(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 March 2014 (27.03.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/047447 A2

(51) International Patent Classification:
A61K 31/34 (2006.01)

(21) International Application Number:
PCT/US2013/060934

(22) International Filing Date:
20 September 2013 (20.09.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/704,014 21 September 2012 (21.09.2012) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,

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(54) Title: FTO MODULATING COMPOUNDS AND METHODS OF USE

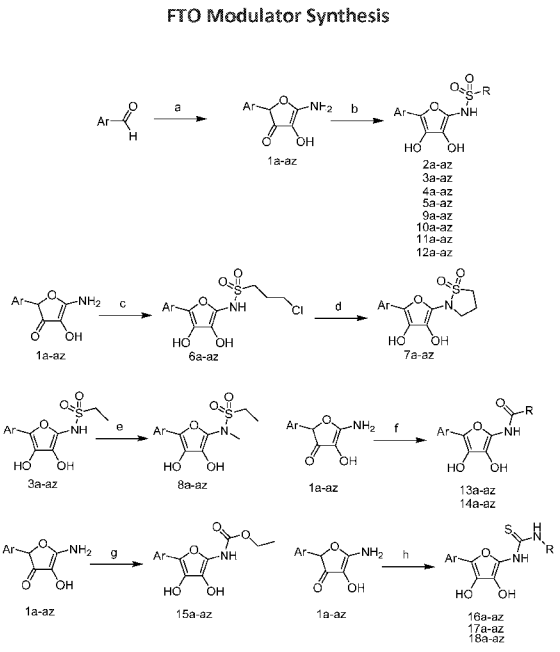

Figure 2

(57) Abstract: The present invention relates to compounds which modulate the level or activity of polypeptides having Fe(II) and 2-oxoglutarate (2QG)-dependent oxygenase activity in a cell, tissue, or subject, exemplified by the Fat Mass and Obesity Associated protein (FTO). Aspects relate to N-(3,4-dihydroxy-5-aryl-2-furanyl)-sulfonamides, methods for their synthesis, and methods of using these compounds to modulate the activity of FTO in a cell-free sample, a cell-based assay, and in a subject. Aspects are also directed to compositions comprising compounds which modulate the activity of FTO, including pharmaceutically-acceptable compositions, and to methods of preventing, ameliorating, or treating FTO-mediated conditions or diseases in a subject, including stroke, epilepsy, depression, and degenerative central nervous system disorders such as Alzheimer's and Parkinson's disease. Other aspects elate to use of the compounds to ameliorate or treat conditions associated with metabolic disorders, such as diabetes and obesity.

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TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

— *with sequence listing part of description (Rule 5.2(a))*

FTO MODULATING COMPOUNDS AND METHODS OF USE

CROSS REFERENCE TO RELATED APPLICATIONS

The pending application claims priority under 35 U.S.C. § 119(e) to United States Provisional Patent Application Number 61/704,014, filed September 21, 2012, the disclosure of which is incorporated herein by reference.

STATEMENT REGARDING FEDERALLY-SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with U.S. Government Support through the NINDS Anticonvulsant Screening Program. The U.S. Government has certain rights in the invention.

INCORPORATION-BY-REFERENCE OF A SEQUENCE LISTING

The sequence listing contained in the file "127190_0006_PtCT_ST25.txt", created on 2013-09-20, modified on 2013-09-20, file size 630 bytes, is incorporated by reference in its entirety herein.

FIELD OF THE INVENTION

The present invention relates to compounds which modulate the level or activity of one or more polypeptides having Fe(II) and 2-oxoglutarate (2OG)-dependent oxygenase activity in a cell, tissue, or subject, exemplified by the Fat Mass and Obesity Associated protein (FTO). Aspects of the invention relate to novel N-(3,4-dihydroxy-5-aryl-2-furanyl)-sulfonamides, methods for their synthesis, and methods of using these compounds to modulate the activity of FTO in a cell-free sample, a cell-based assay, and in a subject. The invention is also directed to compositions comprising compounds which modulate the activity of FTO, including pharmaceutically-acceptable compositions, and to methods of preventing, ameliorating, or treating FTO-mediated conditions or diseases in a subject, including stroke, epilepsy, depression, and degenerative central nervous system disorders such as Alzheimer's and Parkinson's disease. Other aspects of the invention relate to use of the compounds to ameliorate or treat conditions associated with metabolic disorders, such as diabetes and obesity, respectively.

BACKGROUND OF THE INVENTION

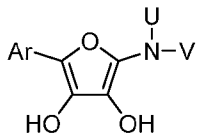
Epilepsy is a chronic disorder of abnormal electrical activity in the brain characterized by recurrent unprovoked seizures (Rogers, S. J.; Cavazos, J. E. (2011) *In*: Pharmacotherapy, A Pathophysiologic Approach; DiPiro J. T. et al., Eds., McGraw-Hill: New York, 979-1005). It manifests as a collection of disorders which vary widely in etiology, appearance, and severity. Treatment with traditional antiepileptic drugs (AED) may reduce symptoms of seizures but does not influence the course of the disorder. Despite some benefit of AED treatment, approximately 30-35% of treated patients will be refractory (Rogers, S. J.; Cavazos, J. E. (2011) *In*: Pharmacotherapy, A Pathophysiologic Approach; DiPiro J. T. et al., Eds., McGraw-Hill: New York, 979-1005). These two factors indicate the need for additional therapeutic agents.

Epilepsy is thought to be caused by some predisposing factor(s) (e.g., genetic, age, environmental) and/or insult (e.g., head trauma, status epilepticus, febrile seizure) that trigger the initial seizure. After this first event, brain neuronal circuitry undergoes changes that may eventually produce a condition of chronic, spontaneous seizures, i.e., epilepsy. This lag time may be 1-2 weeks in animal models, or up to several years in humans. Epileptogenesis refers to the time period between the initial insult and spontaneous, recurring seizures. More recently it has been extended to include both this initial latency period up to the point of epilepsy, as well as the progression of events that occur after epilepsy has been established (Pitkanen, A. (2010), Epilepsia, 51(S3):2–17; Pitkänen, A.; Lukasiuk, K. (2011), Lancet Neurol., 10 :173–186). Antiepileptogenic agents therefore would have such activities as decreasing seizure frequency and severity, increasing responsiveness to traditional AEDs, and decreasing pharmacoresistance (Mani, R.; Pollard, J.; Dichter, M. A. (2011), Neurosci. Lett., 497:251-256).

