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Description

[0001] The present invention relates to methods of regulating interleukin-6 (IL-6) and/or vascular cell adhesion molecule-1 (VCAM-1) and to methods of treating and/or preventing cardiovascular and inflammatory diseases and related disease states, such as, for example, atherosclerosis, asthma, arthritis, cancer, multiple sclerosis, psoriasis, and inflammatory bowel diseases, and autoimmune disease(s) by administering a naturally occurring or synthetic quinazolone derivative. The invention provides novel synthetic quinazolone compounds, as well as pharmaceutical compositions comprising those compounds.

[0002] Coronary heart disease (CHD) remains a leading cause of death in industrialized nations. A primary cause of CHD is atherosclerosis, a disease characterized by the deposition of lipids in the arterial vessel wall, resulting in a narrowing of the vessel passages and, ultimately, hardening of the vascular system.

[0003] It is generally accepted that atherosclerosis can begin with local injury to the arterial endothelium, followed by monocyte recruitment and maturation, and smooth muscle cell proliferation in the intimal arterial layer, along with the deposition of lipids and the accumulation of foam cells in the lesion. As the atherosclerotic plaque develops, it progressively occludes more of the affected blood vessel and can eventually lead to ischemia or infarction. Thus, it continues to be desirable to develop treatments to inhibit or prevent the progression of atherosclerosis in patients in need thereof.

[0004] Cardiovascular disease has been linked to several causative factors, including hypercholesterolemia, hyperlipidemia, and vascular cell adhesion molecule-1 (VCAM-1) in vascular endothelial cells. VCAM-1 promotes the adhesion of lymphocytes, monocytes, eosinophils, and basophils. Certain melanoma cells can use VCAM-1 to adhere to the endothelium, and VCAM-1 may participate in monocyte recruitment to atherosclerotic sites. As a result, VCAM-1 is of interest as a drug target.

[0005] The VCAM-1 gene is a member of the immunoglobulin (Ig) superfamily and encodes a cell-surface sialoglycoprotein expressed by cytokine-activated endothelial cells. This type-1 membrane protein mediates leukocyte-endothelial cell adhesion and signal transduction, and may play a role in the development of artherosclerosis and rheumatoid arthritis. VCAM-1, also known as CD106, has several roles in the immune system. The VCAM-1 protein contains six or seven immunoglobulin domains, and is expressed in both large and small vessels only after endothelial cells are stimulated by cytokines.

[0006] Adhesion of leukocytes to the endothelium represents a fundamental, early event in many inflammatory conditions, including atherosclerosis, autoimmune disorders, and bacterial and viral infections. Leukocyte recruitment to the endothelium begins when inducible adhesion molecule receptors on the surface of endothelial cells interact with their counter-receptors on immune cells. Vascular endothelial cells determine which type(s) of leukocyte(s) (e.g., monocytes, lymphocytes, neutrophils) are recruited, by selectively expressing specific adhesion molecules, such as VCAM-1, intracellular adhesion molecule-1 (ICAM-1), and E-selectin.

[0007] In the early stage of the atherosclerotic lesion, there is localized endothelial expression of VCAM-1 and selective recruitment of mononuclear leukocytes that express the integrin counter-receptor VLA-4. Because of the selective expression of VLA-4 on monocytes and lymphocytes, but not neutrophils, VCAM-1 is important in mediating the selective adhesion of mononuclear leukocytes. Subsequent conversion of leucocytes to foamy macrophages results in the synthesis of a wide variety of inflammatory cytokines, growth factors, and chemoattractants that help expand leukocyte and platelet recruitment, smooth muscle cell proliferation, endothelial cell activation, and the extracellular matrix synthesis characteristic of maturing atherosclerotic plaques.

[0008] VCAM-1 is a mediator in chronic inflammatory disorders, such as asthma, rheumatoid arthritis, and diabetes. For example, it is known that VCAM-1 and ICAM-1 is increased in asthmatics (Pilewski et al. (1995) Am. J. Respir. Cell Mol. Biol. 12, 1-3; Ohkawara et al. (1995) Am J. Respir. Cell Mol. Biol. 12, 4-12). Further examples of non-cardiovascular inflammatory diseases mediated by VCAM-1 include rheumatoid and osteoartitis, asthma, dermatitis, and multiple sclerosis. Blocking the integrin receptors for VCAM-1 and ICAM-1 (VLA-4 and LFA-1, respectively) suppresses both early- and late-phase responses in an ovalbumin-sensitized rat model of allergic airway responses (Rabb et al. (1994) Am. J. Respir. Care Med. 149, 1186-1191). There is also increased expression of endothelial adhesion molecules, including VCAM-1, in the microvasculature of rheumatoid synovium (Koch et al. (1991) Lab. Invest. 64, 313-322; Morales-Ducret etal. (1992) Immunol. 149, 1421-31).

[0009] Neutralizing antibodies directed against VCAM-1 or its counter receptor, VLA-4, can delay the onset of diabetes in a mouse model (NOD mice) which spontaneously develop the disease (Yang et al. (1993) Proc. Natl. Acad. Sci. USA 90, 10494-10498; Burkly et al. (1994) Diabetes 43, 523-534; Baron et al. (1994) J. Clin. Invest. 93, 1700-1708). Monoclonal antibodies to VCAM-1 can also have beneficial effects in animal models of allograft rejection, suggesting that inhibitors of VCAM-1 expression may also have utility in preventing transplant rejection (Oroez et al. (1992) Immunol. Lett. 32, 7-12).

[0010] VCAM-1 is expressed by cells both in a membrane-bound form and a soluble form. The soluble form has been shown to induce chemotaxis of vascular endothelial cells *in vitro* and to stimulate an angiogenic response in rat cornea (Koch etal. (1995) Nature 376, 517-519). Inhibitors of VCAM-1 have potential therapeutic value in treating diseases with an angiogenic component, including tumor growth and metastasis (Folkman & Shing (1992) Biol. Chem. 10931-10934).

[0011] Because cardiovascular disease is currently a leading cause of death and disability in the developed world, there is a strong need to identify new methods and pharmaceutical agents for its treatment. Thus, there is a need to identify and manipulate synthetic compounds that can affect mediators of the inflammatory process, such as, for example, VCAM-1.

[0012] Interleukin-6 (IL-6) is a 22-27-kDa secreted glycoprotein that exhibits growth stimulatory and pro-inflammatory activities. IL-6 has also been called interferon-β2 (IFN-β2), IL-1-inducible 26-kDa protein, hepatocyte-stimulating factor, cytotoxic T-cell differentiation factor, and B-cell stimulatory factor (Trikha et al. (2003) Clin. Cancer Res. 9, 4653-4665). IL-6 was originally identified in monocytes / macrophages, fibroblasts, and endothelial cells.

[0013] IL-6 is secreted by various cell types and exerts its activities by binding to a high-affinity receptor complex, consisting of two membrane glycoproteins, an 80-kDa component receptor that binds IL-6 with low affinity (IL-6R) and a signal-transducing component of 130 kDa (also known as gp130) that does not bind IL-6 itself, but is required for high-affinity binding of IL-6 by the complex. The IL-6R can be cleaved by a transmembrane metalloproteinase to yield a soluble IL-6R.

[0014] IL-6 levels are rapidly elevated in the circulation in numerous infectious, inflammatory, and autoimmune diseases, and in some cancers, in association with increased synthesis of other cytokines, stimulated by infection, trauma, and immunological challenge. (Trikha et al. (2003) Clin. Cancer Res. 9, 4653-4665). IL-6 has been implicated in various diseases and disorders, including multiple myeloma (Rossi et al. (2005) Bone Marrow Transplantation 36, 771-779), lymphomas (Emilie et al. (1994) Blood 84, 2472-2479), neurological disorders, such as neurodegeneration, astrocytosis, and cerebral angiogenesis (Campbell et al. (1993) Proc. Natl. Acad. Sci. USA 90, 10061-10065), autoimmune disorders (such as, e.g., rheumatoid arthritis), inflammatory diseases, Alzheimer's disease, myocardial infarction, Paget's disease, osteoporosis, solid tumors, prostate and bladder cancers (Trikha et al. (2003) Clin. Cancer Res. 9, 4653-4665), septic shock, transplants, acute infections of the central nervous system, cardiac myxoma (Wijdenes etal. (1991) Mol. Immunol. 28, 1183-1192), tumor-induced cachexia (Cahlin et al. (2000) Cancer Res. 60, 5488-5489), cancer-associated depression, and cerebral edema secondary to brain tumors (Musselman et al. (2001) Am. J. Psychiatry 158, 1252-1257). Inflammation and IL-6 are now specifically thought to be linked to heart attacks (Taubes (2002) Science 296, 242).

[0015] Generally, it is known that IL-6 is abnormally produced in some inflammatory, autoimmune, and neoplastic diseases; further, it has been proposed that abnormal production of IL-6 is an aspect of the mechanisms of these diseases (Hirano et al. (1990) Immunol. Today, 11, 443-449; Sehgal (1990) Proc. Soc. Exp. Biol. Med. 195, 183-191; Grau (1990) Eur. Cytokine Net 1, 203-210; Bauer et al. (1991) Ann. Hematol. 62, 203-210; Campbell et al. (1991) J. Clin. Invest. 7, 739-742; Roodman et al. (1992) J. Clin. Invest. 89, 46-52). In particular, it is known that IL-6 is associated with neuropathological processes, and its level in blood is increased in diseases invading the central nervous system. It has been found that IL-6 increases the level of tau epitope, by stimulating the dementia-associated phosphorylation of the tau protein in neuronal cells (Quintanilla et al. (2004) Exp. Cell Res. 295, 245-257), and mice lacking IL-6 have enhanced resistance to glutamate toxicity and increased viability of neuronal cells (Fisher et al. (2001) J. Neuroimmunol. 119, 1-9). It has also been found that IL-6 amplifies a calcium influx signal for the neurotransmitter N-methyl-D-aspartate (NMDA), through voltage-sensitive calcium channels, which provides a clue that the increased IL-6 level may have a role in inducing pathological changes in central nervous system diseases (Qiu *et al.* (1998) 18,10445-10456). It has also been reported that the abnormal levels of IL-6 is a pathogenic mechanism in other diseases, including cardiac myxoma, uterine cancer (Kishimoto et al. (1988) Ann. Rev. Immunol. 6, 485; multiple myeloma; histiocytomas (Taga et al. (1987) J. Exp. Med. 166, 967), plasmacytoma, hematological diseases, including plasma cell dyscrasias, leukemia, and lymphoma (Kishimoto (1989) Blood 74, 1; Taga et al. (1987) J. Exp. Med. 166, 967; Klein etal. (1991) Blood 78, 1198-1204); proliferative glomerulonephritis; activated multiclonal B-cell (types I-IV) allergic diseases, rheumatoid arthritis (Hirano et al. (1988) Eur. J. Immunol. 18, 1797), diabetes (Campbell et al.(1991) J. Clin. Invest. 87, 739-742), multiple sclerosis, SLE, septic shock, bacterial infections, viral infections, osteoporosis (Roodman et al. (1992) J. Clin. Invest. 89, 46-52; Jilka et al. (1992) Science 257, 88-91); chronic immunodeficiency syndrome and autoimmune immunodeficiency syndromes, including AIDS (Med. Immunol. 15, 195-201 (1988)), and inflammatory diseases, including inflammatory bowel diseases (such as Crohn's disease and ulcerative colitis) (WO99/47170). It is known that IL-6 is associated with some central nervous system diseases (Frei et al. (1991) J. Neuroimmunol. 31, 147).

[0016] Interleukin-6 is secreted by many advanced cancers, such as hormone-independent prostate cancer, and is believed to be a growth factor for such cancers. Additionally, the secretion of IL-6 by cancer cells is believed to cause cachexia, the wasting syndrome characteristic of advanced cancers. Thus, reducing the level of IL-6 would be useful in treating such cancers. IL-6 also plays a key role in B cell development. Autoimmune diseases with a significant antibody component, such as rheumatoid arthritis, could be treated by decreasing IL-6 levels. Disorders involving B cell proliferation, such as multiple myeloma and B cell lymphoma, could also be treated by reducing IL-6 activity. Additionally, IL-6 plays an important role in bone remodeling by promoting bone resorption. Reducing IL-6 activity would have the effect of reducing bone resorption and could be used to treat osteoporosis.

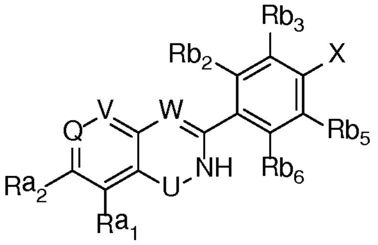
[0017] Accordingly, there have been various attempts to reduce the levels of IL-6, which are believed to be associated with the pathogenic mechanisms of these various diseases and conditions. A steroid formulation has been used for suppressing the cytokines in the art, but such medicines may causes severe side-effects, such as peptic ulcers, if administered for an extended period.

[0018] Anti-IL-6 antibodies have been shown to be effective in treating several diseases and disorders. For example, anti-IL-6 monoclonal antibodies have been shown to block the proliferation of myeloma cells both *in vivo* and *in vitro* (Rossi et al. (2005) Bone Marrow Transplantation 36, 771-779). Administration of anti-IL-6 antibodies to chronic rheumatoid arthritis patients was found to alleviate the symptoms of the disease (Wendling et al. (1993) J. Rheumatol. 20, 259-262). Anti-IL-6 antibodies have also been shown to be effective in treating AIDS-associated lymphoma (Emilie et al. (1994) Blood 84, 2472-2479), and metastatic renal cell carcinoma (Blay et al. (1997) Int. J. Cancer 72, 424-430). Clinical results involving the administration of anti-IL-6 antibodies to treat various other diseases and disorders are summarized in Trikha et al. (2003) Clin. Cancer Res. 9, 4653-4665.

[0019] Thus, the present invention relates to methods of regulating interleukin-6 (IL-6) and vascular cell adhesion molecule-1 (VCAM-1) in a mammal by administering one or more compounds of Formula I or Formula II to the mammal. The invention also relates to methods of treating and/or preventing cardiovascular and inflammatory diseases, such as, for example, atherosclerosis, asthma, arthritis, cancer, multiple sclerosis, psoriasis, and inflammatory bowel diseases, and autoimmune disease(s) in a mammal by administering one or more compounds of Formula I or Formula II to the mammal. Also described herein are provides novel compounds, pharmaceutical compositions comprising those compounds, and methods of preparing those compounds.

[0020] Wtihout wishing to be bound by theory, it is believed that the compounds of Formula I and II act by inhibiting expression of IL-6 and/or VCAM-1 in the subject receiving the compound. However, regardless of the mechanism of action, administration of one or more compounds of Formula I and/or Formula II will reduce the levels of IL-6 and/or VCAM-1 in the subject and as a result treat or reduce the incidence of cardiovascular and/or inflammatory diseases.

[0021] One aspect of the invention provides a pharmaceutical composition for use in a method of reducing IL-6 for the treatment of cancer in a subject, wherein the composition comprises a therapeutically effective amount of at least one compound of Formula I:

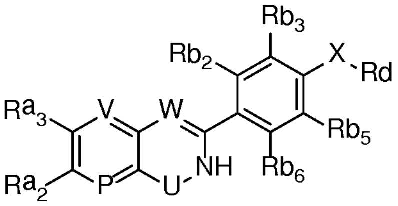


(I)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof, wherein:

Q is selected from N and CRa_3;
V is selected from N and CRa_4;
W is selected from N and CH;
U is selected from C=O, C=S, SO_2, S=O, and SR_1;
X is selected from OH, SH, NH_2, S(O)H, $S(O)_2H$, $S(O)_2NH_2$, $S(O)NH_2$, NHAc, and $NHSO_2Me$;
Ra_1, Ra_3, and Ra_4 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, and halogen;
Ra_2 is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, amino, amide, and halogen;
Rb_2 and Rb_6 are independently selected from hydrogen, methyl and fluorine;
Rb_3 and Rb_5 are independently selected from hydrogen, halogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and C_1-C_6 alkoxy; and
Rb_2 and Rb_3 and/or Rb_5 and Rb_6 may be connected to form a cycloalkyl or a heterocycle,
provided that at least one of Ra_1, Ra_2, Ra_3, and Ra_4 is not hydrogen.

[0022] The invention also provides a pharmaceutical composition for use in reducing IL-6 and/or VCAM-1 in a subject for the treatment of cancer or a disease selected from arthritis, asthma, dermatitis, psoriasis, cystic fibrosis, post transplantation late and chronic solid organ rejection, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel diseases, ocular inflammation, uveitis, rhinitis, chronic obstructive pulmonary disease (COPD), glomerulonephritis, Grave's disease, gastrointestinal allergies, and conjunctivitis, wherein the composition comprises a therapeutically effective amount of at least one compound of Formula II:



(II)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof, wherein:

P is selected from N and CRa_1;
V is selected from N and CRa_4;
W is selected from N and CH;
U is C=O;
Ra_1, Ra_3, and Ra_4 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, and halogen;
Ra_2 is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, heterocycle, amide, amino, fluoro, and bromo;
Rb_2 and Rb_6 are independently selected from hydrogen, methyl, and fluoride;
Rb_3 and Rb_5 are independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, halogen, and amino;
Rb_2 and Rb_3 and/or Rb_5 and Rb_6 may be connected to form a cycloalkyl, phenyl, or heterocycle; and
X-Rd is selected from 2-hydroxyethoxy, methoxy, benzyloxyethoxy, 2,3-dihydroxypropoxy, aminocarbonylethoxy, methylaminocarbonylethoxy, (4-methoxyphenyl)aminocarbonylethoxy, benzylaminocarbonylethoxy, 4-hydroxybutoxy, (5-phenyl-4H-[1,2,4]triazol-3-ylamino)ethoxy, (3-methyl-[1,2,4]oxadiazol-5-ylamino)ethoxy, methylcarbonylaminoethoxy, methylcarbonylaminomethyl, (2,2,2-trifluoro-ethylamino)ethoxy, methanesulfonylaminoethoxy, isobutyrylaminoethoxy, methylaminoethoxy, isopropylsulfonylaminoethoxy, dimethylaminoethoxy, N-(2-hydroxyethyl)-N-methylacetamide, formamide-N-2-ethoxy, methylformamide-N-2-ethoxy, dimethylsulfonylaminoethoxy, cyanoaminoethoxy, (5-methylisoxazol-3-ylamino)ethoxy, (pyrimidin-2-ylamino)ethoxy, (isoxazol-3-ylamino)ethoxy, (4,6-dimethoxypyrimidin-2-ylamino)ethoxy, 3-hydroxypropyl, and 2-hydroxyethyl,
provided that
at least one of Ra_1, Ra_2, Ra_3, and Ra_4 is not hydrogen;
if -XRd is $-OCH_2CH_2OH$, then Rb_3 is not pyrrolidine; and
if -XRd is -OMe, then Ra_2 is not $-CH_2$morpholino.

Definitions

[0023] As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise. The following abbreviations and terms have the indicated meanings throughout:

[0024] The terms "compound of Formula I" and "compound of Formula II" are intended to include any stereoisomer, tautomer, and/or pharmaceutically acceptable salt as defined herein. Compounds of Formula I and Formula II also include crystalline and amorphous forms of those compounds, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof. "Crystalline form," "polymorph," and "novel form" may be used interchangeably herein, and are meant to include all crystalline and amorphous forms of the compound, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to. Compounds of Formula I and compounds of Formula II also inclued pharmaceutically acceptable forms of the recited compounds, including chelates, non-covalent complexes, prodrugs, and mixtures thereof.

[0025] As noted above, prodrugs also fall within the scope of compounds of Formula I and compounds of Formula II. In some embodiments, the "prodrugs" described herein include any compound that becomes a compound of Formula I and /or Formula II when administered to a patient, e.g., upon metabolic processing of the prodrug. Examples of prodrugs include derivatives of functional groups, such as a carboxylic acid group, in the compounds of Formula I and/or Formula II. Exemplary prodrugs of a carboxylic acid group include, but are not limited to, carboxylic acid esters such as alkyl esters, hydroxyalkyl esters, arylalkyl esters, and aryloxyalkyl esters.

[0026] A "solvate" is formed by the interaction of a solvent and a compound. The terms "compound of Formula I" and "compounds of Formula II" are intended to include solvates of compounds. Similarly, "salts" includes solvates of salts. Suitable solvates are pharmaceutically acceptable solvates, such as hydrates, including monohydrates and hemi-hydrates.

[0027] A "chelate" is formed by the coordination of a compound to a metal ion at two (or more) points. The term "compound" is intended to include chelates of compounds. Similarly, "salts" includes chelates of salts.

[0028] A "non-covalent complex" is formed by the interaction of a compound and another molecule wherein a covalent bond is not formed between the compound and the molecule. For example, complexation can occur through van der Waals interactions, hydrogen bonding, and electrostatic interactions (also called ionic bonding). Such non-covalent complexes are included in the term "compound".

[0029] As used herein, "cardiovascular disease" refers to diseases, disorders and conditions of the heart and circulatory system that are mediated by VCAM-1 and/or IL-6. 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.

[0030] As used herein, "inflammatory diseases" includes refers to diseases, disorders and conditions, that are mediated by VCAM-1 and/or IL-6. Exemplary inflammatory diseases, include, but are not limited to, arthritis, asthma, dermatitis, psoriasis, cystic fibrosis, post transplantation late and chronic solid organ rejection, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel diseases, autoimmune diabetes, diabetic retinopathy, diabetic nephropathy, diabetic vasculopathy, ocular inflammation, uveitis, rhinitis, ischemia-reperfusion injury, post-angioplasty restenosis, chronic obstructive pulmonary disease (COPD), glomerulonephritis, Graves disease, gastrointestinal allergies, conjunctivitis, atherosclerosis, coronary artery disease, angina, and small artery disease.

[0031] "Subject" refers to an animal, such as a mammal, that has been or will be the object of treatment, observation, or experiment. The methods described herein may be useful for both human therapy and veterinary applications. In one embodiment, the subject is a human.

[0032] As used herein, "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 reducing 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.

[0033] As used herein, "prevention" or "preventing" refers to a reduction of the risk of acquiring a given disease or disorder.

[0034] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-CONH_2$ is attached through the carbon atom.

[0035] By "optional" or "optionally" is meant that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which is does not. For example, "optionally substituted aryl" encompasses both "aryl" and "substituted aryl" as defined below. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible and/or inherently unstable.

[0036] The term "acyl" term as used herein refers to a carbonyl radical attached to an alkyl, alkenyl, alkynyl, cycloalkyl, heterocycyl, aryl, or heteroaryl. Exemplary acyl groups include, but are not limited to, acetyl, formyl, propionyl, benzoyl, and the like.

[0037] The term "aldehyde" or "formyl" as used herein refers to -CHO.

[0038] 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, and 4-(2-methyl-3-butene)-pentenyl.

[0039] 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 $(C_1\text{-}C_{22})$alkoxy, $(C_1\text{-}C_8)$alkoxy, and $(C_1\text{-}C_6)$alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy and ethoxy.

[0040] 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 $(C_1\text{-}C_{22})$alkyl, $(C_1\text{-}C_8)$alkyl, and $(C_1\text{-}C_6)$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, and octyl.

[0041] 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 $(C_2\text{-}C_{22})$alkynyl, $(C_2\text{-}C_8)$alkynyl, and $(C_2\text{-}C_6)$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.

[0042] 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, and 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- or 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, an amino group attached to a carboxy group (e.g., -amino-COOH or salts such as -amino-COONa).

[0043] 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, and 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.

[0044] 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."

[0045] 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."

[0046] 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."

[0047] 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."

[0048] 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."

[0049] The term "benzyl" as used herein refers to the group $-CH_2$-phenyl.

[0050] 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.

[0051] 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, and 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.

[0052] 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, and 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).

[0053] The term "carbonyl" as used herein refers to -C(O)-.

[0054] The term "carboxy" as used herein refers to -COOH or its corresponding carboxylate salts (e.g., -COONa). 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.

[0055] The term "cyano" as used herein refers to -CN.

[0056] The term "cycloalkoxy" as used herein refers to a cycloalkyl group attached to an oxygen.

[0057] 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.

[0058] 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 (for example, succinic anhydride and succinimide).

[0059] 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 Rj and R_k can independently be selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, cycloalkyl, ether, haloalkyl, heteroaryl, and heterocyclyl. R_k can be a hydrogen, but Rj cannot be hydrogen. The ester may be cyclic, for example the carbon atom and Rj, the oxygen atom and R_k, or Rj 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 R_k is alkyl, such as -O-C(O)-alkyl, -C(O)-O-alkyl-, and -alkyl-C(O)-O-alkyl-. Exemplary esters also include aryl or heteroaryl esters, e.g. wherein at least one of Rj or R_k 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 molecule. Exemplary reverse esters include succinate, D-argininate, L-argininate, L-lysinate and D-lysinate. Esters also include carboxylic acid anhydrides and acid halides.

[0060] 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, and 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.

[0061] The terms "halo" or "halogen" or "Hal" as used herein refer to F, Cl, Br, or I.

[0062] 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.

[0063] The term "heteroaryl" as used herein refers to a mono-, bi-, or multi-cyclic, aromatic ring system containing one or more heteroatoms, for example 1-3 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 2-5 carbon atoms and 1-3 heteroatoms, referred to herein as "(C_2-C_5)heteroaryl."

[0064] 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.

[0065] The terms "hydroxy" and "hydroxyl" as used herein refers to -OH.

[0066] The term "hydroxyalkyl" as used herein refers to a hydroxy attached to an alkyl group.

[0067] The term "hydroxyaryl" as used herein refers to a hydroxy attached to an aryl group.

[0068] 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.

[0069] 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.

[0070] The term "nitro" as used herein refers to -NO_2.

[0071] The term "perfluoroalkoxy" as used herein refers to an alkoxy group in which all of the hydrogen atoms have been replaced by fluorine atoms.

[0072] 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-C_5 perfluoroalkyl, such as trifluoromethyl.

[0073] The term "perfluorocycloalkyl" as used herein refers to a cycloalkyl group in which all of the hydrogen atoms have been replaced by fluorine atoms.

[0074] 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.

[0075] 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_x-OP(O)O_2R_y-, wherein R_x and R_y can be alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl, hydrogen.

[0076] 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.

[0077] 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.

[0078] 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).

[0079] The term "sulfonate" as used herein refers to -OSO_3-. Sulfonate includes salts such as -OSO_3Na, -OSO_3K and the acid -OSO_3H.

[0080] The term "sulfonic acid" refers to -SO_3H- and its corresponding salts (e.g., -SO_3K- and -SO_3Na-).

[0081] 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.

[0082] 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.

[0083] "Alkyl" 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, ketone, heteroaryl, heterocyclyl, hydroxyl, 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.

[0084] "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, carbonyl, 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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., "Prodrugs 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.

[0089] 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.

[0090] In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare non-toxic pharmaceutically acceptable addition salts.

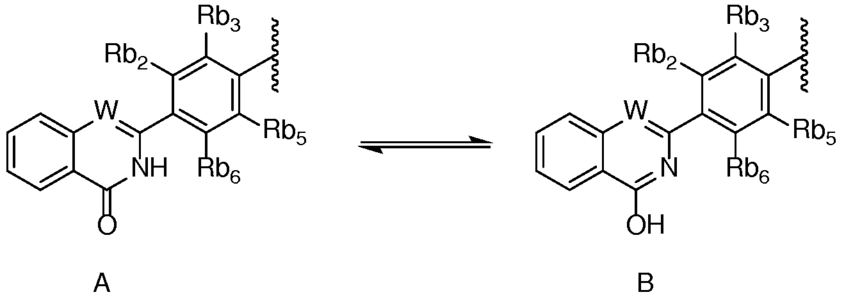
[0091] The compounds of the disclosure may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as geometric isomers, enantiomers or diastereomers. The term "stereoisomers" when used herein consist of all geometric isomers, enantiomers or diastereomers. 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.

[0092] 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.

[0093] 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.

[0094] 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."

[0095] The compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted. For example, any claim to compound A below is understood to include tautomeric structure B, and vice versa, as well as mixtures thereof.



Exemplary Embodiments

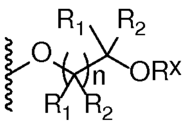
Formula I Methods and Compounds

[0096] In certain embodiments, the pharmaceutical composition for use in a method for reducing IL-6 for the treatment of cancer in a subject comprises a therapeutically effective amount of at least one compound of Formula I or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof, wherein:

Q is selected from CRa_3;
V is selected from N and CRa_4;
W is selected from N and CH;
U is C=O;
X is selected from OH, NH_2, $S(O)_2NH_2$, NHAc, and $NHSO_2Me$;
Ra_1 is selected from hydrogen and C_1-C_6 alkoxy;
Ra_2 is selected from hydrogen, C_1-C_6 alkoxy, amino, amide, and C_1-C_6 alkyl;
Ra_3 and Ra_4 are independently selected from hydrogen and C_1-C_6 alkoxy;
Rb_2 and Rb_6 are both hydrogen; and
Rb_3 and Rb_5 are independently selected from C_1-C_6 alkyl and halogen.

[0097] In some embodiments, said pharmaceutical composition comprises a therapeutically effective amount of at least one compound of Formula I, wherein:

U is C=O;
Q is selected from CRa_3;
Ra_3 is selected from hydrogen, methoxy,



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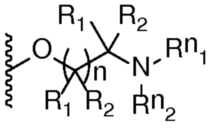


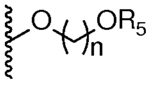
wherein

n is 0, 1, or 3;
R_1, R_1', R_2, and R_2' are independently selected from hydrogen, C_1-C_3 alkyl, cyclopropyl, and halogen wherein if n is 1, then R_2 and R_2', R_1 and R_1', R_1 and R_2', or R_2 and R_1' may form a double bond, wherein said double bond can be cis, trans, or a mixture thereof;
Rx is selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and aryl;
Rn_1 and Rn_2 are independently selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and aryl; and
V, W, X, Ra_1, Ra_2, Ra_4, Rb_2, Rb_3, Rb_5, and Rb_6 are as defined in paragraph [021]

[0098] In some embodiments, said pharmaceutical composition comprises a therapeutically effective amount of at least one compound of Formula I, wherein:

U is C=O;

Ra_3 is selected from hydrogen, methoxy,



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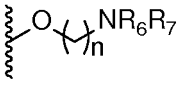


wherein

n is 1, 2, or 3;
R_5 is selected from C_1-C_6 alkyl substituted with one or more groups selected fron methyl, phenyl, and pyridinyl;
R_6 and R_7 are independently selected from unsubstituted C_1-C_6 alkyl; and
Q, V, W, X, Ra_1, Ra_2, Ra_4, Rb_2, Rb_3, Rb_5, and Rb_6 are as defined in paragraph [021].

[0099] In some embodiments, said pharmaceutical composition comprises a therapeutically effective amount of at least one compound of Formula I, wherein:

U is C=O;
Ra_3 is selected from hydrogen, methoxy, 2-methoxy-ethoxy, 2-dimethylamino-ethoxy, 2-benzyloxy-ethoxy, and 2-(pyridin-3-ylmethoxy)ethoxy; and
Q, V, W, X, Ra_1, Ra_2, Ra_4, Rb_2, Rb_3, Rb_5, and Rb_6 are as defined in paragraph [021].

[0100] In some embodiments, said pharmaceutical composition comprises a therapeutically effective amount of at least one compound of Formula I, wherein:

U is C=O;
V is selected from N and CRa_4;
Ra_4 is selected from hydrogen and unsubstituted C_1-C_6 alkoxy; and
Q, W, X, Ra_1, Ra_2, Ra_3, Rb_2, Rb_3, Rb_5, and Rb_6 are as defined in paragraph [021].

[0101] In some embodiments, said pharmaceutical composition comprises a therapeutically effective amount of at least one compound of Formula I, wherein:

U is C=O;
Ra_4 is selected from hydrogen and methoxy; and
Q, V, W, X, Ra_1, Ra_2, Ra_3, Rb_2, Rb_3, Rb_5, and Rb_6 are as defined in paragraph [021].

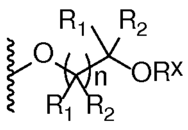
[0102] In some embodiments, said pharmaceutical composition comprises a therapeutically effective amount of at least one compound of Formula I, wherein:

U is C=O;
X is OH; and
Q, V, W, Ra_1, Ra_2, Ra_3, Ra_4, Rb_2, Rb_3, Rb_5, and Rb_6 are as defined in paragraph [021].

[0103] In some embodiments, said pharmaceutical composition comprises administering a therapeutically effective amount of at least one compound of Formula I, wherein:

U is C=O;

Ra_1 is selected from hydrogen, methoxy,



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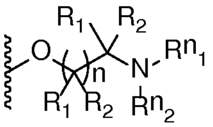
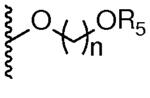


wherein

n is 0, 1, or 3;
R_1, R_1', R_2, and R_2' are independently selected from hydrogen, C_1-C_3 alkyl, cyclopropyl, and halogen wherein if n is 1, then R_2 and R_2', R_1 and R_1', R_1 and R_2', or R_2 and R_1' may form a double bond, wherein said double bond can be cis, trans, or a mixture thereof;
Rx is selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and aryl;
Rn_1 and Rn_2 are independently selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and aryl; and
Q, V, W, X, Ra_2, Ra_3, Ra_4, Rb_2, Rb_3, Rb_5, and Rb_6 are as defined in paragraph [021].

[0104] In some embodiments, said pharmaceutical composition comprises a therapeutically effective amount of at least one compound of Formula I, wherein:

U is C=O;
Ra_1 is selected from hydrogen, methoxy,



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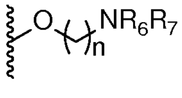


;

n is 1, 2, or 3;
R_5, R_6, and R_7 are independently selected from unsubstituted C_1-C_6 alkyl; and
Q, V, W, X, Ra_2, Ra_3, Ra_4, Rb_2, Rb_3, Rb_5, and Rb_6 are as defined in paragraph [021].

[0105] In some embodiments, said pharmaceutical composition comprises a therapeutically effective amount of at least one compound of Formula I, wherein:

U is C=O;
Ra_1 is selected from hydrogen, methoxy, 2-methoxy-ethoxy, and 2-dimethylamino-ethoxy; and
Q, V, W, X, Ra_2, Ra_3, Ra_4, Rb_2, Rb_3, Rb_5, and Rb_6 are as defined in paragraph [021].

[0106] In some embodiments, said pharmaceutical composition comprises a therapeutically effective amount of at least one compound of Formula I, wherein:

U is C=O;
Ra_2 is selected from hydrogen, unsubstituted C_1-C_6 alkoxy, NHR_9, and C_1-C_6 alkyl substituted with heterocycle or amino;
R_9 is selected from acyl, and heteroaryl; and
Q, V, W, X, Ra_1, Ra_3, Ra_4, Rb_2, Rb_3, Rb_5, and Rb_6 are as defined in paragraph [021].

[0107] In some embodiments, said pharmaceutical composition comprises a therapeutically effective amount of at least one compound of Formula I, wherein:

U is C=O;
Ra_2 is selected from hydrogen, methoxy, acetamido, morpholin-4-ylmethyl, pyridin-2-ylamino, (4-methylpiperazin-1-yl)methyl, and methanesulfonamido; and
Q, V, W, X, Ra_1, Ra_3, Ra_4, Rb_2, Rb_3, Rb_5, and Rb_6 are as defined in paragraph [021].

[0108] In some embodiments, said pharmaceutical composition comprises a therapeutically effective amount of at least one compound of Formula I, wherein:

U is C=O;
Rb_3 and Rb_5 are independently selected from unsubtituted C_1-C_6 alkyl and halogen; and
Q, V, W, X, Ra_1, Ra_2, Ra_3, Ra_4, Rb_2, and Rb_6 are as defined in paragraph [021].

[0109] In some embodiments, said pharmaceutical composition comprises a therapeutically effective amount of at least one compound of Formula I, wherein:

U is C=O;
Rb_3 and Rb_5 are independently selected from methyl, *tert*-butyl, fluorine, and chlorine; and
Q, V, W, X, Ra_1, Ra_2, Ra_3, Ra_4, Rb_2, and Rb_6 are as defined in paragraph [021].

[0110] In certain embodiments, said pharmaceutical composition comprises a therapeutically effective amount of at least one compound selected from:

3-(3-fluoro-4-hydroxyphenyl)-5-methoxyisoquinolin-1(2H)-one;

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

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

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

2-(3,5-di-tert-butyl-4-hydroxyphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;

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

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

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

2-(4-hydroxy-3,5-dimethylphenyl)-6-(morpholinomethyl)quinazolin-4(3H)-one;

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

2-(4-hydroxy-3,5-dimethylphenyl)-5,7-dimethoxy-6-(morpholinomethyl)quinazolin-4(3H)-one;

5-(2-dimethylamino-ethoxy)-2(4-hydroxy-3, 5-dimethylphenyl)-7-methoxy-3*H*-quinazolin-4-one;

2-(4-hydroxy-3,5-dimethyl-phenyl)-7-methoxy-5-(2-methoxy-ethoxy)-3*H*-quinazolin-4-one;

7-(2-amino-ethoxy)-2-(4-hydroxy-3, 5-dimethyl-phenyl)-5-methoxy-3H-quinazolin-4-one;

2-(4-hydroxy-3,5-dimethyl-phenyl)-5-methoxy-7-(2-methoxy-ethoxy)-3H-quinazolin-4-one;

7-(2-benzyloxy-ethoxy)-2-(4-hydroxy-3,5-dimethyl-phenyl)-5-methoxy-3*H*-quinazolin-4-one;

2-(4-hydroxy-3,5-dimethylphenyl)-5-methoxy-7-[2-(pyridin-3-ylmethoxy)ethoxy]-3H-quinazolin-4-one;

7-(2-dimethylamino-ethoxy)-2-(4-hydroxy-3,5-dimethylphenyl)-3*H*-quinazolin-4-one;

2-(4-hydroxy-3,5-dimethyl-phenyl)-6-(pyridin-4-ylamino)-3*H*-quinazolin-4-one;

2-(4-hydroxy-3,5-dimethyl-phenyl)-6-(pyridin-2-ylamino)-3H-quinazolin-4-one;

2-(4-hydroxy-3,5-dimethylphenyl)-6-((4-methylpiperazin-1-yl)methyl)quinazolin-4(3H)-one; and

N-((2-(4-hydroxy-3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl)methyl)methanesulfonamide, or a

tatutomer, stereoisomer, pharmaceutically acceptable salt, or hydrate thereof.

[0111] Another aspect of the invention provides compounds of Formula I selected from:

5-(2-dimethylamino-ethoxy)-2(4-hydroxy-3,5-dimethylphenyl)-7-methoxy-3H-quinazolin-4-one;
2-(4-hydroxy-3,5-dimethyl-phenyl)-7-methoxy-5-(2-methoxy-ethoxy)-3*H*-quinazolin-4-one;
7-(2-amino-ethoxy)-2-(4-hydroxy-3,5-dimethyl-phenyl)-5-methoxy-3*H*-quinazolin-4-one;
2-(4-hydroxy-3,5-dimethyl-phenyl)-5-methoxy-7-(2-methoxy-ethoxy)-3*H*-quinazolin-4-one;
7-(2-benzyloxy-ethoxy)-2-(4-hydroxy-3,5-dimethyl-phenyl)-5-methoxy-3*H*-quinazolin-4-one;
2-(4-hydroxy-3,5-dimethylphenyl)-5-methoxy-7-[2-(pyridin-3-ylmethoxy)ethoxy]-3H-quinazolin-4-one;
7-(2-dimethylamino-ethoxy)-2-(4-hydroxy-3,5-dimethylphenyl)-3*H*-quinazolin-4-one;
2-(4-hydroxy-3,5-dimethyl-phenyl)-6-(pyridin-4-ylamino)-3*H*-quinazolin-4-one;
2-(4-hydroxy-3,5-dimethyl-phenyl)-6-(pyridin-2-ylamino)-3*H*-quinazolin-4-one;
2-(4-hydroxy-3,5-dimethylphenyl)-6-((4-methylpiperazin-1-yl)methyl)quinazolin-4(3H)-one; and
N-((2-(4-hydroxy-3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl)methyl)methanesulfonamide, and

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

Formula II Methods and Compounds

[0112] Also described herein are pharmaceutical compositions for use in a method for reducing IL-6 and/or VCAM-1 or a method for treating an inflammatory or cardiovascular diseasein a subject, wherein the composition comprises a therapeutically effective amount of at least one compound of Formula II or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof, wherein:

P is CRa_1;
V is selected from N and CRa_4;
W is selected from N and CH;
U is C=O;
X is selected from O, S, CH_2, and NH;
Ra_1 is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, and halogen;
Ra_2 is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, heterocycle, amide, and amino;
Ra_3 and Ra_4 are independently selected from hydrogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, and halogen;
Rb_2 and Rb_6 are independently selected from hydrogen, methyl, and fluoride;
Rb_3 and Rb_5 are independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, halogen, and amino, wherein Rb_2 and Rb_3 and/or Rb_5 and Rb_6 may be connected to form a phenyl ring; and
Rd is selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, and C_3-C_6 cycloalkyl, wherein Rd may be connected to Rb_3 or Rb_5 to form a heterocycle.

