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(54) **Title:** Substituted Dihydroxyflavone Derivatives, Compositions, and Methods Related Thereto

(57) **Abstract:** In certain embodiments, the disclosure relates to heterocyclic flavone derivatives, such as those described by formula provided herein, pharmaceutical compositions, and methods related thereto. In certain embodiments, the disclosure relates to methods of treating or preventing diseases or conditions related to BDNF and TrkB activity, such as depression, stroke, Rett syndrome, Parkinson's disease, and Alzheimer's disease by administering effective amounts of pharmaceutical compositions comprising compounds disclosed herein to a subject in need thereof.

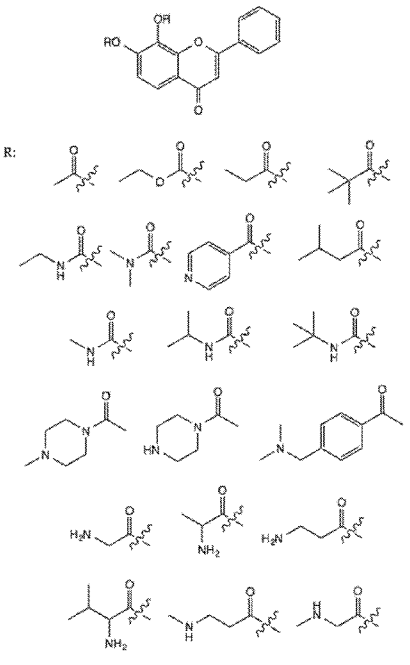


FIG. 1

WO 2020/033960 A1

SUBSTITUTED DIHYDROXYFLAVONE DERIVATIVES, COMPOSITIONS, AND METHODS RELATED THERETO

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/717,423 filed August 10, 2018. The entirety of this application is hereby incorporated by reference for all purposes.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under AG051538 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

Neurotrophins are growth factors regulate the development and maintenance of the peripheral and the central nervous system. Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family, which includes nerve growth factor (NGF), NT-3 and NT-4/5. BDNF binding to its cognate receptor, TrkB, triggers its dimerization through conformational changes and autophosphorylation of tyrosine residues, resulting in activation of the three major signaling pathways – mitogen-activated protein (MAPK), phosphatidylinositol 3-kinase (PI3K) and phospholipase C-γ1 (PLC-γ1). Various studies have shown links between BDNF and TrkB to conditions such as depression, schizophrenia, obsessive-compulsive disorder, Alzheimer's disease, Huntington's disease, Rett syndrome, and dementia, as well as anorexia nervosa and bulimia nervosa. See Dwivedi, Neuropsychiatric Disease and Treatment, 2009, 5: 433–49; Xiu et al., Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2009, 33(8):1508-12; Maina et al., Journal of Affective Disorders, 2010, 122(1-2):174-8; Zuccato et al., Nature Reviews Neurology, 2009, 5(6):311-22; Zajac et al., 2010, Hippocampus 20 (5): 621–36; Zeev et al., Neurology, 2009, 72 (14): 1242–7; Arancio et al., 2007, Current Opinion in Neurobiology, 17 (3): 325–30; Mercader et al, Neuropsychobiology , 2007, 56 (4): 185–90; Kaplan et al., International Journal of Eating Disorders, 2008 41 (1): 22–8.

It has been reported that certain 7,8-dihydroxyflavone derivatives promote neurogenesis and exhibits potent antidepressant effects. See Liu et al., J Med Chem, 2010, 53 (23), pp 8274–8286. See also WO/2014/018741, WO/2010/011836, WO/2010/107866, WO 2011/156479, and U.S. Patent 9,682,948. As 7,8-dihydroxyflavone derivatives are catechol and phenyl containing compounds, they are prone to be cleared in the circulatory system following oxidation, glucuronidation, sulfation, or methylation. Thus, there is a need to identify improved flavone derivatives with improved pharmacokinetic properties.

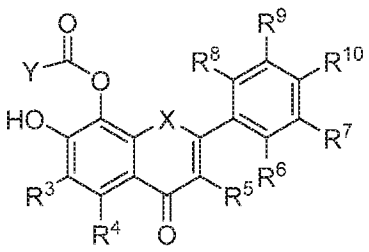
The health benefits of flavonoid compounds have been reported in a number of references, including neuroprotective and anti-cancer properties. See Chiruta et al., 2012, Journal of Medicinal Chemistry, 55, 378-89; Sousa et al., 2012, European Journal of Organic Chemistry, 1, 132-43; Sivakumar et al., PCT Appl. No. US 2010/0179210. Derivatives of 3-hydroxyquinolone compounds have also been previously synthesized with reports of their fluorescence and biological activities disclosed. See Yushchenko et al., 2006, Tetrahedron Letters, 47, 905-8; Krejci et al., PCT Appl. No. US 2010/0022587.

The references cited hereby are not an admission of prior art.

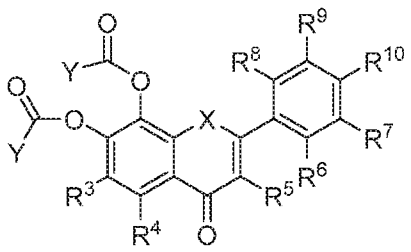
SUMMARY

In certain embodiments, the disclosure relates to substituted dihydroxyflavone derivatives, such as those described by formula provided herein, pharmaceutical compositions, and methods related thereto. In certain embodiments, the disclosure relates to methods of treating or preventing diseases or conditions related to BDNF and TrkB activity, such as depression, stroke, Rett syndrome, Parkinson's disease, and Alzheimer's disease by administering effective amounts of pharmaceutical compositions comprising compounds disclosed herein.

In certain embodiments, the disclosure related to a compound comprising Formula I or II:



Formula I



Formula II

or salt, prodrug, or ester thereof wherein

X is O, S, or NH;

Y is R^1, OR^1, NHR^1, or NR^1R^2;

R^1 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, or aryl, wherein R^1 is optionally substituted with one or more, the same or different, R^{15};

R^2 is hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^2 is optionally substituted with one or more, the same or different, R^{15};

R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are each individually and independently hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are optionally substituted with one or more, the same or different, R^{15};

R^{15} is independently selected alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, alkanoyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, or aryl, wherein R^{15} is optionally substituted with one or more, the same or different, R^{16}; and

R^{16} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, the disclosure relates to pharmaceutical compositions comprising compounds disclosed herein and a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition is in the form of a tablet, capsule, pill, or solution for injection. In

certain embodiments, the pharmaceutical composition is in sterilized and pH buffered aqueous solution optionally comprising a saccharide or polysaccharide.

In certain embodiments, the disclosure relates to methods of preventing or treating a BDNF and TrkB related disease or condition comprising the administering an effective amount of a pharmaceutical composition disclosed herein, to a subject in need thereof. In some embodiments, the subject is diagnosed with, exhibiting symptoms of, or at risk of the disease or condition. In some embodiments, the disease or condition is depression, schizophrenia, obsessive-compulsive disorder, anorexia nervosa, bulimia nervosa, anxiety, amyotrophic later sclerosis, Alzheimer's disease, Huntington's disease, Rett syndrome, epilepsy, Parkinson's disease, dementia, diabetic neuropathy, peripheral neuropathy, obesity, peripheral nerve injury, pain, or stroke. In certain embodiments, the methods described herein include a method of improving memory, e.g., in a subject diagnosed with a dementia or related TrkB related disease or condition.

In certain embodiments, the disease is depression and the pharmaceutical composition is administered in combination with an anti-depressant such as a selective serotonin reuptake inhibitor such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, or vilazodone, a serotonin-norepinephrine reuptake inhibitor such as desvenlafaxine, duloxetine, milnacipran, venlafaxine, a noradrenergic and specific serotonergic antidepressant such as mianserin and mirtazapine, a norepinephrine reuptake inhibitor such as atomoxetine, mazindol, reboxetine, viloxazine, a norepinephrine-dopamine reuptake inhibitor such as bupropion, a selective serotonin reuptake enhancer such as tianeptine and amineptine, a norepinephrine-dopamine disinhibitor such as agomelatine, a tricyclic antidepressant such as amitriptyline, clomipramine, doxepin, imipramine, trimipramine, desipramine, nortriptyline, protriptyline, a monoamine oxidase inhibitor such as isocarboxazid, moclobemide, phenelzine, selegiline, tranylcypromine.

In some embodiments, the disclosure relates to the use of a compound disclosed herein in the production of a medicament for the treatment or prevention of a BDNF and TrkB related disease or condition.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates compounds of this disclosure.

Figure 2A shows data on 7,8-DHF concentrations in plasma after oral administration of R13. Twenty-four male CD1 mice were administrated 78 mg/kg of R13 (equal to 7,8-DHF 50 mg/kg), which was dissolved in DMSO and resuspended in 5% DMSO/95% methylcellulose (0.5%, w/v). At indicated time points, 3 mice/group were sacrificed, the serum and brain samples were collected. 7,8-DHF was quantitatively analyzed by LC-MS/MS. Even 8 h after oral administration, more than 19 ng/ml of 7,8-DHF was detected in the plasma. 7,8-DHF above 8 ng/g was detected in mouse brain at 2h and lasted more than 4 h.

Figure 2B shows data on 7,8-DHF concentrations in the brain.

Figure 2C show data for an experiment where six 5XFAD mice were administrated 7.25 mg/kg, 21.8 mg/kg and 72.5 mg/kg of R13 while another six 5XFAD mice were administrated of 7,8-DHF at 5 mg/kg, 15 mg/kg, 50 mg/kg, respectively. After 4 hour, 2 mice/ group were sacrificed, the serum and brain samples were collected. 7,8-DHF was quantitatively analyzed by LC-MS/MS. Homogenization Dilution factor (1:3) already calculated for brain samples: BQL - Below Quantitation Limit, < 0.500 ng/mL, for serum: BQL - Below Quantitation Limit, < 2.00 ng/mL, for brain: - Not Applicable

Figure 2D illustrates R13 hydrolysis route. T1 is the major intermediate that is released from R13 from pH 1.2 to pH 7.4 buffer, mimicking the transition from stomach to intestine's pH change.

Figure 2E shows data in an experiment where nine 5XFAD mice were administrated with R13 at different dose of 21.8 mg/kg, 43.6 mg/kg and 72.5 mg/kg, respectively. After 4 hour of administration, 3 mice/group were sacrificed, the serum and brain were collected. 7,8-DHF and T1 were quantitatively analyzed by LC-MS/MS.

Figure 3A shows data on the quantity of R13 and T1 and 7,8DHF over time in Phosphate Buffer pH 1.2.

Figure 3B shows data on the quantity of R13 and T1 and 7,8DHF in phosphate buffer pH 6.

DETAILED DISCUSSION

Terms

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this disclosure

belongs. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present disclosure will be limited only by the appended claims.

As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present disclosure.

Embodiments of the present disclosure will employ, unless otherwise indicated, techniques of synthetic organic chemistry, biochemistry, biology, molecular biology, pharmacology, and the like, which are within the skill of the art. Such techniques are explained fully in the literature.

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. In this specification and in the claims that follow, reference will be made to a number of terms that shall be defined to have the following meanings unless a contrary intention is apparent.

As used herein a "flavone" refers to any compound comprising a 2-phenyl-4H-chromen-4-one ring system.

As used herein, “alkyl” means a noncyclic straight chain or branched, unsaturated or saturated hydrocarbon such as those containing from 1 to 10 carbon atoms, typically 1 to 6 carbon atoms. Within any embodiments, herein alkyl may refer to an alkyl with 1 to 6 carbons ($C_{1\text{-}6}$alkyl). Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-septyl, n-octyl, n-nonyl, and the like; while saturated branched alkyls include isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl, and the like. Unsaturated alkyls contain at least one double or triple bond between adjacent carbon atoms (referred to as an “alkenyl” or “alkynyl”, respectively). Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3 -methyl- 1-butenyl, 2-methyl-2-butenyl, 2,3- dimethyl-2-butenyl, and the like; while representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3- methyl-1-butynyl, and the like.

