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Compounds for the prevention and treatment of cardiovascular diseases

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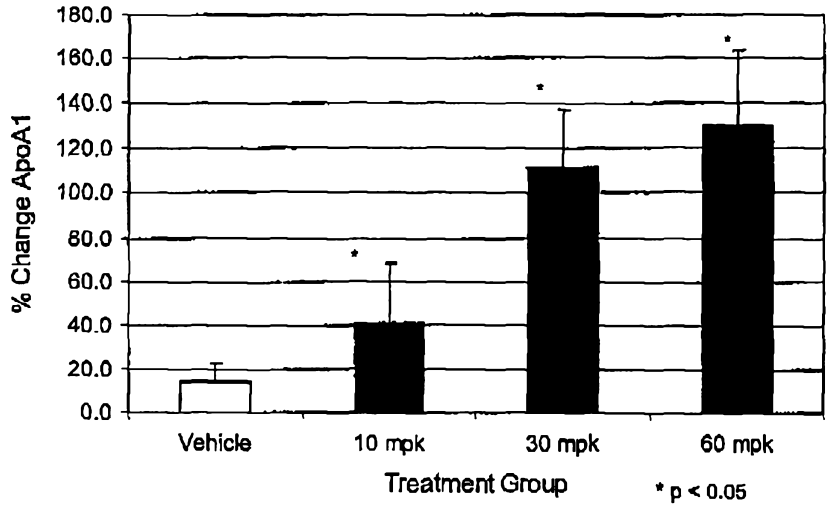
(54) **Title:** COMPOUNDS FOR THE PREVENTION AND TREATMENT OF CARDIOVASCULAR DISEASES

FIGURE 1



(57) **Abstract:** The present disclosure relates to compounds, which are useful for regulating the expression of apolipoproteiπ A-I (ApoA-l), and their use for 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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COMPOUNDS FOR THE PREVENTION AND TREATMENT OF CARDIOVASCULAR DISEASES

Technical Field

[001] The present disclosure relates to compounds, which are useful for regulating the expression of apolipoprotein A-I (ApoA-I), and their use for the treatment and prevention of cardiovascular disease and related disease states, including cholesterol- or lipid-related disorders, such as, for example, atherosclerosis.

BACKGROUND

[002] 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 reduces coronary heart disease (CHD) 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 results in a 6% increase in the HDL-C level and a corresponding 22% reduction of the 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 the link between elevated risk of CHD and low HDL-C.

[003] 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 exerts anti-

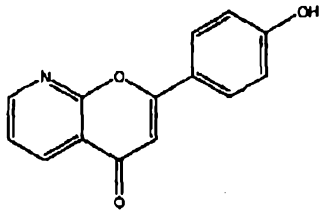
inflammatory and anti-oxidant effects and promotes fibrinolysis. HDL-C particles protect against oxidation of LDL, an important initial step in promoting cholesterol uptake by arterial macrophages. HDL-C exists in two main forms, one containing both apolipoprotein A-I (ApoA-I) and apolipoprotein A-II (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 mostly, but not exclusively, attributable to ApoA-I.

[004] Clinical and experimental data suggest that the production of ApoA-I is a critical 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.

[005] 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 very attractive as new therapeutic agents for cardiovascular disease. Such small molecule compounds have been described in WO 2006/045096.

[006] The compounds of the present invention represent a major improvement over compounds disclosed in WO 2006/045096. Specifically, the compounds of the present invention are more than an order of magnitude more potent than the most active compounds described in that publication, such as 2-(4-hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one.

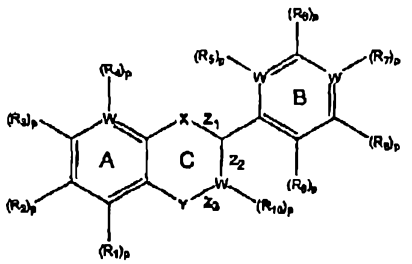


2-(4-hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one

SUMMARY

[007] The present invention includes non-naturally occurring compounds that are useful for regulating the expression of apolipoprotein A-I (ApoA-I), and their use in the treatment and prevention of cardiovascular disease and related disease states, including cholesterol- and lipid-related disorders, such as, for example, atherosclerosis.

[008] The methods of invention include administering to a mammal (e.g., a human) in need thereof a therapeutically effective amount of a compound of **Formula II**:



Formula II

wherein:

X is selected from CR_{11}, N and NR_{11};

Y is selected from CO, CS, and SO_2;

R_{11} is selected from hydrogen, unsubstituted alkyl (preferably C_{1-3} alkyl), unsubstituted alkenyl (preferably C_{1-3} alkenyl), and unsubstituted alkynyl (preferably C_{1-3} alkynyl);

R_1 and R_3 are each independently selected from alkoxy (preferably methoxy), alkyl, amino, halogen (preferably chloride), and hydrogen;

R_2 is selected from alkoxy, alkyl, alkenyl, amide, amino, halogen (preferably bromide or chloride), and hydrogen;

R_6 and R_8 are each independently selected from alkoxy, alkyl (preferably methyl), amino, halogen (preferably chloride and fluoride), and hydrogen;

R_5 and R_9 are each independently selected from halogen (preferably chloride), and hydrogen;

R_7 is selected from alkoxy, alkyl, alkenyl, amide, amino, ether, hydrogen, and hydroxyl;

R_{10} is selected from hydrogen and alkyl (preferably methyl); or

two adjacent substituents selected from R_1, R_2, R_3, R_6, R_7, R_8, R_{10}, and R_{11} are connected to form a group selected from aryl, heteroaryl, cycloalkyl, and heterocyclyl;

each W is independently selected from C and N, wherein if W is N, then p is 0 or 1, and if W is C, then p is 1;

for $W\text{-}(R_4)_p$, W is C, p is 1 and R_4 is H, or W is N and p is 0;

Z_1, Z_2 and Z_3 are each independently selected from a single bond and a double bond, wherein at least one of Z_1 or Z_2 is a double bond;

and pharmaceutically acceptable salts and hydrates thereof.

[009] The invention further includes certain compounds falling within the scope of **Formula II** and methods of administering a therapeutically effective amount of those compounds to a mammal (e.g., a human) in need thereof wherein:

X is selected from N and CH;

Y is CO;

R_1 and R_3 are each independently selected from alkoxy and hydrogen;

R_2 is selected from alkoxy, alkyl, and hydrogen;

R_6 and R_8 are each independently selected from alkyl, alkoxy, chloride, and hydrogen;

R_5 and R_9 are each hydrogen;

R_7 is selected from amino, hydroxyl, alkoxy (preferably a substituted ethoxy group), and alkyl substituted with a heterocyclyl;

R_{10} is hydrogen; or

two adjacent substituents selected from R_6, R_7, and R_8 are connected to form a heterocyclyl;

each W is independently selected from C and N, wherein if W is N, then p is 0 or 1, and if W is C, then p is 1;

for $W-(R_{10})_p$, W is N and p is 1;

for $W-(R_4)_p$, W is C, p is 1 and R_4 is H, or W is N and p is 0;

Z_1 is a double bond, and Z_2 and Z_3 are each a single bond;

with the proviso that if R_2 is selected from alkoxy and hydrogen, then at least one of R_1 and R_3 is alkoxy;

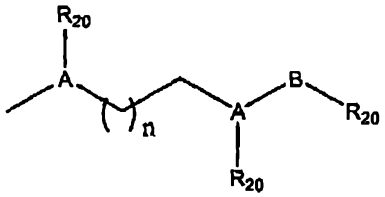
with the proviso that if R_7 is selected from hydroxyl and alkoxy, then at least one of R_6 and R_8 are independently selected from alkyl, alkoxy, and chloride;

with the proviso that if R_7 is an amino, then X is N;

with the proviso that if for $W-(R_7)_p$, W is N and p is 0, then at least one of R_6 and R_8 is chloride;

and pharmaceutically acceptable salts and hydrates thereof.

[010] In some embodiments of the invention, R_7 is an amino or an alkoxy selected from the group represented by **Formula III**:



Formula III

wherein:

A is selected from O and N;

n is selected from 0, 1, 2, 3, 4 and 5;

B is selected from $-C(O)N(R_h)_2-$, $-S(O)_2N(R_h)_2-$, $-C(O)-$, $-S(O)_2-$, $-C(O)O-$, wherein each R_h is selected from alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, haloalkyl, heteroaryl, heterocyclyl, and hydrogen; and

R_{20} is selected from (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, aryl, arylalkyl, cycloalkyl, haloalkyl, heteroaryl, heterocyclyl, and hydrogen.

In another embodiment, if A is O and B is $-C(O)NH-$, then R_{20} is not an unsaturated cycloalkyl.

[011] In certain embodiments, the methods, compounds, and compositions of the invention are useful for the prevention or treatment of diseases that benefit from raised ApoA-I or HDL, and diseases characterized by reduced ApoA-I and/or HDL-C, abnormal lipid parameters, or lipid parameters indicative of high cholesterol. The methods, compounds, and compositions of the invention can be used to increase expression of ApoA-I. Increasing expression of ApoA-I may refer to, but is not limited to, transcriptionally modulating the expression of the ApoA-I gene, thereby affecting the level of the ApoA-I protein produced (synthesized and secreted). An increase in ApoA-I levels may lead to an increase the levels of HDL-C and/or increase in the functionality of HDL-C particles. Thus, the methods, compounds, and compounds of the invention may further be used to reduce cholesterol levels. Accordingly, the methods, compounds, and compositions of the invention can be used for treatment and prevention of cardiovascular disease and related disease states, particularly, cholesterol- or lipid-related disorders, such as, for example, atherosclerosis.

BRIEF DESCRIPTION OF THE FIGURES

[012] **Figure 1** depicts plasma levels of ApoA-I in hApoA-I transgenic mice receiving 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (Example 7) (10, 30, and 60 mg/kg body weight) twice daily for 7 days by oral gavage.

[013] **Figure 2** depicts plasma levels of HDL cholesterol in hApoA-I transgenic mice receiving 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (Example 7) (10 and 30 mg/kg body weight) twice daily for 7 days by oral gavage.

[014] **Figure 3** depicts plasma levels of ApoA-I in wild-type C57BL/6 mice receiving 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (Example 7) (10, 30, and 60 mg/kg of body weight) twice daily for 3 days by intraperitoneal administration.

[015] **Figure 4** depicts plasma levels of HDL cholesterol in wild-type C57/Bl mice receiving 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (Example 7) (10, 30, and 60 mg/kg of body weight) twice daily for 3 days by oral gavage.

[016] **Figure 5** depicts plasma levels of ApoA-I and tissue levels of ApoA-I mRNA in hApoA-I transgenic mice administered 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (Example 7) (30 mg/kg body weight) twice daily for 7 days by oral gavage.

DETAILED DESCRIPTION

Definitions

[017] The term "aldehyde" or "formyl" as used herein refers to -CHO.

[018] The term "alkenyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond, such as a straight or branched group of 2-22, 2-8, or 2-6 carbon atoms, referred to herein as (C_2-C_{22})alkenyl, (C_2-C_8)alkenyl, and (C_2-C_6)alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl, etc.

[019] The term "alkoxy" as used herein refers to an alkyl group attached to an oxygen (-O-alkyl-). "Alkoxy" groups also include an alkenyl group attached to an oxygen ("alkenyloxy") or an alkynyl group attached to an oxygen ("alkynyloxy") groups. Exemplary alkoxy groups include, but are not limited to, groups with an alkyl, alkenyl or alkynyl group of 1-22, 1-8, or 1-6 carbon atoms, referred to herein as (C_1-C_{22})alkoxy, (C_1-C_8)alkoxy, and (C_1-C_6)alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, etc.

[020] The term "alkyl" as used herein refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-22, 1-8, or 1-6 carbon atoms, referred to herein as (C_1-C_{22})alkyl, (C_1-C_8)alkyl, and (C_1-C_6)alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

[021] The term "alkynyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond, such as

a straight or branched group of 2-22, 2-8, or 2-6 carbon atoms, referred to herein as (C_2-C_{22})alkynyl, (C_2-C_8)alkynyl, and (C_2-C_6)alkynyl, respectively. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butynyl, 4-propyl-2-pentynyl, and 4-butyl-2-hexynyl, etc.

[022] The term "amide" as used herein refers to the form -$NR_aC(O)(R_b)$- or -$C(O)NR_bR_c$, wherein R_a, R_b and R_c are each independently selected from alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, haloalkyl, heteroaryl, heterocyclyl, hydrogen. The amide can be attached to another group through the carbon, the nitrogen, R_b, or R_c. The amide also may be cyclic, for example R_b and R_c, may be joined to form a 3- to 12-membered ring, such as a 3- to 10-membered ring or a 5- to 6-membered ring. The term "amide" encompasses groups such as sulfonamide, urea, ureido, carbamate, carbamic acid, and cyclic versions thereof. The term "amide" also encompasses an amide group attached to a carboxy group, e.g., –amide-COOH or salts such as –amide-COONa, etc., an amino group attached to a carboxy group, e.g., –amino-COOH or salts such as –amino-COONa, etc.

[023] The term "amine" or "amino" as used herein refers to the form -NR_dR_e or -$N(R_d)R_e$-, where R_d and R_e are independently selected from alkyl, alkenyl, alkynyl, aryl, arylalkyl, carbamate, cycloalkyl, haloalkyl, heteroaryl, heterocyclyl, hydrogen. The amino can be attached to the parent molecular group through the nitrogen. The amino also may be cyclic, for example any two of R_d and R_e may be joined together or with the N to form a 3- to 12-membered ring, e.g., morpholino or piperidinyl. The term amino also includes the corresponding

quaternary ammonium salt of any amino group. Exemplary amino groups include alkylamino groups, wherein at least one of R_d or R_e is an alkyl group.

[024] The term "aryl" as used herein refers to a mono-, bi-, or other multi-carbocyclic, aromatic ring system. The aryl group can optionally be fused to one or more rings selected from aryls, cycloalkyls, and heterocyclyls. The aryl groups of this invention can be substituted with groups selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Exemplary aryl groups include, but are not limited to, phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl, and naphthyl, as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl. Exemplary aryl groups also include, but are not limited to a monocyclic aromatic ring system, wherein the ring comprises 6 carbon atoms, referred to herein as "(C_6)aryl."

[025] The term "arylalkyl" as used herein refers to an alkyl group having at least one aryl substituent, e.g. -aryl-alkyl-. Exemplary arylalkyl groups include, but are not limited to, arylalkyls having a monocyclic aromatic ring system, wherein the ring comprises 6 carbon atoms, referred to herein as "(C_6)arylalkyl."

[026] The term "aryloxy" as used herein refers to an aryl group attached to an oxygen atom. Exemplary aryloxy groups include, but are not limited to, aryloxys having a monocyclic aromatic ring system, wherein the ring comprises 6 carbon atoms, referred to herein as "(C_6)aryloxy."

[027] The term "arylthio" as used herein refers to an aryl group attached to an sulfur atom. Exemplary arylthio groups include, but are not limited to, arylthios

having a monocyclic aromatic ring system, wherein the ring comprises 6 carbon atoms, referred to herein as "(C_6)arylthio."

[028] The term "arylsulfonyl" as used herein refers to an aryl group attached to a sulfonyl group, e.g., $-S(O)_2$-aryl-. Exemplary arylsulfonyl groups include, but are not limited to, arylsulfonyls having a monocyclic aromatic ring system, wherein the ring comprises 6 carbon atoms, referred to herein as "(C_6)arylsulfonyl."

[029] The term "benzyl" as used herein refers to the group $-CH_2$-phenyl.

[030] The term "bicyclic aryl" as used herein refers to an aryl group fused to another aromatic or non-aromatic carbocylic or heterocyclic ring. Exemplary bicyclic aryl groups include, but are not limited to, naphthyl or partly reduced forms thereof, such as di-, tetra-, or hexahydronaphthyl.

[031] The term "bicyclic heteroaryl" as used herein refers to a heteroaryl group fused to another aromatic or non-aromatic carbocylic or heterocyclic ring. Exemplary bicyclic heteroaryls include, but are not limited to, 5,6 or 6,6-fused systems wherein one or both rings contain heteroatoms. The term "bicyclic heteroaryl" also encompasses reduced or partly reduced forms of fused aromatic system wherein one or both rings contain ring heteroatoms. The ring system may contain up to three heteroatoms, independently selected from oxygen, nitrogen, or sulfur. The bicyclic system may be optionally substituted with one or more groups selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Exemplary bicyclic heteroaryl's include, but are not limited to, quinazolinyl, benzothiophenyl,

benzoxazolyl, benzimidazolyl, benzothiazolyl, benzofuranyl, indolyl, quinolinyl, isoquinolinyl, phthalazinyl, benzotriazolyl, benzopyridinyl, and benzofuranyl.

[032] The term "carbamate" as used herein refers to the form $-R_gOC(O)N(R_h)-$, $-R_gOC(O)N(R_h)R_i-$, or $-OC(O)NR_hR_i$, wherein R_g, R_h and R_i are each independently selected from alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, haloalkyl, heteroaryl, heterocyclyl, hydrogen. Exemplary carbamates include, but are not limited to, arylcarbamates or heteroaryl carbamates, e.g., wherein at least one of R_g, R_h and R_i are independently selected from aryl or heteroaryl, such as pyridine, pyridazine, pyrimidine, and pyrazine.

[033] The term "carbonyl" as used herein refers to -C(O)-.

[034] The term "carboxy" as used herein refers to -COOH or its corresponding carboxylate salts, e.g. –COONa, etc. The term carboxy also includes "carboxycarbonyl," e.g. a carboxy group attached to a carbonyl group, e.g., –C(O)-COOH or salts such as -C(O)-COONa, etc..

[035] The term "cyano" as used herein refers to -CN.

[036] The term "cycloalkoxy" as used herein refers to a cycloalkyl group attached to an oxygen.

[037] The term "cycloalkyl" as used herein refers to a saturated or unsaturated cyclic, bicyclic, or bridged bicyclic hydrocarbon group of 3-12 carbons, or 3-8 carbons, referred to herein as "$(C_3$-$C_8)$cycloalkyl," derived from a cycloalkane. Exemplary cycloalkyl groups include, but are not limited to, cyclohexanes, cyclohexenes, cyclopentanes, and cyclopentenes. Cycloalkyl groups may be substituted with alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate,

sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Cycloalkyl groups can be fused to other cycloalkyl saturated or unsaturated, aryl, or heterocyclyl groups.

[038] The term "dicarboxylic acid" as used herein refers to a group containing at least two carboxylic acid groups such as saturated and unsaturated hydrocarbon dicarboxylic acids and salts thereof. Exemplary dicarboxylic acids include alkyl dicarboxylic acids. Dicarboxylic acids may be substituted with alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Dicarboxylic acids include, but are not limited to succinic acid, glutaric acid, adipic acid, suberic acid, sebacic acid, azelaic acid, maleic acid, phthalic acid, aspartic acid, glutamic acid, malonic acid, fumaric acid, (+)/(-)-malic acid, (+)/(-) tartaric acid, isophthalic acid, and terephthalic acid. Dicarboxylic acids further include carboxylic acid derivatives thereof, such as anhydrides, imides, hydrazides, etc., for example, succinic anhydride, succinimide, etc.