[0113] Described are compositions comprising a therapeutically effective amount of at least one compound of Formula II, wherein:

U is C=O;
Ra_1 is selected from hydrogen, unsubstituted C_1-C_6 alkyl, unsubstituted C_1-C_6 alkoxy, and halogen; and
P, V, W, X, Ra_2, Ra_3, Ra_4, Rb_2, Rb_3, Rb_5, Rb_6, and Rd are as defined in paragraph [022].

[0114] Described are compositions comprising a therapeutically effective amount of at least one compound of Formula II, wherein:

U is C=O; and
Ra_1 is selected from hydrogen, methyl, methoxy, chlorine, and fluorine; and
P, V, W, X, Ra_2, Ra_3, Ra_4, Rb_2, Rb_3, Rb_5, Rb_6, and Rd are as defined in paragraph [022].

[0115] Described are compositions comprising a therapeutically effective amount of at least one compound of Formula II, wherein:

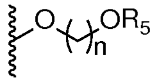
U is C=O;
Ra_2 is selected from hydrogen, C_1-C_6 alkyl substituted with heterocyclyl, unsubstituted C_1-C_6 alkoxy, amino, and heterocycle; and
P, V, W, X, Ra_1, Ra_3, Ra_4, Rb_2, Rb_3, Rb_5, Rb_6, and Rd are as defined in paragraph [022].

[0116] Described are compositions comprising a therapeutically effective amount of at least one compound of Formula II, wherein:

U is C=O; and
Ra_2 is selected from hydrogen, methoxy, acetamido, morpholino, morpholin-4-ylmethyl, and (4-methylpiperazin-1-yl)methyl; and
P, V, W, X, Ra_1, Ra_3, Ra_4, Rb_2, Rb_3, Rb_5, Rb_6, and Rd are as defined in paragraph [022].

[0117] Described are compositions comprising a therapeutically effective amount of at least one compound of Formula II, wherein:

U is C=O;
Ra_3 is selected from selected from hydrogen, methoxy, unsubstituted C_1-C_6 alkyl, halogen, and



;

n is 1, 2, or 3;
R_5 is C_1-C_6 alkyl substituted with phenyl or heteroaryl; and
P, V, W, X, Ra_1, Ra_2, Ra_4, Rb_2, Rb_3, Rb_5, Rb_6, and Rd are as defined in paragraph [022].

[0118] Described are compositions comprising a therapeutically effective amount of at least one compound of Formula II, wherein:

U is C=O;
Ra_3 is selected from selected from hydrogen, methoxy, chlorine, fluorine, isopropoxy, methyl, 2-benzyloxy-ethoxy, and 2-(pyridin-3-ylmethoxy)ethoxy; and
P, V, W, X, Ra_1, Ra_2, Ra_4, Rb_2, Rb_3, Rb_5, Rb_6, and Rd are as defined in paragraph [022].

[0119] Described are compositions comprising a therapeutically effective amount of at least one compound of Formula II, wherein:

U is C=O;
Ra_4 is selected from hydrogen, unsubstituted C_1-C_6 alkoxy, and halogen; and

P, V, W, X, Ra_1, Ra_2, Ra_3, Rb_2, Rb_3, Rb_5, Rb_6, and Rd are as defined in paragraph [022].

[0120] Described are compositions comprising a therapeutically effective amount of at least one compound of Formula II, wherein:

U is C=O;
Ra_4 is hydrogen, methoxy, and chlorine; and
P, V, W, X, Ra_1, Ra_2, Ra_3, Rb_2, Rb_3, Rb_5, Rb_6, and Rd are as defined in paragraph [022].

[0121] Described are compositions comprising a therapeutically effective amount of at least one compound of Formula II, wherein:

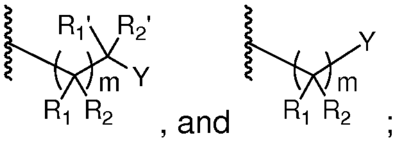
U is C=O;
Rb_3 and Rb_5 are independently selected from hydrogen, methyl, C_1-C_6 alkyl substituted with heterocyclyl, and unsubstituted C_1-C_6 alkoxy wherein Rb_2 and Rb_3 and/or Rb_5 and Rb_6 may be connected to form a phenyl ring; and
P, V, W, X, Ra_1, Ra_2, Ra_3, Ra_4, Rb_2, Rb_6, and Rd are as defined in paragraph [022].

[0122] Described are compositions comprising a therapeutically effective amount of at least one compound of Formula II, wherein:

U is C=O;
Rb_3 and Rb_5 are independently selected from hydrogen, methyl, methoxy, and morpholinomethyl, and wherein Rb_2 and Rb_3 and/or Rb_5 and Rb_6 may be connected to form a phenyl ring; and
P, V, W, X, Ra_1, Ra_2, Ra_3, Ra_4, Rb_2, Rb_6, and Rd are as defined in paragraph [022].

[0123] Described are compositions comprising a therapeutically effective amount of at least one compound of Formula II, wherein:

U is C=O;
Rd is selected from C_1-C_6 alkoxy, C_3-C_6 cycloalkyl,



m is selected from 1, 2, or 3;
R_1, R_1', R_2, and R_2' are independently selected from hydrogen, fluorine, C_1-C_6 alkyl, hydroxyl, -NH_2, and C_1-C_6 alkoxy wherein R_2 and R_2' may be eliminated to form a double bond;
Y is selected from OH, SH, NH_2, -Oalkyl, -Oaryl, -CH_2aryl, -C(O)NHalkyl, -C(O)N(alkyl)$_2$, -C(O)NHaryl, -NHacyl, -NHalkyl, -NHS(O)$_2$alkyl, -N(alkyl)$_2$, -NHS(O)$_2$N(alkyl)$_2$, -NHCN, and -NHC(O)N(alkyl)$_2$, -NHheterocyclyl, and heterocyclyl;
P, V, W, X, Ra_1, Ra_2, Ra_3, Ra_4, Rb_2, Rb_3, Rb_5, and Rb_6 are as defined in paragraph [022]; and
Rd may be connected to Rb_3 or Rb_5 to form a heterocycle,
provided that for -N(alkyl)$_2$ the alkyl chains cannot be joined to form an aryl or heterocyclic ring.

[0124] Described are compositions comprising a therapeutically effective amount of at least one compound of Formula II, wherein:

U is C=O;
Rd is connected to Rb_3 or Rb_5 to form a heterocycle selected from substituted furanyl or substituted pyrrolyl; and
P, V, W, X, Ra_1, Ra_2, Ra_3, Ra_4, Rb_2, Rb_3, Rb_5, and Rb_6 are as defined in paragraph [022].

[0125] Described are compositions comprising a therapeutically effective amount of at least one compound of Formula II, wherein:

U is C=O;

Rd is connected to Rb_3 or Rb_5 to form a heterocycle selected from 2-hydroxymethyl-furan-5-yl or 2-(4,5-dihydro-1H-pyrrol-2-yl)ethanol; and
P, V, W, X, Ra_1, Ra_2, Ra_3, Ra_4, Rb_2, Rb_3, Rb_5, and Rb_6 are as defined in paragraph [022].

[0126] In some embodiments, the pharmaceutical composition for use in a method for reducing IL-6 and/or VCAM-1 for the treatment of cancer or a disease selected from arthritis, asthma, dermatitis, psoriasis, cystic fibrosis, post transplantation late and chronic solid organ rejection, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel diseases, ocular inflammation, uveitis, rhinitis, chronic obstructive pulmonary disease (COPD), glomerulonephritis, Grave's disease, gastrointestinal allergies, and conjunctivitiscomprises a therapeutically effective amount of at least one compound of Formula II, wherein:

U is C=O;
X-Rd is selected from 2-hydroxy-2-methylpropoxy, 2-hydroxyethoxy, methoxy, benzyloxyethoxy, 2,3-dihydroxypropoxy, aminocarbonylethoxy, methylaminocarbonylethoxy, (4-methoxyphenyl)aminocarbonylethoxy, benzylaminocarbonylethoxy, 4-hydroxybutoxy, (5-phenyl-4H-[1,2,4]triazol-3-ylamino)ethoxy, (3-methyl-[1,2,4]oxadiazol-5-ylamino)ethoxy, methylcarbonylaminoethoxy, methylcarbonylaminomethyl, (2,2,2-trifluoro-ethylamino)ethoxy, methanesulfonylaminoethoxy, isobutyrylaminoethoxy, methylaminoethoxy, isopropylsulfonylaminoethoxy, dimethylaminoethoxy, N-(2-hydroxyethyl)-N-methylacetamide, formamide-N-2-ethoxy, methylformamide-N-2-ethoxy, dimethylsulfonylaminoethoxy, cyanoaminoethoxy, (5-methylisoxazol-3-ylamino)ethoxy, (pyrimidin-2-ylamino)ethoxy, (isoxazol-3-ylamino)ethoxy, (4,6-dimethoxypyrimidin-2-ylamino)ethoxy, 3-hydroxypropyl, and 2-hydroxyethyl; and
P, V, W, X, Ra_1, Ra_2, Ra_3, Ra_4, Rb_2, Rb_3, Rb_5, and Rb_6 are as defined in paragraph [022].

[0127] In some embodiments, the pharmaceutical composition for use in a method for reducing IL-6 and/or VCAM-1 for the treatment of cancer or a disease selected from arthritis, asthma, dermatitis, psoriasis, cystic fibrosis, post transplantation late and chronic solid organ rejection, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel diseases, ocular inflammation, uveitis, rhinitis, chronic obstructive pulmonary disease (COPD), glomerulonephritis, Grave's disease, gastrointestinal allergies, and conjunctivitis comprises a therapeutically effective amount of at least one compound of Formula II, wherein:

U is C=O;
X-Rd is selected from hydroxyethoxy, methylcarbonylaminoethoxy, (4-methoxyphenyl)aminocarbonylethoxy, and isobutyrylaminoethoxy; and
P, V, W, X, Ra_1, Ra_2, Ra_3, Ra_4, Rb_2, Rb_3, Rb_5, and Rb_6 are as defined in paragraph [022].

[0128] In certain embodiments, the pharmaceutical composition comprises a therapeutically effective amount of at least one compound of Formula II, selected from:

3-(4-(2-hydroxy-2-methylpropoxy)-3,5-dimethylphenyl)-6,8-dimethoxyisoquinolin-1(2H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
5,7-dimethoxy-2-(4-methoxyphenyl)quinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6,7-dimethoxyquinazolin-4(3H)-one;
5,7-dimethoxy-2-(4-methoxy-3-(morpholinomethyl)phenyl)quinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxypyrido[2,3-d]pyrimidin-4(3H)-one;
N-(2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl)acetamide;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-morpholinoquinazolin-4(3H)-one;
2-(4-(2-(benzyloxy)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxypyrido[2,3-d]pyrimidin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethylpyrido[2,3-d]pyrimidin-4(3H)-one;
5,7-difluoro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
5,7-dichloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
2-[4-(2-hydroxy-ethoxy)-3,5-dimethyl-phenyl]-5,7-diisopropoxy-3H-quinazolin-4-one;
2-[4-(2-hydroxyethoxy)-3,5-dimethyl-phenyl]-6-morpholin-4-ylmethyl-3H-quinazolin-4-one;
2-[4-(2,3-Dihydroxy-propoxy)-3,5-dimethyl-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one;
2-[4-(2-hydroxy-ethoxy)-3,5-dimethylphenyl]-5,7-dimethoxy-6-morpholin-4-ylmethyl-3H-quinazolin-4-one;
2-[4-(2-hydroxy-ethoxy)-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one;
2-[4-(2-hydroxy-ethoxy)-naphthalen-1-yl]-5,7-dimethoxy-3*H*-quinazolin-4-one;
7-(2-benzyloxy-ethoxy)-2-[4-(2-hydroxy-ethoxy)-3,5-dimethyl-phenyl]-5-methoxy-3*H*-quinazolin-4-one;
2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-dimethyl-phenoxy]-acetamide;
2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-dimethyl-phenoxy]-*N*-methyl-acetamide;

2-[4-(5,7-Dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-dimethyl-phenoxy]-N-(4-methoxy-phenyl)-acetamide;
N-benzyl-2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy]acetamide;
2-[4-(4-hydroxy-butoxy)-3,5-dimethyl-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-methoxyquinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5-methoxyquinazolin-4(3H)-one;
7-chloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
8-chloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-8-methoxyquinazolin-4(3H)-one;
5-chloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-7-methoxyquinazolin-4(3H)-one;
5,7-dimethoxy-2-(4-methoxy-3,5-dimethylphenyl)quinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3-methylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-((4-methylpiperazin-1-yl)methyl)quinazolin-4(3H)-one;
5,7-Dimethoxy-2-{3-methyl-4-[2-(5-phenyl-4H-[1,2,4]triazol-3-ylamino)-ethoxy]-phenyl}-3H-quinazolin-4-one;
2-{3,5-Dimethyl-4-[2-(3-methyl-[1,2,4]oxadiazol-5-ylamino)-ethoxy]-phenyl}-5,7-dimethoxy-3H-quinazolin-4-one;
N-{2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2,6-dimethyl-phenoxy]-ethyl}-acetamide;
N-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylbenzyl)acetamide;
N-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2,6-dimethylbenzyl]-acetamide;
2-{3,5-Dimethyl-4-[2-(2, 2, 2-trifluoro-ethylamino)-ethoxy]-phenyl}-5,7-dimethoxy-3H-quinazolin-4-one;
N-{2-[4-(6,8-Dimethoxy-1-oxo-1,2-dihydro-isoquinolin-3-yl)-2,6-dimethyl-phenoxy]-ethyl}-formamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)methanesulfonamide;
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)isobutyramide;
2-(3,5-dimethyl-4-(2-(methylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)propane-2-sulfonamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylphenoxy)ethyl)acetamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylphenoxy)ethyl)isobutyramide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylphenoxy)ethyl)methanesulfonamide;
2-(4-(2-(dimethylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N-methylacetamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)formamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N-methylformamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)cyanamide;
2-(3,5-dimethyl-4-(2-(5-methylisoxazol-3-ylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(3,5-dimethyl-4-(2-(pyrimidin-2-ylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(4-(2-(isoxazol-3-ylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(4-(2-(4,6-dimethoxypyrimidin-2-ylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-[4-(3-hydroxy-propyl)-3,5-dimethoxyphenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one; and
2-[4-(3-hydroxy-propyl)-3-methoxy-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one;
, or a

tautomer, stereoisomer, pharmaceutically acceptable salt, or hydrate thereof.

[0129] Another aspect of the invention provides compounds of Formula II selected from:

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-morpholinoquinazolin-4(3H)-one;
2-(4-(2-(benzyloxy)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxypyrido[2,3-d]pyrimidin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethylpyrido[2,3-d]pyrimidin-4(3H)-one;
5,7-difluoro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
2-[4-(2-hydroxy-ethoxy)-3,5-dimethyl-phenyl]-5,7-diisopropoxy-3H-quinazolin-4-one;
2-[4-(2-hydroxyethoxy)-3,5-dimethyl-phenyl]-6-morpholin-4-ylmethyl-3H-quinazolin-4-one;
2-[4-(2,3-Dihydroxy-propoxy)-3,5-dimethyl-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one;
2-[4-(2-hydroxy-ethoxy)-3,5-dimethylphenyl]-5,7-dimethoxy-6-morpholin-4-ylmethyl-3H-quinazolin-4-one;
2-[4-(2-hydroxy-ethoxy)-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one;
2-[4-(2-hydroxy-ethoxy)-naphthalen-1-yl]-5,7-dimethoxy-3*H*-quinazolin-4-one;
7-(2-benzyloxy-ethoxy)-2-[4-(2-hydroxy-ethoxy)-3,5-dimethyl-phenyl]-5-methoxy-3*H*-quinazolin-4-one;
2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-dimethyl-phenoxy]-*N*-methyl-acetamide;
2-[4-(5,7-Dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-dimethyl-phenoxy]-N-(4-methoxy-phenyl)-acetamide;

N-benzyl-2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy]acetamide;
2-[4-(4-hydroxy-butoxy)-3,5-dimethyl-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one;
7-chloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
8-chloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-8-methoxyquinazolin-4(3H)-one;
5-chloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-7-methoxyquinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-((4-methylpiperazin-1-yl)methyl)quinazolin-4(3H)-one;
5,7-Dimethoxy-2-{3-methyl-4-[2-(5-phenyl-4H-[1,2,4]triazol-3-ylamino)-ethoxy]-phenyl}-3*H*-quinazolin-4-one;
2-{3,5-Dimethyl-4-[2-(3-methyl-[1,2,4]oxadiazol-5-ylamino)-ethoxy]-phenyl}-5,7-dimethoxy-3*H*-quinazolin-4-one;
N-{2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2,6-dimethyl-phenoxy]-ethyl}-acetamide;
N-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylbenzyl)acetamide;
N-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2,6-dimethylbenzyl]-acetamide;
2-{3, 5-Dimethyl-4-[2-(2, 2, 2-trifluoro-ethylamino)-ethoxy]-phenyl}-5,7-dimethoxy-3H-quinazolin-4-one;
N-{2-[4-(6,8-Dimethoxy-1-oxo-1,2-dihydro-isoquinolin-3-yl)-2,6-dimethyl-phenoxy]-ethyl}-formamide;
2-(3,5-dimethyl-4-(2-(methylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)propane-2-sulfonamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylphenoxy)ethyl)acetamide;
2-(4-(2-(dimethylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N-methylacetamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)formamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N-methylformamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)cyanamide;
2-(3,5-dimethyl-4-(2-(5-methylisoxazol-3-ylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(3,5-dimethyl-4-(2-(pyrimidin-2-ylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(4-(2-(isoxazol-3-ylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(4-(2-(4,6-dimethoxypyrimidin-2-ylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-[4-(3-hydroxy-propyl)-3,5-dimethoxyphenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one; and
2-[4-(3-hydroxy-propyl)-3-methoxy-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one; and
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)formamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N-methylformamide;
N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)dimethylamino-*N*-sulfonamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)cyanamide;
2-(3,5-dimethyl-4-(2-(5-methylisoxazol-3-ylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(3,5-dimethyl-4-(2-(pyrimidin-2-ylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(4-(2-(isoxazol-3-ylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(4-(2-(4,6-dimethoxypyrimidin-2-ylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-[4-(3-hydroxy-propyl)-3,5-dimethoxyphenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one;
2-[4-(3-hydroxy-propyl)-3-methoxy-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one; and
2-[2-(2-hydroxyethyl)-1*H*-indol-6-yl]-5,7-dimethoxy-3*H*-quinazolin-4-one, or a

tautomer, stereoisomer, pharmaceutically acceptable salt, or hydrate thereof.

[0130] Another aspect of the invention provides compounds of Formula II selected from:

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

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

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

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

2-[4-(2-hydroxy-ethoxy)-3,5-dimethyl-phenyl]-5,7-diisopropoxy-3H-quinazolin-4-one;

2-[4-(2-hydroxyethoxy)-3,5-dimethyl-phenyl]-6-morpholin-4-ylmethyl-3H-quinazolin-4-one;

2-[4-(2,3-Dihydroxy-propoxy)-3,5-dimethyl-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one;

2-[4-(2-hydroxy-ethoxy)-3,5-dimethylphenyl]-5,7-dimethoxy-6-morpholin-4-ylmethyl-3H-quinazolin-4-one;

2-[4-(2-hydroxy-ethoxy)-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one;

2-[4-(2-hydroxy-ethoxy)-naphthalen-1-yl]-5,7-dimethoxy-3*H*-quinazolin-4-one;

2-(2-hydroxymethyl-benzofuran-5-yl)-5,7-dimethoxy-3*H*-quinazolin-4-one;

7-(2-benzyloxy-ethoxy)-2-[4-(2-hydroxy-ethoxy)-3,5-dimethyl-phenyl]-5-methoxy-3*H*-quinazolin-4-one;

7-(2-benzyloxy-ethoxy)-2-(2-hydroxymethyl-benzofuran-5-yl)-5-methoxy-3*H*-quinazolin-4-one;

2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-dimethyl-phenoxy]-*N*-methyl-acetamide;

2-[4-(5,7-Dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-dimethyl-phenoxy]-N-(4-methoxy-phenyl)-acetamide;

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

2-[4-(4-hydroxy-butoxy)-3,5-dimethyl-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one;

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

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

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-8-methoxyquinazolin-4(3H)-one;

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

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

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-((4-methylpiperazin-1-yl)methyl)quinazolin-4(3H)-one;

5,7-Dimethoxy-2-{3-methyl-4-[2-(5-phenyl-4H-[1,2,4]triazol-3-ylamino)-ethoxy]-phenyl}-3*H*-quinazolin-4-one;

2-{3,5-Dimethyl-4-[2-(3-methyl-[1,2,4]oxadiazol-5-ylamino)-ethoxy]-phenyl}-5,7-dimethoxy-3*H*-quinazolin-4-one;

N-{2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2,6-dimethyl-phenoxy]-ethyl}-acetamide;

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

N-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2,6-dimethyl-benzyl]-acetamide;

2-{3, 5-Dimethyl-4-[2-(2, 2, 2-trifluoro-ethylamino)-ethoxy]-phenyl}-5,7-dimethoxy-3H-quinazolin-4-one;

N-{2-[4-(6, 8-Dimethoxy-1-oxo-1, 2-dihydro-isoquinolin-3-yl)-2,6-dimethyl-phenoxy]-ethyl}-formamide;

2-(3,5-dimethyl-4-(2-(methylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;

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

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

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

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

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

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

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

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

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

2-(3,5-dimethyl-4-(2-(5-methylisoxazol-3-ylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;

2-(3,5-dimethyl-4-(2-(pyrimidin-2-ylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;

2-(4-(2-(isoxazol-3-ylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;

2-(4-(2-(4,6-dimethoxypyrimidin-2-ylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;

2-[4-(3-hydroxy-propyl)-3,5-dimethoxyphenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one;

2-[4-(3-hydroxy-propyl)-3-methoxy-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one; and
2-[2-(2-hydroxyethyl)-1*H*-indol-6-yl]-5,7-dimethoxy-3*H*-quinazolin-4-one, and

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

Pharmaceutical Compositions

[0131] Pharmaceutical compositions are provided comprising at least one compound of Formula I or II, or tautomer, stereoisomer, pharmaceutically acceptable salt or hydrate thereof 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. 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.

[0132] Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of a compound of the invention 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 method of pharmacy which includes the step of bringing into association at least one compound of the invention as the active compound and a 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 at least one compound described herein as the active compound in a unit-dose formulation, for example, a tablet, which may contain from about 0.05% to about 95% by weight of the at least one 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.

[0133] 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, for example, dissolving or dispersing, at least one active compound of the invention 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 at least one active compound of the invention 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 at least one compound of the invention, which may be optionally combined with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, at least one compound of the invention in a free-flowing form, such as a powder or granules, which may be 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, where the powdered form of at least one compound of the invention is moistened with an inert liquid diluent.

[0134] Formulations suitable for buccal (sub-lingual) administration include lozenges comprising at least one compound of the invention in a flavored base, usually sucrose and acacia or tragacanth, and pastilles comprising the at least one compound in an inert base such as gelatin and glycerin or sucrose and acacia.

[0135] Formulations of the invention suitable for parenteral administration comprise sterile aqueous preparations of at least one comound of Formula I or II, or tautomers, stereoisomers, pharmaceutically acceptable salts, and hydrates thereof, 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 at least one compound described herein 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.

[0136] Formulations suitable for rectal administration are presented as unit-dose suppositories. These may be prepared by admixing at least one compound as described herein with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

[0137] 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 (i.e., at least one compound of Formula I or II, or tautomers, stereoisomers, pharmaceutically acceptable salts, and hydrates thereof) 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%.

[0138] 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.

[0139] 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.

[0140] 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.

[0141] 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. Equivalent Surface Area Dosage Factors

To: From:	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

[0142] 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 gender, 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.

[0143] In one embodiment, a compound of Formula I or II, or a tautomer, stereoisomer, 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 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; a cholesteryl ester transfer protein (CETP), 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.

[0144] In another embodiment, a compound of Formula I, II, III, IV, V or a tautomer, stereoisomer, pharmaceutically acceptable salt or hydrate thereof, is administered in combination with one or more anti-inflammatory agents. Anti-inflammatory agents can include immunosuppressants, TNF inhibitors, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDS), and the like. Exemplary anti-inflammatory agents include, for example, prednisone; methylprenisolone (Medrol®), triamcinolone, methotrexate (Rheumatrex®, Trexall®), hydroxychloroquine (Plaquenil®), sulfasalzine (Azulfidine®), leflunomide (Arava®), etanercept (Enbrel®), infliximab (Remicade®), adalimumab (Humira®), rituximab (Rituxan®), abatacept (Orencia®), interleukin-1, anakinra (Kineret™), ibuprofen, ketoprofen, fenoprofen, naproxen, aspirin, acetominophen, indomethacin, sulindac, meloxicam, piroxicam, tenoxicam, lornoxicam, ketorolac, etodolac, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, diclofenac, oxaprozin, apazone, nimesulide, nabumetone, tenidap, etanercept, tolmetin, phenylbutazone, oxyphenbutazone, diflunisal, salsalate, olsalazine or sulfasalazine.

Therapeutic Methods

[0145] The invention provides compositions for use in methods of treating or preventing cardiovascular and inflammatory diseases and related disease states, characterized by altered levels of markers of inflammation such as IL-6 and/or VCAM-1. These methods comprise administering to a subject (e.g., a mammal, such as e.g., a human) a therapeutically effective amount of at least one compound of the invention, i.e., a compound of Formula I or II, or a tautomer, stereoisomer, pharmaceutically acceptable salt or hydrate thereof. In another embodiment, at least one compound of the invention may be administered as a pharmaceutically acceptable composition, comprising one or more compounds of Formula I or II and a pharmaceutically acceptable carrier.

[0146] In one embodiment, the inflammatory diseases and related disease states are those where inhibition of IL-6 and/or VCAM-1 is desirable.

[0147] In some embodiments, the methods comprise administering at least one compound of Formula I or Formula II to a subject, such as a human, as a preventative measure against cardiovascular and inflammatory diseases and related disease states, such as, for example, atherosclerosis, asthma, arthritis, cancer, multiple sclerosis, psoriasis, and inflammatory bowel diseases, and autoimmune disease(s).

[0148] At least one compound of Formula I or Formula II may be administered as a preventative measure to a subject, such as a human, having a genetic predisposition to cardiovascular and inflammatory diseases and related disease states, such as, for example, familial hypercholesterolemia, familial combined hyperlipidemia, atherosclerosis, a dyslipidemia, a dyslipoproteinemia, arthritis, cancer, multiple sclerosis, or Alzheimer's disease.

[0149] At least one compound of Formula I or Formula II may be administered as a preventative measure to a subject, such as a human, having a non-genetic predisposition to a disease including a cardiovascular disease or an inflammatory disorder. Examples of such non-genetic predispositions include cardiac bypass surgery and PTCA (which can lead to restenosis), an accelerated form of atherosclerosis, diabetes in women, (which can lead to polycystic ovarian disease), and cardiovascular disease (which can lead to impotence). Accordingly, compositions of the invention 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).

[0150] 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 Formula I or Formula II 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.

[0151] In another embodiment, the compounds of Formula I or Formula II may be used for the prevention of one disease or disorder while concurrently treating another (e.g., prevention of polycystic ovarian disease while treating diabetes; prevention of impotence while treating a cardiovascular disease).

EXAMPLES

[0152] The invention is further illustrated by the following non-limiting examples, wherein the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

AcOH = acetic acid

BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

Boc = N-tert-butoxycarbonyl

TBDMS = tert-butyldimethylsilyl

dba = dibenzylidene acetone

DCM = dichloromethane

DMAP = dimethylaminopyridine

DMF = dimethylformamide

DMSO = dimethylsulfoxide

EDCI = 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide

EtOH = ethanol

EtOAc = ethyl acetate

IBX = 2-Iodoxybenzoic acid

MeOH = methanol

HOBt = N-hydroxybenzotriazole

THF = tetrahydrofuran

TEA = triethylamine

p-TSA = p-toluenesulfonic acid

TBAF = tetrabutylammonium fluoride

DMA = N,N-dimethylacetamide

DIBAL-H = diisobutylaluminum hydride

TPAP = tetrapropylammonium perruthenate

NMO = N-methylmorpholine N-oxide

DDQ = 2,3-dicyano-5,6-dichloro-parabenzoquinone

DME = 1,2-dimethoxyethane

TFA = trifluoroacetic acid

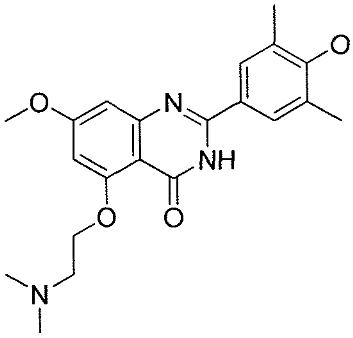
DPPF = 1,1'-bis(diphenylphosphino)ferrocene

$Pd(OAc)_2$ = palladium(II) acetate

$Pd(PPh_3)_4$ = tetrakis(triphenylphosphine)palladium(0)

Example 1. Preparation of 5-(2-dimethylamino-ethoxy)-2(4-hydroxy-3,5-dimethylphenyl)-7-methoxy-3H-quinazolin-4-one

[0153]



[0154] To a solution of 3,5-dimethyl-4-hydroxybenzaldehyde (10.0 g, 66.6 mmol) in anhydrous DMF (20 mL) was added NaH (4.00 g, 99.9 mmol) in portions and the mixture was stirred for 1 hour at room temperature. Benzyl bromide (9.5 mL, 80 mmol) was added dropwise and stirred for 16 hours at room temperature. Water was added, the mixture was acidified with acetic acid to pH approximately 4-5, and the product was isolated by extraction with ethyl acetate. The solvent was evaporated in *vacuo* and the residue was purified by column chromatography (silica gel 230-400 mesh; 2-5% ethyl acetate/hexane as eluent) to give 4-benzyloxy-3,5-dimethyl-benzaldehyde as white solid. Yield: 15.2 g (95%).

[0155] A mixture of 2-amino-4,6-difluorobenzamide (2.13 g, 12.4 mmol), 4-benzyloxy-3,5-dimethylbenzaldehyde (2.98 g, 12.4 mmol), $NaHSO_3$ (2.50 g, 13.6 mmol) and p-toluene sulfonic acid (0.236 g, 1.24 mmol) in *N,N*-dimethylacetamide (20 mL) was stirred at 110-120 °C for 16 hours. The solvent was evaporated *in vacuo,* water was added and the precipitated solid was filtered off, washed with water and ether to give 2-(4-benzyloxy-3,5-dimethylphenyl)-5,7-difluoro-3*H*-quinazolin-4-one as a light yellow solid. Yield: 1.99 g (41%).

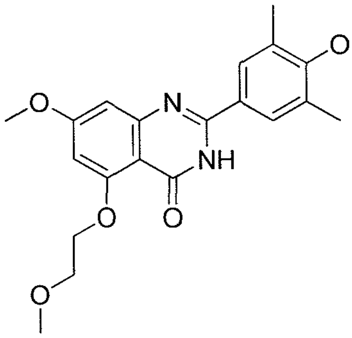
[0156] To a solution of 2-dimethylaminoethanol (180 mg, 2.03 mmol) in DMF (2 mL) was added NaH (61 mg, 1.5 mmol) at 0°C. The reaction mixture was stirred at room temperature for 30 minutes. Then, 2-(4-benzyloxy-3, 5-dimethylphenyl)-5,7-difluoro-3H-quinazolin-4-one (200 mg, 0.510 mmol) was added and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over Na_2SO_4, and concentrated *in vacuo* to give product 2-(4-bezyloxy-3,5-dimethyl phenyl)-5-(2-dimethylamino-ethoxy)-7-fluoro-3*H*-quinazolin-4-one. Yield: 220 mg (93%).

[0157] To a solution of 2-(4-bezyloxy-3,5-dimethylphenyl)-5-(2-dimethylaminoethoxy)-7-fluoro-3*H*-quinazolin-4-one (220 mg, 0.470 mmol) in DMF (3 mL) was added 25% (w/w) sodium methoxide in methanol (205 mg, 3.81 mmol). The reaction mixture was heated at 95°C for 4 hours. The reaction mixture was cooled to the room temperature, diluted with water, and extracted with ethyl acetate. The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give crude product, which was purified by column chromatography (silica gel 230-400 mesh; 5% NH_3 in methanol/ CH_2Cl_2 as eluent) to give pure product 2-(4-bezyloxy-3,5-dimethylphenyl)-5-(2-dimethylamino-ethoxy)-7-methoxy-3*H*-quinazolin-4-one. Yield: 110 mg (49%).

[0158] To a solution of 2-(4-bezyloxy-3, 5-dimethylphenyl)-5-(2-dimethylaminoethoxy)-7-methoxy-3H-quinazolin-4-one (110 mg, 0.23 mmol) in methanol (5 mL) and THF (5 mL) was added Pd/C (50 mg, 10% on charcoal). The reaction mixture was hydrogenated for 2 hours at 50 psi at room temperature. The mixture was filtered through celite and solvent was evaporated *in vacuo* to give crude product, which was purified by column chromatography (silica gel 230-400 mesh; 5% NH_3 in methanol/CH_2Cl_2 as eluent) to give the title compound as a light brown solid. Yield: 70 mg (78%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (s, 2H), 6.80 (s, 1H), 6.40 (s, 1H), 4.20 (t, 2H), 3.90 (s, 3H), 2.90 (t, 2H), 2.40 (s, 3H), 2.25 (s, 3H). MS (ES^+) *m/z:* 384.09 (M+1).

Example 2. Preparation of 2-(4-hydroxy-3,5-dimethyl-phenyl)-7-methoxy-5-(2-methoxy-ethoxy)-3*H*-quinazolin-4-one

[0159]



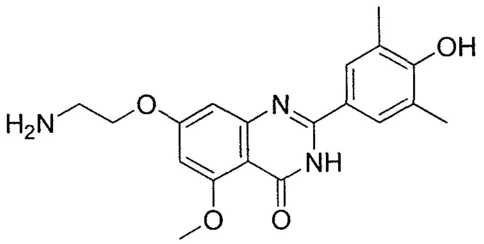
[0160] To a solution of 2-methoxy-ethanol (2 mL) in anhydrous DMF (2 mL) was added NaH (0.276 g, 6.90 mmol) in portions at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 30 minutes. The compound 2-(4-benzyloxy-3,5-dimethyl-phenyl)-5,7-difluoro-3*H*-quinazolin-4-one (0.25 g, 0.64 mmol) was added and the reaction mixture was stirred at room temperature for 16 hours. Water was added and the mixture was acidified with acetic acid to pH approximately 4-5. The precipitated solid was filtered off and washed with water and dried over anhydrous Na_2SO_4 to give 2-(4-benzyloxy-3,5-dimethyl-phenyl)-7-fluoro-5-(2-methoxy-ethoxy)-3*H*-quinazolin-4-one as a white solid. Yield: 0.28 g (98%).

[0161] To a solution of 2-(4-benzyloxy-3,5-dimethyl-phenyl)-7-fluoro-5-(2-methoxy-ethoxy)-3*H*-quinazolin-4-one (0.28 g, 0.62 mmol) in anhydrous DMF (3 mL) was added a 25% solution of sodium methoxide in methanol (1.5 mL, 7.0 mmol) and the reaction mixture was heated to 80-90 ° C for 6 hours. Water was added and the mixture was acidified with acetic acid, to pH approximately 4-5. The precipitated solid was filtered off and purified by column chromatography (silica gel 230-400 mesh; 20-50% ethyl acetate/CH_2Cl_2 as eluent) to give 2-(4-benzyloxy-3,5-dimethyl-phenyl)-7-methoxy-5-(2-methoxy-ethoxy)-3*H*-quinazolin-4-one as a white solid. Yield: 0.1 g (35%).

[0162] The compound 2-(4-benzyloxy-3,5-dimethyl-phenyl)-7-methoxy-5-(2-methoxy-ethoxy)-3*H*-quinazolin-4-one (0.1 g, 0.22 mmol) was hydrogenated in THF/methanol (20/20 mL) at room temperature using Pd/C (10 wt %, 0.05 g) for 4 hours. After filtering through celite, the solvent was evaporated *in vacuo* and the crude material was purified by column chromatography (silica gel 230-400 mesh; 20-50% ethyl acetate/CH_2Cl_2 as eluent) to give the title compound as a white solid. Yield: 0.05 g (61.7%). ^1H NMR (400 MHz, DMSO-d_6): δ 7.81 (s, 2H), 6.70 (s, 1H), 6.51 (s, 1H), 4.19 (t, 2H), 3.87 (s, 3H), 3.70 (t, 2H), 3.40 (s, 3H), 2.21 (s, 6H). MS (ES^+) *m/z:* 371.11 (M+1).

Example 3. Preparation of 7-(2-amino-ethoxy)-2-(4-hydroxy-3,5-dimethyl-phenyl)-5-methoxy-3*H*-quinazolin-4-one

[0163]



[0164] To a solution of 2-amino-4,6-difluoro-benzamide (0.400 g, 2.32 mmol) and 4-benzyloxy-3,5-dimethylbenzaldehyde (0.560 g, 2.32 mmol) in *N,N*-dimethylacetamide (5 mL) were added $NaHSO_3$ (0.450 g, 2.55 mmol) and p-TSA (44 mg, 0.23 mmol) and the reaction mixture was heated at 115-120°C for 16 hours. The reaction mixture was cooled to room temperature. *N,N*-Dimethylacetamide was removed under reduced pressure. The residue was diluted with water and the solid was collected and mixed and stirred for 0.5 hours with methanol (20 mL). The solid was filtered to give 2-(4-benzyloxy-3,5-dimethyl-phenyl)-5,7-difluoro-3*H*-quinazolin-4-one. Yield: 0.41 g (45%).

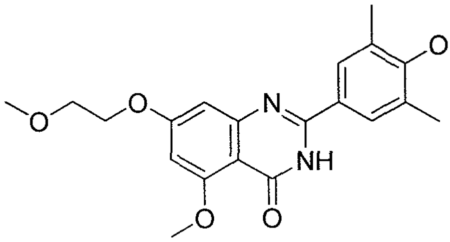
[0165] A solution of 2-(4-benzyloxy-3,5-dimethyl-phenyl)-5,7-difluoro-3*H*-quinazolin-4-one (0.39 g, 1.0 mmol) and 25% sodium methoxide in methanol (0.70 g, 3.2 mmol) in DMF (1.5 mL) was stirred at room temperature for 16 hours. Acetic acid (1.0 mL) was added and the mixture was poured into water (20 mL) and stirred for 0.5 hours. The solid was filtered and further rinsed with water (30 mL), and dried to give 2-(4-benzyloxy-3,5-dimethyl-phenyl)-7-fluoro-5-methoxy-3*H*-quinazolin-4-one. Yield: 0.39 g (92%).

[0166] To a solution of 2-(4-benzyloxy-3,5-dimethyl-phenyl)-7-fluoro-5-methoxy-3*H*-quinazolin-4-one (0.390 g, 0.960 mmol) and 2-dimethylamin-ethanol (0.258 g, 2.89 mmol) in DMF (1.5 mL) was added sodium hydride (0.135 g, 2.97 mmol). The reaction mixture was kept at 80°C for 16 hours and then poured into water (20 mL). The aqueous layer was adjusted to pH 9.0, and extracted with dichloromethane. The crude product was purified by column chromatography on silica gel (230-400 mesh) using 10% methanol in dichloromethane with 1% triethylamine as eluent to give 7-(2-amino-ethoxy)-2-(4-benzyloxy-3, 5-dimethyl-phenyl)-5-methoxy-3*H*-quinazolin-4-one. Yield: 0.25 g (58%).