Non-aromatic mono or polycyclic alkyls are referred to herein as "carbocycles" or "carbocyclyl" groups. Representative saturated carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like; while unsaturated carbocycles include cyclopentenyl and cyclohexenyl, and the like.

"Heterocarbocycles" or heterocarbocyclyl" groups are carbocycles which contain from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur which may be saturated or unsaturated (but not aromatic), monocyclic or polycyclic, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized. Heterocarbocycles include morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Aryl" means an aromatic carbocyclic monocyclic or polycyclic ring such as phenyl or naphthyl. Polycyclic ring systems may, but are not required to, contain one or more non-aromatic rings, as long as one of the rings is aromatic.

As used herein, "heteroaryl" refers an aromatic heterocarbocycle having 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and polycyclic ring systems. Polycyclic ring systems may, but are not required to, contain one or more non-aromatic rings, as long as one of the rings is aromatic. Representative heteroaryls are furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinolinyl, isoquinolinyl, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl. It is contemplated that the use of the term "heteroaryl" includes N-alkylated derivatives such as a 1-methylimidazol- 5-yl substituent.

As used herein, "heterocycle" or "heterocyclyl" refers to mono- and polycyclic ring systems having 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom. The mono- and polycyclic ring systems may be aromatic, non-aromatic or mixtures of aromatic and non-aromatic rings. Heterocycle includes heterocarbocycles, heteroaryls, and the like.

"Alkylthio" refers to an alkyl group as defined above with the indicated number of carbon atoms attached through a sulfur bridge. An example of an alkylthio is methylthio, (i.e., -S-CH_3).

"Alkoxy" refers to an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n- pentoxy, and s-pentoxy. Preferred alkoxy groups are methoxy, ethoxy, n-propoxy, i- propoxy, n-butoxy, s-butoxy, t-butoxy.

"Alkylamino" refers an alkyl group as defined above attached through an amino bridge. An example of an alkylamino is methylamino, (i.e., -NH-CH_3).

"Alkyloxycarbonyl" refers to an alkyl as defined above attached through a carboxy bridge (i.e., -(C=O)Oalkyl.

"Alkylcarbamoyl" refers to an alkyl as defined above attached through a carbonyl bridge (i.e., -(C=O)NHalkyl).

"Alkanoyl" refers to an alkyl as defined above attached through a carbonyl bridge (i.e., -(C=O)alkyl).

"Alkylsulfonyl" refers to an alkyl as defined above attached through a sulfonyl bridge (i.e., -$S(=O)_2$alkyl) such as mesyl and the like, and "Arylsulfonyl" refers to an aryl attached through a sulfonyl bridge (i.e., - $S(=O)_2$aryl).

"Alkylsulfonamide" refers to an alkyl as defined above attached through a sulfamoyl bridge (i.e., -$S(=O)_2$NHalkyl), and an "Arylsulfonamide" refers to an alkyl attached through a sulfamoyl bridge (i.e., (i.e., - $S(=O)_2$NHaryl).

"Alkylsulfinyl" refers to an alkyl as defined attached through a sulfinyl bridge (i.e. -S(=O)alkyl).

The terms "halogen" and "halo" refer to fluorine, chlorine, bromine, and iodine.

The term "substituted" refers to a molecule wherein at least one hydrogen atom is replaced with a substituent. When substituted, one or more of the groups are "substituents." The molecule may be multiply substituted. In the case of an oxo substituent ("=O"), two hydrogen atoms are replaced. Example substituents within this context may include halogen, hydroxy, alkyl, alkoxy, nitro, cyano, oxo, carbocyclyl, carbocycloalkyl, heterocarbocyclyl, heterocarbocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -NR_aR_b, -$NR_aC(=O)R_b$, -$NR_aC(=O)NR_aNR_b$, -$NR_aC(=O)OR_b$, - $NR_aSO_2R_b$, -$C(=O)R_a$, -$C(=O)OR_a$, -$C(=O)NR_aR_b$, -$OC(=O)NR_aR_b$, -OR_a, -SR_a, -SOR_a, - $S(=O)_2R_a$, -$OS(=O)_2R_a$ and -$S(=O)_2OR_a$. R_a and R_b in this context may be the same or different and independently hydrogen, halogen hydroxyl, alkyl, alkoxy, alkyl, amino, alkylamino,

dialkylamino, carbocyclyl, carbocycloalkyl, heterocarbocyclyl, heterocarbocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl.

The term "optionally substituted," as used herein, means that substitution is optional and therefore it is possible for the designated atom to be unsubstituted.

As used herein, "salts" refer to derivatives of the disclosed compounds where the parent compound is modified making acid or base salts thereof. Examples of salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkylamines, or dialkylamines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. In preferred embodiment, the salts are conventional nontoxic pharmaceutically acceptable salts including the quaternary ammonium salts of the parent compound formed, and non-toxic inorganic or organic acids. Preferred salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

"Subject" refers any animal, preferably a human patient, livestock, or domestic pet.

As used herein, the terms "prevent" and "preventing" include the prevention of the recurrence, spread or onset. It is not intended that the present disclosure be limited to complete prevention. In some embodiments, the onset is delayed, or the severity of the disease is reduced.

As used herein, the terms "treat" and "treating" are not limited to the case where the subject (e.g. patient) is cured and the disease is eradicated. Rather, embodiments, of the present disclosure also contemplate treatment that merely reduces symptoms, and/or delays disease progression.

As used herein, the term "combination with" when used to describe administration with an additional treatment means that the agent may be administered prior to, together with, or after the additional treatment, or a combination thereof.

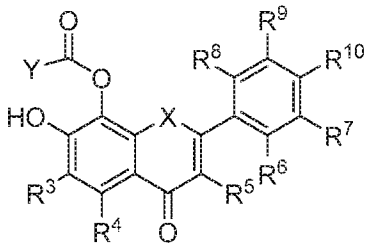
As used herein, the term “derivative” refers to a structurally similar compound that retains sufficient functional attributes of the identified analogue. The derivative may be structurally similar because it is lacking one or more atoms, substituted, a salt, in different hydration/oxidation states, or because one or more atoms within the molecule are switched, such as, but not limited to, replacing an oxygen atom with a sulphur atom or replacing an amino group with a hydroxyl group.

The derivative may be a prodrug. Derivatives may be prepared by any variety of synthetic methods or appropriate adaptations presented in synthetic or organic chemistry text books, such as those provide in March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Wiley, 6th Edition (2007) Michael B. Smith or Domino Reactions in Organic Synthesis, Wiley (2006) Lutz F. Tietze hereby incorporated by reference.

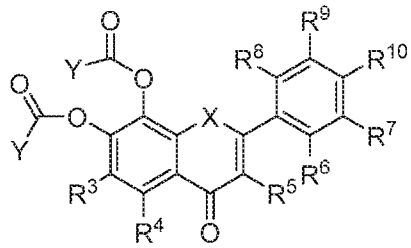
An "excipient" refers to an inert substance added to a pharmaceutical composition facilitating administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

Compounds

In certain embodiments, the disclosure related to a compound comprising Formula I or II:



Formula I



Formula II

or salt, prodrug, or ester thereof wherein

X is O, S, or NH;

Y is R^1, OR^1, NHR^1, or NR^1R^2;

R^1 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, or aryl, wherein R^1 is optionally substituted with one or more, the same or different, R^{15};

R^2 is hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^2 is optionally substituted with one or more, the same or different, R^{15};

R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are each individually and independently hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio,

alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are optionally substituted with one or more, the same or different, R^{15};

R^{15} is independently selected alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, alkanoyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, (alkyl)$_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, or aryl, wherein R^{15} is optionally substituted with one or more, the same or different, R^{16}; and

R^{16} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

In certain embodiments, X is O.

In certain embodiments, Y is NHR^1.

In certain embodiments, R^1 is alkyl, optionally substituted.

In certain embodiments, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are hydrogen.

In certain embodiments, X is O and Y is NHR^1.

In certain embodiments, X is O, Y is NHR^1, and R^1 is alkyl, methyl, ethyl, or isopropyl, optionally substituted.

In certain embodiments, X is O, Y is NHR^1, R^1 is alkyl, methyl, ethyl, or isopropyl, optionally substituted, and R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are hydrogen.

In certain embodiments, Y is R^1 and R^1 is methyl, optionally substituted.

In certain embodiments, Y is R^1, R^1 is methyl, X is O, and R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are hydrogen.

In certain embodiments, Y is R^1 and R^1 is ethoxy, optionally substituted.

In certain embodiments, Y is R^1, R^1 is ethoxy, optionally substituted, X is O, and R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are hydrogen.

In certain embodiments, Y is R^1 and R^1 is ethyl, optionally substituted.

In certain embodiments, Y is R^1, R^1 is ethyl, optionally substituted, X is O, and R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are hydrogen.

In certain embodiments, Y is R^1 and R^1 is tert-butyl, optionally substituted.

In certain embodiments, Y is R^1, R^1 is tert-butyl, optionally substituted, X is O, and R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are hydrogen.

In certain embodiments, Y is R^1 and R^1 is iso-butyl, optionally substituted.

In certain embodiments, Y is R^1, R^1 is iso-butyl, optionally substituted, X is O, and R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are hydrogen.

In certain embodiments, Y is NR^1R^2.

In certain embodiments, Y is NR^1R^2 and R^1 and R^2 are alkyl, methyl, ethyl, or isopropyl, optionally substituted.

In certain embodiments, R^1 is alkyl and R^2 is hydrogen.

In certain embodiments, R^1 and R^2 are alkyl, methyl, ethyl, or isopropyl, optionally substituted.

In certain embodiments, Y is NR^1R^2, R^1 and R^2 are alkyl, methyl, ethyl, or isopropyl, optionally substituted, X is O, and R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are hydrogen.

In certain embodiments, Y is R^1 and R^1 is heterocyclyl such as pyridinyl, pyridin-4-yl, piperazinyl, piperazin-1-yl, 4-alkylpiperazin-1-yl, or 4-methylpiperazin-1-yl.

In certain embodiments, Y is R^1 and R^1 is heterocyclyl, optionally substituted, such as pyridinyl, pyridin-4-yl, piperazinyl, piperazin-1-yl, 4-alkylpiperazin-1-yl, or 4-methylpiperazin-1-yl, optionally substituted, and X is O, and R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are hydrogen.

In certain embodiments, Y is R^1 and R^1 is aryl or phenyl, optionally substituted.

In certain embodiments, Y is R^1 and R^1 is aryl or phenyl, optionally substituted and X is O, and R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are hydrogen.

In certain embodiments, Y is R^1 and R^1 is 4-((dimethylamino)methyl)phenyl, optionally substituted.

In certain embodiments, Y is R^1 and R^1 is 4-((dimethylamino)methyl)phenyl, optionally substituted, X is O, and R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are hydrogen.

In certain embodiments, Y is R^1 and R^1 is amino-methyl, 2-amino-ethan-1-yl, 2-amino-propan-1-yl, 2-amino-isobut-1-yl, 1-methylamino-meth-1-yl, 2-methylamino-eth-1-yl, optionally substituted.

In certain embodiments, Y is R^1 and R^1 is amino-methyl, 2-amino-ethan-1-yl, 2-amino-propan-1-yl, 2-amino-isobut-1-yl, 1-methylamino-meth-1-yl, 2-methylamino-eth-1-yl, optionally substituted, X is O, and R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are hydrogen.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl methylcarbamate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl ethylcarbamate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl isopropylcarbamate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl dimethylcarbamate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl tert-butylcarbamate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl alaninate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl 3-aminopropanoate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl 3-(methylamino)propanoate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl glycinate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl methylglycinate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl valinate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl acetate, or salts, or derivatives thereof.

In certain embodiments, the compound is ethyl (7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl) carbonate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl propionate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl pivalate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl isonicotinate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl 3-methylbutanoate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl piperazine-1-carboxylate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl 4-methylpiperazine-1-carboxylate, or salts, or derivatives thereof.