[039] The term "ester" refers to the structure -C(O)O-, -C(O)O-R_j-, -R_kC(O)O-R_j-, or -R_kC(O)O-, where O is not bound to hydrogen, and R_j and R_k can independently be selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, cycloalkyl, ether, haloalkyl, heteroaryl, heterocyclyl. R_k can be a hydrogen, but R_j cannot be hydrogen. The ester may be cyclic, for example the carbon atom and R_j, the oxygen atom and R_k, or R_j and R_k may be joined to form a 3- to 12-membered ring. Exemplary esters include, but are not limited to,

alkyl esters wherein at least one of Rj or Rk is alkyl, such as –O-C(O)-alkyl, –C(O)-O-alkyl–, –alkyl–C(O)-O-alkyl–, etc. Exemplary esters also include aryl or heteoraryl esters, e.g. wherein at least one of Rj or Rk is a heteroaryl group such as pyridine, pyridazine, pyrmidine and pyrazine, such as a nicotinate ester. Exemplary esters also include reverse esters having the structure $-R_kC(O)O-$, where the oxygen is bound to the parent molecular. Exemplary reverse esters include succinate, D-argininate, L-argininate, L-lysinate and D-lysinate. Esters also include carboxylic acid anhydrides and acid halides.

[040] The term "ether" refers to the structure $-R_lO-R_m-$, where R_l and R_m can independently be alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl, or ether. The ether can be attached to the parent molecular group through R_l or R_m. Exemplary ethers include, but are not limited to, alkoxyalkyl and alkoxyaryl groups. Ethers also includes polyethers, e.g., where one or both of R_l and R_m are ethers.

[041] The terms "halo" or "halogen" or "Hal" as used herein refer to F, Cl, Br, or I.

[042] The term "haloalkyl" as used herein refers to an alkyl group substituted with one or more halogen atoms. "Haloalkyls" also encompass alkenyl or alkynyl groups substituted with one or more halogen atoms.

[043] The term "heteroaryl" as used herein refers to a mono-, bi-, or multi-cyclic, aromatic ring system containing one or more heteroatoms, for example 1 to 3 heteroatoms, such as nitrogen, oxygen, and sulfur. Heteroaryls can be substituted with one or more substituents including alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester,

ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Heteroaryls can also be fused to non-aromatic rings. Illustrative examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrimidyl, pyrazyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3)- and (1,2,4)-triazolyl, pyrazinyl, pyrimidilyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, furyl, phenyl, isoxazolyl, and oxazolyl. Exemplary heteroaryl groups include, but are not limited to, a monocyclic aromatic ring, wherein the ring comprises 2 to 5 carbon atoms and 1 to 3 heteroatoms, referred to herein as "(C_2-C_5)heteroaryl."

[044] The terms "heterocycle," "heterocyclyl," or "heterocyclic" as used herein refer to a saturated or unsaturated 3-, 4-, 5-, 6- or 7-membered ring containing one, two, or three heteroatoms independently selected from nitrogen, oxygen, and sulfur. Heterocycles can be aromatic (heteroaryls) or non-aromatic. Heterocycles can be substituted with one or more substituents including alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Heterocycles also include bicyclic, tricyclic, and tetracyclic groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from aryls, cycloalkyls, and heterocycles. Exemplary heterocycles include acridinyl, benzimidazolyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, biotinyl, cinnolinyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, furyl, homopiperidinyl, imidazolidinyl, imidazolinyl, imidazolyl, indolyl, isoquinolyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl,

oxazolyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazinyl, pyrazolyl, pyrazolinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolidin-2-onyl, pyrrolinyl, pyrrolyl, quinolinyl, quinoxaloyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydropyranyl, tetrahydroquinolyl, tetrazolyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, thiomorpholinyl, thiopyranyl, and triazolyl.

[045] The terms "hydroxy" and "hydroxyl" as used herein refers to -OH.

[046] The term "hydroxyalkyl" as used herein refers to a hydroxy attached to an alkyl group.

[047] The term "hydroxyaryl" as used herein refers to a hydroxy attached to an aryl group.

[048] The term "ketone" as used herein refers to the structure -C(O)-Rn (such as acetyl, $-C(O)CH_3$) or $-R_n-C(O)-R_o-$. The ketone can be attached to another group through R_n or R_o. R_n or R_o can be alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl or aryl, or R_n or R_o can be joined to form a 3- to 12-membered ring.

[049] The term "monoester" as used herein refers to an analogue of a dicarboxylic acid wherein one of the carboxylic acids is functionalized as an ester and the other carboxylic acid is a free carboxylic acid or salt of a carboxylic acid. Examples of monoesters include, but are not limited to, to monoesters of succinic acid, glutaric acid, adipic acid, suberic acid, sebacic acid, azelaic acid, oxalic and maleic acid.

[050] The term "nitro" as used herein refers to the $-NO_2$.

[051] The term "perfluoroalkoxy" as used herein refers to an alkoxy group in which all of the hydrogen atoms have been replaced by fluorine atoms.

[052] The term "perfluoroalkyl" as used herein refers to an alkyl group in which all of the hydrogen atoms have been replaced by fluorine atoms. Exemplary perfluroalkyl groups include, but are not limited to, C_{1-5} perfluoroalkyl, such as trifluoromethyl, etc.

[053] The term "perfluorocycloalkyl" as used herein refers to a cycloalkyl group in which all of the hydrogen atoms have been replaced by fluorine atoms.

[054] The term "phenyl" as used herein refers to a 6-membered carbocyclic aromatic ring. The phenyl group can also be fused to a cyclohexane or cyclopentane ring. Phenyl can be substituted with one or more substituents including alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone.

[055] The term "phosphate" as used herein refers to the structure $-OP(O)O_2-$, $-R_xOP(O)O_2-$, $-OP(O)O_2R_y-$, or $-R_xOP(O)O_2R_y-$, wherein R_x and R_y can be alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl, hydrogen

[056] The term "sulfide" as used herein refers to the structure $-R_ZS-$, where R_Z can be alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, haloalkyl, heteroaryl, heterocyclyl. The sulfide may be cyclic, forming a 3 to 12-membered ring. The term "alkylsulfide" as used herein refers to an alkyl group attached to a sulfur atom.

[057] The term "sulfinyl" as used herein refers to the structure $-S(O)O-$, $-R_pS(O)O-$, $-R_pS(O)OR_q-$, or $-S(O)OR_q-$, wherein R_p and R_q can be alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, , haloalkyl, heteroaryl, heterocyclyl, hydroxyl, Exemplary

sulfinyl groups include, but are not limited to, alkylsulfinyls wherein at least one of R_p or R_q is alkyl, alkenyl or alkynyl.

[058] The term "sulfonamide" as used herein refers to the structure $-(R_r)-N-S(O)_2-R_s-$ or $-R_t(R_r)-N-S(O)_2-R_s$, where R_t, R_r, and R_s can be, for example, hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, and heterocyclyl. Exemplary sulfonamides include alkylsulfonamides (e.g., where R_s is alkyl), arylsulfonamides (e.g., where $R_s$is aryl), cycloalkyl sulfonamides (e.g., where R_s is cycloalkyl), and heterocyclyl sulfonamides (e.g., where R_s is heterocyclyl), etc.

[059] The term "sulfonate" as used herein refers to $-OSO_3^-$. Sulfonate includes salts such as $-OSO_3Na$, $-OSO_3K$, etc. and the acid $-OSO_3H$

[060] The term "sulfonic acid" refers to $-SO_3H-$ and its corresponding salts, e.g. $-SO_3K-$, $-SO_3Na-$.

[061] The term "sulfonyl" as used herein refers to the structure R_USO_2-, where R_U can be alkyl, alkenyl, alkynyl, aryl, cycloalkyl, and heterocyclyl, e.g., alkylsulfonyl. The term "alkylsulfonyl" as used herein refers to an alkyl group attached to a sulfonyl group. "Alkylsulfonyl" groups can optionally contain alkenyl or alkynyl groups.

[062] The term "thioketone" refers to the structure $-R_V-C(S)-R_W-$. The ketone can be attached to another group through R_V or R_W. R_V or R_W can be alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl or aryl, or R_V or R_W can be joined to form a 3- to 12-membered ring.

[063] "Alkyl," "alkenyl," "alkynyl", "alkoxy", "amino" and "amide" groups can be substituted with or interrupted by or branched with at least one group selected

from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide, thioketone, ureido and N. The substituents may be branched to form a substituted or unsubstituted heterocycle or cycloalkyl.

[064] As used herein, a "suitable substituent" refers to a group that does not nullify the synthetic or pharmaceutical utility of the compounds of the invention or the intermediates useful for preparing them. Examples of suitable substituents include, but are not limited to: C_{1-22}, C_{1-8}, and C_{1-6} alkyl, alkenyl or alkynyl; C_{1-6} aryl, C_{2-5} heteroaryl; C_{3-7} cycloalkyl; C_{1-22}, C_{1-8}, and C_{1-6} alkoxy; C_6 aryloxy; -CN; -OH; oxo; halo, carboxy; amino, such as -NH(C_{1-22}, C_{1-8}, or C_{1-6} alkyl), -N(C_{1-22}, C_{1-8}, and C_{1-6} alkyl)$_2$, -NH((C_6)aryl), or -N((C_6)aryl)$_2$; formyl; ketones, such as -CO(C_{1-22}, C_{1-8}, and C_{1-6} alkyl), --CO((C_6 aryl) esters, such as -CO_2(C_{1-22}, C_{1-8}, and C_{1-6} alkyl) and -CO_2 (C_6 aryl). One of skill in art can readily choose a suitable substituent based on the stability and pharmacological and synthetic activity of the compound of the invention.

[065] The term "pharmaceutically acceptable carrier" as used herein refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

[066] The term "pharmaceutically acceptable composition" as used herein refers to a composition comprising at least one compound as disclosed herein formulated together with one or more pharmaceutically acceptable carriers.

[067] The term "pharmaceutically acceptable prodrugs" as used herein represents those prodrugs of the compounds of the present invention that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, commensurate with a reasonable benefit / risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. A discussion is provided in Higuchi et al., "Pro-drugs as Novel Delivery Systems," *ACS Symposium Series*, Vol. 14, and in Roche, E.B., ed. *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

[068] The term "pharmaceutically acceptable salt(s)" refers to salts of acidic or basic groups that may be present in compounds used in the present compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including but not limited to sulfate, citrate, matate, acetate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate,

methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds included in the present compositions, that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts.

[069] The compounds of the disclosure may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as geometric isomers, enantiomers or diastereomers. The term "stereoisomers" when used herein consist of all geometric isomers, enantiomers or diastereomers. These compounds may be designated by the symbols "R" or "S," depending on the configuration of substituents around the stereogenic carbon atom. The present invention encompasses various stereoisomers of these compounds and mixtures thereof. Stereoisomers include enantiomers and diastereomers. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

[070] Individual stereoisomers of compounds of the present invention can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of

enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, or (3) direct separation of the mixture of optical enantiomers on chiral chromatographic columns. Stereoisomeric mixtures can also be resolved into their component stereoisomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Stereoisomers can also be obtained from stereomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

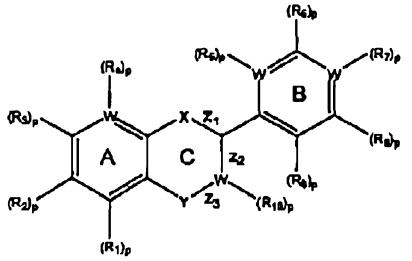
[071] Geometric isomers can also exist in the compounds of the present invention. The present invention encompasses the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a carbocyclic ring. Substituents around a carbon-carbon double bond are designated as being in the "*Z*" or "*E*" configuration wherein the terms "*Z*" and "*E*" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the *E* and *Z* isomers.

[072] Substituents around a carbon-carbon double bond alternatively can be referred to as "cis" or "trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituents on opposite sides of the double bond. The arrangements of substituents around a carbocyclic ring are designated as "cis" or "trans." The term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on

opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

Embodiments of the Invention

[073] Disclosed herein are methods for increasing expression of ApoA-I in a mammal (e.g., a human) comprising administering a therapeutically effective amount of a compound of **Formula II**:



Formula II

wherein:

X is selected from CR_{11}, N and NR_{11},

Y is selected from CO, CS, and SO_2,

R_{11} is selected from hydrogen, unsubstituted alkyl (preferably C_{1-3} alkyl), unsubstituted alkenyl (preferably C_{1-3} alkenyl), and unsubstituted alkynyl (preferably C_{1-3} alkynyl);

R_1 and R_3 are each independently selected from alkoxy (preferably methoxy), alkyl, amino, halogen (preferably chloride), and hydrogen;

R_2 is selected from alkoxy, alkyl, alkenyl, amide, amino, halogen (preferably bromide or chloride), and hydrogen;

R_6 and R_8 are each independently selected from alkoxy, alkyl (preferably methyl), amino, halogen (preferably chloride and fluoride), and hydrogen;

R_5 and R_9 are each independently selected from halogen (preferably chloride), and hydrogen;

R_7 is selected from alkoxy, alkyl, alkenyl, amide, amino, ether, hydrogen, and hydroxyl;

R_{10} is selected from hydrogen and alkyl (preferably methyl); or

two adjacent substituents selected from R_1, R_2, R_3, R_6, R_7, R_8, R_{10}, and R_{11} are connected to form a group selected from aryl, heteroaryl, cycloalkyl, and heterocyclyl;

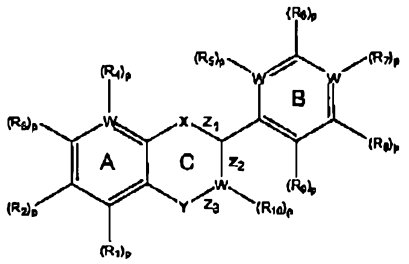
each W is independently selected from C and N, wherein if W is N, then p is 0 or 1, and if W is C, then p is 1;

for $W\text{-}(R_4)_p$, W is C, p is 1 and R_4 is H, or W is N and p is 0;

Z_1, Z_2 and Z_3 are each independently selected from a single bond and a double bond, wherein at least one of Z_1 or Z_2 is a double bond;

and pharmaceutically acceptable salts and hydrates thereof.

[074] Another embodiment includes methods for increasing expression of ApoA-I in a mammal (e.g., a human) comprising administering a therapeutically effective amount of a compound of **Formula II:**



Formula II

wherein:

X is selected from N and CH;

Y is CO;

R_1 and R_3 are each independently selected from alkoxy and hydrogen;

R_2 is selected from alkoxy, alkyl, and hydrogen;

R_6 and R_8 are each independently selected from alkyl, alkoxy, chloride, and hydrogen;

R_8 and R_9 are each hydrogen;

R_7 is selected from amino, hydroxyl, alkoxy (preferably a substituted ethoxy group), and alkyl substituted with a heterocyclyl;

R_{10} is hydrogen; or

two adjacent substituents selected from R_6, R_7, and R_8 are connected to form a heterocyclyl;

each W is independently selected from C and N, wherein if W is N, then p is 0 or 1, and if W is C, then p is 1;

for $W\text{-}(R_{10})_p$, W is N and p is 1;

for $W\text{-}(R_4)_p$, W is C, p is 1 and R_4 is H, or W is N and p is 0;

Z_1 is a double bond, and Z_2 and Z_3 are each a single bond;

with the proviso that if R_2 is selected from alkoxy and hydrogen, then at least one of R_1 and R_3 is alkoxy;

with the proviso that if R_7 is selected from hydroxyl and alkoxy, then at least one of R_6 and R_8 are independently selected from alkyl, alkoxy, and chloride;

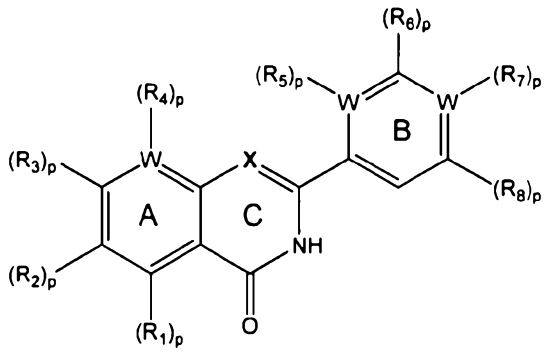
with the proviso that if R_7 is an amino, then X is N;

with the proviso that if for $W\text{-}(R_7)_p$, W is N and p is 0, then at least one of R_6 and R_8 is chloride;

and pharmaceutically acceptable salts and hydrates thereof.

[075] The following is a list of specific exemplary embodiments that are encompassed by the invention:

[075a] According to a first embodiment of the invention, there is provided a compound of **Formula II**:



Formula II

wherein:

X is N;

R_1 and R_3 are each independently selected from alkoxy and hydrogen;

R_2 is selected from alkoxy, alkyl, and hydrogen;

R_6 and R_8 are each independently selected from alkyl, alkoxy, chloride, and hydrogen;

R_4 and R_5 are hydrogen;

R_7 is selected from amino, hydroxyl, alkoxy, and alkyl substituted with a heterocyclyl, or

two adjacent substituents selected from R_6, R_7, and R_8 are connected to form a heterocyclyl;

each W is independently selected from C and N, p is 1 except that when W is N, then p is 0;

with the proviso that if R_2 is selected from alkoxy or hydrogen, then at least one of R_1 and R_3 is alkoxy;

with the proviso that if R_7 is selected from hydroxyl or alkoxy, then at least one of R_6 and R_8 are independently selected from alkyl, alkoxy, and chloride;

with the proviso that for W-$(R_7)_p$, if W is N and p is 0, then at least one of R_6 and R_8 is chloride;

or a pharmaceutically acceptable salt or hydrate thereof.

[075b] According to a second embodiment of the invention, there is provided a pharmaceutical composition comprising a compound according to the first embodiment, or

a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier.

[075c] According to a third embodiment of the invention, there is provided a method of treating or preventing a cardiovascular, cholesterol or lipid related disorder in a mammal comprising administering to said mammal a therapeutically effective amount of a compound according to the first embodiment, or a pharmaceutically acceptable salt or hydrate thereof, or a pharmaceutical composition according to the second embodiment.

[075d] According to a fourth embodiment of the invention, there is provided a method of increasing expression of ApoA-I and/or HDL-C in a mammal comprising administering to said mammal a therapeutically effective amount of a compound according to the first embodiment, or a pharmaceutically acceptable salt or hydrate thereof, or a pharmaceutical composition according to the second embodiment.

Pharmaceutical Formulations and Methods of Treatment

[076] The present disclosure also provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with one or more pharmaceutically acceptable carriers. These formulations include those suitable for oral, rectal, topical, buccal and parenteral (e.g. subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used.

[077] Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of the compound as powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such formulations may be prepared by any suitable

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method of pharmacy which includes the step of bringing into association the active compound and the carrier or excipient (which may constitute one or more accessory ingredients). The carrier must be acceptable in the sense of being compatible with the other ingredients of the formulation and must not be deleterious to the recipient. The carrier may be a solid or a liquid, or both, and may be formulated with the compound as a unit-dose formulation, for example, a tablet, which may contain from about 0.05% to about 95% by weight of the active compound. Other pharmacologically active substances may also be present including other compounds. The formulations of the invention may be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components.

[078] For solid compositions, conventional nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate, and the like. Liquid pharmacologically administrable compositions can, for example, be prepared by dissolving, dispersing, etc., an active compound as described herein and optional pharmaceutical adjuvants in an excipient, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. In general, suitable formulations may be prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet may be prepared by compressing or molding a powder or granules of the compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed

with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

[079] Formulations suitable for buccal (sub-lingual) administration include lozenges comprising a compound in a flavored base, usually sucrose and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

[080] Formulations of the present invention suitable for parenteral administration comprise sterile aqueous preparations of the compounds, which are approximately isotonic with the blood of the intended recipient. These preparations are administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention may contain from about 0.1 to about 5% w/w of the active compound.