[0167] To a solution of 7-(2-amino-ethoxy)-2-(4-benzyloxy-3,5-dimethyl-phenyl)-5-methoxy-3*H*-quinazolin-4-one (0.25 g, 0.56 mmol) in methanol (15 mL) was added 10% palladium charcoal wet (0.17 g) and the reaction mixture was subjected to hydrogenation under hydrogen balloon at room temperature for 16 hours. The catalyst was filtered through celite and methanol was removed. The resulting material was further washed with an ethyl acetate and ether mixture (20 mL/20 mL) to give the title compound. Yield: 0.13 g (75%). ^{1}H NMR (400 Hz, DMSO-d_6): δ 11.70 (s, 1H), 8.98 (s, 1H), 7.83 (s, 2H), 6.78 (s, 1H), 6.48 (s, 1H), 4.25 (t, 2H), 3.82 (s, 3H), 2.81 (t, 2H), 2.35 (s, 6H), 2.24 (s, 6H). MS (ES$^+$) *m*/*z:* 384.14 (M+1).

Example 4. Preparation of 2-(4-hydroxy-3,5-dimethyl-phenyl)-5-methoxy-7-(2-methoxy-ethoxy)-3*H*-quinazolin-4-one

[0168]

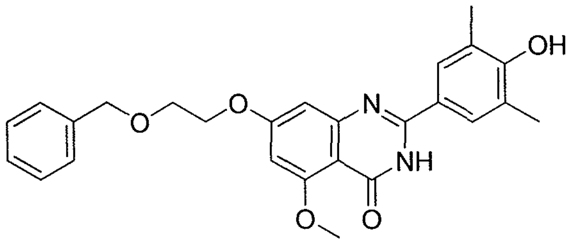


[0169] Sodium hydride (0.340 g, 8.62 mmol) was taken in anhydrous DMF (5 mL). Anhydrous 2-methoxy-ethanol (1.64 g, 21.6 mmol) was added dropwise at 0°C under nitrogen over a period of 15 minutes. Stirring was continued at 0°C for 5 minutes. The ice-bath was removed and stirring continued at room temperature for 10 minutes. Then, 2-(4-benzyloxy-3,5-dimethyl-phenyl)-7-fluoro-5-methoxy-3H-quinazolin-4-one (0.436 g, 1.08 mmol) was added. The color changed to green and stirring continued at 100°C for 4 hours (progress of the reaction was monitored by TLC). The reaction mixture was cooled to room temperature, then quenched with glacial acetic acid (2 mL). Water (75 mL) was added. A white precipitate formed, which was filtered, washed with water, and dried under vacuum. Crude compound was purified by column chromatography (silica gel 230-400 mesh; 0-3% methanol in CH_2Cl_2 as eluent) to give 2-(4-benzyloxy-3,5-dimethyl-phenyl)-5-methoxy-7-(2-methoxy-ethoxy)-3*H*-quinazolin-4-one as a white solid. Yield: 0.09 g (18%).

[0170] To a solution of 2-(4-benzyloxy-3,5-dimethyl-phenyl)-5-methoxy-7-(2-methoxy-ethoxy)-3*H*-quinazolin-4-one (0.083 g, 0.18 mmol) in methanol (15 mL) and THF (5 mL) was added palladium on charcoal (75 mg). The reaction mixture was hydrogenated at 50 psi for 16 hours at room temperature then filtered through celite. The filtrate was concentrated under reduced pressure and the crude compound was purified by preparative HPLC to give the title compound as a white solid. Yield: 0.043 g (45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 2H), 7.00 (s, 1H), 6.52 (s, 1H), 4.20 (m, 2H), 3.80 (m, 5H), 3.48 (s, 3H), 2.22 (s, 6H).

Example 5. Preparation of 7-(2-benzyloxy-ethoxy)-2-(4-hydroxy-3,5-dimethyl-phenyl)-5-methoxy-3*H*-quinazolin-4-one

[0171]



[0172] To a suspension of sodium hydride (2.00 g, 50.0 mmol) in anhydrous DMF (30 mL) at 0°C was added a solution of 4-hydroxy-3,5-dimethyl-benzaldehyde (5.00 g, 33.3 mmol) in anhydrous DMF (20 mL), dropwise over a period of 30 minutes, under nitrogen. Stirring continued at room temperature for 30 minutes and the mixture was cooled to 0°C. Chloromethoxymethane (5.06 mL, 66.6 mmol) was added and the reaction mixture was stirred at room temperature for 16 hours under nitrogen. The reaction mixture was poured into water (200 mL), extracted with ethyl acetate (2 × 50 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude compound was purified by column chromatography (SiO_2, ethyl acetate / hexanes = 1:3) to afford 4-methoxymethoxy-3,5-dimethyl-benzaldehyde as colorless oil. Yield: 5.97 g (92%).

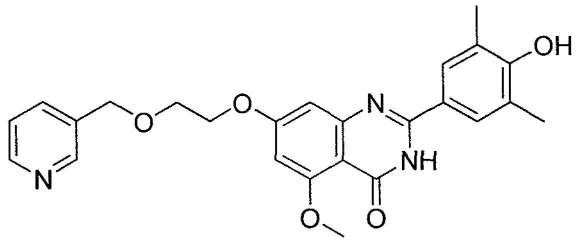
[0173] To a solution of 4-methoxymethoxy-3,5-dimethyl-benzaldehyde (4.00 g, 20.6 mmol) and 2-amino-4,6-difluorobenzamide (3.55 g, 20.6 mmol) in *N,N*-dimethylacetamide (20 mL) were added sodium hydrogen sulfite (58.5 wt%) (5.45 g, 30.9 mmol) and p-toluenesulfonic acid (0.20 g, 1.0 mmol). The reaction mixture was stirred at 120°C for 16 hours under nitrogen and cooled to room temperature. The solvent was evaporated under reduced pressure. Methanol (50 mL) and water (200 mL) were added, the separated solid was filtered, washed with water (30 mL), methanol (30 mL), hexanes (100 mL), and dried under vacuum, to afford 5,7-difluoro-2-(4-methoxymethoxy-3,5-dimethyl-phenyl)-3*H*-quinazolin-4-one as a white solid. Yield: 1.40 g (20%).

[0174] To a solution of 5,7-difluoro-2-(4-methoxymethoxy-3,5-dimethyl-phenyl)-3*H*-quinazolin-4-one (1.40 g, 4.04 mmol) in anhydrous DMF (20 mL) was added a solution of sodium methoxide in methanol (25 wt%, 5.0 mL, 24 mmol). The reaction mixture was stirred at room temperature for 16 hours under nitrogen, diluted with water (100 mL), extracted with ethyl acetate, dried over sodium sulfate, and concentrated on a rotary evaporator to afford 7-fluoro-5-methoxy-2-(4-methoxymethoxy-3,5-dimethyl-phenyl)-3*H*-quinazolin-4-one as a white solid. Yield: 1.1 g (76%).

[0175] To a suspension of sodium hydride (0.176 g, 4.40 mmol) in anhydrous DMF (20 mL) was added benzyloxyethanol (1.02 g, 6.70 mmol) at room temperature under nitrogen. The reaction mixture was stirred 60°C for 30 minutes to get a clear solution. Then, 7-fluoro-5-methoxy-2-(4-methoxymethoxy-3,5-dimethyl-phenyl)-3*H*-quinazolin-4-one (0.200 g, 0.559 mmol) was added and the reaction mixture was stirred at 105°C for 16 hours under nitrogen. The reaction was diluted with water (100 mL), extracted with ethyl acetate (100 mL), and concentrated on a rotary evaporator. The oily residue was subjected to column chromatography (SiO_2, hexanes / ethyl acetate / methanol = 6:2:1) to afford a mixture of two components of very similar polarity. The mixture was dissolved in 50% aqueous acetic acid (60 mL) and mixed with concentrated HCl (3 mL). The resulting mixture was stirred at 70°C for 1 hour and concentrated to dryness on a rotary evaporator. The residue was diluted with saturated sodium bicarbonate aqueous solution (50 mL), extracted with ethyl acetate (150 mL), and concentrated. The residue was purified by column chromatography (SiO_2, hexanes / ethyl acetate / methanol = 7:2:1) to afford the title compound as a light yellow solid. Yield: 45 mg (18%). ^1H NMR (400 MHz, $CDCl_3$): δ 9.68 (br s, 1H), 7.69 (s, 2H), 7.40-7.30 (m, 5H), 6.79 (d, 1H), 6.50 (d, 1H), 4.66 (s, 2H), 4.27 (t, 2H), 3.96 (s, 3H), 3.88 (t, 2H), 2.33 (s, 6H). MS (ES^+) *m/z:* 447.59 (M+1).

Example 6. Preparation of 2-(4-hydroxy-3,5-dimethylphenyl)-5-methoxy-7-[2-(pyridin-3-ylmethoxy)ethoxy]-3H-quinazolin-4-one

[0176]



[0177] To a stirred solution of 5,7-difluoro-2-(4-methoxymethoxy-3,5-dimethylphenyl)-3*H*-quinazolin-4-one (1.04 g, 3.00 mmol) in anhydrous DMF (10 mL) was added a solution of sodium methoxide (25 wt%) in methanol (3.9 mL, 18.0 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 hours under nitrogen. Water (100 mL) was added, the white precipitated solid was filtered off, washed with water and dried under vacuum. The solid was further washed with 10% methanol in ether (20 mL), then ether (20 mL), and dried under vacuum. Yield 0.95 g (88%).

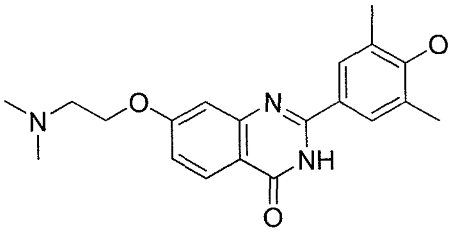
[0178] Sodium hydride (60% in mineral oil; 1.00 g, 25.0 mmol) was added slowly to ethylene glycol (1.48 g, 239 mmol), cooled to 0°C under nitrogen. The cooling bath was removed, and the mixture was stirred for a further 15 minutes at room temperature, before 3-(bromomethyl)pyridine hydrobromide (2.53 g, 10.0 mmol) was added. Then, the mixture was stirred at room temperature for 2.5 days. Water was added, the mixture was extracted with EtOAc (5 × 100 mL), the extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification by column chromatography on silica gel, with CH_2Cl_2 / MeOH (95:5) as the eluent, gave 2-(pyridin-3-ylmethoxy)-ethanol as a colorless liquid. Yield 0.90 g, 59%.

[0179] To a solution of 7-fluoro-5-methoxy-2-(4-methoxymethoxy-3,5-dimethyl-phenyl)-3*H*-quinazolin-4-one (0.30 g, 0.86 mmol) and 2-(pyridin-3-ylmethoxy)ethanol (0.20 g, 1.3 mmol) in DMF (2.0 mL), was added sodium hydride (60% in mineral oil) (0.30 g, 6.9 mmol). The mixture was stirred at room temperature under nitrogen for 3 h, then in an oil bath at 95°C for 2.5 days. The mixture was concentrated under vacuum, water (approximately 50 mL) was added, and the mixture extracted with dichloromethane (3 × 50 mL). The dichloromethane solution was dried over anhydrous Na_2SO_4, concentrated under vacuum, and purified by column chromatography on silica gel, with CH_2Cl_2 / MeOH (95:5) as eluent, to give 5-methoxy-2-(4-methoxymethoxy-3,5-dimethylphenyl)-7-[2-(pyridin-3-ylmethoxy)-ethoxy]-3*H*-quinazolin-4-one. Yield 150 mg (35%).

[0180] To a solution of 5-methoxy-2-(4-methoxymethoxy-3,5-dimethylphenyl)-7-[2-(pyridin-3-ylmethoxy)ethoxy]-3H-quinazolin-4-one (0.10 g, 0.20 mmol) in acetic acid (10 mL) and water (10 mL), sulphuric acid (0.5 mL) was added. The solution was stirred in a 75°C oil bath for 5 hours. The mixture was then concentrated under reduced pressure. The residue was dissolved in methanol, and 2 M Na_2CO_3 was added until the pH reached 8. The mixture was concentrated under reduced pressure. The resulting precipitate was filtered, washed with water, and dried in air. The precipitate was washed further with methanol to give the title compound. Yield: 67 mg (74%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.69 (s, 1H), 8.95 (s, 1H), 8.59 (s, 1H), 8.51 (d, *J* = 3.2 Hz, 1H), 7.84 (s, 2H), 7.79 (dt, *J* = 7.6 and 2.0 Hz, 1H), 7.41-7.38 (m, 1H), 6.72 (d, *J* = 2.0 Hz, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 4.63 (s, 2H), 4.30 (m, 2H), 3.86 (m,. 2H), 3.83 (s, 3H), 2.23 (s, 6H). MS (ES$^-$) *m/z:* 446.52 (M-1).

Example 7. Preparation of 7-(2-dimethylamino-ethoxy)-2-(4-hydroxy-3,5-dimethylphenyl)-3*H*-quinazolin-4-one

[0181]



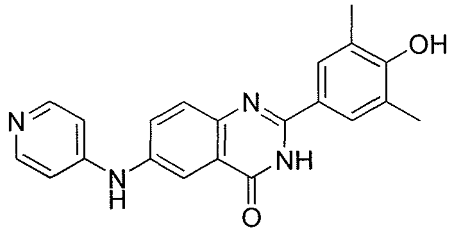
[0182] To a solution of 2-amino-4-fluoro-benzamide (0.77 g, 5.00 mmol) and 4-benzyloxy-3,5-dimethyl-benzaldehyde (1.20 g, 5.00 mmol) in *N,N*-dimethyl acetamide (20 mL) were added sodium hydrogen sulfite (58.5 wt%, 1.10 g, 6.00 mmol) and p-toluenesulfonic acid monohydrate (0.19 g, 1.00 mmol). The reaction mixture was stirred at 120°C for 16 hours under nitrogen, and then cooled to room temperature. Solvent was evaporated under reduced pressure, and water (100 mL) was added. The separated solid was filtered, washed with water (50 mL), and dried under vacuum to give a white solid. Yield: 0.74 g (39%).

[0183] Sodium hydride (60% suspension in mineral oil; 0.36 g, 9.00 mmol) was taken in anhydrous DMF (20 mL). Then, 2-dimethylamino-ethanol (1.07 g, 12.0 mmol) was added drop-wise at room temperature under nitrogen. After the addition, the reaction mixture was stirred at room temperature for 20 minutes. Then, 2-(4-benzyloxy-3,5-dimethylphenyl)-7-fluoro-3*H*-quinazolin-4-one (0.56 g, 1.50 mmol) was added and the reaction mixture was stirred at 80°C for 16 hours. The reaction mixture was cooled to room temperature. Water (100 mL) was added and the mixture was neutralized to pH approximately 8 with aqueous 2 N HCl. The separated solid was filtered, washed with water, and dried under vacuum. The crude compound was purified by the Simpliflash system (0-5% methanol in CH_2Cl_2 and 7 N ammonia in methanol 5% in CH_2Cl_2 as eluent) to give 2-(4-benzyloxy-3,5-dimethylphenyl)-7-(2-dimethylamino-ethoxy)-3*H*-quinazolin-4-one as a white solid. Yield: 0.32 g (48%).

[0184] 2-(4-Benzyloxy-3,5-dimethylphenyl)-7-(2-dimethylamino-ethoxy)-3*H*-quinazolin-4-one (0.30 g, 11.2 mmol) was dissolved in a mixture of methanol and THF (1:1, 60 mL). Palladium on carbon (10 wt%, 0.20 g) was added and the reaction mixture was hydrogenated at 45 psi for 6 hours. The reaction mixture was filtered, and the filtrate was concentrated. The residue was washed with 10% methanol in ether, then ether, and dried under vacuum to give the title compound as a white solid. Yield: 0.18 g (75%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.98 (br s, 1H), 8.94 (br s, 1H), 7.99 (d, *J* = 8.59 Hz, 1H), 7.86 (s, 2H), 7.13 (s, 1H), 7.01 (d, *J* = 8.98 Hz, 1H), 4.21 (t, *J* = 5.46 Hz, 2H), 2.68 (t, *J* = 5.27 Hz, 2H), 2.24 (s, 12H). MS (ES+) *m/z* 354.16 (100%).

Example 8. Preparation of 2-(4-hydroxy-3,5-dimethyl-phenyl)-6-(pyridin-4-ylamino)-3*H*-quinazolin-4-one

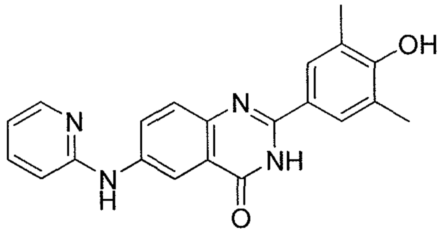
[0185]



[0186] To a solution of 6-amino-2-(4-hydroxy-3,5-dimethyl-phenyl)-3*H*-quinazolin-4-one (300 mg, 1.07 mmol) in pyridine (3 mL), were added 4-bromopridinium hydrochloride (207 mg, 1.07 mmol), $Pd_2(dba)_3$ (19 mg, 0.02 mmol), dppf (18 mg, 0.03 mmol) and NaO-t-Bu (328 mg, 3.41 mmol). The reaction mixture was heated at 140°C for 1 hour in a microwave oven. Solvent was removed under reduced pressure. The crude compound was purified by the Simpliflash system (5% 7 N ammonia in methanol and dichloromethane as eluent) to give the title compound as a yellow solid. Yield: 58 mg (15%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.13 (s, 1H), 9.16 (s, 1H), 8.92 (s, 1H), 8.25 (br s, 2H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.81 (s, 2H), 7.65 (m, 2H), 6.99 (d, *J* = 5.2 Hz, 2H), 2.22 (s, 6H). MS (ES) *m*/*z*: 359.26 (M+1) (100%).

Example 9. Preparation of 2-(4-hydroxy-3,5-dimethyl-phenyl)-6-(pyridin-2-ylamino)-3*H*-quinazolin-4-one

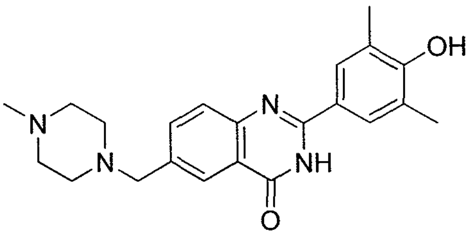
[0187]



[0188] To a solution of 6-amino-2-(4-hydroxy-3,5-dimethyl-phenyl)-3*H*-quinazolin-4-one (300 mg, 1.07 mmol) in pyridine (3.5 mL), were added 2-bromopyridine (202 mg, 1.28 mmol), $Pd_2(dba)_3$ (20 mg, 0.02 mmol), dppf (18 mg, 0.03 mmol) and NaO-t-Bu (329 mg, 3.42 mmol). The reaction mixture was heated at 125°C for 1 hour in a microwave oven (100 W). Solvent was removed under reduced pressure. The crude compound was purified by column chromatography (silica gel 230-400 mesh; 3% methanol, 37% ethyl acetate and 60% CH_2Cl_2 as eluent). The compound was further purified by preparative HPLC to give the title compound as a beige-colored solid. Yield: 35 mg (9%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.01 (br s, 1H), 9.40 (s, 1H), 8.87 (br s, 1H), 8.60 (d, *J* = 2.34 Hz, 1H), 8.23 (d, *J* = 3.91 Hz, 1H), 7.97 (dd, *J* = 8.99 and 2.74 Hz, 1H), 7.82 (s, 2H), 7.72-7.44 (m, 2H), 6.87 (d, *J* = 8.60 Hz, 1H), 6.83 - 6.78 (m, 1H), 2.23 (s, 6H). MS (ES) *m*/*z*: 359.01 (M+1) (100%).

Example 10. Preparation of 2-(4-hydroxy-3,5-dimethylphenyl)-6-((4-methylpiperazin-1-yl)methyl)quinazolin-4(3H)-one

[0189]



[0190] A solution of 2-amino-5-bromobenzamide (12.0 g, 55.8 mmol) and 4-hydroxy-3,5-dimethylbenzaldehyde (8.4

g, 55.8 mmol) in DMA (200 mL) was treated with $NaHSO_3$ (7.7 g, 72.5 mmol) and *p*-TsOH (1.1 g, 5.6 mmol). The reaction was heated at 135°C for 2.5 hours, at which time, H_2O (10 mL) and CH_2Cl_2 (100 mL) were added and the solids were collected by filtration. The solids were washed with CH_2Cl_2 and dried *in vacuo* to afford 6-bromo-2-(4-hydroxy-3,5-dimethylphenyl)quinazolin-4(3*H*)-one (13.1 g, 68%).

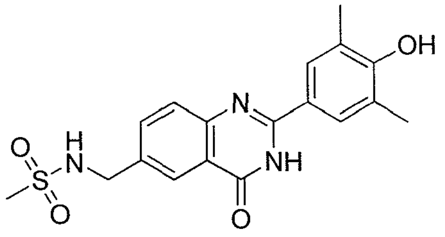
[0191] A solution of 6-bromo-2-(4-hydroxy-3,5-dimethylphenyl)quinazolin-4(3*H*)-one (2.0 g, 5.8 mmol) in DMF (20 mL) was treated with vinyltributyltin (2.6 mL, 8.70 mmol), $Pd(PPh_3)_4$ (0.670 g, 0.58 mmol), and LiCl (0.730 g, 17.4 mmol). The reaction was stirred at reflux for 30 minutes, then concentrated *in vacuo.* The residue was purified by flash chromatography on silica gel, eluting with 30% to 100% of 92:7:1 $CHCl_3$/MeOH/concentrated NH_4OH in CH_2Cl_2, to afford 2-(4-hydroxy-3,5-dimethylphenyl)-6-vinylquinazolin-4(3*H*)-one (0.780 g, 46%).

[0192] To a suspension of 2-(4-hydroxy-3,5-dimethylphenyl)-6-vinylquinazolin-4(3*H*)-one (0.500 g, 1.70 mmol) in THF (30 mL) and H_2O (10 mL) was added $NaIO_4$ (1.09 g, 5.10 mmol), followed by OSO_4 (0.2 mL, 0.017 mmol). The reaction was stirred overnight, then concentrated *in vacuo.* The residue was purified by flash chromatography on silica gel, eluting with 92:7:1 to 6:3:1 $CHCl_3$/MeOH/ concentrated NH_4OH to afford 2-(4-hydroxy-3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carbaldehyde (0.475 g, 95%).

[0193] To a solution of 2-(4-hydroxy-3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carbaldehyde (0.115 g, 0.40 mmol) in DCE/CH_2Cl_2 (1:1, 15 mL) was added 1-methylpiperazine (0.13 mL, 1.20 mmol) and $NaBH(OAc)_3$ (0.250 g, 1.20 mmol). The reaction stirred at room temperature overnight. After this time, the mixture was concentrated in vacuo and purified by flash chromatography on silica gel eluting with 92:7:1 $CHCl_3$/MeOH/concentrated NH_4OH to afford the title compound (0.036 g, 25%) as a white solid: ^1H NMR (300 MHz, DMSO-d_6): δ 11.63 (br s, 1H), 8.77 (br s, 1H), 8.00 (s, 1H), 7.85 (s, 2H), 7.65-7.69 (m, 2H), 3.57 (s, 2H), 2.15-2.39 (m, 17H); APCI MS *m*/*z* 377 $[M-H]^-$.

Example 11. Preparation of N-((2-(4-hydroxy-3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl)methyl)methanesulfonamide

[0194]



[0195] To a solution of methyl-5-methyl-2-nitrobenzoate (2.3 g, 11.8 mmol) in $CHCl_3$ (150 mL) was added NBS (5.3 g, 30.0 mmol) and benzoyl peroxide (0.285 g, 1.2 mmol). The reaction was heated at reflux temperature overnight. Then, the resulting mixture was washed sequentially with H_2O, Na_2CO_3, and brine. The organic layer was then dried (Na_2SO_4), filtered, and concentrated *in vacuo.* Purification by flash chromatography on silica gel, eluting with 5% to 20% ethyl acetate/heptane,afforded methyl 5-(bromomethyl)-2-nitrobenzoate (1.3 g, 40%).

[0196] To a solution of methyl 5-(bromomethyl)-2-nitrobenzoate (1.3 g, 4.7 mmol) in DMF (15 mL) was added potassium phthalimide (1.0 g, 5.2 mmol) and the reaction was stirred at room temperature for 1 hour and concentrated *in vacuo.* Purification by flash chromatography, eluting with 15% to 70% ethyl acetate/heptane, afforded methyl 5-((1,3-dioxoisoindolin-2-yl)methyl)-2-nitrobenzoate (1.4 g, 88%).

[0197] A solution of methyl 5-((1,3-dioxoisoindolin-2-yl)methyl)-2-nitrobenzoate (0.50 g, 1.4 mmol) in EtOH (10 mL) was treated with hydrazine (0.14 mL, 4.4 mol) and the reaction was stirred at room temperature overnight. After this time, the mixture was concentrated *in vacuo* and purified by flash chromatography on silica gel, eluting with 30% to 100% of 92:7:1 $CHCl_3$/MeOH/concentrate NH_4OH in CH_2Cl_2, to afford methyl 5-(aminomethyl)-2-nitrobenzoate (0.23 g, 78%).

[0198] To a solution of methyl 5-(aminomethyl)-2-nitrobenzoate (0.23 g, 1.1 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (0.31 mL, 2.2 mmol) and methanesulfonyl chloride (0.08 mL, 1.1 mmol). The reaction was stirred for 15 minutes at room temperature, concentrated *in vacuo,* and purified by flash chromatography on silica gel, eluting with 2% to 20% MeOH/CH_2Cl_2, to afford methyl 5-(methylsulfonamidomethyl)-2-nitrobenzoate (0.18 g, 57%).

[0199] A mixture of methyl 5-(methylsulfonamidomethyl)-2-nitrobenzoate (0.18 g, 0.62 mmol) in EtOH (10 mL) was flushed with N_2. Pd/C (0.018 g) was added and the reaction was flushed with H_2 for 2 hours. Then, the resulting mixture was filtered through celite and the filtrate was concentrated. Purification by flash chromatography, eluting with 15% to 60% of 92:7:1 $CHCl_3$/MeOH/concentrate NH_4OH in CH_2Cl_2, afforded methyl 2-amino-5-(methylsulfonamidomethyl)-benzoate (0.085 g, 53%).

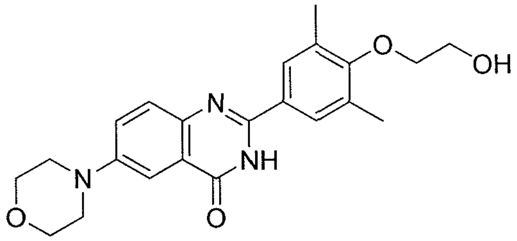
[0200] To a solution of methyl 2-amino-5-(methylsulfonamidomethyl)benzoate (0.085 g, 0.33 mmol) in THF (7 mL) and H_2O (3 mL) was added LiOH•H_2O (0.028 g, 0.65 mol). The reaction was stirred at room temperature for 2 hours and then neutralized with 1 N HCl. The resulting aqueous solution was extracted with EtOAc. The organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated, to afford 2-amino-5-(methylsulfonamidomethyl)benzoic acid (0.066 g, 82%).

[0201] A solution of 2-amino-5-(methylsulfonamidomethyl)benzoic acid (0.066 g, 0.27 mol) in THF (5 mL) was treated with EDCI (0.062 g, 0.32 mmol), HOBT (0.044 g, 0.32 mol) and NMM (0.035 mL, 0.32 mmol.) The reaction was stirred at room temperature for 1.5 hours. Then, NH_4OH (0.03 mL, 0.35 mmol) in H_2O (0.03 mL) was added. The mixture was stirred at room temperature for 5 hours and then concentrated. Purification by flash chromatography, eluting with 92:7:1 to 7:2.5:0.5 $CHCl_3$/MeOH/concentrated NH_4OH, afforded 2-amino-5-(methylsulfonamidomethyl)benzamide (0.035 g, 53%).

[0202] A mixture of 2-amino-5-(methylsulfonamidomethyl)benzamide (0.035 g, 0.14 mmol), 4-hydroxy-3,5-dimethyl benzaldehyde (0.022 g, 0.14 mmol) and $CuCl_2$ (0.039 g, 0.28 mmol) in EtOH (5 mL) was refluxed for 3 h, then concentrated *in vacuo.* Purification by flash chromatography on silica gel, eluting with 92/7/1 $CHCl_3$:MeOH:concentrated NH_4OH, followed by reverse-phase chromatography, eluting with 10% to 50% CH_3CN in H_2O with 0.1% TFA, and finally flash chromatography on silica gel, eluting with 7:2.5:0.5 $CHCl_3$/MeOH/concentrated NH_4OH, afforded the title compound (0.030 g, 57%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6): δ 8.09 (s, 1H), 7.83-7.90 (m, 2H), 7.65-7.78 (m, 3H), 6.81-7.54 (m, 2H), 4.30 (d, J = 6.2 Hz, 2H), 2.91 (s, 3H), 2.24 (s, 6H). ESI MS m/z 374 $[M+H]^+$.

Example 12. Preparation of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-morpholinoquinazolin-4(3H)-one

[0203]



[0204] A mixture of 3,5-dimethoxy-4-hydroxybenzaldehyde (10 g, 66.67 mmol), (2-bromoethoxy)-dimethyl-tert-butyl-silane (15 mL, 70 mmol), potassium iodide (1.1 g, 6.67 mmol), and sodium hydride (4 g, 100 mmol) in DMF (150 mL) was heated and stirred at 70°C for 14 hours. The reaction was then cooled and quenched by adding water (100 mL). The mixture was extracted with EtOAc (3 × 100 mL) and concentrated on a rotary evaporator. The resulting residue was purified by column (SiO_2, hexanes/EtOAc, 6:1) to yield 4-[2-(tert-butyl-dimethyl-silanyloxy)-ethoxy]-3,5-dimethyl-benzaldehyde (15.4 g, 75%).

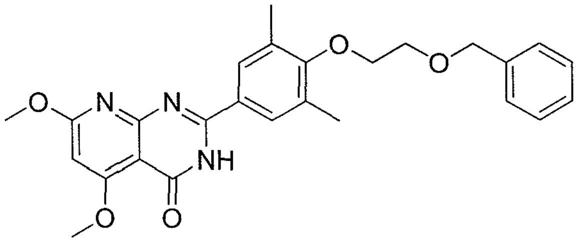
[0205] A solution of 5-morpholin-4-yl-2-nitro-benzamide (2 g, 7.96 mmol) in MeOH (50 mL) and DMF (150 mL) in a Parr bottle was mixed with Pd/C (0.5 g) and was subjected to hydrogenation (35 psi) at room temperature for 14 hours. The suspension was then passed through a celite pad and the filtrated was concentrated on a rotary evaporator, to provide 2-amino-5-morpholin-4-yl-benzamide (1.69 g, 96%).

[0206] A mixture of 2-amino-5-morpholin-4-yl-benzamide (0.2 g, 0.905 mmol), 4-[2-(tert-butyl-dimethyl-silanyloxy)-ethoxy]-3,5-dimethyl-benzaldehyde (0.28 g, 0.905 mol), sodium hydrogensulfite (0.162 g, 0.905 mmol) and p-toluenesulfonic acid (0.224 g, 1.177 mol) in N,N-dimethyl acetamide (10 mL) was stirred at 150°C for 4 hours. The reaction mixture was cooled to room temperature, diluted with water (50 L), basified with sodium bicarbonate to pH approximately 8-9, extracted with EtOAc (3 × 100 mL), and concentrated on a rotary evaporator, affording a solid residue. Further purification on a column (SiO_2, DCM/MeOH/EtOAc = 6:1:2) yielded 2-{4-[2-(tert-butyl-dimethyl-silanyloxy)-ethoxy]-3,5-dimethyl-phenyl}-6-morpholin-4-yl-3H-quinazolin-4-one (66 mg, 14%).

[0207] The above compound (66 mg, 0.129 mmol) in THF (10 mL) was mixed with TBAF in THF (2 mL, 2 mmol) and stirred at room temperature for 5 hours. The mixture was then concentratred on a rotary evaporator and subjected to column chromatography (SiO_2, DCM/MeOH/EtOAc = 6:1:2) to yield the title compound as a light yellow solid (35 mg, 68%). MP 279.5-281 °C.

Example 13. Preparation of 2-(4-(2-(benzyloxy)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxypyrido[2,3-d]pyrimidin-4(3H)-one

[0208]



[0209] A mixture of dimethyl acetone-1,3-dicarboxylate (200 g 1.148 mol), cyanamide (48.3 g, 1.148 mol), and Ni(acac)$_2$ (14.75 g, 0.0574 mol) in dioxane (200 mL) was heated to reflux in a 1-L flask with a reflux condenser. The reaction mixture was heated at reflux for 16 hours and then cooled to room temperature. The precipitate was filtered off, and the solid was mixed with methanol (200 mL), stirred for 30 minutes, and filtered again to give methyl 2-amino-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylate (93 g, 44%).

[0210] In a 1-L flask with a reflux condenser was added methyl 2-amino-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylate (93.0 g, 0.505 mol) and $POCl_3$ (425 mL) and the reaction mixture was heated to reflux for 35 minutes. About 300 mL $POCl_3$ was evaporated under vacuum. The residue was poured into ice and water (400 mL), which was further neutralized with KOH to pH approximately 6-7. The precipitate was filtered off and extracted with ethyl acetate (2 × 300 mL). The organic solution was concentrated and passed through a column, eluting with hexane:ethyl acetate 4:1, to give methyl 2-amino-4,6-dichloropyridine-3-carboxylate (22.5 g, 20.1%).

[0211] In a 500-mL flask with a reflux condenser was added methyl 2-amino-4.6-dichloropyridine-3-carboxylate (22.5 g, 0.101 mol) and 25 wt% sodium methoxide in methanol (88 mL, 0.407 mol), together with methanol (20 mL). The mixture was heated to reflux for 5 hours, then cooled to room temperature. Acetic acid (15 mL) was added to the mixture and pH was adjusted to approximatley 7. Methanol was removed and the residue was poured into water (100 mL). The precipitated solid was filtered and further rinsed with water (3 × 200 mL) to give methyl 2-amino-4, 6-dimethoxypyridine-3-carboxylate (18.5 g, 86.4%).

[0212] In a 500-mL flask with a reflux condenser was added methyl 2-amino-4,6-dimethoxypyridine-3-carboxylate (18.5 g, 0.0872 mol), potassium hydroxide (19.5 g, 0.349 mol) in water (80 mL) and ethanol (100 mL). The mixture was heated to 80°C for 16 hours. The solvent was removed and aqueous HCl was used to adjust the pH to 6. The water was removed by freeze drying. The obtained solid was extracted with methanol to yield 2-amino-4,6-dimethoxy-nicotinic acid (17.2 g, 100%).

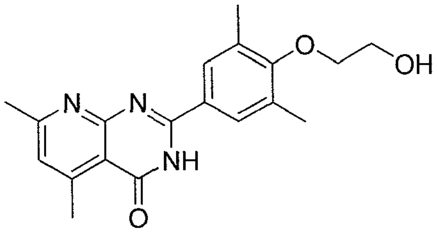
[0213] 2-Amino-4,6-dimethoxy-nicotinic acid (17.2 g, 0.0872 mol) was added to THF (110 mL). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (21.73 g, 0.113 mol), 1-hydroxybenzotriazole hydrate (12.96 g, 0.0959 mol) and 4-methyl morpholine (9.7 g, 0.0959 mol) were then added to the suspension. After stirring for 10 minutes at room temperature, 50% v/v ammonium hydroxide (18.3 g, 0.262 mol) was added. The reaction mixture was kept at room temperature for 16 hours. THF was removed and the residue was poured into cold water (100 mL). The precipitate was filtered off and washed with cold water to yield 2-amino-4,6-dimethoxy-nicotinamide (10.8 g, 62.3%).

[0214] To a solution of 4-hydroxy-3,5-dimethylbenzaldehyde (6.84 g, 0.0455 mol) in anhydrous DMF (15 mL) was added NaH in mineral oil (60%, 2.23 g, 0.0558 mol). (2-Bromo-ethyoxymethyl)-benzene (10.0 g, 0.0465 mol) was added and the reaction was kept at 65°C overnight. The reaction mixture was poured into water and extracted with dichloromethane to yield (4-(2-benzyloxy-ethoxy)-3,5-dimethylbenzaldehyde (10.5 g, 81%), which was used for next step reaction without further purification.

[0215] To a solution of 2-amino-4,6-dimethoxy-nicotinamide (2.55 g, 12.9 mmol) and 4-(2-benzyloxy-ethoxy)-3,5-dimethylbenzaldehyde (3.68 g, 12.9 mmol) in N,N-dimethyl acetamide (20 mL), were added $NaHSO_3$ (2.52 g, 14.2 mmol) and p-TSA (1.98 g, 10.4 mmol). The reaction mixture was heated at 150°C for 14 hours. The reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure. The residue was diluted with water and the solid was collected and further washed with methanol. The crude product was purified by column chromatography (silica gel 230-400 mesh; 2% methanol in CH_2Cl_2 as eluent) to give the title compound as an off-white solid (0.88 g, 14.7%). MP 204.5-205.9°C.

Example 14. Preparation of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethylpyrido[2,3-d]pyrimidin-4(3H)-one

[0216]



[0217] A mixture of 3,5-dimethoxy-4-hydroxybenzaldehyde (10 g, 67 mmol), (2-bromoethoxy)-dimethyl-tert-butylsilane (15 mL, 70 mmol), potassium iodide (1.1 g, 6.7 mmol), and sodium hydride (4 g, 100 mmol) in DMF (150 mL) was heated and stirred at 70°C for 14 hours. The reaction was then cooled and quenched by adding water (100 mL). The mixture was extracted with EtOAc (3 × 100 mL) and concentrated on a rotary evaporator. The resulting residue was purified by column (SiO_2, hexanes/EtOAc = 6:1) to yield 4-[2-(tert-butyl-dimethyl-silanyloxy)-ethoxy]-3,5-dimethyl-benzaldehyde (15.4 g, 75%).

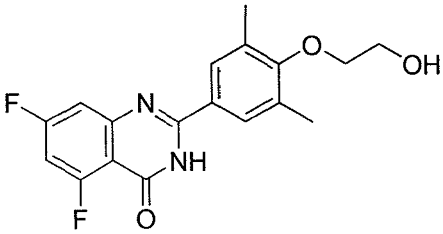
[0218] A mixture of 2-amino-4,6-dimethyl-nicotinamide (0.25 g, 1.5 mmol), 4-[2-(tert-butyl-dimethyl-silanyloxy)-ethoxy]-3,5-dimethyl-benzaldehyde (0.468 g, 1.5 mmol), sodium hydrogensulfite (0.271 g, 1.51 mmol) and p-toluenesulfonic acid (0.358 g, 1.82 mmol) in N,N-dimethyl acetamide (10 mL) was stirred at 150°C for 4 hours. The reaction mixture was cooled to room temperature, diluted with water (50 mL), basified with sodium bicarbonate, to pH approximately 8-9, extracted with EtOAc (3 × 100 mL), and concentrated on a rotary evaporator, to afford a solid residue, which was purified by column chromatography (SiO_2, DCM/MeOH/EtOAc = 6:1:2) to yield 2-{4-[2-(tert-butyl-dimethyl-silanyloxy)-ethoxy]-3,5-dimethyl-phenyl}-5,7-dimethyl-3H-pyrido[2,3-d]pyrimidin-4-one (56 mg, 8%).

[0219] To a solution of 2-{4-[2-(tert-butyl-dimethyl-silanyloxy)-ethoxy]-3,5-dimethyl-phenyl}-5,7-dimethyl-3H-pyrido[2,3-d]pyrimidin-4-one (107 mg, 0.234 mmol) in THF (10 mL) was added TBAF in THF (3 mL, 3 mmol) and the mixture was stirred at room temperature for 15 hours. The mixture was then concentratred on a rotary evaporator and subjected to column chromatography (SiO_2, DCM/MeOH/EtOAc = 6:1:2) to yield 2-[4-(2-hydroxy-ethoxy)-3,5-dimethylphenyl]-5,7-dimethyl-3H-pyrido[2,3-d]pyrimidin-4-one (36 mg, 45%).