The gene fat mass and obesity-associated (FTO) was first identified in mice as one of the genes encoded by the 1.6 Mb deletion that produced a phenotype with partial syndactyly of forelimbs and extensive thymic hyperplasia (Peters et al., Mamm Genome 1999; 10:983-6). Subsequently, a common variant in the FTO gene was identified as a risk allele for type 2 diabetes and increased body mass (Frayling et al., Science 2007; 316:889-94), and many studies of FTO have focused on the association with diabetes, obesity, and metabolism (Larder et al., Trends Endocrinol Metab 2011; 22:53-9). In the course of conducting these large scale genotyping studies, the role of FTO in human disorders was expanded to include the central nervous system (CNS). Variants have been found to be associated with neurological disease conditions including depression (Rivera et al., Mol Psychiatr 2012; 17:604-11) and Alzheimer's disease (Keller et al., JAD 2011; 23:461-9). FTO is highly expressed in brain tissue (Yeo GSH. J Neuroendocrinol 2012; 24:393-4), and is essential for normal development of the CNS in human (Boissel et al., Am J Hum Genet 2009; 85:106-11.). The generation of mice that were specifically deleted only for neuronal FTO had a similar phenotype of growth retardation as the whole body FTO deletion, suggesting that a major function of FTO occurs in the brain (Gao et al, PLoS One 2010; 5:e14005). The obesity-associated risk allele has been shown to have a potential pathological effect on brain volume; healthy elderly subjects with the risk allele had brain volume deficits (average differences of 8% in frontal lobes and 12% in occipital lobes) compared to non-carriers (Ho et al., Proc Natl Acad Sci U S A 2010; 107:8404-9). Recently, brain derived neurotrophic factor (BDNF) was identified as a candidate gene for functional coupling to FTO, leading the authors to speculate on a role of FTO in neuronal plasticity possibly via interaction with CCAAT/enhancer binding protein beta (Rask-Andersen et al., BMC Neurosci 2011; 12:117). These data provide strong evidence that FTO has a functional role in the CNS, and by implication, to CNS disorders.

BRIEF SUMMARY OF THE INVENTION

One aspect of the invention is related to a compound of **Formula I**, a pharmaceutically-acceptable salt thereof, and mixtures of any of the forgoing



(I)

wherein Ar is a substituted or unsubstituted aryl or heteroaryl ring;

wherein said aryl ring comprises at least one R group selected from the group consisting of -H, -OH, -SH, -CN, -F, -Cl, -Br, -CN, NO_2 -NO, $-NH_2$, -NHR, -NRR, -C(O)R, -C(O)OH, -C(O)OR, $-C(O)NH_2$, -C(O)NHR, and -C(O)NRR, -SOR, $-SO_2R$, $-SO_2NH_2$, $-SO_2NHR$, $-SO_2NRR$;

wherein each R is independently selected from the group consisting of $(C_1$-$C_5)$ alkyl, substituted $(C_1$-$C_6)$ alkyl, $(C_2$-$C_6)$ alkenyl, substituted $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, substituted $(C_2$-$C_6)$ alkynyl, $(C_5$-$C_{20})$ aryl, substituted $(C_5$-$C_{20})$ aryl, $(C_6$-$C_{26})$ arylalkyl, substituted $(C_6$-$C_{26})$ arylalkyl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, 6-26 membered heteroarylalkyl, and substituted 6-26 membered heteroarylalkyl; and

wherein V is selected from the group consisting of $-SO_2R$, - SO_2R, -C(O)R, -C(O)OR, -C(S)R, and -C(S)NHR;

wherein both U and V are not hydrogen; and

wherein U and V can join together to form an unsubstituted or substituted ring.

Related aspects of the invention are directed to compositions, including pharmaceutical compositions, comprising the compounds of the invention, noted above, including method for pharmaceutical formulation of previously described compounds for use in oral and intravenous applications, and in implantable materials.

One aspect of the invention is directed to a method of preventing, ameliorating, or treating at least one FTO-mediated condition or disease in a subject, comprising administering to said subject a therapeutically-effective amount of the compound or salt described above and encompassed by any of **Formulas I-VII**, wherein said condition or disease is selected from the group consisting of neurological disorders, degenerative central nervous system disorders, metabolic disorders, and proliferative cell disorders.

One aspect of the invention relates to a method of modulating the level or activity of at least one FTO protein in a cell, comprising contacting the cell with an effective amount of the compound or salt described above and encompassed by any of **Formulas I-VII**.

One aspect of the invention relates to a method of modulating the level or activity of at least one FTO protein in a subject, which comprises administering a therapeutically-effective amount of an effective amount of the compound or salt described above and encompassed by any of **Formulas I-VII** to said subject.

One aspect of the invention is directed to the treatment of CNS diseases by modulating mRNA N6-methyladenosine (m6A), another aspect of the invention is through modulation of microRNA (miRNA), and another aspect of the invention is through the modulation of mRNA expression.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing aspects and many of the advantages of this invention will become more readily appreciated as the same become better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

FIG. 1 Panel A sets forth an illustration showing the mechanism of FTO modulation of m6A. FTO is known to demethylate non-stoichiometrically, for example resulting in 20, 50, or 70% demethylation of appropriate substrates. Panel B illustrates the consequences of FTO modulation of m6A in mRNA.

FIG. 2 sets forth the synthesis of FTO modulators. The following legends describe components used in each of the named reaction schemes: Synthetic schemes for the synthesis of compounds 1a-az through 18a-az. Reactions a-g are as follows: (a) KCN, glyoxal, Na2CO3, H2O; (b) DMAP, ClSO2R1, DMF, THF; (c) DMAP, ClSO2CH2CH2CH2Cl, DMF, THF; (d) NaH, THF; (e) CH2N2, MeOH; (f) TEA, ClSiMe2tBu, THF, ClCOR2, DMAP, DMF, Bu4NF; (g) TEA, ClSiMe2tBu, THF, ClCOOEt, DMAP, DMF, Bu4NF; (h) SCNR3, THF.

FIG. 3 sets forth an illustration showing the neuroprotective effects of FTO modulators. Mesyl tetronimide represents compound 2c, and Ethyl tetronimide represents compound 3c. HCA is homocysteinic acid and is used to simulate oxidative neurological stress.

FIG. 4 sets forth an illustration showing the inhibition of FTO by modulators 2c (Inhibitor 3) and 3c (Inhibitor 4).

FIG. 5 sets forth an illustration showing the modulation of cellular m6A by 3c (inhibitor).

TERMS AND DEFINITIONS

The following is a list of abbreviations, plus terms and their definitions, used throughout the specification and the claims:

General abbreviations and their corresponding meanings include: aa or AA = amino acid; mg = milligram(s); ml or mL = milliliter(s); mm = millimeter(s); mM = millimolar; nmol = nanomole(s); pmol = picomole(s); ppm = parts per million; RT = room temperature; U = units; ug, µg = micro gram(s); ul, µl = micro liter(s); uM, µM = micromolar, TEA = triethylamine, LDA = lithium diisopropyl amine, THF = tetrahydrofuran, DMAP = 4-dimethylaminopyridine, DMF = N,N'-dimethylformamide.