[081] Formulations suitable for rectal administration are presented as unit-dose suppositories. These may be prepared by admixing the compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

[082] Formulations suitable for topical application to the skin may take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers and excipients which may be used include Vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is

generally present at a concentration of from about 0.1% to about 15% w/w of the composition, for example, from about 0.5 to about 2%.

[083] The amount of active compound administered may be dependent on the subject being treated, the subject's weight, the manner of administration and the judgment of the prescribing physician. For example, a dosing schedule may involve the daily or semi-daily administration of the encapsulated compound at a perceived dosage of about 1 µg to about 1000 mg. In another embodiment, intermittent administration, such as on a monthly or yearly basis, of a dose of the encapsulated compound may be employed. Encapsulation facilitates access to the site of action and allows the administration of the active ingredients simultaneously, in theory producing a synergistic effect. In accordance with standard dosing regimens, physicians will readily determine optimum dosages and will be able to readily modify administration to achieve such dosages.

[084] A therapeutically effective amount of a compound or composition disclosed herein can be measured by the therapeutic effectiveness of the compound. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being used. In one embodiment, the therapeutically effective amount of a disclosed compound is sufficient to establish a maximal plasma concentration. Preliminary doses as, for example, determined according to animal tests, and the scaling of dosages for human administration is performed according to art-accepted practices.

[085] Toxicity and therapeutic efficacy can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the

dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. Compositions that exhibit large therapeutic indices are preferable.

[086] Data obtained from the cell culture assays or animal studies can be used in formulating a range of dosage for use in humans. Therapeutically effective dosages achieved in one animal model may be converted for use in another animal, including humans, using conversion factors known in the art (see, e.g., Freireich et al., *Cancer Chemother. Reports* 50(4):219-244 (1966) and Table 1 for Equivalent Surface Area Dosage Factors).

Table 1

From: \ To:	Mouse (20 g)	Rat (150 g)	Monkey (3.5 kg)	Dog (8 kg)	Human (60 kg)
Mouse	1	1/2	1/4	1/6	1/12
Rat	2	1	1/2	1/4	1/7
Monkey	4	2	1	3/5	1/3
Dog	6	4	3/5	1	1/2
Human	12	7	3	2	1

[087] The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Generally, a therapeutically effective amount may vary with the subject's age, condition, and sex, as well as the severity of the medical condition in the subject. The dosage may be determined by a physician and adjusted, as necessary, to suit observed effects of the treatment.

[088] In one embodiment, a compound as disclosed herein, or a pharmaceutically acceptable salt or hydrate thereof, is administered in combination with another therapeutic agent. The other therapeutic agent can provide additive or synergistic value relative to the administration of a compound of the present invention alone. The therapeutic agent can be, for example, a statin; a PPAR agonist, e.g., a thiazolidinedione or fibrate; a niacin, a RVX, FXR or LXR agonist; a bile-acid reuptake inhibitor; a cholesterol absorption inhibitor; a cholesterol synthesis inhibitor; an ion-exchange resin; an antioxidant; an inhibitor of AcylCoA cholesterol acyltransferase (ACAT inhibitor); a tyrophostine; a sulfonylurea-based drug; a biguanide; an alpha-glucosidase inhibitor; an apolipoprotein E regulator; a HMG-CoA reductase inhibitor, a microsomal triglyceride transfer protein; an LDL-lowing drug; an HDL-raising drug; an HDL enhancer; a regulator of the apolipoprotein A-IV and/or apolipoprotein genes; or any cardiovascular drug.

[089] In one embodiment, a method of treating or preventing cardiovascular disease, cholesterol- or lipid-related disorders, comprises administering to a mammal (e.g., a human) a therapeutically effective amount of a disclosed compound. The disclosed compound may be administered as a pharmaceutically acceptable composition, comprising a disclosed compound and a pharmaceutically acceptable carrier.

[090] As used herein, the term "cardiovascular disease" refers to diseases and disorders of the heart and circulatory system. Exemplary cardiovascular diseases, including cholesterol- or lipid-related disorders, include, but are not limited to acute coronary syndrome, angina, arteriosclerosis, atherosclerosis, carotid atherosclerosis, cerebrovascular disease, cerebral infarction, congestive

heart failure, congenital heart disease, coronary heart disease, coronary artery disease, coronary plaque stabilization, dyslipidemias, dyslipoproteinemias, endothelium dysfunctions, familial hypercholeasterolemia, familial combined hyperlipidemia, hypoalphalipoproteinemia, hypertriglyceridemia, hyperbetalipoproteinemia, hypercholesterolemia, hypertension, hyperlipidemia, intermittent claudication, ischemia, ischemia reperfusion injury, ischemic heart diseases, cardiac ischemia, metabolic syndrome, multi-infarct dementia, myocardial infarction, obesity, peripheral vascular disease, reperfusion injury, restenosis, renal artery atherosclerosis, rheumatic heart disease, stroke, thrombotic disorder, transitory ischemic attacks, and lipoprotein abnormalities associated with Alzheimer's disease, obesity, diabetes mellitus, syndrome X, impotence, multiple sclerosis, Parkinson's diseases and an inflammatory diseases.

[091] One embodiment provides methods for altering lipid metabolism in a patient, e.g., increasing the ratio of HDL to LDL or ApoA-I to ApoB in the blood of a patient, comprising administering to the patient a composition of the invention in an amount effective to alter lipid metabolism.

[092] One embodiment provides methods for elevating the levels of ApoA-I associated molecules, such as HDL, in the blood of a mammal, comprising administering to the mammal a composition comprising a disclosed compound or composition in an amount effective to elevate levels of ApoA-I and HDL associated proteins in the mammal.

[093] In one embodiment, "treatment" or "treating" refers to an amelioration of a disease or disorder, or at least one discernible symptom thereof. In another embodiment, "treatment" or "treating" refers to an amelioration of at least one

measurable physical parameter, not necessarily discernible by the patient. In yet another embodiment, "treatment" or "treating" refers to inhibiting the progression of a disease or disorder, either physically, e.g., stabilization of a discernible symptom, physiologically, e.g., stabilization of a physical parameter, or both. In yet another embodiment, "treatment" or "treating" refers to delaying the onset of a disease or disorder. For example, treating a cholesterol disorder may comprise decreasing blood cholesterol levels.

[094] One embodiment provides a compound for administration to a patient, such as a human, as a preventative measure against cardiovascular diseases, including cholesterol- or lipid-related disorders. As used herein, "prevention" or "preventing" refers to a reduction of the risk of acquiring a given disease or disorder. An additional aspect provides a method for prevention of arteriosclerosis lesion development in a mammal, including the development of new arteriosclerotic lesions. In another aspect, the present invention provides a method for regressing arteriosclerosis lesions.

[095] In another embodiment, the present compositions are administered as a preventative measure to a patient, such as a human having a genetic predisposition to a cardiovascular disease, including cholesterol- or lipid-related disorders, for example familial hypercholeasterolemia, familial combined hyperlipidemia, atherosclerosis, a dyslipidemia, a dyslipoproteinemia, or Alzheimer's disease.

[096] In another embodiment, the compositions of the invention are administered as a preventative measure to a patient having a non-genetic predisposition to a cardiovascular disease, including cholesterol- or lipid-related disorders, Examples of such non-genetic predispositions include, but are not

limited to, cardiac bypass surgery and percutaneous transluminal coronary angioplasty, which often leads to restenosis, an accelerated form of atherosclerosis; diabetes in women, which often leads to polycystic ovarian disease; and cardiovascular disease, which often leads to impotence.

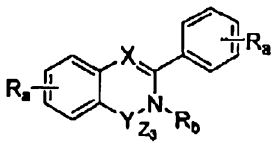
[097] Angioplasty and open heart surgery, such as coronary bypass surgery, may be required to treat cardiovascular diseases, such as atherosclerosis. These surgical procedures entail using invasive surgical devices and/or implants, and are associated with a high risk of restenosis and thrombosis. Accordingly, the compounds of the invention may be used as coatings on surgical devices (e.g., catheters) and implants (e.g., stents) to reduce the risk of restenosis and thrombosis associated with invasive procedures used in the treatment of cardiovascular diseases.

[098] In another embodiment, the present compositions may be used for the prevention of one disease or disorder and concurrently treating another (e.g., prevention of polycystic ovarian disease while treating diabetes; prevention of impotence while treating a cardiovascular disease).

[099] Diseases and conditions associated with "diabetes mellitus" as defined herein refer to chronic metabolic disorder(s) caused by absolute or relative insulin deficiency including, but not limited to hyperglycemia, hyperinsulinemia, hyperlipidemia, insulin resistance, impaired glucose metabolism, obesity, diabetic retinopathy, macular degeneration, cataracts, diabetic nephropathy, glomerulosclerosis, diabetic neuropathy, erectile dysfunction, premenstrual syndrome, vascular restenosis, ulcerative colitis, skin and connective tissue disorders, foot ulcerations, metabolic acidosis, arthritis, osteoporosis and impaired glucose tolerance.

PREPARATION OF COMPOUNDS

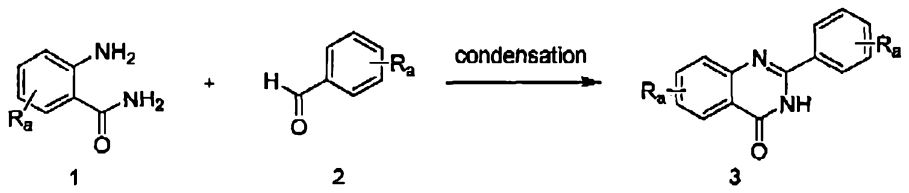
[0100] Exemplary compounds of the invention represented by the general formula A:



A

wherein:

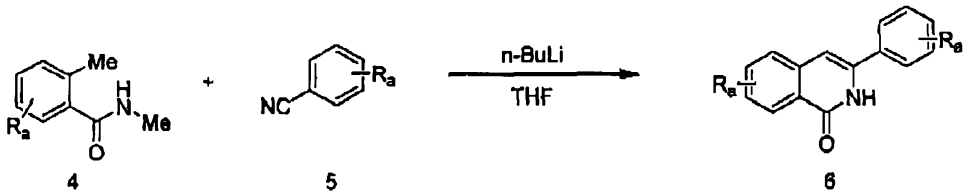
R_a may be selected from groups including, but not limited to, alkoxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, cycloalkyl, ether, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen and hydroxyl; R_b may be selected from groups including, but not limited to, alkyl and hydrogen; X may be selected from, e.g., CR_c, N and NR_c, where R_c represents substituents such as alkyl, alkenyl, alkynyl, and hydrogen; Y may be selected from, e.g., CO, CS, and SO_2; and Z_3 may be a single or double bond; may be synthesized from readily available starting materials as outlined in the exemplary schemes below. It should be appreciated that these designations are non-limiting examples.



Scheme 1

[0101] Scheme 1 illustrates that condensation followed by oxidation of amide **1** and aldehyde **2** can provide quinazolinone **3**. Condensation can occur under a variety of conditions, such as $NaHSO_3$ and p-TsOH in dimethylacetamide,

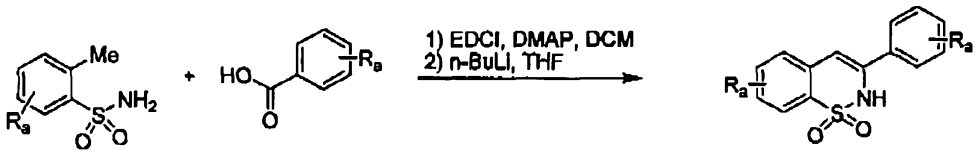
I_2 in the presence of K_2CO_3, and treatment with catalytic trifluoroacetic acid followed by DDQ oxidation.



4 5 6

Scheme 2

[0102] Condensation of amide **4** with nitrile **5** in the presence of n-BuLi can afford isoquinolinone **6**, as shown in Scheme 2.



7 8 9

Scheme 3

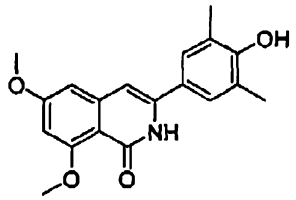
[0103] Scheme 3 provides a method for synthesizing benzothiazine-1,1-dioxide **9**. Amide coupling of sulfonamide **7** with carboxylic acid **8** can be followed by treatment with n-BuLi to afford **9**.

EXAMPLES

[0104] Abbreviations used herein denote the following compounds, reagents and substituents: acetic acid (AcOH); 2,2'-azobisisobutyronitrile (AIBN); *N*-bromosuccinimide (NBS); N-tert-butoxycarbonyl (Boc); t-butyldimethylsilyl (TBDMS); *m*-chloroperoxybenzoic acid (*m*CPBA); dimethylaminopyridine (DMAP); dichloromethane (DCM); dimethylformamide (DMF); dimethylsulfoxide (DMSO); ethanol (EtOH); ethyl acetate (EtOAc); 1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide (EDCI); 1-hydroxybenzotriazole (HOBt); iodomethane (MeI); lithium hexamethyldisilazide (LHMDS); methanol (MeOH); methoxymethyl (MOM); tetrahydrofuran (THF); triethylamine (Et_3N); lithium aluminum hydride (LAH); p-toluenesulfonic acid (p-TSA); tetrabutylammonium fluoride (TBAF); N-Methyl morpholine (NMM); N,N-dimethylacetamide (DMA); twice daily (BID), once daily (QD).

Example 1

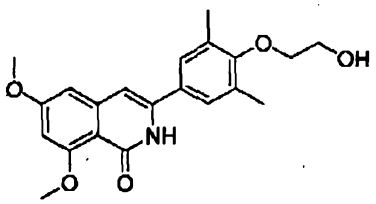


3-(4-hydroxy-3,5-dimethylphenyl)-6,8-dimethoxyisoquinolin-1(2H)-one

[0105] To a suspension of 2-methyl-4,6-dimethoxy benzoic acid (2.61 g, 13.1 mmol) in CH_2Cl_2 (50 mL), oxalyl chloride (3.38 g, 26.6 mmol) was added and the mixture was stirred at room temperature for 16 h. The solvent and excess oxalyl chloride were removed at reduced pressure. The solid was dissolved in CH_2Cl_2 (10 mL) and methyl amine (1.24 g, 39.9 mmol) with cooling and was stirred at room temperature for 4 h. The solvent was removed and crude product was purified by chromatography by using 5% methanol in CH_2Cl_2 to give the amide (2.27 g, 82%). To a solution of the above amide (2.27 g, 10.9 mmol) in THF (50 mL), n-butyl lithium (9.98 mL, 25.0 mmol, 2.5 M solution in hexane) was added slowly under nitrogen with cooling, maintaining the temperature below 20°C. The mixture was stirred for 1 h at 0°C, then cooled to -50°C, and a solution of 4-O-TBDMS-3,5-dimethyl benzonitrile (2.97 g, 11.39 mmol) in THF (10 mL) was added quickly, the cooling bath was removed and the mixture was stirred for 16 h

at room temperature. A saturated aqueous NH_4Cl solution was added with cooling, and the layers were separated. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to give 3.9 g of the crude product mixture. A suspension of the crude product mixture (3.9 g) in ethanol (20 mL) was heated with conc. HCl (2 mL) at 80°C for 2 h. The reaction mixture was cooled to room temperature and the solvent was removed. The solid was dissolved in water and neutralized by $NaHCO_3$, followed by extraction with CH_2Cl_2. The product was purified by chromatography to give two products: 3-(4-hydroxy-3,5-dimethylphenyl)-6,8-dimethoxy-2-methylisoquinolin-1(2H)-one (128 mg, 5%) and 3-(4-hydroxy-3,5-dimethylphenyl)-6,8-dimethoxyisoquinolin-1(2H)-one (340 mg, 9%). Selected data for 3-(4-hydroxy-3,5-dimethylphenyl)-6,8-dimethoxyisoquinolin-1(2H)-one: MS (ES) *m/z*: 326.00; MP 226-227°C.

Example 2



3-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6,8-dimethoxyisoquinolin-1(2H)-one

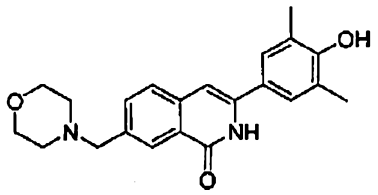
[0106] To a solution of 3,5-dimethyl-4-hydroxy benzonitrile (1.0 g, 6.79 mmol) in DMF (100 mL), were added a NaH (1.065 g, 26.63 mmol) and (2-bromoethoxy)-tert-butyl dimethyl silane (1.95 g, 8.15 mmol). The reaction mixture was stirred for 10 d at room temperature under nitrogen. The reaction mixture was poured into ice-water and the products were extracted with ethyl acetate. The organic layer was separated, washed with water, dried and concentrated to give

crude product, which was purified by column chromatography to give 1.9 g of the B-ring building block in 92% yield.

[0107] n-Butyl lithium (2.84 mL, 7.1 mmol, 2.5 M solution in hexane) was added slowly to a solution of 2,4-dimethoxy-6-methyl benzamide (650 mg, 3.1 mmol) in THF (30 mL), under nitrogen with cooling (ice-salt bath), maintaining the temperature below 20°C. After completion of addition, the mixture was stirred for 1 h at 0°C, and then cooled to -50°C and a solution of 4-(2-tert-butyldimethyl silanyloxy) ethoxy)-3,5-dimethyl benzonitrile (the B-ring building block, above) (996 mg, 3.26 mmol) in THF (10 mL) was added quickly. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and was stirred for 16 h at room temperature. A saturated NH_4Cl solution was added with cooling, and the layers were separated. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to give 1.2 g of crude product.

[0108] The above crude product (1.2 g) was treated with ethanol (10 mL) and conc. HCl (2 mL) at 80°C for 1 h. The solvent was removed and the residue was dissolved in methanol and neutralized by $NaHCO_3$. The solvent was evaporated and crude product was purified by column chromatography to give 3-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6,8-dimethoxyisoquinolin-1(2H)-one (100 mg, 11%). Selected data: MP 193-195°C.