[0220] A solution of 2-[4-(2-hydroxy-ethoxy)-3,5-dimethyl-phenyl]-5,7-dimethyl-3H-pyrido-[2,3-d]pyrimidin-4-one (36 mg, 0.105 mmol) in MeOH (5 mL) and DCM (5 mL) was mixed with HCl in ether (2 mL, 2 mmol) and stirred at room temperature for 30 minutes. The reaction mixture was then concentrated on a rotary evaporator. The resulting solid residue was re-dissolved in minimal volume of MeOH-DCM (1:1) and triturated with hexanes. The solid was collected by filtration and washed with MeOH-DCM (1:20) to yield the title compound as a yellow solid (16.6 mg, 41%).

Example 15. Preparation of 5,7-difluoro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one

[0221]



[0222] A mixture of 3,5-dimethoxy-4-hydroxybenzaldehyde (10 g, 66.67 mmol), (2-bromoethoxy)-dimethyl-tert-butylsilane (15 mL, 70 mmol), potassium iodide (1.1 g, 6.67 mmol), and sodium hydride (4.00 g, 100 mmol) in DMF (150 mL) was heated and stirred at 70°C for 14 hours. The reaction was then cooled and quenched by addition of water (100 mL). The mixture was extracted with EtOAc (3 × 100 mL) and concentrated on a rotary evaporator. The resulting residue was purified by column (SiO_2, hexanes/EtOAc = 6:1) to yield 4-[2-(tert-butyl-dimethyl-silanyloxy)-ethoxy]-3,5-dimethyl-benzaldehyde (15.4 g, 75%).

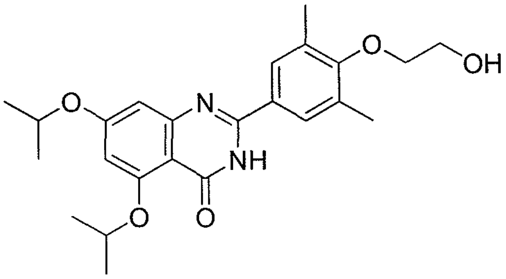
[0223] A solution of 2-amino-4,6-difluorobenzoic acid (0.5 g, 2.9 mmol), EDCI·HCl (0.887 g, 4.62 mmol), HOBt (0.975 g, 7.22 mmol), and triethylamine (1.6 mL, 11.552 mmol) in THF (50 mL) was stirred at room temperature for 1 hour. Ammonium hydroxide (50% aqueous, 10 mL) was then added to the reaction mixture. The resulting mixture was stirred at room temperature for 6 hours. The reaction was quenched by adding water (50 mL), extracted with DCM (3 × 100 mL), and concentrated on a rotary evaporator to afford 2-amino-4,6-difluorobenzamide (0.25 g, 50%).

[0224] A mixture of 2-amino-4,6-difluoro benzamide (0.25 g, 1.45 mmol), 4-[2-(tert-butyl-dimethyl-silanyloxy)-ethoxy]-

3,5-dimethyl-benzaldehyde (0.448 g, 1.45 mmol), sodium hydrogensulfite (0.26 g, 1.45 mmol) and p-toluenesulfonic acid (0.276 g, 1.45 mmol) in N,N-dimethyl acetamide (10 mL) was stirred at 155°C for 14 hours. The reaction mixture was cooled to room temperature, diluted with water (50 mL), extracted with EtOAc (3 × 100 mL), and concentrated on a rotary evaporator, to afford impure product. The residue was re-dissolved in THF (20 mL) and mixed with TBAF in THF (10 mL, 10 mmol). The reaction mixture was stirred at room temperature for 3 hours and concentrated on a rotary evaporator to afford an oily residue. Further purification by column (SiO_2, EtOAc/DCM = 3:1) yielded a light yellow solid. This solid was diluted with MeOH (10 mL) to make a slurry. The solid was collected by filtration and washed with MeOH to afford the title compound as a light yellow solid (49 mg, 5% overall yield).

Example 16. Preparation of 2-[4-(2-hydroxy-ethoxy)-3,5-dimethyl-phenyl]-5,7-diisopropoxy-3H-quinazolin-4-one

[0225]



[0226] To a solution of 3,5-dihydroxybenzoic acid (10.0 g, 64.9 mmol) in anhydrous ethanol (100 mL) at room temperature was slowly added concentrated sulfuric acid (10 mL). The resulting mixture was stirred at reflux for 36 hours. The reaction was cooled to room temperature, diluted with water (200 mL), extracted with CH_2Cl_2 (3 × 100 mL), and concentrated on a rotary evaporator, to afford 3,5-dihydroxybenzoic acid ethyl ester as a colorless oil. Yield: 8.2 g (69%).

[0227] A solution of 3,5-dihydroxybenzoic acid ethyl ester (6.0 g, 33 mmol) and 2-iodo-propane (9.9 mL, 99 mmol) in DMF (200 mL) was mixed with potassium carbonate (13.7 g, 98.9 mmol) and the mixture was stirred at room temperature for 14 hours. The reaction mixture was then diluted with water (300 mL), and extracted with ethyl acetate (3 × 100 mL). The residue obtained upon concentration was subjected to column chromatography (SiO_2, hexanes / ethyl acetate = 3:1) to afford 3,5-diisopropoxybenzoic acid ethyl ester. Yield: 8.80 g (100%).

[0228] A solution of 3,5-diisopropoxybenzoic acid ethyl ester (8.80 g, 33.1 mmol) and lithium hydroxide (3.18 g, 132 mmol) in water (100 mL), methanol (50 mL), and THF (50 mL) was stirred at reflux for 3 hours. It was then cooled to room temperature, diluted with water (200 mL), acidified with 2 N hydrochloric acid, to pH approximately 2, extracted with CH_2Cl_2 (3 × 100 mL), and concentrated on a rotary evaporator, to afford 3,5-diisopropoxybenzoic acid as a white solid. Yield: 7.60 g (97%).

[0229] A solution of 3,5-diisopropoxybenzoic acid (7.60 g, 31.9 mmol), triethylamine (5.3 mL, 38 mmol), and diphenylphosphoroyl azide (8.3 mL, 38 mmol) in 1,4-dioxane (120 mL) and *tert*-butanol (30 mL) was stirred at reflux for 16 hours. The reaction mixture was then cooled to room temperature, diluted with 0.2 N sodium bicarbonate aqueous (200 mL), extracted with CH_2Cl_2 (3 × 100 mL), and concentrated on a rotary evaporator. The residue obtained was subjected to column chromatography (SiO_2, hexanes / ethyl acetate = 3:1) to afford 3,5-diisopropoxyphenyl)-carbamic acid tert-butyl ester as a white solid. Yield: 5.60 g (57%).

[0230] A solution of 3,5-diisopropoxyphenyl)-carbamic acid *tert*-butyl ester (5.60 g, 18.2 mmol) in trifluoroacetic acid (30 mL) was stirred at reflux for 30 minutes and concentrated on a rotary evaporator to dryness to afford 3,5-diisopropoxyphenylamine trifluoroacetic acid salt as an oil. Yield: 5.27 g (90%).

[0231] To a round-bottomed flask contained 3,5-diisopropoxyphenylamine trifluoroacetic acid salt (5.27 g, 16.4 mmol) was slowly added oxalyl chloride (20 mL) and the mixture was stirred at reflux for 1 hour. Extra oxalyl chloride was removed by distillation and methanol (100 mL) was added to the residue. It was then stirred at room temperature for 30 minutes and concentrated to dryness on a rotary evaporator to afford 4,6-diisopropoxy-1H-indole-2,3-dione as a semi-solid. Yield: 4.33 g (100%).

[0232] A solution of potassium hydroxide (15.3 g, 273 mmol) in water (60 mL) was mixed with 4,6-diisopropoxy-1H-indole-2,3-dione (4.33 g, 16.4 mmol). To this mixture was slowly added hydrogen peroxide. The resulting mixture was stirred at 70°C for 30 minutes and cooled to 0°C. The mixture was acidified at 0°C with 2 N hydrochloric acid to pH approximately 4, extracted with CH_2Cl_2 (3 × 100 mL), and concentrated on a rotary evaporator to afford 2-amino-4,6-diisopropoxy-benzoic acid as a semi-solid. Yield: 2.91 g (70%).

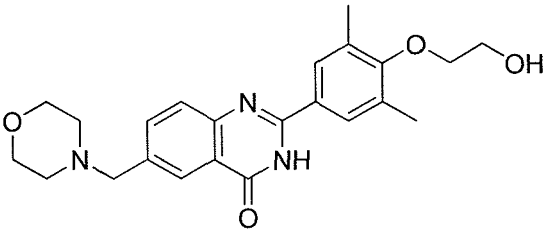
[0233] A solution of 2-amino-4,6-diisopropoxybenzoic acid (2.91 g, 11.5 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (3.20 g, 16.7 mmol), HOBt (3.10 g, 23.0 mmol), and triethylamine (4.2 mL, 30 mmol) in THF

(200 mL) was stirred at room temperature for 20 minutes. 50% (v/v) ammonia aqueous (20 mL) was then added. The resulting solution was stirred at room temperature for 14 hours, diluted with water (200 mL), extracted with CH_2Cl_2 (3 × 100 mL), and concentrated on a rotary evaporator. The residue obtained was subjected to column chromatography (SiO_2, ethyl acetate / dichloromethane / methanol = 6:2:1) to afford 2-amino-4,6-diisopropoxybenzamide. Yield: 1.2 g (41%).

[0234] A solution of 2-amino-4,6-diisopropoxybenzamide (0.30 g, 1.2 mmol), 4-(2-hydroxy-ethoxy)-3,5-dimethylbenzaldehyde (0.28 g, 1.4 mmol), sodium bisulfite (0.25 g, 1.4 mmol), and p-toluenesulfonic acid (20 mg, 0.11 mmol) in dimethyl acetamide (10 mL) was stirred at 150°C for 12 hours. Extra solvent was evaporated on a rotary evaporator and the residue was diluted with saturated sodium bicarbonate aqueous solution (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The residue obtained upon concentration was subjected to column chromatography (SiO_2, ethyl acetate / dichloromethane / hexanes / methanol = 4:4:4:1) to afford the title compound as a light yellow solid. Yield: 35 mg (6.9%). ^1H NMR (400 MHz, $CDCl_3$): δ 9.78 (br s, 1H), 7.66 (s, 2H), 6.78 (d, 1H), 6.42 (d, 1H), 4.72 (m, 1H), 4.63 (m, 1H), 3.97 (t, 3H), 3.92 (t, 2H), 2.33 (s, 6H), 1.45 (d, 3H), 1.41 (d, 3H). MS (ES^+) *m/z:* 427.13 (M+1).

Example 17. Preparation of 2-[4-(2-hydroxyethoxy)-3,5-dimethyl-phenyl]-6-morpholin-4-ylmethyl-3H-quinazolin-4-one

[0235]



[0236] To a solution of 5-methyl-2-nitrobenzoic acid (25.0 g, 138 mmol) in ethanol (200 mL) was slowly added concentrated sulfuric acid (30 mL). The resulting solution was stirred at reflux for 48 hours. The reaction mixture was then poured into icy water (300 mL), extracted with CH_2Cl_2 (3 × 100 mL), and concentrated on a rotary evaporator, to afford 5-methyl-2-nitrobenzoic acid ethyl ester. Yield: 28.9 g (100%).

[0237] A solution of 5-methyl-2-nitrobenzoic acid ethyl ester (28.9 g, 138 mmol), N-bromosuccinimide (24.6 g, 138 mmol), and benzoyl peroxide (7.41 g, 30.6 mmol) in carbon tetrachloride (400 mL) was stirred at 80°C under irradiation from a medium pressure mercury lamp for 3 hours. The lamp was then removed and the reaction was cooled to 40°C. To this solution was slowly added morpholine (14.6 mL, 168 mmol) and triethylamine (43.0 mL, 306 mmol). The resulting mixture was stirred at 40°C for 14 hours, diluted with saturated sodium bicarbonate aqueous (300 mL), extracted with CH_2Cl_2 (3 × 100 mL), and concentrated on a rotary evaporator. The residue was subjected to column chromatography (SiO_2, hexanes / ethyl ether = 1:2) to afford 5-morpholin-4-ylmethyl-2-nitrobenzoic acid ethyl ester as an oil. Yield: 20 g (49%).

[0238] To a solution of 5-morpholin-4-ylmethyl-2-nitrobenzoic acid ethyl ester (20 g, 68 mmol) in acetic acid (100 mL) was added iron powder (13.0 g, 231 mmol). The resulting suspension was stirred at 60°C for 3 hours, cooled to room temperature, and diluted with water (200 mL) and CH_2Cl_2 (200 mL). The solid was filtered off, and the filtrate was extracted with CH_2Cl_2 (3 × 100 mL) and concentrated on a rotary evaporator to remove all solvent. The residue was re-dissolved in CH_2Cl_2 (400 mL), and backwashed with 2 N potassium hydroxide aqueous (2 × 200 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated, to afford 2-amino-5-morpholin-4-ylmethylbenzoic acid ethyl ester as an oil. Yield: 17.7 g (100%).

[0239] A solution of 2-amino-5-morpholin-4-ylmethylbenzoic acid ethyl ester (3.82 g, 15.3 mmol) and lithium hydroxide (0.733 g, 30.6 mmol) in THF (25 mL), methanol (15 mL), and water (10 mL) was stirred at reflux for 2.5 hours. The reaction mixture was then concentrated to dryness on a rotary evaporator and further dried under high vacuum for 24 hours to afford lithium 2-amino-5-morpholin-4-ylmethylbenzoate. Complete conversion was assumed and the solid obtained was used in the next step without further purification.

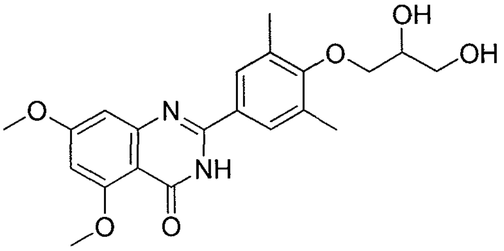
[0240] A solution of lithium 2-amino-5-morpholin-4-ylmethylbenzoate (3.70 g, 15.3 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (5.87 g, 30.6 mmol), HOBt (4.54 g, 33.6 mmol), and 4-methylmorpholine (5.0 mL, 46 mmol) in THF (200 mL) was stirred at room temperature for 40 minutes. 50% (v/v) aqueous ammonia (20 mL) was then added. The resulting solution was stirred at room temperature for 14 hours, diluted with water (200 mL), extracted with CH_2Cl_2 (3 × 100 mL), and concentrated on a rotary evaporator, to afford 2-amino-5-morpholin-4-ylmethylbenzamide as a light yellow solid. Yield: 1.2 g (33%).

[0241] A solution of 2-amino-5-morpholin-4-ylmethylbenzamide (0.60 g, 2.6 mmol), 4-(2-hydroxyethoxy)-3,5-dimethylbenzaldehyde (0.58 g, 3.9 mmol), sodium bisulfite (1.14 g, 6.44 mmol), and *p*-toluenesulfonic acid (0.88 g, 4.6 mmol) in dimethyl acetamide (10 mL) was stirred at 150°C for 12 hours. Extra solvent was evaporated on a rotary evaporator and the residue was diluted with saturated sodium bicarbonate aqueous solution (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The residue obtained on concentration was subjected to column chromatography (SiO_2, hexanes / ethyl acetate / dichloromethane / methanol = 4:4:8:1) to afford 2-[4-(2-hydroxyethoxy)-3,5-dimethylphenyl]-6-morpholin-4-ylmethyl-3H-quinazolin-4-one as a light yellow solid. Yield: 0.15 g (14%).

[0242] A solution of 2-[4-(2-hydroxyethoxy)-3,5-dimethylphenyl]-6-morpholin-4-ylmethyl-3H-quinazolin-4-one (0.15 g, 0.37 mmol) in CH_2Cl_2 (10 mL) was mixed with 1 N HCl in ethyl ether (3 mL, 3 mmol) and was stirred at room temperature for 10 minutes to form a suspension. The solid was filtered, and washed with CH_2Cl_2 to afford the title compound as a light yellow solid. Yield: 52 mg (29%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.49 (s, 1H), 8.13 (d, 1H), 7.93 (d, 1H), 7.77 (s, 2H), 4.58 (s, 2H), 4.05 (m, 2H), 3.98 (t, 2H), 3.91 (t, 2H), 3.80 (m, 2H), 3.41 (m, 2H), 3.30 (m, 2H), 2.44 (s, 6H). MS (ES$^+$) *m/z:* 410.05 (M+1).

Example 18. Preparation of 2-[4-(2,3-Dihydroxy-propoxy)-3,5-dimethyl-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one

[0243]

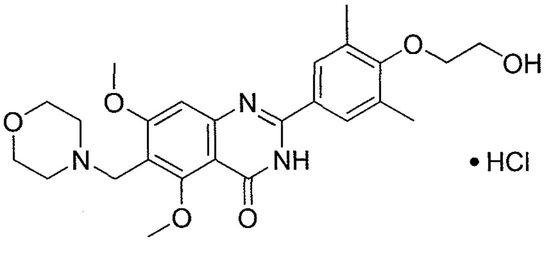


[0244] To a solution of 4-hydroxy-3,5-dimethylbenzaldehyde (1.50 g, 10.0 mmol) in anhydrous DMF (20 mL) were added cesium carbonate (6.52 g, 20.0 mmol) and 4-chloromethyl-2,2-dimethyl-[1,3]dioxolane (1.50 g, 10.0 mmol). The reaction mixture was stirred at 80°C for 4 days under nitrogen, then cooled to room temperature. Water (100 mL) was added, and the mixture extracted with ethyl acetate (200 mL). The organic phase was separated, washed with 1 N aqueous NaOH solution (100 mL), water (2 × 100 mL), brine (100 mL), and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure, and the crude compound was purified using the Simpliflash system (20% ethyl acetate in hexanes as eluent) to give 4-(2,2-dimethyl-[1,3]dioxolane-4-ylmethoxy)-3,5-dimethyl-benzaldehyde as a yellow oil. Yield: 0.95 g (36%).

[0245] To a solution of 2-amino-4,6-dimethoxybenzamide (0.35 g, 1.8 mmol) in *N,N*-dimethyl acetamide (10 mL) were added 4-(2,2-dimethyl-[1,3]dioxolane-4-ylmethoxy)-3,5-dimethyl-benzaldehyde (0.520 g, 1.98 mmol), sodium hydrogensulfite (58.5 wt%) (0.350 g, 1.98 mmol) and p-toluenesulfonic acid (0.17 g, 0.90 mmol). The reaction mixture was stirred at 120°C for 16 hours under nitrogen, then cooled to room temperature. Solvent was evaporated under reduced pressure, water (50 mL) was added, the separated solid was filtered, washed with water, then dichloromethane (10 mL), and dried under vacuum to give the title compound as a yellow solid. Yield: 0.34 g (47%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.8 (s, 1H), 7.83 (s, 2H), 6.64 (s, 1H), 6.44 (s, 1H), 4.95 (d, 1H), 4.40 (t, 1H), 3.88 (s, 3H), 3.84-3.66 (m, 6H), 3.46 (t, 2H), 2.28 (s, 6H). MS (ES) *m/z:* 401.04 (M+1) (100%).

Example 19. Preparation of 2-[4-(2-hydroxy-ethoxy)-3,5-dimethylphenyl]-5,7-dimethoxy-6-morpholin-4-ylmethyl-3H-quinazolin-4-one hydrochloride

[0246]



[0247] Bromine (33.7 mL, 657 mmol) and 1,4-dioxane (56.0 mL, 657 mmol) was mixed at room temperature to provide fresh dioxane dibromide, which was then diluted with ethyl ether (900 mL). To a solution of 2,6-dimethoxytoluene (50.0 g, 328 mmol) in ether (450 mL) was added the freshly prepared dioxane dibromide in ether (900 mL) over 30 minutes while stirring at room temperature. After the addition, the mixture was stirred at room temperature for an additional 1.5 hours, and was poured into a beaker containing water (500 mL) and partitioned. The aqueous was discarded and the ethereal layer was washed sequentially with water (2 × 500 mL), saturated sodium bicarbonate aqueous (2 × 500 mL), dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator, to afford 3-bromo-2,6-dimethoxytoluene as a colorless oil. Yield: 76 g, (100%).

[0248] A cooling well was used to collect 300 mL of ammonia at -78°C, which was then mixed with 0.5 g potassium and 0.5 g ferric nitrate. After the initial blue color discharged, potassium (14.2 g, 364 mmol) was added at -78°C, portionwise so that the blue color discharged before to each addition. After complete addition of potassium, the solution was stirred at -78°C for 15 minutes. To this solution was slowly added 3-bromo-2,6-dimethoxytoluene (42.0 g, 182 mmol) in THF (100 mL). The resulting mixture was stirred at -78°C for 3 hours and then 0°C for 1 hour. The reaction was quenched by adding water (150 mL) and was extracted with CH_2Cl_2 (3 × 200 mL) to afford a brown oil as the crude product. The product was further purified by column chromatography (SiO_2, hexanes / ethyl acetate = 1:1) to yield 3,5-dimethoxy-4-methylaniline. Yield: 22.1 g (73%).

[0249] A solution of 3,5-dimethoxy-4-methylaniline (22.1 g, 132 mmol) in 1,4-dioxane (380 mL) and water (380 mL) was mixed with potassium carbonate (45.6 g, 331 mmol) and $(Boc)_2O$ (34.6 g 159 mmol) and stirred at room temperature for 14 hours. The reaction mixture was then extracted with CH_2Cl_2 (3 × 100 mL) and concentrated on a rotary evaporator. The resulting solid residue was purified by column chromatography (SiO_2, hexanes / ethyl acetate = 2:1) to yield a solid. A mixed solvent of CH_2Cl_2-hexanes (20 mL / 300 mL) was used to make a slurry and the solid was collected by filtration and washed with hexanes to provide (3,5-dimethoxy-4-methylphenyl)-carbamic acid *tert*-butyl ester as a light yellow needle-like solid. Yield: 28.6 g (81%).

[0250] A solution of (3,5-dimethoxy-4-methylphenyl)-carbamic acid *tert*-butyl ester (28.6 g, 107 mmol) in carbon tetrachloride (450 mL) was mixed with NBS (19.05 g, 107.1 mmol) and AIBN (1.55 g, 9.37 mmol) and was stirred at 80°C under irradiation from a medium-pressure mercury lamp for 2 hours. The reaction was then quenched by adding water (150 mL) and extracted with CH_2Cl_2 (3 × 100 mL), and concentrated on a rotary evaporator to afford a solid residue. Further purification on column (SiO_2, hexanes / ethyl acetate = 2:1) yielded (2-bromo-3,5-dimethoxy-4-methylphenyl)-carbamic acid *tert*-butyl ester. Yield: 34.9 g (94%).

[0251] solution of (2-bromo-3,5-dimethoxy-4-methylphenyl)-carbamic acid *tert*-butyl ester (34.9 g, 101 mmol) in carbon tetrachloride (450 mL) was mixed with N-bromosuccinimide (21.5 g, 121 mmol) and AIBN (1.55 g, 9.37 mmol) and was stirred at 80°C under irradiation from a medium-pressure mercury lamp for 4 hours. The reaction was then quenched by adding water (150 mL) and extracted with CH_2Cl_2 (3 × 100 mL), and concentrated on a rotary evaporator to afford a solid residue. Further purification on a column (SiO_2, hexanes / ethyl acetate = 2:1) yielded (2-bromo-4-bromomethyl-3,5-dimethoxyphenyl)-carbamic acid *tert*-butyl ester. Yield: 39.0 g (91%).

[0252] A solution of (2-bromo-4-bromomethyl-3,5-dimethoxyphenyl)-carbamic acid *tert*-butyl ester (39.0 g, 91.8 mmol) in THF (600 mL) was mixed with morpholine (45.0 mL, 515 mmol) and stirred at room temperature for 7 hours. The reaction was diluted with water (300 mL), extracted with CH_2Cl_2 (3 × 200 mL), and concentrated on a rotary evaporator. The residue was further purified by column (SiO_2, dichloromethane / methanol = 20:1) to provide (2-bromo-3,5-dimethoxy-4-morpholin-4-ylmethylphenyl)-carbamic acid *tert*-butyl ester. Yield: 35 g (88%).

[0253] A solution of (2-bromo-3,5-dimethoxy-4-morpholin-4-ylmethylphenyl)-carbamic acid *tert*-butyl ester (3.0 g, 6.9 mmol) in THF (150 mL) was mixed with sodium hydride (0.333 g, 8.33 mmol) and stirred at room temperature for 1.5 hours. The resulting mixture was then cooled to -78°C and mixed with nBuLi (3.33 mL, 8.33 mmol). The reaction was stirred for 1.5 hours at -78°C before addition of tBuLi (8.16 mL, 13.9 mmol). After addition of tBuLi, the reaction was stirred at -78°C for 1 hour and carbon dioxide gas was then bubbled through for 8 hours, allowing the temperature to rise gradually to room temperature. The reaction was quenched by adding water (0.50 mL, 28 mmol) and concentrated on a rotary evaporator. The solid residue was made into a slurry in a minimal amount of methanol and the solid was filtered off. The filtrate was then concentrated on a rotary evaporator and the solid was made into a slurry again in methanol and filtered. After repeating three times, the filtrate was concentrated to yield impure 6-*tert*-butoxycarbonylamino-2,4-dimethoxy-3-morpholin-4-ylmethyl-benzoic acid. Crude yield: 1.80 g (40%).

[0254] A solution of crude 6-*tert*-butoxycarbonylamino-2,4-dimethoxy-3-morpholin-4-ylmethyl-benzoic acid (1.80 g, 4.54 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.31 g, 6.82 mmol), HOBt (1.23 g, 9.09 mmol), and triethylamine (3.3 mL, 24 mmol) in THF (50 mL) was stirred at room temperature for 1 hour. 50% (v/v) aqueous ammonia (20 mL) was then added. The resulting solution was stirred at room temperature for 14 hours, diluted with water (100 mL), extracted with CH_2Cl_2 (3 × 100 mL), and concentrated on a rotary evaporator. The residue was further purified by column chromatography (SiO_2, dichlorometane / methanol / ethyl acetate = 2:1:4) to provide (2-carbamoyl-3,5-dimethoxy-4-morpholin-4-ylmethyl-phenyl)-carbamic acid *tert*-butyl ester. Yield: 0.90 g (50%).

[0255] A solution of (2-carbamoyl-3,5-dimethoxy-4-morpholin-4-ylmethylphenyl)-carbamic acid *tert*-butyl ester (0.90

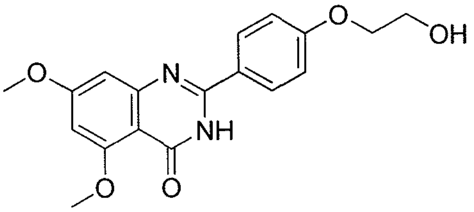
g, 2.7 mmol) in acetic acid (20 mL) and 12 N HCl aqueous (20 mL) was stirred at 50°C for 1 hour, and then concentrated to dryness on a rotary evaporator. The residue was mixed with saturated sodium bicarbonate aqueous (40 mL), extracted with CH_2Cl_2 (3 × 100 mL), and concentrated on a rotary evaporator. The residue was further purified on a column (SiO_2, dichloromethane / methanol / ethyl acetate = 3:2:3), to provide 6-amino-2,4-dimethoxy-3-morpholin-4-ylmethylbenzamide. Yield: 0.6 g (89%).

[0256] A solution of 6-amino-2,4-dimethoxy-3-morpholin-4-ylmethylbenzamide (0.50 g, 1.7 mmol), 4-(2-hydroxyethoxy)-3,5-dimethylbenzaldehyde (0.50 g, 2.5 mmol), sodium bisulfite (0.90 g, 5.1 mmol), and *p*-toluenesulfonic acid (0.80 g, 4.2 mmol) in dimethyl acetamide (15 mL) was stirred at 150°C for 14 hours. Extra solvent was evaporated on a rotary evaporator and the residue was diluted with saturated sodium bicarbonate aqueous solution (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The residue obtained upon concentration was subjected to column chromatography (SiO_2, hexanes / ethyl acetate / dichloromethane / methanol = 1:2:5:1) to afford 2-[4-(2-hydroxy-ethoxy)-3,5-dimethylphenyl]-5,7-dimethoxy-6-morpholin-4-ylmethyl-3H-quinazolin-4-one as a light yellow solid. Yield: 0.12 g (15%).

[0257] A solution of 2-[4-(2-hydroxy-ethoxy)-3,5-dimethylphenyl]-5,7-dimethoxy-6-morpholin-4-ylmethyl-3H-quinazolin-4-one (0.12 g, 0.26 mmol) in CH_2Cl_2 (10 mL) was mixed with 1 N HCl in ethyl ether (3 mL, 3 mmol) and was stirred at room temperature for 10 minutes to form a suspension. The solid was filtered, and washed with CH_2Cl_2 to afford the title compound as a light yellow solid. Yield: 32 mg (23%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (s, 2H), 7.08 (s, 1H), 4.00 (m, 4H), 3.96 (s, 3H), 3.87 (s, 3H), 3.80 (br s, 2H), 3.70 (br s, 4H), 2.67 (br s, 4H), 2.40 (s, 6H). MS (ES^+) *m/z:* 470.17 (M+1).

Example 20. Preparation of 2-[4-(2-hydroxy-ethoxy)-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one

[0258]

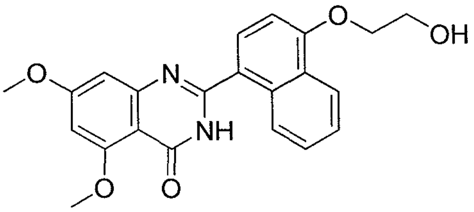


[0259] To a flask (250 mL) with a magnetic stirrer were added 4-hydroxybenzalde (10.0 g, 81.8 mmol), 2-chloroethanol (26.3 g, 327 mmol), potassium carbonate (22.6 g, 163 mmol), and ethanol (80 mL). The reaction mixture was stirred at 70°C for 16 hours. Potassium carbonate was filtered and ethanol was removed. The residue was diluted with ethyl acetate (200 mL) and washed with 5% sodium hydroxide (100 mL), water (100 mL), and brine (100 mL). The crude product was purified by column chromatography (silica gel, 230-400 mesh), using hexane / ethyl acetate (1:1) as eluent, to afford 4-(2-hydroxy-ethoxy)-benzaldehyde. Yield: 10.0 g (73%).

[0260] To a solution of 2-amino-4,6-dimethoxy-benzamide (0.400 g, 2.00 mmol) and 4-(2-hydroxy-ethoxy)-benzaldehyde (0.340 g, 2.00 mmol) in *N,N*-dimethylacetamide (8 mL) were added $NaHSO_3$ (0.390 g, 2.20 mmol) and *p*-TSA (38 mg, 0.20 mmol). The reaction mixture was stirred at 115-120°C for 5 hours and cooled to room temperature. The solvent was removed under reduced pressure. The residue was diluted with water (40 mL) and the solid was collected, mixed with methanol (50 mL), and stirred for 30 min. The solid was filtered and rinsed with ether (30 mL) to give the title compound as white solid. Yield: 0.42 g (61%). ^{1}H NMR (400 Hz, DMSO-d_6): δ 11.98 (s, 1H), 8.18 (d, 2H), 7.08 (d, 2H), 6.78 (s, 1H), 6.52 (s, 1H), 4.98 (s, 1H), 4.10 (t, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.74 (t, 2H). MS (ES^+) *m/z:* 343.13 (M+1).

Example 21. Preparation of 2-[4-(2-hydroxy-ethoxy)-naphthalen-1-yl]-5,7-dimethoxy-3*H*-quinazolin-4-one

[0261]

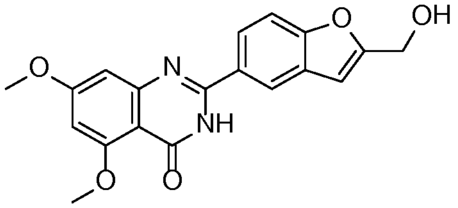


[0262] To a mixture of 4-hydroxy-naphthalene-1-carbaldehyde (1.0 g, 5.8 mmol) and potassium carbonate (2.40 g, 17.4 mmol) in *N,N*-dimethylformamide (3 mL) under nitrogen was added 2-chloroethanol (0.80 mL, 12 mmol). The reaction mixture was heated at reflux for 20 hours and the solvent was then removed under reduced pressure. The residue was diluted with ethyl acetate, washed with water, 0.2 N aqueous sodium hydroxide, brine, and dried over anhydrous sodium sulfate. The crude oil (1.03 g) was purified by column chromatography (silica gel 230-400 mesh; methylene chloride / EtOAc = 3/7), to give 4-(2-hydroxy-ethoxy)-naphthalene-1-carbaldehyde as a colorless oil. Yield: 0.6 g (48%).

[0263] To a solution of 2-amino-4,6-dimethoxy-benzamide (0.45 g, 2.3 mmol) in *N,N*-dimethylacetamide (25 mL) under nitrogen was added 4-(2-hydroxy-ethoxy)-naphthalene-1-carbaldehyde (0.50 g, 2.3 mmol) followed by sodium hydrogensulfite (0.26 g, 2.5 mmol) and *p*-toluenesulfonic acid (0.22 g, 1.1 mmol). The resulting mixture was heated at 130°C for 15 hours and the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate, washed with water, and dried over sodium sulfate. The crude orange solid (0.37 g) was purified by column chromatography (silica gel, 230-400 mesh; 3/7 methylene chloride /EtOAc then 9/1 methylene chloride / MeOH as eluent) and by triturating with methylene chloride and ether to afford the title compound as a light orange solid. Yield: 0.16 g (36%). ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD): δ 8.34 (d, 1H), 8.19 (d, 1H), 7.62 (d, 1H), 7.44-7.53 (m, 2H), 6.84 (d, 1H), 6.75 (s, 1H), 6.43 (s, 1H), 4.22-4.24 (m, 2H), 4.01-4.03 (m, 2H), 9.90 (s, 3H), 3.85 (s, 3H). MS (ES$^+$) *m/z:* 393.27 (M+1).

Example 22 (Reference Example). Preparation of 2-(2-hydroxymethyl-benzofuran-5-yl)-5,7-dimethoxy-3*H*-quinazolin-4-one

[0264]



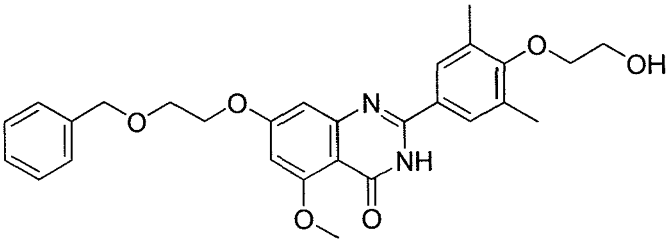
[0265] To a solution of 4-hydroxy-benzaldehyde (3.66 g, 30.0 mmol) in 50% (v/v) aqueous ammonium hydroxide (250 mL) was quickly added a solution of potassium iodide (24.9 g, 150 mmol) and iodine (7.62 g, 30.0 mmol) in water (60 mL). The dark colored solution was stirred at room temperature for 1 hour and the color changed to yellow. Stirring was continued at room temperature for 16 hours. The color changed to gray. Then, the reaction mixture was filtered through a celite pad. The filtrate was acidified with concentrated HCl to pH approximately 1 and extracted with ethyl acetate (1 × 300 mL). The organic phase was washed with water (150 mL) and brine (150 mL), dried over anhydrous Na_2SO_4, and concentrated to give 4-hydroxy-3-iodo-benzaldehyde as an off-white solid (1:1 mixture of starting material and product). Yield: 5.34 g (crude).

[0266] To a degassed solution of 4-hydroxy-3-iodo-benzaldehyde (5.34 g, 15.0 mmol) in anhydrous DMF (100 mL) were added bis(triphenylphosphine)palladium(II) dichloride (0.53 g, 0.75 mmol), copper (I) iodide (0.14 g, 0.75 mmol), 1,1,3,3-tetramethyl guanidine (8.64 g, 75.0 mmol), and propargyl alcohol (1.18 g, 21.0 mmol). The reaction mixture was stirred at room temperature for 24 hours under nitrogen and then concentrated to dryness under reduced pressure. The residue was diluted with 2 N aqueous HCl (150 mL) and extracted with ethyl acetate (1 × 200 mL). Organic phase was washed with water (2 × 100 mL), brine (100 mL), and dried over anhydrous Na_2SO_4. Solvent was evaporated and crude compound was purified using the Simpliflash system (30% ethyl acetate in hexanes as eluent) to give 2-hydroxymethyl-benzofuran-5-carbaldehyde as a pale yellow solid. Yield: 1.36 g (26% for two steps).

[0267] To a solution of 2-hydroxymethyl-benzofuran-5-carbaldehyde (0.450 g, 2.55 mmol) and 2-amino-4,6-dimethoxy-benzamide (0.500 g, 2.55 mmol) in *N,N*-dimethylacetamide (5 mL) were added sodium hydrogen sulfite (58.5 wt %; 0.510 g, 2.80 mmol) and p-toluenesulfonic acid (50 mg, 0.25 mmol). The reaction mixture was stirred at 120°C for 6 hours under nitrogen and cooled to room temperature. The separated solid was filtered, washed with ether (30 mL), water (30 mL), and ethyl acetate (20 mL), and then dried under vacuum to give the title compound as a yellow solid. Yield: 0.572 g (64%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (br s, 1H), 8.44 (d, *J* = 2.0 Hz, 1H), 8.10 (dd, *J* = 8.8 and 1.6 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 6.89 (s, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 4.61 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H). MS (ES$^+$) *m/z:* 353.20 (M+1).

Example 23. Preparation of 7-(2-benzyloxy-ethoxy)-2-[4-(2-hydroxy-ethoxy)-3,5-dimethyl-phenyl]-5-methoxy-3*H*-quinazolin-4-one

[0268]



[0269] To a solution of 4-hydroxy-3,5-dimethyl-benzaldehyde (1.00 g, 6.70 mmol) in DMF (20 mL) was added cesium carbonate (8.70 g, 26.6 mmol) followed by (2-bromo-ethoxy)-*tert*-butyl-dimethyl-silane (2.9 mL, 13 mmol). The reaction mixture was stirred at room temperature for 16 hours. Water was added and the product was extracted with ethyl acetate. The solvent was evaporated *in vacuo* to obtain 4-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethoxy]-3,5-dimethyl-benzaldehyde as a colorless oil. It was contaminated with (2-bromo-ethoxy)-*tert*-butyl-dimethyl-silane, but was used in the next step without further purification. Yield: 2.5 g (71%).

[0270] To a stirred solution of 2-amino-4,6-difluoro-benzamide (0.50 g, 2.9 mmol) and 4-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethoxy]-3,5-dimethyl-benzaldehyde (1.3 g, 2.9 mmol) in *N,N*-dimethylacetamide (10 mL) were added sodium hydrogen sulfite (0.60 g, 3.5 mmol) and *p*-toluenesulfonic acid (0.1 g, 0.6 mmol) and the reaction mixture was stirred at 120°C for 16 hours. The solvent was evaporated *in vacuo,* water was added, and the precipitated solid was filtered off to obtain 2-{4-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethoxy]-3,5-dimethyl-phenyl}-5,7-difluoro-3*H*-quinazolin-4-one as a yellow solid, which was used in the next step without further purification. Yield: 0.490 g (36%).

