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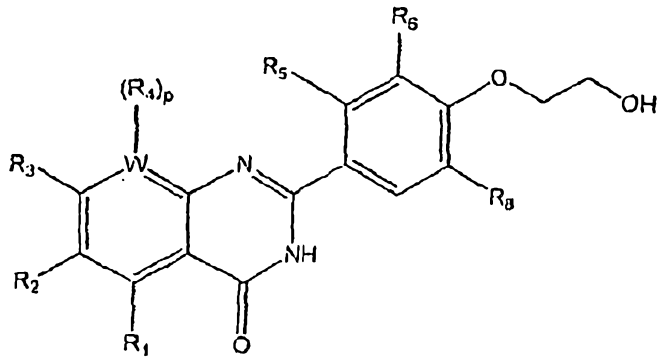
(54) **Title**: METHODS OF PREPARING QUINAZOLINONE DERIVATIVES



Formula I

(57) **Abstract**: The present disclosure relates to methods for preparing compounds, which are useful for regulating the expression of apolipoprotein A-I (ApoA-I), and in the treatment and prevention of cardiovascular disease and related disease states, including cholesterol- or lipid-related disorders, such as, for example, atherosclerosis.

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METHODS OF PREPARING QUINAZOLINONE DERIVATIVES

[001] This application claims the benefit of U.S. Provisional Application No. 61/075,952, filed June 26, 2008, which is incorporated herein by reference in its entirety.

[002] The present disclosure relates to methods of preparing quinazolinone derivatives, which are useful for regulating the expression of apolipoprotein A-I (ApoA-I) and in the treatment and prevention of cardiovascular disease and related disease states, such as, for example, atherosclerosis.

[003] Epidemiologic data demonstrate an inverse relationship between circulating levels of high-density lipoprotein cholesterol (HDL-C) and the incidence of clinically significant atherosclerosis. Each 1 mg/dL increment in the HDL-C serum level is associated with a 2-3% decrement in cardiovascular risk; a 1% reduction in LDL-C reduced cardiovascular risk by 2% (Gordon *et al.* (1997) *Am. J. Med.* **62**, 707-714). Experimental evidence further supports the protective effect of HDL-C against cardiovascular disease. For example, in subjects with low HDL-C, administration of gemfibrozil resulted in a 6% increase in the HDL-C level and a corresponding 22% reduction of the coronary heart disease (CHD) risk (Rubins *et al.* (1999) *N. Engl. J. Med.* **341**, 410-418). Observations in genetic disorders associated with low HDL-C due to reduced ApoA-I expression also indicate a link between elevated risk of CHD and low HDL-C.

[004] HDL-C appears to exert its anti-atherogenic effect by mediating reverse cholesterol transport (RCT), in which cholesterol is recruited from peripheral tissues and transported to the liver. In addition, HDL-C also possesses pleiotropic biological properties that contribute to its antiatherogenic effects, such as anti-inflammatory, anti-oxidant, and anti-thrombotic activities. HDL-C exists in two main forms, one

containing both apolipoprotein A-I (ApoA-I) and apolipoprotein A-II (ApoA-II), and the other containing ApoA-I without ApoA-II (Schultz *et al.* (1993) *Nature* **365**, 762-764). The cardioprotective effect of HDL-C is primarily, but not exclusively, attributable to ApoA-I.

[005] Clinical and experimental data suggest that the production of ApoA-I is an important determinant of circulating HDL-C. For example, persons with familial hyperalphalipoproteinemia (elevated ApoA-I) appear to be protected from atherosclerosis, while those deficient in ApoA-I (hypoalphalipoproteinemia) show accelerated cardiovascular disease. In addition, various experimental manipulations to increase production of ApoA-I are associated with reduced atherogenicity. For example, human ApoA-I is protective in transgenic animal models (Shah *et al.* (1998) *Circulation* **97**, 780-785; Rubin *et al.* (1991) *Nature* **353**, 265-267), and treatment with ApoA-I_{Milano} prevents atherosclerotic lesions and leads to regression of atherosclerotic plaques in human patients (Nissen *et al.* (2003) *JAMA* **290**, 2292-2300). Further lines of research demonstrate that ApoA-I plays a role in enhancing reverse cholesterol transport, attenuating oxidative stress, increasing paraoxonase activity, enhancing anticoagulant activity, and increasing anti-inflammatory activity (Andersson (1997) *Curr. Opin. Lipidol.* **8**, 225-228). Accordingly, ApoA-I is an attractive target for therapeutic intervention.

[006] Currently available therapeutic agents that increase the plasma concentration of ApoA-I, for example, recombinant ApoA-I or peptides that mimic ApoA-I, have potential drawbacks with respect to, e.g., stability during storage, delivery of active product, and *in vivo* half-life. Thus, small molecule compounds that up-regulate the production of endogenous ApoA-I, such as, for example,

up-regulators of ApoA-I expression, would be attractive as new therapeutic agents for cardiovascular disease.

[007] The methods of the present invention provide improved procedures for preparing up-regulators of ApoA-I expression. For the disclosed compounds of Formulae I, VI and VIII, alkylation of the phenol starting material with ethylene carbonate, rather than alkylating agents of known procedures, is more efficient, and thus less expensive on a large scale. The coupling procedures of the invention described herein to form the quinazolinones result in lower levels of impurities and increased yield of the final compounds.

Definitions

[008] It should be noted that, as used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to a method containing “a compound” includes a mixture of two or more compounds. It should also be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise. Unless otherwise specified, the chemical groups refer to their unsubstituted and substituted forms.

[009] The terms “compound of Formula I”, “compound of Formula VI”, and “compound of Formula VIII” are intended to include any stereoisomer, tautomer, and/or pharmaceutically acceptable salt as defined herein. Compounds of Formula I, Formula VI, and Formula VIII also include crystalline and amorphous forms of those compounds, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof. "Crystalline form," "polymorph," and "novel form" may be used interchangeably

herein, and are meant to include all crystalline and amorphous forms of the compound, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to. Compounds of Formula I, Formula VI, and Formula VIII also include pharmaceutically acceptable forms of the recited compounds, including chelates, non-covalent complexes, prodrugs, and mixtures thereof.

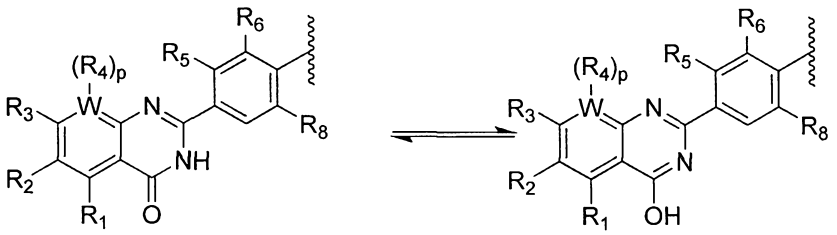
[010] As noted above, prodrugs also fall within the scope of compounds of Formula I, Formula VI, and Formula VIII. In some embodiments, the "prodrugs" described herein include any compound that becomes a compound of Formula I, Formula VI and/or Formula VIII when administered to a patient, e.g., upon metabolic processing of the prodrug. Examples of prodrugs include derivatives of functional groups, such as a carboxylic acid group, in the compounds of Formula I, Formula VI and/or Formula VIII. Exemplary prodrugs of a carboxylic acid group include, but are not limited to, carboxylic acid esters such as alkyl esters, hydroxyalkyl esters, arylalkyl esters, and aryloxyalkyl esters.