Example 3



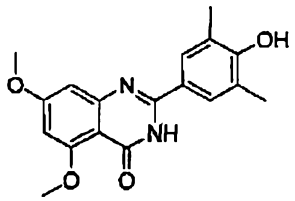
3-(4-hydroxy-3,5-dimethylphenyl)-7-(morpholinomethyl)isoquinolin-1(2H)-one

[0109] Hydrogen bromide in acetic acid (13 mL, 33 wt%) was added to a mixture of 2-methyl benzoic acid (4.08 g, 30 mmol), paraformaldehyde (2.50 g, 83.0 mmol), and o-phosphoric acid (7 mL, 85%). The reaction mixture was stirred at 115°C for 15 h. It was cooled to room temperature and poured into ice-cold water. A white precipitate was formed. The mixture was extracted with ethyl acetate (300 mL). The organic layer was washed with water (100 mL), brine (100 mL) and dried over anhydrous Na_2SO_4. Removal of solvent gave 6.84 g of a white solid, which was used in the next step without further purification. The above compound (6.8 g) was dissolved in anhydrous dichloromethane (150 mL). Oxalyl chloride (7.8 mL) was added drop-wise. After the addition was complete, 3 drops of anhydrous DMF were added. A vigorous reaction occurred and the stirring was continued overnight. Solvent and excess oxalylchloride were removed under reduced pressure and the residue was dried under vacuum to give 7.02 g of brown liquid, which was used in the next step without further purification. The above compound (7.02 g, 28.36 mmol) was dissolved in anhydrous THF (60 mL) and cooled to 0°C. A solution of *N*-methylamine (2.0 M in THF, 19 mL, 38.03 mmol) was added drop-wise under nitrogen. The stirring was continued for 15 min at 0°C. The ice-bath was removed, and the stirring was continued at room temperature for 3 h. A white precipitate was formed. Water (100 mL) was added

and the mixture was extracted with ethyl acetate (150 mL). The organic layer was separated, washed with water (50 mL), saturated $NaHCO_3$ solution (2×50 mL), water (50 mL), and brine (50 mL), and dried over anhydrous Na_2SO_4. Removal of solvent gave 5.64 g of 5-bromomethyl-2,N-dimethylbenzamide as a white solid which was used in the next step without further purification. To a solution of the above compound (2.42 g, 10 mmol) in anhydrous THF was added morpholine (1.92 g, 22 mmol) at room temperature under nitrogen. A white precipitate was formed. Stirring continued overnight. Water (100 mL) was added and the mixture was extracted with ethyl acetate (150 mL). The organic layer was separated, washed with water (50 mL) and brine (50 mL) and dried (Na_2SO_4). Removal of solvent gave a colorless oil, which was purified by column chromatography (silica gel 230-400 mesh; 0-5% methanol in CH_2Cl_2 as eluent) to give the desired benzamide intermediate (yield 0.50 g, 20%). N-Butyl lithium (1.6 M solution in hexanes, 4.1 mL, 6.6 mmol) was added drop-wise to a solution of the benzamide (0.5 g, 2.0 mmol) in anhydrous THF (4 mL) at -10°C over a period of 10 min under nitrogen. Stirring was continued at 0°C for 1 h. The reaction mixture was cooled to -50°C. A solution of 4-(*tert*-butyldimethylsilanyloxy)-3,5-dimethylbenzonitrile (0.653 g, 2.5 mmol) in anhydrous THF (3 mL) was quickly added. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature. Stirring was continued at room temperature for 1 h. An aqueous ammonium chloride solution (5 mL) was added followed by ethyl acetate (50 mL). The organic layer was separated, washed with water (5 mL) and dried (Na_2SO_4). Removal of the solvent gave 1.23 g pale yellow gummy material, which was used in next step without further purification. The above compound (1.2 g) was dissolved in 10 mL anhydrous ethanol. Conc. HCl (1 mL) was added and the

mixture was refluxed for 15 min, then cooled to room temperature. The solvent was removed under reduced pressure. The crude compound was basified with methanolic ammonia and purified by column chromatography (silica gel 230-400 mesh; 0-5% methanol in CH_2Cl_2 as eluent) to give 3-(4-hydroxy-3,5-dimethylphenyl)-7-morpholin-4-ylmethyl-2H-isoquinolin-1-one (35 mg) as a white solid (the free base). To a solution of the above compound (35 mg) in CH_2Cl_2 (5 mL) and MeOH (1 mL) was added drop-wise hydrogen chloride in ether (0.5 mL, 1.0 M) under nitrogen. The reaction mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and dried under vacuum to give the hydrochloride of 3-(4-hydroxy-3,5-dimethylphenyl)-7-(morpholinomethyl)isoquinolin-1(2H)-one (36 mg, 93%) as a yellow solid. Selected data: MP 281-283°C (hydrochloride).

Example 4



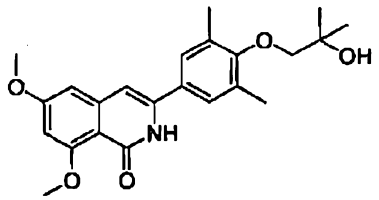
2-(4-hydroxy-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one

[0110] A solution of 3,5-dimethoxyaniline (199 g, 1.30 mol) in ether (5.0 L) in a 5 L 3-necked flask was cooled to 0°C. HCl gas (227 g) was bubbled through the solution over 45 min. After 45 min at 10°C, the mixture was filtered, washed with isopropylacetate (4 L), and dried overnight on high vacuum at 45°C to give the hydrochloride (242.3 g, 98%), as a white solid. A mixture of the hydrochloride above (20 g, 0.105 mol) and oxalyl chloride (33 mL) in a 3-necked flask equipped with a reflux condenser was heated for 2 h with stirring (170°C external

temperature), and the oxalyl chloride was distilled from the reaction mixture. The flask was cooled to 0°C and methanol (40 mL) was added. The reaction mixture was heated to reflux for 45 min, filtered while hot, and washed with methanol (80 mL) to give the 4,6-dimethoxyisatin (17.2 g, 79%) as a yellow-green solid. To a heated solution (external temp 70°C) of the isatin (162 g, 0.78 mol) in aqueous NaOH (40%, 1.5 L) was added H_2O_2 (35%, 405 mL) slowly over 2 h. After the addition of each portion of H_2O_2, the internal reaction temperature (initially 64°C) increased (to a maximum temp of 80°C). After the addition was complete, the foaming reaction mixture was then stirred for an additional 2 h at 70°C, and the mixture was allowed to stir overnight while cooling to RT. The mixture was heated to 70°C. Additional H_2O_2 (75 mL) was added, and the mixture was stirred at 70°C for a further 2 h until the reaction was complete. After cooling to 10°C (bath temperature), aqueous $Na_2S_2O_3$ (150 mL, saturated) was added. The mixture was brought to pH 8 with HCl (37%, 1.6 L) and pH 6 with acetic acid (glacial, 75 mL), without allowing the reaction mixture to warm to greater than 40°C. Filtration of the reaction mixture and washing with water (4 L) gave the expected amino acid as a tan solid (83.7 g, 55%). To a solution of the amino acid (82.7 g, 0.42 mol) in anhydrous THF (4.2 L) was added EDCI (89.2 g, 0.48 mol), HOBT (65 g, 0.48 mol), and NMM (51.3 mL), and the mixture was allowed to stir at RT for 3 h. Aqueous NH_3 (83 mL, 50%) was added, and the mixture was stirred at RT for 16 h. Water (1.25 L) was added, and the mixture was extracted with DCM (2×250 mL). The combined extracts were then washed with water (2×500 mL). Concentration, formation of a slurry with ether (550 mL), filtration, and drying under high vacuum gave 2-amino-4,6-dimethoxybenzamide (46.7 g, 57%) as a brown solid.

[0111] 2-Amino-4,6-dimethoxy-benzamide (1.06 g, 5.4 mmol), 3,5-dimethyl-4-hydroxybenzaldehyde (0.810 g, 5.4 mmol), K_2CO_3 (0.747 g, 5.4 mmol) and I_2 (1.645 g, 6.5 mmol) were mixed in DMF (20 mL) and the reaction mixture was heated at 80°C for 12 h. It was cooled to RT and poured into crushed ice. The solid was collected and purified by column chromatography to give 2-(4-hydroxy-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (0.9 g, 51%) as a white solid. Selected data: MP 291-293°C.

Example 5



3-(4-(2-hydroxy-2-methylpropoxy)-3,5-dimethylphenyl)-6,8-dimethoxyisoquinolin-1(2H)-one

[0112] To a solution of 4-hydroxy-3,5-dimethylbenzonitrile (2.00 g, 13.5 mmol) and 1-chloro-2-methyl propan-2-ol (8.85 g, 81.5 mmol) in ethanol (50 mL) was added potassium carbonate (7.5 g, 54 mmol) and water (5 mL). The reaction mixture was stirred at reflux for 24 h and cooled to RT. The precipitated solid was filtered off and washed with water. The solid was dissolved in ethyl acetate (100 mL), washed with water (50 mL), brine (50 mL), and dried over anhydrous Na_2SO_4. Removal of solvent gave 4-(2-hydroxy-2-methylpropoxy)-3,5-dimethyl benzonitrile (2.9 g, 97%) as a white solid.

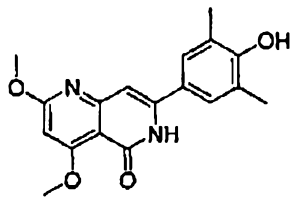
[0113] To a solution of 4-(2-hydroxy-2-methylpropoxy)-3,5-dimethyl benzonitrile (2.90 g, 13.2 mmol) in anhydrous DMF (20 mL) was added imidazole (2.7 g, 40 mmol) and *tert*-butyldimethylsilylchloride (2.19 g, 14.6 mmol). The reaction mixture was stirred at RT under nitrogen for 3 d. Water (200 mL) was

added and the mixture was extracted with ethyl acetate (200 mL). The organic layer was washed with water (2×100 mL) and brine (100 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude compound was purified by column chromatography to give 4-[2-(*tert*-butyldimethylsilanyloxy)-2-methylpropoxy]-3,5-dimethylbenzonitrile (2.24 g, 54%). n-Butyl lithium (6.2 mL, 6.6 mmol, 1.6 M solution in hexanes) was added to a solution of 2,4-dimethoxy-6-*N*-dimethylbenzamide (0.9 g, 4.3 mmol) in anhydrous THF (10 mL) drop-wise at -10°C over a period of 10 min under nitrogen. The stirring was continued at 0°C for 1 h. The reaction mixture was cooled to -50°C. A solution of 4-[2-(*tert*-butyldimethylsilanyloxy)-2-methylpropoxy]-3,5-dimethylbenzonitrile (1.58 g, 4.73 mmol) in anhydrous THF (5 mL) was quickly added. The cooling bath was removed and the reaction mixture was allowed to warm to RT. The stirring was continued at RT for 1 h. An aqueous ammonium chloride solution (10 mL) was added followed by ethyl acetate (100 mL). The organic layer was separated, washed with water (10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude compound was purified by column chromatography (silica gel 230-400 mesh; 0-5% methanol in CH_2Cl_2 as eluent) to give 3-{4-[2-(*tert*-butyldimethylsilanyloxy)-2-methylpropoxy]-3,5-dimethylphenyl}-6,8-dimethoxy-2H-isoquinolin-1-one (0.82 g, 37%), as a white solid.

[0114] The above compound (0.42 g, 0.82 mmol) was dissolved in anhydrous THF (20 mL). Tetrabutylammonium fluoride (4.1 mL, 1.0 M solution in THF) was added at 0°C. The reaction mixture was stirred at 0°C for 10 min, then at RT for 2 h and then stirred at 70°C for 24 h. The mixture was cooled to RT. Saturated aqueous ammonium chloride (30 mL) was added. The organic layer

was separated, washed with water, brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel 230-400 mesh; 0-4% methanol in CH_2Cl_2 as eluent) to give 3-(4-(2-hydroxy-2-methylpropoxy)-3,5-dimethylphenyl)-6,8-dimethoxyisoquinolin-1(2H)-one (0.15 g, 46%), as a white solid. Selected data: MS (ES) *m/z*: 397.98; MP 252-254 °C at decomposition.

Example 6



7-(4-hydroxy-3,5-dimethylphenyl)-2,4-dimethoxy-1,6-naphthyridin-5(6H)-one

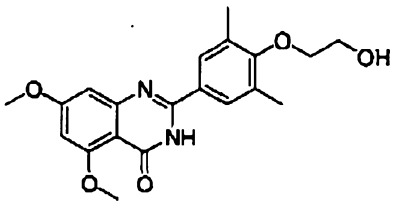
[0115] A mixture of malonic acid (20 g, 192 mmol), 2,4,6-trichlorophenol (72 g, 365 mmol), and phosphorus oxychloride (38 mL, 403.2 mmol) was stirred at reflux for 12 h. The reaction mixture was cooled to 70°C and poured into ice water. The solid was collected by filtration, washed with water, and dried to give malonic acid bis-(2,4,6-trichloro-phenyl) ester (85 g, 95%). A solution of malonic acid bis-(2,4,6-trichloro-phenyl) ester (85 g, 184 mmol) and ethyl 3-aminocrotonate (26.08 g, 201.9 mmol) in bromobenzene (100 mL) was stirred at reflux for 50 min. The reaction mixture was cooled to 50°C and diluted with EtOAc (260 mL). The solid was collected by filtration, washed with water, and dried to give 4,6-dihydroxy-2-methyl nicotinic acid ethyl ester (31 g, 86%). A solution of 4,6-dihydroxy-2-methyl nicotinic acid ethyl ester (31 g, 157 mmol) in phosphorus oxychloride (60 mL, 629 mmol) was stirred at reflux for 1.5 h. The extra phosphorus oxychloride was removed and the reaction mixture was poured into

ice water. The solid was removed by filtration. The filtrate was extracted with dichloromethane (3×100 mL) and concentrated. The residue was further purified by column chromatography, to yield 4,6-dichloro-2-methyl nicotinic acid ethyl ester (16.9 g, 46%). A solution of 4,6-dichloro-2-methyl nicotinic acid ethyl ester (16.9 g, 71.3 mmol) in MeOH (60 mL) was mixed with sodium methoxide (58 mL, 256.68 mmol) and stirred at reflux for 12 h. The reaction was quenched by adding HOAc (50 mL). The mixture was diluted with water (200 mL), extracted with dichloromethane (3×100 mL), and concentrated. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc = 6:1), to yield 4,6-dimethoxy-2-methyl nicotinic acid methyl ester (10 g, 67%). A solution of 4,6-dimethoxy-2-methyl nicotinic acid methyl ester (2.6 g, 12.3 mmol), lithium hydroxide (1.06 g, 44.08 mmol) in water (40 mL), MeOH (30 mL) and THF (20 mL) was stirred at reflux for 4 h. The reaction mixture was concentrated to dryness. The residue was mixed with HCl (conc., 20 mL) and was concentrated again on high vacuum to dryness to yield crude 4,6-dimethoxy-2-methyl nicotinic acid (quantitative yield). To a solution of 4,6-dimethoxy-2-methyl nicotinic acid (2.5 g, 12.0 mmol) in dichloromethane (50 mL) and THF (50 mL) at room temperature was added oxalyl chloride (2.57 mL, 29.4 mmol) and DMF (3 drops). The reaction mixture was stirred at room temperature for 0.5 h, concentrated to dryness using a rotary evaporator to afford crude 4,6-dimethoxy-2-methyl nicotinic acid chloride HCl salt (2.8 g, quantitative). A solution of 4,6-dimethoxy-2-methyl nicotinic acid chloride HCl salt (4.8 g, 23.5 mmol) in dichloromethane (100 mL) at room temperature was poured into a beaker of ammonium hydroxide (200 mL). The reaction mixture was stirred at room temperature for 1 h, extracted with dichloromethane (3×100 mL), and concentrated using a rotary evaporator to yield 4,6-dimethoxy-2-methyl-

nicotinamide (2.4 g, 52%) as a light yellow solid. A solution of 4-hydroxy-3,5-dimethylbenzonitrile (2.00 g, 13.59 mmol) in DMF (20 mL) at room temperature was mixed with sodium hydride (0.706 g, 17.6 mmol) and stirred for 0.5 h. Benzyl bromide (1.62 mL, 13.59 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. The reaction was quenched by adding water (200 mL), extracted with EtOAc (3×100 mL), and concentrated. The residue was purified by column chromatography to yield 4-benzyloxy-3,5-dimethylbenzonitrile (3.25 g, 100%) as a white solid. To a solution of 4,6-dimethoxy-2-methyl-nicotinamide (1 g, 5.1 mmol) in THF (120 mL) at -20°C was added n-BuLi (9.6 mL, 15.3 mmol). The reaction was stirred at -20-0°C for 2.5 h and then was cooled to -78°C. 4-Benzyloxy-3,5-dimethylbenzonitrile (1.21 g, 5.1 mmol) was added, the cooling bath was removed, and the reaction was allowed to warm up gradually to room temperature. After stirring at room temperature for 20 h the reaction was quenched by adding water (100 mL), extracted with dichloromethane (3×100 mL), and concentrated using a rotary evaporator. The residue was further purified by column (SiO_2, Hexanes/EtOAc/MeOH = 3:2:1) to yield 7-(4-benzyloxy-3,5-dimethyl-phenyl)-2,4-dimethoxy-[1,6]naphthyridin-5-ylamine (0.4 g, 19%) and 7-(4-benzyloxy-3,5-dimethyl-phenyl)-2,4-dimethoxy-6H-[1,6]naphthyridin-5-one (0.34 g, 16%). A solution of 7-(4-benzyloxy-3,5-dimethyl-phenyl)-2,4-dimethoxy-6H-[1,6]naphthyridin-5-one (0.34 g, 0.82 mmol) in DMF (100 mL) and MeOH (100 mL) was mixed with palladium/carbon (0.1 g) and subjected to hydrogenation (50 psi) for 2 h. The mixture was filtered through a Celite-pad. The filtrate was concentrated on high vacuum to afford 7-(4-hydroxy-3,5-dimethyl-phenyl)-2,4-dimethoxy-6H-[1,6]naphthyridin-5-one (0.23 g, 88%). A solution of 7-(4-hydroxy-3,5-dimethyl-phenyl)-2,4-dimethoxy-6H-[1,6]naphthyridin-5-one (0.23 g, 0.7 mmol)

in MeOH (20 mL) and DCM (20 mL) was mixed with HCl in ether (7 mL, 7 mmol) and stirred for 0.5 h. The reaction was concentrated using a rotary evaporator to get a solid residue. The solid was rinsed with DCM, collected by filtration, washed with DCM to yield the HCl salt of 7-(4-hydroxy-3,5-dimethylphenyl)-2,4-dimethoxy-1,6-naphthyridin-5(6H)-one (0.15 g, 59%) as a light yellow solid. Selected data: MS (ES) *m/z*: 327.06; MP >324°C at decomposition (HCl salt).

Example 7



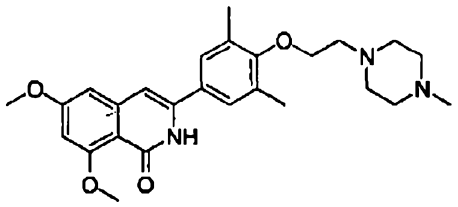
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one

[0116] A solution of 2-amino-4,6-dimethoxybenzamide (0.60 g, 3.06 mmol) and 4-[2-(*tert*-butyldimethylsilanoxy)ethoxy]-3,5-dimethylbenzaldehyde (0.856 g, 2.78 mmol) in *N,N*-dimethyl formamide (20 mL) was stirred at 70°C for 1 h. Iodine (0.846 g, 3.33 mmol) and potassium carbonate (0.384 g, 2.78 mmol) were added and the reaction mixture was stirred at 70°C for 16 h. The reaction mixture was poured into ice, and extracted with ethyl acetate. The organic layer was washed with water, brine, and dried over anhydrous Na_2SO_4. Removal of the solvent gave the crude product which was purified by column chromatography to give 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (444 mg, 39%) as a white solid. Selected data: 229-231°C.