In certain embodiments, the compound is 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl 4-((dimethylamino)methyl)benzoate, or salts, or derivatives thereof.

Formulations

Pharmaceutical compositions disclosed herein may be in the form of pharmaceutically acceptable salts, as generally described below. Some preferred, but non-limiting examples of suitable pharmaceutically acceptable organic and/or inorganic acids are hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, acetic acid and citric acid, as well as other pharmaceutically acceptable acids known per se (for which reference is made to the references referred to below).

When the compounds of the disclosure contain an acidic group as well as a basic group, the compounds of the disclosure may also form internal salts, and such compounds are within the scope of the disclosure. When a compound contains a hydrogen-donating heteroatom (e.g. NH), salts are contemplated to covers isomers formed by transfer of said hydrogen atom to a basic group or atom within the molecule.

Pharmaceutically acceptable salts of the compounds include the acid addition and base salts thereof. Suitable acid addition salts are formed from acids that form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate,

mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts. Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminum, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts. Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts. For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002), incorporated herein by reference.

The compounds described herein may be administered in the form of prodrugs. A prodrug can include a covalently bonded carrier that releases the active parent drug when administered to a mammalian subject. Prodrugs can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Prodrugs include, for example, compounds wherein a hydroxyl group is bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl group. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol functional groups in the compounds. Methods of structuring a compound as prodrugs can be found in the book of Testa and Mayer, Hydrolysis in Drug and Prodrug Metabolism, Wiley (2006). Typical prodrugs form the active metabolite by transformation of the prodrug by hydrolytic enzymes, the hydrolysis of amide, lactams, peptides, carboxylic acid esters, epoxides or the cleavage of esters of inorganic acids.

Pharmaceutical compositions for use in the present disclosure typically comprise an effective amount of a compound and a suitable pharmaceutical acceptable carrier. The preparations may be prepared in a manner known per se, which usually involves mixing the at least one compound according to the disclosure with the one or more pharmaceutically acceptable carriers, and, if desired, in combination with other pharmaceutical active compounds, when necessary under aseptic conditions. Reference is again made to U.S. Pat. No. 6,372,778, U.S. Pat. No. 6,369,086, U.S. Pat. No. 6,369,087 and U.S. Pat. No. 6,372,733 and the further references mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

Generally, for pharmaceutical use, the compounds may be formulated as a pharmaceutical preparation comprising at least one compound and at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant, and optionally one or more further pharmaceutically active compounds.

The pharmaceutical preparations of the disclosure are preferably in a unit dosage form, and may be suitably packaged, for example in a box, blister, vial, bottle, sachet, ampoule or in any other suitable single-dose or multi-dose holder or container (which may be properly labeled); optionally with one or more leaflets containing product information and/or instructions for use. Generally, such unit dosages will contain between 1 and 1000 mg, and usually between 5 and 500 mg, of the at least one compound of the disclosure, e.g. about 10, 25, 50, 100, 200, 300 or 400 mg per unit dosage.

The compounds can be administered by a variety of routes including the oral, ocular, rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes, depending mainly on the specific preparation used. The compound will generally be administered in an "effective amount", by which is meant any amount of a compound that, upon suitable administration, is sufficient to achieve the desired therapeutic or prophylactic effect in the subject to which it is administered. Usually, depending on the condition to be prevented or treated and the route of administration, such an effective amount will usually be between 0.01 to 1000 mg per kilogram body weight of the patient per day, more often between 0.1 and 500 mg, such as between 1 and 250 mg, for example about 5, 10, 20, 50, 100, 150, 200 or 250 mg, per kilogram body weight of the patient per day, which may be administered as a single daily dose, divided over one or more daily doses. The amount(s) to be administered, the route of administration and the further treatment regimen may be determined by the treating clinician, depending on factors such as the age, gender and general condition of the patient and the nature and severity of the disease/symptoms to be treated. Reference is again made to U.S. Pat. No. 6,372,778, U.S. Pat. No. 6,369,086, U.S. Pat. No. 6,369,087 and U.S. Pat. No. 6,372,733 and the further references mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

Depending upon the manner of introduction, the compounds described herein may be formulated in a variety of ways. Formulations containing one or more inhibitors can be prepared in various pharmaceutical forms, such as granules, tablets, capsules, suppositories, powders, controlled release formulations, suspensions, emulsions, creams, gels, ointments, salves, lotions,

or aerosols and the like. Preferably, these formulations are employed in solid dosage forms suitable for simple, and preferably oral, administration of precise dosages. Solid dosage forms for oral administration include, but are not limited to, tablets, soft or hard gelatin or non-gelatin capsules, and caplets. However, liquid dosage forms, such as solutions, syrups, suspension, shakes, etc. can also be utilized. In another embodiment, the formulation is administered topically. Suitable topical formulations include, but are not limited to, lotions, ointments, creams, and gels. In a preferred embodiment, the topical formulation is a gel. In another embodiment, the formulation is administered intranasally.

Formulations containing one or more of the compounds described herein may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, diluents, binders, lubricants, disintegrators, fillers, pH modifying agents, preservatives, antioxidants, solubility enhancers, and coating compositions.

Carrier also includes all components of the coating composition which may include plasticizers, pigments, colorants, stabilizing agents, surfactants, and glidants. Delayed release, extended release, and/or pulsatile release dosage formulations may be prepared as described in standard references such as "Pharmaceutical dosage form tablets", eds. Liberman et. al. (New York, Marcel Dekker, Inc., 1989), "Remington – The science and practice of pharmacy", 20th ed., Lippincott Williams & Wilkins, Baltimore, MD, 2000, and "Pharmaceutical dosage forms and drug delivery systems", 6th Edition, Ansel et al., (Media, PA: Williams and Wilkins, 1995). These references provide information on carriers, materials, equipment and process for preparing tablets and capsules and delayed release dosage forms of tablets, capsules, and granules.

Examples of suitable coating materials include, but are not limited to, cellulose polymers such as cellulose acetate phthalate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate; polyvinyl acetate phthalate, acrylic acid polymers and copolymers, and methacrylic resins that are commercially available under the trade name EUDRAGIT® (Roth Pharma, Westerstadt, Germany), zein, shellac, and polysaccharides.

Optional pharmaceutically acceptable excipients present in the drug-containing tablets, beads, granules or particles include, but are not limited to, diluents, binders, lubricants, disintegrants, colorants, stabilizers, and surfactants. Diluents, also referred to as "fillers," are typically necessary to increase the bulk of a solid dosage form so that a practical size is provided for compression of tablets or formation of beads and granules. Suitable diluents include, but are not limited to, dicalcium phosphate dihydrate, calcium sulfate, lactose, sucrose, mannitol, sorbitol, cellulose, microcrystalline cellulose, kaolin, sodium chloride, dry starch, hydrolyzed starches, pregelatinized starch, silicone dioxide, titanium oxide, magnesium aluminum silicate and powdered sugar.

Binders are used to impart cohesive qualities to a solid dosage formulation, and thus ensure that a tablet or bead or granule remains intact after the formation of the dosage forms. Suitable binder materials include, but are not limited to, starch, pregelatinized starch, gelatin, sugars (including sucrose, glucose, dextrose, lactose and sorbitol), polyethylene glycol, waxes, natural and synthetic gums such as acacia, tragacanth, sodium alginate, cellulose, including hydroxypropyl methylcellulose, hydroxypropyl cellulose, ethylcellulose, and magnesium aluminum silicate, and synthetic polymers such as acrylic acid and methacrylic acid copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, aminoalkyl methacrylate copolymers, polyacrylic acid/polymethacrylic acid and polyvinylpyrrolidone.

Lubricants are used to facilitate tablet manufacture. Examples of suitable lubricants include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, glycerol behenate, polyethylene glycol, talc, and mineral oil.

Disintegrants are used to facilitate dosage form disintegration or "breakup" after administration, and generally include, but are not limited to, starch, sodium starch glycolate, sodium carboxymethyl starch, sodium carboxymethylcellulose, hydroxypropyl cellulose, pregelatinized starch, clays, cellulose, arginine, gums or cross-linked polymers, such as cross-linked PVP.

Stabilizers are used to inhibit or retard drug decomposition reactions which include, by way of example, oxidative reactions.

Surfactants may be anionic, cationic, amphoteric or nonionic surface active agents. Suitable anionic surfactants include, but are not limited to, those containing carboxylate, sulfonate and sulfate ions. Examples of anionic surfactants include sodium, potassium, ammonium of long

chain alkyl sulfonates and alkyl aryl sulfonates such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium bis-(2-ethylthioxyl)-sulfosuccinate; and alkyl sulfates such as sodium lauryl sulfate. Cationic surfactants include, but are not limited to, quaternary ammonium compounds such as benzalkonium chloride, benzethonium chloride, cetrimonium bromide, stearyl dimethylbenzyl ammonium chloride, polyoxyethylene and coconut amine. Examples of nonionic surfactants include ethylene glycol monostearate, propylene glycol myristate, glyceryl monostearate, glyceryl stearate, polyglyceryl-4-oleate, sorbitan acylate, sucrose acylate, PEG-150 laurate, PEG-400 monolaurate, polyoxyethylene monolaurate, polysorbates, polyoxyethylene octylphenylether, PEG-1000 cetyl ether, polyoxyethylene tridecyl ether, polypropylene glycol butyl ether, stearoyl monoisopropanolamide, and polyoxyethylene hydrogenated tallow amide. Examples of amphoteric surfactants include sodium N-dodecyl-beta-alanine, sodium N-lauryl-beta-iminodipropionate, myristoamphoacetate, lauryl betaine, and lauryl sulfobetaine.

If desired, the tablets, beads, granules, or particles may also contain minor amount of nontoxic auxiliary substances such as wetting or emulsifying agents, dyes, pH buffering agents, or preservatives.

The concentration of the inhibitor(s) to carrier and/or other substances may vary from about 0.5 to about 100 wt % (weight percent). For oral use, the pharmaceutical formulation will generally contain from about 5 to about100% by weight of the active material. For other uses, the pharmaceutical formulation will generally have from about 0.5 to about 50 wt. % of the active material.

The compositions described herein can be formulation for modified or controlled release. Examples of controlled release dosage forms include extended release dosage forms, delayed release dosage forms, pulsatile release dosage forms, and combinations thereof.

The extended release formulations are generally prepared as diffusion or osmotic systems, for example, as described in “Remington – The science and practice of pharmacy” (20th ed., Lippincott Williams & Wilkins, Baltimore, MD, 2000). A diffusion system typically consists of two types of devices, a reservoir and a matrix, and is well known and described in the art. The matrix devices are generally prepared by compressing the drug with a slowly dissolving polymer carrier into a tablet form. The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers, and fatty compounds. Plastic matrices

include, but are not limited to, methyl acrylate-methyl methacrylate, polyvinyl chloride, and polyethylene. Hydrophilic polymers include, but are not limited to, cellulosic polymers such as methyl and ethyl cellulose, hydroxyalkylcelluloses such as hydroxypropyl-cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and Carbopol® 934, polyethylene oxides and mixtures thereof. Fatty compounds include, but are not limited to, various waxes such as carnauba wax and glyceryl tristearate and wax-type substances including hydrogenated castor oil or hydrogenated vegetable oil, or mixtures thereof.

In certain preferred embodiments, the plastic material is a pharmaceutically acceptable acrylic polymer, including but not limited to, acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

Alternatively, extended release formulations can be prepared using osmotic systems or by applying a semi-permeable coating to the dosage form. In the latter case, the desired drug release profile can be achieved by combining low permeable and high permeable coating materials in suitable proportion.

The devices with different drug release mechanisms described above can be combined in a final dosage form comprising single or multiple units. Examples of multiple units include, but are not limited to, multilayer tablets andcapsules containing tablets, beads, or granulesAn immediate release portion can be added to the extended release system by means of either applying an immediate release layer on top of the extended release core using a coating or compression process or in a multiple unit system such as a capsule containing extended and immediate release beads.