[011] A "solvate" is formed by the interaction of a solvent and a compound. The terms "compound of Formula I", "compound of Formula VI", and "compound of Formula VIII" are intended to include solvates of compounds. Similarly, "salts" includes solvates of salts. Suitable solvates are pharmaceutically acceptable solvates, such as hydrates, including monohydrates and hemi-hydrates.

[012] A "chelate" is formed by the coordination of a compound to a metal ion at two (or more) points. The term "compound" is intended to include chelates of compounds. Similarly, "salts" includes chelates of salts.

[013] A "non-covalent complex" is formed by the interaction of a compound and another molecule wherein a covalent bond is not formed between the compound and the molecule. For example, complexation can occur through van der Waals interactions, hydrogen bonding, and electrostatic interactions (also called ionic bonding). Such non-covalent complexes are included in the term "compound'.

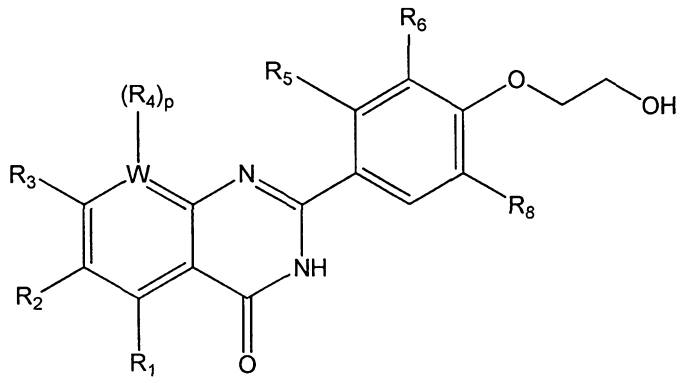
[014] The compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted. For example, any claim to compound A below is understood to include tautomeric structure B, and vice versa, as well as mixtures thereof.



[015] As used herein, the terms have the meaning given in US Patent Publication No. 2006/0205767 at pp. 3-7, which disclosure is incorporated herein by reference. The term "radical" used in these definitions refers to a substituent group or variable group.

[016] In addition, the term "imido" refers to a group having the structure -C(O)NC(O)-R_z, where R_z can be selected from alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, haloalkyl, heteroaryl, and heterocyclyl.

[017] One embodiment provides a method of preparing a compound of Formula I:



Formula I

and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof, wherein:

R_1, R_2, R_3, and R_4 are each independently selected from alkoxy, alkyl, amido, aryloxy, cycloalkyl, halogen, heterocyclyl, hydrogen, and nitro;

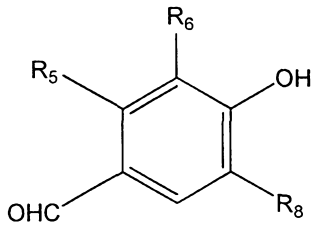
R_6 is selected from alkyl, alkoxy, and halogen;

R_5 is hydrogen, or R_5 and R_6 may be taken together with the carbon atoms to which they are attached, to form a ring selected from aryl, cycloalkyl, and heterocycyl;

R_8 is selected from alkyl, alkoxy, halogen, and hydrogen;

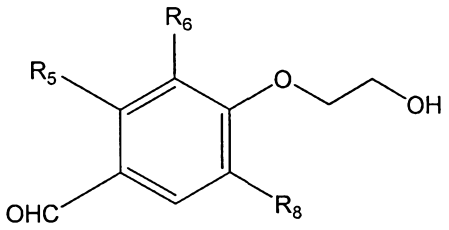
W is C or N, where if W is N, then p is 0, and if W is C, then p is 1; comprising

a) reacting an aldehyde of Formula II:



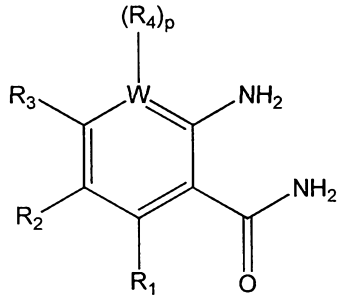
Formula II

wherein R_5, R_6 and R_8 are as defined above, with ethylene carbonate to form a compound of Formula III:



Formula III ; and

b) reacting the compound of Formula III with a compound of Formula IV:



Formula IV

wherein R_1, R_2, R_3, and R_4 are as defined above, to form the compound of Formula I.

[018] In one embodiment, R_1 and R_3 can each be independently selected from alkoxy, alkyl, halogen, and hydrogen. In another embodiment, R_1 and R_3 can each be independently selected from chloro, hydrogen, methoxy, and methyl. In a further embodiment, R_1 and R_3 can each be methoxy.

[019] In one embodiment, R_2 can be selected from bromo, hydrogen, methoxy, and methylamido. In a further embodiment, R_2 can be hydrogen. In one embodiment, W can be N. In another embodiment, W can be C and R_4 can be hydrogen.

[020] In one embodiment, R_6 can be selected from chloro, methoxy, and methyl. In another embodiment, R_6 can be methyl. In another embodiment, R_6 and R_8 can be each independently selected from alkyl and halogen. In one embodiment,

R_8 can be selected from chloro, hydrogen, methoxy, and methyl. In a further embodiment, R_6 and R_8 can be each methyl.

[021] In one embodiment, the compound of Formula I can be selected from:

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;

2-(3-chloro-4-(2-hydroxyethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3-methoxyphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6,7-dimethoxyquinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxypyrido[2,3-d]pyrimidin-4(3H)-one;

N-(2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl)acetamide;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethylquinazolin-4(3H)-one;

5,7-dichloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-methoxyquinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5-methoxyquinazolin-4(3H)-one;

6-bromo-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one; and

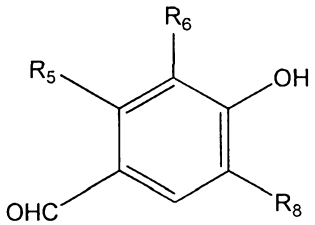
2-(4-(2-hydroxyethoxy)-3-methylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one,

and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof.

[022] In another embodiment, the compound of Formula I is 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one, or a solvate, hydrate, tautomer, or pharmaceutically acceptable salt thereof.