[0117] Alternatively, 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one can be synthesized by the following method. In a 2 L dry round-bottom flask with a reflux condenser and magnetic stirrer was

placed 3, 5-dimethyl-4-hydroxy benzaldehyde (26.9 g, 0.179 mol) in ethanol (350 mL). 2-chloroethanol (87.6 g, 1.074 mol) and K_2CO_3 (99 g, 0.716 mol) were added and the reaction mixture was heated to reflux for 24 h. The reaction mixture was cooled to room temperature and filtered. The solvent was removed under reduced pressure. The crude product was diluted with ethyl acetate and the organic layer was washed with water, brine, and dried over Na_2SO_4. Upon removal of solvent it gave 45 g of crude product. The crude product was purified by column chromatography (silica gel 230-400 mesh; 50% ethyl acetate in hexane as eluent) to give 33.3 g (95%) of product. To a solution of 2-amino-4, 6-dimethoxy-benzamide (33.45 g, 0.170 mol) and 4-(2-hydroxy ethoxy)-3, 5-dimethyl benzaldehyde (33.3 g, 0.170 mol) in *N,N*-dimethyl acetamide (300 mL), $NaHSO_3$ (33.3 g, 0.187 mol) and *p*-TSA (3.2 g, 17.1 mmol) were added and the reaction mixture was heated at 150°C for 14 h. The reaction was cooled to room temperature. The solvent was removed under reduced pressure. The residue was diluted with water and stirred for 30 min at room temperature. The solids separated were filtered and dried to give crude product. The crude product was purified by column chromatography (silica gel 230-400 mesh; 5 % methanol in CH_2Cl_2 as eluent) to give 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (33 g, 52%).

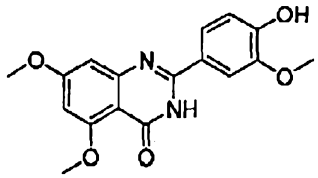
Example 8



3-(3,5-dimethyl-4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)-6,8-dimethoxyisoquinolin-1(2H)-one

[0118] The compound 3-[4-(2-chloro-ethoxy)-3,5-dimethyl-phenyl]-6,8-dimethoxy-isochromen-1-one (298 mg, 0.767 mmol) was dissolved in DMSO (5 mL) and *N*-methyl piperazine (388 mg, 3.83 mmol) and Et_3N (392 mg, 3.83 mmol) were added. The reaction mixture was heated at 110°C for 16 h before being cooled to room temperature. Water was added and the mixture was extracted with ethyl acetate. The solvent was evaporated *in vacuo* to leave a residue which was purified by column chromatography. The yield was 60 mg (17%). The compound 3-[3,5-dimethyl-4-(2-(4-methyl piperazin-1-yl-ethoxy)-phenyl]-6,8-dimethoxy-isochromen-1-one (60 mg, 0.13 mmol) and NH_3 (2.0 M solution in ethanol, 20 mL) were mixed in a steel bomb and heated at 130°C for 16 h. The solvent was removed and the crude compound was purified by column chromatography. The compound was then converted to the hydrochloride salt of 3-(3,5-dimethyl-4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)-6,8-dimethoxyisoquinolin-1(2H)-one (40 mg, 62%), an off-white solid. Selected data: MS (ES) *m/z*: 452.1; MP 195-198°C (HCl salt).

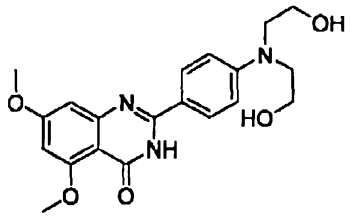
Example 9



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

[0119] 2-(4-Hydroxy-3-methoxyphenyl)-5,7-dimethoxyquinazolin-4(3H)-one was synthesized from 2-amino-4,6-dimethoxybenzamide and 4-hydroxy-3-methoxybenzaldehyde, using the method described for 5,7-dimethoxy-2-(pyridin-2-yl)quinazolin-4(3H)-one. 2-(4-Hydroxy-3-methoxyphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (90 mg, 36%) was isolated as a white solid. Selected data: MS (*m/z*): 329.06; MP 294-296°C.

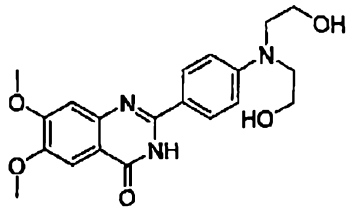
Example 10



2-(4-(bis(2-hydroxyethyl)amino)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one

[0120] 2-(4-(Bis(2-hydroxyethyl)amino)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one was synthesized from 2-amino-4,6-dimethoxybenzamide and 4-[bis-(2-hydroxy-ethyl)-amino]-benzaldehyde, using the method described for 5,7-dimethoxy-2-(pyridin-2-yl)quinazolin-4(3H)-one. 2-(4-(bis(2-hydroxyethyl)amino)phenyl)-5,7-dimethoxy-quinazolin-4(3H)-one (120 mg, 41%) was isolated as a yellow solid. Selected data: MS (*m/z*): 386.15; MP 249-251°C.

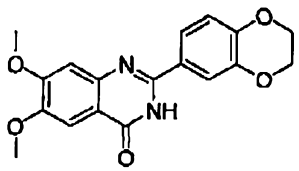
Example 11



2-(4-(bis(2-hydroxyethyl)amino)phenyl)-6,7-dimethoxyquinazolin-4(3H)-one

[0121] 2-(4-(Bis(2-hydroxyethyl)amino)phenyl)-6,7-dimethoxyquinazolin-4(3H)-one was synthesized from 2-amino-4,5-dimethoxy-benzamide and 4-(N,N-bis(2-hydroxyethyl)amino)benzaldehyde, using the method described for 5,7-dimethoxy-2-(pyridin-2-yl)quinazolin-4(3H)-one. 2-(4-(Bis(2-hydroxyethyl)amino)phenyl)-6,7-dimethoxyquinazolin-4(3H)-one (72 mg, 24%) was isolated as a yellow solid. Selected data: MS (*m/z*): 386.15; MP 268-270°C.

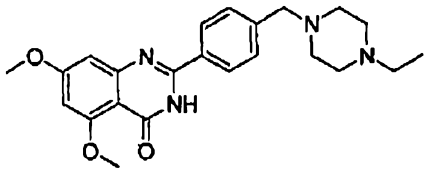
Example 12



2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6,7-dimethoxyquinazolin-4(3H)-one

[0122] 2-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-6,7-dimethoxyquinazolin-4(3H)-one was synthesized from 2-amino-4,5-dimethoxybenzamide and 2,3-dihydro-benzo[1,4]dioxine-6-carbaldehyde, using the method described for 5,7-dimethoxy-2-(pyridin-2-yl)quinazolin-4(3H)-one. 2-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-6,7-dimethoxy-quinazolin-4(3H)-one (180 mg, 69%) was isolated as a light yellow solid. Selected data: MS (*m/z*): 341.03; MP 316.4-318.2°C.

Example 13



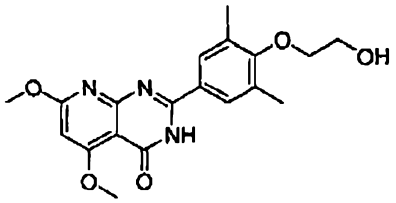
2-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one

[0123] To a solution of 4-bromoethyl-benzoic acid ethyl ester (4.0 g, 16.46 mmol) in THF (30 mL), *N*-ethyl piperazine (3.76 g, 32.92 mmol) was added and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was diluted with water and the product was extracted with ethyl acetate. The combined organic layers were washed with water, brine, and dried over Na_2SO_4. The solvent was removed to give 4.61 g of crude 4-(4-ethyl piperazin-1-ylmethyl)-benzoic acid ethyl ester (100% yield). LAH (0.792 g, 20.86 mmol) was taken up in a 3-neck dry flask and THF (60 mL) was added on cooling. A solution of 4-(4-ethyl piperazin-1-ylmethyl)-benzoic acid ethyl ester (4.61 g, 16.69 mmol) in THF (10 mL) was added slowly on cooling. After completion of addition, the reaction mixture was heated at reflux for 2 h. The reaction mixture was cooled to 0°C, 10% NaOH solution was added, and then water was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, brine and dried over Na_2SO_4. The solvent was removed to give 2.78 g of crude (4-(4-ethyl piperazin-1-ylmethyl) phenyl)-methanol in 78% yield. To a 3-neck flask containing anhydrous CH_2Cl_2 (100 mL) cooled to the -78°C oxalyl chloride (1.8 g, 14.25 mmol) and DMSO (1.85 g, 23.76 mmol) were added and the mixture was stirred for 15 min at -78°C. The solution of (4-(4-ethyl piperazin-1-ylmethyl) phenyl)-methanol (2.78 g, 11.88 mmol) in CH_2Cl_2 (10 mL) was added at -78°C and stirred at -78°C for 1 h.

Then Et_3N (4.8 g, 47.52 mmol) was added at -78°C. The reaction mixture was allowed to come to room temperature. Water was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water, brine and dried over Na_2SO_4. Then, solvent was removed to give crude 4-(4-ethyl piperazin-1-ylmethyl)benzaldehyde (2.5 g, 91%).

[0124] To a solution of 2-amino-4,6-dimethoxy-benzamide (150 mg, 0.76 mmol) and 4-(4-ethyl piperazin-1-ylmethyl)benzaldehyde (177 mg, 0.76 mmol) in *N,N*-dimethyl acetamide (10 mL), $NaHSO_3$ (150 mg, 0.84 mmol) and *p*-TSA (319 mg, 1.68 mmol) were added and the reaction mixture was heated at 150°C for 5 h. The reaction mixture was cooled to room temperature, water was added and the mixture was neutralized with $NaHCO_3$. The solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography to give 2-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)-5,7-dimethoxy-quinazolin-4(3H)-one (87 mg, 27 %), which was converted to the hydrochloride salt. Selected data: MS (ES) *m/z*: 409.11; MP 278-280°C (at decomposition).

Example 14

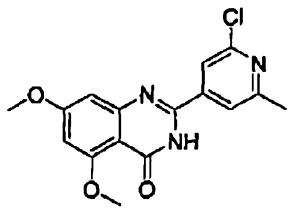


2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxypyrido[2,3-d]pyrimidin-4(3H)-one

[0125] To a solution of 2-amino-4, 6-dimethoxy-nicotinamide (1.07 g, 5.42 mmol) and 4-[2-(*tert*-butyldimethylsilanoxy) ethoxy]-3, 5-dimethylbenzaldehyde (1.67 g, 5.42 mmol) in *N,N*-dimethyl acetamide (25 mL),

$NaHSO_3$ (1.06 g, 5.97 mmol) and *p*-TSA (1.14 g, 5.97 mmol) were added and the reaction mixture was heated at 150°C for 16 h, cooled to room temperature and poured into water. The solid was collected to give 3.25 g of crude product. To a solution of the crude product (3.25 g, 6.70 mmol) in THF (50 mL), TBAF (3.5 g, 13.4 mmol) was added at 0°C and the mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, brine and dried over Na_2SO_4. The solvent was removed, and the crude was purified by column chromatography (silica gel 230-400 mesh; 2% methanol in CH_2Cl_2 as eluent) to give 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxypyrido[2,3-d]pyrimidin-4(3H)-one (132 mg, 6%). Selected data: MS (ES) *m/z*: 371.99; MP 255-256°C.

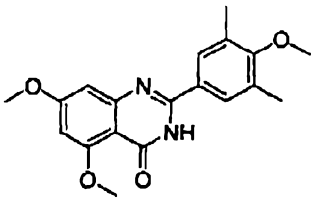
Example 15



2-(2-chloro-6-methylpyridin-4-yl)-5,7-dimethoxyquinazolin-4(3H)-one

[0126] Following the method described for 5,7-dimethoxy-2-(4-methoxy-3,5-dimethylphenyl)quinazolin-4(3H)-one, 2-(2-chloro-6-methylpyridin-4-yl)-5,7-dimethoxyquinazolin-4(3H)-one was synthesized from 2-amino-4,6-dimethoxybenzamide and 2-chloro-6-methylisonicotinoyl chloride in 75% yield as a white solid. Selected data: ^1H NMR (300 MHz, $CDCl_3$) δ 10.95 (s, 1H), 7.90 (s, 2H), 6.74 (d, J = 2.33 Hz, 1H), 6.51 (d, J = 2.32 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 2.29 (s, 3H); MS (APCI) *m/z* 332 $[M+H]^+$.

Example 16

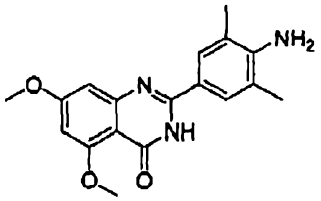


5,7-dimethoxy-2-(4-methoxy-3,5-dimethylphenyl)quinazolin-4(3H)-one

[0127] To a solution of 4-methoxy-3,5-dimethylbenzoic acid (0.100 g, 0.555 mmol) in CH_2Cl_2 (2.77 mL) cooled to 0–5°C was added oxalyl chloride (67.8 μL, 0.777 mmol) followed by drop-wise addition of DMF (4.3 μL, 0.056 mmol). The mixture was stirred for 50 min, the volatiles were removed under vacuum, and the crude acid chloride was used immediately without further purification.

[0128] To a mixture of 2-amino-4,6-dimethoxybenzamide (0.0990 g, 0.555 mmol) and pyridine (44.9 μL, 0.555 mmol) in THF (2.02 mL) was added drop-wise a solution of the acid chloride (crude residue described above) in THF (925 μL). After 16 h, the mixture was diluted with EtOAc (300 mL), washed with saturated aqueous NH_4Cl (3×75 mL), saturated aqueous $NaHCO_3$ (3×75 mL), and brine (75 mL). The insoluble yellow solid was isolated by filtration to provide the amide (0.150 g, 83%). A mixture of the amide (0.148 g, 0.413 mmol) and 2 M NaOH (7.00 mL) was heated at 85°C for 19 h, cooled to 5°C, and neutralized with 4 M HCl in dioxanes. The white solid was filtered and rinsed with acetone to provide 5,7-dimethoxy-2-(4-methoxy-3,5-dimethylphenyl)quinazolin-4(3H)-one (0.144 g, 100%). Selected data: ^1H NMR (300 MHz, $CDCl_3$) δ 11.00 (s, 1H), 7.90 (s, 2H), 6.74 (d, J = 2.33 Hz, 1H), 6.51 (d, J = 2.32 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.72 (s, 3H), 2.29 (s, 6H); MS (APCI) *m/z* 341 $[M+H]^+$.

Example 17

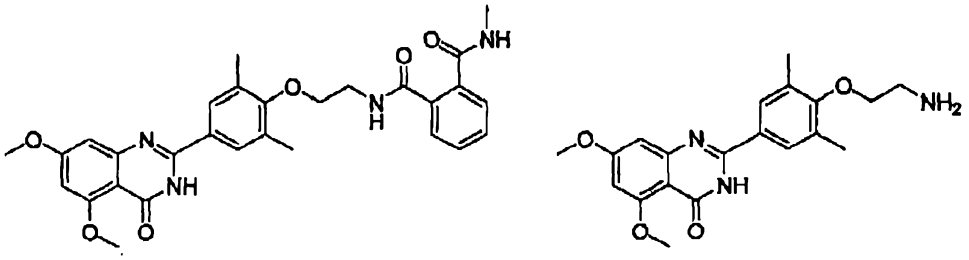


2-(4-amino-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one

[0129] To a solution of 3,5-dimethyl-4-nitrobenzoic acid (1.00 g, 5.12 mmol) in CH_2Cl_2 (25.6 mL) cooled to 0-5°C was added oxalyl chloride (0.626 mL, 7.17 mmol) followed by drop-wise addition of DMF (39.8 μL). The mixture was stirred for 2 h, the volatiles were removed under vacuum, and the crude acid chloride was used immediately without further purification. To a mixture of 2-amino-4,6-dimethoxybenzamide (0.913 g, 4.65 mmol) and pyridine (414 μL, 5.12 mmol) in THF (18.6 mL) was added drop-wise a solution of the acid chloride (crude residue described above) in THF (8.53 mL). After 16 h, the mixture was diluted with EtOAc (500 mL), washed with saturated aqueous NH_4Cl (3×100 mL), saturated aqueous $NaHCO_3$ (3×100 mL), and brine (100 mL). The insoluble yellow solid was isolated by filtration to provide the amide (1.51 g, 87%). A mixture of the amide (1.50 g, 4.03 mmol) and 2 M aqueous NaOH (25.0 mL) was heated at 85°C for 17 h, then added THF (50 mL) and stirred at reflux for 25 h. The volatiles were removed under vacuum, the mixture was cooled to 5°C, and neutralized with 4 M HCl in dioxanes. After stirring for 30 min, the white solid was filtered and lyophilized from $MeCN/H_2O$ to afford the cyclized compound (1.36 g, 95%). A mixture of the cyclized compound (0.200 g, 0.563 mmol), $Na_2S_2O_4$ (0.980 g, 5.63 mmol), water (5.00 mL) and MeOH (15.0 mL) was stirred at 70°C

for 2 h. The volatiles were removed under vacuum, then diluted with EtOAc (200 mL), washed with saturated $NaHCO_3$ (2×100 mL) and brine (75 mL). The organic layer was dried over sodium sulfate, filtered, and the volatiles were removed under vacuum to provide 2-(4-amino-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (0.062 g, 34%) as a yellow solid. Selected data: ^1H NMR (300 MHz, DMSO-d_6) δ 11.45 (s, 1H), 7.78 (s, 2H), 6.66 (d, J = 2.25 Hz, 1H), 6.42 (d, J = 2.24 Hz, 1H), 5.26 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 2.14 (s, 6H); MS (APCI) m/z 326 $[M+H]^+$.

Example 18



N1-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N2-methylphthalamide (left)

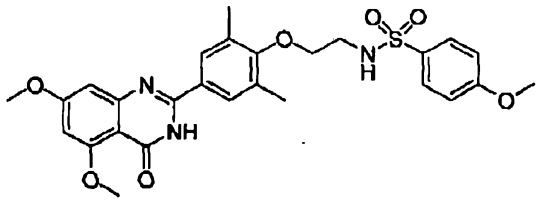
and

2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (right)

[0130] A mixture of 3,5-dimethyl-4-hydroxybenzaldehyde (0.600 g, 4.00 mmol), *N*-(2-bromoethyl)-phthalimide (1.22 g, 4.80 mmol), K_2CO_3 (0.829 g, 6.00 mmol), NaI (3.00 g, 20.0 mmol) in DMF (40.0 mL) was heated at 80°C for 2.5 h. The reaction was cooled to room temperature, diluted with EtOAc (200 mL), washed with 1 M NaOH (2×100 mL), 1 M HCl (2×100 mL), brine (75 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The residue was chromatographed on silica gel (40 g, hexanes/EtOAc) to provide the expected

ether (0.300 g, 23%) as a yellow solid. A mixture of the above ether (0.293 g, 0.907 mmol), 2-amino-4,6-dimethoxybenzamide (0.178 g, 0.907 mmol), $NaHSO_3$ (94%, 0.100 g, 0.907 mmol), and *p*-TsOH•H_2O (0.0173 g, 0.0907 mmol) in DMA (11.3 mL) was stirred at reflux for 1.5 h then cooled to room temperature. The mixture was diluted with EtOAc (250 mL), washed with saturated aqueous ammonium chloride (3×75 mL) and brine (75 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The residue was chromatographed on silica gel (40 g, CH_2Cl_2/CH_3OH) to provide the expected product (0.075 g, 17%) as a light yellow solid. A mixture of the above compound (0.213 g, 0.426 mmol) and 2 M methylamine in THF (25.0 mL) was stirred at room temperature for 17 h. The volatiles were removed under vacuum and the residue was chromatographed on silica gel to provide compound N1-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N2-methylphthalamide (0.0493 g, 22%) and compound 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (0.0360 g, 23%) as white solids. Selected data for N1-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N2-methylphthalamide: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.80 (s, 1H), 8.51 (t, J = 5.57 Hz, 1H), 8.18 (q, J = 4.57 Hz, 1H), 7.89 (s, 2H), 7.53-7.42 (m, 4H), 6.74 (d, J = 2.31 Hz, 1H), 6.52 (d, J = 2.29 Hz, 1H), 3.96-3.80 (m, 8H), 3.61 (q, J = 5.73 Hz, 2H), 2.71 (d, J = 4.62 Hz, 3H), 2.32 (s, 6H); MS (APCI) *m/z* 531 $[M+H]^+$. Selected data for 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (s, 2H), 6.74 (d, J = 2.31 Hz, 1H), 6.51 (d, J = 2.32 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.77 (t, J = 5.76 Hz, 2H), 2.91 (t, J = 5.75 Hz, 2H), 2.30 (s, 6H); MS (APCI) *m/z* 370 $[M+H]^+$.

