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(54) Title: ORAL IMMEDIATE RELEASE FORMULATIONS FOR SUBSTITUTED QUINAZOLINONES

(57) Abstract: The present disclosure relates to oral immediate release solid pharmaceutical formulations and the process for their preparation. The present disclosure also provides, in part, methods of using the pharmaceutical formulations for regulating the expression of apolipoprotein A-I (ApoA-I), and their use for the treatment and prevention of cardiovascular disease and related disease states, including cholesterol- or lipid-related disorders, such as atherosclerosis.



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## Pharmaceutical Compositions for Substituted Quinazolinones

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

[002] HDL-C appears to exert its anti-atherogenic effect by mediating reverse cholesterol transport (RCT), in which cholesterol is recruited from peripheral tissues and transported to the liver. In addition, HDL-C also exerts anti-inflammatory and anti-oxidant effects and promotes fibrinolysis. HDL-C particles protect against oxidation of LDL, an important initial step in promoting cholesterol uptake by arterial macrophages. HDL-C exists in two main forms, one containing both apolipoprotein A-I (ApoA-I) and apolipoprotein A-II (ApoA-II), and the other containing ApoA-I without ApoA-II (Schultz *et al.* (1993) *Nature* **365**, 762-764). The cardioprotective effect of HDL-C is mostly, but not exclusively, attributable to ApoA-I.

[003] Clinical and experimental data suggest that the production of ApoA-I is a critical determinant of circulating HDL-C. For example, persons with familial

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

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

[005] One class of compounds that are thought to contribute to the prevention of various diseases, including cancer and cardiovascular disease, is polyphenols. Polyphenols are present in most food and beverages of plant origin and are the most abundant dietary antioxidants (Scalbert & Williamson (2000) *J. Nutr.* **130**, 2073S-2085S). However, the protective properties of polyphenols have

not been fully realized due to poor bioavailability (Manach *et al.* (2005) *Am. J. Clin. Nutr.* **81**, 230S-242S), lack of clinical significance in various reported studies assessing them (Williamson & Manach (2005) *Am. J. Clin. Nutr.* **81**, 243S-255S), and deleterious effects at higher dose concentrations. For example, an abundant and available source of resveratrol, a well known stilbene polyphenol, is red wine (Wu *et al.* (2001) *Int. J. Mol. Med.* **8**, 3-17). However, red wine cannot be consumed in therapeutically efficacious quantities on a daily basis due to the numerous well documented deleterious effects of excessive alcohol consumption. The effects of resveratrol may be better or safer in the absence of alcohol.

[006] Several human clinical studies involving the anti-oxidant effect of various polyphenols in various foods or beverages, have failed to demonstrate an unequivocal benefit with respect to primary clinical endpoints, such as oxidative stress, lipemia, and inflammation (Williamson & Manach (2005) *Am. J. Clin. Nutr.* **81**, 243S-255S). For example, out of twelve recent intervention studies with differing polyphenol sources, six showed no effect on lipid parameters and six showed an improvement in the lipid parameters (Manach (2005) *Curr. Opin. Lipidol.* **16**, 77-84). Such inconclusive data has limited the potential use of polyphenols, despite their many beneficial properties.

[007] The use of naturally occurring polyphenols as potential therapeutics has also been impeded by the inability to achieve efficacious levels in the body, partly due to poor bioavailability (Manach *et al.* (2005) *Am. J. Clin. Nutr.* **81**, 230S-242S). The bioavailability of any given polyphenol varies widely (from 1-26%) in different individuals. This variability is also seen with administration of different polyphenols to the same individual due to differences in absorption, metabolism, and excretion rates. For example, polyphenol flavonoids, such as quercetin, have been

reported to have less than 1% intestinal absorption following oral administration (Gugler *et al.* (1975) *Eur. J. Clin. Pharm.* **9**, 229-234). In addition, some polyphenol metabolites are known to negatively influence the biological activity of the parent compounds (Manach *et al.* (2005) *Am. J. Clin. Nutr.* **81**, 230S-242S). Such metabolites often differ from the parent compound in terms of toxicity, efficacy, and length of residence in the plasma. Another limiting factor is the poor solubility of many polyphenols that limits the potential routes of administration. These and other factors have made it difficult to determine appropriate dosages of the naturally occurring polyphenols, naringenin or resveratrol, for use in humans.

[008] Thus, there exists a need for polyphenol-like compounds to be developed as therapeutic agents for the treatment and prevention of cardiovascular disease and related diseases, particularly, cholesterol- or lipid-related disorders, such as, for example, atherosclerosis. It is therefore one of the objects of the present disclosure to provide compounds that up-regulate the expression of ApoA-I. In addition, the compounds may have more favorable pharmacological properties than naturally occurring polyphenols.

[009] Cancer is a group of diseases caused by dysregulated cell proliferation. Therapeutic approaches aim to decrease the numbers of cancer cells by inhibiting cell replication or by inducing cancer cell differentiation or death, but there is still significant unmet medical need for more efficacious therapeutic agents. Cancer cells accumulate genetic and epigenetic changes that alter cell growth and metabolism in order to promote cell proliferation and increased resistance to programmed cell death, or apoptosis. Some of these changes include inactivation of tumor suppressor genes, activation of oncogenes, as well as modifications of the

regulation of chromatin structure. Watson, *Cancer Discovery* 1:477-480 (2011); Morin et al., *Nature* 476:298-303 (2011).