The terms "cell" and "cells", which are meant to be inclusive, refer to one or more cells which can be in an isolated or cultured state, as in a cell line comprising a homogeneous or heterogeneous population of cells, or in a tissue sample, or as part of an organism, such as a transgenic mammal.

The term "amino acid" encompasses both naturally occurring and non-naturally occurring amino acids unless otherwise designated.

The term "an effective amount" means an amount of the substance in question which produces a statistically significant effect. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising an active compound herein required to provide a clinically significant alteration in a measurable trait. Such effective amounts will be determined using routine optimization techniques and are dependent on the particular condition to be treated, the condition of the patient, the route of administration, the formulation, and the judgment of the practitioner and other factors evident to those skilled in the art. The dosage required for the compounds of the invention is manifested as that which induces a statistically significant difference between treatment and control groups.

A "therapeutically-effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically-effective amount of modulator may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the modulator to elicit a desired response in the individual. Dosage regimens may be adjusted to provide the optimum therapeutic response. A therapeutically-effective amount is also one in which any toxic or detrimental effects of the modulator are outweighed by the therapeutically beneficial effects.

A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. A prophylactically effective amount can be determined as described above for the therapeutically-effective amount. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically-effective amount.

The term "treatment" includes both prophylaxis and therapy.

The term "animal" includes human beings.

The term "substituted aromatic or heteroaromatic" refers to aromatic or heteroaromatic rings may contain one or more substituents such as -OH, SH, -CN, -F, -Cl, -Br, -R, $-NO_2$ -NO, $-NH_2$, -NHR, -NRR, -C(O)R, -C(O)OH, -C(O)OR, $-C(O)NH_2$, -C(O)NHR, -C(O)NRR, and the like where each R is independently (C_1-C_5) alkyl, substituted (C_1-C_6) alkyl, (C_2-C_6) alkenyl, substituted (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, substituted (C_2-C_6) alkynyl, (C_5-C_{20}) aryl, substituted (C_5-C_{20}) aryl, (C_6-C_{26}) arylalkyl, substituted (C_6-C_{26}) arylalkyl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, 6-26 membered heteroarylalkyl or substituted 6-26 membered heteroarylalkyl.

A "derivative" of a compound X (e.g., a peptide or amino acid) refers to a form of X in which one or more reactive groups on the compound have been derivatized with a substituent group. Peptide derivatives include pep tides in which an amino acid side chain, the peptide backbone, or the amino' or carboxy-terminus has been derivatized (e.g., peptidic compounds with 5 methylated amide linkages).

An "analogue" of a compound X refers to a compound which retains chemical structures of X necessary for functional activity of X yet which also contains certain chemical structures which differ from X. An analogue of a naturally-occurring peptide, is a peptide which includes one or more non-naturally-occurring amino acids.

The term "mimetic refers to a compound having similar functional and/or structural properties to another known compound or a particular fragment of that known compound. A "mimetic" of a compound X refers to a compound in which chemical structures of X necessary for functional activity of X have been replaced with other chemical structures which mimic the conformation of X. The term mimetic, and in particular, peptidomimetic, is intended to include isosteres.

The term "cyclic group", as used herein, is intended to include cyclic saturated or unsaturated (i.e., aromatic) group having from about 3 to 10, preferably about 4 to 8, and more preferably about 5 to 7, carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclooctyl. Cyclic groups may be unsubstituted or substituted at one 35 or more ring positions. Thus, a cyclic group may be substituted with halogens, alkyls, cycloalkyls, alkenyls, alkynyls, aryls, heterocycles, hydroxyls, aminos, nitros, thiols amines, imines, amides, phosphonates, phosphines, carbonyls, carboxyls, silyls, ethers, thioethers, sulfonyls, sulfonates. selenoethers, ketones, aldehydes, esters, $'CF_3$, 'CN, or the like.

The term "heterocyclic group" is intended to include cyclic saturated or unsaturated (i.e., aromatic) group having from about 3 to 10, preferably about 4 to 8, and more preferably about 5 to 7, carbon atoms, wherein the ring structure includes about one to four heteroatoms. Heterocyclic groups include pyrrolidine, oxolane, thiolane, imidazole, oxazole, piperidine, piperazine, morpholine and pyridine. The heterocyclic ring can be substituted at one or more positions with such substituents as, for example, halogens, alkyls, cycloalkyls, alkenyls, alkynyls, aryls, other heterocycles, hydroxyl, amino, nitro thiol, amines, imines, amides, phosphonates, phosphines, carbonyls, carboxyls, eilyls, ethers, thioethers, sulfonyls, selenoethers, ketones, aldehydes, esters, $'CF_3$, 'CN, or the like. Heterocycles may also be bridged or fused to other cyclic groups as described below.

The term "polycyclic group" as used herein is intended to refer to two or more saturated or unsaturated (i.e., aromatic) cyclic rings in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycyclic group can he substituted with such substituents as described above, as for example, halogens, alkyls, cycloalkyls, alkenyls, alkynyls, hydroxyl, amino, nitro, thiol, amines, imines, amides, phosphonates, phosphines, carbonyls, carboxyls, silyls, ethers, thioethers, sulfonyls, selenoethers, ketones, aldehydes, esters, $'CF_3$, 'CN, or the like.

As used herein, the term "modulating group" and "modifying group" are used interchangeably to describe a chemical group directly or indirectly attached to a peptidic structure. For example, a modifying

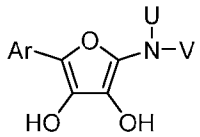
group(s) can be directly attached by covalent coupling to the peptidic structure or a modifying group(s) can be attached indirectly by a stable non-covalent association.

For the purposes of the present disclosure the terms "compound," "analog," and "composition of matter" stand equally well for the enzyme modulators or inhibitors described herein, including all enantiomeric forms, diastereomeric forms, salts, and the like. The terms "compound," "analog," and "composition of matter" are used interchangeably throughout the present specification.

The compounds disclosed herein include all salt forms, for example, salts of both basic groups, inter alia, amines, as well as salts of acidic groups, inter alia, carboxylic acids. The following are non-limiting examples of anions that can form pharmaceutically acceptable salts with basic groups: chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, formate, acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, citrate, and the like. The following are non-limiting examples of cations that can form pharmaceutically-acceptable salts of the anionic form of acidic substituent groups on the compounds described herein: sodium, lithium, potassium, calcium, magnesium, zinc, bismuth, and the like.