Extended release tablets containing hydrophilic polymers are prepared by techniques commonly known in the art such as direct compression, wet granulation, or dry granulation. Their

formulations usually incorporate polymers, diluents, binders, and lubricants as well as the active pharmaceutical ingredient. The usual diluents include inert powdered substances such as starches, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders include substances such as starch, gelatin and sugars such as lactose, fructose, and glucose. Natural and synthetic gums, including acacia, alginates, methylcellulose, and polyvinylpyrrolidone can also be used. Polyethylene glycol, hydrophilic polymers, ethylcellulose and waxes can also serve as binders. A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. In certain embodiments, the lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Extended release tablets containing wax materials are generally prepared using methods known in the art such as a direct blend method, a congealing method, and an aqueous dispersion method. In the congealing method, the drug is mixed with a wax material and either spray-congealed or congealed and screened and processed.

Delayed release formulations are created by coating a solid dosage form with a polymer film, which is insoluble in the acidic environment of the stomach, and soluble in the neutral environment of the small intestine.

The delayed release dosage units can be prepared, for example, by coating a drug or a drug-containing composition with a selected coating material. The drug-containing composition may be, e.g., a tablet for incorporation into a capsule, a tablet for use as an inner core in a "coated core" dosage form, or a plurality of drug-containing beads, particles or granules, for incorporation into a tablet or capsule. Preferred coating materials include bioerodible, gradually hydrolyzable, gradually water-soluble, and/or enzymatically degradable polymers, and may be conventional "enteric" polymers. Enteric polymers, as will be appreciated by those skilled in the art, become soluble in the higher pH environment of the lower gastrointestinal tract or slowly erode as the dosage form passes through the gastrointestinal tract, while enzymatically degradable polymers are degraded by bacterial enzymes present in the lower gastrointestinal tract, particularly in the colon. Suitable coating materials for effecting delayed release include, but are not limited to,

cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose acetate succinate, hydroxypropylmethyl cellulose phthalate, methylcellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate vinyl polymers and copolymers such as polyvinyl pyrrolidone, vinyl acetate, vinylacetate phthalate, vinyl acetate crotonic acid copolymer, and ethylene-vinyl acetate copolymer; enzymatically degradable polymers such as azo polymers, pectin, chitosan, amylose and guar gum; zein and shellac. Combinations of different coating materials may also be used. Multi-layer coatings using different polymers may also be applied.

The preferred coating weights for particular coating materials may be readily determined by those skilled in the art by evaluating individual release profiles for tablets, beads and granules prepared with different quantities of various coating materials. It is the combination of materials, method and form of application that produce the desired release characteristics, which one can determine only from the clinical studies.

The coating composition may include conventional additives, such as plasticizers, pigments, colorants, stabilizing agents, glidants, etc. A plasticizer is normally present to reduce the fragility of the coating, and will generally represent about 10 wt. % to 50 wt. % relative to the dry weight of the polymer. Examples of typical plasticizers include polyethylene glycol, propylene glycol, triacetin, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl acetyl citrate, castor oil and acetylated monoglycerides. A stabilizing agent is preferably used to stabilize particles in the dispersion. Typical stabilizing agents are nonionic emulsifiers such as sorbitan esters, polysorbates and polyvinylpyrrolidone. Glidants are recommended to reduce sticking effects during film formation and drying, and will generally represent approximately 25 wt % to 100 wt % of the polymer weight in the coating solution. One effective glidant is talc. Other glidants such as magnesium stearate and glycerol monostearates may also be used. Pigments such as titanium dioxide may also be used. Small quantities of an anti-foaming agent, such as a silicone (e.g., simethicone), may also be added to the coating composition.

The formulation can provide pulsatile delivery of the one or more inhibitors. By "pulsatile" is meant that a plurality of drug doses are released at spaced apart intervals of time. Generally, upon ingestion of the dosage form, release of the initial dose is substantially immediate, i.e., the first drug release "pulse" occurs within about one hour of ingestion. This initial pulse is followed by a first time interval (lag time) during which very little or no drug is released from the dosage form, after which a second dose is then released. Similarly, a second nearly drug release-free interval between the second and third drug release pulses may be designed. The duration of the nearly drug release-free time interval will vary depending upon the dosage form design e.g., a twice daily dosing profile, a three times daily dosing profile, etc. For dosage forms providing a twice daily dosage profile, the nearly drug release-free interval has a duration of approximately 3 hours to 14 hours between the first and second dose. For dosage forms providing a three times daily profile, the nearly drug release-free interval has a duration of approximately 2 hours to 8 hours between each of the three doses.

In one embodiment, the pulsatile release profile is achieved with dosage forms that are closed and preferably sealed capsules housing at least two drug-containing "dosage units" wherein each dosage unit within the capsule provides a different drug release profile. Control of the delayed release dosage unit(s) is accomplished by a controlled release polymer coating on the dosage unit, or by incorporation of the active agent in a controlled release polymer matrix. Each dosage unit may comprise a compressed or molded tablet, wherein each tablet within the capsule provides a different drug release profile. For dosage forms mimicking a twice a day dosing profile, a first tablet releases drug substantially immediately following ingestion of the dosage form, while a second tablet releases drug approximately 3 hours to less than 14 hours following ingestion of the dosage form. For dosage forms mimicking a three times daily dosing profile, a first tablet releases drug substantially immediately following ingestion of the dosage form, a second tablet releases drug approximately 3 hours to less than 10 hours following ingestion of the dosage form, and the third tablet releases drug at least 5 hours to approximately 18 hours following ingestion of the dosage form. It is possible that the dosage form includes more than three tablets. While the dosage form will not generally include more than a third tablet, dosage forms housing more than three tablets can be utilized.

Alternatively, each dosage unit in the capsule may comprise a plurality of drug-containing beads, granules or particles. As is known in the art, drug-containing "beads" refer to beads made

with drug and one or more excipients or polymers. Drug-containing beads can be produced by applying drug to an inert support, e.g., inert sugar beads coated with drug or by creating a "core" comprising both drug and one or more excipients. As is also known, drug-containing "granules" and "particles" comprise drug particles that may or may not include one or more additional excipients or polymers. In contrast to drug-containing beads, granules and particles do not contain an inert support. Granules generally comprise drug particles and require further processing. Generally, particles are smaller than granules, and are not further processed. Although beads, granules and particles may be formulated to provide immediate release, beads and granules are generally employed to provide delayed release.

In one embodiment, the compound is formulated for topical administration. Suitable topical dosage forms include lotions, creams, ointments, and gels. A "gel" is a semisolid system containing a dispersion of the active agent, i.e., inhibitor, in a liquid vehicle that is rendered semisolid by the action of a thickening agent or polymeric material dissolved or suspended in the liquid vehicle. The liquid may include a lipophilic component, an aqueous component or both. Some emulsions may be gels or otherwise include a gel component. Some gels, however, are not emulsions because they do not contain a homogenized blend of immiscible components. Methods for preparing lotions, creams, ointments, and gels are well known in the art.

The compounds described herein can be administered in combination with other active compounds. These compounds include but are not limited to analgesics, anti-inflammatory drugs, antipyretics, antidepressants, antiepileptics, antihistamines, antimigraine drugs, antimuscarinics, anxiolytics, sedatives, hypnotics, antipsychotics, bronchodilators, anti-asthma drugs, cardiovascular drugs, corticosteroids, dopaminergics, electrolytes, gastro-intestinal drugs, muscle relaxants, nutritional agents, vitamins, parasympathomimetics, stimulants, anorectics and anti-narcoleptics.

Specific examples of compounds that can be adjunctively administered with the compounds include, but are not limited to, aceclofenac, acetaminophen, adomexetine, almotriptan, alprazolam, amantadine, amcinonide, aminocyclopropane, amitriptyline, amolodipine, amoxapine, amphetamine, aripiprazole, aspirin, atomoxetine, azasetron, azatadine, beclomethasone, benactyzine, benoxaprofen, bermoprofen, betamethasone, bicifadine, bromocriptine, budesonide, buprenorphine, bupropion, buspirone, butorphanol, butriptyline, caffeine, carbamazepine, carbidopa, carisoprodol, celecoxib, chlordiazepoxide, chlorpromazine, choline salicylate,

citalopram, clomipramine, clonazepam, clonidine, clonitazene, clorazepate, clotiazepam, cloxazolam, clozapine, codeine, corticosterone, cortisone, cyclobenzaprine, cyproheptadine, demexiptiline, desipramine, desomorphine, dexamethasone, dexanabinol, dextroamphetamine sulfate, dextromoramide, dextropropoxyphene, dezocine, diazepam, dibenzepin, diclofenac sodium, diflunisal, dihydrocodeine, dihydroergotamine, dihydromorphine, dimetacrine, divalproxex, dizatriptan, dolasetron, donepezil, dothiepin, doxepin, duloxetine, ergotamine, escitalopram, estazolam, ethosuximide, etodolac, femoxetine, fenamates, fenoprofen, fentanyl, fludiazepam, fluoxetine, fluphenazine, flurazepam, flurbiprofen, flutazolam, fluvoxamine, frovatriptan, gabapentin, galantamine, gepirone, ginko bilboa, granisetron, haloperidol, huperzine A, hydrocodone, hydrocortisone, hydromorphone, hydroxyzine, ibuprofen, imipramine, indiplon, indomethacin, indoprofen, iprindole, ipsapirone, ketaserin, ketoprofen, ketorolac, lesopitron, levodopa, lipase, lofepramine, lorazepam, loxapine, maprotiline, mazindol, mefenamic acid, melatonin, melitracen, memantine, meperidine, meprobamate, mesalamine, metapramine, metaxalone, methadone, methadone, methamphetamine, methocarbamol, methyldopa, methylphenidate, methylsalicylate, methysergid(e), metoclopramide, mianserin, mifepristone, milnacipran, minaprine, mirtazapine, moclobemide, modafinil (an anti-narcoleptic), molindone, morphine, morphine hydrochloride, nabumetone, nadolol, naproxen, naratriptan, nefazodone, neurontin, nomifensine, nortriptyline, olanzapine, olsalazine, ondansetron, opipramol, orphenadrine, oxaflozane, oxaprazin, oxazepam, oxitriptan, oxycodone, oxymorphone, pancrelipase, parecoxib, paroxetine, pemoline, pentazocine, pepsin, perphenazine, phenacetin, phendimetrazine, phenmetrazine, phenylbutazone, phenytoin, phosphatidylserine, pimozide, pirlindole, piroxicam, pizotifen, pizotyline, pramipexole, prednisolone, prednisone, pregabalin, propanolol, propizepine, propoxyphene, protriptyline, quazepam, quinupramine, reboxitine, reserpine, risperidone, ritanserin, rivastigmine, rizatriptan, rofecoxib, ropinirole, rotigotine, salsalate, sertraline, sibutramine, sildenafil, sulfasalazine, sulindac, sumatriptan, tacrine, temazepam, tetrabenozine, thiazides, thioridazine, thiothixene, tiapride, tiasipirone, tizanidine, tofenacin, tolmetin, toloxatone, topiramate, tramadol, trazodone, triazolam, trifluoperazine, trimethobenzamide, trimipramine, tropisetron, valdecoxib, valproic acid, venlafaxine, viloxazine, vitamin E, zimeldine, ziprasidone, zolmitriptan, zolpidem, zopiclone and isomers, salts, and combinations thereof.

The additional active agent(s) can be formulated for immediate release, controlled release, or combinations thereof.

Methods of Use

In certain embodiments, the disclosure relates to methods of preventing or treating a BDNF and TrkB related disease or condition comprising the administering an effective amount of a pharmaceutical composition disclosed herein, to a subject in need thereof. In some embodiments, the subject is diagnosed with, exhibiting symptoms of, or at risk of the disease or condition. In some embodiments, the disease or condition is depression, anxiety, amyotrophic later sclerosis, Alzheimer's disease, Huntington's disease, Rett syndrome, epilepsy, Parkinson's disease, dementia, diabetic neuropathy, peripheral neuropathy, obesity, or stroke.