[010] Many modifications of histones in chromatin have been characterized, including acetylation at multiple lysines in histones H3 and H4. Peserico and Simone, *J. Biomed. Biotechnol.* 2011:371832 (2011). Histone acetylation is controlled by acetylases (HATs) as well as deacetylases (HDACs), and small molecule HDAC inhibitors have been developed with cancer as an indication. Hoshino and Matsubara, *Surg. Today* 40:809-815 (2010). Histone acetylation controls gene expression by recruiting protein complexes that bind directly to acetylated lysine via bromodomains. Sanchez and Zhou, *Curr. Opin. Drug Discov. Devel.* 12(5):659-665 (2009). One such family, the bromodomain and extra terminal domain (BET) proteins, comprises Brd2, Brd3, Brd4, and BrdT each of which contains two bromodomains in tandem that can independently bind to acetylated lysines. Wu and Chiang, *J. Biol. Chem.* 282(18):13141-13145 (2007). BET proteins exert some of their effects on transcription by recruiting the positive transcription elongation factor b (p-TEFb), which stimulates transcription elongation by phosphorylating the C-terminal domain of RNA polymerase II and results in increased expression of growth promoting genes, such as, e.g., c-Myc and the well established cancer target Aurora B. Filippakopoulos et al., *Nature* 468:1067-1073 (2010).

[011] Molecules that bind to BET proteins and prevent them from binding to chromatin, inhibit transcription and prevent cell replication, which is useful in cancer therapy and other settings. For example, it has been shown that BET proteins can be displaced from the chromatin by small molecule inhibitors, such as, e.g., JQ1, I-BET, and I-BET151, which specifically compete with the acetyl-lysine binding pocket

of the BET protein bromodomains thereby preventing transcription elongation of their target genes. Filippakopoulos et al. (2010); Nicodeme et al., *Nature* 468:1119-1123 (2010); Dawson et al., *Nature* 478:529-533 (2011).

[012] Inhibition of BET bromodomain-promoter interactions results in a subsequent reduction of myc transcription and protein levels. This results in G<sub>1</sub> arrest and extensive apoptosis in a variety of leukemia and lymphoma cell lines. Mertz et al., *PNAS* 108(40):16669-16674 (2011). The Myc family of proto-oncogenes (c-myc, l-myc, n-myc) is activated in 25-35% of all human cancers. Vita and Henrickson, *Seminars in Cancer Biol.* 16:318-330 (2006). Mouse models of cancer driven by overexpression of c-myc demonstrate that transiently inhibiting c-myc expression can cause tumor regression, cell death, and in some cancers such as leukemia, complete disease remission. Soucek et al., *Nature* 455:679-683 (2008). The absence of a clear ligand-binding domain of c-myc has made the development of an inhibitor a formidable challenge, thus alternative strategies to targeting c-myc transcription must be developed. Delmore et al., *Cell* 146:904-917 (2011). A mouse model of aggressive human medulloblastoma, in which c-myc is overexpressed, suggests that BET inhibitors may be useful for treating myc-amplified medulloblastoma. Kawauchi et al., *Cancer Cell* 21:168-180 (2012); Pei et al., *Cancer Cell* 21:155-167 (2012). Similarly, inhibition of n-myc through RNA interference significantly reduced tumor growth in neuroblastoma mouse models. Jiang et al., *Biochem. Biophys. Res. Commun.* 410:364-370 (2011). A similar role for l-myc was suggested in small cell lung carcinoma cell lines using antisense oligonucleotides to inhibit l-myc amplification. Dosaka-Akita et al., *Cancer Res.* 55:1559-1564 (1995). Therefore BET inhibitors have potential to be efficacious in treating multiple types of cancer.



[013] In fact, small molecules that target the bromodomains of BET family members have demonstrated potential therapeutic use in treating cancer. See, e.g., Dawson et al. (2011), showing that a small molecule inhibitor of the BET family has a profound efficacy against human and murine mixed lineage leukemia (MLL)-fusion cell lines by early cell cycle arrest and apoptosis. Its mechanism of efficacy is the selective abrogation of Brd3/4 recruitment to chromatin. BET inhibitor JQ1 has demonstrated potent antitumor activity in murine xenograft models of NUT (nuclear protein in testis) midline carcinoma (NMC), a rare but lethal form of cancer. NMC tumor cell growth is driven by a translocation of the Brd4 gene to the nutlin 1 gene. Filippakopoulos et al., (2010). JQ1 was also shown to be a potent antiproliferator in multiple myeloma, associated with cell cycle arrest and cellular senescence. Delmore et al. (2011).

[014] BET inhibitors are also expected to be potential therapeutics for other types of cancer. For example, in acute myeloid leukemia (AML), Brd4 is required to sustain myc expression and continued disease progression. Zuber et al., *Nature* 478:524-8 (2011). Moreover, inactivation of Brd4 results in a rapid and drastic down-regulation of the transcription of the proto-oncogenes c-myc and n-myc in cell lines they are amplified. Dawson et al. (2011); Delmore et al. (2011); Zuber et al. (2011); Mertz et al. (2011). Consequently, treatment of tumors that have activation of c-myc with a BET inhibitor resulted in tumor regression through inactivation of c-myc transcription. BET inhibitors are also expected to have application in multiple myeloma, as the multiple myeloma SET domain (MMSET) which is implicated in this disease also binds to BET proteins. Dawson et al. (2011).

[015] In addition to cancer, BET inhibitors are also expected to have have anti-inflammatory and immunomodulatory properties. Lamotte et al., *Bioorganic &*

*Med. Chem. Letters* (February 24, 2012); Prinjha et al., *Trends Pharmacol. Sci.* 33(3):146-153 (2012). BET inhibitors I-BET and I-BET151 decrease IL-6 expression *in vivo*. I-BET was shown to confer protection against lipopolysaccharide-induced endotoxic shock and bacteria-induced sepsis and I-BET151 was shown to suppress bacterial-induced inflammation and sepsis in a murine model. Nicodeme et al. (2010); Lamotte et al.(2012). In addition, BET inhibitors may modulate responses to viral and bacterial infections, including HIV, herpes, and papilloma viruses.

[015a] Definitions of the specific embodiments of the invention as claimed herein follow.