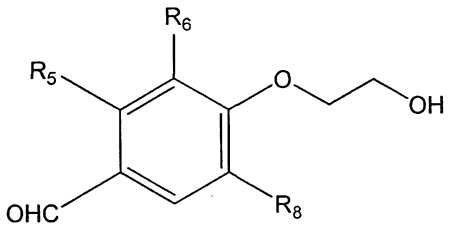
[023] In one embodiment, a reaction step can be performed in a large scale. In one embodiment, "large scale" refers to the use of at least 50 grams of a starting material, intermediate or reagent, such as the use of at least 100 grams, at least 500 g, at least 1 kg, at least 10 kg, at least 25 kg, at least 50 kg, at least 100 kg, at least 250 kg, or at least 500 kg.

[024] In one embodiment, the aldehyde of Formula II:



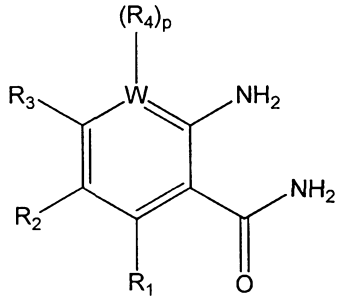
Formula II

can be combined with ethylene carbonate in a solvent, such as dimethylformamide, dichloromethane, isopropanol, methanol, tetrahydrofuran, toluene, xylene and water, and stirred at elevated temperature, such as 110 °C, to form the alkylated compound of Formula III. This compound can be purified by crystallization from, for example, dichloromethane/heptane. Use of ethylene carbonate allows for improved control of the alkylation process and is much more cost effective than other known methods.



Formula III

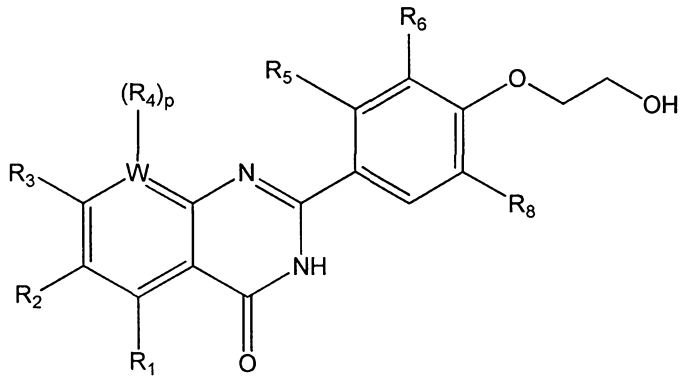
[025] The compound of Formula III can then be combined with a compound of Formula IV in *N,N*-dimethylacetamide (DMAC). Other suitable solvents include acetonitrile, benzene and methanol.



Formula IV

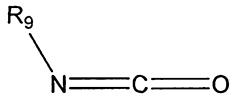
[026] Sodium bisulfite can then be added in portions, such as one-third portions, with heating, e.g., at approximately 115 °C. An acid, such as p-toluenesulfonic acid monohydrate, can be added with the first portion of sodium bisulfite. The reaction can be stirred for at least about 90 minutes, such as 90-105 minutes, between addition of the portions. Gradual addition of the portions over at least a 4 hour period significantly reduces the amount of impurities present in the final compound of Formula I, some of which are otherwise difficult to remove during the purification stage of the process.

[027] Upon completion of the reaction, the reaction mixture can be cooled and the resulting product can be recrystallized from, for example, DMAC/heptane. Alternatively, the unpurified product can be triturated with acetone. In another embodiment, this first purification step can be omitted. Following the first purification step, the product can then be recrystallized from ethanol/water to provide the compound of Formula I.



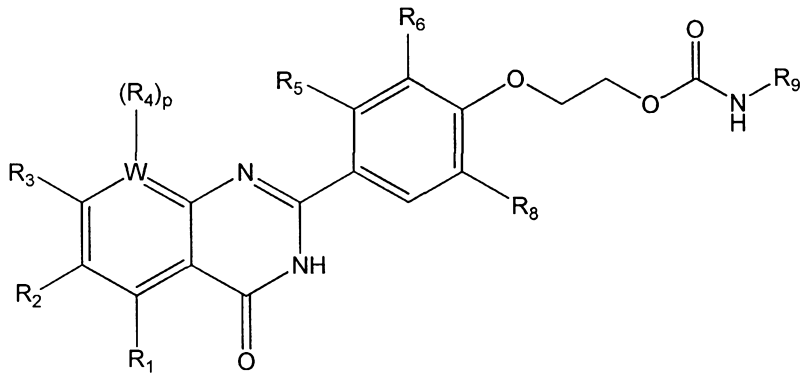
Formula I

[028] In a further embodiment, the compound of Formula I can be treated with an isocyanate of Formula V



Formula V

and a base, such as triethylamine or Hunig's base, to form a carbamate compound of Formula VI.

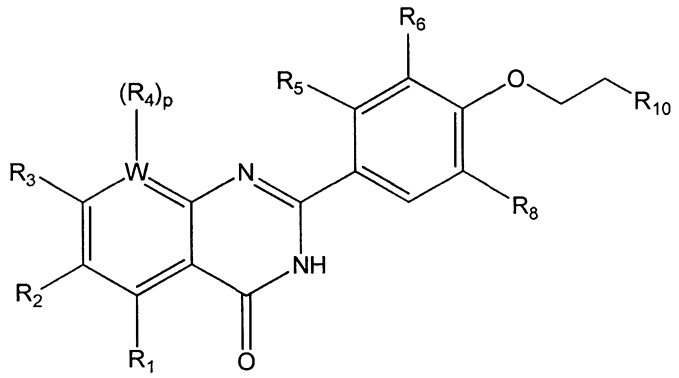


Formula VI

[029] In one embodiment, R_9 can be selected from alkyl, aryl, cycloalkyl, heteroaryl, and heterocyclyl. In another embodiment, R_9 can be aryl substituted with one or more groups selected from alkoxy, alkyl, and halogen. In another embodiment, the compound of Formula VI is 2-(4-(5,7-dimethoxy-4-oxo-3,4-

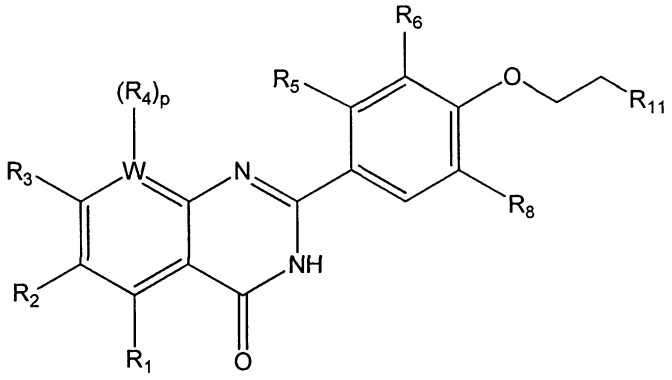
dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl cyclohexylcarbamate, or a solvate, hydrate, tautomer, or pharmaceutically acceptable salt thereof.