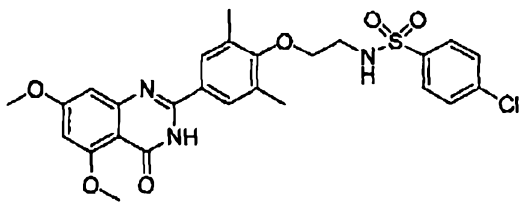
Example 19



N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-4-methoxybenzenesulfonamide

[0131] A mixture of 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (0.060 g, 0.162 mmol), 4-methoxybenzenesulfonyl chloride (0.044 mg, 0.211 mmol), and triethylamine (29.4 μL, 0.211 mmol) in CH_2Cl_2 (812 μL) was stirred at room temperature for 3 h. The mixture was chromatographed directly on silica gel to yield N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy) ethyl)-4-methoxybenzenesulfonamide (0.046 g, 53%) as a white solid after lyophilization from MeCN/H_2O. Selected data: ^1H NMR (300 MHz, DMSO-d_6) δ ppm 11.81 (s, 1H), 7.88 (s, 2H), 7.83-7.73 (m, 3H), 7.17-7.07 (m, 2H), 6.73 (d, J = 2.31 Hz, 1H), 6.52 (d, J = 2.29 Hz, 1H), 3.91-3.75 (m, 11H), 3.12 (q, J = 5.75 Hz, 2H), 2.24 (s, 6H); MS (APCI) *m/z* 540 $[M+H]^+$.

Example 20

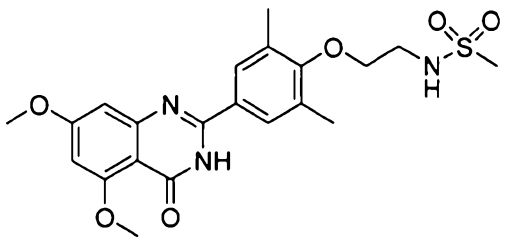


4-chloro-*N*-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)benzenesulfonamide

[0132] Following the method described for N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy) ethyl)-4-methoxybenzenesulfonamide, compound 4-chloro-*N*-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)benzene-sulfonamide was made from 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in 51% yield and isolated as a white solid after lyophilization from MeCN/H_2O. Selected data: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.8 (s, 1H), 8.1 (s, 1H), 7.9 – 7.6 (m, 6H), 6.75 (1H), 6.5 (1H), 3.9 – 3.7 (m, 8H), 3.15 (m, 2H), 2.2 (s, 6H); MS (APCI) *m/z* 544 $[M+H]^+$.

[Paragraphs 133 to 135 of the application as filed, which comprise examples 21 to 23, deleted.]

Example 24



N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)methanesulfonamide

[0136] Following the method described for N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy) ethyl)-4-methoxybenzenesulfonamide, compound N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-

[Text continues on page 80.]

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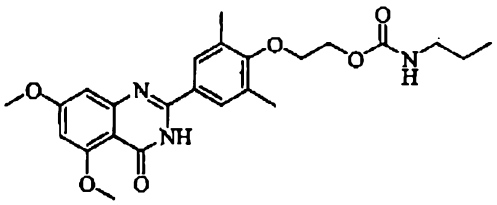
dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)methanesulfonamide was made from 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in 42% yield and isolated as a white solid after lyophilization from MeCN/H_2O. Selected data: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 11.82 (s, 1H), 7.90 (s, 2H), 7.33 (t, J = 5.94 Hz, 1H), 6.74 (d, J = 2.31 Hz, 1H), 6.52 (d, J = 2.30 Hz, 1H), 3.92-3.81 (m, 8H), 3.41-3.34 (m, 2H), 2.97 (s, 3H), 2.32 (s, 6H); MS (APCI) *m/z* 448 $[M+H]^+$.

Example 25

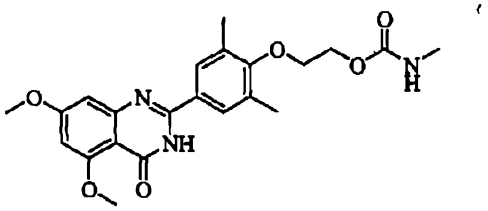


2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethyl-phenoxy)ethyl propylcarbamate

[0137] A mixture of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (0.070 g, 0.19 mmol), propyl isocyanate (0.088 mL, 0.94 mmol), and TEA (0.14 g, 1.1 mmol) in THF (4.0 mL) was stirred at 70°C for 16 h. The mixture was filtered, washed with THF, and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with saturated aqueous sodium bicarbonate (50 mL), dried and the solvent was removed under reduced pressure. The resulting solid was chromatographed on silica gel to yield 2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethyl-phenoxy)ethyl propylcarbamate (0.035 g, 41%) as an off-white solid: Selected data: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.82 (s, 1H), 7.90 (s, 2H), 7.23 (t, J = 5.27 Hz, 1H), 6.74 (d, J = 2.32 Hz, 1H), 6.52 (d, J

= 2.31 Hz, 1H), 4.27 (t, *J* = 4.29 Hz, 2H), 3.99 (t, *J* = 4.29 Hz, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.02-2.86 (m, 2H), 2.29 (s, 6H), 1.50-1.30 (m, 2H), 0.84 (t, *J* = 7.33 Hz, 3H); MS (APCI) *m/z* 456 $[M+H]^+$.

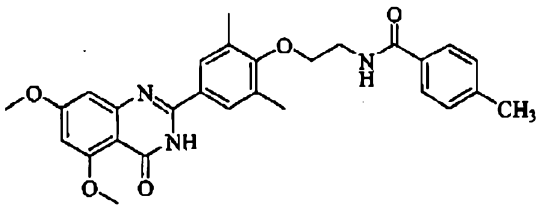
Example 26



2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethyl-phenoxy)ethyl methylcarbamate

[0138] Following the method described for 2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethyl-phenoxy)ethyl propylcarbamate, compound 2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethyl-phenoxy)ethyl methylcarbamate was made from 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in 11% yield and isolated as an off-white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.82 (s, 1H), 7.90 (s, 2H), 7.08 (m, 1H), 6.74 (d, *J* = 2.29 Hz, 1H), 6.52 (d, *J* = 2.27 Hz, 1H), 4.27 (t, *J* = 4.55 Hz, 2H), 3.99 (t, *J* = 4.55 Hz, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 2.60 (d, *J* = 4.57 Hz, 3H), 2.29 (s, 6H); MS (APCI) *m/z* 428 $[M+H]^+$.

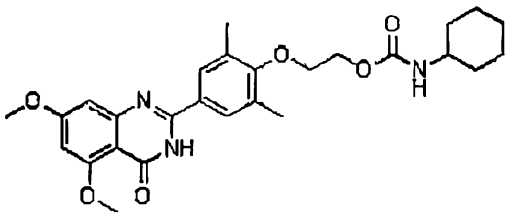
Example 27



N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-4-methylbenzamide

[0139] A mixture of compound 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (0.060 g, 0.16 mmol), p-toluoyl chloride (0.028 mL, 0.21 mmol), and PS-DIEA (0.057 g, 0.21 mmol) in CH_2Cl_2 (4.0 mL) was stirred at room temperature for 16 h. The mixture was filtered, washed with CH_2Cl_2 and the solvent was removed under reduced pressure. The resulting residue was chromatographed on silica gel to yield N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-4-methylbenzamide (0.037 g, 51%) as an off-white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.80-11.00 (s, 1H), 8.69 (t, J = 5.43 Hz, 1H), 7.88 (s, 2H), 7.79 (d, J = 8.19 Hz, 2H), 7.28 (d, J = 8.00 Hz, 2H), 6.73 (d, J = 2.31 Hz, 1H), 6.51 (d, J = 2.31 Hz, 1H), 3.94 (t, J = 5.59 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.72-3.60 (m, 2H), 2.36 (s, 3H), 2.27 (s, 6H); MS (APCI) *m/z* 488 $[M+H]^+$.

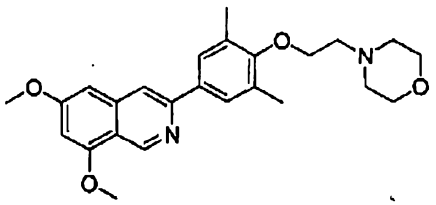
Example 28



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

[0140] A mixture of 4-(6,8-dimethoxyisoquinolin-3-yl)-2,6-dimethylphenol (0.100 g, 0.270 mmol), cyclohexylisocyanate (172 μL, 1.35 mmol), and Et_3N (263 μL, 1.89 mmol) in THF (1.00 mL) was stirred at reflux for 4 h then diluted with EtOAc (200 mL) and washed with saturated aqueous ammonium chloride (3 × 75 mL) and brine (75 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under vacuum. The residue was chromatographed on silica gel (12 g, CH_2Cl_2/CH_3OH) and the product freeze dried from $MeCN/H_2O$ to provide 2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl cyclohexylcarbamate (0.0981 g, 73%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6 δ) 11.82 (s, 1H), 7.90 (s, 2H), 7.24-7.05 (m, 1H), 6.73 (d, J = 2.30 Hz, 1H), 6.52 (d, J = 2.31 Hz, 1H), 4.30-4.22 (m, 1H), 4.03-3.95 (m, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.29 (s, 6H), 1.82-1.46 (m, 5H), 1.18 (m, 5H); MS (APCI) *m/z* 496 $[M+H]^+$.

Reference Example A

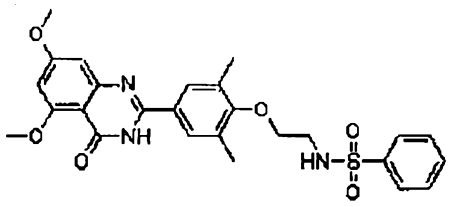


4-(2-(4-(6,8-dimethoxyisoquinolin-3-yl)-2,6-dimethylphenoxy)ethyl)morpholine

[0141] To a solution of 4-(6, 8-dimethoxyisoquinolin-3-yl)-2, 6-dimethylphenol (0.309 g, 1.0 mol) in anhydrous THF (20 mL), triphenyl phosphene (0.52 g, 2.0 mmol), 4-(2-hydroxyethyl) morpholine (0.262 g, 2.0 mmol) and *N,N*-diisopropylethylamine (0.387 g, 3.0 mmol) were added. To this stirred solution was added diethylazodicarboxylate (0.348 g, 2.0 mmol). The reaction mixture was stirred at room temperature overnight under nitrogen, then diluted with ethyl acetate (100 mL). The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude material was purified by column chromatography to give 3-[3,5-dimethyl-4-(2-morpholin-4-ylethoxy) phenyl]-6,8-dimethoxyisoquinoline (0.54 g) as a white solid.

[0142] To a solution of the above compound (0.54 g, impure) in 1:1 ether-CH_2Cl_2 (10 mL), was added 1.0 M solution of hydrogen chloride in ether (2 mL) and the reaction mixture was stirred at room temperature for 30 min. Solvent was removed under reduced pressure. The residue was triturated with 10% methanol in ether to give 4-(2-(4-(6,8-dimethoxyisoquinolin-3-yl)-2,6-dimethylphenoxy)ethyl)morpholine (0.323 g, 70% over two steps) as a yellow solid. Selected data: MS (ES) *m/z*: 423.1; MP 239-240°C (HCl salt).

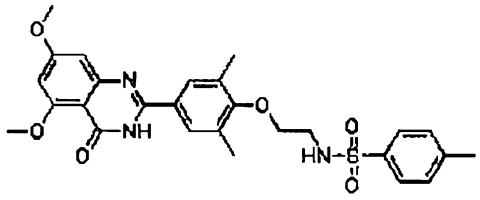
Example 29



N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)benzenesulfonamide

[0143] Following the methodology described for Reference Example A, the title compound was made from 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in 41% yield and isolated as an off-white solid: MS (APCI) *m/z* 510 $[M+H]^+$.

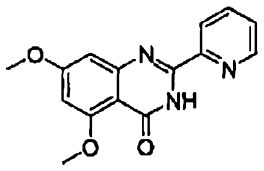
Example 30



N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-4-methylbenzenesulfonamide

[0144] Following the methodology described for Reference Example A, the title compound was made from 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in 50% yield and isolated as an off-white solid: MS (APCI) *m/z* 524 $[M+H]^+$.

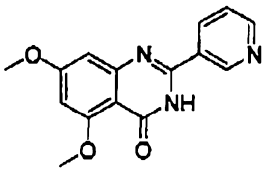
Reference Example B



5,7-dimethoxy-2-(pyridin-2-yl)quinazolin-4(3H)-one

[0145] To a solution of 2-amino-4,6-dimethoxybenzamide (0.15 g, 0.764 mmol) in *N,N*-dimethyl acetamide (5 mL) were added 2-pyridine carboxaldehyde (0.082 g, 0.764 mmol), sodium hydrogen sulphite (58.5%, 0.15 g, 0.84 mmol), and *p*-toluenesulfonic acid (15 mg, 0.0764 mmol). The reaction mixture was stirred at 150°C overnight. The mixture was cooled to room temperature. Water (40 mL) was added and the reaction mixture was extracted with dichloromethane (2×50 mL). The combined organic layers were washed with water and dried over anhydrous Na_2SO_4. The solvent was removed and the crude compound was purified by column chromatography (silica gel 230-400 mesh; 1% methanol in CH_2Cl_2 as eluent) to give 5,7-dimethoxy-2-(pyridin-2-yl)quinazolin-4(3H)-one (0.077 g, 36%) as a white solid. 5,7-dimethoxy-2-(pyridin-2-yl)quinazolin-4(3H)-one was converted to the corresponding hydrochloride. Selected data: MS (*m/z*): 284.0; MP 215-217°C (hydrochloride).

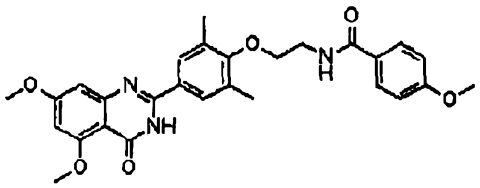
Reference Example C



5,7-dimethoxy-2-(pyridin-3-yl)quinazolin-4(3H)-one

[0146] 5,7-Dimethoxy-2-(pyridin-3-yl)quinazolin-4(3H)-one was synthesized from 2-amino-4,6-dimethoxybenzamide and 3-pyridine carboxaldehyde, using the method described for Reference Example B. 5,7-Dimethoxy-2-(pyridin-3-yl)quinazolin-4(3H)-one (105 mg, 48%) was isolated as a white solid. Selected data: MS (*m/z*): 284.0; MP 257-259°C (hydrochloride).

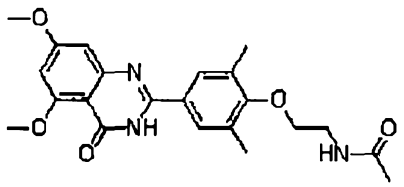
Example 31



N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-4-methoxybenzamide

[0147] Following the methodology described for Reference Example C, the title compound was made from 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in 46% yield and isolated as a white solid: MS (APCI) *m/z* 526 $[M+Na]^+$.

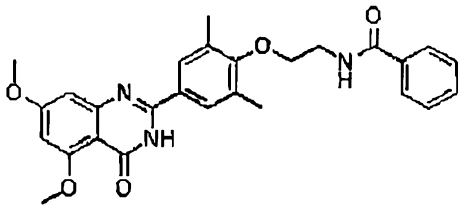
Example 32



N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)acetamide

[0148] Following the methodology described for Example 27, the title compound was made from 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in 40% yield and isolated as a white solid: MS (APCI) *m/z* 412 $[M+H]^+$.

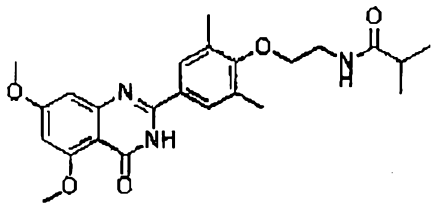
Example 33



N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)benzamide

[0149] Following the methodology described for Example 27, the title compound was made from 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in 66% yield and isolated as a white solid: MS (APCI) *m/z* 474 $[M+H]^+$.

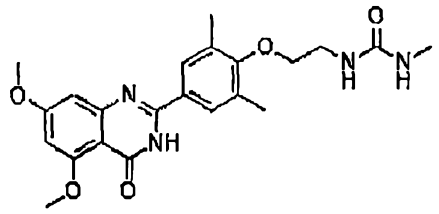
Example 34



N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)isobutyramide

[0150] Following the methodology described for Example 27, the title compound was made from 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in 59% yield and isolated as a white solid: MS (APCI) *m/z* 440 $[M+H]^+$.

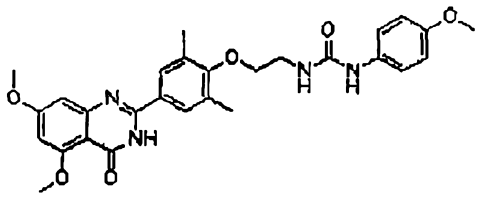
Example 35



1-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-3-methylurea

[0151] A mixture of compound 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (0.10 g, 0.27 mmol), methylisocyanate (0.020 g, 0.35 mmol), and Et_3N (0.034 g, 0.35 mmol) in THF (4.0 mL) was stirred at room temperature for 16 hours. The mixture was filtered, washed with CH_2Cl_2 and the solvent was removed under reduced pressure. The resulting residue was chromatographed on silica gel to yield the title compound (0.082 g, 71%) as a white solid: MS (APCI) *m/z* 449 $[M+Na]^+$.

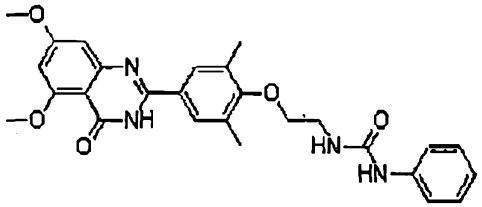
Example 36



1-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-3-(4-methoxyphenyl)urea

[0152] Following the methodology described for Example 35, the title compound was made from 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in 57% yield and isolated as a white solid: MS (APCI) *m/z* 541 $[M+Na]^+$.

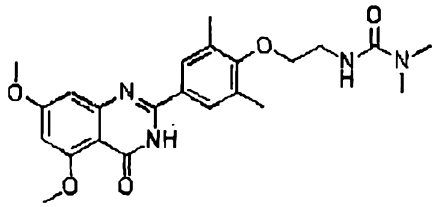
Example 37



1-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-3-phenylurea

[0153] Following the methodology described for Example 35, the title compound was made from 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in 59% yield and isolated as a light yellow solid: MS (APCI) *m/z* 489 $[M+H]^+$.