[015b] According to a first embodiment of the invention, there is provided an oral immediate release formulation comprising an active ingredient selected from:

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

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

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

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

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

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

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

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

and

pharmaceutically acceptable salts, stereoisomers, hydrates, or tautomers thereof;

wherein the formulation further comprises:

- (i) from about 10% w/w to about 85% w/w of microcrystalline cellulose;
- (ii) about 4% w/w of sodium starch glycolate;
- (iii) about 0.5% w/w of magnesium stearate; and
- (iv) about 2.5% w/w of colloidal silicon dioxide;

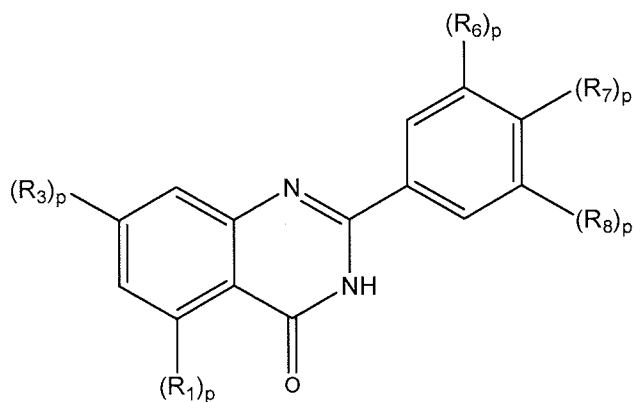
and wherein the sum of all components of the formulation is equal to 100% w/w.

[015c] According to a second embodiment of the invention, there is provided use of a pharmaceutical formulation of the first embodiment in the manufacture of a medicament for the treatment or prevention of a cardiovascular disease, metabolic syndrome, inflammatory disease, Alzheimer's disease, diabetes, or cancer, in a human in need thereof.

[015d] According to a third embodiment of the invention, there is provided a method of treating or preventing cardiovascular disease, metabolic syndrome, inflammatory disease, Alzheimer's disease, diabetes, or cancer, in a subject, comprising administering to said subject a formulation according to the first embodiment.

[016] The invention provides an immediate release formulation comprising,

- (i) a compound Formula I as an active ingredient



**Formula I**

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

R<sub>1</sub> and R<sub>3</sub> are each independently selected from alkoxy, alkyl, and hydrogen;

R<sub>6</sub> and R<sub>8</sub> are each independently selected from alkoxy, alkyl, halogen, and hydrogen;

R<sub>7</sub> is selected from alkoxy, alkyl, ether, hydrogen, and hydroxyl; or

**[Text continues on page 9.]**

two adjacent substituents selected from R<sub>1</sub>, R<sub>3</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, and are connected to form a group selected from aryl, heteroaryl, cycloalkyl, and heterocyclyl;

provided that if R<sub>1</sub> is hydrogen, then R<sub>3</sub> is alkoxy;

provided that if R<sub>3</sub> is hydrogen then R<sub>1</sub> is alkoxy; and

provided that if R<sub>7</sub> is selected from alkyl, hydroxyl, and alkoxy, then at least one of R<sub>6</sub> and R<sub>8</sub> are independently selected from alkyl or alkoxy;

(ii) at least one glidant; and

(iii) at least one disintegrant.

[017] Important considerations during the manufacturing of a solid pharmaceutical formulation include preservation of the chemical and physical properties of the active ingredient, enhancement of bioavailability, ease of administration, and overall stability. In each case, the formulation must be based on the properties of the active/drug substance, balancing factors like disintegration, dissolution, particle size, size of unit, compatibility of components, and stability (see, *e.g.*, The Pharmaceutical Codex, Principles and Practice of Pharmaceutics. Ed: Walter Lund; 2008, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Lippincott Williams & Wilkins, 2010, Pharmaceutical Dosage forms: Tablets. Vol 1, 2. Eds: Liberman, Lachman and Schwartz. 2d edition).

[018] Disintegration and dissolution are prerequisite steps for absorption, and the efficacy of these steps can affect the bioavailability of an active/drug substance. The solubility and thus the dissolution rate for weak acids and bases are influenced by the pH of the gastrointestinal fluids. For compounds that have reduced solubility in neutral and basic environments, like the small intestine, and a higher solubility at gastric pH, rapid disintegration and dissolution in the acidic gastric fluids may be critical for absorption in the small intestine (Principles of Drug Absorption, Michael

Mayersohn. In *Modern Pharmaceutics: Drugs and the Pharmaceutical Sciences*, Vol 72, edited by James Swarbrick).

[019] Many active compounds, including compounds of Formula I, have poor aqueous solubility, thus reducing their potential for absorption from the gastrointestinal tract. A challenge to working with compounds having poor aqueous solubility is that it can be difficult to improve solubility without decreasing stability of the compound, thus reducing shelf life to an unacceptable levels. The hydrophobicity of compounds of Formula I can be altered when substituted with ionizable basic substituents, such as amines and/or amides, providing an opportunity for increased solubilization and absorption from the acidic gastric environment when dosed orally. However, due to the increasing pH gradient (pH 3 to 7) in the gastrointestinal cavity, the opportunity for dissolution and absorption is dependent on the rate of dissolution. As a result, if these compounds are not dissolved in the right gastric environment, absorption and bioavailability in the small intestine is reduced or lost. Thus, any improved biological activity gained from substituting compounds of Formula I with ionizable basic substituents is compromised because of their diminished solubility in the small intestine, which leads to a decrease in the overall efficacy and therapeutic effects of the active drug substance.

[020] Because compounds of Formula I have been shown to regulate expression of Apo-A1 and given the correlation between increased expression of Apo-A1 and treating or preventing cardiovascular and cholesterol- or lipid-related disorders, there is a need to develop solid pharmaceutical formulations comprising substituted quinazolinones, such as those described herein, where the pharmaceutical formulations improve dissolution of the quinazolinone drug

substance, have favorable bioavailability, are convenient to administer, and which are stable for an extended period of time.