DETAILED DESCRIPTION OF THE INVENTION

One aspect of the invention is related to a compound of **Formula I**, a pharmaceutically-acceptable salt thereof, and mixtures of any of the forgoing



(I)

wherein Ar is a substituted or unsubstituted aryl or heteroaryl ring;

wherein said aryl ring comprises at least one R group selected from the group consisting of -H, -OH, -SH, -CN, -F, -Cl, -Br, -CN, NO_2 -NO, $-NH_2$, -NHR, -NRR, -C(O)R, -C(O)OH, -C(O)OR, $-C(O)NH_2$, -C(O)NHR, and -C(O)NRR, -SOR, $-SO_2R$, $-SO_2NH_2$, $-SO_2NHR$, $-SO_2NRR$;

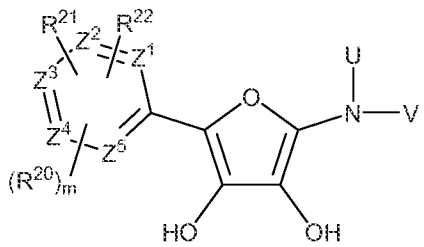
wherein each R is independently selected from the group consisting of (C_1-C_5) alkyl, substituted (C_1-C_6) alkyl, (C_2-C_6) alkenyl, substituted (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, substituted (C_2-C_6) alkynyl, (C_5-C_{20}) aryl, substituted (C_5-C_{20}) aryl, (C_6-C_{26}) arylalkyl, substituted (C_6-C_{26}) arylalkyl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, 6-26 membered heteroarylalkyl, and substituted 6-26 membered heteroarylalkyl; and

wherein V is selected from the group consisting of $-SO_2R$, - SO_2R, -C(O)R, -C(O)OR, -C(S)R, and -C(S)NHR;

wherein both U and V are not hydrogen; and

wherein U and V can join together to form an unsubstituted or substituted ring.

Another aspect of the invention is related to a compound of represented by the structure of **Formula II**:



(II)

wherein R^{20}, R^{21}, and R^{22} are independently selected from the group consisting of H, -F, -Cl, -Br, -I, -OH, -SH, -CN, NO_2 -NO, $-NH_2$. -NHR, -NRR, -C(O)R, -C(O)OH, -C(O)OR, -C(O)NH2, -C(O)NHR, -C(O)NRR, -SOR, $-SO_2R$, $-SO_2NH_2$, $-SO_2NHR$, and $-SO_2NRR$;

wherein each R is independently selected from the group consisting of (C_1-C_5) alkyl, substituted (C_1-C_6) alkyl, (C_2-C_6) alkenyl, substituted (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, substituted (C_2-C_6) alkynyl, (C_5-C_{20}) aryl, substituted (C_5-C_{20}) aryl, (C_6-C_{26}) arylalkyl, substituted (C6-C26) arylalkyl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, 6-26 membered heteroarylalkyl, and substituted 6-26 membered heteroarylalkyl; and

wherein U is selected from the group consisting of hydrogen, (C_1-C_5) alkyl, substituted (C_1-C_6) alkyl, (C_2-C_6) alkenyl, substituted (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, substituted (C_2-C_6) alkynyl, (C_5-C_{20}) aryl, substituted (C_5-C_{20}) aryl, (C_6-C_{26}) arylalkyl, substituted (C_6-C_{26}) arylalkyl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, 6-26 membered heteroarylalkyl, and substituted 6-26 membered heteroarylalkyl;

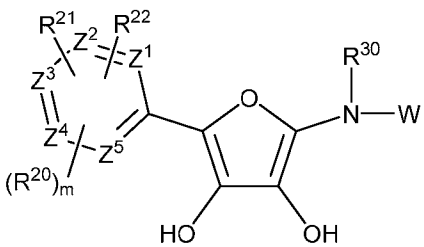
wherein V is selected from the group consisting of $-SO_2R$, - SO_2R, -C(O)R, -C(O)OR, -C(S)R, and -C(S)NHR;

wherein Z^1, Z^2, Z^3, Z^4, Z^5 are independently selected from C, N;

wherein both U and V are not hydrogen; and

wherein U and V can join together to form an unsubstituted or substituted ring.

Another aspect of the invention relates to a compound represented by the structure of **Formula III**:



(III)

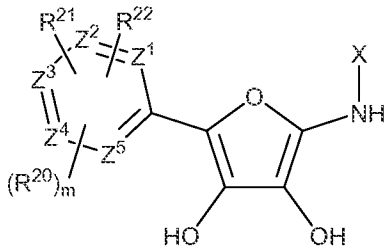
wherein R^{20}, R^{21}, and R^{22} are independently selected from the group consisting of H, -F, -Cl, -Br, -I, -OH, -SH, -CN, NO_2 -NO, $-NH_2$. -NHR, -NRR, -C(O)R, -C(O)OH, -C(O)OR, -C(O)NH2, -C(O)NHR, -C(O)NRR, -SOR, $-SO_2R$, $-SO_2NH_2$, $-SO_2NHR$, and $-SO_2NRR$;

wherein Z^1, Z^2, Z^3, Z^4, Z^5 are independently selected from C, N;

wherein R^{30} is selected from the group consisting of hydrogen, (C_1-C_5) alkyl, substituted (C_1-C_6) alkyl, (C_2-C_6) alkenyl, substituted (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, substituted (C_2-C_6) alkynyl, (C_5-C_{20}) aryl, substituted (C_5-C_{20}) aryl, (C_6-C_{26}) arylalkyl, substituted (C_6-C_{26}) arylalkyl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, 6-26 membered heteroarylalkyl or substituted 6-26 membered heteroarylalkyl ;

wherein W is selected from the group consisting of hydrogen, alkyl, haloalkyl, -C(O)R, -C(O)OR, -SOR, $-SO_2R$, -C(O)NHR, -C(O)NRR where each R is independently (C_1-C_5) alkyl, substituted (C_1-C_6) alkyl, (C_2-C_6) alkenyl, substituted (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, substituted (C_2-C_6) alkynyl, (C_5-C_{20}) aryl, substituted (C_5-C_{20}) aryl, (C_6-C_{26}) arylalkyl, substituted (C6-C26) arylalkyl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, 6-26 membered heteroarylalkyl or substituted 6-26 membered heteroarylalkyl.