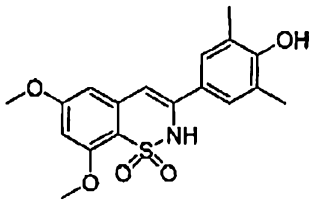
Example 38



3-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-1,1-dimethylurea

[0154] Following the methodology described for Example 35, the title compound was made from 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in 59% yield and isolated as a white solid: MS (APCI) *m/z* 441 $[M+H]^+$.

Example 39



6,8-dimethoxy-3-(4-hydroxy-3,5-dimethylphenyl)-2H-1,2-benzothiazine-1,1-dioxide

[0155] To a 3-necked, round-bottomed flask was added 3,5-dimethoxytoluene (6.088 g, 40 mmol) and cyclohexane (28 mL) under nitrogen. Dimethyl carbonate (30.3 g, 336 mmol) was added and the reaction mixture was heated at 60°C. Excess chlorosulfonic acid was added over a period of 15 min. The liberated HCl gas was removed by inserting a tube into solid sodium hydroxide. On completion of the addition, the reaction mixture was heated to 70-72°C for 1 h and then cooled to room temperature. The solid was filtered off and washed with dimethyl carbonate/cyclohexane (1:1, 20 mL). The solid was dried *in vacuo* to obtain pure material (6.13 g, 66%). To a mixture of the sulfonic acid (product from above, 4.65 g, 20 mmol) and triethyl amine (2.03 g, 2.79 mL) in acetone (40 mL) was added 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride, 3.69 g, 20 mmol). The reaction mixture was heated under reflux for 20 h before being cooled to room temperature. The solution was passed through a Celite pad and evaporated *in vacuo* to leave a solid, which was filtered off and washed with hexane. The mixture of product and salt of cyanuric hydroxide and triethyl amine (7.58 g) was used for the next step without further purification.

[0156] To a 3-necked, round-bottomed flask, equipped with a condenser (acetone-dry ice cooling), was added the mixture from the step above (7.58 g) and acetone (100 mL). The reaction mixture was cooled to -78°C and ammonia gas

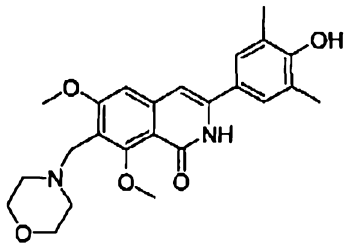
was bubbled through the solution for 0.5 h. The reaction mixture was kept standing overnight, allowing slow evaporation of ammonia gas, followed by the evaporation of solvent. Water was added and the product was extracted with DCM. The solvent was dried and evaporated to leave a mixture of solid and a dense liquid. The solid was filtered off and washed with hexane to leave pure sulfonamide (3.23 g, 70%).

[0157] To a round-bottomed flask was added 3,5-dimethyl-4-hydroxybenzoic acid (2.99 g, 18 mmol). Anhydrous DMF (20 mL) was added, followed by sodium hydride (1.8 g, 45 mmol). The reaction mixture was stirred at room temperature for 1 h. *p*-Methoxybenzyl chloride (6.20 g, 39.6 mmol) was added and the mixture was stirred at room temperature overnight (~20 h). The reaction mixture was poured into water, acidified with 1 N HCl and stirred for 1 h. The precipitated solid was filtered off, washed with water and hexane to obtain pure B-ring building block (6.93 g, 95%).

[0158] The B-ring building block (6.93 g, 17.1 mmol) was dissolved in a mixture of methanol (50 mL) and tetrahydrofuran (50 mL). Potassium hydroxide (1.25 g, 22.2 mmol) in water (20 mL) was added. The reaction mixture was refluxed at 70°C for 24 h. The solvent was evaporated *in vacuo*. Water was added and the reaction mixture was acidified with 1 N HCl (pH 4-5). The solid was filtered off, washed with water and hexane. The yield was 4.61 g (94%). The product (1.932 g, 6.75 mmol) and the sulfonamide from above (1.04 g, 4.5 mmol) were taken in a 3-necked, round-bottomed flask under nitrogen. Dichloromethane (100 mL) was added with stirring. To this stirred mixture was added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI. HCl, 1.36 g, 7.09 mmol), followed by *N,N*-dimethylaminopyridine (2.06 g, 16.9 mmol). The

reaction mixture was stirred at room temperature for 24 h before being washed with 1 N HCl, 2.5% NaOH and saturated sodium bicarbonate solutions. The organic layers were dried and evaporated *in vacuo* to leave a residue, which was purified by silica gel (100 g) column chromatography, employing 20-50% ethyl acetate in hexane and 5% methanol in dichloromethane as eluents. Fractions 30-66 were combined to obtain pure materials (1.35 g, 60%). The compound from the step above (0.105 g, 0.21 mmol) was dissolved in tetrahydrofuran under nitrogen and cooled to -78°C. n-Butyllithium was added and the reaction mixture was allowed to warm to room temperature slowly and stirred overnight (~14 h). TLC showed incomplete conversion. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The solvent was evaporated *in vacuo* to leave a residue that was purified by silica gel (15 g) column chromatography, employing 20-50% ethyl acetate in hexane as eluents. The product was not pure enough, so another column was used, employing 0.5% methanol in hexane as eluent, and finally preparative TLC was employed to purify the material. The compound from the step above (0.277 g) was dissolved in trifluoroacetic acid (10 mL) under nitrogen and the reaction mixture was refluxed (bath temperature 80°C) for 4 d. The solvent was evaporated *in vacuo* and the residue was dissolved in 0.25 N NaOH (20 mL), and acidified with acetic acid. The solid had precipitated out at this point. The solid was filtered off and washed with water, hexane and dried. From one batch, 0.005 g of pure material was isolated. From another batch, 0.060 g compound was isolated, which was not pure enough. This compound was further purified by preparative HPLC to give pure 6,8-dimethoxy-3-(4-hydroxy-3,5-dimethylphenyl)-2H-1,2-benzothiazine-1,1-dioxide (0.010 g). Selected data: MP 246.6-247.4°C.

Example 40



3-(4-hydroxy-3,5-dimethylphenyl)-6,8-dimethoxy-7-(morpholinomethyl)isoquinolin-1(2H)-one

[0159] Methyl acetoacetate (69.67 g, 0.6 mol) in dry THF (350 mL) was cooled to -5°C and sodium hydride in mineral oil (24.5 g, 60%) was added at -5 to 0°C over 30 min. Diketene (50.4 g) in dry THF (80 mL) was added drop-wise at 5°C over 20 min. The resulting solution was allowed to stir for 1.0 h at -5°C, after which it was allowed to warm to room temperature and stir overnight. Acetic acid (35 mL) was added and the THF solvent was removed. Water (200 mL) and ethyl acetate (300 mL) were added to the residue and the pH was adjusted to 5.0 by addition of HCl solution. The organic layer was separated and washed with brine and dried over sodium sulfate. After column purification and recrystalization, compound A (26.6 g, 24.3%) was obtained.

[0160] Sodium hydride in mineral oil (11.2 g, 0.279 mol, 60%) was added to compound A (24.8 g, 0.136 mol) in DMF (150 mL). The reaction was cooled to -30°C and methyl iodide (21.3 mL, 0.341 mol) was added and the reaction was kept at room temperature overnight. Sodium iodide was filtered off and DMF was removed. The residue was mixed with water (100 mL) and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The crude mixture was purified by column chromatography to yield compound B (11.40 g, 39.9%). To a solution of compound B (11.4 g, 0.054 mole) in dry CCl_4

(90 mL) was added *N*-bromosuccinimide (10.6 g, 0.0596 mol). The mixture was refluxed overnight and CCl_4 solvent was removed. Water (100 mL) was added to the residue. After stirring for a while the solid was filtered off and washed with water, ethyl acetate (10 mL) and hexane (30 mL) to yield compound (13.1 g, 83.9%). Compound C (12.5 g, 0.043 mol), chloromethyl methyl ether (81.0 g) and anhydrous zinc chloride (7.0 g, 0.051 mol) were kept at room temperature overnight. Chloromethyl methyl ether was removed and the residue was mixed with water and the pH was adjusted to 7.0 using sodium bicarbonate. The mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. Compound D (7.39 g, 50.6%) was obtained after column chromatography. A solution of compound D (7.39 g, 0.022 mol), morpholine (7.62 g, 0.088 mol) and anhydrous THF (20 mL) was kept at room temperature overnight. The solvent was evaporated. Water and ethyl acetate were added to the residue, and pH was adjusted to 9.0 with sodium bicarbonate. The organic layer was washed with brine and dried over sodium sulfate, and concentrated. Compound E (5.4 g, 63.8%) was obtained after column chromatography. The hydrogenation reaction was carried out at 50 psi with compound E (5.4 g, 0.014 mol) in THF (100 mL) and triethyl amine (3.9 mL) with 10% Pd/C (2.6 g) as a catalyst for 2 d. After the catalyst was filtered off, the organic layer was purified by column chromatography to yield product F (3.20 g, 74.4%). Compound F (3.20 g, 0.0103 mol) was dissolved in ethanol (30 mL) and potassium hydroxide (2.31 g, 0.041 mol) in water (20 mL) was added and the reaction mixture was heated to 100°C overnight. The solvent was removed, pH was adjusted to 6.0 and the water was removed. The residue was further dried under high vacuum and the compound was extracted with ethanol to yield

compound G (2.95 g, 99%). Compound G (1.80 g, 6.1 mmol) with thionyl chloride (3 mL, 0.0411 mol) was refluxed for 1 h before the excess thionyl chloride was removed and the residue was dried under high vacuum. Anhydrous THF (20 mL) was added and ammonia gas was bubbled into the reaction mixture for 2 h. THF was removed and pH was adjusted to 8.0-9.0. The mixture was extracted with dichloromethane and dried over sodium sulfate to give compound H (1.30 g, 72.4%).

[0161] NaH in mineral oil (1.14 g, 0.0285 mol, 60%) was added to 4-hydroxy-3,5-dimethylbenzonitrile (4.0 g, 0.027 mol) in anhydrous DMF (20 mL) followed by benzyl bromide (3.27 mL, 0.027 mol). The reaction was kept at room temperature overnight. The reaction mixture was poured into water and the solid was filtered off and washed with hexane to yield Compound I (5.7 g, 89%). Compound I was used for the next step reaction without further purification. BuLi (1.60 M, 10.2 mL) was added drop-wise to compound H (0.8 g, 2.72 mmol) in anhydrous THF (25 mL) at -10°C. The reaction mixture was kept at 0°C for one h before the cooling bath was removed. The reaction mixture was stirred for 45 minutes. Compound I (0.65 g, 2.72 mmol) in anhydrous THF (5 mL) was added drop-wise at -10°C and the reaction was continued for a further 45 min. Water (20 mL) was added. The mixture was extracted with ethyl acetate. The solvent was removed and the residue was purified by column chromatography to yield compound J (0.180 g, 12.8%). Compound J (180 mg) in methanol (80 mL) was hydrogenated at 50 psi for 3 h, using 10% Pd/C as the catalyst. The catalyst and solvent were removed and the residue was purified by column chromatography to yield 3-(4-hydroxy-3,5-dimethylphenyl)-6,8-dimethoxy-7-

(morpholinomethyl)isoquinolin-1(2H)-one (28 mg, 18.8%) as a white solid. Selected data: MS (*m/z*): 424.21; MP 158-161°C.

Example 41: Quantification of ApoA-I mRNA

[0162] In this example, ApoA-I mRNA in tissue culture cells was quantitated to measure the transcriptional up-regulation of ApoA-I when treated with a compound of the invention.

[0163] HepG2 cells (~2×10^5 per well) were placed in a 24-well plate in ~400 µL MEM, supplemented with 0.5% (v/v) FBS, 24 h before addition of the compound of interest. At time of harvesting, the spent media was removed from the HepG2 cells and immediately placed on ice (for immediate use) or at -80°C (for future use) in ApoA-I and albumin ELISAs. The cells remaining in the plate wells were rinsed in 200 µL PBS. PBS was carefully removed to avoid removing any loosely attached cells.

[0164] Once the PBS was removed, 85 µL cell lysis solution was added the cells in each well and incubated for 5-10 min at room temperature, to allow for complete cell lysis and detachment. mRNA was then prepared using the "mRNA Catcher PLUS plate" from Invitrogen, according to the protocol supplied. After the last wash, as much wash buffer as possible was aspirated without allowing the wells to dry. Elution Buffer (E3, 80 µL) was then added to each well. mRNA was then eluted by incubating the mRNA Catcher PLUS plate with Elution Buffer for 5 min at 68°C and then immediately placing the plate on ice.

[0165] The eluted mRNA isolated was then used in a one-step real-time room temperature-PCR reaction, using components of the Ultra Sense Kit together with Applied Biosystems primer-probe mixes. Real-time PCR data was

analyzed, using the Ct values, to determine the fold induction of each unknown sample, relative to the control (that is, relative to the control for each independent DMSO concentration).

[0166] An active compound is one that causes a >15% increase in ApoA-I mRNA at a concentration less than or equal to 100 μM.

Example #	Compound Name	Effect on ApoA-I mRNA levels
38	3-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-1,1-dimethylurea	Active
37	1-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-3-phenylurea	Active
36	1-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-3-(4-methoxyphenyl)urea	Active
35	N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-3-methylurea	Active
34	N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)isobutyramide	Active
33	N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)benzamide	Active
32	N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)acetamide	Active
31	N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-4-methoxybenzamide	Active
30	N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-4-methylbenzenesulfonamide	Active
29	N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)benzenesulfonamide	Active
28	2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl cyclohexylcarbamate	Active
27	N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-4-methylbenzamide	Active
26	2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethyl-phenoxy)ethyl methylcarbamate	Active
25	2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethyl-phenoxy)ethyl propylcarbamate	Active
24	N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)methanesulfonamide	Active
23	4-chloro-N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)benzenesulfonamide	Active
22	N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-4-methoxybenzenesulfonamide	Active
21	N1-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N2-methylphthalamide	Active
20	4-chloro-N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)benzenesulfonamide	Active
18	2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one	Active
18	N1-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N2-methylphthalamide	Active
17	2-(4-amino-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one	Active
16	5,7-dimethoxy-2-(4-methoxy-3,5-dimethylphenyl)quinazolin-4(3H)-one	Active
15	2-(2-chloro-6-methylpyridin-4-yl)-5,7-dimethoxyquinazolin-4(3H)-one	Active

Example #	Compound Name	Effect on ApoA-I mRNA levels
14	2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxypyrido[2,3-d]pyrimidin-4(3H)-one	Active
13	2-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one	Active
12	2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6,7-dimethoxyquinazolin-4(3H)-one	Active
11	2-(4-(bis(2-hydroxyethyl)amino)phenyl)-6,7-dimethoxyquinazolin-4(3H)-one	Active
10	2-(4-(bis(2-hydroxyethyl)amino)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one	Active
9	2-(4-hydroxy-3-methoxyphenyl)-5,7-dimethoxyquinazolin-4(3H)-one	Active
8	3-(3,5-dimethyl-4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)-6,8-dimethoxyisoquinolin-1(2H)-one	Active
7	2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one	Active
6	7-(4-hydroxy-3,5-dimethylphenyl)-2,4-dimethoxy-1,6-naphthyridin-5(6H)-one	Active
5	3-(4-(2-hydroxy-2-methylpropoxy)-3,5-dimethylphenyl)-6,8-dimethoxyisoquinolin-1(2H)-one	Active
4	2-(4-hydroxy-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one	Active
3	3-(4-hydroxy-3,5-dimethylphenyl)-7-(morpholinomethyl)isoquinolin-1(2H)-one	Active
2	3-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6,8-dimethoxyisoquinolin-1(2H)-one	Active
1	3-(4-hydroxy-3,5-dimethylphenyl)-6,8-dimethoxyisoquinolin-1(2H)-one	Active

Example 42: ApoA-I mRNA and protein induction

[0167] In this example, ApoA-I mRNA and secreted protein from tissue culture cells were quantitated. The assay can be used to determine the potency for compounds of interest, including those of the present invention.

[0168] HepG2 cells and primary human hepatocytes (BD Gentest, lot 107) (~2×10^5 per well) were placed in a 24-well plate in ~400 µL MEM, supplemented with 0.5% (v/v) FBS, 24 h before addition of the compound of interest. The compounds of interest were dissolved in DMSO at 0.05% (v/v). Appropriate volumes of the stock solutions of the compounds in DMSO were then added to appropriate volumes of MEM, supplemented with 0.5% (v/v) FBS, to achieve the desired concentration (for example, 1 µL of a compound stock into 1 mL of MEM, supplemented with 0.5% (v/v) FBS).

[0169] Just prior to compound addition to the cells, the growth media was aspirated and replaced with 300 µL of fresh MEM, supplemented with 0.5% (v/v) FBS, followed by addition of 300 µL of the compound of interest in MEM, supplemented with 0.5% (v/v) FBS, to achieve the desired final compound concentration in a total volume of 600 µL. The final concentration of diluent (DMSO) was 0.05% (v/v).

[0170] Cells were incubated for the desired time. The cell media was then harvested, as were the cells. ApoA-I mRNA was measured as described in Example 39. Secreted ApoA-I was measured using an ApoA-I ELISA, as described below:

ApoA-I ELISA

[0171] In this example, the ApoA-I secreted into the media from tissue culture cells was quantitated to assess induction of endogenous ApoA-I protein secretion from cells treated with various small molecule compounds, such as those of the present invention.

[0172] At time of harvesting, spent media from the HepG2 cell cultures or primary cell culture was removed and stored at -80°C in 1.5 mL microfuge tubes.

[0173] For the human ApoA-I ELISA, an ELISA plate was coated with ~100 µL/well human ApoA-I capture antibody diluted to ~2 µg/mL in coating buffer for ~1 h at room temperature. The plate was then washed three times in wash buffer. The plate was then blocked with ~200 µL/well human ApoA-I blocking buffer for at least ~30 min at room temperature.

[0174] Samples for use in generating a standard curve were prepared from spent media (MEM, supplemented with 0.5% (v/v) FBS) from HepG2 or

primary cells treated with DMSO for 48 h. Serial 2 fold dilutions of the media were prepared in MEM, supplemented with 0.5% (v/v) FBS. The unknown samples, from the cultures treated with the compounds of interest, were also diluted in MEM, supplemented with 0.5% (v/v) FBS. The plate was washed three times in wash buffer. The standard curve and unknown samples (100 µL/well), in triplicate, were added to the plate and it was incubated for 1.5 h at room temperature.

[0175] The plate was washed three times in wash buffer. Human ApoA-I detection antibody, diluted 1:1000 in PBS, was added (100 µL/well) and the plate was incubated for 1 h at room temperature. The plate was washed three times in wash buffer.

[0176] Goat anti-rabbit IgG H & L chain specific peroxidase conjugate, diluted 1:2000 in PBS, was added (100 µL/well) and the plate was incubated for 40 min at room temperature in the dark. The plate was washed six times in wash buffer.

[0177] TMB liquid substrate was added (100 µL/well) and the plate was incubated on a shaker underneath tin foil during development. Once a sufficient "blue" color had been achieved, stop solution (50 µL/well, 1 M H_2SO4) was added and mixed thoroughly on the plate shaker. Air bubbles were removed and the absorbance at 450 nm was determined, using a Molecular Devices SpectraMax 190 Plate Reader and the human ApoA-I ELISA Softmax software.