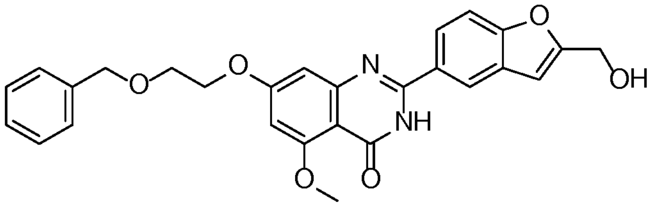
[0271] To a suspension of 2-{4-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethoxy]-3,5-dimethyl-phenyl}-5,7-difluoro-3*H*-quinazolin-4-one (0.490 g, 1.06 mmol) in DMF (3 mL) was added sodium methoxide in methanol (2.3 mL, 11 mmol) and the reaction mixture was stirred at room temperature for 16 hours. Water was added, the mixture was acidified with acetic acid, to pH approximately 4-5, and the precipitated solid was filtered off to obtain 7-fluoro-2-[4-(2-hydroxy-ethoxy)-3,5-dimethyl-phenyl]-5-methoxy-3*H*-quinazolin-4-one as a white solid. Yield: 0.21 g (55%).

[0272] To a solution of 7-fluoro-2-[4-(2-hydroxy-ethoxy)-3,5-dimethyl-phenyl]-5-methoxy-3*H*-quinazolin-4-one (0.21 g, 0.59 mmol) in THF (12 mL) was added imidazole (80 mg, 1.2 mmol), followed by *tert*-butyldiphenylsilyl chloride (0.20 mL, 0.65 mmol). The reaction mixture was stirred at room temperature for 16 hours. Saturated NH_4Cl aqueous solution was added and the product was extracted with ethyl acetate. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (silica gel; 230-400 mesh; eluting with 5-10% ethyl acetate / CH_2Cl_2) to afford 2-{4-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethoxy]-3,5-dimethyl-phenyl}-7-fluoro-5-methoxy-3*H*-quinazolin-4-one. Yield: 0.36 g (quantitative).

[0273] To a solution of 2-benzyloxy-ethanol (3 mL) in dimethyl sulfoxide (3 mL) was added sodium hydride (0.24 g, 6.0 mmol) in portions and the reaction mixture was stirred at room temperature for 45 minutes. To this mixture was added 2-{4-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethoxy]-3,5-dimethyl-phenyl}-7-fluoro-5-methoxy-3*H*-quinazolin-4-one (0.36 g, 0.60 mmol) and the reaction mixture was heated at 70°C for 16 hours. Water was added, and the mixture was acidified with acetic acid, to pH approximately 4-5, and the precipitated solid was filtered off to obtain a crude product, which was purified by preparative HPLC to obtain the title compound as a white solid. Yield: 0.12 g (42%). ^1H NMR (400 MHz, DMSO-d_6): δ 11.83 (s, 1H), 7.89 (s, 2H), 7.37 (m, 5H), 6.75 (s, 1H), 6.53 (s, 1H), 4.91 (s, 1H), 4.58 (s, 2H), 4.30 (s, 2H), 3.84-3.73 (m, 9H), 2.31 (s, 6H). MS (ES^+) *m/z:* 491.55 (M+1).

Example 24 (Reference Example). Preparation of 7-(2-benzyloxy-ethoxy)-2-(2-hydroxymethyl-benzofuran-5-yl)-5-methoxy-3*H*-quinazolin-4-one

[0274]



[0275] To a stirred solution of 2-hydroxymethyl-benzofuran-5-carbaldehyde (2.00 g, 11.4 mmol) in anhydrous CH_2Cl_2 (25 mL) were added N,N-diisopropylethyl amine (5.17 g, 40.0 mmol) and chloromethyl methyl ether (2.76 g, 34.3 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 hours under nitrogen. Phosphate buffer (pH 7, 100 mL) was added and the mixture was extracted with dichloromethane (100 mL). The organic phase was separated, washed with brine, and dried over anhydrous Na_2SO_4. Removal of solvent gave 2-methoxymethoxymethyl-benzofuran-5-carbaldehyde as an orange oil. Yield 2.41 g (96%).

[0276] To a solution of 2-methoxymethoxymethyl-benzofuran-5-carbaldehyde (2.31 g, 10.5 mmol) and 2-amino-4,6-difluoro-benzamide (1.20 g, 7.00 mmol) in N,N-dimethyl acetamide (15 mL) were added sodium hydrogen sulfite (58.5 wt%; 1.54 g, 8.40 mmol) and p-toluenesulfonic acid monohydrate (0.26 g, 1.40 mmol). The reaction mixture was stirred at 120°C for 4 hours under nitrogen, then cooled to room temperature. Solvent was evaporated under reduced pressure and water (100 mL) was added. The separated solid was filtered, washed with water (50 mL), and dried under vacuum, to give 5,7-difluoro-2-(2-methoxymethoxymethyl-benzofuran-5-yl)-3*H*-quinazolin-4-one as a white solid. Yield 0.96 g (37%).

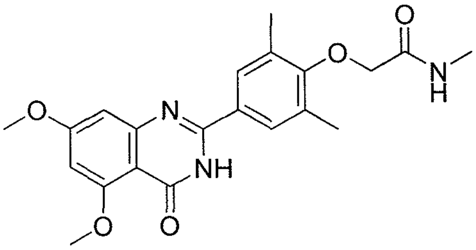
[0277] To a suspension of 5,7-difluoro-2-(2-methoxymethoxymethyl-benzofuran-5-yl)-3*H*-quinazolin-4-one (0.95 g, 2.56 mmol) in anhydrous DMF (5 mL) was added a solution of sodium methoxide (25 wt%) in methanol at 0°C under nitrogen. Then, the reaction mixture was stirred at 0°C for 6 hours. Water (20 mL) was added, the mixture was acidified to pH approximately 6 with glacial acetic acid. The separated solid was filtered, washed with water (20 mL), and dried under vacuum to give 7-fluoro-5-methoxy-2-(2-methoxymethoxymethyl-benzofuran-5-yl)-3*H*-quinazolin-4-one as a white solid. Yield 0.94 g (95%).

[0278] Sodium hydride (60% suspension in mineral oil; 0.48 g, 12.0 mmol) was taken in anhydrous DMF (5 mL). 2-Benzyloxyethanol (3.65 g, 24.0 mmol) was added dropwise at room temperature under nitrogen. After the addition, the reaction mixture was stirred at room temperature for 30 minutes. Then, 7-fluoro-5-methoxy-2-(2-methoxymethoxymethyl-benzofuran-5-yl)-3*H*-quinazolin-4-one (0.46 g, 1.2 mmol) was added and the reaction mixture was stirred at 80°C for 16 hours. The reaction mixture was then cooled to room temperature. Water (50 mL) was added, the mixture was acidified to pH approximately 6 with glacial acetic acid and extracted with CH_2Cl_2 (2 × 100 mL). The organic phase was washed with brine (100 mL) and then dried over anhydrous Na_2SO_4. Removal of solvent, followed by purification, by the Simpliflash system (0-2% methanol in CH_2Cl_2 as eluent) gave 7-(2-benzyloxy-ethoxy)-5-methoxy-2-(2-methoxymethoxymethyl-benzofuran-5-yl)-3H-quinazolin-4-one as a white solid. Yield 0.28 g (45%).

[0279] To a solution of 7-(2-benzyloxy-ethoxy)-5-methoxy-2-(2-methoxymethoxymethyl-benzo-furan-5-yl)-3*H*-quinazolin-4-one (0.27 g, 0.53 mmol) in 50% aqueous acetic acid (15 mL), conc. H_2SO_4 (0.3 mL) was added. The reaction mixture was stirred at 75°C for 2 hours, then cooled to room temperature. Water (50 mL) was added, and the mixture was neutralized to pH approximatley 7 with 4 N aqueous NaOH solution. The separated solid was filtered, washed with water (20 mL), and dried under vacuum. Crude compound was purified by column chromatography (silica gel 230-400 mesh; 2:20:78 methanol / ethyl acetate / CH_2Cl_2 as eluent) to give the title compound as a white solid. Yield 0.13 g (52%). ^1H NMR (400 MHz, DMSO-d_6): δ 12.03 (bs, 1H), 8.43 (s, 1H), 8.09 (dd, J = 8.58 and 1.95 Hz, 1H), 7.65 (d, J = 8.58 Hz, 1H), 7.37-7.29 (m, 5H), 6.88 (s, 1H), 6.77 (d, J = 1.95 Hz, 1H), 6.55 (d, J = 1.56 Hz, 1H), 5.51 (s, 1H), 4.60 (t, J = 4.68 Hz, 4H), 4.31 (s, 2H), 3.90-3.83 (m, 5H). MS (ES+) *m/z* 473.48 (100%).

Example 25. Preparation of 2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-dimethyl-phenoxy]-*N*-methyl-acetamide

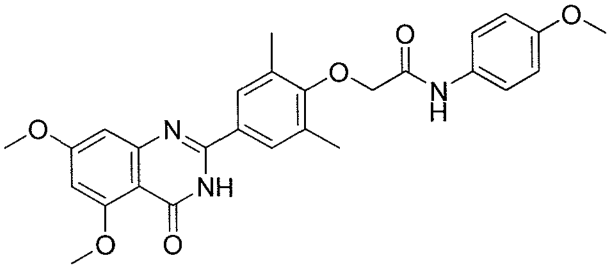
[0280]



[0281] To a solution of [4-(5,7-dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-dimethyl-phenoxy]-acetic acid (0.20 g, 0.52 mmol) in anhydrous DMF (8 mL) were added EDCI (0.12 g, 0.62 mmol) and HOBt (0.084 g, 0.62 mmol). Then, a solution of N-methyl amine (2.0 M solution in THF, 1.3 mL, 2.60 mmol) was added and the reaction mixture was stirred at room temperature for 16 hours under nitrogen. Solvent was evaporated under reduced pressure, water (20 mL) was added, and the separated solid was filtered, washed with water (30 mL), ether (20 mL) and dried under vacuum to give the title compound as a white solid. Yield: 0.13 g (63%). ^1H NMR (400 MHz, DMSO-d_6): δ 11.86 (br s, 1H), 8.19 (br s, 1H), 7.91 (s, 2H), 6.74 (d, J = 1.95 Hz, 1H), 6.52 (d, *J* = 1.95 Hz, 1H), 4.26 (s, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 2.72 (d, *J* = 4.30 Hz, 3H), 2.30 (s, 6H). MS (ES) *m/z:* 398.53 (M+1) (100%).

Example 26. Preparation of 2-[4-(5,7-Dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-dimethyl-phenoxy]-N-(4-methoxy-phenyl)-acetamide

[0282]



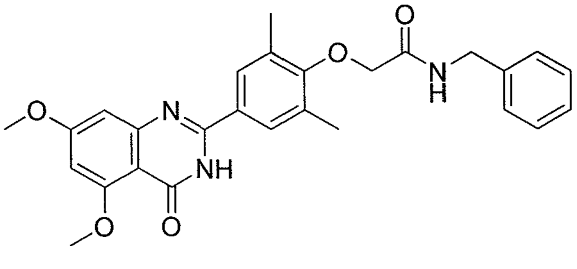
[0283] To a solution of 4-hydroxy-3,5-dimethyl-benzaldehyde (9.00 g, 60.0 mmol) in ethanol (300 mL) were added potassium carbonate (24.9 g, 180 mmol) and methyl bromoacetate (11.4 mL, 120 mmol). The reaction mixture was stirred at 95°C under nitrogen for 16 hours. The mixture was concentrated to dryness under reduced pressure. Water (150 mL) and 1 N NaOH solution (90 mL) were added to the residue. The mixture was stirred at room temperature for 30 minutes, then washed with ether. Concentrated HCl was added slowly to the aqueous solution until a large amount of white precipitate formed. The solid was filtered, washed with water, and air-dried, to give (4-formyl-2,6-dimethyl-phenoxy)-acetic acid as a white solid. Yield: 11.1 g (89%).

[0284] To a solution of (4-formyl-2,6-dimethyl-phenoxy)-acetic acid (3.12 g, 15.0 mmol) and 2-amino-4,6-dimethoxy-benzamide (2.94 g, 15.0 mmol) in *N,N*-dimethylacetamide (50 mL) were added sodium hydrogen sulfite (58.5 wt%, 3.02 g, 16.5 mmol) and *p*-toluenesulfonic acid monohydrate (0.285 g, 1.50 mmol). The reaction mixture was stirred at 120°C for 17 hours under nitrogen and cooled to room temperature. The precipitate was filtered, washed with water, then methanol, and air-dried to give 1.29 g [4-(5,7-dimethoxy-4-oxo-3, 4-dihydro-quinazolin-2-yl)-2,6-dimethyl-phenoxy]-acetic acid. The filtrate was concentrated to dryness and water was added. The suspension was stirred for 30 minutes and filtered. The solid was washed with water, then methanol. After air drying, 3.78 g more [4-(5,7-dimethoxy-4-oxo-3, 4-dihydro-quinazolin-2-yl)-2,6-dimethyl-phenoxy]-acetic acid was obtained. Yield: 5.07 g (88%).

[0285] To a mixture of [4-(5,7-dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-dimethyl-phenoxy]-acetic acid (0.400 g, 1.04 mmol), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (EDCI; 0.240 g, 1.24 mmol), 1-hydroxy-benzotriazole hydrate (HOBt; 0.17 g, 1.24 mmol) in DMF (10 mL) was added 4-methylmorpholine (0.20 mL, 1.8 mmol). After 10 minutes, p-anisidine (0.26 g, 2.08 mmol) was added. The mixture was stirred at room temperature under nitrogen for 2.5 days. The solvent was removed under reduced pressure. Water was added, stirred for 30 minutes. The solid was filtered, washed with water, and dried in air. The crude product was purified by column chromatography (silica gel, 230-400 mesh; 5% MeOH in CH_2Cl_2 as eluent). The product fractions were combined, concentrated to dryness. The solid was dissolved in small amount of dichloromethane, precipitate out by adding ether. The precipitate was filtered, washed with ether, dried under vacuum to afford the title compound as a white solid. Yield: 0.26 g (51%). ^1H NMR (400 MHz, $CDCl_3$): δ 10.30 (br s, 1H), 8.52 (s, 1H), 7.83 (s, 2H), 7.58 (dd, J = 6.8 and 2.0 Hz, 2H), 6.93 (dd, J = 6.8 and 2.0 Hz, 2H), 6.84 (d, J = 2.4 Hz, 1H), 6.48 (d, J = 2.0 Hz, 1H), 4.44 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H), 3.83 (s, 3H), 2.42 (s, 3H). MS (ES^+) *m/z*: 490.55 (M+1).

Example 27. Preparation of N-benzyl-2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy]acetamide

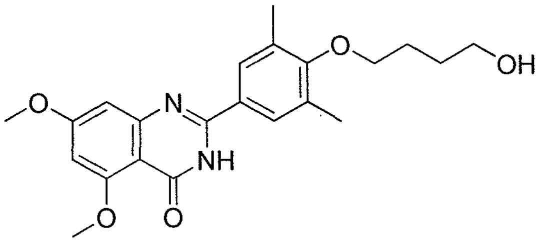
[0286]



[0287] To a mixture of [4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy]acetic acid (0.25 g, 0.65 mmol), 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride (EDCI; 0.137 g, 0.715 mmol), 1-hydroxybenzotriazole hydrate (HOBT; 0.110 g, 0.715 mmol) in DMF (3 mL) was added 4-methylmorpholine (0.08 mL, 0.715 mmol) at room temperature. After 10 minutes, benzylamine (0.142 mL, 1.30 mmol) was added. The mixture was stirred at room temperature under nitrogen for 15 hours. The solvent was removed under reduced pressure. The crude compound was purified by column chromatography (silica gel 230-400 mesh; 3% methanol in dichloromethane as eluent), followed by triturating with an ether-hexane mixture to afford the title compound as a white solid. Yield: 60 mg (39%). ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 11.86 (s, 1H), 8.79 (t, *J* = 6.2 Hz, 1H), 7.89 (s, 2H), 7.34 - 7.21 (m, 5H), 6.72 (d, *J* = 2.0 Hz, 1H), 6.50 (d, *J* = 2.0 Hz , 1H), 4.38 (d, *J* = 6.0 Hz, 2H), 4.33 (s, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 2.30 (s, 6H). MS (ES$^+$) *m*/*z:* 474.49 (M+1).

Example 28. Preparation of 2-[4-(4-hydroxy-butoxy)-3,5-dimethyl-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one

[0288]

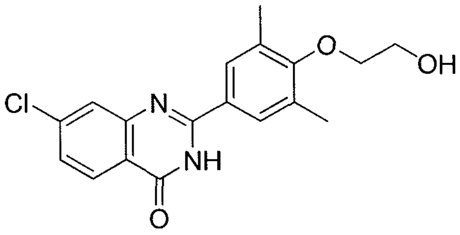


[0289] To a solution of 4-hydroxy-3,5-dimethyl benzaldehyde (5.00 g, 33.3 mmol) in DMF (30 mL) were added 4-bromo butan-1-ol (6.11 g, 39.9 mmol) and Cs_2CO_3 (16.24 g, 50.0 mmol). The reaction mixture was stirred at room temperature for 48 hours. Water was added and the products were extracted with ethyl acetate (2 × 200 mL). The combined organic phase was washed with water (100 mL), brine (100 mL), and dried over anhydrous Na_2SO_4. Solvent was removed and the crude compound was purified using the Simpliflash system (40% ethyl acetate in hexane as eluent) to give 4-(4-hydroxybutoxy)-3,5-dimethyl benzaldehyde as a colorless liquid. Yield: 0.66 g (7%).

[0290] To a solution of 2-amino-4,6-dimethoxy-benzamide (0.50 g, 2.53 mmol) and 4-(4-hydroxybutoxy)-3,5-dimethyl benzaldehyde (0.66 g, 2.53 mmol) in N,N-dimethyl acetamide (10 mL), $NaHSO_3$ (0.50 g, 2.79 mmol) and *p*-TSA (96 mg, 0.50 mmol) were added and the reaction mixture was heated at 115°C for 16 hours, then cooled to room temperature. Solvent was removed under reduced pressure. Water (100 mL) was added and the mixture was stirred for 1 hour. The solid separated was filtered and dried. The solid was again washed with diethyl ether to give the title compound as a white solid. Yield: 1.69 g (82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H), 7.66 (s, 2H), 6.83 (d, *J* = 2.4 Hz, 1H), 6.46 (d, *J* = 2.0 Hz, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 3.85 (t, *J* = 6.0 Hz, 2H), 3.78 (m, 2H), 2.36 (s, 6H), 1.94 (m, 2H), 1.85 (m, 2H). MS (ES) *m*/*z:* 399.12 (M+1) (100%).

Example 29. Preparation of 7-chloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one

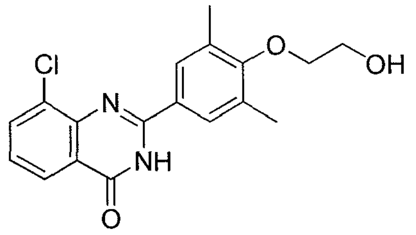
[0291]



[0292] Following the method described in Example 33, the title compound was made starting from 2-amino-4-chlorobenzoic acid and isolated as a white solid. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 12.46 (s, 1H), 8.12 (d, *J* = 8.49 Hz, 1H), 7.90 (s, 2H), 7.77 (d, *J* = 2.00 Hz, 1H), 7.52 (dd, *J* = 8.49, 2.00 Hz, 1H), 4.90 (t, *J* = 5.51 Hz, 1H), 3.86 (t, *J* = 4.88 Hz, 2H), 3.76-3.69 (m, 2H), 2.32 (s, 6H). MS (APCI) *m*/*z* 345 [$C_{18}H_{17}ClN_2O_3$+H]$^+$.

Example 30. Preparation of 8-chloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one

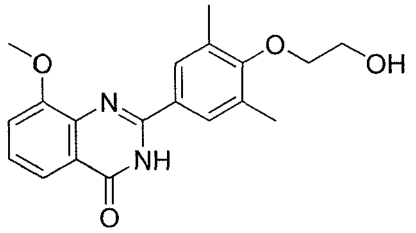
[0293]



[0294] Following the procedure described in Example 33, the title compound was made starting from 2-amino-3-chlorobenzoic acid and isolated as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6: δ 12.55 (s, 1H), 8.09 (dd, *J* = 7.88, 1.37 Hz, 1H), 8.00-7.93 (m, 3H), 7.46 (t, *J* = 7.88 Hz, 1H), 4.91 (t, *J* = 5.54 Hz, 1H), 3.86 (t, *J* = 4.90 Hz, 2H), 3.77-3.69 (m, 2H), 2.33 (s, 6H). MS (APCI) *m/z* 345 $[C_{18}H_{17}ClN_2O_3+H]^+$.

Example 31. Preparation of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-8-methoxyquinazolin-4(3H)-one

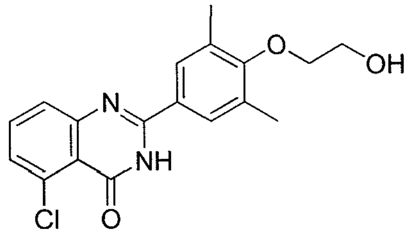
[0295]



[0296] Following the procedure described in Example 33, the title compound was made starting from 2-amino-3-methoxybenzoic acid and isolated as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.34 (s, 1H), 7.87 (s, 2H), 7.69 (dd, *J* = 7.63, 1.59 Hz, 1H), 7.45-7.34 (m, 2H), 4.90 (t, *J* = 5.53 Hz, 1H), 3.94 (s, 3H), 3.85 (t, *J* = 4.92 Hz, 2H), 3.77-3.69 (m, 2H), 2.33 (s, 6H). MS (APCI) *m/z* 341 $[C_{19}H_{20}N_2O_4+H]^+$.

Example 32. Preparation of 5-chloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one

[0297]



[0298] A mixture of 2-amino-6-chlorobenzoic acid (5.00 g, 29.1 mmol) in acetonitrile (50.0 mL) was stirred at room temperature under nitrogen. Pyridine (4.72 mL, 58.3 mmol) was added, followed by drop-wise addition of triphosgene (2.85 g, 9.60 mmol) in CH_2Cl_2 (20.0 mL). After the addition, the mixture was heated at 55°C for 2 hours, then cooled to 25°C and stirred overnight. Water (100 mL) was added to quench, the mixture was filtered, and washed with cold CH_2Cl_2, to provide 5-chloro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (3.54 g, 62%) as a white solid.

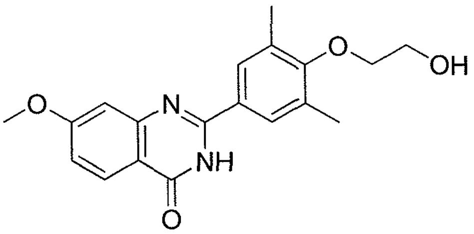
[0299] A mixture of 5-chloro-1H-benzo[*d*][1,3]oxazine-2,4-dione (3.50 g, 17.7 mmol) and 2 M NH_3 in EtOH (11.5 mL, 23.0 mmol) and EtOH (10.0 mL) was stirred at room temperature for 2 hours. The volatiles were removed under reduced pressure, the residue was triturated with water (50 mL), and the solid was filtered, to provide 2-amino-6-chlorobenzamide (1.60 g, 49%) as a tan solid.

[0300] A mixture of 2-amino-6-chlorobenzamide (0.490 g, 3.00 mmol), 4-(2-(tert-butyldimethylsilyloxy)ethoxy)-3,5-dimethylbenzaldehyde (0.925 g, 3.00 mmol), $NaHSO_3$ (94%, 0.468 g, 4.50 mmol), and *p*-TsOH•H_2O (0.171 g, 0.900 mmol) in DMA (10.0 mL) was heated at 140°C for 16 hours. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was diluted with EtOAc (50 mL), washed with water (50 mL), then brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure, to provide 2-(4-(2-(*tert*-butyldimethylsilyloxy)ethoxy)-3,5-dimethylphenyl)-5-chloroquinazolin-4(3*H*)-one as an off-white solid. The crude material was used directly in the next step without characterization.

[0301] Following the method described for desilylation using TBAF in Example 33 below, the title compound was made from 2-(4-(2-(*tert*-butyldimethylsilyloxy)ethoxy)-3,5-dimethylphenyl)-5-chloroquinazolin-4(3*H*)-one in 21% yield and was isolated as a white solid. ^1H NMR (300 MHz, DMSO-d_6): δ 12.32 (s, 1H), 7.90 (s, 2H), 7.82-7.55 (m, 2H), 7.48 (dd, *J* = 7.54, 1.35 Hz, 1H), 4.90 (t, *J* = 5.51 Hz, 1H), 3.86 (t, *J* = 4.90 Hz, 2H), 3.77-3.68 (m, 2H), 2.32 (s, 6H). MS (APCI) m/z 345 $[C_{18}H_{17}ClN_2O_3+H]^+$.

Example 33. Preparation of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-7-methoxyquinazolin-4(3H)-one

[0302]



[0303] A mixture of 2-nitro-4-methoxybenzoic acid (1.00 g, 5.10 mmol) in methanol (10.0 mL) was stirred at room temperature under nitrogen. Palladium on carbon (10% wt, 50% wet, 0.559 g, 0.255 mmol) was added. The roundbottomed flask was capped with a new septa and degassed under vacuum. The flask was charged with hydrogen and degassed again. This was repeated twice and a hydrogen-filled balloon was attached to the flask. The mixture was stirred at room temperature for 4 hours. Nitrogen was then bubbled through the mixture to displace any excess hydrogen. The mixture was filtered through celite 521 and the filtrate was concentrated under reduced pressure to provide 2-amino-4-methoxybenzoic acid (0.890 g, >99%) as an off-white solid. The crude material was used directly in the next step without characterization.

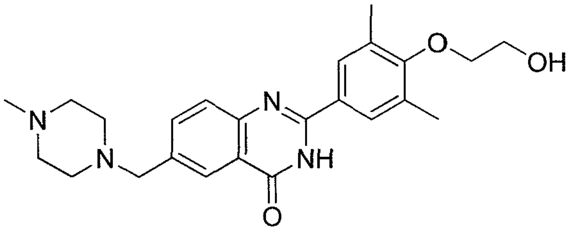
[0304] A mixture of 2-amino-4-methoxybenzoic acid (0.490 g, 3.00 mmol), EDCI (1.12 g, 5.83 mmol), HOBt (0.788 g, 5.83 mmol), *N*-methylmorpholine (0.590 g, 5.83 mmol) and 14.8 N NH_4OH (0.781 mL, 10.6 mmol) in THF was stirred at room temperature for 16 hours. The solvent was removed under reduced pressure, then the residue was diluted with EtOAc (100 mL), washed with water (2 × 100 mL), then brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure to provide 2-amino-4-methoxybenzamide as a tan solid.

[0305] A mixture of 2-amino-4-methoxybenzamide (0.490 g, 3.00 mmol), 4-(2-(tert-butyldimethylsilyloxy)ethoxy)-3,5-dimethylbenzaldehyde (0.925 g, 3.00 mmol), $NaHSO_3$ (94%, 0.468 g, 4.50 mmol), and *p*-TsOH•H_2O (0.171 g, 0.900 mmol) in benzene (10.0 mL) was heated at 80°C for 36 hours. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was diluted with EtOAc (50 mL), washed with water (50 mL) then brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure to provide 2-(4-(2-(*tert*-butyldimethylsilyloxy)ethoxy)-3,5-dimethylphenyl)-7-methoxyquinazolin-4(3*H*)-one as a pink solid. The crude material was used directly in the next step without characterization.

[0306] A mixture of 2-(4-(2-(*tert*-butyldimethylsilyloxy)ethoxy)-3,5-dimethylphenyl)-7-methoxyquinazolin-4(3*H*)-one (1.09 g, 2.30 mmol) in 1 M TBAF (11.6 mL, 11.6 mmol) was stirred at room temperature for 3 hours. The mixture was diluted with water (100 mL) and extracted with EtOAc (2 × 100 mL). The organic layers were combined, washed with saturated aqueous NH_4Cl (2 × 75 mL), then brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The residue was purified over silica gel (12 g, EtOAc/hexanes), triturated in ether, and the product was freeze-dried from MeCN/H_2O to yield the title compound (0.0960 g, 12%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6): δ 12.18 (s, 1H), 8.02 (d, *J* = 8.79 Hz, 1H), 7.91 (s, 2H), 7.16 (d, *J* = 2.46 Hz, 1H), 7.07 (dd, *J* = 8.79, 2.46 Hz, 1H), 4.90 (t, *J* = 5.53 Hz, 1H), 3.91 (s, 3H), 3.89-3.82 (m, 2H), 3.77-3.67 (m, 2H), 2.32 (s, 6H), 2.22 (d, *J* = 6.92 Hz, 1H). MS (APCI) *m/z* 341 $[C_{19}H_{20}N_2O_4+H]^+$.

Example 34. Preparation of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-((4-methylpiperazin-1-yl)methyl)quinazolin-4(3H)-one

[0307]



[0308] To a solution of 4-(2-(tert-butyldimethylsilyloxy)ethoxy)-3,5-dimethylbenzaldehyde (7.5 g, 24.4 mmol) in DMA (50 mL) was added 2-amino-5-bromobenzamide (5.2 g, 24.4 mmol), $NaHSO_3$ (3.9 g, 36.5 mmol) and p-TsOH (0.46 g, 2.4 mmol), and the reaction was heated at 160°C. After 1 hour, the resulting mixture was cooled to room temperature, diluted with water, and filtered to afford 6-bromo-2-(4-(2-(tert-butyldimethylsilyloxy)ethoxy)-3,5-dimethylphenyl) quinazolin-4(3H)-one (6.7 g, 55%) as a white solid (6.7 g, 55%).

[0309] A mixture of 6-bromo-2-(4-(2-(*tert*-butyldimethylsilyloxy)ethoxy)-3,5-dimethylphenyl) quinazolin-4(3*H*)-one (5.0 g, 9.9 mmol), vinyltributyltin (4.3 mL, 14.9 mmol) and $PdCl_2(PPh_3)_2$ (0.70 g, 1.0 mmol) in CH_3CN (150 mL) was stirred at reflux overnight. Then, additional $PdCl_2(PPh_3)_2$ (0.10 g, 0.14 mmol) and vinyltributyltin (2.0 mL, 6.8 mmol) were added and the reaction continued to reflux overnight. The resulting mixture was cooled to room temperature, filtered through celite, and the filtrate concentrated. The residue was purified by flash chromatography (silica, eluting with 98:2 CH_2Cl_2/MeOH) to afford 2-(4-(2-(*tert*-butyldimethylsilyloxy)ethoxy)-3,5-dimethylphenyl)-6-vinylquinazolin-4(3*H*)-one (2.0 g, 45%).

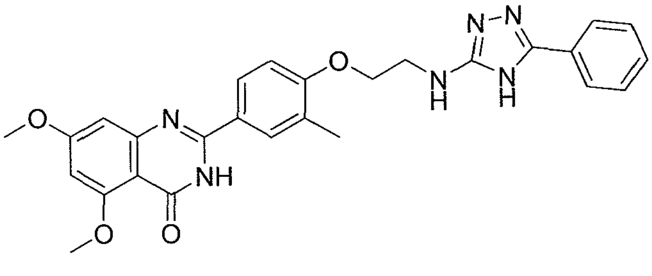
[0310] To a solution of 2-(4-(2-(*tert*-butyldimethylsilyloxy)ethoxy)-3,5-dimethylphenyl)-6-vinylquinazolin-4(3*H*)-one (0.63 g, 1.4 mmol) in THF (50 mL) and H_2O (5 mL) was added $NaIO_4$ (0.90 g, 4.2 mmol) and OsO_4 (0.11 mL, 0.014 mmol), and the reaction was stirred overnight at room temperature. Then, the mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (silica gel, eluting with 98:2 to 95:5 CH_2Cl_2/MeOH) to afford 2-(4-(2-(*tert*-butyldimethylsilyloxy)ethoxy)-3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carbaldehyde (0.52 g, 82%).

[0311] A solution of 2-(4-(2-(*tert*-butyldimethylsilyloxy)ethoxy)-3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carbaldehyde (0.11 g, 0.24 mmol) in DCE/CH_2Cl_2 (1:1, 15 mL) was treated with 1-methylpiperazine (0.05 mL, 0.48 mmol) and $NaBH(OAc)_3$ (0.103 g, 0.48 mmol) and the reaction mixture was stirred at room temperature overnight. Then, the mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (silica gel, eluting with 60% of 92:7:1 $CHCl_3$/MeOH/concentrated NH_4OH in CH_2Cl_2) to afford 2-(4-(2-(*tert*-butyldimethylsilyloxy)ethoxy)-3,5-dimethylphenyl)-6-((4-methylpiperazin-1-yl)methyl)quinazolin-4(3*H*)-one (0.14 g, 98%).

[0312] A solution of 2-(4-(2-(*tert*-butyldimethylsilyloxy)ethoxy)-3,5-dimethylphenyl)-6-((4-methylpiperazin-1-yl)methyl)quinazolin-4(3*H*)-one (0.087 g, 0.16 mmol) in a 1 M TBAF/THF solution (1.3 mL, 1.3 mmol) was stirred for 2 hours at room temperature. Then, the resulting mixture was concentrated *in vacuo* and purified by flash chromatography (silica gel, eluting with 70% of 92:7:1 $CHCl_3$/MeOH/concentrated NH_4OH in CH_2Cl_2) to afford the title compound (0.070 g, 100%): ^1H NMR (300 MHz, DMSO-d_6): δ 12.31 (s, 1H), 8.02 (s, 1H), 7.89 (s, 2H), 7.56-7.79 (m, 2H), 4.92 (t, J = 5.3 Hz, 1H), 3.77-3.93 (m, 2H), 3.64-3.75 (m, 2H), 3.58 (s, 2H), 2.21-2.45 (m, 14H), 2.15 (s, 3H). APCI MS m/z 423 $[M+H]^+$.

Example 35. Preparation of 5,7-Dimethoxy-2-{3-methyl-4-[2-(5-phenyl-4H-[1,2,4]triazol-3-ylamino)-ethoxy]-phenyl}-3*H*-quinazolin-4-one

[0313]

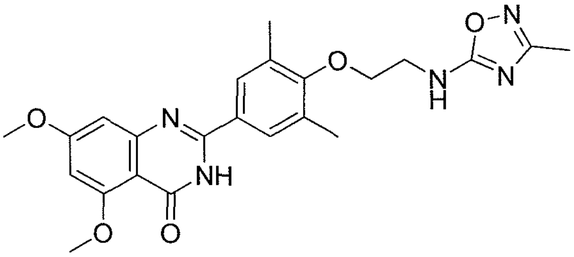


[0314] To a solution of 2-[4-(2-amino-ethoxy)-3,5-dimethyl-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one (0.37 g, 1.00 mmol) in anhydrous dichloroethane (20 mL) was added benzoyl isothiocyanate (0.18 g 1.10 mmol). The reaction mixture was stirred at room temperature for 3 hours. The solvent was removed and ether (30 mL) was added. The mixture was stirred for 30 minutes and the solid was filtered and dried to give 1-benzoyl-3-{2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-phenoxy]-ethyl}-thiourea as a white solid. Yield: 0.53 g (99%).

[0315] To a solution of 1-benzoyl-3-{2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-phenoxy]-ethyl}-thiourea (0.42 g, 0.785 mmol) in chloroform (20 mL) was added hydrazine hydrate (1.30 mL, 26.5 mmol). The reaction mixture was stirred at reflux for 16 hours. After the solvent was removed, the residue was purified by preparative HPLC to afford the title compound as a white solid. Yield: 35 mg (29%). ^{1}H NMR (400 MHz, $CDCl_3$): δ12.26 (s, 1H), 11.82 (s, 1H), 7.91 (m, 2H), 7.89 (s, 2H), 7.40 (m, 3H), 6.84 (s, 1H), 6.73 (d, *J* = 2.0 Hz, 1H), 6.51 (d, *J* = 2.0 Hz, 1H), 3.98 (t, *J* = 5.6 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.62(m, 2H), 2.29 (s, 6H). MS (ES$^+$) *m/z* 513.53 (M+1).

Example 36. Preparation of 2-{3,5-Dimethyl-4-[2-(3-methyl-[1,2,4]oxadiazol-5-ylamino)-ethoxy]-phenyl}-5,7-dimethoxy-3*H*-quinazolin-4-one

[0316]

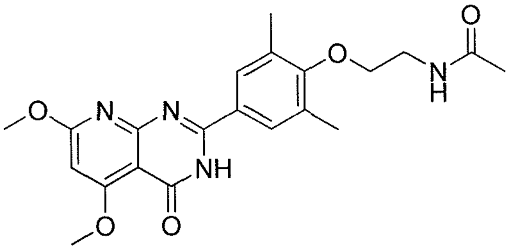


[0317] Acetamide oxime (5.00 g, 67.5 mmol) and trichloroacetic anhydride (49.3 mL, 270 mmol) were stirred at 120-130°C for 3 hours. The mixture was then distilled under vacuum. The fraction at approximately 50-70°C / approximately 5 mmHg was collected. The collected fraction was added to cold saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic phase was washed with saturated aqueous $NaHCO_3$ solution and dried over Na_2SO_4. The solvent was evaporated to give 3-methyl-5-trichloromethyl-[1,2,4]oxadiazole as a colorless liquid. Yield: 7.69 g (52%)

[0318] A mixture of 3-methyl-5-trichloromethyl-[1,2,4]oxadiazole (56 mg, 0.28 mmol), 2-[4-(2-amino-ethoxy)-3,5-dimethyl-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one (92 mg, 0.25 mmol), and cesium carbonate (179 mg, 0.55 mmol) in DMF (3 mL) was stirred at room temperature under nitrogen for 3.5 days. Water was added, and the mixture was extracted with MeOH/CH_2Cl_2. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, purified by column chromatography (silica gel; 5% MeOH in CH_2Cl_2 as eluent) to give the title compound as a beige solid. Yield: 75 mg (60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (s, 1H), 7.71 (s, 2H), 6.82 (d, *J* = 2.4 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 5.80 (t, *J* = 5.6 Hz, 1H), 4.00-3.97 (m, 5H), 3.93 (s, 3H), 3.83 (m, 2H), 2.34 (s, 6H), 2.24 (s, 3H). MS (ES$^+$) *m/z*: 452.57 (M+1).

Example 37. Preparation of N-{2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2,6-dimethyl-phenoxy]-ethyl}-acetamide

[0319]



[0320] To a solution of 4-hydroxy-3,5-dimethyl-benzaldehyde (15.0 g, 0.10 mol) in anhydrous DMF (30 mL) was added 60% sodium hydride (4.80 g, 0.12 mol) and the reaction mixture was kept stirring for 20 minutes. 2-(2-Bromoethyl)-isoindole-1,3-dione (25.4 g, 0.10 mol) in anhydrous DMF (30 mL) was added drop-wise. The reaction mixture was heated to 65°C for 5 hours. Acetic acid (3 mL) was added, DMF was removed, and the residue was poured into water (150 mL), and extracted with dichloromethane (200 mL). The crude compound was purified by column chromatography (silica gel 230-400 mesh; eluting with ethyl acetate and hexane 1:1) to give 4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethoxy]-3,5-dimethyl-benzaldehyde. Yield: 11.0 g (34%).

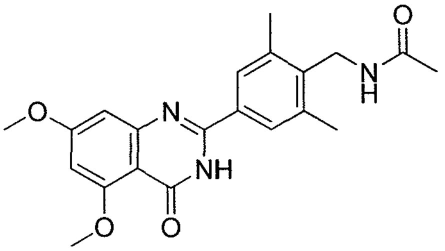
[0321] To a solution of 2-amino-4,6-dimethoxy-nicotinamide (0.40 g, 2.02 mmol, and 4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethoxy]-3,5-dimethyl-benzaldehyde (0.65 g, 2.02 mmol) in *N,N*-dimethylacetamide (30 mL) was added $NaHSO_3$ (58.5 wt%, 0.40 g, 2.20 mol) and *p*-TSA (0.12 g, 6.00 mmol). The reaction mixture was heated to 145°C for 16 hours, and then cooled to room temperature. Solvent was removed under reduced pressure. Aqueous sodium bicarbonate solution (50 mL) was added and the solid separated was filtered and washed with ether (50 mL). Crude compound was purified by column chromatography (silica gel, 230-400 mesh; methanol, ethyl acetate and dichloromethane 5:20:75) to give 2-{2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2,6-dimethyl-phenoxy]-ethyl}-isoindole-1,3-dione as a light yellow solid. Yield: 0.43 g (43%).