Another aspect of the invention relates to a compound represented by the structure of **Formula IV**:



(IV)

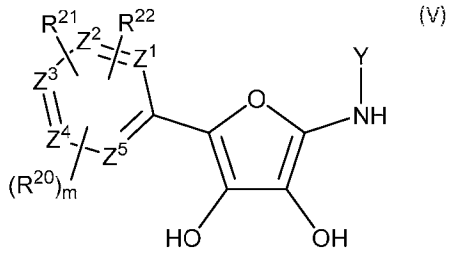
wherein R^{20}, R^{21}, and R^{22} are independently selected from the group consisting of H, -F, -Cl, -Br, -I, -OH, -SH, -CN, NO_2 -NO, $-NH_2$. -NHR, -NRR, -C(O)R, -C(O)OH, -C(O)OR, -C(O)NH2, -C(O)NHR, -C(O)NRR, -SOR, $-SO_2R$, $-SO_2NH_2$, $-SO_2NHR$, and $-SO_2NRR$;

wherein Z^1, Z^2, Z^3, Z^4, Z^5 are independently selected from C, N;

wherein X is selected from the group consisting of SO_2R,

where each R is independently (C_1-C_5) alkyl, substituted (C_1-C_6) alkyl, (C_2-C_6) alkenyl, substituted (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, substituted (C_2-C_6) alkynyl, (C_5-C_{20}) aryl, substituted (C_5-C_{20}) aryl, (C_6-C_{26}) arylalkyl, substituted (C_6-C_{26}) arylalkyl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, 6-26 membered heteroarylalkyl or substituted 6-26 membered heteroarylalkyl.

Another aspect of the invention relates to a compound represented by the structure of **Formula V**:



(V)

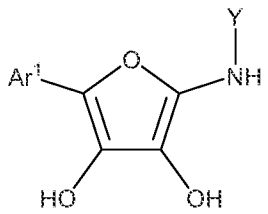
wherein R^{20}, R^{21}, and R^{22} are independently selected from the group consisting of H, -F, -Cl, -Br, -I, -OH, -SH, -CN, NO_2 -NO, $-NH_2$. -NHR, -NRR, -C(O)R, -C(O)OH, -C(O)OR, $-C(O)NH_2$, -C(O)NHR, -C(O)NRR, -SOR, $-SO_2R$, $-SO_2NH_2$, $-SO_2NHR$, and $-SO_2NRR$; and

wherein Z^1, Z^2, Z^3, Z^4, Z^5 are independently selected from C, N; and

wherein Y is selected from the group consisting of SO_2R,

where each R is independently (C_1-C_5) alkyl, substituted (C_1-C_6) alkyl, (C_2-C_6) alkenyl, substituted (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, and substituted (C_2-C_6) alkynyl.

Another aspect of the invention relates to a compound represented by the structure of **Formula VI**:

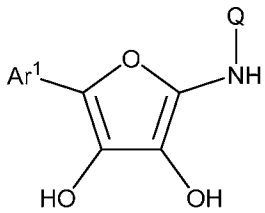


(VI)

wherein Ar^1 is selected from the group consisting of phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-thiophene, 2-furan, 2-thiazole, 1-naphthyl, 2-napthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3-cyanophenyl, and 4-cyanophenyl; and

wherein Y is selected from the group consisting of SO_2R, where R is independently (C_1-C_5) alkyl, substituted (C_1-C_6) alkyl, (C_2-C_6) alkenyl, substituted (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, and substituted (C_2-C_6) alkynyl.

Another aspect of the invention relates to a compound represented by the structure of **Formula VII**:



(VII)

wherein Ar^1 is selected from the group consisting of phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 3-cyanophenyl; and

wherein Q is selected from the group consisting of SO_2R, where R is independently (C_1-C_5) alkyl, substituted (C_1-C_6) alkyl.

Specific compounds encompassed by Formulas I-VII

Specific aspects of the invention relate to a compound of Formulas I-VII selected from the group consisting of the following named compounds: N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)methanesulfonamide; N-(3,4-dihydroxy-5-(2-chlorophenyl)-2-furanyl)ethanesulfonamide; N-(3,4-dihydroxy-5-(3-chlorophenyl)-2-furanyl)ethanesulfonamide; N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)ethanesulfonamide; N-(3,4-dihydroxy-5-(2-fluorophenyl)-2-furanyl)ethanesulfonamide; N-(3,4-dihydroxy-5-(3-fluorophenyl)-2-furanyl)ethanesulfonamide; N-(3,4-dihydroxy-5-(4-fluorophenyl)-2-furanyl)ethanesulfonamide; N-(3,4-dihydroxy-5-(4-trifluoromethylphenyl)-2-furanyl)ethanesulfonamide; N-(3,4-dihydroxy-5-(4-nitrilephenyl)-2-furanyl)ethanesulfonamide; N-(3,4-dihydroxy-5-(3-nitrilephenyl)-2-furanyl)ethanesulfonamide; N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-1-propylsulfonamide; N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-2-propylsulfonamide; N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-1-butylsulfonamide; N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-1-propyl-2-methylsulfonamide; N-methyl-N'-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)ethanesulfonamide; N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)benzenesulfonamide; N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)benzylsulfonamide; N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-1,1-dioxide-isothiazolidine; N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)acetamide; N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)benzamide; N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)- carbamic acid ethyl ester; Thiourea, N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)- N'-methyl; Thiourea, N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)- N'-ethyl; and Thiourea, N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)- N'-phenyl.

Another aspect of the invention relates to a pharmaceutical composition comprising at least one pharmaceutically-acceptable excipient and a therapeutically effective amount of the compound or salt according to any one of Formulas I-VII, as noted above.

One aspect of the invention relates to a method of modulating the level or activity of at least one polypeptide having Fe(II) and 2-oxoglutarate (2OG) dependent oxygenase activity in a cell or tissue comprising (a) contacting the cell with the compound of any of Formulas I-VII; noted above, and (b) measuring the level or activity of said polypeptide.

Related aspects include a method of modulating the activity of at least one of said polypeptides in a cell or tissue wherein said polypeptide is an Fe(II) and 2-oxoglutarate (2OG)-dependent oxygenase (Iron 2OG dioxygenase domain polypeptide) selected from the group consisting of (a) polypeptide hydroxylases; (b) polypeptide demethylases; and (c) nucleic acid hydroxylases. Exemplary polypeptide hydroxylases include FIH, ASPH, PHD, C-P4H, C-P3H, and PLODs (Loenarz and Schofield, 2011). Exemplary polypeptide demethylases include lysine demethylases (KDMs) and PHF8. Exemplary nucleic acid hydroxylases include FTO and TET1-3. Other exemplary demethylases include AlkBH1-8, such as AlkBH5. A specific aspect of the invention relates to a method wherein at least one of said polypeptides is FTO.

The methods of the invention may be carried out using cells or tissues from a variety of sources. Typically these include cells derived from vertebrates, including mammals, particularly primates, and human-derived cells or tissues.