Example #	Compound Name	EC50 Protein (µM)
20	4-chloro-N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)benzenesulfonamide	0.32
18	2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one	7.22

Example #	Compound Name	EC50 Protein (μM)
18	N1-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N2-methylphthalamide	7.29
17	2-(4-amino-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one	7.63
16	5,7-dimethoxy-2-(4-methoxy-3,5-dimethylphenyl)quinazolin-4(3H)-one	16.46
15	2-(2-chloro-6-methylpyridin-4-yl)-5,7-dimethoxyquinazolin-4(3H)-one	3.96
14	2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxypyrido[2,3-d]pyrimidin-4(3H)-one	9.20
13	2-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one	13.72
12	2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6,7-dimethoxyquinazolin-4(3H)-one	9.07
11	2-(4-(bis(2-hydroxyethyl)amino)phenyl)-6,7-dimethoxyquinazolin-4(3H)-one	13.30
10	2-(4-(bis(2-hydroxyethyl)amino)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one	12.11
9	2-(4-hydroxy-3-methoxyphenyl)-5,7-dimethoxyquinazolin-4(3H)-one	12.08
8	3-(3,5-dimethyl-4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)-6,8-dimethoxyisoquinolin-1(2H)-one	2.82
7	2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one	12.16
6	7-(4-hydroxy-3,5-dimethylphenyl)-2,4-dimethoxy-1,6-naphthyridin-5(6H)-one	6.52
5	3-(4-(2-hydroxy-2-methylpropoxy)-3,5-dimethylphenyl)-6,8-dimethoxyisoquinolin-1(2H)-one	6.27
4	2-(4-hydroxy-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one	7.93
3	3-(4-hydroxy-3,5-dimethylphenyl)-7-(morpholinomethyl)isoquinolin-1(2H)-one	11.09
2	3-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6,8-dimethoxyisoquinolin-1(2H)-one	11.35
1	3-(4-hydroxy-3,5-dimethylphenyl)-6,8-dimethoxyisoquinolin-1(2H)-one	5.42
	2-(4-Hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one	179.47

EXAMPLE 43: ***In vivo* efficacy**

[0178] To test whether the efficacy of compounds of the invention observed *in vitro* extended to an *in vivo* model, transgenic mice carrying multiple copies of the human ApoA-I gene (Bisaha *et al.* (1995) *J. Biol. Chem.* **34**, 19979-88) or wild-type mice (C57BL/6 (Stock Number 000664) Jackson Laboratory (Bar Harbor, ME)) were exposed to compounds of the invention. In the transgenic mice, the exogenous human ApoA-I gene in these mice enables them to express the human ApoA-I protein under the control of its own promoter.

[0179] Seven to eight week old male mice were housed five per cage (10"x20"x8" with aspen chip bedding) with pelleted Rodent chow [Purina 5001] and water available at all times. After an acclimation period of 1 week, animals were individually identified by numbering on tail and weighed. Mice were pre-bled via the retro-orbital plexus, and 100 µL of blood was collected in 1.5 mL Eppendorf tube containing 5 µL of 0.5 mM EDTA and chilled on ice. Plasma was collected after centrifuging the whole blood at 14000 rpm [TOMY high speed micro-refrigerated centrifuge NTX-150] for 10 min at 4°C and frozen at -80°C. Mice were grouped based on having an average body weight of 25 g.

[0180] A day following pre-bleed, mice were dosed by oral gavage or by i.p. administration daily using a 20 gauge, 11/2" curved disposable feeding needle (Popper & Sons); when B.I.D., mice were gavaged morning and afternoon (8 am and 5 pm); when Q.D. mice were gavaged in morning (8 am). Compounds were prepared each day in vehicle. One day prior to necropsy mice were weighed and fasted overnight. On final day of dosing, mice were sacrificed post 2 h of dosing by inhalation of CO_2 and blood was obtained via cardiac puncture (0.7-1.0 mL). Plasma was collected and frozen at -80°C. Samples were assayed for ApoA-I by ELISA, and HDL-C by HPLC (Polaris 200 with an auto sampler Prostar 410 from Varian on a Superose 6 10/30 column from Amersham). During necropsy, liver and enterocytes from the duodenum and jejunum of small intestine were collected, cleaned with cold PBS and frozen at -80°C for further analysis of compound and mRNA levels by Q-PCR.

[0181] **Experiment A** 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (10, 30 and 60 mg/kg of body weight, mpk) were BID administered to hApoA-I transgenic mice daily for seven days by oral gavage

in 1% DMSO, 2.5% Tween-80, 10% PEG-300 QS to water. Plasma was assayed for ApoA-I (Fig. 1), and HDL cholesterol (Fig. 2).

[0182] **Experiment B** 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (10, 30 and 60 mg/kg of body weight) were BID administered to wild-type C57BL/6 mice daily for three days by i.p. administration in 1% DMSO, 2.5% Tween-80, 10% PEG-300 QS to water. Plasma was assayed for ApoA-I (Fig. 3), and HDL cholesterol (Fig. 4).

[0183] **Experiment C** 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (30 mg/kg of body weight) were BID administered to hApoA-I transgenic mice daily for seven days by oral gavage in 1% DMSO, 2.5% Tween-80, 10% PEG-300 QS to water. Plasma was assayed for ApoA-I and tissues were assayed for mRNA (Fig. 5).

[0184] These results indicate that the compounds of the invention are useful for increasing the transcription of ApoA-I in vivo, and elevating plasma levels of ApoA-I and circulating levels of HDL-C in wild-type and hApoA-I transgenic mice. These results demonstrate that compounds of the invention activate the human ApoA-I transgene in mice, leading to an increase in circulating ApoA-I.

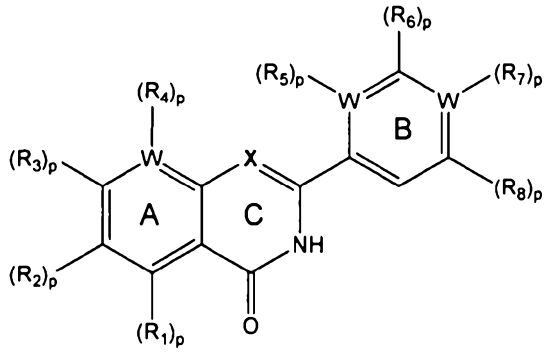
[0185] The term "comprise" and variants of the term such as "comprises" or "comprising" are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

[0186] Any reference to publications cited in this specification is not an admission that the disclosures constitute common general knowledge in Australia.

[0187] 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.

CLAIMS:

1. A compound of **Formula II**:



Formula II

wherein:

X is N;

R_1 and R_3 are each independently selected from alkoxy and hydrogen;

R_2 is selected from alkoxy, alkyl, and hydrogen;

R_6 and R_8 are each independently selected from alkyl, alkoxy, chloride, and hydrogen;

R_4 and R_5 are hydrogen;

R_7 is selected from amino, hydroxyl, alkoxy, and alkyl substituted with a heterocyclyl, or

two adjacent substituents selected from R_6, R_7, and R_8 are connected to form a heterocyclyl;

each W is independently selected from C and N, p is 1 except that when W is N, then p is 0;

with the proviso that if R_2 is selected from alkoxy or hydrogen, then at least one of R_1 and R_3 is alkoxy;

with the proviso that if R_7 is selected from hydroxyl or alkoxy, then at least one of R_6 and R_8 are independently selected from alkyl, alkoxy, and chloride;

with the proviso that for W-$(R_7)_p$, if W is N and p is 0, then at least one of R_6 and R_8 is chloride;

or a pharmaceutically acceptable salt or hydrate thereof.

2. The compound according to claim 1, wherein at least one of R_6 and R_8 is selected from alkyl, alkoxy, and chloride.

3. The compound according to claim 1, wherein R_6 and R_8 are each hydrogen, and W-$(R_7)_p$ is C-$(R_7)_1$.

4. The compound according to claim 1, wherein both R_6 and R_8 are not hydrogen.

5. The compound according to claim 1, wherein:
R_1 and R_3 are alkoxy;
R_6 and R_8 are alkyl; and
R_7 is alkoxy substituted with a hydroxyl.

6. The compound according to any one of claims 1 to 4, wherein R_7 is not diethylamino or an alkoxy substituted with a carboxylate group.

7. The compound according to any one of claims 1 to 4, wherein R_7 is selected from hydroxyl, amino, and alkoxy.

8. The compound according to claim 1, wherein the compound is 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one, or a pharmaceutically acceptable salt or hydrate thereof.

9. The compound according to claim 1, wherein the compound is selected from:
2-(4-hydroxy-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(4-hydroxy-3-methoxyphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(4-(bis(2-hydroxyethyl)amino)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(4-(bis(2-hydroxyethyl)amino)phenyl)-6,7-dimethoxyquinazolin-4(3H)-one;
2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6,7-dimethoxyquinazolin-4(3H)-one;
2-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxypyrido[2,3-d]pyrimidin-4(3H)-one;
2-(2-chloro-6-methylpyridin-4-yl)-5,7-dimethoxyquinazolin-4(3H)-one;
5,7-dimethoxy-2-(4-methoxy-3,5-dimethylphenyl)quinazolin-4(3H)-one;
2-(4-amino-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
N1-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N2-methylphthalamide;
2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one; and
4-chloro-N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)benzenesulfonamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-4-methoxybenzenesulfonamide;
4-chloro-*N*-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-

2,6-dimethylphenoxy)ethyl)benzenesulfonamide;

N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)methanesulfonamide;

2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethyl-phenoxy)ethyl propylcarbamate;

2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethyl-phenoxy)ethyl methylcarbamate;

N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-4-methylbenzamide;

2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl cyclohexylcarbamate;

N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)benzenesulfonamide;

N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-4-methylbenzenesulfonamide;

N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-4-methoxybenzamide;

N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)acetamide;

N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)benzamide;

N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)isobutyramide;

1-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-3-methylurea;

1-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-3-(4-methoxyphenyl)urea;

1-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-3-phenylurea; and

3-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-1,1-dimethylurea;

or a pharmaceutically acceptable salt or hydrate thereof.

10. The compound according to any one of claims 1 to 4, wherein R_7 is selected from an alkoxy substituted with a heterocycle.

11. The compound according to claim 10, wherein the heterocycle substituent on the alkoxy at R_7 is substituted or unsubstituted.

12. The compound according to claim 10 or claim 11, wherein the heterocycle substituent on the alkoxy at R_7 is selected from 5 and 6 membered amines.

13. The compound according to claim 12, wherein the heterocyclic amine substituent on the alkoxy at R_7 contains 1-2 nitrogen atoms.

14. The compound according to any one of claims 10 to 13 wherein the heterocycle substituent on the alkoxy at R_7 is selected from pyrrolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazinyl, pyrazolyl, pyrazolinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidin-2-onyl, and pyrrolinyl.

15. The compound according to claim 14, wherein the heterocycle substituent on the alkoxy at R_7 is selected from pyrrolidinyl, piperazinyl, and piperidinyl.

16. A pharmaceutical composition comprising a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier.

17. A method of treating or preventing a cardiovascular, cholesterol or lipid related disorder in a mammal comprising administering to said mammal a therapeutically effective amount of a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt or hydrate thereof, or a pharmaceutical composition according to claim 16.

18. The method according to claim 17, wherein said disorder is atherosclerosis.

19. A method of increasing expression of ApoA-I and/or HDL-C in a mammal comprising administering to said mammal a therapeutically effective amount of a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt or hydrate thereof, or a pharmaceutical composition according to claim 16.

20. The method according to any one of claims 17 to 19, wherein said mammal is a human.

Date: 31 January 2013

FIGURE 1

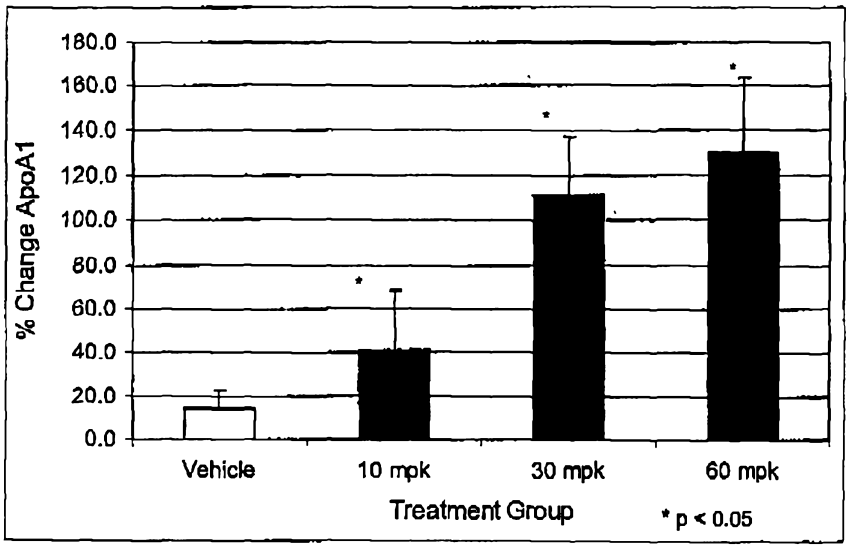

180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
% Change ApoA1
Vehicle
10 mpk
30 mpk
60 mpk
Treatment Group
* p < 0.05

FIGURE 2

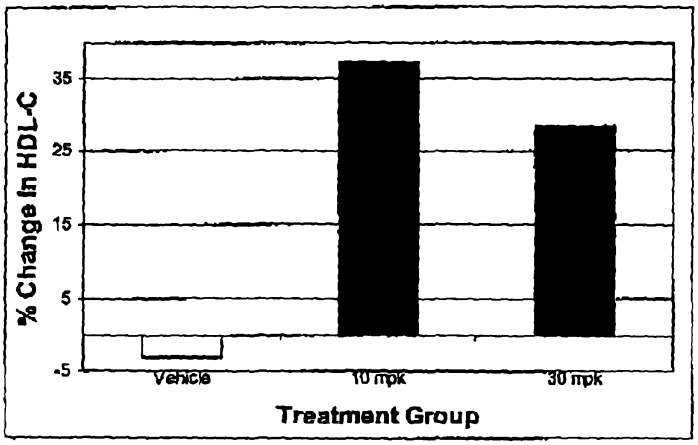

% Change in HDL-C
35
25
15
5
-5
Vehicle
10 mpk
30 mpk
Treatment Group

FIGURE 3

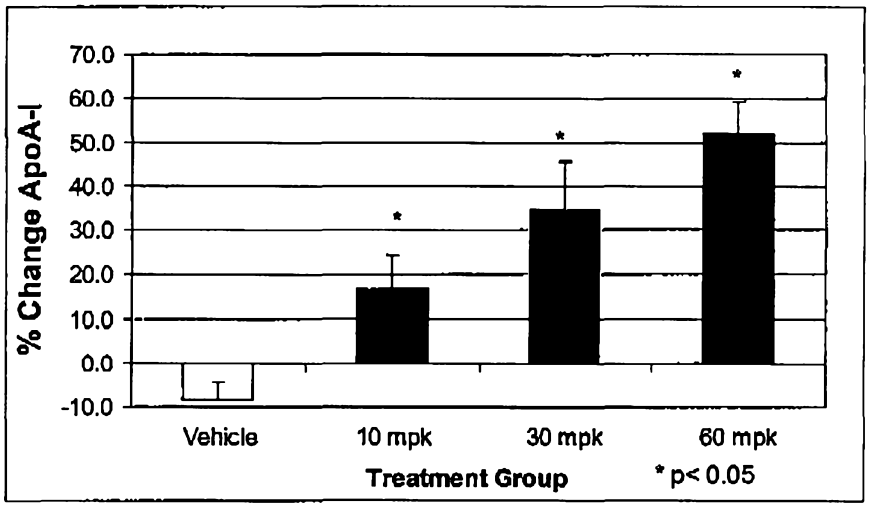

70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
-10.0
% Change ApoA-I
*
*
*
Vehicle
10 mpk
30 mpk
60 mpk
Treatment Group
* p< 0.05

FIGURE 4

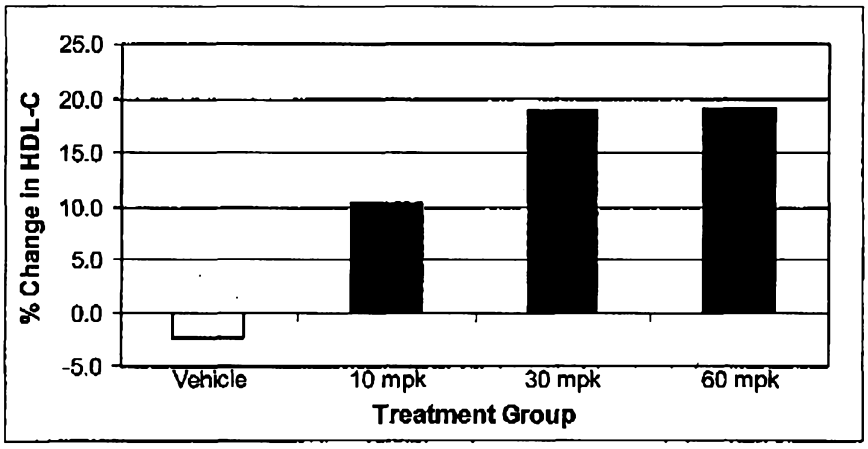
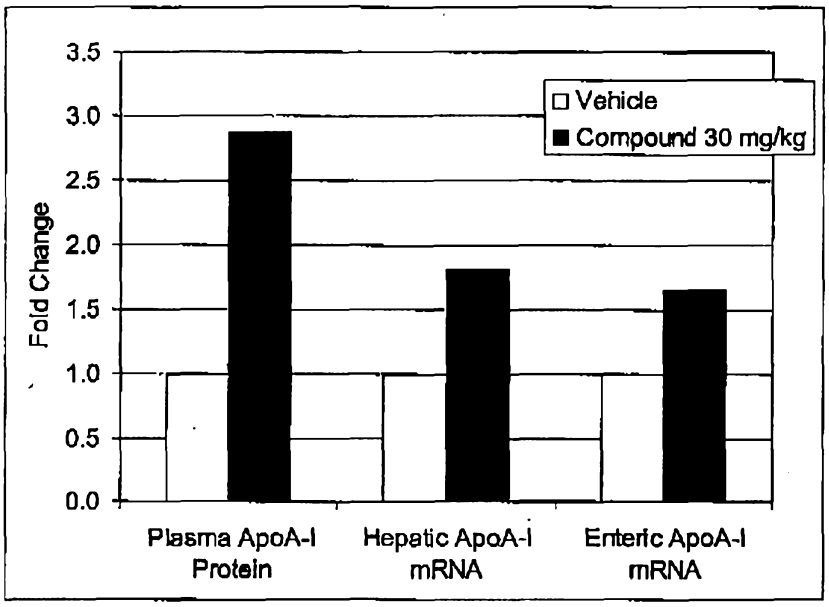

25.0
20.0
15.0
10.0
5.0
0.0
-5.0
% Change in HDL-C
Vehicle
10 mpk
30 mpk
60 mpk
Treatment Group

FIGURE 5


3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Fold Change
Vehicle
Compound 30 mg/kg
Plasma ApoA-I Protein
Hepatic ApoA-I mRNA
Enteric ApoA-I mRNA