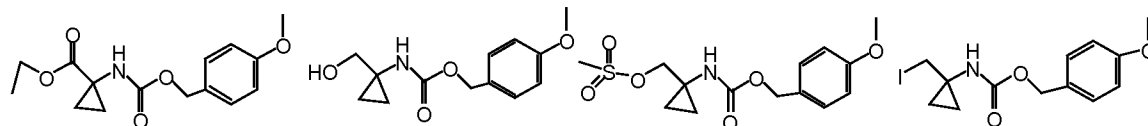


Wherein

R₁ is selected from H, halogen, halogeno-C₁-C₆alkyl, C₁-C₆alkyl, C₁-C₆alkoxy, cyano or nitro;

R₂ is selected from C₁-C₆alkoxy, or nitro.

14. An intermediate compound selected from the following compounds:



ethyl 6-(6-methoxy-7-((1-((4-methoxybenzyloxy)carbonylamino)cyclopropyl)methoxy)-quinolin-4-yloxy)-1-naphthoate

6-(6-methoxy-7-((1-((4-methoxybenzyloxy)carbonylamino)cyclopropyl)methoxy)-quinolin-4-yloxy)-1-naphthoic acid

4-methoxybenzyl 1-((4-chloro-6-methoxyquinolin-7-yloxy)methyl)cyclopropylcarbamate

15. A crystalline form of 6-(7-((1-aminocyclopropyl)methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide exhibiting at least one of

a melting point at 185 °C-205 °C;

a no observable endotherm DSC from about 40 °C to about 185 °C;

an observable endotherm DSC from about 185 °C to about 210 °C;

a TGA themogram that doesn't exhibit significant weight loss until at 210 °C to 250 °C;

a XRPD graph having 20-40 characteristic peaks.

16. A crystalline form of 6-(7-((1-aminocyclopropyl)methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide according claim 15 exhibiting at least one of a melting point at 192⁰C-196⁰C ; a DSC having observable endotherm from about 193⁰C-202⁰C; a TGA demonstrating as an unsolvated material with weight loss at about 230⁰C; a XRPD having pattern comprising characteristic peaks with all intensity% expressed in d values and angles as follows:

NO.	Angle	d value	NO.	Angle	d value	NO.	Angle	d value
1	10.429	8.476	14	20.545	4.320	27	29.137	3.062
2	11.811	7.487	15	21.214	4.185	28	30.331	2.944
3	12.287	7.198	16	21.843	4.066	29	31.172	2.867
4	13.293	6.655	17	22.058	4.026	30	31.803	2.811
5	13.658	6.478	18	22.682	3.917	31	32.613	2.743
6	15.778	5.612	19	23.453	3.790	32	37.959	2.369
7	16.186	5.472	20	24.065	3.695	33	39.470	2.281
8	16.682	5.310	21	24.708	3.600			
9	17.102	5.181	22	25.072	3.549			
10	17.907	4.949	23	25.435	3.499			
11	18.631	4.759	24	25.886	3.439			
12	19.027	4.661	25	27.929	3.192			
13	19.847	4.470	26	28.420	3.138			

17. A crystalline form of 6-(7-((1-aminocyclopropyl)methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide according claim 15 exhibiting at least one of a melting point at 192⁰C-196⁰C ; a DSC having observable endotherm from about 193⁰C-202⁰C; a TGA demonstrating as an unsolvated material with weight loss at about 230⁰C; a XRPD having pattern comprising characteristic peaks with intensity% greater than 10% expressed in d values and angles as follows:

NO.	Angle	d value	NO.	Angle	d value	NO.	Angle	d value
1	10.429	8.476	15	21.214	4.185			
			16	21.843	4.066			
4	13.293	6.655	17	22.058	4.026			
			18	22.682	3.917	31	32.613	2.743
6	15.778	5.612	19	23.453	3.790			
7	16.186	5.472	20	24.065	3.695	33	39.470	2.281
			21	24.708	3.600			
			22	25.072	3.549			
10	17.907	4.949	23	25.435	3.499			
12	19.027	4.661	25	27.929	3.192			
13	19.847	4.470						

18. A crystalline form of 6-(7-((1-aminocyclopropyl)methoxy)-6-methoxyquinolin-4-yloxy)-N-methyl-1-naphthamide according claim 15 is recrystallized from isopropanol.