[030] In another embodiment, the compound of Formula I can be treated with a reagent to form a leaving group R_{10}, as shown in Formula VII. The leaving group R_{10} may be selected from halogen, sulfonyl, and phosphonium, such as chloride, methanesulfonyl, p-toluenesulfonyl, and triphenylphosphonium. The reagent can be selected from thionyl chloride, methanesulfonyl chloride, p-toluenesulfonyl chloride, and PPh_3/diethyl azodicarboxylate.



Formula VII

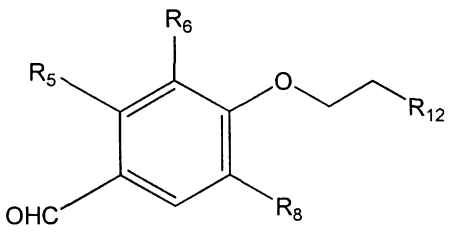
[031] The compound of Formula VII may then be treated with a nucleophilic reagent, such as an alkoxide, an amine, or a heterocycle having at least one nitrogen, including imido compounds, to provide a compound of Formula VIII. Alternatively, when R_{10} is triphenylphosphonium, the compound of Formula VII can be treated in situ with HN_3 followed by reduction with reagents such as Pd-C/H_2 to form an intermediate amine, which can then be treated with an acylating agent to form the compound of Formula VIII having an amido group or an imido group. As shown in Formula VIII, R_{11} can be selected from alkoxy, amido, amino, imido, and heterocyclyl. In one embodiment, R_{11} is selected from methoxy, methylamino, morpholino, piperazino, and piperidino.



Formula VIII

[032] In one embodiment, a compound of Formula I can be treated with methanesulfonyl chloride and triethylamine in dichloromethane to form the corresponding mesylate. The mesylate may then be treated with an amine, such as methylamine, in refluxing ethanol to give the compound of Formula VIII. In a further embodiment, the compound of Formula VIII is 2-(3,5-dimethyl-4-(2-(methylamino)ethoxy)phenyl)-5,7-dimethoxy-quinazolin-4(3*H*)-one, or a solvate, hydrate, tautomer, or pharmaceutically acceptable salt thereof.

[033] In another embodiment, a compound of Formula VIII can be prepared by reacting the aldehyde of Formula II with ethylene carbonate to provide the compound of Formula III. The compound of Formula III can then be reacted with a reagent to create a leaving group R_{12} on the compound of Formula IX.

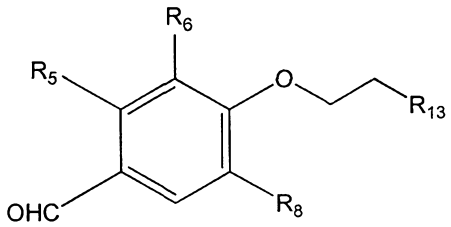


Formula IX

[034] In one embodiment, R_{12} can be selected from halogen, sulfonyl, and phosphonium, such as chloride, methanesulfonyl, p-toluenesulfonyl, and triphenylphosphonium. In another embodiment, the reagent is selected from thionyl

chloride, methanesulfonyl chloride, p-toluenesulfonyl chloride, and PPh_3/diethyl azodicarboxylate.

[035] The compound of Formula IX may be treated with an nucleophilic reagent, such as an alkoxide, amine or a heterocycle having at least one nitrogen, including imido compounds, to provide a compound of Formula X. Alternatively, when R_{12} is triphenylphosphonium, the compound of Formula VII can be treated in situ with HN_3 followed by reduction with reagents such as Pd-C/H_2 to form an intermediate amine, which can be treated with an acylating agent to form the compound of Formula VIII having an amido group or an imido group.



Formula X

[036] As shown in Formula X, R_{13} can be selected from alkoxy, amido, amino, imido, and heterocyclyl. In one embodiment, R_{13} is selected from methoxy, methylamino, morpholino, piperazino, and piperidino.

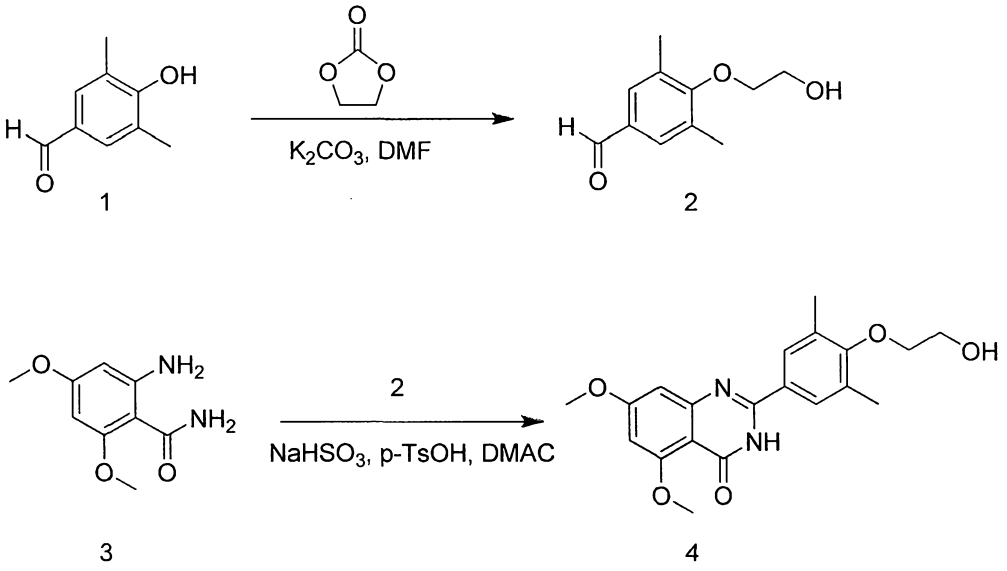
[037] The compound of Formula X may then be condensed with a compound of Formula IV to form the compound of Formula VIII. In one embodiment, R_6 and R_8 are each methyl. In another embodiment, R_1 and R_3 are each hydrogen. In a further embodiment, the compound of Formula VIII is 2-(3,5-dimethyl-4-(2-morpholinoethoxy)phenyl) quinazolin-4(3H)-one, or a solvate, hydrate, tautomer, or pharmaceutically acceptable salt thereof.

EXAMPLES

[038] The invention is further illustrated by the following non-limiting examples, wherein the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

[039] Abbreviations used herein denote the following compounds, reagents and substituents: acetonitrile (MeCN); diisopropylethylamine (DIPEA); *N,N*-dimethylacetamide (DMAC); dimethylformamide (DMF); ethyl acetate (EtOAc); methanesulfonyl anhydride (Ms_2O); methanesulfonyl chloride (MsCl); p-toluenesulfonic acid (p-TsOH); and triethylamine (Et_3N).