In certain embodiments, the methods described herein include a method of treating or reducing the risk of disorders associated with activation of the TrkB receptor including neurological disorders, neuropsychiatric disorders, and metabolic disorders in a subject. Examples of neurological and neuropsychiatric disorders include depression, anxiety, Alzheimer's, CNS injuries, and the like. Examples of metabolic disorders include obesity and hyperphagia. This method includes the steps of selecting a subject with or at risk of developing the neurological disorder, neuropsychiatric disorder, or obesity, and administering to the subject a therapeutically effective amount of a compound disclosed herein. The compound can be administered systemically (e.g., orally, parenterally (e.g. intravenously), intramuscularly, intraperitoneally, transdermally (e.g., by a patch), extracorporeally, topically, by inhalation, subcutaneously or the like), by administration into the central nervous system (e.g., into the brain (intracerebrally or intraventricularly), spinal cord, or into the cerebrospinal fluid), or any combination thereof.

In certain embodiments, the methods described herein include a method of improving memory, e.g., in a subject diagnosed with a dementia or related disorder.

The subject in need thereof can be a patient diagnosed as suffering from depression or anxiety. These diseases and their diagnoses are very clearly defined in the "Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)" published by the American Psychiatric Association. This manual sets forth diagnostic criteria, descriptions and other information to guide the classification and diagnosis of mental disorders and is commonly used in the field of neuropsychiatry. In certain embodiments, the patient is being administered an antidepressant or

anti-anxiolytic medication. In certain embodiments, the patient has been diagnosed by a mental health professional (e.g., a psychiatrist) with an anxiety or depression disorder. Anxiety can be a symptom of an underlying health issue such as chronic obstructive pulmonary disease (COPD), heart failure, or heart arrhythmia.

The subject in need thereof can be a patient diagnosed as suffering from being overweight or obese. Being overweight and obesity can be diagnosed by health or nutritional professionals (e.g., physicians, nurses, dieticians, and the like) when the patient's body mass index (BMI), a measurement which compares weight and height, is between 25 kg/m and 30 kg/m^2, and obese when it is greater than 30 kg/m^2.

Also provided is a method of promoting neuroprotection in a subject. This method includes the steps of selecting a subject in need of neuroprotection, and administering to the subject a therapeutically effective amount of a compound disclosed herein. A subject in need of neuroprotection can be a subject that has amyotrophic lateral sclerosis (ALS) or a central nervous system injury. A central nervous system injury includes, for example, a brain injury, a spinal cord injury, or a cerebrovascular event (e.g., a stroke). Methods can further comprise testing the effectiveness of a compound disclosed herein. Testing the effectiveness can include, but is not limited to, imaging (e.g., Magnetic Resonance Imaging (MRI)) and functional measurements (e.g., survival or clinical symptoms like analysis of speech patterns, logic, comprehension, memory, mood, and orientation).

EXAMPLES

Prodrugs of 7,8-dihydroxyflavone

7,8-DHF is oral bioactive and penetrates brain blood barrier. However, its oral bioavailability is not optimal. The catechol group makes 7,8-DHF labile for fast metabolism including glucuronidation, sulfation, methylation etc. A prodrug strategy was investigated to elevate the bioavailability. Hence, esters or carbamates were synthesized by changing the hydroxy groups on the catechol ring in 7,8-DHF (Figure 1).

In vitro pharmacokinetic profiles

It is desirable to identify prodrugs that are stable in both aqueous solution and at room temperature for a long shelf-life. Stability in intestine microsomes during the absorption, and

hydrolyzable in liver microsomes or plasma into 7,8-DHF are desirable properties. In addition, favorable Caco-2 permeability to allow prominent absorption is desirable. After intestine microsome, liver microsome and plasma stability screening, several synthetic derivatives relatively stable in intestine microsomes and hydrolyzable in both liver microsomes and plasma. Unfortunately, R16 or R17 failed to yield any detectable 7,8-DHF, indicating that these two compounds possess different hydrolytic chemistry (Table 1, 2 and 3).

In vivo Pharmacokinetics and brain exposure of R13

To test in vivo PK/BBB profiles of 7,8-DHF and R13 after dosing, R13 (prodrug of 7,8-DHF), was administered to six mice. Three animals in Group 1 were dosed orally at 50 mg/kg of 7,8-DHF and three animals in Group 2 were dosed orally at 72 mg/kg of R13. Blood samples were collected from all animals up to 8 h post-dose. Concentrations of 7,8-DHF and R13 in the plasma samples were determined by using LC-MS/MS. Pharmacokinetic analysis was performed using non-compartmental method.

Following a single P.O. administration of R13 at a dose of 72 mg/kg, the mean value of Cmax and Tmax for 7,8-DHF were 56 ng/mL and 2 h, respectively; the mean values of AUC(0-t) was 14777.5 min*ng/mL. The mean value of oral bioavailability for R13 was 10.50%. Strikingly, 7,8-DHF was detectable in the plasma at 8 h, indicating the prodrug can sustainably release 7,8-DHF in the circulation system. The ratio of R13/parent compound of AUClast is 14777.5/6885.5 = 2.14.

The metabolites of R13 were determined. Intermediate T1 was synthesized this from 7,8-DHF by the reaction with methylcarbamic chloride. T1 was identified as a major component. This finding indicates that 7-positioned mono-methyl carbamate hydrolyzed in water, when pH values gradually escalate in the buffers.

As illustrated in Figure 2D, T1 is the major intermediate that is released from R13 from pH 1.2 to pH 7.4 buffer, mimicking the transition from stomach to intestine's pH change. See Figure 3A and 3B. Nine 5XFAD mice were administrated with R13 at different dose of 21.8 mg/kg, 43.6 mg/kg and 72.5 mg/kg, respectively. After 4 hour of administration, 3 mice/group were sacrificed, the serum and brain were collected. 7,8-DHF and T1 were quantitatively analyzed by LC-MS/MS. As T1 is an intermediate, it can be used as a pharmaceutical product as it sustains

high levels in plasma. See Figure 2E. Other monosubstituted dihydroxyflavones are contemplated for these purposes.

Preparation of 4-oxo-2-phenyl-4H-chromene-7,8-diyl diacetate

7,8-Dihydroxyflavone (100 mg, 0.4 mmol) was added to a suspension of K_2CO_3 (342 mg, 2.5 mmol) and acetic anhydride (0.1 mL, 0.8 mmol) in DCM. After stiring at r.t. overnight, the mixture was filtered and evaporated under reduced pressure. The residue was washed by ethyl ether to afford the product as a white solid (71 mg, yield: 53.3%,). ^{1}H NMR (400 MHz, CD_3OD): δppm 8.06 (d, J = 8.8 Hz,1H), 7.93-7.95 (m, 2H), 7.58-7.61(m, 3H), 7.38 (d, J = 8.4 Hz, 1H), 6.93 (s, 1H), 2.48(s, 3H), 2.37(s, 3H). Purity: 99.8% (254 nm); MS: 339.0 [M+1]+

Diethyl (4-oxo-2-phenyl-4H-chromene-7,8-diyl) bis(carbonate)

7,8-Dihydroxyflavone (200 mg, 0.8 mmol) was added to a suspension of K_2CO_3 (458 mg, 3.3 mmol) and ethyl chloroformate (0.3 mL, 1.7 mmol) in DCM. After stirring at r.t. overnight, the mixture was filtered and evaporated under reduced pressure. The residue was washed by ethyl ether to afford the product as a white solid (50 mg, yield: 15.9%). ^{1}H NMR (400 MHz, $CDCl_3$): δppm 8.14 (d, J = 8.8 Hz,1H), 7.85-7.87 (m, 2H), 7.50-7.56(m, 3H), 7.35-7.38 (m, 1H), 6.83 (s, 1H), 4.35-4.43 (m, 4H), 1.41-1.44(m, 6H). Purity: 96.0%(254 nm); MS: 399.0 [M+1]+

4-Oxo-2-phenyl-4H-chromene-7,8-diyl dipropionate

7,8-Dihydroxyflavone (200 mg, 0.8 mmol) was added to a suspension of K2CO3 (458 mg, 3.3 mmol) and Propionyl chloride (0.3 mL, 1.7 mmol) in DCM. After stirring at r.t. overnight, the mixture was filtered and evaporated under reduced pressure. The residue was washed by ethyl ether to afford the product as a yellow solid (51 mg, yield: 17.4%). ^{1}H NMR (400 MHz, $CDCl_3$): δppm 8.13 (d, J =8.8 Hz, 1H), 7.79-7.81 (m, 2H), 7.51-7.55(m, 3H), 7.25-7.27 (m, 1H), 6.79 (s, 1H), 2.75 (q, J = 7.6 Hz, 2H), 2.65(q, J = 7.6 Hz, 2H), 1.38(t, J= 7.6 Hz, 3H), 1.31(t, J =7.6 Hz, 3H). Purity: 95.5% (254 nm); MS: 367.0 [M+1]+

4-Oxo-2-phenyl-4H-chromene-7,8-diyl bis(2,2-dimethylpropanoate)

7,8-Dihydroxyflavone (150 mg, 0.6 mmol) was added to a suspension of K_2CO_3 (341 mg, 2.48 mmol) and pivaloyl chloride (0.2 mL, 1.2 mmol) in DCM. After stirring at r.t. overnight, the

mixture was filtered and evaporated under reduced pressure. The residue was washed by ethyl ether to afford the product as a red solid (52 mg, yield: 20.9%). ^{1}H NMR (400 MHz, $CDCl_3$):δppm 8.12 (d, J = 8.8 Hz, 1H), 7.80-7.82 (m, 2H), 7.50-7.55(m, 3H), 7.20 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H), 1.45(s, 9H), 1.35(s, 9H). Purity: 99.6% (254 nm); MS: 445.1 [M+1]+

4-Oxo-2-phenyl-4H-chromene-7,8-diyl bis(ethylcarbamate)

7,8-Dihydroxyflavone (200 mg, 0.8 mmol) was added to a suspension of K_2CO_3 (458 mg, 3.3 mmol) and ethyl isocyanate (0.3 mL, 1.7 mmol) in DCM. After stirring at r.t. overnight, the mixture was filtered and evaporated under reduced pressure. The residue was washed by ethyl ether to afford the product as a white solid (70 mg, yield: 22.5%). ^{1}H NMR (400 MHz, $CDCl_3$): δppm 8.05 (d, J = 8.8 Hz, 1H), 7.84-7.86 (m, 2H), 7.47-7.53(m, 3H), 7.28-7.30 (m, 1H), 6.79 (s, 1H), 5.45-5.46 (m, 1H), 5.22-5.23 (m, 1H), 3.32-3.54 (m, 4H), 1.23-1.30(m, 6H). Purity: 99.8% (254 nm); MS: 397.1 [M+1]+.

The following may be prepared using above procedure by substituting the appropriate isocyanate.

4-Oxo-2-phenyl-4H-chromene-7,8-diyl bis(methylcarbamate)

^{1}H NMR (300 MHz, d_6-DMSO): δ ppm 8.21 (q, J = 4.50 Hz, 1H), 7.95-8.02 (m, 3H), 7.90 (d, J = 9.0 Hz, 1H), 7.58-7.64 (m, 3H), 7.38 (d, J = 8.70 Hz, 1H), 7.10 (s, 1H), 2.77 (d, J = 4.80 Hz, 3H), 2.69 (d, J = 4.80 Hz, 3H). Purity: 99.9% (254 nm); MS: 369.1 $[M+1]^+$.

4-Oxo-2-phenyl-4H-chromene-7,8-diyl bis(iso-propylcarbamate)

^{1}H NMR (300 MHz, d_6-DMSO): δ ppm 8.26 (d, J = 7.80 Hz, 1H), 8.04 (d, J = 8.40 Hz, 3H), 7.90 (d, J = 9.0 Hz, 1H), 7.60 (m, 3H), 7.36 (d, J = 8.70 Hz, 1H), 7.12 (s, 1H), 3.68 (m, 2H), 1.20 (m, 12 H). Purity: 99.4% (254 nm); MS: 425.1 $[M+1]^+$.