[0322] Hydrazine hydrate (0.2 mL, 4.1 mmol) was added to a solution of 2-{2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2,6-dimethyl-phenoxy]-ethyl}-isoindole-1,3-dione (0.43 g, 0.86 mmol) in ethanol (10 mL). The reaction mixture was heated to 70°C for 4 hours, solvent was removed, and the residue was purified by column chromatography (silica gel, 230-400 mesh; eluting with 5% 7 N ammonia in methanol and dichloromethane) to give 2-[4-(2-amino-ethoxy)-3,5-dimethyl-phenyl]-5,7-dimethoxy-3H-pyrido[2,3-d]pyrimidin-4-one as a white solid. Yield: 0.22 g (69%).

[0323] To a solution of 2-[4-(2-amino-ethoxy)-3,5-dimethyl-phenyl]-5,7-dimethoxy-3H-pyrido[2,3-d]pyrimidin-4-one (0.21 g, 0.56 mmol) in pyridine (4 mL) and dichloromethane (10 mL) was added acetyl chloride (51 mg, 0.65 mmol), and the reaction mixture was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure, the residue was poured into water (50 mL) and stirred for 30 minutes. The solid separated was filtered and washed with cold water and ether, and then dried under vacuum to give the title compound as a white solid. Yield: 0.19 g (81%). ^1H NMR (400 MHz, DMSO-d_6): δ8.15 (s, 1H), 7.90 (s, 2H), 6.36 (s, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.79 (t, *J* = 5.6 Hz, 3H), 3.42 (q, *J* = 5.6Hz, 2H), 2.28 (s, 6H), 1.84 (s, 3H). MS (ES) *m/z:* 411.15 (M-1).

Example 38. Preparation of *N*-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylbenzyl)acetamide

[0324]



[0325] 4-Bromo-2,6-dimethylaniline (4.49 g, 22.4 mmol), water (25 mL) and concentrated HCl (8.0 mL) were sonicated and cooled to 0°C. Sodium nitrite (1.67 g, 24.2 mmol) in water (5 mL) was added over 20 minutes. The mixture was stirred at 0°C for 30 minutes, and solid Na_2CO_3 was added to adjust the pH to approximately 7. The liquid portion was added, in portions, to copper (I) cyanide (2.42 g, 27.0 mmol) and potassium cyanide (3.65 g, 56.1 mmol) in water (25 mL) at 70°C over a period of 25 minutes and the mixture was heated at 70°C for 45 minutes. The mixture was cooled and extracted with toluene (2 × 150 mL). The organic phase was washed with water (100 mL), then brine (100 mL), dried (Na_2SO_4), filtered, and evaporated to afford a brown oil. Purification by column chromatography (silica gel 230-400 mesh; 25% dichloromethane in hexanes as the eluent) gave 4-bromo-2,6-dimethylbenzonitrile as an orange solid. Yield: 2.3 g (49%).

[0326] To 4-bromo-2,6-dimethylbenzonitrile (1.84 g, 8.75 mmol) in anhydrous THF (95 mL), at -78°C under nitrogen, was added n-butyllithium (2.5 M in hexanes; 3.85 mL, 9.63 mmol) dropwise over 10 minutes. The solution was stirred at -78°C for 1 hour, and anhydrous DMF (1.00 mL, 12.91 mmol) was added dropwise. The mixture was stirred at -78°C for 1 hour and at 0°C for 25 minutes. The reaction was quenched with 1 M HCl, to pH approximately 3. The solution was poured into water (370 mL) and extracted with $CHCl_3$ (7 × 100 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated, to give 4-formyl-2,6-dimethylbenzonitrile as a yellow-orange solid (1.20 g, 86%).

[0327] 4-Formyl-2,6-dimethylbenzonitrile (1.20 g, 7.53 mmol), anhydrous MeOH (80 mL), trimethylorthoformate (18.0 mL, 164.5 mmol), and camphorsulfonic acid (0.050 g, 0.215 mmol) were stirred at room temperature under nitrogen for 23 hours. Triethylamine (7.5 mL) was added and the solution was evaporated to an oil. The oil was diluted with $NaHCO_3$

(100 mL) and extracted with $CHCl_3$ (5 × 75 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated to afford 4-(dimethoxymethyl)-2,6-dimethylbenzonitrile as a golden-red oil. Yield: 1.40 g (90%).

[0328] To 4-(dimethoxymethyl)-2,6-dimethylbenzonitrile (0.86 g, 4.18 mmol) in anhydrous THF (40 mL), at 0°C under nitrogen, was added solid lithium aluminum hydride (0.34 g, 8.94 mmol) in portions over 15 minutes. The mixture was stirred at 0°C for 30 minutes and at room temperature for 20 hours. The mixture was cooled to 0°C and quenched with solid $Na_2SO_4 \cdot 10H_2O$, stirred for 10 minutes, and then stirred at room temperature for 15 minutes. Solids were removed by filtration and washed with THF (100 mL). The filtrate was evaporated to give (4-(dimethoxymethyl)-2,6-dimethylphenyl)methanamine as a golden-brown semi-solid. Yield: 0.87 g (100%)

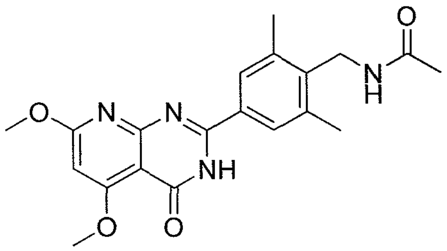
[0329] To (4-(dimethoxymethyl)-2,6-dimethylphenyl)methanamine (0.87 g, 4.18 mmol), anhydrous CH_2Cl_2 (20 mL), Et_3N (5.84 mL, 41.89 mmol), at 0°C under nitrogen, was added acetic anhydride (0.44 mL, 4.65 mmol), followed by DMAP (0.018 g, 0.147 mmol). The mixture was stirred at 0°C for 15 minutes and then at room temperature for 23 hours. The mixture was evaporated to a solid. The solid was stirred with $NaHCO_3$ (100 mL) and $CHCl_3$ (50 mL) for 15 minutes. The organic phase was separated and the aqueous phase extracted with $CHCl_3$ (4 × 50 mL). The combined organic phase was washed with brine (75 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to afford *N*-(4-(dimethoxymethyl)-2,6-dimethylbenzyl)acetamide as a light orange solid (1.00 g, 95%).

[0330] To *N*-(4-(dimethoxymethyl)-2,6-dimethylbenzyl)acetamide (0.83 g, 3.30 mmol) in $CHCl_3$ (65 mL), at 0°C was added trifluoroacetic acid/water (1:1, 10 mL) added dropwise. The solution was stirred at 0°C for 1.75 hours. The solution was diluted with water (200 mL) and the organic phase separated. The aqueous phase was extracted with $CHCl_3$ (4 × 75 mL). The combined organic phase was washed with $NaHCO_3$ (200 mL). The aqueous phase was back-extracted with $CHCl_3$ (3 × 30 mL). The combined organic phase was dried (Na_2SO_4), filtered, and evaporated to give a *N*-(4-formyl-2,6-dimethylbenzyl)acetamide as a brown solid. Yield: 0.56 g (82%)

[0331] 2-Amino-4,6-dimethoxybenzamide (0.334 g, 1.70 mmol), *N*-(4-formyl-2,6-dimethylbenzyl)acetamide (0.35 g, 1.70 mmol), anhydrous *N,N*-dimethylacetamide (10 mL), sodium bisulfite (58.5 wt%, 0.343 g, 1.87 mmol) and *p*-TsOH•H_2O (0.065 g, 0.341 mmol) were heated at 120°C for 19.5 hours. The solution was evaporated *in vacuo* and the residue was triturated with water (50 mL). The yellow solid was filtered off and washed with water (50 mL). The product was purified by column chromatography (silica gel, 230-400 mesh; 6% methanol in dichloromethane as the eluent) and triturated with Et_2O (6 mL) to afford the title compound as a white solid. Yield: 0.202 g (31%). ^1H NMR (400 MHz, DMSO-d_6): δ 11.89 (s, 1H), 7.93 (t, *J* = 4.49 Hz, 1H), 7.85 (s, 2H), 6.74 (d, *J* = 1.95 Hz, 1H), 6.51 (d, *J* = 1.95 Hz, 1H), 4.28 (d, *J* = 4.69 Hz, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 2.37 (s, 6H), 1.80 (s, 3H). MS (ES+) *m*/*z*: 382.18 (100%), 383.19.

Example 39. Preparation of N-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2,6-dimethyl-benzyl]-acetamide

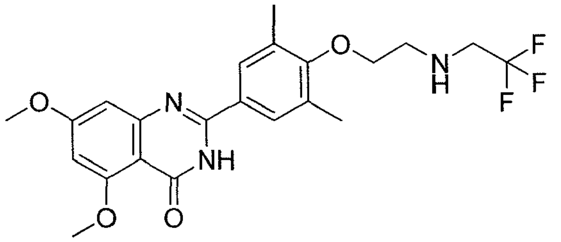
[0332]



[0333] To a solution of 2-amino-4,6-dimethoxy-nicotinamide (300 mg, 1.52 mmol), N-(4-formyl-2,6-dimethyl-benzyl)-acetamide (342 mg, 1.67 mmol) in *N,N*-dimethylacetamide (5 mL) were added sodium hydrogen sulfite (58.5 wt%, 300 mg, 1.68 mmol) and p-toluenesulfonic acid monohydrate (60 mg, 0.32 mmol). The reaction mixture was stirred at 150°C for 17 hours under nitrogen and then cooled to room temperature. The solvent was evaporated under reduced pressure to dryness. Water (50 mL) was added, and extracted with dichloromethane. The organic phase was dried over anhydrous anhydrous sodium sulfate. Solvent was evaporated and the crude compound was purified by column chromatography (silica gel 230-400 mesh; eluting with 5% methanol in dichloromethane) to give the title compound as a white solid. Yield: 78 mg (13%). ^1H NMR (400 MHz, CD_3OD): δ 7.79 (s, 2H), 6.40 (s, 1H), 4.46 (s, 2H), 4.05 (s, 3H), 3.98 (s, 3H), 2.46 (s, 6H), 1.95 (s, 3H). MS (ES^+) *m*/*z*: 383.13 (M+1).

Example 40. Preparation of 2-{3,5-dimethyl-4-[2-(2, 2, 2-trifluoro-ethylamino)-ethoxy]-phenyl}-5,7-dimethoxy-3H-quinazolin-4-one

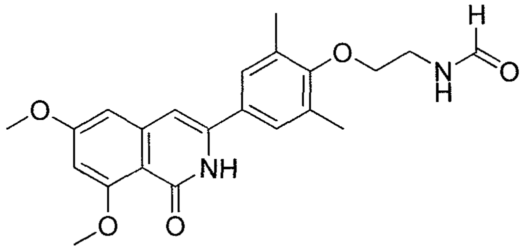
[0334]



[0335] A solution of 2-[4-(2-bromo-ethoxy)-3,5-dimethyl-phenyl]-5,7-dimethoxy-3H-quinazolin-4-one (500 mg, 1.15 mmol) and 2,2,2-trifluoro ethyl amine (1.14 g, 11.53 mmol) and TEA (5 mL) in DMF:THF (10:5 ml) was heated at 40°C for 24 hours. Then, water (100 mL) was added and product was extracted with ethyl acetate (2 × 250 mL). The combined organic layer was washed with water, then brine, dried over Na_2SO_4, and evaporated, to give crude product. The crude product was purified by the Simpliflash system, using 2% methanol in dichloromethane as eluent, to give the title compound as a white solid. Yield: 81 mg (15%). ^1H NMR (400 MHz, $CDCl_3$) δ9.44 (s, 1H), 7.69 (s, 2H), 6.83 (d, *J* = 2.4 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.91 (s, br, 2H), 3.33 (d, *J* = 4.4 Hz, 2H), 3.14 (d, *J* = 1.2 Hz, 2H), 2.37 (s, 6 H). MS (ES) m/z: 450.07 (M-1) (100%).

Example 41. Preparation of N-{2-[4-(6, 8-dimethoxy-1-oxo-1,2-dihydro-isoquinolin-3-yl)-2,6-dimethyl-phenoxy]-ethyl}-formamide

[0336]



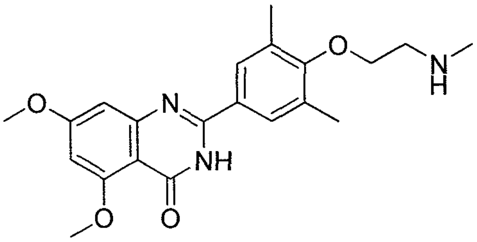
[0337] To a suspension of 3-[4-(2-Hydroxy-ethoxy)-3,5-dimethyl-phenyl]-6,8-dimethoxy-2H-isoquinolin-1-one (0.80 g, 2.16 mmol), isoindole-1,3-dione (0.35 g, 2.38 mmol), and triphenyl phosphine (0.85 g, 3.25 mmol) in THF (30 mL), was added diethyl azodicarboxylate (0.56 g, 3.25 mmol), and the reaction mixture was stirred at room temperature for 16 hours. The solvent was evaporated *in vacuo* and the residue was washed with ether to give 2-{2-[4-(6,8-dimethoxy-1-oxo-1,2-dihydro-isoquinolin-3-yl)-2,6-dimethyl-phenoxy]-ethyl}-isoindole-1,3-dione as an off-white solid. Yield: 1.11 g (crude).

[0338] Hydrazine hydrate (0.29 mL, 6.07 mmol) was added to the solution of 2-{2-[4-(6,8-dimethoxy-1-oxo-1, 2-dihydro-isoquinolin-3-yl)-2,6-dimethyl-phenoxy]-ethyl}-isoindole-1,3-dione (1.01 g, 2.03 mmol) in ethanol (20 mL). The reaction mixture was heated to 70°C for 5 hours. The solvent was removed and the residue was purified by the Simpliflash system, using 5% 7 N ammonia in methanol with dichloromethane as eluent, to give 3-[4-(2-amino-ethoxy)-3,5-dimethyl-phenyl]-6,8-dimethoxy-2H-isoquinolin-1-one as a white solid. Yield: 0.59 g (80.2%).

[0339] To a solution of 3-[4-(2-amino-ethoxy)-3, 5-dimethyl-phenyl]-6,8-dimethoxy-2H-isoquinolin-1-one (0.30 g, 0.8 mmol) in formic acid (20 mL), was heated at reflux for 72 hours. The reaction mixture was cooled to room temperature and solvent was removed under reduced pressure. Water (100 mL) was added to the residue and neutralized with solid $NaHCO_3$. The product was extracted with dichloromethane (2 × 200 mL). The combined organic layer was washed with water, then brine, dried over Na_2SO_4, and evaporated to give crude product. The crude product was purified by the Simpliflash system, using 5% 7 N ammonia in methanol with dichloromethane as eluent, to give the title compound as a white solid. Yield: 97 mg (30%). ^1H NMR (400 MHz, DMSO): δ 10.70 (s, 1H), 8.31 (br s, 1H), 8.09 (s, 1H), 7.45 (s, 2H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.64 (s, 1H), 6.45 (d, *J* = 2.0 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.77 (m, 2H), 3.48 (m, 3H), 2.25 (s, 6H). MS (ES) *m/z:* 397.11 (M+1) (100%).

Example 42. Preparation of 2-(3,5-dimethyl-4-(2-(methylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one

[0340]

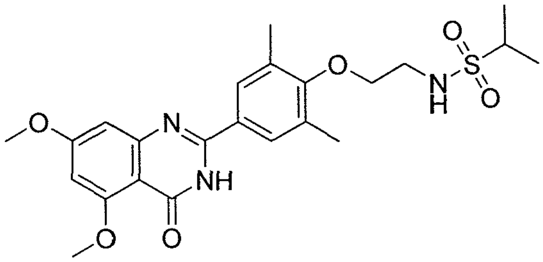


[0341] To a mixture of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (2.00 g, 5.40 mmol) and Et_3N (0.977 mL, 7.02 mmol) in CH_2Cl_2 (27.0 mL) was added slowly MsCl (0.543 mL, 7.02 mmol) at room temperature. After 1 day, additional Et_3N (0.977 mL, 7.02 mmol) and MsCl (0.543 mL, 7.02 mmol) was added and the mixture was stirred for 2 hours, then diluted with EtOAc (300 mL) and washed with 10% aqueous citric acid (3 × 75 mL), saturated aqueous $NaHCO_3$ (75 mL), and brine (75 mL). An insoluble white solid was collected by filtration to provide 2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethyl-phenoxy)ethyl methanesulfonate (0.890 g, 37%).

[0342] A mixture of compound 2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethyl-phenoxy)ethyl methanesulfonate (0.200 g, 0.446 mmol) and 33% CH_3NH_2 in EtOH (5.00 mL) was heated at reflux overnight. The solvent was removed under vacuum and the residue was purified on silica gel (12 g, CH_2Cl_2/CH_3OH) and the product freeze-dried from MeCN/H_2O to provide the title compound (0.0968 g, 57%) as a light yellow solid. ^1H NMR (300 MHz, DMSO-d_6: δ 7.90 (s, 2H), 6.73 (d, J = 2.29 Hz, 1H), 6.52 (d, J = 2.29 Hz, 1H), 3.94-3.80 (m, 8H), 2.98 (t, J = 5.46 Hz, 2H), 2.45 (s, 3H), 2.33-2.28 (m, 8H). MS (APCI) m/z 384 $[C_{21}H_{25}N_3O_4+H]^+$.

Example 43. Preparation of N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)propane-2-sulfonamide

[0343]

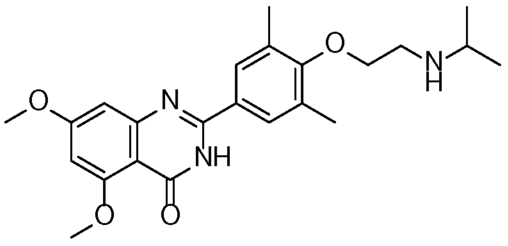


[0344] A mixture of 3,5-dimethyl-4-hydroxybenzaldehyde (0.600 g, 4.00 mmol), *N*-(2-bromoethyl)-phthalimide (1.22 g, 4.80 mmol), K_2CO_3 (0.829 g, 6.00 mmol), NaI (3.00 g, 20.0 mmol) in DMF (40.0 mL) was heated at 80°C for 2.5 hours. The reaction was cooled to room temperature, diluted with EtOAc (200 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 this 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 hours, then cooled to room temperature. The mixture was diluted with EtOAc (250 mL), washed with saturated aqueous ammonium chloride (3 × 75 mL), them 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 hours. The volatiles were removed under vacuum and 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one was isolated (0.036 g, 23%) as a white solid.

[0345] A mixture of 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3*H*)-one (0.125 g, 0.338 mmol), 2-propylsulfonyl chloride (0.040 mL, 0.36 mmol), and DBU (0.100 mL, 0.67 mmol) in THF (2.5 mL) was stirred at 60°C for 18 hours. Then, the mixture was cooled to room temperature and purified by silica gel chromatography, eluting with 92:7:1 $CHCl_3$/MeOH/concentrated NH_4OH. The mixture was further purified by reverse-phase HPLC, eluting with 10% to 90% CH_3CN in H_2O with 0.1% TFA, to afford the desired product. The product was freeze-dried from CH_3CN/H_2O to afford the title compound (0.080 g, 50%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6: δ 11.85 (s, 1H), 8.09 (s, 2H), 7.33 (t, J = 6.0 Hz, 1H), 6.74 (d, J = 2.3 Hz, 1H), 6.52 (d, J = 2.3 Hz, 1H), 3.89 (s, 3H), 3.82-3.86 (m, 5H), 3.21-3.39 (m, 3H), 2.31 (s, 6H), 1.26 (d, J = 6.8 Hz, 6H). APCI MS *m*/*z* 476 $[M+H]^+$.

Example 44 (Reference Example). Preparation of 2-(4-(2-(isopropylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one

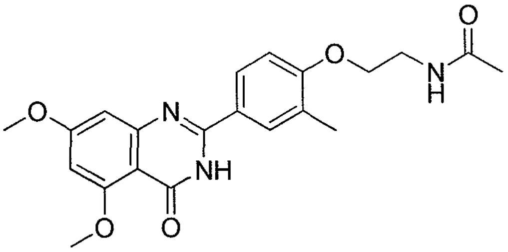
[0346]



[0347] A solution of 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3*H*)-one (0.200 g, 0.54 mmol) in EtOH (10 mL) and acetone (0.198 mL, 2.71 mmol) was treated with PtO_2 (0.050 g). The reaction mixture was stirred under 1 atmosphere of hydrogen for 48 hours. Then, the mixture was filtered through celite with ethanol washings, concentrated, and purified by silica gel chromatography, to afford the title compound (0.155 g, 70%). The product was further purified by reverse-phase HPLC, eluting with 10% to 90% CH_3CN in H_2O with 0.1% TFA, to afford the title compound as a white solid. ^1H NMR (300 MHz, DMSO-d_6□□: δ□ 7.90 (s, 2H), 6.74 (d, J = 2.3 Hz, 1H), 6.52 (s, J = 2.3 Hz, 1H), 3.83-3.89 (m, 8H), 2.89 (t, J = 5.6 Hz, 2H), 2.75-2.84 (m, 1H), 2.30 (s, 6H), 1.01 (d, J = 6.2 Hz, 6H); APCI MS *m*/*z* 412 $[M+H]^+$.

Example 45. Preparation of N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylphenoxy)ethyl)acetamide

[0348]

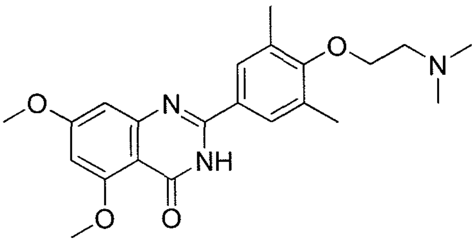


[0349] 2-(4-(2-Aminoethoxy)-3-methylphenyl)-5,7-dimethoxyquinazolin-4(3*H*)-one was synthesized as described for 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one from 3-methyl-4-hydroxybenzaldehyde (See Example 43).

[0350] A suspension of 2-(4-(2-aminoethoxy)-3-methylphenyl)-5,7-dimethoxyquinazolin-4(3*H*)-one (0.12 g, 0.33 mmol) in CH_2Cl_2 (5 mL) was treated with Et_3N (0.05 mL, 0.41 mmol) and acetyl chloride (0.026 mL, 0.37 mmol) and the mixture stirred at room temperature for 3 hours. Then, the mixture was concentrated *in vacuo* and the residue purified by flash chromatography on silica gel, eluting with 97:3 to 90:10 CH_2Cl_2/MeOH to 92:7:1 $CHCl_3$/MeOH/concentrated NH_4OH, to afford crude product. Further purification on a reverse-phase C_{18} column, eluting with 10% to 90% CH_3CN in H_2O with 0.05% TFA, afforded the title compound (0.080 g, 61%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 11.65 (s, 1H), 7.93-8.18 (m, 3H), 7.05 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 2.3 Hz, 1H), 6.50 (d, J = 2.3 Hz, 1H), 4.07 (t, J = 5.6 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.35-3.52 (m, 2H), 2.23 (s, 3H), 1.83 (s, 3H). APCI MS *m*/*z* 398 $[M+H]^+$.

Example 46. Preparation of 2-(4-(2-(dimethylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one

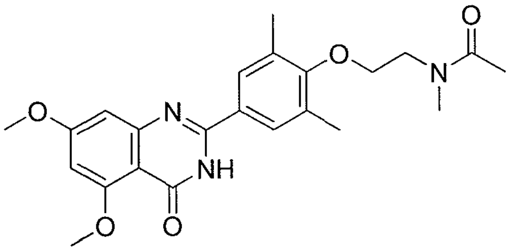
[0351]



[0352] To a solution of 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3*H*)-one (0.150 g, 0.41 mmol) in MeOH (16 mL) and CH_2Cl_2 (5 mL) was added 37% aqueous formaldehyde (0.300 mL, 4.0 mmol) and the mixture stirred for 1 hour. Then, $NaBH_4$ (0.078 g, 2.05 mmol) was added and the reaction was stirred for 16 hours at room temperature. Additional 37% aqueous formaldehyde (1.0 mL) was added and stirred for 1 hour, at which time, additional $NaBH_4$ (0.100 g, 2.63 mmol) was added and stirred for 1 hour. The reaction mixture was concentrated, redissolved in CH_2Cl_2, washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography, eluting with 9:1 CH_2Cl_2/MeOH to 92:7:1 $CHCl_3$/MeOH/concentrated aqueous NH_4OH. The residue was further purified by reverse-phase HPLC, eluting with 10% to 90% CH_3CN in H_2O with 0.1% TFA, to afford the title compound as a white solid (0.070 g, 43%). ^1H NMR (300 MHz, DMSO-d_6) δ 11.70 (br s, 1H), 7.90 (s, 2H), 6.74 (d, J = 2.3 Hz, 1H), 6.52 (d, J = 2.3 Hz, 1H), 3.84-3.89 (m, 8H), 2.64 (t, J = 5.8 Hz, 2H), 2.30 (s, 6H), 2.24 (s, 6H). APCI MS m/z 398 $[M+H]^+$.

Example 47. Preparation of N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N-methylacetamide

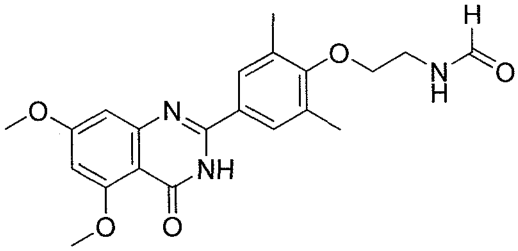
[0353]



[0354] To a solution of 2-(3,5-dimethyl-4-(2-(methylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3*H*)-one (0.110 g, 0.287 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.080 mL, 0.574 mmol), followed by acetyl chloride (0.022 mL, 0.315 mmol). The mixture was stirred at room temperature under nitrogen for 10 minutes, concentrated, and purified by silica gel chromatography, eluting with 9:1 CH_2Cl_2/MeOH, followed by reverse-phase HPLC, eluting with 10% to 90% CH_3CN in H_2O with 0.1% TFA, to afford the title compound as a white solid (0.078 g, 64%). ^1H NMR (mixture of amide rotomers, 300 MHz, DMSO-d_6: δ 11.85 (s, 1H), 7.90 (d, J = 2.7 Hz, 2H), 6.74 (d, J = 2.2 Hz, 1H), 6.52 (d, J = 2.2 Hz, 1H), 3.84-3.95 (m, 8H), 3.65-3.74 (m, 2H), 3.12 (s, 1.5H), 2.92 (s, 1.5H), 2.27 (d, J = 1.1 Hz, 6H), 2.11 (s, 1.5H), 2.03 (s, 1.5H). APCI MS m/z 424 $[M-H]^-$.

Example 48. Preparation of N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)formamide

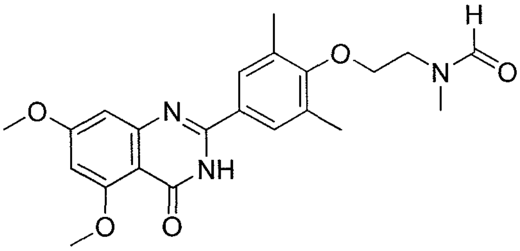
[0355]



[0356] A solution of 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3*H*)-one (0.086 g, 0.23 mmol) in ethanol (10 mL) and methyl formate (0.028 mL, 0.46 mmol) was stirred at room temperature for 5 hours. At this time, an additional portion of methyl formate (5 mL, 80.6 mmol) was added and the mixture heated at reflux for 4 days. The mixture was concentrated and purified by silica gel chromatography, eluting with 92:7:1 $CHCl_3$/MeOH/concentrated NH_4OH. The product was freeze-dried from CH_3CN/H_2O to yield the title compound (0.065 g, 71%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6: δ 11.84 (s, 1H), 8.29-8.37 (m, 1H), 8.11 (d, *J* = 1.3 Hz, 1H), 7.90 (s, 2H), 6.74 (d, *J* = 2.3 Hz, 1H), 6.52 (d, *J* = 2.3 Hz, 1H), 3.89 (s, 3H), 3.79-3.84 (m, 5H), 3.47-3.53 (m, 2H), 2.29 (s, 6H). APCI MS *m/z* 396 $[M - H]^-$.

Example 49. Preparation of N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N-methylformamide

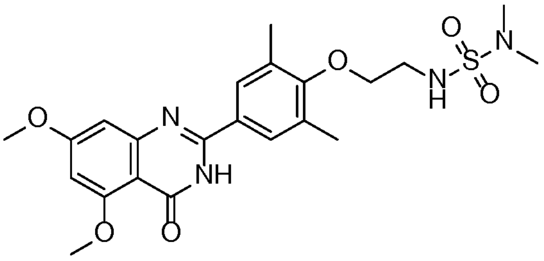
[0357]



[0358] To a solution of 2-(3,5-dimethyl-4-(2-(methylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3*H*)-one (0.080 g, 0.21 mmol) in EtOH (15 mL) was added methyl formate (5 mL). The mixture was heated at reflux for 24 hours, concentrated, and purified by silica gel chromatography, eluting with 9:1 CH_2Cl_2/MeOH, to afford the title compound as a white solid (0.080 g, 93%): ^1H NMR (mixture of amide rotomers, 300 MHz, DMSO-d_6: δ 11.85 (s, 1H), 8.12 (d, *J* = 1.9 Hz, 1H), 7.90 (s, 2H), 6.74 (d, *J* = 2.2 Hz, 1H), 6.52 (d, *J* = 2.2 Hz, 1H), 3.88-3.93 (m, 5H), 3.84 (s, 3H), 3.62-3.68 (m, 2H), 3.08 (s, 0.5H), 2.88 (s, 0.5H), 2.25-2.35 (m, 6H); APCI MS *m/z* 410 $[M-H]^-$.

Example 50 (Reference Example). Preparation of *N*-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)dimethylamino-*N*-sulfonamide

[0359]



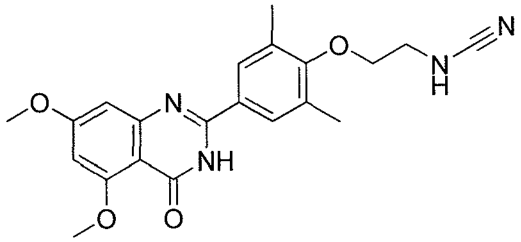
[0360] A solution of 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3*H*)-one (0.150 g, 0.41 mmol) in CH_2Cl_2 (10 mL) was treated with Et_3N (0.083 g, 0.82 mmol), then dimethylsulfamoylchloride (0.065 g, 0.45

mmol), and the reaction mixture stirred under nitrogen at room temperature for 1 hour. Then, DBU (0.100 mL) was added and stirring continued for 1 hour at room temperature. Then, the reaction mixture was heated at reflux for 18 hours, additional dimethylsulfamoylchloride (0.150 mL) was added, and heating continued at reflux for a further 2 hours. The reaction mixture was cooled and purified by flash chromatography on silica gel, eluting with 100% CH_2Cl_2 to 100% (92:7:1 $CHCl_3$/MeOH/concentrated NH_4OH). The resulting solid was further purified by reverse-phase HPLC, eluting with 10% to 90% CH_3CN in H_2O with 0.1% TFA. The solids were then triturated with CH_3CN to afford the title compound as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.69 (s,

2H), 6.82 (d, J = 2.3 Hz, 1H), 6.5 (d, J = 2.3 Hz, 1H), 4.72-4.80 (m, 1H), 3.93-3.98 (m, 8H), 3.46-3.56 (m, 2H), 2.87 (s, 6H), 2.38 (s, 6H); ESI MS *m/z* 477 $[M+H]^+$.

Example 51. Preparation of N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)cyanamide

[0361]

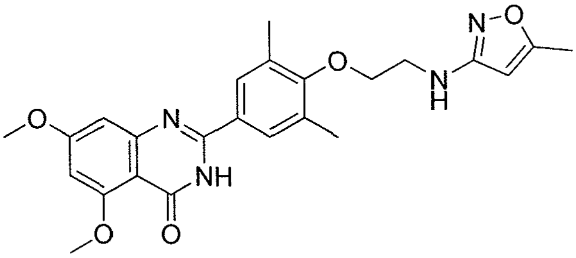


[0362] To a solution of 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3*H*)-one (0.150 g, 0.41 mmol) in MeOH (15 mL) was added BrCN (0.043 g, 0.41 mmol) and $NaHCO_3$ (0.044 g, 0.52 mmol). The reaction was stirred at room temperature for 1 hour and then concentrated *in vacuo.* Purification by flash chromatography on silica gel, eluting with 2% to 10% MeOH/CH_2Cl_2, afforded the title compound (0.120 g, 74%) as a white solid.

^1H NMR (300 MHz, DMSO-d_6): δ 11.85 (s, 1H), 7.82-7.92 (m, 2H), 7.03-7.14 (m, 1H), 6.72 (d, J = 1.4 Hz, 1H), 6.59 (d, J = 1.4 Hz, 1H), 3.81-3.93 (m, 8H), 3.15-3.29 (m, 2H), 2.28 (s, 6H). APCI MS *m/z* 395 $[M+H]^+$.

Example 52. Preparation of 2-(3,5-dimethyl-4-(2-(5-methylisoxazol-3-ylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one

[0363]



[0364] To a solution of 5-methylisoxazol-3-amine (1.0 g, 10.2 mmol) in CH_2Cl_2 was added Et_3N (1.03 g, 10.2 mmol) and bromoacetyl chloride (1.60 g, 10.2 mmol). The mixture was stirred at room temperature for 1 hour, washed with water (100 mL), then brine (100 mL), dried (Na_2SO_4), filtered, and concentrated, to afford 2-bromo-*N*-(5-methylisoxazol-3-yl)acetamide as a white solid (1.2 g, 55%).

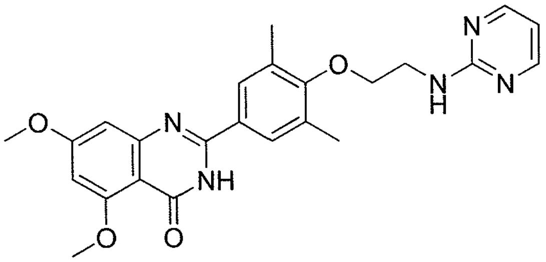
[0365] To a solution of 2-bromo-*N*-(5-methylisoxazol-3-yl)acetamide (0.223 g, 1.0 mmol) in THF (10 mL) under nitrogen was added 1.0 M BH_3•THF (3.0 mL, 3.0 mmol). The reaction mixture was stirred at room temperature for 18 hours, quenched with 1 M NaOH, extracted with ethyl acetate (2 × 100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 1:1 ethyl acetate/hexane to 100% ethyl acetate, to afford *N*-(2-bromoethyl)-5-methylisoxazol-3-amine as a white solid (0.061 g, 30%).

[0366] To a solution of 4-hydroxy-3,5-dimethylbenzaldehyde (0.036 g, 0.24 mmol) in DMF (1.5 mL) was added K_2CO_3 (0.050 g, 0.36 mmol) and the mixture stirred at room temperature under nitrogen for 30 minutes. After this time, a solution of *N*-(2-bromoethyl)-5-methylisoxazol-3-amine (0.060 g, 0.29 mmol) in DMF (1.5 mL) was added and the reaction heated at reflux for 2 hours. The mixture was concentrated and purified by flash chromatography on silica gel, eluting with 1:1 ethyl acetate/heptane to 100% ethyl acetate, to afford 3,5-dimethyl-4-(2-(5-methylisoxazol-3-ylamino)ethoxy)benzaldehyde (0.028 g, 26%).

[0367] A mixture of 3,5-dimethyl-4-(2-(5-methylisoxazol-3-ylamino)ethoxy)benzaldehyde (0.121 g, 0.44 mmol), 2-amino-4,6-dimethoxybenzamide (0.087 g, 0.44 mmol), $NaHSO_3$ (0.050 g, 0.48 mmol), and *p*-TsOH (0.008 g, 0.044 mmol) in DMA (3 mL) was heated at 155°C under nitrogen for 9 hours. Then, the reaction mixture was cooled, diluted with ethyl acetate (200 mL), and washed with water (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 100% CH_2Cl_2 to 100% 92:7:1 $CHCl_3$/MeOH/concentrated NH_4OH, to afford the title compound (0.129 g, 65%). ^1H NMR (300 MHz, DMSO-d_6: δ 11.99 (s, 1H), 7.99 (s, 2H), 6.77 (d, J = 2.3 Hz, 1H), 6.55 (d, J = 2.3 Hz, 1H), 5.29 (s, 1H), 4.70-4.72 (m, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.55-3.61 (m, 4H), 2.22 (s, 6H), 2.21 (s, 3H). APCI MS *m/z* 451 $[M+H]^+$.

Example 53. Preparation of 2-(3,5-dimethyl-4-(2-(pyrimidin-2-ylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one

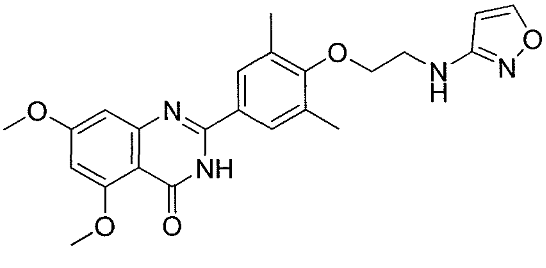
[0368]



[0369] To a solution of 2-(4-(2-aminoethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3*H*)-one (0.145 g, 0.40 mmol) in *t*-butanol (10 mL) was added Et_3N (0.06 mL, 0.47 mmol) and 2-chloropyrimidine (0.045 g, 0.40 mmol). The reaction was stirred and heated at reflux temperature overnight, then concentrated *in vacuo.* Purification by flash chromatography on silica gel, eluting with 95:5 CH_2Cl_2/MeOH, afforded the title compound (0.038 g, 21%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6): δ 8.29 (d, J = 4.7 Hz, 2H), 7.87 (s, 2H), 7.31 (t, J = 6.1 Hz, 1H), 6.72 (d, J = 2.3 Hz, 1H), 6.58 (t, J = 4.7 Hz, 1H), 6.51 (s, 1H), 3.95 (t, J = 5.9 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.65-3.71 (m, 2H), 2.25 (s, 6H). ESI MS *m/z* 448 $[M+H]^+$.

Example 54. Preparation of 2-(4-(2-(isoxazol-3-ylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one

[0370]



[0371] To a solution of isoxazol-3-amine (2.28 g, 27.1 mmol) in CH_2Cl_2 at 0°C under nitrogen was added Et_3N (2.74 g, 27.1 mmol), followed by bromoacetyl chloride (4.26 g, 27.1 mmol). The mixture was warmed to room temperature, stirred for 2 hours, washed sequentially with water (200 mL) and brine (200 mL), dried (Na_2SO_4), filtered, and concentrated, to afford 2-bromo-*N*-(isoxazol-3-yl)acetamide as a tan solid (4.5 g, 81%).

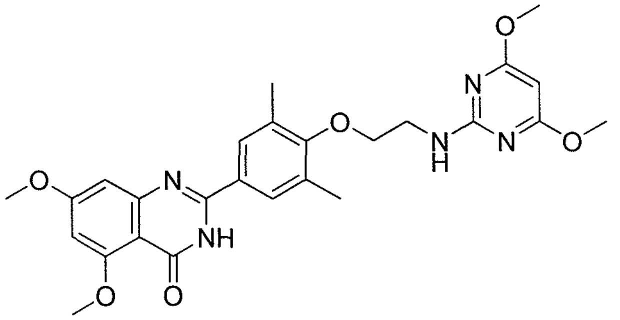
[0372] To a solution of 2-bromo-*N*-(isoxazol-3-yl)acetamide (1.0 g, 4.9 mmol) in THF (50 mL) under nitrogen was added 1.0 M BH_3•THF (14.6 mL, 14.6 mmol). The mixture was stirred at room temperature for 3.5 hours and then an additional portion of BH_3•THF (5.0 mL, 5.0 mmol) was added. After an additional 15 hours at room temperature, the reaction was quenched with 1 M NaOH, extracted with ethyl acetate (2 × 150 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 1:1 ethyl acetate/heptane to 100% ethyl acetate, to afford *N*-(2-bromoethyl)isoxazol-3-amine (0.133 g, 14%).