[021] The invention provides novel solid pharmaceutical formulations comprising compounds of the Formula I, as defined above, and processes for their preparation. The formulations of the invention are stable and have improved disintegration and dissolution profiles for compounds of Formula I and improved bioavailability of the drug substance. The present invention also provides, in part, methods of using the pharmaceutical formulations of the invention that are useful for regulating the expression of apolipoprotein A-I (ApoA-I) and as BET inhibitors, for the treatment and prevention of cardiovascular disease, and cholesterol- or lipid-related disorders, including, for example, metabolic syndrome, inflammatory disease, Alzheimer's disease, atherosclerosis, diabetes, and cancer. Cancers that may be treated or prevented with the methods of the invention include cancers that are sensitive to a compound that binds to bromodomains of BET family proteins, including NUT midline carcinoma; cancers that exhibit c-myc overexpression, including, but not limited to, Burkitt's lymphoma, acute myelogenous leukemia, multiple myeloma, aggressive human medulloblastoma; cancers overexpressing n-myc; and cancers that rely on the recruitment of p-TEFb to regulate activated oncogenes such as, e.g., NOTCH1.

[022] As used in this specification, the term "active ingredient" refers to a compound of Formula I. These compounds may be prepared as described in U.S. Patent Application No. 11/670,238 (U.S. Patent 8,053,440), U.S. Patent Application No. 12/490,877 (U.S. Patent 8,114,995), and U.S. Provisional Application No. 61/635,726, filed April 19, 2012, incorporated herein by reference.

[023] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -CONH<sub>2</sub> is attached through the carbon atom.

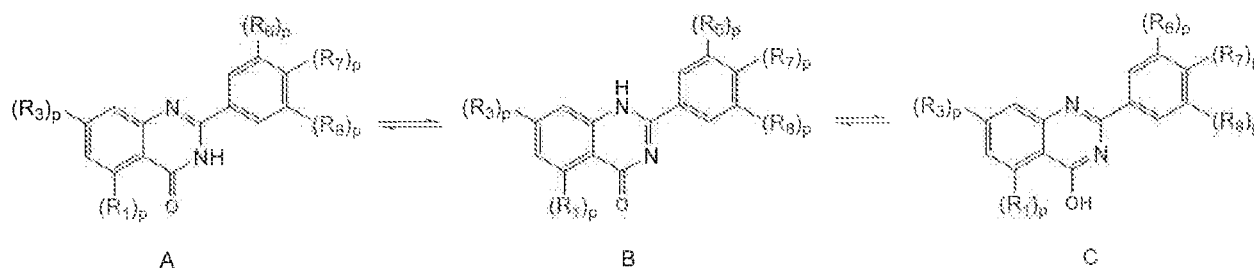
[024] The expression "unit dosage form" as used herein, refers to a physically discrete unit of a pharmaceutical formulation appropriate for the subject to be treated. The total weight of a single unit dosage form, is determined by adding all the weights of the components in the unit dosage form, and does not include the weight of any coating(s) which may be applied to the unit dosage form or capsule that may be loaded with the unit dosage form. The total weight of a single unit dosage form is used as the basis for calculating the weight percentage of each of the components that comprise the unit dosage form.

[025] As used herein, "w/w %" means by weight as a percentage of the total weight.

[026] The term "about" is intended to mean approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is intended to modify a numerical value above and below the stated value by a variance of  $\leq 10\%$ .

[027] Compounds of Formula I may exist as tautomers. It is intended that a description of any active ingredient, i.e., a compound of Formula I encompasses all tautomeric forms of the compound even if only one tautomeric structure is depicted or one compound name is recited. For example, any description of active ingredient A below is understood to equally represent tautomeric structures B and C, and *vice versa*, individually or as mixtures.





[028] As used herein, the term “hydrate” refers to a crystal form of a compound of Formula I with either a stoichiometric or non-stoichiometric amount of water incorporated.

[029] 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<sub>1</sub>-C<sub>22</sub>)alkoxy, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, and (C<sub>1</sub>-C<sub>6</sub>)alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy and ethoxy.

[030] 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<sub>1</sub>-C<sub>22</sub>)alkyl, (C<sub>1</sub>-C<sub>8</sub>)alkyl, and (C<sub>1</sub>-C<sub>6</sub>)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.

[031] 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 heterocycllys. The aryl groups of the compounds used in the formulations of the 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<sub>6</sub>)aryl."

[032] 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<sub>3</sub>-C<sub>8</sub>)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.

[033] The term "ether" refers to the structure -R<sub>l</sub>O-R<sub>m</sub>-, where R<sub>l</sub> and R<sub>m</sub> can independently be alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl, and ether.

The ether can be attached to the parent molecular group through  $R_I$  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  $R_I$  and  $R_M$  are ethers.

[034] The terms "halo" and "halogen" are interchangeable and refer to F, Cl, Br, or I.

[035] 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, pyrimidyl, 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<sub>2</sub>-C<sub>5</sub>)heteroaryl."

[036] 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 aryl, cycloalkyl, and heterocycle. Exemplary heterocycles include acridinyl, benzimidazolyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, biotinyl, cinnolinyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, furyl, homopiperidinyl, imidazolidinyl, imidazolynyl, imidazolyl, indolyl, isoquinolyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazinyl, pyrazolyl, pyrazolynyl, 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.

[037] "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.

[038] "Alkoxy" 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.

[039] The term "pharmaceutically acceptable salt(s)" refers to salts of acidic or basic groups that may be present in compounds of Formula I. Compounds of Formula I 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, malate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds of Formula I that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds of Formula I 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.

[040] Compounds of Formula I 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. Compounds of Formula I encompass stereoisomers 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 contain an implicit chiral center.

[041] Individual stereoisomers of compounds of Formula I 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 include, but are not limited to (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, including, but not limited to chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, and/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.

[042] Compounds of Formula I may also exist as geometric isomers or 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.

[043] 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 of Formula I wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

[044] One exemplary embodiment of the invention is a pharmaceutical formulation comprising, as an active ingredient, a compound of Formula I wherein:

$R_1$  and  $R_3$  are each independently selected from alkoxy, alkyl, and hydrogen;

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

$R_7$  is selected from alkyl, hydroxyl, and alkoxy;

provided that if  $R_1$  is hydrogen, then  $R_3$  is alkoxy;

provided that if  $R_3$  is hydrogen then  $R_1$  is alkoxy; and

provided that if  $R_7$  is selected from alkyl, hydroxyl, and alkoxy, then at least one of  $R_6$  and  $R_8$  are independently selected from alkyl or alkoxy.