4-Oxo-2-phenyl-4H-chromene-7,8-diyl bis(t-butylcarbamate)

^{1}H NMR (300 MHz, d_6-DMSO): δ ppm 8.09 (d, J = 8.40 Hz, 3H), 7.89 (d, J = 8.70 Hz, 2 H), 7.55-7.64 (m, 3H), 7.31 (d, J = 8.70 Hz, 1H), 7.11 (s, 1H), 1.32 (s, 18 H). Purity: 97.5% (254 nm); MS: 453.5 $[M+1]^+$.

4-Oxo-2-phenyl-4H-chromene-7,8-diyl bis(dimethylcarbamate)

7,8-Dihydroxyflavone (200 mg, 0.8 mmol) was added to a suspension of K_2CO_3 (458 mg, 3.3 mmol) and dimethylcarbamoyl chloride (0.3 mL, 1.7 mmol) in DCM. After stirring at r.t. overnight, the mixture was filtered and evaporated under reduced pressure. The residue was washed by ethyl ether to afford the product as a white solid (53 mg, yield: 15.9%). ^{1}H NMR (400 MHz, $CDCl_3$): δppm 8.07 (d, J = 8.8 Hz, 1H), 7.82-7.84 (m, 2H), 7.49-7.54(m, 3H), 7.32-7.34 (m, 1H), 6.79 (s, 1H), 3.24 (s, 3H), 3.15(s, 3H), 3.11(s, 3H), 3.05(s, 3H). Purity: 98.2% (254 nm); MS: 397.0[M+1]+

4-Oxo-2-phenyl-4H-chromene-7,8-diyl diisonicotinate

A solution of isonicotinic acid (600 mg, 4.9 mmol) in $SOCl_2$ (20 mL) was refluxed overnight under Ar atmosphere. Then the resulting mixture was evaporated under reduced pressure to remove the $SOCl_2$, the residue was used for the next step directly without further purification. 7,8-Dihydroxyflavone (200 mg, 0.8 mmol) was added to a solution of DMAP (1.2 g, 4.8 mmol) and isonicotinoyl chloride (690 mg, 4.9 mmol) in DCM (5 mL), and the mixture was stirred at r.t. overnight. The mixture was filtered and evaporated under reduced pressure. The residue was washed by ethyl ether to afford the product as a white solid (80 mg, yield: 21.9%). The product was confirmed by HPLC, LCMS and ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$): δppm 8.89 (d, J = 6.0 Hz, 2H), 8.83 (d, J = 6.0 Hz, 2H), 8.28 (d, J = 8.8 Hz, 1H), 7.99-8.00 (m, 2H), 7.91-7.92 (m, 2H), 7.67-7.69 (m, 2H), 7.46-7.48 (m, 2H), 7.36-7.40 (m, 2H), 6.86(s, 1H). Purity: 93.7% (254 nm); MS: 465.0 [M+1]+

The following may be prepared using above procedure by substituting the appropriate carboxylic acids wherein the amine optionally contains a protecting group

4-Oxo-2-phenyl-4H-chromene-7,8-diyl bis(4-methylpiperazine-1-carboxylate)

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.08 (d, *J* = 9.0 Hz, 1H), 7.84 (d, *J* = 6.3 Hz, 2H), 7.53-7.49 (m, 3H), 7.30 (d, *J* = 9.0 Hz, 1H), 6.79 (s, 1H), 3.85-3.58 (m, 8H), 2.53-2.45 (m, 8H), 2.39 (s, 3H), 2.36 (s, 3H); purity >98% at 214 nm, MS (ESI) m/z = 507.2 $[M+H]^+$.

4-Oxo-2-phenyl-4H-chromene-7,8-diyl bis(piperazine-1-carboxylate) dihydrochloride

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ (ppm) 9.78-9.45 (br, 4H), 7.99-7.95 (m, 3H), 7.67-7.63 (m, 3H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.11 (s, 1H), 4.05-3.70 (m, 8H), 3.27-3.14 (m, *8*H); purity >98% at 214 nm, MS (ESI) m/z = 479.1 $[M+H]^+$.

4-Oxo-2-phenyl-4H-chromene-7,8-diyl bis(4-((dimethylamino)methyl)benzoate

^{1}H NMR (600MHz, DMSO-d$_6$): d 8.10 (m, 3H), 8.01 (d, 2H), 7.84 (d, 2H), 7.71 (d, 1H), 7.52-7.41 (m, 7H), 7.17 (s, 1H), 3.50 (d, 4H), 2.17 (d, 12H) and LC-MS [MW=576.6].

4-Oxo-2-phenyl-4H-chromene-7,8-diyl-bis(2-aminoacetate) dihydrochloride

^{1}H NMR (300MHz, D_2O) δ7.95 (d, 1H), 7.74 (d, 2H), 7.74 (m, 5H), 6.81 (s, 1H), 4.79 (s, 15H), 4.45 (d, 2H), 4.34 (d, 2H), 3.70 (s, 1H). HPLC 90%; MS: calculated: 368.34; found: 396.1 (M + 1). Elemental Analysis: calculated C: 49.69, found C: 49.62; MS: calculated H: 4.39, found H: 4.45, LC: calculated N 6.10, found: 6.10, calculated Cl: 15.44, found Cl: 15.36.

(2S, 2'S)-4-Oxo-2-phenyl-4H-chromene-7,8-diyl-bis(2-aminopropanoate)

^{1}H NMR (300MHz, D_2O) δ7.94 (d, 1H), 7.71 (d, 2H), 7.46 (m, 4H), 6.78(s, 1H), 4.77 (m, 2H), 1.83 (d, 3H), 1.76 (d, 3H), 1.45 (m, 1H). HPLC: 0.13 alanine. MS: calculated: 396.36, found: 397.1 (M+1). Elemental Analysis: calculated C: 52.73, found C: 52.83; MS: calculated H: 4.85, found H: 4.79, LC: calculated N 5.86, found: 5.82, calculated Cl: 14.82, found Cl: 14.90.

4-Oxo-2-phenyl-4H-chromene-7,8-diyl-bis(3-aminopropanoate) dihydrochloride

^{1}H NMR (300MHz, D_2O) δ7.73 (d, 1H), 7.71 (m, 2H), 7.50(m, 3H), 7.40 (d,1H), 6.81 (s, 1H), 4.83 (m, H), 3.39 (m, 4H), 3.374 (d, 2H), 3.37 (m, 2H). LC: 100%. MS: calculated: 396.36, found: 397.1 (M+1). Elemental Analysis: calculated C: 52.73, found C: 52.55; MS: calculated H: 4.85, found H: 4.80, LC: calculated N 5.86, found: 5.92, calculated Cl: 14.82, found Cl: 14.99.

(2S,2'S)-4-Oxo-2-phenyl-4H-chromene-7,8-diyl-bis(2-amino-3-methylbutanoate) dihydrochloride

^{1}H NMR (300MHz, D_2O) δ7.88 (d, 1H), 7.58 (m, 3H), 7.41 (m, 3H), 6.68 (s, 1H), 4.77 (s, H), 4.49 (d, 1H), 4.44 (d, 1H), 2.65 (m, 2H), 1.19 (m, 9H), 1.06 (m, 4H). HPLC: 0.15 eq. valine.

MS: calculated: 452.5, found: 453.2 (M+1). Elemental Analysis: calculated C: 55.07, found C: 54.87; MS: calculated H: 5.95, found H: 45.82, LC: calculated N 5.14, found: 5.22, calculated Cl: 13.00, found Cl: 13.08.

4-Oxo-2-phenyl-4H-chromene-7,8-diyl-bis(3-methylaminopropanoate) Dihydrochloride

^{1}H NMR (300MHz, D2O) δ7.94 (d, 1H), 7.70 (d, 2H), 7.47(m, 3H), 7.39 (d, 1H), 6.80 (s, 1H), 4.83 (m, H), 3.43 (m, 4H), 3.28 (d, 2H), 3.21 (m, 2H). 2.77(s, 3H), 2.72 (s, 3H). HPLC: 100%. MS: calculated: 424.45, found: 425.2 (Parent+1). Elemental Analysis: calculated C: 52.85, found C: 53.09; MS: calculated H: 5.44, found H: 5.18, LC: calculated N 5.36, found: 5.30, calculated Cl: 14.92, found Cl: 14.96.

4-Oxo-2-phenyl-4H-chromene-7,8-diyl-bis(2-(methylamino)acetate) dihydrochloride

^{1}H NMR (300MHz, D_2O) δ7.94 (d, 1H), 7.75 (d, 2H), 7.48(m, 5H), 6.80 (s, 1H), 4.80 (m, H), 4.55 (s, 2H), 4.53 (d, 2H), 2.93 (d, 7H). HPLC: 90%. MS: calculated: 396.36, found: fragmented. NMR: Elemental Analysis: calculated C: 53.74, found C: 53.58; calculated H: 4.72, found H: 4.69, LC: calculated N 5.97, found: 5.90, calculated Cl: 15.11, found Cl: 15.02.

4-Oxo-2-phenyl-4H-chromene-7,8-diyl bis(3-methylbutanoate)

7,8-Dihydroxyflavone (150 mg, 0.6 mmol) was added to a suspension of K_2CO_3 (341 mg, 2.48 mmol) and isovaleryl chloride (0.2 mL, 1.2 mmol) in DCM. After stirring at r.t. overnight, the mixture was filtered and evaporated under reduced pressure. The residue was washed by ethyl ether to afford the product as a white solid (57 mg, yield: 23.1%). ^{1}H NMR (400 MHz, $CDCl_3$): δppm 8.12 (d, J = 8.8 Hz, 1H), 7.80-7.82 (m, 2H), 7.48-7.55(m, 3H), 7.23-7.26 (m, 1H), 6.78 (s, 1H), 2.59 (d, J = 6.8 Hz, 2H), 2.49 (d, J = 6.8 Hz, 2H), 2.24-2.32(m, 2H), 1.09-1.11(m, 12H). Purity: 99.6% (254 nm); MS: 445.0 [M+1]+

4-Oxo-2-phenyl-4H-chromene-7,8-diyl-bis(2-aminoacetate) dihydrochloride

^{1}H NMR (300MHz, D_2O) δ7.95 (d, 1H), 7.74 (d, 2H), 7.74 (m, 5H), 6.81 (s, 1H), 4.79 (s, 15H), 4.45 (d, 2H), 4.34 (d, 2H), 3.70 (s, 1H). HPLC 90%; MS: calculated: 368.34; found: 396.1 (M + 1). Elemental Analysis: calculated C: 49.69, found C: 49.62; MS: calculated H: 4.39, found H: 4.45, LC: calculated N 6.10, found: 6.10, calculated Cl: 15.44, found Cl: 15.36.

(2S, 2'S)-4-Oxo-2-phenyl-4H-chromene-7,8-diyl-bis(2-aminopropanoate)

^{1}H NMR (300MHz, D_2O) δ7.94 (d, 1H), 7.71 (d, 2H), 7.46 (m, 4H), 6.78(s, 1H), 4.77 (m, 2H), 1.83 (d, 3H), 1.76 (d, 3H), 1.45 (m, 1H). HPLC: 0.13 alanine. MS: calculated: 396.36, found: 397.1 (M+1). Elemental Analysis: calculated C: 52.73, found C: 52.83; MS: calculated H: 4.85, found H: 4.79, LC: calculated N 5.86, found: 5.82, calculated Cl: 14.82, found Cl: 14.90.

4-Oxo-2-phenyl-4H-chromene-7,8-diyl-bis(3-aminopropanoate) dihydrochloride

^{1}H NMR (300MHz, D_2O) δ7.73 (d, 1H), 7.71 (m, 2H), 7.50(m, 3H), 7.40 (d,1H), 6.81 (s, 1H), 4.83 (m, H), 3.39 (m, 4H), 3.374 (d, 2H), 3.37 (m, 2H). LC: 100%. MS: calculated: 396.36, found: 397.1 (M+1). Elemental Analysis: calculated C: 52.73, found C: 52.55; MS: calculated H: 4.85, found H: 4.80, LC: calculated N 5.86, found: 5.92, calculated Cl: 14.82, found Cl: 14.99.