[0373] To a solution of 4-hydroxy-3,5-dimethylbenzaldehyde (0.471 g, 3.14 mmol) in DMF (20 mL) was added K_2CO_3 (0.650 g, 4.71 mmol). The reaction mixture was stirred at room temperature under nitrogen for 30 minutes. Then, a solution of *N*-(2-bromoethyl)isoxazol-3-amine (0.600 g, 3.14 mmol) in DMF (10 mL) was added. The mixture was heated at reflux for 3 hours, concentrated, and purified by flash chromatography on silica gel, eluting with 30% ethyl acetate/heptane to 100% ethyl acetate, to afford 4-(2-(isoxazol-3-ylamino)ethoxy)-3,5-dimethylbenzaldehyde as a white solid (0.260 g, 32%).

[0374] A mixture of 4-(2-(isoxazol-3-ylamino)ethoxy)-3,5-dimethylbenzaldehyde (0.253 g, 0.97 mmol), 2-amino-4,6-dimethoxybenzamide (0.190 g, 0.97 mmol), $NaHSO_3$ (0.111 g, 1.07 mmol), and p-TsOH (0.018 g, 0.097 mmol) in DMA (10 mL) was heated at 150°C under nitrogen for 44 hours. Then, the reaction mixture was concentrated, diluted with ethyl acetate (200 mL), and washed with water (150 mL), then brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 100% CH_2Cl_2 to 100% 92:7:1 $CHCl_3$/MeOH/concentrated NH_4OH, to afford the title compound (0.150 g, 35%). ^1H NMR (300 MHz, DMSO-d_6: δ 11.82 (s, 1H), 8.39 (d, *J* = 1.7 Hz, 1H), 7.89 (s, 2H), 6.73 (d, *J* = 2.2 Hz, 1H), 6.51 (d, *J* = 2.2 Hz, 1H), 6.44 (t, *J* = 6.1 Hz, 1H), 6.02 (d, *J* = 1.7 Hz, 1H), 3.94 (t, *J* = 5.5 Hz, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.46-3.51 (m, 2H), 2.27 (s, 6H). APCI MS m/z 437 $[M+H]^+$.

Example 55. Preparation of 2-(4-(2-(4,6-dimethoxypyrimidin-2-ylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one

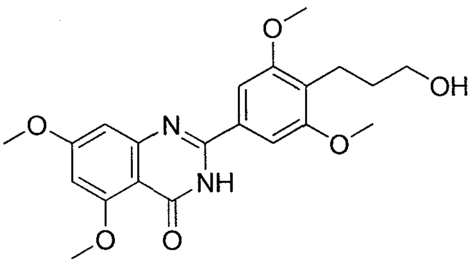
[0375]



[0376] Following the method described for Example 51 above, the title compound was made from 2-chloro-4,6-dimethoxypyrimidine (0.071 g, 0.40 mmol) in 35% yield. ^1H NMR (300 MHz, DMSO-d_6): δ 11.82 (s, 1H), 7.88 (s, 2H), 7.22 (t, *J* = 6.1 Hz, 1H), 6.72 (d, *J* = 2.3 Hz, 1H), 6.51 (s, 1H), 5.38 (s, 1H), 3.90-4.02 (m, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.77 (s, 6H), 3.59-3.72 (m, 2H), 2.27 (s, 6H). APCI MS *m/z* 506 $[M-H]^-$.

Example 56. Preparation of 2-[4-(3-hydroxy-propyl)-3,5-dimethoxyphenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one

[0377]



[0378] To a stirred solution of 4-hydroxy-3,5-dimethoxylbenzaldehyde (5.87 g, 32.2 mmol) in CH_2Cl_2 (50 mL) and pyridine (8.6 mL) was added trifluoromethanesulfonic anhydride (10.0 g, 35.4 mmol) at 0°C. After the addition was complete, stirring was continued for 16 hours at room temperature. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with water (3 × 100 mL). The separated organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product, trifluoromethanesulfonic acid 4-formyl-2,6-dimethoxyphenyl ester, was used in the next step without further purification. Yield: 10.0 g (98.9%).

[0379] To a stirred solution of trifluoromethanesulfonic acid 4-formyl-2,6-dimethoxyphenyl ester (8.00 g, 25.4 mmol) in anhydrous DMF (80 mL) under nitrogen at room temperature were sequentially added triethylamine (5.14 g, 50.8 mmol), methyl acrylate (21.9 g, 254.0 mmol), 1,3-bis-(diphenylphosphino)-propane (0.84 g, 2.03 mmol), and palladium acetate (0.40 g, 1.77 mmol). The reaction mixture was stirred at 115°C for 16 hours. DMF was removed under reduced pressure and the residue was taken in ethyl acetate (200 mL) and washed with 1 N HCl solution (2 × 50 mL), and saturated sodium bicarbonate solution (100 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (silica gel 230-400 mesh; eluting with hexane / ethyl acetate = 3:1) to give 3-(4-formyl-2,6-dimethoxyphenyl)-acrylic acid methyl ester. Yield: 4.0 g (62%).

[0380] To a solution of 3-(4-formyl-2,6-dimethoxyphenyl)-acrylic acid methyl ester (5.00 g, 20.0 mmol) in methanol (80 mL), 1.5 N sodium hydroxide (45 mL) was added. The suspension was stirred at room temperature for 16 hours. Methanol was evaporated and acetic acid (4.0 mL) was added. The aqueous layer was extracted with dichloromethane (200 mL) then acidified, to pH 3, with 2 N HCl. The solid was filtered and further washed with cold water (100 mL) to obtain 3-(4-formyl-2,6-dimethoxyphenyl)-acrylic acid as a yellow solid. Yield: 4.20 g (89%).

[0381] To a solution of 3-(4-formyl-2,6-dimethoxyphenyl)-acrylic acid (4.20 g, 17.7 mmol) and N,N-diisopropylethylamine (3.5 mL) in ethanol (80 mL) were added Pd/C (400 mg, 10 wt%). The suspension was vigorously stirred under 1 bar of hydrogen pressure for 16 hours. The mixture was filtered through a celite pad and the filtrate was evaporated. The residue was poured into chilled 1 N HCl (200 mL), the solid was filtered, and further washed with cold water (100 mL) to give a mixture of 3-(4-formyl-2,6-dimethoxyphenyl)-propionic acid and 3-(4-hydroxymethyl-2,6-dimethoxyphenyl)-propionic acid as a white solid. Yield: 3.30 g.

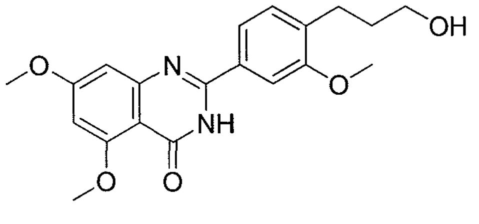
[0382] To a suspension of $LiAlH_4$ (1.00 g, 26.3 mmol) in anhydrous THF (40 mL) was added dropwise a solution of a mixture of 3-(4-formyl-2,6-dimethoxyphenyl)-propionic acid and 3-(4-hydroxymethyl-2,6-dimethoxyphenyl)-propionic acid (3.30 g, 13.8 mmol). After the addition was complete, the reaction mixture was stirred at reflux for 2 hours. The suspension was diluted with THF (20 mL) and another portion of $LiAlH_4$ (0.60 g, 15.8 mmol) was added. The mixture was refluxed for an additional 1 hour. The reaction was cooled to room temperature, carefully quenched with aqueous saturated NH_4Cl solution (8 mL), acidified to pH 1-2 with 2 N HCl, and extracted with ethyl acetate (200 mL). The organic phase was dried over sodium sulfate, filtered and concentrated to provide 3-(4-hydroxymethyl-2,6-dimethoxyphenyl)-propan-1-ol as a colorless crystalline solid. Yield: 3.08 g (98.7%).

[0383] To a solution of 3-(4-hydroxymethyl-2,6-dimethoxyphenyl)-propan-1-ol (3.08 g, 13.6 mmol) in ethanol (50 mL) was added activated MnO_2 (4.15 g, 47.6 mmol) and the resulting suspension was stirred at reflux for 16 hours. The reaction mixture was filtered through a celite pad and the filtrate was concentrated. The residue was purified by column chromatography (silica gel 230-400 mesh; eluting with 2:1 hexane and ethyl acetate) to give 4-(3-hydroxy-propyl)-3,5-dimethoxybenzaldehyde. Yield: 1.10 g (36%).

[0384] To a solution of 2-amino-4,6-dimethoxy-benzamide (0.35 g, 1.78 mmol) and 4-(3-hydroxy-propyl)-3,5-dimethylbenzaldehyde (0.40 g, 1.78 mmol) in *N,N*-dimethylacetamide (8 mL) were added $NaHSO_3$ (0.35 g, 1.96 mmol) and *p*-TSA (34 mg, 0.18 mmol) and the reaction mixture was heated at 115-120°C for 5 hours, then cooled to room temperature. *N,N*-dimethylacetamide was removed under reduced pressure. The residue was diluted with water (50 mL) and the pH was adjusted to 7 by adding sodium bicarbonate solution. The solid was collected and washed with ether and further mixed with methanol (30 mL) and stirred for 1 hour, filtered, and dried under vacuum to give the title compound as a white solid. Yield: 0.25 g (35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.13 (s, 1H), 7.30 (s, 2H), 6.86 (d, *J* = 2.4 Hz, 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 3.98 (s, 6H), 3.95 (s, 3H), 3.94 (s, 3H), 3.52 (m, 2H), 2.86 (t, *J* = 6.6 Hz 2H), 2.27 (t, *J* = 6.6 Hz, 1H), 1.81(m, 2H). MS (ES$^+$) *m/z:* 401.49 (M+1).

Example 57. Preparation of 2-[4-(3-hydroxy-propyl)-3-methoxy-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one

[0385]



[0386] To a stirred solution of 4-hydroxy-3-methoxy-benzaldehyde (5.00 g , 32.8 mmol) in CH_2Cl_2 (50 mL) and pyridine (8 mL) was added trifluoromethanesulfonic anhydride (10.19 g, 36.1 mmol) at 0°C. After addition was complete, stirring was continued for 16 hours at room temperature. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with water (3 × 100 mL) and brine (100 mL). The separated organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (silica gel 230-400 mesh; 20% ethyl acetate in hexanes as eluent) to give trifluoromethanesulfonic acid 4-formyl-2-methoxyphenyl ester. Yield: 8.00 g, (85%).

[0387] To a stirred solution of trifluoromethanesulfonic acid 4-formyl-2-methoxy-phenyl ester (5.00 g, 17.5 mmol) in anhydrous DMF (75 mL) under nitrogen at room temperature were sequentially added triethylamine (3.50 g, 34.5 mmol), ethyl acrylate (17.50 g, 174.7 mmol), 1,3-bis-(diphenylphosphino)-propane (0.40 g, 0.96 mmol), and palladium (II) acetate (0.20 g, 0.87 mmol). The reaction mixture was stirred at 100°C for 5 hours. DMF was removed under reduced pressure, and the residue was taken in ethyl acetate (200 mL) and washed with 1 N HCl solution (2 × 50 mL), and saturated sodium bicarbonate solution (100 mL) and brine (100 mL). The organic phase was dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (silica gel 230-400 mesh; 20% ethyl acetate in hexanes as eluent) to give 3-(4-formyl-2-methoxy-phenyl)-acrylic acid ethyl ester as a beige solid. Yield: 3.00 g (73%).

[0388] To a solution of 3-(4-formyl-2-methoxy-phenyl)-acrylic acid ethyl ester (3.00 g, 13.6 mmol) and N,N-diisopropylethylamine (3.0 mL) in ethanol (100 mL) were added Pd/C (10 wt%, 400 mg). The suspension was hydrogenated under 25 psi pressure for 5 hours. The mixture was filtered through a celite pad and the filtrate was evaporated. The residue was poured into chilled 1 N HCl (200 mL), the solid was filtered, and further washed with cold water (100 mL) to give a 3-(4-hydroxymethyl-2-methoxy-phenyl)-propionic acid ethyl ester as a beige solid. Yield: 2.80 g (93%).

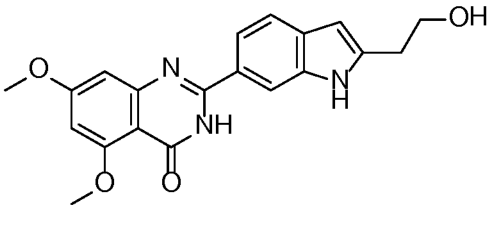
[0389] To a suspension of $LiAlH_4$ (0.51 g, 26.3 mmol) in anhydrous THF (100 mL) was added dropwise a solution of 3-(4-hydroxymethyl-2-methoxyphenyl)-propionic acid ethyl ester (2.5 g, 11.1 mmol) in THF (10 mL). After the addition was complete, the reaction mixture was stirred at reflux for 3 hours. Then, the reaction was cooled to room temperature, carefully quenched with aqueous saturated NH_4Cl solution (8 mL), acidified to pH approximately 1-2 with 2 N HCl, and extracted with ethyl acetate (200 mL). The organic phase was dried over sodium sulfate, filtered, and concentrated, to provide 3-(4-hydroxymethyl-2-methoxy-phenyl)-propan-1-ol as a colorless crystalline solid. Yield: 1.80 g (90%).

[0390] To a solution of 3-(4-hydroxymethyl-2-methoxy-phenyl)-propan-1-ol (1.8 g, 9.1 mmol) in ethanol (50 mL) was added activated MnO_2 (2.79 g, 32.0 mmol) and the resulting suspension was stirred at reflux for 16 hours. The reaction mixture was filtered through celite pad and the filtrate was concentrated. The residue was purified by column chromatography (silica gel 230-400 mesh; 2:1 hexane and ethyl acetate as eluent) to give 4-(3-hydroxy-propyl)-3-methoxybenzaldehyde. Yield: 1.2 g (67%).

[0391] To a solution of 2-amino-4,6-dimethoxy-benzamide (0.48 g, 2.44 mmol) and 4-(3-hydroxy-propyl)-3-methoxybenzaldehyde (0.40 g, 2.05 mmol) in *N,N*-dimethylacetamide (10 mL) were added $NaHSO_3$ (58.5 wt%, 0.40 g, 2.25 mmol) and p-toluenesulfonic acid monohydrate (78 mg, 0.41 mmol) and the reaction mixture was heated at 115°C for 16 hours, then cooled to room temperature. The solvent was removed under reduced pressure. The residue was diluted with water (50 mL) and the pH was adjusted to approximatley 7 by adding sodium bicarbonate solution. The solid was filtered and washed with water. The crude compound was purified by column chromatography (silica gel 230-400 mesh; 5% methanol in dichloromethane as eluent) to give the title compound as an off-white solid. Yield: 0.35 g (46%). ^1H NMR (400 MHz, DMSO-d_6): δ 12.02(s, 1H), 7.75-7.73 (m, 2H), 7.28 (d, J = 7.8 Hz, 1H), 6.75 (d, J = 2.3 Hz, 1H), 6.53 (d, J = 1.9 Hz, 1H), 4.48 (t, J = 5.0 Hz, 1H), 3.90 (d, J = 4.2 Hz, 6H), 3.85 (s, 3H), 3.44 (q, J = 6.6Hz, 2H), 2.65 (t, J = 7.4Hz 2H), 1.71-1.67 (m, 2H). MS (ES^+) *m/z*: 371.51 (M+1).

Example 58 (Reference Example). Preparation of 2-[2-(2-hydroxyethyl)-1*H*-indol-6-yl]-5,7-dimethoxy-3*H*-quinazolin-4-one

[0392]



[0393] To a degassed solution of methyl-3-amino-4-iodobenzoate (2.00 g, 7.22 mmol) in a mixture of 5:1 DMF-triethylamine (30 mL) were added $PdCl_2(PPh_3)_2$ (0.25 g, 0.36 mmol) and copper (I) iodide (0.41 g, 2.16 mmol) and the mixture was degassed again. A degassed solution of 2-(3-butynyloxy)tetrahydro-2*H*-pyran (1.7 mL, 10.83 mmol) in a mixture of 5:1 DMF-triethylamine (12 mL) was added drop-wise at 75°C over a period of 45 minutes under nitrogen. Soon after the addition, TLC showed completion of the reaction. The reaction mixture was cooled to room temperature, solvent was removed under reduced pressure, and the residue was diluted with water (75 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was washed with water (50 mL), brine (50 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated and the crude product was purified by column chromatography (silica gel 230-400 mesh; 2:1 hexanes and ethyl acetate as eluent) to obtain 3-amino-4-[4-(tetrahydropyran-2-yloxy)-but-1-ynyl]benzoic acid methyl ester as a brown solid. Yield: 1.70 g (78%).

To a stirred solution of 3-amino-4-[4-(tetrahydropyran-2-yloxy)-but-1-ynyl]benzoic acid methyl ester (1.68 g, 5.55 mmol) in anhydrous pyridine (5 mL) was added acetyl chloride (0.43 mL, 6.11 mmol) at 0°C under nitrogen. Stirring was continued at 0°C. After 30 minutes TLC showed completion of the reaction. Pyridine was removed under reduced pressure and the residue was diluted with ethyl acetate (100 mL). The resulting mixture was washed with aq 2 N HCl (20 mL), water (2 × 15 mL) and brine (20 mL). After drying over anhydrous $MgSO_4$, solvent was removed to obtain 3-acetylamino-4-[4-(tetrahydropyran-2-yloxy)-but-1-ynyl]benzoic acid methyl ester as a beige solid. Yield: 1.67 g (87%). Crude product was used in the next step without further purification.

[0394] A 1.0 M solution of tetrabutylammonium fluoride (9.67 mL, 9.67 mmol) in THF was added to a solution of 3-acetylamino-4-[4-(tetrahydropyran-2-yloxy)-but-1-ynyl]benzoic acid methyl ester (1.67 g, 4.83 mmol) in anhydrous THF (20 mL) at room temperature. The resulting reddish-brown solution was heated at reflux for 2 hours and then allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue was taken in water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phase was washed with water (25 mL), brine (50 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated and the crude product was purified by column chromatography on (silica gel 230-400 mesh; dichloromethane as eluent) to give 2-[2-(tetrahydropyran-2-yloxy)ethyl]-1*H*-indole-6-carboxylic acid methyl ester as a light brown solid. Yield: 1.27 g (87%).

[0395] To a suspension of lithium aluminum hydride (0.32 g, 8.37 mmol) in anhydrous THF (20 mL) was added a solution of 2-[2-(tetrahydropyran-2-yloxy)ethyl]-1*H*-indole-6-carboxylic acid methyl ester (1.27 g, 4.19 mmol) in anhydrous THF (10 mL) at -30°C to -20°C dropwise over a period of 15 minutes under nitrogen. The temperature was allowed to warm to room temperature and stirring continued for 15 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution at 0°C, diluted with ethyl acetate (50 mL), and filtered. The solid was washed with ethyl acetate. The combined organic phase was dried over anhydrous $MgSO_4$. The solvent was evaporated and the crude product was purified by the Simpliflash system (3:2 ethyl acetate-hexanes as eluent) to give {2-[2-(tetrahydropyran-2-yloxy)ethyl]-1*H*-indol-6-yl}-methanol as a white solid. Yield: 0.61 g (53%).

[0396] IBX (0.62 g, 2.21 mmol) was added to a solution of {2-[2-(tetrahydropyran-2-yloxy)ethyl]-1*H*-indol-6-yl}-methanol (0.61 g, 2.21 mmol) in DMSO (10 mL). After 30 min, the reaction mixture became a clear solution. Stirring was continued at room temperature for 2 hours and during this time, some solid precipitated. Water (50 mL) was added, the solid was filtered, and washed with ethyl acetate (50 mL). The filtrate was collected and extracted with ethyl acetate (3 × 20 mL). The organic phase was washed with brine (30 mL) and dried over anhydrous $MgSO_4$. Removal of solvent gave 2-[2-(tetrahydropyran-2-yloxy)ethyl]-1*H*-indole-6-carbaldehyde as a light brown solid. Yield: 0.60 g (99%).

[0397] To a solution of 2-amino-4,6-dimethoxy-benzamide (0.48 g, 2.42 mmol) and 2-[2-(tetrahydropyran-2-yloxy)ethyl]-1*H*-indole-6-carbaldehyde (0.60 g, 2.20 mmol) in *N,N*-dimethylacetamide (20 mL) were added $NaHSO_3$ (58.5 wt%, 0.60 g, 3.30 mmol) and *p*-toluenesulfonic acid monohydrate (0.17 g, 0.88 mmol). The reaction mixture was heated at 110°C for 20 hours and then cooled to room temperature. *N,N*-dimethylacetamide was removed under reduced pressure. The residue was diluted with saturated sodium carbonate solution (50 mL) and extracted with dichloromethane (4 × 25 mL). The combined organic phase was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed and the crude product was purified by column chromatography (silica gel 230-400 mesh; 7% methanol in dichloromethane as eluent). Yield: 0.45 g (56%). The compound was further purified by preparative HPLC to give the title compound as an off-white solid. Yield: 123 mg. ^1H NMR (400 MHz, DMSO-d_6): δ 11.89 (s, 1H), 11.25 (s, 1H), 8.18 (s, 1H), 7.82 (d, J = 8.40 Hz, 1H), 7.50 (d, J = 8.40 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 6.49 (d, J = 2.0 Hz, 1H), 6.27 (s, 1H), 4.80 (t, J = 5.2 Hz, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.78-3.73 (m, 2H), 2.92 (t, J = 7.2 Hz, 2H). MS (ES+) *m*/*z* 366.54 (100%, M+1).

Example 59. Quantification of hIL-6 mRNA

[0398] In this example, hIL-6 mRNA in tissue culture cells was quantitated to measure the transcriptional inhibition of hIL-6 when treated with a compound of the invention.

[0399] A human leukemic monocytic lymphoma cell line (U937) was plated (3.2×10^5 cells per well) in a 96-well plate in 100 μL RPMI 1640 + 10% FBS, and differentiated into macrophages with PMA (60 ng/mL) for 3 days prior to the addition of the compound of interest. The cells were pretreated for 1 h with the test compound in DMSO prior to stimulation with lipopolysaccharide from *Escherichia coli* at 1 μg/mL. The cells were incubated for 3 h before harvest. At the time of harvest, cells were rinsed in 200 μL PBS. Cell lysis solution (70 μL) was added the cells for 10 min, and mRNA was then prepared using the "mRNA Catcher PLUS plate" (Invitrogen), according to the protocol supplied.

[0400] The eluted mRNA isolated was then used in a one-step quantitative real-time PCR reaction, using components of the UltraSense kit together with Applied Biosystems primer-probe mixes. 10 μL of template was amplified with 1.75 μL of IL-6 primer-probe, and 1 μL of hCyclophilin primer probe, and the reaction was carried out in multiplex. Real-time PCR data was analyzed, normalizing the Ct values for hIL-6 to hCyclophilin, prior to determining the fold induction of each unknown sample, relative to the control.

[0401] In Table 2, an active compound is one that causes a ≥ 20% inhibition in IL-6 mRNA at a concentration less than or equal to 10 μM.

Table 2.

Example	Inhibition of IL-6 expression
1	Active
2	Active
3	Active
4	Active
5	Active
6	Active
7	Active
8	Active
9	Active
10	Active
11	Active
12	Active
13	Active
14	Active
15	Active
16	Active
17	Active
18	Active
19	Active
20	Active
21	Active
22	Active
23	Active
24	Active
25	Active
26	Active
27	Active
28	Active
29	Active
30	Active
31	Active
32	Active
33	Active

(continued)

Example	Inhibition of IL-6 expression
34	Active
35	Active
36	Active
37	Active
38	Active
39	Active
40	Active
41	Active
42	Active
43	Active
44	Active
45	Active
46	Active
47	Active
48	Active
49	Active
50	Active
51	Active
52	Active
53	Active
54	Active
55	Active
56	Active
57	Active
58	Active

Example 60. Quantification of hVCAM-1 mRNA

[0402] In this example, hVCAM-1 mRNA in tissue culture cells was quantitated to measure the transcriptional inhibition of hVCAM when treated with a compound of the invention.

[0403] A human umbilical vein endothelial cell line (HUV-EC-C) was plated in a 96-well plate (5.0×10^3 cells/well) in 100 µL EGM complete media and incubated for 24 h prior to the addition of the compound of interest. The cells were pretreated for 1 h with the test compound in DMSO prior to stimulation with tumor necrosis factor-α (10 ng/mL). The cells were incubated for an additional 24 h before harvest. At time of harvest, the cells were rinsed in 200 µL PBS, and cell lysis solution (70 µL) was then added the cells for 10 min. mRNA was then prepared using the "mRNA Catcher PLUS plate" (Invitrogen), according to the protocol supplied.

[0404] The eluted mRNA was then used in a one-step quantitative real-time PCR reaction, using components of the UltraSense kit together with Applied Biosystems primer-probe mixes. 10 µL of template was amplified with 1.75 µL of hVCAM-1 primer-probe, and 1 µL of hCyclophilin primer probe, and the reaction was carried out in multiplex. Real-time PCR data was analyzed, normalizing the Ct values for hVCAM-1 to hCyclophilin, prior to determining the fold induction of each unknown sample, relative to the control.

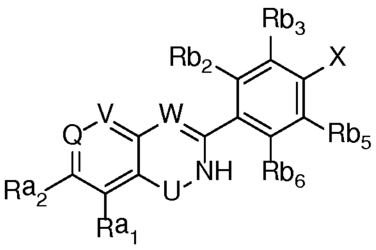
[0405] In Table 3, an active compound is one that causes a ≥ 20% inhibition in VCAM-1 mRNA at a concentration less than or equal to 10 µM.

Table 3.

Example	Inhibition of VCAM-1 expression
3	Active
4	Active
5	Active
7	Active
9	Active
10	Active
15	Inactive
17	Inactive
18	Active
20	Active
21	Inactive
22	Active
23	Active
25	Active
26	Active
28	Active
29	Active
30	Inactive
31	Active
32	Active
33	Active
34	Active
35	Active
36	Active
37	Inactive
38	Active
39	Active
40	Active
42	Active
44	Active
47	Active
51	Active
58	Active

Claims

1. A pharmaceutical composition for use in reducing IL-6 for the treatment of cancer in a subject, wherein the composition comprises a therapeutically effective amount of at least one compound of Formula I:

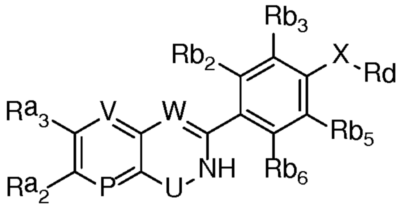


(I)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof, wherein:

Q is selected from N and CRa_3;
V is selected from N and CRa_4;
W is selected from N and CH;
U is selected from C=O, C=S, SO_2 and S=O;
X is selected from OH, SH, NH_2, S(O)H, $S(O)_2H$, $S(O)_2NH_2$, $S(O)NH_2$, NHAc, and $NHSO_2Me$;
Ra_1, Ra_3, and Ra_4 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, and halogen;
Ra_2 is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, amino, amide, and halogen;
Rb_2 and Rb_6 are independently selected from hydrogen, methyl and fluorine;
Rb_3 and Rb_5 are independently selected from hydrogen, halogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and C_1-C_6 alkoxy; and
Rb_2 and Rb_3 and/or Rb_5 and Rb_6 may be connected to form a cycloalkyl or a heterocycle,
provided that at least one of Ra_1, Ra_2, Ra_3, and Ra_4 is not hydrogen.

2. A pharmaceutical composition for use in reducing IL-6 and/or VCAM-1 for the treatment of cancer or a disease selected from arthritis, asthma, dermatitis, psoriasis, cystic fibrosis, post transplantation late and chronic solid organ rejection, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel diseases, ocular inflammation, uveitis, rhinitis, chronic obstructive pulmonary disease (COPD), glomerulonephritis, Grave's disease, gastrointestinal allergies, and conjunctivitis in a subject, wherein the composition comprises a therapeutically effective amount of at least one compound of Formula II:



(II)

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof, wherein:

P is selected from N and CRa_1;
V is selected from N and CRa_4;
W is selected from N and CH;
U is C=O;
Ra_1, Ra_3, and Ra_4 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, and halogen;
Ra_2 is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, heterocycle, amino, amide, fluoro, and bromo;
Rb_2 and Rb_6 are independently selected from hydrogen, methyl, and fluoride;
Rb_3 and Rb_5 are independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, halogen, and amino;
Rb_2 and Rb_3 and/or Rb_5 and Rb_6 may be connected to form a cycloalkyl, phenyl or heterocycle; and
X-Rd is selected from 2-hydroxyethoxy, methoxy, benzyloxyethoxy, 2,3-dihydroxypropoxy, aminocarbonylethoxy, methylaminocarbonylethoxy, (4-methoxyphenyl)aminocarbonylethoxy, benzylaminocarbonylethoxy, 4-hydroxybutoxy, (5-phenyl-4H-[1,2,4]triazol-3-ylamino)ethoxy, (3-methyl-[1,2,4]oxadiazol-5-ylamino)ethoxy,

methylcarbonylaminoethoxy, methylcarbonylaminomethyl, (2,2,2-trifluoro-ethylamino)ethoxy, methanesulfonylaminoethoxy, isobutyrylaminoethoxy, methylaminoethoxy, isopropylsulfonylaminoethoxy, dimethylaminoethoxy, N-(2-hydroxyethyl)-N-methylacetamide, formamide-N-2-ethoxy, methylformamide-N-2-ethoxy, dimethylsulfonylaminoethoxy, cyanoaminoethoxy, (5-methylisoxazol-3-ylamino)ethoxy, (pyrimidin-2-ylamino)ethoxy, (isoxazol-3-ylamino)ethoxy, (4,6-dimethoxypyrimidin-2-ylamino)ethoxy, 3-hydroxypropyl, and 2-hydroxyethyl,
provided that
at least one of Ra_1, Ra_2, Ra_3, and Ra_4 is not hydrogen;
if -XRd is $-OCH_2CH_2OH$, then Rb_3 is not pyrrolidine; and
if -XRd is -OMe, then Ra_2 is not $-CH_2$morpholino.

3. The pharmaceutical composition for use according to claim 2, wherein:

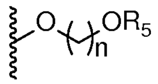
U is C=O
P is CRa_1;
Ra_1 is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, and halogen;
Ra_2 is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, heterocycle, amide, and amino;
Ra_3 and Ra_4 are independently selected from hydrogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, and halogen; and
Rb_3 and Rb_5 are independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, halogen, and amino, wherein Rb_2 and Rb_3 and/or Rb_5 and Rb_6 may be connected to form a phenyl ring.

4. The pharmaceutical composition for use according to claim 2, wherein Ra_1 is selected from hydrogen, unsubstituted C_1-C_6 alkyl, unsubstituted C_1-C_6 alkoxy, and halogen.

5. The pharmaceutical composition for use according to claim 2, wherein Ra_2 is selected from hydrogen, C_1-C_6 alkyl substituted with heterocyclyl, unsubstituted C_1-C_6 alkoxy, amino, and heterocycle.

6. The pharmaceutical composition for use according to claim 2, wherein:

Ra_3 is selected from selected from hydrogen, methoxy, unsubstituted C_1-C_6 alkyl, halogen, and



;

n is 1, 2, or 3; and
R_5 is C_1-C_6 alkyl substituted with phenyl or heteroaryl.

7. The pharmaceutical composition for use according to claim 2, wherein Ra_4 is selected from hydrogen, unsubstituted C_1-C_6 alkoxy, and halogen;

8. The pharmaceutical composition for use according to claim 2, wherein Rb_3 and Rb_5 are independently selected from hydrogen, methyl, C_1-C_6 alkyl substituted with heterocyclyl, and unsubstituted C_1-C_6 alkoxy wherein Rb_2 and Rb_3 and/or Rb_5 and Rb_6 may be connected to form a phenyl ring.

9. The pharmaceutical composition for use according to claim 2, wherein the compound is selected from:

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
5,7-dimethoxy-2-(4-methoxyphenyl)quinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6,7-dimethoxyquinazolin-4(3H)-one;
5,7-dimethoxy-2-(4-methoxy-3-(morpholinomethyl)phenyl)quinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxypyrido[2,3-d]pyrimidin-4(3H)-one;
N-(2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl)acetamide;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-morpholinoquinazolin-4(3H)-one;
2-(4-(2-(benzyloxy)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxypyrido[2,3-d]pyrimidin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethylpyrido[2,3-d]pyrimidin-4(3H)-one;
5,7-difluoro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;

5,7-dichloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
2-[4-(2-hydroxy-ethoxy)-3,5-dimethyl-phenyl]-5,7-diisopropoxy-3H-quinazolin-4-one;
2-[4-(2-hydroxyethoxy)-3,5-dimethyl-phenyl]-6-morpholin-4-ylmethyl-3H-quinazolin-4-one;
2-[4-(2,3-Dihydroxy-propoxy)-3,5-dimethyl-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one;
2-[4-(2-hydroxy-ethoxy)-3,5-dimethylphenyl]-5,7-dimethoxy-6-morpholin-4-ylmethyl-3H-quinazolin-4-one;
2-[4-(2-hydroxy-ethoxy)-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one;
2-[4-(2-hydroxy-ethoxy)-naphthalen-1-yl]-5,7-dimethoxy-3*H*-quinazolin-4-one;
7-(2-benzyloxy-ethoxy)-2-[4-(2-hydroxy-ethoxy)-3,5-dimethyl-phenyl]-5-methoxy-3*H*-quinazolin-4-one;
2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-dimethyl-phenoxy]-acetamide;
2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-dimethyl-phenoxy]-*N*-methyl-acetamide;
2-[4-(5,7-Dimethoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-dimethyl-phenoxy]-*N*-(4-methoxy-phenyl)-acetamide;
N-benzyl-2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy]acetamide;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-methoxyquinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5-methoxyquinazolin-4(3H)-one;
7-chloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
8-chloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-8-methoxyquinazolin-4(3H)-one;
5-chloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-7-methoxyquinazolin-4(3H)-one;
5,7-dimethoxy-2-(4-methoxy-3,5-dimethylphenyl)quinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3-methylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-((4-methylpiperazin-1-yl)methyl)quinazolin-4(3H)-one;
5,7-Dimethoxy-2-{3-methyl-4-[2-(5-phenyl-4H-[1,2,4]triazol-3-ylamino)-ethoxy]-phenyl}-3*H*-quinazolin-4-one;
2-{3,5-Dimethyl-4-[2-(3-methyl-[1,2,4]oxadiazol-5-ylamino)-ethoxy]-phenyl}-5,7-dimethoxy-3*H*-quinazolin-4-one;
N-{2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2,6-dimethyl-phenoxy]-ethyl}-acetamide;
N-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylbenzyl)acetamide;
N-[4-(5,7-dimethoxy-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2,6-dimethylbenzyl]-acetamide;
2-{3,5-Dimethyl-4-[2-(2,2,2-trifluoro-ethylamino)-ethoxy]-phenyl}-5,7-dimethoxy-3H-quinazolin-4-one;
N-{2-[4-(6,8-Dimethoxy-1-oxo-1,2-dihydro-isoquinolin-3-yl)-2,6-dimethyl-phenoxy]-ethyl}-formamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)methanesulfonamide;
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)isobutyramide;
2-(3,5-dimethyl-4-(2-(methylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)propane-2-sulfonamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylphenoxy)ethyl)acetamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylphenoxy)ethyl)isobutyramide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylphenoxy)ethyl)methanesulfonamide;
2-(4-(2-(dimethylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N-methylacetamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)formamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N-methylformamide;
N-(2-(4-(5,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)cyanamide;
2-(3,5-dimethyl-4-(2-(5-methylisoxazol-3-ylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(3,5-dimethyl-4-(2-(pyrimidin-2-ylamino)ethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(4-(2-(isoxazol-3-ylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-(4-(2-(4,6-dimethoxypyrimidin-2-ylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
2-[4-(3-hydroxy-propyl)-3,5-dimethoxyphenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one; and
2-[4-(3-hydroxy-propyl)-3-methoxy-phenyl]-5,7-dimethoxy-3*H*-quinazolin-4-one;

and
tautomers, stereoisomers, pharmaceutically acceptable salts, or hydrates thereof.

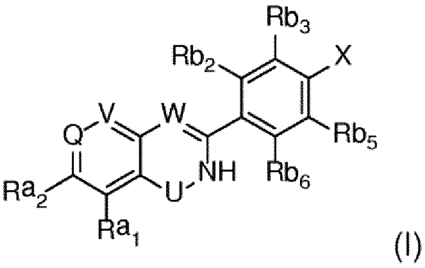
10. The pharmaceutical composition for use according to claim 1, wherein the compound is selected from:

5-(2-dimethylamino-ethoxy)-2(4-hydroxy-3,5-dimethylphenyl)-7-methoxy-3H-quinazolin-4-one;
2-(4-hydroxy-3,5-dimethyl-phenyl)-7-methoxy-5-(2-methoxy-ethoxy)-3*H*-quinazolin-4-one;
7-(2-amino-ethoxy)-2-(4-hydroxy-3, 5-dimethyl-phenyl)-5-methoxy-3*H*-quinazolin-4-one;
2-(4-hydroxy-3,5-dimethyl-phenyl)-5-methoxy-7-(2-methoxy-ethoxy)-3*H*-quinazolin-4-one;
7-(2-benzyloxy-ethoxy)-2-(4-hydroxy-3,5-dimethyl-phenyl)-5-methoxy-3*H*-quinazolin-4-one;
2-(4-hydroxy-3,5-dimethylphenyl)-5-methoxy-7-[2-(pyridin-3-ylmethoxy)ethoxy]-3H-quinazolin-4-one;
7-(2-dimethylamino-ethoxy)-2-(4-hydroxy-3,5-dimethylphenyl)-3*H*-quinazolin-4-one;
2-(4-hydroxy-3,5-dimethyl-phenyl)-6-(pyridin-4-ylamino)-3*H*-quinazolin-4-one;
2-(4-hydroxy-3,5-dimethyl-phenyl)-6-(pyridin-2-ylamino)-3*H*-quinazolin-4-one;
2-(4-hydroxy-3,5-dimethylphenyl)-6-((4-methylpiperazin-1-yl)methyl)quinazolin-4(3H)-one;
N-((2-(4-hydroxy-3,5-dimethylphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl)methyl)methanesulfonamide;

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

Patentansprüche

1. Pharmazeutische Zusammensetzung zur Verwendung beim Reduzieren von IL-6 für die Behandlung von Krebs bei einem Subjekt, wobei die Zusammensetzung eine therapeutisch wirksame Menge von mindestens einer Verbindung der Formel I umfasst:

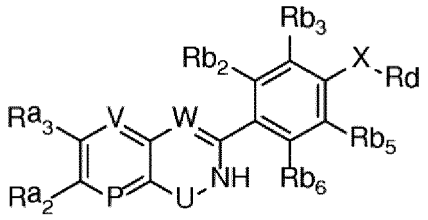


(I)

oder ein Stereoisomer, Tautomer, pharmazeutisch annehmbares Salz oder Hydrat davon, wobei:

Q ausgewählt ist aus N und CRa_3;
V ausgewählt ist aus N und CRa_4;
W ausgewählt ist aus N und CH;
U ausgewählt ist aus C=O, C=S, SO_2 und S=O;
X ausgewählt ist aus OH, SH, NH_2, S(O)H, $S(O)_2H$, $S(O)_2NH_2$, $S(O)NH_2$, NHAc und $NHSO_2Me$;
Ra_1, Ra_3 und Ra_4 unabhängig ausgewählt sind aus Wasserstoff, C_1-C_6-Alkyl, C_1-C_6-Alkoxy, C_3-C_6-Cycloalkyl und Halogen;
Ra_2 ausgewählt ist aus Wasserstoff, C_1-C_6-Alkyl, C_1-C_6-Alkoxy, C_3-C_6-Cycloalkyl, Amino, Amid und Halogen;
Rb_2 und Rb_6 unabhängig ausgewählt sind aus Wasserstoff, Methyl und Fluor;
Rb_3 und Rb_5 unabhängig ausgewählt sind aus Wasserstoff, Halogen, C_1-C_6-Alkyl, C_3-C_6-Cycloalkyl und C_1-C_6-Alkoxy; und
Rb_2 und Rb_3 und/oder Rb_5 und Rb_6 verbunden sein können, um ein Cycloalkyl oder einen Heterocyclus zu bilden, vorausgesetzt, dass mindestens eines von Ra_1, Ra_2, Ra_3 und Ra_4 nicht Wasserstoff ist.