[045] In one embodiment, formulations of the invention comprise, as an active ingredient, a compound of Formula I, wherein:

R<sub>1</sub> and R<sub>3</sub> are each alkoxy;

R<sub>6</sub> and R<sub>8</sub> are each alkyl; and

R<sub>7</sub> is selected from alkoxy substituted with a hydroxyl.

[046] In certain embodiments, formulations of the invention comprise, as an active ingredient, a compound of Formula I, wherein:

R<sub>1</sub> and R<sub>3</sub> are each methoxy;

R<sub>6</sub> and R<sub>8</sub> are each methyl; and

R<sub>7</sub> is selected from alkoxy substituted with a hydroxyl.

[047] In certain embodiments, formulations of the invention comprise an active ingredient wherein R<sub>7</sub> is selected from hydroxyl and alkoxy substituted with a hydroxyl. In other embodiments, R<sub>7</sub> is hydroxyl substituted with alkoxy. In further embodiments, R<sub>7</sub> is 2-hydroxyethoxy.

[048] In some embodiments, the active ingredient is 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one or a pharmaceutically acceptable salt, stereoisomer, hydrate, or tautomer thereof.

[049] In other embodiments, the active ingredient is the hydrochloride salt of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one, or a stereoisomer or tautomer thereof.

[050] In other embodiments, formulations of the invention comprise an active ingredient selected from:

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

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

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



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

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

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

and

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

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

[051] In certain embodiments, the pKa of the corresponding acid of the active ingredient of Formula I is < 3. In some embodiments the particle size of the active ingredient ranges from about 1-250 microns, about 1-100 microns, or about 1-10 microns.

[052] In certain embodiments, formulations of the invention are stable over extended periods of time. For example, in some embodiments, the formulations are stable for at least two years.

[053] In some embodiments, the at least one glidant in the formulations of the invention is present an amount of 1-10% w/w, or 2-4% w/w, or 2.5% w/w. In some embodiments, the glidant is colloidal silicon dioxide such as, for example, Cab-O-Sil.

[054] The at least one disintegrant in the formulations of the invention may be present in an amount of about 0-25% w/w, about 4-25% w/w, about 0-10% w/w, about 0-8% w/w, about 1-8% w/w, about 2-5% w/w, about 2-4% w/w, or about 4% w/w. In some embodiments, at least one disintegrant is present in an amount of about 4% w/w to about 25% w/w. Suitable disintegrants include, for example, powdered cellulose, calcium silicate, croscopovidone, calcium alginate, methyl cellulose, chitosan, carboxy methyl cellulose, croscarmellose sodium, carboxymethyl

starch, sodium alginate, sodium starch glycolate (e.g., ExploTab), pregelatinized starch, and mixtures thereof. See, e.g., The Pharmaceutical Codex, Principles and Practice of Pharmaceutics. Ed: Walter Lund; 2008.

[055] In certain embodiments, formulations of the present disclosure comprise an active ingredient of the Formula I, colloidal silicon dioxide and at least one disintegrant selected from sodium starch glycolate, croscarmellose sodium, and mixtures thereof.

[056] In certain embodiments, colloidal silicon dioxide is present in an amount of about 2.5% w/w and sodium starch glycolate and croscarmellose sodium are each present in an amount of about 4% w/w to about 25% w/w respectively.

[057] In other embodiments, colloidal silicon dioxide is present in an amount of about 2.5% w/w and sodium starch glycolate is present in an amount of about 4% w/w.

[058] In addition to the active ingredient, at least one glidant, and at least one disintegrant, the formulations may comprise one or more fillers or diluents. In some embodiments, the filler/diluent is present in an amount up to 85% w/w, or about 15-65% w/w, or about 20-45% w/w. Suitable fillers/diluents include, for example, microcrystalline cellulose, mannitol, ethyl cellulose, sorbitol, starch, sucrose, calcium phosphate, powdered cellulose, silicified microcrystalline cellulose, and mixtures thereof.

[059] In some embodiments, the filler/diluent is microcrystalline cellulose. In certain embodiments, the microcrystalline cellulose is Avicel PH-301.

[060] The formulations may further comprise one or more lubricants. In some embodiments, the lubricant is present in an amount of about 0-2% w/w, about

0-1% w/w, or about 0.5% w/w. Suitable lubricants include, for example, magnesium stearate, stearic acid, sodium stearyl fumarate, glyceryl behenate, hydrogenated vegetable oil, zinc stearate, calcium stearate, sucrose stearate, polyvinyl alcohol, magnesium lauryl sulfate, and mixtures thereof. In some embodiments, the lubricant is magnesium stearate.

[061] The formulations of the invention may further comprise a surfactant. In some embodiments, the surfactant is present in an amount of about 0-5% w/w, about 0-3% w/w, or about 1% w/w. Suitable surfactants include, for example, sodium lauryl sulfate, sodium dodecyl sulfate, polysorbates (such as Tween 20 and Tween 80), poloxamers (such as Poloxamer 188), glyceryl monooleate, and mixtures thereof. In some embodiments, the surfactant is Poloxamer 188, sodium lauryl sulfate, and mixtures thereof.

[062] In an exemplary embodiment of the invention, the pharmaceutical formulation comprises an active ingredient of Formula I, 10-85% microcrystalline cellulose, 1-8% sodium starch glycolate, 0.5-2% magnesium stearate, 1-10% colloidal silicon dioxide, 0-2% sodium lauryl sulfate, and 0-25% croscarmellose sodium.

[063] In other embodiments, the formulation comprises an active ingredient of Formula I, 10-85% microcrystalline cellulose, 4% sodium starch glycolate, 0.5% magnesium stearate, and 2.5% colloidal silicon dioxide.