(2S,2'S)-4-Oxo-2-phenyl-4H-chromene-7,8-diyl-bis(2-amino-3-methylbutanoate) dihydrochloride

^{1}H NMR (300MHz, D_2O) δ7.88 (d, 1H), 7.58 (m, 3H), 7.41 (m, 3H), 6.68 (s, 1H), 4.77 (s, H), 4.49 (d, 1H), 4.44 (d, 1H), 2.65 (m, 2H), 1.19 (m, 9H), 1.06 (m, 4H). HPLC: 0.15 eq. valine. MS: calculated: 452.5, found: 453.2 (M+1). Elemental Analysis: calculated C: 55.07, found C: 54.87; MS: calculated H: 5.95, found H: 45.82, LC: calculated N 5.14, found: 5.22, calculated Cl: 13.00, found Cl: 13.08.

4-Oxo-2-phenyl-4H-chromene-7,8-diyl-bis(3-methylaminopropanoate) dihydrochloride

^{1}H NMR (300MHz, D_2O) δ7.94 (d, 1H), 7.70 (d, 2H), 7.47(m, 3H), 7.39 (d, 1H), 6.80 (s, 1H), 4.83 (m, H), 3.43 (m, 4H), 3.28 (d, 2H), 3.21 (m, 2H). 2.77(s, 3H), 2.72 (s, 3H). HPLC: 100%. MS: calculated: 424.45, found: 425.2 (Parent+1). Elemental Analysis: calculated C: 52.85, found C: 53.09; MS: calculated H: 5.44, found H: 5.18, LC: calculated N 5.36, found: 5.30, calculated Cl: 14.92, found Cl: 14.96.

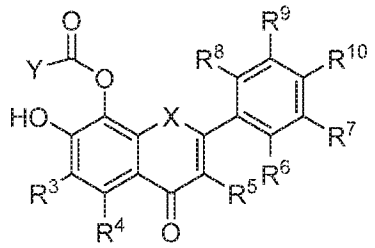
4-Oxo-2-phenyl-4H-chromene-7,8-diyl-bis(2-(methylamino)acetate) dihydrochloride

^{1}H NMR (300MHz, D_2O) δ7.94 (d, 1H), 7.75 (d, 2H), 7.48(m, 5H), 6.80 (s, 1H), 4.80 (m, H), 4.55 (s, 2H), 4.53 (d, 2H), 2.93 (d, 7H). HPLC: 90%. MS: calculated: 396.36, found:

fragmented. NMR: Elemental Analysis: calculated C: 53.74, found C: 53.58; calculated H: 4.72, found H: 4.69, LC: calculated N 5.97, found: 5.90, calculated Cl: 15.11, found Cl: 15.02.

CLAIMS

1. A compound having Formula I:



Formula I

or salt, prodrug, or ester thereof wherein

X is O, S, or NH;

Y is R^1, OR^1, NHR^1, or NR^1R^2;

R^1 is alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, or aryl, wherein R^1 is optionally substituted with one or more, the same or different, R^{15};

R^2 is hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^2 is optionally substituted with one or more, the same or different, R^{15};

R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are each individually and independently hydrogen, alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, or heterocyclyl, wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are optionally substituted with one or more, the same or different, R^{15};

R^{15} is independently selected alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, alkanoyl, carboxy, carbamoyl, alkoxy, alkylthio, alkylamino, $(alkyl)_2$amino, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, carbocyclyl, or aryl, wherein R^{15} is optionally substituted with one or more, the same or different, R^{16}; and

R^{16} is halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino,

N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N-methyl-N-ethylsulfamoyl, carbocyclyl, aryl, or heterocyclyl.

2. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable excipient.

3. The composition of Claim 2, wherein the pharmaceutical composition is in the form of a tablet, capsule, or pill.

4. The composition of Claim 2, wherein the pharmaceutical composition is in sterilized and pH buffered aqueous solution.

5. A method of preventing or treating a BDNF and TrkB related disease or condition comprising the administering an effective amount of a pharmaceutical composition of Claim 1, to a subject in need thereof.

6. The method of Claim 5, wherein the disease or condition is depression, schizophrenia, obsessive-compulsive disorder, anorexia nervosa, bulimia nervosa, anxiety, amyotrophic later sclerosis, Alzheimer's disease, Huntington's disease, Rett syndrome, epilepsy, Parkinson's disease, dementia, diabetic neuropathy, peripheral neuropathy, obesity, or stroke.

7. The method of Claim 5, wherein the method is improving memory in a subject diagnosed with dementia or related condition.

8. The use of a compound of Claim 1, in the production of a medicament for use in the treatment or prevention of a BDNF and TrkB related disease or condition.

9. A compound 7-hydroxy-4-oxo-2-phenyl-4H-chromen-8-yl methylcarbamate or salt thereof.

10. A pharmaceutical composition comprising a compound of Claim 9 and a pharmaceutically acceptable excipient.

11. The composition of Claim 10, wherein the pharmaceutical composition is in the form of a tablet, capsule, or pill.

12. The composition of Claim 10, wherein the pharmaceutical composition is in sterilized and pH buffered aqueous solution.

13. A method of preventing or treating a BDNF and TrkB related disease or condition comprising the administering an effective amount of a pharmaceutical composition of Claim 9 to a subject in need thereof.

14. The method of Claim 13, wherein the disease or condition is depression, schizophrenia, obsessive-compulsive disorder, anorexia nervosa, bulimia nervosa, anxiety, amyotrophic later sclerosis, Alzheimer's disease, Huntington's disease, Rett syndrome, epilepsy, Parkinson's disease, dementia, diabetic neuropathy, peripheral neuropathy, obesity, or stroke.

15. The method of Claim 13, wherein the method is improving memory in a subject diagnosed with dementia or related condition

16. The use of a compound of Claim 9, in the production of a medicament for use in the treatment or prevention of a BDNF and TrkB related disease or condition.

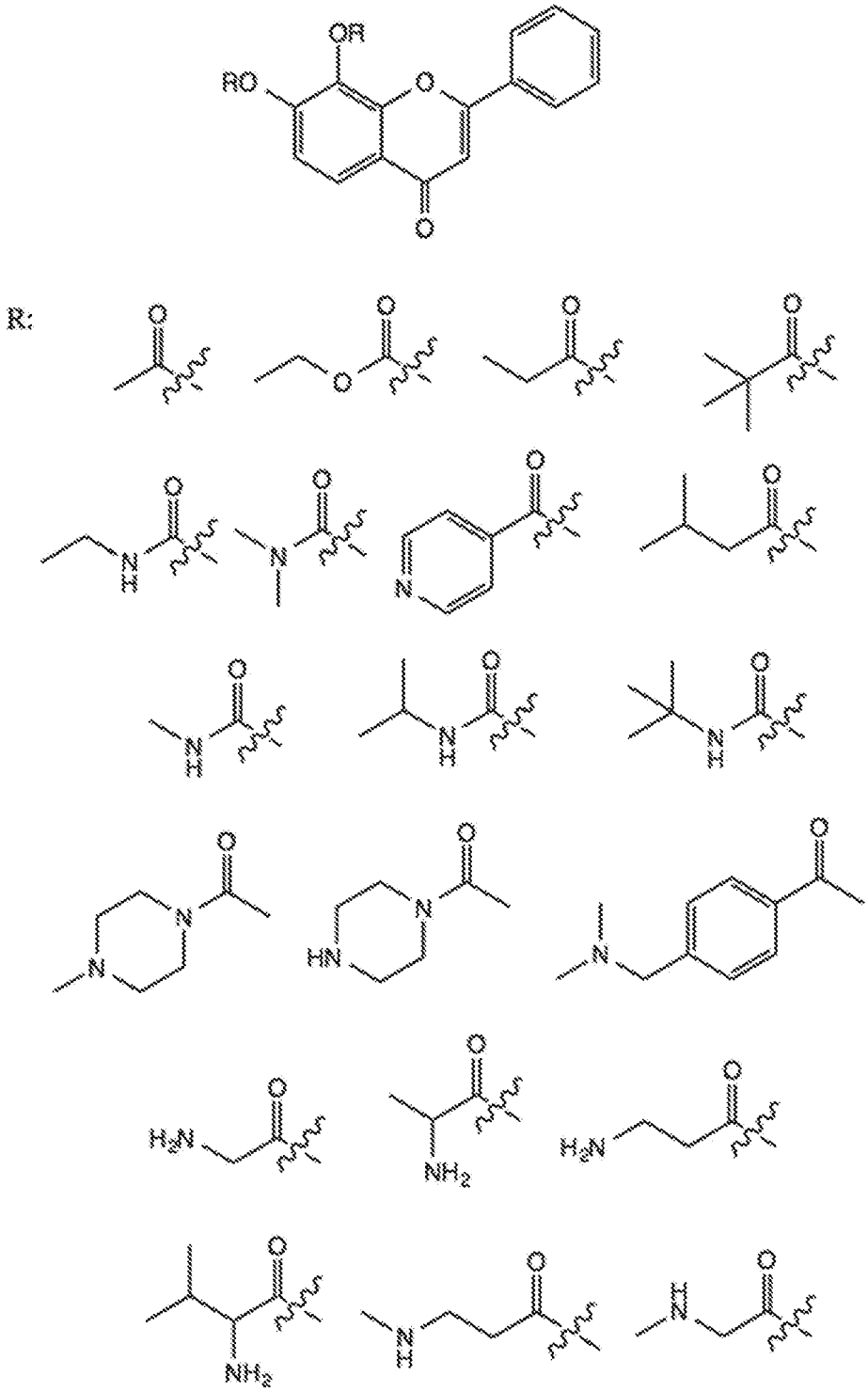

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FIG. 1

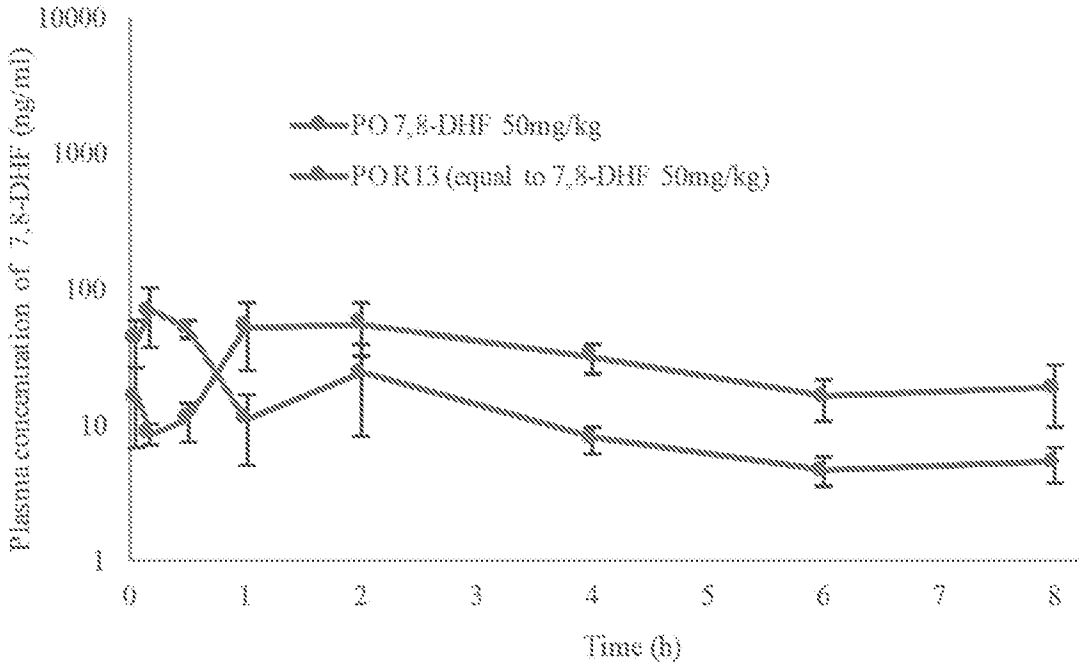

10000
1000
100
10
1
Plasma concentration of 7,8-DHF (ng/ml)
PO 7,8-DHF 50mg/kg
PO R13 (equal to 7,8-DHF 50mg/kg)
0
1
2
3
4
5
6
7
8
Time (h)