One aspect of the invention relates to a method of modulating the level or activity of at least one polypeptide having Fe(II) and 2-oxoglutarate (2OG)-dependent oxygenase activity in a subject, which comprises: (a) administering a therapeutically-effective amount of a compound any of Formulas I-VII; noted above, to said subject; (b) measuring the level or activity of said polypeptide.

Related aspects include a method of modulating the activity of at least one of said polypeptides in a subject wherein said polypeptide is an Fe(II) and 2-oxoglutarate (2OG)-dependent oxygenase (Iron 2OG dioxygenase domain polypeptide) selected from the group consisting of (a) polypeptide hydroxylases; (b) polypeptide demethylases; and (c) nucleic acid hydroxylases. Exemplary polypeptide hydroxylases include FIH, ASPH, PHD, C-P4H, C-P3H, and PLODs. Exemplary polypeptide demethylases include lysine demethylase (KDM) and PHF8. Exemplary nucleic acid hydroxylases include FTO and TET1-3. A specific aspect of the invention relates to a method wherein at least one of said polypeptides is FTO. The subject may be an animal, such as a vertebrate, including mammals, particularly primates, and humans.

One aspect of the invention relates to a method of preventing, ameliorating, or treating at least one Fe(II) and 2-oxoglutarate (2OG)-dependent oxygenase-mediated condition or disease in a subject, comprising administering to said subject a therapeutically-effective amount of the compound or salt represented by a compound encompassed by any of formulas I-VII.

Another aspect of the invention relates to a method of preventing, ameliorating, or treating at least one FTO-mediated-mediated condition or disease in a subject, comprising administering to said subject a therapeutically-effective amount of the compound or salt represented by a compound encompassed by any of formulas I-VII, wherein said condition or disease is selected from the group

consisting of neurological disorders, degenerative central nervous system disorders, metabolic disorders, and drug abuse.

Related aspects include methods wherein said condition or disease is a neurological disorder. Exemplary conditions include but are not limited to epilepsy, epileptogenesis, depression, and stroke. Other aspects relate to methods wherein said condition or disease is a degenerative disorder selected from the group consisting of Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, traumatic brain injury, and multiple sclerosis. Still other aspects relate to methods wherein said condition or disease is a metabolic disorder, such as diabetes, anemia, renal failure-associated anemia, and obesity, plus methods wherein said conditions or disease are related to drug substance abuse, drug addiction, and symptoms of drug withdrawal.

Methods of the invention that relate to administration of a compound or composition comprising a compound represented by any of Formulas I-VII to a subject may be carried out in a variety of animals, particularly vertebrates, including mammals, particularly primates, and humans. Exemplary mammals also include rodents, such as laboratory mice and rats, plus farm animals, including cows, pigs, goats, sheep, and horses, plus other types of domesticated animals, such as dogs and cats.

Other aspects of the invention are directed to the treatment of CNS diseases by modulating mRNA N6-methyladenosine (m6A), the modulation of microRNA (miRNA), and the modulation of mRNA expression.

Therapeutic Uses of Compositions Comprising Compounds of the Invention

Epileptogenesis is a major cause of epilepsy. One major contributor to epilepsy is neuronal death due to an unprovoked seizure, traumatic brain injury, infantile febrile seizures, stroke, or brain insult. Epileptogenesis may occur after any of these events, leading to an asymptomatic latent period during which the disease state progresses. Preventing neuronal death by modulating antioxidant enzyme expression can be accomplished by inhibiting FTO, resulting in a neuroprotective effect.

One aspect of the invention is directed to a method of preventing, ameliorating, or treating at least one Fe(II) and 2-oxoglutarate (2OG)-dependent oxygenase-mediated condition or disease in a subject, comprising administering to said subject a therapeutically-effective amount of the compound or salt described above and encompassed by any of Formulas I-VII, wherein said condition or disease is selected from the group consisting of neurological disorders, degenerative central nervous system disorders, metabolic disorders, and proliferative cell disorders. Another aspect of the invention is directed to the methods noted above, wherein said condition or disease is a degenerative disorder selected from the group consisting of Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, traumatic brain injury, and multiple sclerosis. Another aspect is related to the methods noted above, wherein said condition or disease is a neurological disorder. Still another aspect relates to a method wherein said neurological disorder is selected from the group consisting of epilepsy, epileptogenesis, depression, and

stroke. Another aspect is related to the methods noted above, wherein said condition or disease is a metabolic disorder, such as obesity, diabetes, anemia, and renal failure-associated anemia. Another aspect is related to the methods noted above wherein said condition or disease is a proliferative disease, such as cancer, and specific types of cancer, such as colon cancer. Another aspect of the invention is directed to the treatment of CNS diseases by modulating neuronal levels of m6A, and microRNA.

In one aspect, the invention is directed to a method of treating, suppressing, reducing the severity, reducing the risk of developing or inhibiting epilepsy comprising administering a compound of this invention to a subject suffering from epilepsy under conditions effective to treat the epilepsy.

In one aspect, this invention provides methods for a) treating, suppressing, reducing the severity, reducing the risk, preventing, or inhibiting epilepsy; b) treating, suppressing, reducing the severity, reducing the risk, preventing, or inhibiting epileptogenesis; c) treating, suppressing, reducing the severity, reducing the risk, preventing, or inhibiting temporal lobe epilepsy; d) treating, suppressing, reducing the severity, reducing the risk, preventing, or inhibiting partial seizures; e) treating, suppressing, reducing the severity, reducing the risk, preventing, or inhibiting generalized seizures; f) treating, suppressing, reducing the severity, reducing the risk, preventing, or inhibiting unclassified seizures; g) treating, suppressing, reducing the severity, reducing the risk, preventing, or inhibiting status epilepticus; h) treating, suppressing, reducing the severity, reducing the risk, preventing, or inhibiting pharmacoresistant seizures

The compounds of the present invention are useful in the treatment, reducing the severity, reducing the risk, or inhibition of epileptogenesis and drug resistant epilepsy and seizures. Treatment of these different epilepsies is supported by the Examples herein. Moreover, based upon the designed mode of action as Fe(II) and 2-oxoglutarate (2OG)-dependent oxygenase inhibitors, it is believed that other CNS disease states, such as depression, schizophrenia, stroke, traumatic brain injury, Alzheimer's and Parkinson's disease will likewise be treatable or preventable upon administration of the compounds or compositions of the present invention to a patient. Preferred compounds of the present invention are able to preserve neurons at risk of death thereby preventing subsequent CNS pathological states due to the death of neurons, and also disrupt the process of epileptogenesis.

In some aspects, this invention provides for the use of a compound as herein described, or its isomer, metabolite, tautomer, pharmaceutically acceptable salt, pharmaceutical product, polymorph, crystal, N-oxide, hydrate, or any combination thereof, for treating, suppressing, preventing, reducing the severity, reducing the risk, or inhibiting epilepsy in a subject.