[064] In certain embodiments, the formulation comprises an active ingredient of Formula I, 10-85% microcrystalline cellulose, 4% sodium starch glycolate, 25% croscarmellose sodium, 0.5% magnesium stearate, and 2.5% colloidal silicon dioxide.

[065] In an exemplary embodiment, the formulation of the invention comprises:

- (i) about 10-12% w/w 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
- (ii) about 82-83% w/w Avicel PH 301;
- (iii) about 2.5% w/w colloidal silicon dioxide;
- (iv) about 4% w/w sodium starch glycolate; and
- (v) about 0.5% w/w magnesium stearate.

[066] In an alternate embodiment the hydrochloride salt of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one may be substituted for 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in this formulation.

[067] In another exemplary embodiment, the formulation of the invention comprises:

- (i) about 20-22% w/w 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
- (ii) about 70-72% w/w Avicel PH 301;
- (iii) about 2.5% w/w colloidal silicon dioxide;
- (iv) about 4% w/w sodium starch glycolate; and
- (v) about 0.5% w/w magnesium stearate.

[068] In an alternate embodiment the hydrochloride salt of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one may be

substituted for 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in this formulation.

[069] In another exemplary embodiment, the formulation of the invention comprises:

- (i) about 31-33% w/w 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
- (ii) about 60-62% w/w Avicel PH 301;
- (iii) about 2.5% w/w colloidal silicon dioxide;
- (iv) about 4% w/w sodium starch glycolate; and
- (v) about 0.5% w/w magnesium stearate.

[070] In an alternate embodiment the hydrochloride salt of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one may be substituted for 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in this formulation.

[071] In another exemplary embodiment, the formulation of the invention comprises:

- (i) about 41-43% w/w 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;
- (ii) about 50-51% w/w Avicel PH 301;
- (iii) about 2.5% w/w colloidal silicon dioxide;
- (iv) about 4% w/w sodium starch glycolate; and
- (v) about 0.5% w/w magnesium stearate.

[072] In an alternate embodiment the hydrochloride salt of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one may be substituted for 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in this formulation.

[073] In another exemplary embodiment, the formulation of the invention comprises:

- (i) about 10-12% w/w 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one or a hydrochloride salt thereof;
- (ii) about 56-57% w/w Avicel PH 301;
- (iii) about 2.5% w/w colloidal silicon dioxide;
- (iv) about 4% w/w sodium starch glycolate;
- (v) about 0.5% w/w magnesium stearate; and
- (vi) about 25% w/w croscarmellose sodium.

[074] In an alternate embodiment the hydrochloride salt of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one may be substituted for 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in this formulation.

[075] In another exemplary embodiment, the formulation of the invention comprises:

- (i) about 42-43% w/w 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one or a hydrochloride salt thereof;
- (ii) about 24-25% w/w Avicel PH 301;
- (iii) about 2.5% w/w colloidal silicon dioxide;

- (iv) about 4% w/w sodium starch glycolate;
- (v) about 0.5% w/w magnesium stearate;
- (vi) about 25% w/w croscarmellose sodium; and
- (vii) about 1% w/w sodium lauryl sulfate.

[076] In an alternate embodiment the hydrochloride salt of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one may be substituted for 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one in this formulation.

[077] The physical and chemical stability of the formulation may be tested in a conventional manner, for example, the measurement of dissolution or disintegration time, or moisture content, or assay for the active ingredient or degradation products after storage at different temperatures and relative humidity for different lengths of time.

[078] The pharmaceutical formulations of the invention may be administered using any amount effective for treating the disease. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease and/or disorder, the particular active ingredient, its mode of administration, and the like. In one aspect, the pharmaceutical formulations are formulated in an oral pharmaceutical unit dosage form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the pharmaceutical formulation of the present invention will be decided by the attending physician within the scope of sound medical judgment.

[079] The specific effective dose level for any particular subject will depend on a variety of factors including, for example, the disease being treated and the severity of the disease; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, gender, and diet of the subject; the time of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts.

[080] In some embodiments, the unit dosage form comprises between 25-150 mg of the active pharmaceutical ingredient. In some embodiments, the unit dosage form comprises about 25, 50, 75, 100 or 150 mg of the active pharmaceutical ingredient.

[081] In one embodiment, the present disclosure provides for pharmaceutical formulations in solid oral pharmaceutical dosage forms. Examples of solid oral pharmaceutical dosage forms include, for example, tablets, capsules, pills, powders, and granules. In certain embodiments, the pharmaceutical formulation is in the form of a capsule. While formulations of the invention are described with reference to capsules as the exemplary dosage form, other dosage forms are also within the scope of this invention.

[082] In some embodiments, the capsules are filled with a total weight between 100 and 500 mg per capsule. In some embodiments, the capsules are filled with a total weight of about 200-250 mg per capsule; and in some embodiments, the capsules are filled with a total weight of about 230 mg per capsule.



[083] As used herein, the term "cardiovascular disease" refers to diseases and disorders of the heart and circulatory system. Exemplary cardiovascular diseases, including cholesterol- or lipid-related disorders, include, but are not limited to acute coronary syndrome, angina, arteriosclerosis, atherosclerosis, carotid atherosclerosis, cerebrovascular disease, cerebral infarction, congestive heart failure, congenital heart disease, coronary heart disease, coronary artery disease, coronary plaque stabilization, dyslipidemias, dyslipoproteinemias, endothelium dysfunctions, familial hypercholesterolemia, 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 inflammatory diseases.

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

disorders, foot ulcerations, metabolic acidosis, arthritis, osteoporosis and impaired glucose tolerance.