FIG. 2A

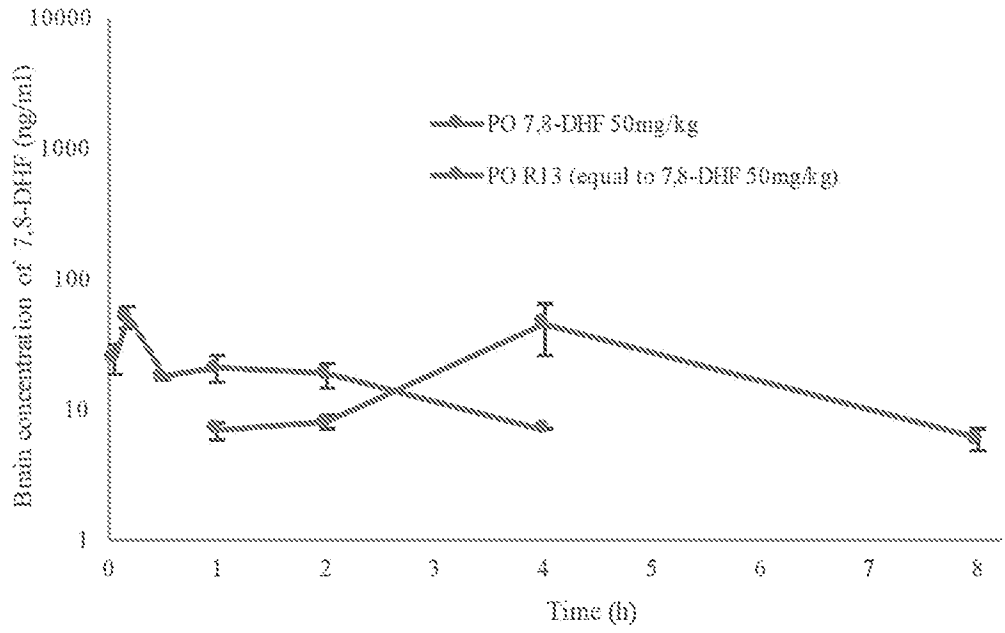

10000
1000
100
10
1
Brain concentration of 7,8-DHF (ng/ml)
PO 7,8-DHF 50mg/kg
PO R13 (equal to 7,8-DHF 50mg/kg)
0
1
2
3
4
5
6
7
8
Time (h)

FIG. 2B

7,8-DHF Assayed Concentrations (ng/mL)

Treatment		Serum	Brain	Conc. Ratio (Brain/Plasma)
R13 PO mg/kg	7.25	21.2	*BQL*	-
		BQL	*BQL*	-
	21.8	4.98	2.44	0.490
		418	5.97	0.0143
	72.5	288	6.22	0.0216
		8.58	4.22	0.492
7,8-DHF PO mg/kg	5	BQL	*BQL*	-
		BQL	2.02	-
	15	BQL	*BQL*	-
		BQL	2.02	-
	50	22.4	6.92	0.309
		48.9	8.81	0.180
MEAN		93.7	81.1	0.251
STDEV		151	47.8	0.215

FIG. 2C

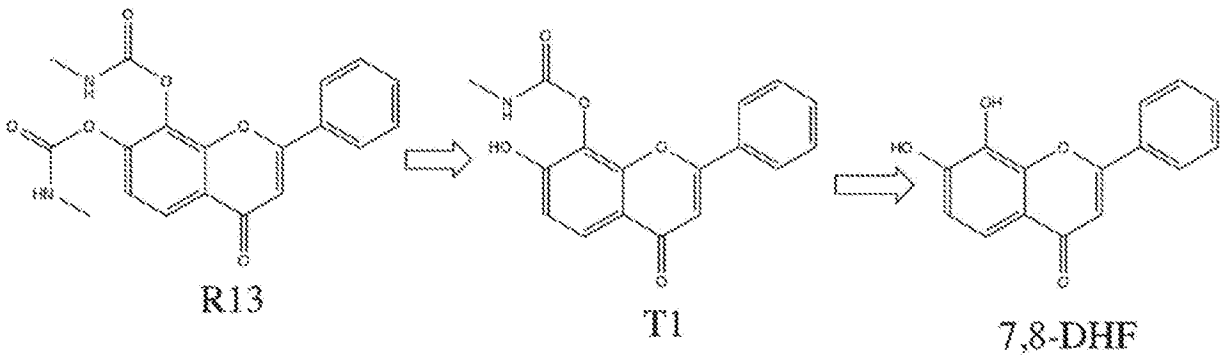


FIG. 2D

R13 Dose level (mg/kg)	7,8-DHF Assayed concentrations						T1 Assayed concentrations					
	Plasma (ng/ml)			Brain (ng/g)			Plasma (ng/ml)			Brain (ng/g)		
		Mean	SD		Mean	SD		Mean	SD		Mean	SD
21.8	2.8	2.1	0.91	*BQL*	-	-	15.5	10.2	4.71	*BQL*	-	-
	1.0			*BQL*			8.8			*BQL*		
	2.4			*BQL*			6.4			*BQL*		
43.6	4.0	4.8	2.01	*BQL*	-	-	33.0	34.0	17.80	*BQL*	-	-
	3.3			*BQL*			16.7			*BQL*		
	7.1			*BQL*			52.2			*BQL*		
72.5	5.4	6.9	4.09	2.7	3.4	1.0	39.1	42.3	22.60	*BQL*	-	-
	3.7			*BQL*			21.4			*BQL*		
	11.5			4.1			66.3			*BQL*		

FIG. 2E

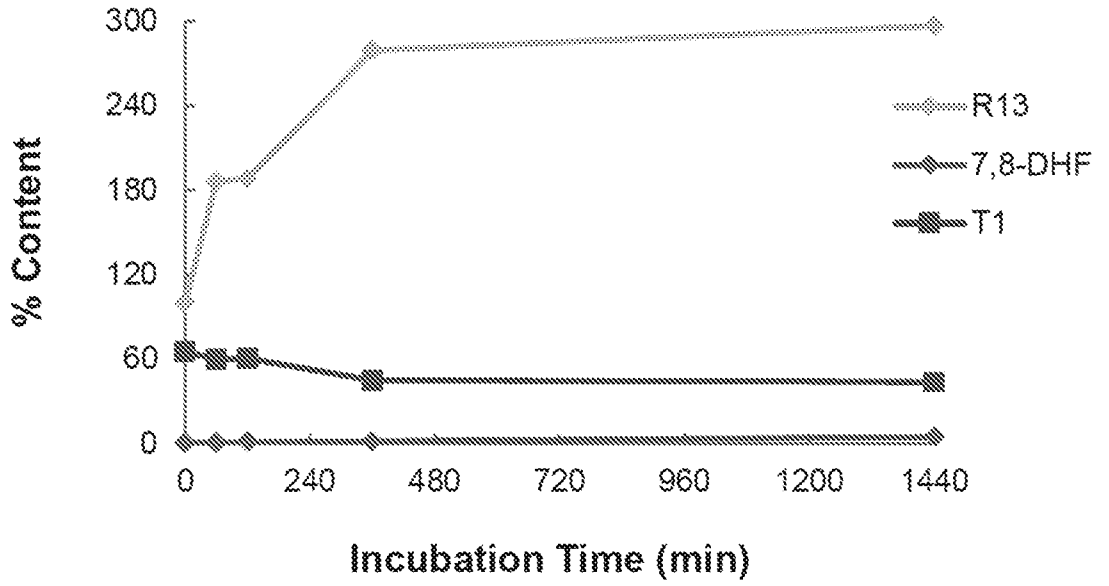

300
240
180
120
60
0
% Content
0
240
480
720
960
1200
1440
Incubation Time (min)
R13
7,8-DHF
T1

FIG. 3A

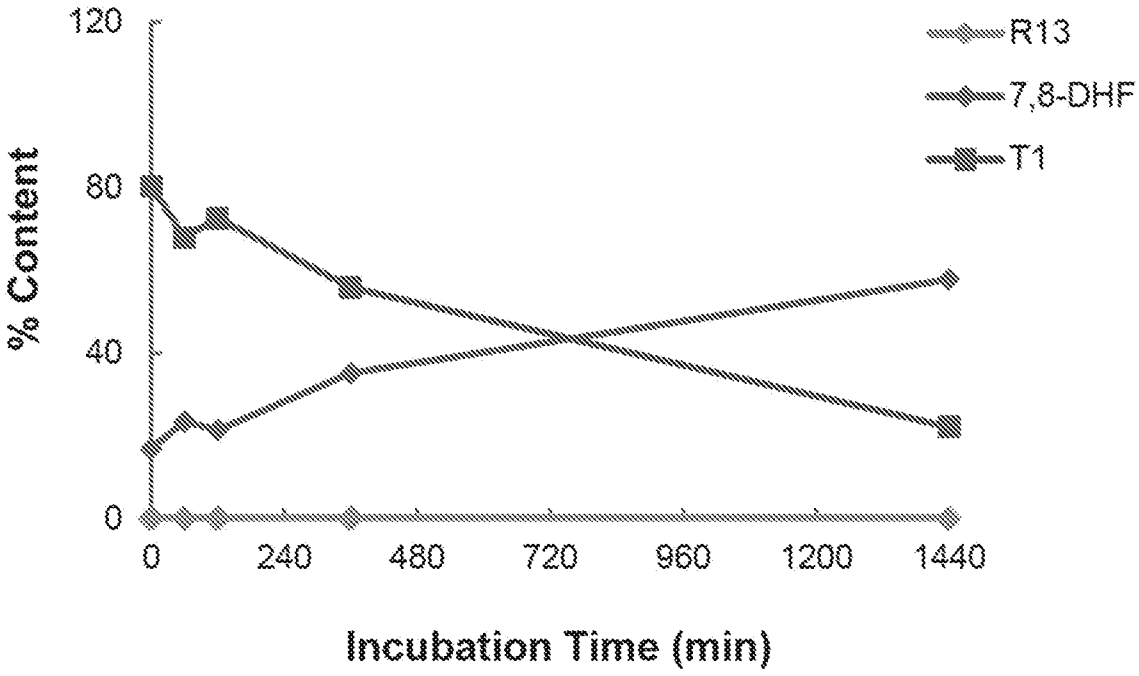

120
80
40
0
% Content
0
240
480
720
960
1200
1440
Incubation Time (min)
R13
7,8-DHF
T1

FIG. 3B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/46194

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/35; A61P 25/22; A61P 25/24 (2019.01)
CPC - A61K 31/352; A61K 31/353

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEN et al. "The prodrug of 7,8-dihydroxyflavone development and therapeutic efficacy for treating Alzheimer's disease", PNAS. January 16, 2018. vol. 115(3), pp578-583, entire document, especially: abstract; pg 578, col 1, para 1; pg 578, col 1, para 4; pg 578, col 2, para 1; pg 578, col 2, para 2; pg 580, col 2, Fig. 3A; pg 580, Fig. 2D, formula T1; pg 583, col 2, para 1.	1-16
A	WO 2010/011836 A2 (EMORY UNIVERSITY) 28 January 2010 (28.01.2010), entire document.	1-16
A	LIU et al. "A Synthetic 7,8-Dihydroxyflavone Derivative Promotes Neurogenesis and Exhibits Potent Antidepressant Effect", J Med Chem. 2010. Vol. 53(23), pp 8274-8286, entire document.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 October 2019	18 NOV 2019

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)