Example 1



2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (**4**)

[040] The starting material 4-hydroxy-3,5-dimethylbenzaldehyde (**1**; 70 kg), K_2CO_3 (9.8 kg) and DMF (133 kg) were mixed and stirred at 110 °C under nitrogen. Ethylene carbonate (45.6 kg) in DMF (46 kg) was added to the mixture over a period of 4 hours, using a diaphragm pump. The reaction mixture was stirred at 110 °C for 12 hours, until less than 5% of the starting material **1** remained. The reaction mixture

was cooled to 25 °C and water (1300 kg) was added followed by a mixture of dichloromethane and heptane (3V/2V; 1300 kg). The mixture was agitated for 30 minutes. The organic layer was isolated and the aqueous layer was back extracted with a mixture of dichloromethane and heptane (3V/2V; 1300 kg). The combined organic layers were washed with aqueous sodium hydroxide (3 M; 460 kg), followed by three washes with water (3 × 710 kg), and dried over sodium sulfate (60 kg). Dichloromethane was removed from the dried organic layer by distillation, keeping the temperature below 40 °C. Heptane (260 kg) and seed crystals were added to initiate crystallization and the mixture was stirred at 20 °C for 2 hours. The mixture was filtered, washed with heptane (60 kg), and dried under vacuum until constant weight to afford intermediate **2** (71.3 kg, 78.8%). ^{1}H-NMR (DMSO-d_6): δ 9.82 (1H), 7.54 (2H), 4.96 (1H), 3.85 (2H), 3.74 (2H), 2.29 (6H).

[041] Intermediate **2** (58.74 kg), *N*,*N*-dimethylacetamide (280 kg), and starting material **3** (56.00 kg) were combined and *p*-toluenesulfonic acid monohydrate (5.90 kg) and 1/3 of the required sodium bisulfite (24.1 kg) were added. The mixture was heated to 115 °C and stirred for 90-105 minutes before the second 1/3 of the required sodium bisulfite (24.1 kg) was added. The remaining sodium bisulfite (24.1 kg) was added after another 90-105 minutes. The reaction mixture was stirred at 115 °C until the reaction was complete as determined by HPLC (approximately 1 hour, less than 4% of intermediate **2** remaining). The reaction mixture was cooled to 25 °C and added to water (1770 kg). The mixture was stirred at 20 °C for 6 hours to complete the crystallization. The crude material was isolated by filtration, washed with water (234 kg) and dried under vacuum to constant weight. The crude material was dissolved in *N*,*N*-dimethylacetamide (252 kg) at 80 °C until all material had dissolved. The solution was cooled to 60 °C and heptane (918 kg)

was slowly added over a period of 1 hour, maintaining a temperature above 35 °C. The solution was cooled to 35 °C and stirred at 35 °C for a minimum of 1 hour. The solid was isolated by filtration, washed with heptane (250 kg) and dried to constant weight under vacuum. Yield: 92.5%; purity: 98.6%. The dry solid (83.1 kg) was added to a 1:1 mixture of ethanol and water (1V/1V; 1670 kg), and the mixture was heated to approximately 84°C (reflux) until all material was in solution. The solution was cooled to 70 °C and polish-filtered, and then cooled to 30 °C over 2 hours. The solution was cooled to 0 °C. The mixture was stirred at 0 °C for at least 1 hour, before the material was isolated by filtration, washed with ethanol/water (1V/1V; 33 kg) and dried under vacuum to constant weight. The material was passed through a 60-mesh screen to afford 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (**4**). Yield: 66.4 kg; 79.9%.

Example 2

Compounds that can be prepared similar to Example 1

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;

2-(3-chloro-4-(2-hydroxyethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3-methoxyphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6,7-dimethoxyquinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxypyrido[2,3-d]pyrimidin-4(3H)-one;

N-(2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl)acetamide;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethylquinazolin-4(3H)-one;

5,7-dichloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;

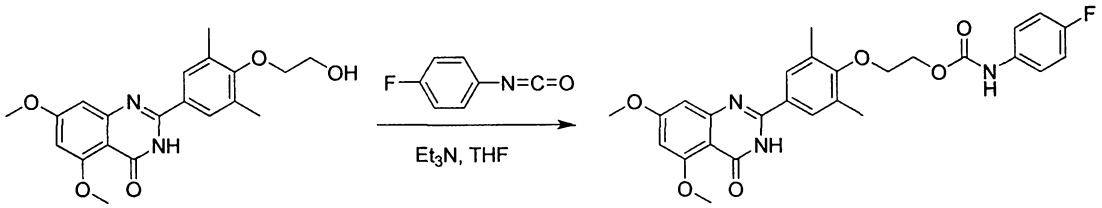
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-methoxyquinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5-methoxyquinazolin-4(3H)-one;

6-bromo-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one; and

2-(4-(2-hydroxyethoxy)-3-methylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one.

Example 3



4 5

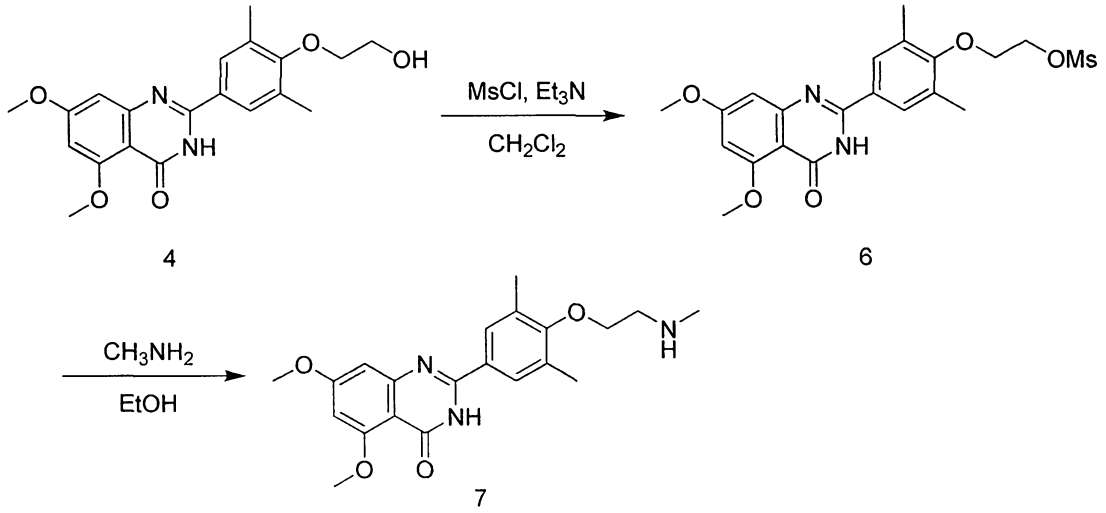
2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl 4-fluoro-phenylcarbamate (**5**)

[042] A mixture of 4-fluorophenylisocyanate (0.138 mL, 1.14 mmol), Et_3N (0.185 mL, 1.32 mmol) and **4** (0.0700 g, 0.189 mmol) in THF (1.00 mL) was heated at reflux for 8 hours. The mixture was cooled, diluted with EtOAc (200 mL), washed with saturated aqueous NH_4Cl (3 × 75 mL), brine (75 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified on silica gel (12 g, CH_2Cl_2/MeOH) and the product was freeze-dried from MeCN/H_2O to provide 2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl 4-fluoro-phenylcarbamate (**5**) (0.0710 g, 74%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.83 (s, 1H), 9.78 (s, 1H), 7.91 (s, 2H), 7.54-7.44 (m, 2H), 7.18–7.08 (m, 2H), 6.73 (d, J = 2.31 Hz, 1H), 6.51 (d, J = 2.31 Hz, 1H), 4.47–4.38 (m, 2H), 4.12–4.03 (m, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 2.31 (s, 6H); MS (APCI) *m/z* 508 $[C_{27}H_{26}FN_3O_6+H]^+$.