[085] In certain embodiments, the cancer to be treated is a midline carcinoma. In some embodiments, the cancer is characterized by c-myc activation or overexpression. In other embodiments, the cancer is characterized by overexpression or activation of n-myc. In certain embodiments, the cancer is Burkitt's lymphoma, acute myelogenous leukemia, multiple myeloma, or aggressive human medulloblastoma. In some embodiments, the cancer relies on the recruitment of p-TEFb to regulate activated oncogenes such as, e.g., NOTCH1. In some embodiments, the cancer to be treated or prevented by the methods of the invention is selected from the group consisting of hematological, epithelial including lung, breast and colon carcinomas, midline carcinomas, mesenchymal, hepatic, renal and neurological tumours.

[086] The certain embodiments, administration of a compound of Formula I or Formula II or a tautomer, stereoisomer, pharmaceutically acceptable salt or hydrate thereof, to a mammal suffering from a cancer induces apoptosis in cancer cells by decreasing expression of the anti-apoptosis gene Bcl2. Thus, some embodiments of the invention provide a method of treating or preventing a disease or disorder in a mammal that benefits from increased cell death or differentiation, or decreased cell proliferation, comprising administering a compound of Formula I or Formula II or a tautomer, stereoisomer, pharmaceutically acceptable salt or hydrate thereof.

[087] The invention is further illustrated by the following non-limiting examples.

## Examples

[088] 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (**Compound 1**) was prepared according to the synthetic methods described in U.S. Patent Application Nos. 11/670,238 and 12/490,877, incorporated herein by reference.

[089] Capsules containing formulations of the invention may be produced using any suitable apparatus or procedure. Typically, the appropriate amount of the active pharmaceutical ingredient and optionally, sodium starch glycolate are weighed out and transferred to a V-blender or bin-blender and blended, for example, for about 2 min at about 25 rpm. Colloidal silicon oxide and approximately 1/3 of the desired amount of a filler/diluent, such as microcrystalline cellulose are screened and added to the same V-blender, and the ingredients are blended for about 2 min at about 25 rpm. The remaining filler/diluent, such as microcrystalline cellulose is added to the same V-blender, and the ingredients are blended for about 4 min at about 25 rpm.

[090] A lubricant, such as magnesium stearate, is screened through a 30 mesh screen and transferred to the V-blender containing the other ingredients. The final formulation is blended for about 3 min at about 25 rpm.

[091] Disintegration of capsules was monitored visually during the first 5 min while conducting dissolution testing, as seen by bursting of the capsule to release and disperse the formulation blend from the capsule shell. Dissolution testing was conducted in a USP Paddle type II apparatus at 50 and/or 75 rpm in 0.1 N HCl at 37°C. The dissolution profile of the formulations were determined by sampling the API released from the formulation in the dissolution media at frequent time points, such as 5, 10, 15, 30, 45, 60, and 90 min. Samples were assayed for drug content

by HPLC and a dissolution profile was generated. For these experiments, the upper threshold for dissolution profiles included those which exhibited >85% drug released in 30 min or less, at 75 rpm paddle speed. A lower paddle speed (50 rpm) was used to differentiate dissolution performance of closely performing formulations.

[092] Considering factors such as, for example, number of excipients, density of blend, stability, and scaleability, the numerous formulations were produced at various API weight percentages. The following formulations provided higher levels of drug load and a higher density leading to increased manufacturability, reducing the exposure of inactive ingredients to subjects. In addition, the combination of two or more disintegrants in conjunction with high levels of glidant (e.g., silicon dioxide) improved disintegration and dissolution profiles.

Formulation D4 (25 mg/capsule)

Ingredients	mg / capsule	% wt./wt
Compound 1	25.00	10.73
Microcrystalline cellulose (Avicel PH 301)	191.69	82.27
Colloidal silicon dioxide (Cab-O-Sil M5P)	5.83	2.5
Sodium starch glycolate (ExploTab)	9.32	4.0
Magnesium stearate (Vegetable Source)	1.17	0.5
Hard shell gelatin capsule white/white Size 1 Capsugel	-	-
Total	233.01	100.0

Formulation D4 (50 mg/capsule)

Ingredients	mg / capsule	% wt./wt
Compound 1	50	21.46
Microcrystalline cellulose (Avicel PH 301)	166.69	71.54
Colloidal silicon dioxide (Cab-O-Sil M5P)	5.83	2.5
Sodium starch glycolate (ExploTab)	9.32	4.0
Magnesium stearate (Vegetable Source)	1.17	0.5
Hard shell gelatin capsule white/white Size 1 Capsugel	-	-
Total	233.01	100.0

Formulation D4 (75 mg/capsule)

Ingredients	mg / capsule	% wt./wt
Compound 1	75.00	32.19
Microcrystalline cellulose (Avicel PH 301)	141.69	60.81
Colloidal silicon dioxide (Cab-O-Sil M5P)	5.83	2.5
Sodium starch glycolate (ExploTab)	9.32	4.0
Magnesium stearate (Vegetable Source)	1.17	0.5
Hard shell gelatin capsule white/white Size 1 Capsugel	-	-

Total	233.01	100.0
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Formulation D4 (100 mg/capsule)

Ingredients	mg / capsule	% wt./wt
Compound 1	100.00	42.9
Microcrystalline cellulose (Avicel PH 301)	116.69	50.1
Colloidal silicon dioxide (Cab-O-Sil M5P)	5.83	2.5
Sodium starch glycolate (ExploTab)	9.32	4.0
Magnesium stearate (Vegetable Source)	1.17	0.5
Hard shell gelatin capsule white/white Size 1 Capsugel	-	-
Total	233.01	100.0

Formulation F3 (25 mg/capsule)

Ingredients	mg / capsule	% wt./wt
Compound 1	25.00	10.73
Microcrystalline cellulose (Avicel PH 301)	197.0	56.29
Colloidal silicon dioxide (Cab-O-Sil M5P)	5.83	2.5
Sodium starch glycolate (ExploTab)	9.32	4.0
Magnesium stearate (vegetable source)	1.17	0.5

Croscarmellose sodium	58.25	25
Hard shell gelatin capsule white/white Size 1 Capsugel	-	-
Total	233.01	100.0

Formulation F3" (100 mg/capsule)

Ingredients	mg / capsule	% wt./wt
Compound 1	100	42.9
Microcrystalline cellulose (Avicel PH 301)	56.25	24.14
Colloidal silicon dioxide (Cab-O-Sil M5P)	5.83	2.5
Sodium starch glycolate (ExploTab)	9.32	4.0
Magnesium stearate (Vegetable Source)	1.17	0.5
Croscarmellose sodium	58.25	25
Sodium lauryl sulfate	2.33	1
Hard shell gelatin capsule white/white Size 1 Capsugel	-	-
Total	233.01	100.0

[093] Of the formulations above, D4 had the fewest inactive ingredients, and thus, the highest levels of drug load and density, thereby reducing unnecessary exposure to inactive ingredients. Dissolution profiles of the formulations above are provided in Table 1.