In another aspect, this invention provides for the post-operative recovery and suppression of epileptogenesis following temporal lobe epilepsy surgery. Presently, temporal lobe epilepsy surgery fails in about 20-30% of patients, with a major cause being the persistence of epileptogenic mesial structures. Treatment with a pharmaceutical composition comprising a compound of the present invention and a pharmaceutically acceptable carrier under conditions to treat epilepsy is useful by one skilled in the art.

Pharmaceutical Compositions

Related aspects of the invention are directed to compositions, including pharmaceutical compositions, comprising the compounds of the invention, noted above. One aspect of the invention is directed to a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and a therapeutically effective amount of the compound or salt disclosed above. Still another aspect of the invention relates to a method for pharmaceutical formulation of previously described compounds for use in oral and intravenous applications, and in implantable materials.

Another aspect of the present invention relates to a pharmaceutical composition including a pharmaceutically acceptable carrier and a compound according to the aspects of the present invention. The pharmaceutical composition can contain one or more of the above-identified compounds of the present invention.

Typically, the pharmaceutical composition of the present invention will include a compound of the present invention or its pharmaceutically acceptable salt, as well as a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" refers to any suitable adjuvants, carriers, excipients, or stabilizers, and can be in solid or liquid form such as, tablets, capsules, powders, solutions, suspensions, emulsions, or implantable disc.

Typically, the composition will contain from about 0.01 to 99 percent, preferably from about 20 to 75 percent of active compound(s), together with the adjuvants, carriers and/or excipients. While individual needs may vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typical dosages comprise about 0.01 to about 100 mg/kg body wt. The preferred dosages comprise about 0.1 to about 100 mg/kg body wt. The most preferred dosages comprise about 1 to about 100 mg/kg body wt. Treatment regimen for the administration of the compounds of the present invention can also be determined readily by those with ordinary skill in art. That is, the frequency of administration and size of the dose can be established by routine optimization, preferably while minimizing any side effects.

Dosage forms

The solid unit dosage forms can be of the conventional type. The solid form can be a capsule and the like, such as an ordinary gelatin type containing the compounds of the present invention and a carrier, for example, lubricants and inert fillers such as, lactose, sucrose, or cornstarch. In another embodiment, these compounds are tabulated with conventional tablet bases such as lactose, sucrose, or cornstarch in combination with binders like acacia, cornstarch, or gelatin, disintegrating agents, such as cornstarch, potato starch, or alginic acid, and a lubricant, like stearic acid or magnesium stearate.

The tablets, capsules, and the like can also contain a binder such as gum tragacanth, acacia, com starch, or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as com starch,

potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose, or saccharin. When the dosage unit form is a capsule, it can contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Optional Coatings

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets can be coated with shellac, sugar, or both. A syrup can contain, in addition to active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye, and flavoring such as cherry or orange flavor.

Excipients

For oral therapeutic administration, these active compounds can be incorporated with excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups, and the like. Such compositions and preparations should contain at least 0.1 % of active compound. The percentage of the compound in these compositions can, of course, be varied and can conveniently be between about 2% to about 60% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions according to the present invention are prepared so that an oral dosage unit contains between about 1 mg and 800 mg of active compound.

Modes of administration

The active compounds of the present invention may be orally administered, for example, with an inert diluent, or with an assailable edible carrier, or they can be enclosed in hard or soft shell capsules, or they can be compressed into tablets, or they can be incorporated directly with the food of the diet.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form should be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The compounds or pharmaceutical compositions of the present invention may also be administered in injectable dosages by solution or suspension of these materials in a physiologically acceptable diluent with a pharmaceutical adjuvant, carrier or excipient. Such adjuvants, carriers and/or excipients include, but are not limited to, sterile liquids, such as water and oils, with or without the addition of a surfactant and other pharmaceutically and physiologically acceptable components. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil,

soybean oil, or mineral oil. In general, water, saline, aqueous dextrose and related sugar solution, and glycols, such as propylene glycol or polyethylene glycol, are preferred liquid carriers, particularly for injectable solutions.

The pharmaceutical forms suitable for implantable use include sterile wafers of polycarboxyphenoxypropane-sebacic-acid (pCPP:SA) polymers, poly(D,L-lactic acid), polyhydroxybutyrate, lysine diisocyanate (LDI)-glycerol polyurethane, and poly(D-L lactide-co-glycolide). In all cases, the form should be sterile and should be a wafer or disc of suitable dimensions for surgical implantation in the brain. The polymers should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The wafers should be biodegradable in the central nervous system, and should permit the slow release of the above mentioned compounds, ranging from 24 hours up to 6 months. Such wafers may be of particular value in enhancing the success of temporal lobe epilepsy surgery by suppressing persistent epileptogenic structures.

In one aspect, the invention provides compounds and compositions, including any aspect described herein, for use in any of the methods of this invention. In one aspect, use of a compound of this invention or a composition comprising the same, will have utility in inhibiting, suppressing, enhancing or stimulating a desired response in a subject, as will be understood by one skilled in the art. In another embodiment, the compositions may further comprise additional active ingredients, whose activity is useful for the particular application for which the compound of this invention is being administered.

Pharmaceutical compositions comprising modulator compounds of the invention

Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin. Moreover, the modulators can be administered in a time release formulation, for example in a composition 5 which includes a slow release polymer. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters,

polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are patented or generally known to those skilled in the art.

The mode of administration may be oral, for intestinal delivery; intranasal, for nasal delivery; and intravenous for delivery through the blood-brain barrier. Other modes of administration as are known in the art may also be used, including, but not limited to intrathecal, intramuscular, intrabronchial, intrarectal, intraocular, and intravaginal delivery,

The modulator compounds can be administered as oral dosage compositions for small intestinal delivery. Such oral dosage compositions for small intestinal delivery are well-known in the art, and generally comprise gastroresistent tablets or capsules (Remington's Pharmaceutical Sciences, 16th Ed., Eds. Osol, Mack Publishing Co., Chapter 89 (1980); Digenis et al, J. Pharm. Sci., 83:915-921 (1994); Vantini et al, Clinica Terapeutica, 145:445-451 (1993); Yoshitomi et al, Chem. Pharm. Bull., 40:1902'1905 (1992); Thoma et al, Pharmazie, 46:331-336 (1991); Morishita et al, Drug Design and Delivery, 7:309-319 (1991); and Lin et al, Pharmaceutical Res., 8:919'924 (1991)); each of which is incorporated by reference herein in its entirety).