Example 4

[043] 2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl cyclohexylcarbamate can be prepared using a procedure similar to Example 3.

Example 5



2-(3,5-Dimethyl-4-(2-(methylamino)ethoxy)phenyl)-5,7-dimethoxy-quinazolin-4(3*H*)-one (**7**)

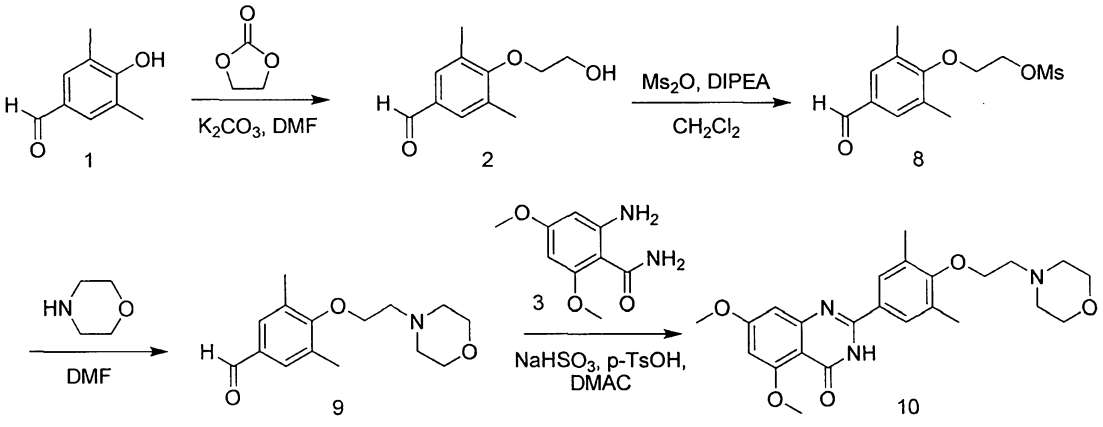
[044] To a mixture of **4** (2.00 g, 5.40 mmol) and Et_3N (0.977 mL, 7.02 mmol) in CH_2Cl_2 (27.0 mL) was added slowly MsCl (0.543 mL, 7.02 mmol) at room temperature. After 1 day, additional Et_3N (0.977 mL, 7.02 mmol) and MsCl (0.543 mL, 7.02 mmol) was added and the mixture was stirred for 2 hours, then diluted with EtOAc (300 mL) and washed with 10% aqueous citric acid (3 × 75 mL), saturated aqueous $NaHCO_3$ (75 mL), and brine (75 mL). An insoluble white solid was collected by filtration to provide mesylate **6** (0.890 g, 37%): ^1H NMR (300 MHz, DMSO-d_6) δ 11.84 (s, 1H), 7.91 (s, 2H), 6.74 (d, J = 2.32 Hz, 1H), 6.52 (d, J = 2.32 Hz, 1H), 4.59-4.48 (m, 2H), 4.15-4.04 (m, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.25 (s, 3H), 2.32 (s, 6H).

[045] The mesylate (**6**) (0.200 g, 0.446 mmol) and 33% CH_3NH_2 in EtOH (5.00 mL) was heated at reflux overnight. The solvent was removed under vacuum and the residue was purified on silica gel (12 g, CH_2Cl_2/CH_3OH) and the product freeze-dried from $MeCN/H_2O$ to provide 2-(3,5-dimethyl-4-(2-(methylamino)ethoxy)phenyl)-5,7-dimethoxy-quinazolin-4(3*H*)-one (**7**) (0.0968 g, 57%) as a light yellow solid: ^1H NMR (300 MHz, DMSO-d_6) δ 7.90 (s, 2H), 6.73 (d, J = 2.29 Hz, 1H), 6.52 (d, J = 2.29 Hz, 1H), 3.94-3.80 (m, 8H), 2.98 (t, J = 5.46 Hz, 2H), 2.45 (s, 3H), 2.33-2.28 (m, 8H); MS (APCI) *m/z* 384 $[C_{21}H_{25}N_3O_4+H]^+$.

Example 6

[046] 2-(3,5-Dimethyl-4-(2-(methoxy)ethoxy)phenyl)-5,7-dimethoxy-quinazolin-4(3*H*)-one can be prepared using a procedure similar to Example 5, where the mesylate (**6**) is treated with NaOMe in MeOH or $MeOH/K_2CO_3$ instead of CH_3NH_2.

Example 7



2-(3,5-Dimethyl-4-(2-(morpholino)ethoxy)phenyl)-5,7-dimethoxy-quinazolin-4(3H)-one (**10**)

[047] Intermediate **2** is obtained from **1** according to the procedure in Example 1. To a mixture of **2** and diisopropylethylamine in CH_2Cl_2 at 0 °C is added Ms_2O. The reaction mixture is stirred until the reaction is complete, as determined by thin layer chromatography (TLC). The reaction mixture is diluted with ethyl acetate and washed with cold sat. $NaHCO_3$ and brine. The organic layer is dried over Na_2SO_4, filtered and concentrated to provide mesylate **8**.

[048] A mixture of compound **8** and morpholine in DMF is heated to 50 °C. The reaction mixture is stirred until the reaction is complete, as determined by TLC. The reaction mixture is cooled to room temperature and ethyl acetate is added. The mixture is washed with water, dried over Na_2SO_4, filtered and concentrated to provide crude intermediate **9**. The crude product is purified by column chromatography to provide pure intermediate **9**.

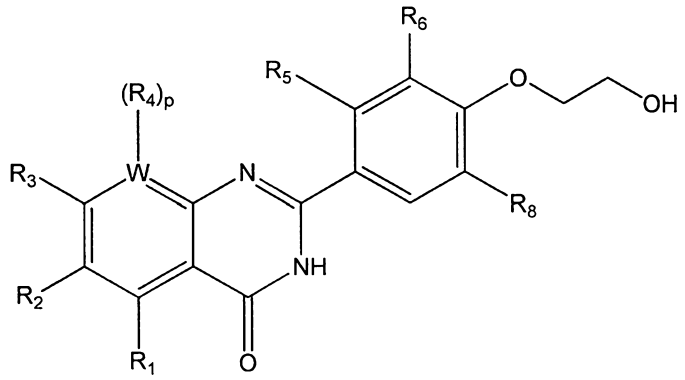
[049] Starting material **3** and intermediate **9** are combined in DMAC followed by the addition of p-TsOH and sodium bisulfite. The reaction mixture is heated to 115 °C. The reaction is stirred until complete as determined by TLC. The reaction mixture is cooled to room temperature and water is added. The mixture is extracted with CH_2Cl_2 three times. The combined organic layers are washed with water, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography to provide 2-(3,5-dimethyl-4-(2-(methylamino)ethoxy)phenyl)-5,7-dimethoxy-quinazolin-4(3H)-one (**10**).