Table 1. Dissolution Results

Capsule Strength (mg)	Formulation	Paddle Speed RPM	% Compound 1 Dissolved (Average of 3 vessels)		
			15	30	45
200 (used 2 caps)	F3	50	59.84	64.10	66.15
200 (used 2 caps)	F3''	50	62.83	66.79	69.65
200 (used 2 caps)	D4	50	53.09	66.08	74.05

[094] Thus, the present disclosure provides in part, a technical solution to the existing problem of developing formulations that increase the bioavailability of compounds of Formula I, while preserving compound stability and shelf-life. Because of the known ability of compounds of Formula I to regulate expression of ApoA-1 and as BET inhibitors, the aforementioned immediate release formulations also provide an avenue for the treatment and prevention of cardiovascular disease, and cholesterol- or lipid-related disorders, including, for example, metabolic syndrome, inflammatory disease, Alzheimer's disease, atherosclerosis, diabetes, and cancer.

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

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



# CLAIMS

1. An oral immediate release formulation comprising an active ingredient selected from:

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;  
 2-(3-chloro-4-(2-hydroxyethoxy)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;  
 2-(4-(2-hydroxyethoxy)-3-methoxyphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;  
 2-(4-hydroxy-3-(2-hydroxyethyl)phenyl)-5,7-dimethoxyquinazolin-4(3H)-one;  
 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethylquinazolin-4(3H)-one;  
 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5-methoxyquinazolin-4(3H)-one;  
 2-(4-(2-hydroxyethoxy)-3-methylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;  
 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one;

and

pharmaceutically acceptable salts, stereoisomers, hydrates, or tautomers thereof;

wherein the formulation further comprises:

- (i) from about 10% w/w to about 85% w/w of microcrystalline cellulose;
- (ii) about 4% w/w of sodium starch glycolate;
- (iii) about 0.5% w/w of magnesium stearate; and
- (iv) about 2.5% w/w of colloidal silicon dioxide;

and wherein the sum of all components of the formulation is equal to 100% w/w.

2. The formulation of claim 1, wherein the active ingredient is present:

(a) in an amount from about 10% w/w to about 12% w/w and the formulation further comprises:

- (i) from about 82% w/w to about 83% w/w of microcrystalline

cellulose;

- (ii) about 2.5% w/w of colloidal silicon dioxide;
- (iii) about 4.0% w/w of sodium starch glycolate; and
- (iv) about 0.5% w/w of magnesium stearate;

(b) in an amount from about 20% w/w to about 22% w/w and the formulation further comprises:

- (i) from about 70% w/w to about 72% w/w of microcrystalline cellulose;
- (ii) about 2.5% w/w of colloidal silicon dioxide;
- (iii) about 4.0% w/w of sodium starch glycolate; and
- (iv) about 0.5% w/w of magnesium stearate;

(c) in an amount from about 31% w/w to about 33% w/w and the formulation further comprises:

- (i) from about 60% w/w to about 62% w/w of microcrystalline cellulose;
- (ii) about 2.5% w/w of colloidal silicon dioxide;
- (iii) about 4.0% w/w of sodium starch glycolate; and
- (iv) about 0.5% w/w of magnesium stearate.

or

(d) in an amount from about 41% w/w to about 43% w/w and the formulation further comprises:

- (i) from about 50% w/w to about 51% w/w of microcrystalline cellulose;
- (ii) about 2.5% w/w of colloidal silicon dioxide;
- (iii) about 4.0% w/w of sodium starch glycolate; and

(iv) about 0.5% w/w of magnesium stearate;

wherein the sum of all components of the formulation is equal to 100% w/w.

3. The formulation of claim 1 or claim 2, wherein the formulation comprises from about 25-150 mg of the active pharmaceutical ingredient.
4. The formulation of any one of claims 1 to 3, wherein the active ingredient is present in the formulation in an amount selected from about 25 mg, about 50 mg, about 75 mg, about 100 mg, or about 150 mg.
5. The formulation of any one of claims 1 to 4, wherein the active ingredient is 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one.
6. The formulation of any one of claims 1 to 4, wherein the active ingredient is the hydrochloride salt of 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one.
7. The formulation of any one of claims 1 to 6, wherein the particle size of the active ingredient ranges from about 1-250 microns, about 1-100 microns, or about 1-10 microns.
8. The formulation of any one of claims 1 to 7, wherein the formulation has a disintegration time of 120 seconds or less.
9. The formulation of any one of claims 1 to 8, wherein said formulation is in the

form of a tablet, capsule, pill, powder, or granule.

10. The formulation of claim 9, wherein said formulation is in the form of a capsule.
11. The formulation of claim 9, wherein said formulation is in the form of a tablet.
12. Use of a pharmaceutical formulation of any one of claims 1 to 11 in the manufacture of a medicament for the treatment or prevention of a cardiovascular disease, metabolic syndrome, inflammatory disease, Alzheimer's disease, diabetes, or cancer, in a human in need thereof.
13. A method of treating or preventing cardiovascular disease, metabolic syndrome, inflammatory disease, Alzheimer's disease, diabetes, or cancer, in a subject, comprising administering to said subject a formulation according to any one of claims 1 to 11.

Date: 13 September 2016