2. Eine pharmazeutische Zusammensetzung zur Verwendung beim Reduzieren von IL-6 und/oder VCAM-1 für die Behandlung von Krebs oder einer Krankheit, ausgewählt aus Arthritis, Asthma, Dermatitis, Psoriasis, zystischer Fibrose, später und chronischer Abstoßung von solidem Organ nach Transplantation, multipler Sklerose, systemischer Lupus erythematosus, entzündlichen Darmerkrankungen, Augenentzündung, Uveitis, Rhinitis, chronischer obstruktiver Lungenerkrankung (chronic obstructive pulmonary disease, COPD), Glomerulonephritis, Basedow’sche Krankheit, gastrointestinaler Allergien und Bindehautentzündung bei einem Subjekt, wobei die Zusammensetzung eine therapeutisch wirksame Menge von mindestens einer Verbindung der Formel II umfasst:



(II)

oder ein Stereoisomer, Tautomer, pharmazeutisch annehmbares Salz oder Hydrat davon, wobei:

P ausgewählt ist aus N und CRa_1,
V ausgewählt ist aus N und CRa_4;
W ausgewählt ist aus N und CH;
U C=O ist;
Ra_1, Ra_3 und Ra_4 unabhängig ausgewählt sind aus Wasserstoff, C_1-C_6-Alkyl, C_1-C_6-Alkoxy, C_3-C_6-Cycloalkyl und Halogen;
Ra_2 ausgewählt ist aus Wasserstoff, C_1-C_6-Alkyl, C_1-C_6-Alkoxy, Heterocyclus, Amino, Amid, Fluor und Brom;
Rb_2 und Rb_6 unabhängig ausgewählt sind aus Wasserstoff, Methyl und Fluor;
Rb_3 und Rb_5 unabhängig ausgewählt sind aus Wasserstoff, C_1-C_6-Alkyl, C_3-C_6-Cycloalkyl, C_1-C_6-Alkoxy, Halogen und Amino;
Rb_2 und Rb_3 und/oder Rb_5 und Rb_6 verbunden sein können, um ein Cycloalkyl, Phenyl oder einen Heterocyclus zu bilden; und
X-Rd ausgewählt ist aus 2-Hydroxyethoxy, Methoxy, Benzyloxyethoxy, 2,3-Dihydroxypropoxy, Aminocarbonylethoxy, Methylaminocarbonylethoxy, (4-Methoxyphenyl)aminocarbonylethoxy, Benzylaminocarbonylethoxy, 4-Hydroxybutoxy, (5-Phenyl-4H-[1,2,4]triazol-3-ylamino)ethoxy, (3-Methyl-[1,2,4]oxadiazol-5-ylamino)ethoxy, Methylcarbonylaminoethoxy, Methylcarbonylaminomethyl, (2,2,2-Trifluorethylamino)ethoxy, Methansulfonylaminoethoxy, Isobutyrylaminoethoxy, Methylaminoethoxy, Isopropylsulfonylaminoethoxy, Dimethylaminoethoxy, N-(2-Hydroxyethyl)-N-methylacetamid, Formamid-N-2-ethoxy, Methylformamid-N-2-ethoxy, Dimethylsulfonylaminoethoxy, Cyanoaminoethoxy, (5 -Methylisoxazol-3 -ylamino)ethoxy, (Pyrimidin-2-ylamino)ethoxy, (Isoxazol-3-ylamino)ethoxy, (4,6-Dimethoxypyrimidin-2-ylamino)ethoxy, 3-Hydroxypropyl und 2-Hydroxyethyl, vorausgesetzt, dass
mindestens eines von Ra_1, Ra_2, Ra_3 und Ra_4 nicht Wasserstoff ist;
wenn -XRd $-OCH_2CH_2OH$ ist, dann Rb_3 nicht Pyrrolidin ist; und
wenn -XRd -OMe ist, dann Ra_2 nicht $-CH_2$-Morpholino ist.

3. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 2, wobei:

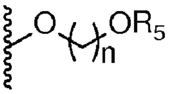
U C=O ist
P CRa_1 ist;
Ra_1 ausgewählt ist aus Wasserstoff, C_1-C_6-Alkyl, C_1-C_6-Alkoxy und Halogen;
Ra_2 ausgewählt ist aus Wasserstoff, C_1-C_6-Alkyl, C_1-C_6-Alkoxy, Heterocyclus, Amid und Amino;
Ra_3 und Ra_4 unabhängig ausgewählt sind aus Wasserstoff, C_1-C_6-Alkoxy, C_1-C_6-Alkyl und Halogen; und
Rb_3 und Rb_5 unabhängig ausgewählt sind aus Wasserstoff, C_1-C_6-Alkyl, C_3-C_6-Cycloalkyl, C_1-C_6-Alkoxy, Halogen und Amino, wobei Rb_2 und Rb_3 und/oder Rb_5 und Rb_6 verbunden sein können, um einen Phenyl-Ring zu bilden.

4. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 2, wobei Ra_1 ausgewählt ist aus Wasserstoff, unsubstituiertem C_1-C_6-Alkyl, unsubstituiertem C_1-C_6-Alkoxy und Halogen.

5. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 2, wobei Ra_2 ausgewählt ist aus Wasserstoff, C_1-C_6-Alkyl substituiert mit Heterocyclyl, unsubstituiertem C_1-C_6-Alkoxy, Amino und Heterocyclus.

6. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 2, wobei:

Ra_3 ausgewählt ist aus Wasserstoff, Methoxy, unsubstituiertem C_1-C_6-Alkyl, Halogen und



;

n 1, 2 oder 3 ist; und
R_5 C_1-C_6-Alkyl substituiert mit Phenyl oder Heteroaryl ist.

7. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 2, wobei Ra_4 ausgewählt ist aus Wasserstoff, unsubstituiertem C_1-C_6-Alkoxy und Halogen.

8. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 2, wobei Rb_3 und Rb_5 unabhängig ausgewählt sind aus Wasserstoff, Methyl, C_1-C_6-Alkyl substituiert mit Heterocyclyl und unsubstituiertem C_1-C_6-Alkoxy, wobei Rb_2 und Rb_3 und/oder Rb_5 und Rb_6 verbunden sein können, um einen Phenyl-Ring zu bilden.

9. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 2, wobei die Verbindung aus Folgenden ausgewählt ist:

2-(4-(2-Hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxychinazolin-4(3H)-on;
5,7-Dimethoxy-2-(4-methoxyphenyl)chinazolin-4(3H)-on;
2-(4-(2-Hydroxyethoxy)-3,5-dimethylphenyl)-6,7-dimethoxychinazolin-4(3H)-on;
5,7-Dimethoxy-2-(4-methoxy-3-(morpholinomethyl)phenyl)chinazolin-4(3H)-on;
2-(4-(2-Hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxypyrido[2,3-d]pyrimidin-4(3H)-on;
N-(2-(4-(2-Hydroxyethoxy)-3,5-dimethylphenyl)-4-oxo-3,4-dihydrochinazolin-6-yl)acetamid;
2-(4-(2-Hydroxyethoxy)-3,5-dimethylphenyl)-6-morpholinochinazolin-4(3H)-on;
2-(4-(2-(Benzyloxy)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxypyrido[2,3-d]pyrimidin-4(3H)-on;
2-(4-(2-Hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethylpyrido[2,3-d]pyrimidin-4(3H)-on;
5,7-Difluor-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)chinazolin-4(3H)-on;
5,7-Dichlor-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)chinazolin-4(3H)-on;
2-[4-(2-Hydroxy-ethoxy)-3,5-dimethyl-phenyl]-5,7-diisopropoxy-3H-chinazolin-4-on;
2-[4-(2-Hydroxyethoxy)-3,5-dimethyl-phenyl]-6-morpholin-4-ylmethyl-3H-chinazolin-4-on;
2-[4-(2,3-Dihydroxy-propoxy)-3,5-dimethyl-phenyl]-5,7-dimethoxy-3*H*-chinazolin-4-on;
2-[4-(2-Hydroxy-ethoxy)-3,5-dimethylphenyl]-5,7-dimethoxy-6-morpholin-4-ylmethyl-3H-chinazolin-4-on;
2-[4-(2-Hydroxy-ethoxy)-phenyl]-5,7-dimethoxy-3*H*-chinazolin-4-on;
2-[4-(2-Hydroxy-ethoxy)-naphthalen-1-yl]-5,7-dimethoxy-3*H*-chinazolin-4-on,
7-(2-Benzyloxy-ethoxy)-2-[4-(2-hydroxy-ethoxy)-3,5-dimethyl-phenyl]-5-methoxy-3*H*-chinazolin-4-on;
2-[4-(5,7-Dimethoxy-4-oxo-3,4-dihydro-chinazolin-2-yl)-2,6-dimethyl-phenoxy]-acetamid;
2-[4-(5,7-Dimethoxy-4-oxo-3,4-dihydro-chinazolin-2-yl)-2,6-dimethyl-phenoxy]-*N*-methyl-acetamid;
2-[4-(5,7-Dimethoxy-4-oxo-3,4-dihydro-chinazolin-2-yl)-2,6-dimethyl-phenoxy]-N-(4-methoxy-phenyl)-acetamid;
N-Benzyl-2-[4-(5,7-dimethoxy-4-oxo-3,4-dihydrochinazolin-2-yl)-2,6-dimethylphenoxy]acetamid;
2-(4-(2-Hydroxyethoxy)-3,5-dimethylphenyl)-6-methoxychinazolin-4(3H)-on;
2-(4-(2-Hydroxyethoxy)-3,5-dimethylphenyl)-5-methoxychinazolin-4(3H)-on;
7-Chlor-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)chinazolin-4(3H)-on;
8-Chlor-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)chinazolin-4(3H)-on;
2-(4-(2-Hydroxyethoxy)-3,5-dimethylphenyl)-8-methoxychinazolin-4(3H)-on;
5-Chlor-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)chinazolin-4(3H)-on;
2-(4-(2-Hydroxyethoxy)-3,5-dimethylphenyl)-7-methoxychinazolin-4(3H)-on;
5,7-Dimethoxy-2-(4-methoxy-3,5-dimethylphenyl)chinazolin-4(3H)-on;
2-(4-(2-Hydroxyethoxy)-3-methylphenyl)-5,7-dimethoxychinazolin-4(3H)-on;
2-(4-(2-Hydroxyethoxy)-3,5-dimethylphenyl)-6-((4-methylpiperazin-1-yl)methyl)chinazolin-4(3H)-on;
5,7-Dimethoxy-2-{3-methyl-4-[2-(5-phenyl-4H-[1,2,4]triazol-3-ylamino)-ethoxy]-phenyl}-3*H*-chinazolin-4-on;
2-{3,5-Dimethyl-4-[2-(3-methyl-[1,2,4]oxadiazol-5-ylamino)-ethoxy]-phenyl}-5,7-dimethoxy-3*H*-chinazolin-4-on;
N-{2-[4-(5,7-Dimethoxy-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2,6-dimethyl-phenoxy]-ethyl}-acetamid;
N-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydrochinazolin-2-yl)-2,6-dimethylbenzyl)acetamid;
N-[4-(5,7-Dimethoxy-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2,6-dimethyl-benzyl]-acetamid;

2-{3,5-Dimethyl-4-[2-(2,2,2-trifluor-ethylamino)-ethoxy]-phenyl}-5,7-dimethoxy-3H-chinazolin -4-on;
N-{2-[4-(6,8-Dimethoxy-1-oxo-1,2-dihydro-isochinolin-3-yl)-2,6-dimethyl-phenoxy]-ethyl}-for mamid;
N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydrochinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)methans ulfonamid;
N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydrochinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-4-meth oxybenzamid;
N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydrochinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)acetami d;
N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydrochinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)isobutyr amid;
2-(3,5-Dimethyl-4-(2-(methylamino)ethoxy)phenyl)-5,7-dimethoxychinazolin-4(3H)-on;
N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydrochinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)propan-2-sulfonamid;
N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydrochinazolin-2-yl)-2-methylphenoxy)ethyl)acetamid;
N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydrochinazolin-2-yl)-2-methylphenoxy)ethyl)isobutyrami d;
N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydrochinazolin-2-yl)-2-methylphenoxy)ethyl)methansulfo namid;
2-(4-(2-(Dimethylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxychinazolin-4(3H)-on;
N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydrochinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N-meth ylacetamid;
N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydrochinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)formam id;
N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydrochinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)-N-meth ylformamid;
N-(2-(4-(5,7-Dimethoxy-4-oxo-3,4-dihydrochinazolin-2-yl)-2,6-dimethylphenoxy)ethyl)cyanami d;
2-(3,5-Dimethyl-4-(2-(5-methylisoxazol-3-ylamino)ethoxy)phenyl)-5,7-dimethoxychinazolin-4(3H)-on;
2-(3,5-Dimethyl-4-(2-(pyrimidin-2-ylamino)ethoxy)phenyl)-5,7-dimethoxychinazolin-4(3H)-on;
2-(4-(2-(Isoxazol-3-ylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxychinazolin-4(3H)-on;
2-(4-(2-(4,6-Dimethoxypyrimidin-2-ylamino)ethoxy)-3,5-dimethylphenyl)-5,7-dimethoxychinaz olin-4(3H)-on;
2-[4-(3-Hydroxy-propyl)-3,5-dimethoxyphenyl]-5,7-dimethoxy-3*H*-chinazolin-4-on,
und
2-[4-(3-Hydroxy-propyl)-3-methoxy-phenyl]-5,7-dimethoxy-3*H*-chinazolin-4-on, und

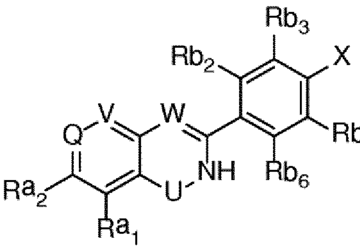
Tautomeren, Stereoisomeren, pharmazeutisch annehmbaren Salzen oder Hydraten davon.

10. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 1, wobei die Verbindung aus Folgenden ausgewählt ist:

5-(2-Dimethylamino-ethoxy)-2(4-hydroxy-3,5-dimethylphenyl)-7-methoxy-3H-chinazolin-4-on,
2-(4-Hydroxy-3,5-dimethyl-phenyl)-7-methoxy-5-(2-methoxy-ethoxy)-3*H*-chinazolin-4-on,
7-(2-Amino-ethoxy)-2-(4-hydroxy-3,5-dimethyl-phenyl)-5-methoxy-3*H*-chinazolin-4-on;
2-(4-Hydroxy-3,5-dimethyl-phenyl)-5-methoxy-7-(2-methoxy-ethoxy)-3*H*-chinazolin-4-on,
7-(2-Benzyloxy-ethoxy)-2-(4-hydroxy-3,5-dimethyl-phenyl)-5-methoxy-3*H*-chinazolin-4-on;
2-(4-Hydroxy-3,5-dimethylphenyl)-5-methoxy-7-[2-(pyridin-3-ylmethoxy)ethoxy]-3H-chinazolin-4-on;
7-(2-Dimethylamino-ethoxy)-2-(4-hydroxy-3,5-dimethylphenyl)-3*H*-chinazolin-4-on;
2-(4-Hydroxy-3,5-dimethyl-phenyl)-6-(pyridin-4-ylamino)-3*H*-chinazolin-4-on,
2-(4-Hydroxy-3,5-dimethyl-phenyl)-6-(pyridin-2-ylamino)-3*H*-chinazolin-4-on,
2-(4-Hydroxy-3,5-dimethylphenyl)-6-((4-methylpiperazin-1-yl)methyl)chinazolin-4(3H)-on;
N-((2-(4-Hydroxy-3,5-dimethylphenyl)-4-oxo-3,4-dihydrochinazolin-6-yl)methyl)methanesulfon amid; und
Tautomeren, Stereoisomeren, pharmazeutisch annehmbaren Salzen und Hydraten davon.

Revendications

1. Composition pharmaceutique pour utilisation dans la réduction de l'IL-6 pour le traitement d'un cancer chez un sujet, ladite composition comprenant une quantité thérapeutiquement efficace d'au moins un composé de formule I :

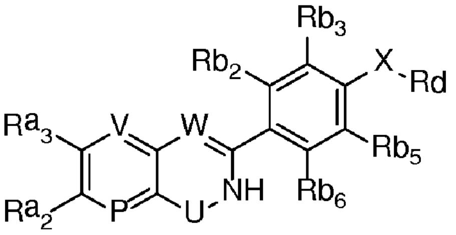


(I)

ou stéréoisomère, tautomère, sel pharmaceutiquement acceptable, ou hydrate de celui-ci, dans laquelle :

Q est choisi parmi un atome N et un groupe CRa_3 ;
V est choisi parmi un atome N et un groupe CRa_4 ;
W est choisi parmi un atome N et un groupe CH ;
U est choisi parmi un groupe C=O, C=S, SO_2 et S=O ;
X est choisi parmi un groupe OH, SH, NH_2, S(O)H, $S(O)_2H$, $S(O)_2NH_2$, $S(O)NH_2$, NHAc, et $NHSO_2Me$;
Ra_1, Ra_3, et Ra_4 sont indépendamment choisis parmi un atome d'hydrogène, un groupe (C_1 à C_6)alkyle, un groupe (C_1 à C_6)alcoxy, un groupe (C_3 à C_6)cycloalkyle, et un atome d'halogène ;
Ra_2 est choisi parmi un atome d'hydrogène, un groupe (C_1 à C_6)alkyle, un groupe (C_1 à C_6)alcoxy, un groupe (C_3 à C_6)cycloalkyle, un groupe amino, un groupe amide, et un atome d'halogène ;
Rb_2 et Rb_6 sont indépendamment choisis parmi un atome d'hydrogène, un groupe méthyle et un atome de fluor ;
Rb_3 et Rb_5 sont indépendamment choisis parmi un atome d'hydrogène, un atome d'halogène, un groupe (C_1 à C_6)alkyle, un groupe (C_3 à C_6)cycloalkyle, et un groupe (C_1 à C_6)alcoxy ; et
Rb_2 et Rb_3 et/ou Rb_5 et Rb_6 peuvent être reliés pour former un groupe cycloalkyle ou un groupe hétérocyclique, à condition qu'au moins l'un des groupes Ra_1, Ra_2, Ra_3 et Ra_4 ne représente pas un atome d'hydrogène.

2. Composition pharmaceutique pour utilisation dans la réduction de l'IL-6 et/ou de la VCAM-1 pour le traitement d'une maladie ou d'un cancer choisi parmi l'arthrite, l'asthme, une dermatite, le psoriasis, la mucoviscidose, le rejet d'organe solide tardif ou chronique après transplantation, la sclérose en plaques, le lupus érythémateux systémique, les maladies inflammatoires intestinales, une inflammation oculaire, une uvéite, une rhinite, une bronchopneumopathie chronique obstructive (BPCO), un glomérulonéphrite, la maladie de Grave, les allergies gastrointestinales et une conjonctivite chez un sujet, ladite composition comprenant une quantité thérapeutiquement efficace d'au moins un composé de formule II :



(II)

ou stéréoisomère, tautomère, sel pharmaceutiquement acceptable, ou hydrate de celui-ci, dans laquelle :

P est choisi parmi un atome N et un groupe CRa_1 ;
V est choisi parmi un atome N et un groupe CRa_4 ;
W est choisi parmi un atome N et un groupe CH ;
U représente un groupe C=O
Ra_1, Ra_3, et Ra_4 sont indépendamment choisis parmi un atome d'hydrogène, un groupe (C_1 à C_6)alkyle, un groupe (C_1 à C_6)alcoxy, un groupe (C_3 à C_6)cycloalkyle, et un atome d'halogène ;
Ra_2 est choisi parmi un atome d'hydrogène, un groupe (C_1 à C_6)alkyle, un groupe (C_1 à C_6)alcoxy, un groupe hétérocyclique, un groupe amino, un groupe amide, et un groupe fluoro et un groupe bromo ;
Rb_2 et Rb_6 sont indépendamment choisis parmi un atome d'hydrogène, un groupe méthyle et un atome de fluor ;
Rb_3 et Rb_5 sont indépendamment choisis parmi un atome d'hydrogène, un groupe (C_1 à C_6)alkyle, un groupe (C_3 à C_6)cycloalkyle, et un groupe (C_1 à C_6)alcoxy, un atome d'halogène, et un groupe amino ; et
Rb_2 et Rb_3 et/ou Rb_5 et Rb_6 peuvent être reliés pour former un groupe cycloalkyle, un groupe phényle ou un groupe hétérocyclique ; et
X-Rd est choisi parmi un groupe 2-hydroxyéthoxy, méthoxy, benzyloxyéthoxy, 2,3-dihydroxypropoxy, aminocarbonyléthoxy, méthylaminocarbonyléthoxy, (4-méthoxyphényl)aminocarbonyléthoxy, benzylaminocarbonyléthoxy, 4-hydroxybutoxy, (5-phényl-4H-[1,2,4]triazol-3-ylamino)éthoxy, (3-méthyl-[1,2,4]oxadiazol-5-ylamino)éthoxy, méthylcarbonylaminoéthoxy, méthylcarbonylaminométhyl, (2,2,2-trifluoro-éthylamino)éthoxy, méthanesulfonylaminoéthoxy, isobutyrylaminoéthoxy, méthylaminoéthoxy, isopropylsulfonylaminoéthoxy, diméthylaminoéthoxy, N-(2-hydroxyéthyl)-N-méthylacétamide, formamide-N-2-éthoxy, méthylformamide-N-2-éthoxy, diméthylsulfonylaminoéthoxy, cyanoaminoéthoxy, (5-méthylisoxazol-3-ylamino)éthoxy, (pyrimidin-2-ylamino)éthoxy, (isoxazol-3-ylamino)éthoxy, (4,6-diméthoxypyrimidin-2-ylamino)éthoxy, 3-hydroxypropyle et 2-

hydroxyéthyle,
à condition que
au moins l'un des groupes Ra_1, Ra_2, Ra_3 et Ra_4 ne représente pas un atome d'hydrogène ;
si -XRd représente un groupe $-OCH_2CH_2OH$, alors Rb_3 ne représente pas un groupe pyrrolidine ; et
si -XRd représente un groupe -OMe, alors Ra_2 ne représente pas un groupe $-CH_2$morpholino.

3. Composition pharmaceutique pour utilisation selon la revendication 2, dans laquelle :

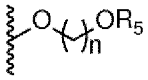
U représente un groupe C=O ;
P représente un groupe CRa_1 ;
Ra_1 est choisi parmi un atome d'hydrogène, un groupe (C_1 à C_6)alkyle, un groupe (C_1 à C_6)alcoxy, et un atome d'halogène ;
Ra_2 est choisi parmi un atome d'hydrogène, un groupe (C_1 à C_6)alkyle, un groupe (C_1 à C_6)alcoxy, un groupe hétérocyclique, un groupe amide, et un groupe amino ;
Ra_3 et Ra_4 sont indépendamment choisis parmi un atome d'hydrogène, un groupe (C_1 à C_6)alcoxy, un groupe (C_1 à C_6)alkyle, et un atome d'halogène ; et
Rb_3 et Rb_5 sont indépendamment choisis parmi un atome d'hydrogène, un groupe (C_1 à C_6)alkyle, un groupe (C_3 à C_6)cycloalkyle, un groupe (C_1 à C_6)alcoxy, un atome d'halogène, et un groupe amino, Rb_2 et Rb_3 et/ou Rb_5 et Rb_6 pouvant être reliés pour former un noyau phényle.

4. Composition pharmaceutique pour utilisation selon la revendication 2, Ra_1 étant choisi parmi un atome d'hydrogène, un groupe (C_1 à C_6)alkyle non substitué, un groupe (C_1 à C_6)alcoxy non substitué, et un atome d'halogène.

5. Composition pharmaceutique pour utilisation selon la revendication 2, Ra_2 étant choisi parmi un atome d'hydrogène, un groupe (C_1 à C_6)alkyle substitué par un groupe hétérocyclyle, un groupe (C_1 à C_6)alcoxy non substitué, un groupe amino et un groupe hétérocyclique.

6. Composition pharmaceutique pour utilisation selon la revendication 2, dans laquelle :

Ra_3 est choisi parmi un atome d'hydrogène, un groupe méthoxy, un groupe (C_1 à C_6)alkyle non substitué, un atome d'halogène et



;

n vaut 1, 2 ou 3 ; et
R_5 représente un groupe (C_1 à C_6)alkyle substitué par un groupe phényle ou hétéroaryle.

7. Composition pharmaceutique pour utilisation selon la revendication 2, Ra_4 étant choisi parmi un atome d'hydrogène, un groupe (C_1 à C_6)alcoxy non substitué, et un atome d'halogène.

8. Composition pharmaceutique pour utilisation selon la revendication 2, Rb_3 et Rb_5 étant indépendamment choisis parmi un atome d'hydrogène, un groupe méthyle, un groupe (C_1 à C_6)alkyle substitué par un groupe hétérocyclyle, et un groupe (C_1-C_6)alcoxy non substitué, Rb_2 et Rb_3 et/ou Rb_5 et Rb_6 pouvant être reliés pour former un noyau phényle.

9. Composition pharmaceutique pour utilisation selon la revendication 2, ledit composé étant choisi parmi :

2-(4-(2-hydroxyéthoxy)-3,5-diméthylphényl)-5,7-diméthoxyquinazolin-4(3H)-one ;
5,7-diméthoxy-2-(4-méthoxyphényl)quinazolin-4(3H)-one ;
2-(4-(2-hydroxyéthoxy)-3,5-diméthylphényl)-6,7-diméthoxyquinazolin-4(3H)-one ;
5,7-diméthoxy-2-(4-méthoxy-3-(morpholinométhyl)phényl)quinazolin-4(3H)-one ;
2-(4-(2-hydroxyéthoxy)-3,5-diméthylphényl)-5,7-diméthoxypyrido[2,3-d]pyrimidin-4(3 H)-one ;
N-(2-(4-(2-hydroxyéthoxy)-3,5-diméthylphényl)-4-oxo-3,4-dihydroquinazolin-6-yl)acétamide ;
2-(4-(2-hydroxyéthoxy)-3,5-diméthylphényl)-6-morpholinoquinazolin-4(3H)-one ;
2-(4-(2-(benzyloxy)éthoxy)-3,5-diméthylphényl)-5,7-diméthoxypyrido[2,3-d]pyrimidin-4 (3H)-one ;
2-(4-(2-hydroxyéthoxy)-3,5-diméthylphényl)-5,7-diméthylpyrido[2,3-d]pyrimidin-4(3H)-one ;

5,7-difluoro-2-(4-(2-hydroxyéthoxy)-3,5-diméthylphényl)quinazolin-4(3H)-one ;
5,7-dichloro-2-(4-(2-hydroxyéthoxy)-3,5-diméthylphényl)quinazolin-4(3H)-one ;
2-[4-(2-hydroxy-éthoxy)-3,5-diméthyl-phényl]-5,7-diisopropoxy-3H-quinazolin-4-one ;
2-[4-(2-hydroxyéthoxy)-3,5-diméthyl-phényl]-6-morpholin-4-ylméthyl-3H-quinazolin-4-one ;
2-[4-(2,3-dihydroxy-propoxy)-3,5-diméthyl-phényl]-5,7-diméthoxy-3*H*-quinazolin-4-one 2-[4-(2-hydroxy-éthoxy)-3,5-diméthylphényl]-5,7-diméthoxy-6-morpholin-4-ylméthyl-3H-quinazolin-4-one ;
2-[4-(2-hydroxy-éthoxy)-phényl]-5,7-diméthoxy-3*H*-quinazolin-4-one ;
2-[4-(2-hydroxy-éthoxy)-naphtalén-1-yl]-5,7-diméthoxy-3*H*-quinazolin-4-one ;
7-(2-benzyloxy-éthoxy)-2-[4-(2-hydroxy-éthoxy)-3,5-diméthyl-phényl]-5-méthoxy-3*H*-quinazolin-4-one ;
2-[4-(5,7-diméthoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-diméthyl-phénoxy]-acétamide ;
2-[4-(5,7-diméthoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-diméthyl-phénoxy]-*N*-méthyl-acétamide ;
2-[4-(5,7-diméthoxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-2,6-diméthyl-phénoxy]-N-(4-méthoxy-phényl)-acétamide ;
N-benzyl-2-[4-(5,7-diméthoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-diméthylphénoxy] acétamide ;
2-(4-(2-hydroxyéthoxy)-3,5-diméthylphényl)-6-méthoxyquinazolin-4(3H)-one ;
2-(4-(2-hydroxyéthoxy)-3,5-diméthylphényl)-5-méthoxyquinazolin-4(3H)-one ;
7-chloro-2-(4-(2-hydroxyéthoxy)-3,5-diméthylphényl)quinazolin-4(3H)-one ;
8-chloro-2-(4-(2-hydroxyéthoxy)-3,5-diméthylphényl)quinazolin-4(3H)-one ;
2-(4-(2-hydroxyéthoxy)-3,5-diméthylphényl)-8-méthoxyquinazolin-4(3H)-one ;
5-chloro-2-(4-(2-hydroxyéthoxy)-3,5-diméthylphényl)quinazolin-4(3H)-one ;
2-(4-(2-hydroxyéthoxy)-3,5-diméthylphényl)-7-méthoxyquinazolin-4(3H)-one ;
5,7-diméthoxy-2-(4-méthoxy-3,5-diméthylphényl)quinazolin-4(3H)-one ;
2-(4-(2-hydroxyéthoxy)-3-méthylphényl)-5,7-diméthoxyquinazolin-4(3H)-one ;
2-(4-(2-hydroxyéthoxy)-3,5-diméthylphényl)-6-((4-méthylpiperazin-1-yl)méthyl)quinazolin-4(3H)-one ;
5,7-diméthoxy-2-{3-méthyl-4-[2-(5-phényl-4H-[1,2,4]triazol-3-ylamino)-éthoxy]-phényl}-3*H*-quinazolin-4-one ;
2-{3,5-diméthyl-4-[2-(3-méthyl-[1,2,4]oxadiazol-5-ylamino)-éthoxy]-phényl}-5,7-diméthoxy-3*H*-quinazolin-4-one ;
N-{2-[4-(5,7-diméthoxy-4-oxo-3,4-dihydro-pyndo[2,3-d]pyrimidin-2-yl)-2,6-diméthyl-phénoxy]-éthyl}-acétamide ;
N-(4-(5,7-diméthoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-diméthylbenzyl)acétamide ;
N-[4-(5,7-diméthoxy-4-oxo-3,4-dihydro-pyrido[2,3-d]pyrimidin-2-yl)-2,6-diméthyl-benzyl]-acétamide ;
2-{3,5-diméthyl-4-[2-(2,2,2-trifluoro-éthylamino)-éthoxy]-phényl}-5,7-diméthoxy-3*H*-quinazolin-4-one ;
N-{2-[4-(6,8-diméthoxy-1-oxo-1,2-dihydro-isoquinolin-3-yl)-2,6-diméthyl-phénoxy]-éthyl}-formamide ;
N-(2-(4-(5,7-diméthoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-diméthylphénoxy)éthyl) methanesulfonamide ;
N-(2-(4-(5,7-diméthoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-diméthylphénoxy)éthyl)-4-méthoxybenzamide ;
N-(2-(4-(5,7-diméthoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-diméthylphénoxy)éthyl)acétamide ;
N-(2-(4-(5,7-diméthoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-diméthylphénoxy)éthyl)isobutyramide ;
2-(3,5-diméthyl-4-(2-(méthylamino)éthoxy)phényl)-5,7-diméthoxyquinazolin-4(3H)-one
N-(2-(4-(5,7-diméthoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-diméthylphénoxy)éthyl)propane-2-sulfonamide ;
N-(2-(4-(5,7-diméthoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2-méthylphénoxy)éthyl)acétamide ;
N-(2-(4-(5,7-diméthoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2-méthylphénoxy)éthyl)isobutyramide ;
N-(2-(4-(5,7-diméthoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2-méthylphénoxy)éthyl)méthanesulfonamide ;
2-(4-(2-(diméthylamino)éthoxy)-3,5-diméthylphényl)-5,7-diméthoxyquinazolin-4(3H)-one;
N-(2-(4-(5,7-diméthoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-diméthylphénoxy)éthyl)-N-méthylacétamide ;
N-(2-(4-(5,7-diméthoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-diméthylphénoxy)éthyl)formamide ;
N-(2-(4-(5,7-diméthoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-diméthylphénoxy)éthyl)-N-méthylformamide ;
N-(2-(4-(5,7-diméthoxy-4-oxo-3,4-dihydroquinazolin-2-yl)-2,6-diméthylphénoxy)éthyl)cyanamide ;
2-(3,5-diméthyl-4-(2-(5-méthylisoxazol-3-ylamino)éthoxy)phényl)-5,7-diméthoxyquinazolin-4(3H)-one ;
2-(3,5-diméthyl-4-(2-(pyrimidin-2-ylamino)éthoxy)phényl)-5,7-diméthoxyquinazolin-4(3 H)-one ;
2-(4-(2-(isoxazol-3-ylamino)éthoxy)-3,5-diméthylphényl)-5,7-diméthoxyquinazolin-4(3 H)-one ;
2-(4-(2-(4,6-diméthoxypyrimidin-2-ylamino)éthoxy)-3,5-diméthylphényl)-5,7-diméthoxyquinazolin-4(3H)-one ;
2-[4-(3-hydroxy-propyl)-3,5-diméthoxyphényl]-5,7-diméthoxy-3*H*-quinazolin-4-one et
2-[4-(3-hydroxy-propyl)-3-méthoxy-phényl]-5,7-diméthoxy-3*H*-quinazolin-4-one ; et tautomères, stéréoisomères, sels pharmaceutiquement acceptables, ou hydrates de ceux-ci.

10. Composition pharmaceutique pour utilisation selon la revendication 1, ledit composé étant choisi parmi :

5-(2-diméthylamino-éthoxy)-2(4-hydroxy-3,5-diméthylphényl)-7-méthoxy-3*H*-quinazolin-4-one ;

2-(4-hydroxy-3,5-diméthyl-phényl)-7-méthoxy-5-(2-méthoxy-éthoxy)-3*H*-quinazolin-4-one ;
7-(2-amino-éthoxy)-2-(4-hydroxy-3,5-diméthyl-phényl)-5-méthoxy-3*H*-quinazolin-4-one
; 2-(4-hydroxy-3,5-diméthyl-phényl)-5-méthoxy-7-(2-méthoxy-éthoxy)-3*H*-quinazolin-4-one ;
7-(2-benzyloxy-éthoxy)-2-(4-hydroxy-3,5-diméthyl-phényl)-5-méthoxy-3*H*-quinazolin-4 -one ;
2-(4-hydroxy-3,5-diméthylphényl)-5-méthoxy-7-[2-(pyridin-3-ylméthoxy)éthoxy]-3*H*-quinazolin-4-one ;
7-(2-diméthylamino-éthoxy)-2-(4-hydroxy-3,5-diméthylphényl)-3*H*-quinazolin-4-one ;
2-(4-hydroxy-3,5-diméthyl-phényl)-6-(pyridin-4-ylamino)-3*H*-quinazolin-4-one ;
2-(4-hydroxy-3,5-diméthyl-phényl)-6-(pyridin-2-ylamino)-3*H*-quinazolin-4-one ;
2-(4-hydroxy-3,5-diméthylphényl)-6-((4-méthylpiperazin-1-yl)méthyl)quinazolin-4(3H)-one ;
N-((2-(4-hydroxy-3,5-diméthylphényl)-4-oxo-3,4-dihydroquinazolin-6-yl)méthyl)méthanesulfonamide ; et

tautomères, stéréoisomères, sels pharmaceutiquement acceptables, et hydrates de ceux-ci.

REFERENCES CITED IN THE DESCRIPTION

Patent documents cited in the description

- WO 9947170 A **[0015]**

Non-patent literature cited in the description

- **PILEWSKI et al.** *Am. J. Respir. Cell Mol. Biol.,* 1995, vol. 12, 1-3 **[0008]**
- **OHKAWARA et al.** *Am J. Respir. Cell Mol. Biol.,* 1995, vol. 12, 4-12 **[0008]**
- **RABB et al.** *Am. J. Respir. Care Med.,* 1994, vol. 149, 1186-1191 **[0008]**
- **KOCH et al.** *Lab. Invest.,* 1991, vol. 64, 313-322 **[0008]**
- **DUCRET et al.** *Immunol.,* 1992, vol. 149, 1421-31 **[0008]**
- **YANG et al.** *Proc. Natl. Acad. Sci. USA,* 1993, vol. 90, 10494-10498 **[0009]**
- **BURKLY et al.** *Diabetes,* 1994, vol. 43, 523-534 **[0009]**
- **BARON et al.** *J. Clin. Invest.,* 1994, vol. 93, 1700-1708 **[0009]**
- **OROEZ et al.** *Immunol. Lett.,* 1992, vol. 32, 7-12 **[0009]**
- **KOCH et al.** *Nature,* 1995, vol. 376, 517-519 **[0010]**
- **FOLKMAN ; SHING.** *Biol. Chem.,* 1992, 10931-10934 **[0010]**
- **TRIKHA et al.** *Clin. Cancer Res.,* 2003, vol. 9, 4653-4665 **[0012] [0014] [0018]**
- **ROSSI et al.** *Bone Marrow Transplantation,* 2005, vol. 36, 771-779 **[0014] [0018]**
- **EMILIE et al.** *Blood,* 1994, vol. 84, 2472-2479 **[0014] [0018]**
- **CAMPBELL et al.** *Proc. Natl. Acad. Sci. USA,* 1993, vol. 90, 10061-10065 **[0014]**
- **WIJDENES et al.** *Mol. Immunol.,* 1991, vol. 28, 1183-1192 **[0014]**
- **CAHLIN et al.** *Cancer Res.,* 2000, vol. 60, 5488-5489 **[0014]**
- **MUSSELMAN et al.** *Am. J. Psychiatry,* 2001, vol. 158, 1252-1257 **[0014]**
- **TAUBES.** *Science,* 2002, vol. 296, 242 **[0014]**
- **HIRANO et al.** *Immunol. Today,* 1990, vol. 11, 443-449 **[0015]**
- **SEHGAL.** *Proc. Soc. Exp. Biol. Med.,* 1990, vol. 195, 183-191 **[0015]**
- **GRAU.** *Eur. Cytokine Net,* 1990, vol. 1, 203-210 **[0015]**
- **BAUER et al.** *Ann. Hematol.,* 1991, vol. 62, 203-210 **[0015]**
- **CAMPBELL et al.** *J. Clin. Invest.,* 1991, vol. 7, 739-742 **[0015]**
- **ROODMAN et al.** *J. Clin. Invest.,* 1992, vol. 89, 46-52 **[0015]**
- **QUINTANILLA et al.** *Exp. Cell Res.,* 2004, vol. 295, 245-257 **[0015]**
- **FISHER et al.** *J. Neuroimmunol.,* 2001, vol. 119, 1-9 **[0015]**
- **KISHIMOTO et al.** *Ann. Rev. Immunol.,* 1988, vol. 6, 485 **[0015]**
- **TAGA et al.** *J. Exp. Med.,* 1987, vol. 166, 967 **[0015]**
- **KISHIMOTO.** *Blood,* 1989, vol. 74, 1 **[0015]**
- **KLEIN et al.** *Blood,* 1991, vol. 78, 1198-1204 **[0015]**
- **HIRANO et al.** *Eur. J. Immunol.,* 1988, vol. 18, 1797 **[0015]**
- **CAMPBELL et al.** *J. Clin. Invest.,* 1991, vol. 87, 739-742 **[0015]**
- **JILKA et al.** *Science,* 1992, vol. 257, 88-91 **[0015]**
- *Med. Immunol.,* 1988, vol. 15, 195-201 **[0015]**
- **FREI et al.** *J. Neuroimmunol.,* 1991, vol. 31, 147 **[0015]**
- **WENDLING et al.** *J. Rheumatol.,* 1993, vol. 20, 259-262 **[0018]**
- **BLAY et al.** *Int. J. Cancer,* 1997, vol. 72, 424-430 **[0018]**
- Prodrugs as Novel Delivery Systems. **HIGUCHI et al.** ACS Symposium Series. vol. 14 **[0088]**
- Bioreversible Carriers in Drug Design. American Pharmaceutical Association and Pergamon Press, 1987 **[0088]**
- **FREIREICH et al.** *Cancer Chemother. Reports,* 1966, vol. 50 (4), 219-244 **[0141]**