[050] All references referred to herein are incorporated by reference in their entirety. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as

exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

WHAT IS CLAIMED IS:

1. A method of preparing a compound of Formula I:



Formula I

and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof, wherein:

R_1, R_2, R_3, and R_4 are each independently selected from alkoxy, alkyl, amido, aryloxy, cycloalkyl, halogen, heterocyclyl, hydrogen, and nitro;

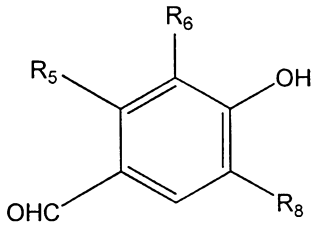
R_6 is selected from alkyl, alkoxy, and halogen;

R_5 is hydrogen, or R_5 and R_6 may be taken together with the carbon atoms to which they are attached, to form a ring selected from aryl, cycloalkyl, and heterocycyl;

R_8 is selected from alkyl, alkoxy, halogen, and hydrogen;

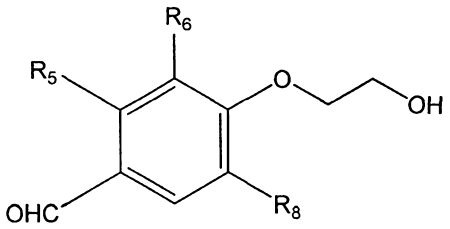
W is C or N, where if W is N, then p is 0, and if W is C, then p is 1; comprising

a) reacting an aldehyde of Formula II:



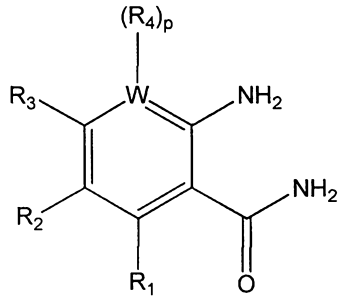
Formula II

wherein R_5, R_6 and R_8 are as defined above, with ethylene carbonate to form a compound of Formula III:



Formula III ; and

b) reacting the compound of Formula III with a compound of Formula IV



Formula IV

wherein R_1, R_2, R_3, and R_4 are as defined above, to form the compound of Formula I.

2. The method according to claim 1, wherein R_6 and R_8 are each independently selected from alkyl and halogen.

3. The method according to claim 2, wherein R_6 and R_8 are each methyl.

4. The method according to claim 1, wherein R_1 and R_3 are each independently selected from alkoxy, alkyl, halogen, and hydrogen.

5. The method according to claim 4, wherein R_1 and R_3 are each methoxy.

6. The method according to claim 1, wherein the compound of Formula I is selected from:

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;

2-(3-chloro-4-(2-hydroxyethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3-methoxyphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6,7-dimethoxyquinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxypyrido[2,3-d]pyrimidin-4(3H)-one;

N-(2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl)acetamide;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethylquinazolin-4(3H)-one;

5,7-dichloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-methoxyquinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5-methoxyquinazolin-4(3H)-one;

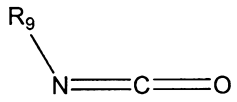
6-bromo-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one; and

2-(4-(2-hydroxyethoxy)-3-methylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one,

and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof.

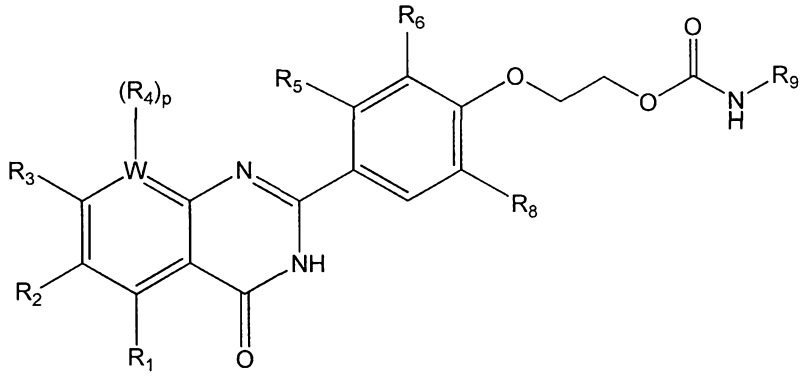
7. The method according to claim 6, wherein the compound of Formula I is 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one, or a solvate, hydrate, tautomer, or pharmaceutically acceptable salt thereof.

8. The method according to claim 1, further comprising reacting the compound of Formula I with a compound of Formula V:



Formula V

wherein R_9 is selected from alkyl, aryl, cycloalkyl, heteroaryl, and heterocyclyl, to form a compound of Formula VI:



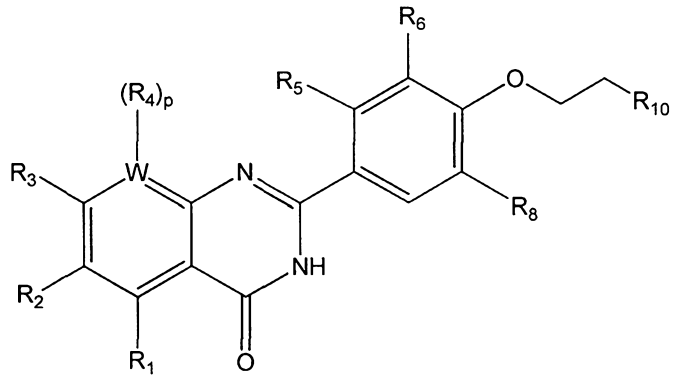
Formula VI

and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof, wherein R_1, R_2, R_3, R_4, R_5, R_6, R_8, and R_9 are as defined above.

9. The method according to claim 8, wherein R_9 is aryl substituted with one or more groups selected from alkoxy, alkyl, and halogen.

10. The method according to claim 1, further comprising

c) reacting the compound of Formula I with a reagent to create a leaving group R_{10} to form a compound of Formula VII;

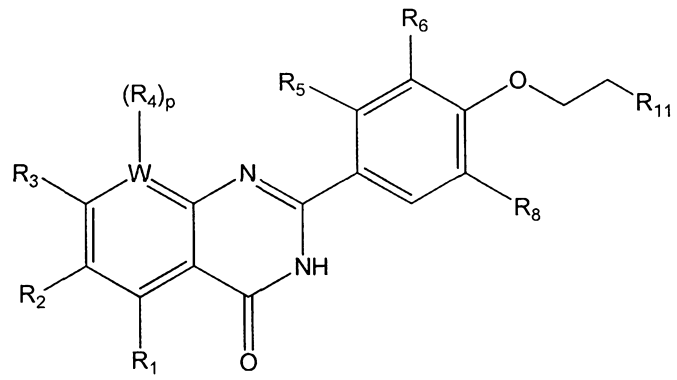


Formula VII

wherein R_{10} is selected from halogen, sulfonyl, and phosphonium;

R_1, R_2, R_3, R_4, R_5, R_6, and R_8 are as defined above; and

d) reacting the compound of Formula VII with a nucleophilic reagent to form a compound of Formula VIII:



Formula VIII

and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof,

wherein R_{11} is selected from alkoxy, amido, amino, imido, and heterocyclyl; and

R_1, R_2, R_3, R_4, R_5, R_6, and R_8 are as defined above.

11. The method according to claim 10, wherein the reagent creating the leaving group is selected from thionyl chloride, methanesulfonyl chloride, p-toluenesulfonyl chloride and PPh_3/diethyl azodicarboxylate.

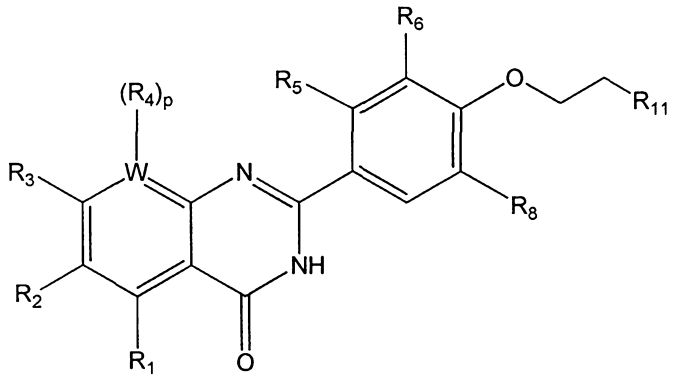
12. The method according to claim 10, wherein R_{10} is selected from chloride, methanesulfonyl, p-toluenesulfonyl, and triphenylphosphonium.

13. The method according to claim 10, wherein the nucleophilic reagent is selected from an alkoxide, an amine, an azide, and a heterocycle having at least one nitrogen.

14. The method according to claim 10, wherein R_{11} is selected from methoxy, methylamino, morpholino, piperazino, and piperidino.

15. The method according to claim 10, wherein the compound of Formula VIII is 2-(3,5-dimethyl-4-(2-(methylamino)ethoxy)phenyl)-5,7-dimethoxy-quinazolin-4(3*H*)-one, or a solvate, hydrate, tautomer, or pharmaceutically acceptable salt thereof.

16. A method of preparing a compound of Formula VIII:



Formula VIII

and solvates, hydrates, tautomers, and pharmaceutically acceptable salts thereof, wherein:

R_1, R_2, R_3, and R_4 are each independently selected from alkoxy, alkyl, amido, aryloxy, cycloalkyl, halogen, heterocyclyl, hydrogen, and nitro;

R_6 is selected from alkyl, alkoxy, and halogen;

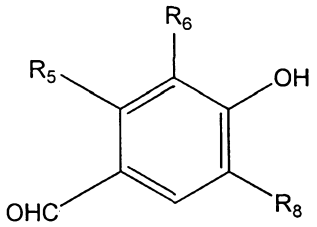
R_5 is hydrogen, or R_5 and R_6 may be taken together with the carbon atoms to which they are attached, to form a ring selected from aryl, cycloalkyl, and heterocycyl;

R_8 is selected from alkoxy, alkyl, halogen, and hydrogen;

R_{11} is selected from alkoxy, amido, amino, imido, and heterocyclyl;

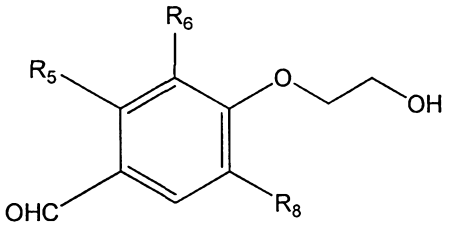
W is C or N, where if W is N, then p is 0, and if W is C, then p is 1; comprising

a) reacting an aldehyde of Formula II:



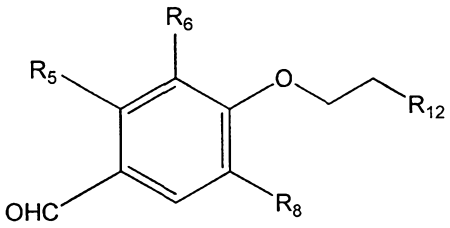
Formula II

wherein R_5, R_6 and R_8 are as defined above, with ethylene carbonate to form a compound of Formula III:



Formula III ;

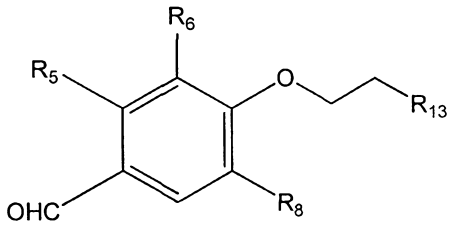
b) reacting the compound of Formula III with a reagent to create a leaving group R_{12} to form a compound of Formula IX:



Formula IX

wherein R_{12} is selected from halogen, sulfonyl, and phosphonium;

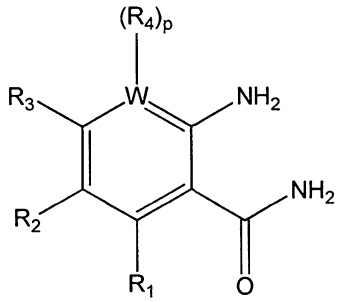
c) reacting the compound of Formula VIII with a nucleophilic reagent to form a compound of Formula X:



Formula X

wherein R_{13} is selected from alkoxy, amido, amino, imido, and heterocyclyl; and

d) reacting the compound of Formula X with a compound of Formula IV:



Formula IV

wherein R_1, R_2, R_3, and R_4 are as defined above, to form the compound of Formula VIII.

17. The method according to claim 16, wherein the reagent creating the leaving group is selected from thionyl chloride, methanesulfonyl chloride, p-toluenesulfonyl chloride, and PPh_3/diethyl azodicarboxylate.

18. The method according to claim 16, wherein R_{12} is selected from chloride, methanesulfonyl, p-toluenesulfonyl, and triphenylphosphonium.

19. The method according to claim 16, wherein the nucleophilic reagent is selected from an alkoxide, an amine, an azide, and a heterocycle having at least one nitrogen.

20. The method according to claim 16, wherein R_{13} is selected from methoxy, methylamino, morpholino, piperazino, and piperidino.

21. The method according to claim 16, wherein R_6 and R_8 are each methyl.

22. The method according to claim 16, wherein R_1 and R_3 are each hydrogen.

23. The method according to claim 16, wherein the compound is 2-(3,5-dimethyl-4-(2-morpholinoethoxy)phenyl)quinazolin-4(3H)-one, or a solvate, hydrate, tautomer, or pharmaceutically acceptable salt thereof.