Tablets are made gastroresistent by the addition of compounds such as cellulose acetate phthalate or cellulose acetate terephthalate.

Capsules are solid dosage forms in which the modulator compound is enclosed in either a hard or soft, soluble container or shell of gelatin. The gelatin used in the manufacture of capsules is obtained from collagenous material by hydrolysis. There are two types of gelatin. Type A, derived from pork skins by acid processing, and Type B, obtained from bones and animal skins by alkaline processing. The use of hard gelatin capsules permit a choice in prescribing a modulator compound or a combination thereof at the exact dosage level considered best for the individual subject. The hard gelatin capsule consists of two sections, one slipping over the other, thus completely surrounding the modulator compound. These capsules are filled by introducing the modulator compound, or gastroresistent beads containing the modulator compound, into the longer end of the capsule, and then slipping on the cap. Hard gelatin capsules are made largely from gelatin, FD&C colorants, and sometimes an opacifying agent, such as titanium dioxide. The USP permits the gelatin for this purpose to contain 0.15% (w/v) sulfur dioxide to prevent decomposition during manufacture.

In the context of the present invention, oral dosage compositions for small intestinal delivery also include liquid compositions which contain aqueous buffering agents that prevent the modulator compound from being significantly inactivated by gastric fluids in the stomach, thereby allowing the modulator compound to reach the small intestines in an active form. Examples of such aqueous buffering agents which can be employed in the present invention include bicarbonate buffer (pH 5.5 to 8.7, preferably about pH 7.4).

When the oral dosage composition is a liquid composition, it is preferable that the composition be prepared just prior to administration so as to minimize stability problems. In this case, the liquid composition can be prepared by dissolving lyophilized modulator compound in the aqueous buffering agent. Oral dosage compositions for small intestinal delivery also include liquid compositions which may optionally contain aqueous buffering agents that prevent the therapeutic agent and modulator compound from being significantly inactivated by gastric fluids in the stomach, thereby allowing the biologically active ingredient and modulator compound to reach the small intestines in an active form. Examples of such aqueous buffering agents which can be employed in the present invention include bicarbonate buffer (pH 5.5 to 8.7, preferably about pH 7.4).

When the oral dosage composition is a liquid composition, it is preferable that the composition be prepared just prior to administration so as to minimize stability problems. In this case, the liquid composition can be prepared by dissolving lyophilized therapeutic agent and modulator compound in the aqueous buffering agent.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. For sterile powders used in the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

A "nasal" delivery composition differs from an "intestinal" delivery composition in that the latter must have gastroresistent properties in order to prevent the acidic degradation of the active agents in the stomach, whereas the former generally comprises water-soluble polymers with a diameter of about 50 µm order to reduce the mucociliary clearance, and to achieve a reproducible bioavailability of the nasally administered agents.

An "intravenous" delivery composition differs from both the "nasal" and "intestinal" delivery compositions in that there is no need for gastroresistance or water-soluble polymers in the "intravenous" delivery composition.

Nasal dosage compositions for nasal delivery are well-known in the art. Such nasal dosage compositions generally comprise water-soluble polymers that have been used extensively to prepare pharmaceutical dosage forms (Martin et al, In: Physical Chemical Principles of 20 Pharmaceutical Sciences, 3rd Ed., pages 592-638 (1983)) that can serve as carriers for peptides for nasal administration (Davis, In: Delivery Systems for Peptide Drugs, 125:1-21 (1986)). The nasal absorption of pap tides embedded in polymer matrices has been shown to be enhanced through retardation of nasal mucociliary clearance (Illum et al, Int. J. Pharm., 46:261-265 (1988). Other possible enhancement mechanisms include an

increased concentration gradient or 25 decreased diffusion path for peptides absorption (Ting et al, Pharm. Res., 9:1330-1335 (1992). However, reduction in mucociliary clearance rate has been predicted to be a good approach toward achievement or reproducible bioavailability of nasally administered systemic drugs (Gonda et al, Pharm. Res., 7:69-75 (1990)). Microparticles with a diameter of about 50 pm are expected to deposit in the nasal cavity (Bjork et al, Int. J. Pharm., 62:187-192 (1990); and illum et al, Int. J. Pharm., 39:189'199 (1987), while microparticles with a diameter under 10 pm can escape the filtering system of the nose and deposit in the lower airways. Microparticles larger than 200 p m in diameter will not be retained in the nose after nasal administration (Lewis et al, Proc. Int. Symp. Control Rel. Bioact. Mater., 17:280-290 (1990)).

The particular water-soluble polymer employed is not critical to the present invention, and can be selected from any of the well-known water-soluble polymers employed for nasal dosage forms. A typical example of a water-soluble polymer useful for nasal delivery is polyvinyl alcohol (pvA). This material is a swellable hydrophilic polymer whose physical properties depend on the molecular weight, degree of hydrolysis, cross-linking density, and crystallinity (Peppas et al, in: Hydrogels in Medicine and Pharmacy, 3:109'131 (1987). PYA can be used in the coating of dispersed materials through phase separation, spray-drying, spray-embedding, and spray-densation (Ting et al, supra).

A "skin" delivery composition comprising a modulator compound of the invention may include in addition a therapeutic or immunogenic agent, fragrance, creams, ointments, colorings, and other compounds so long as the added component does not deleteriously affect transdermal delivery of the therapeutic or immunogenic agent. Conventional pharmaceutically acceptable emulsifiers, surfactants, suspending agents, antioxidants, osmotic enhancers, extenders, diluents and preservatives may also be added. Water soluble polymers can also be used as carriers.

The particular therapeutic or immunogenic agent employed is not critical to the present invention, and can be, e.g., any drug compound, biologically active peptide, vaccine, or any other moiety otherwise not absorbed through the transcellular pathway, regardless of size or charge.

The amount of active compound in the composition may vary according to factors such as the disease state, age, sex, and weight of the individual. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically 35 discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and (b) the

limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

As used herein "pharmaceutically-acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. In one embodiment, the carrier is 10 suitable for parenteral administration. A carrier may be suitable for administration into the central nervous system (e.g., intraspinally or intracerebrally). Alternatively, the carrier can be suitable for intravenous, intraperitoneal or intramuscular administration. In another embodiment, the carrier is suitable for oral administration. Pharmaceutically-acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

While specific aspects of the invention have been described in detail, it will be appreciated by those skilled in the art that various modifications and alternatives to those details could be developed in light of the overall teachings of the disclosure. Accordingly, the particular arrangements disclosed are meant to be illustrative only, and not limiting as to the scope of the invention, which is to be given the full breadth of the appended claims, and any equivalent, thereof.

EXAMPLES

The foregoing discussion may be better understood in connection with the following representative examples which are presented for purposes of illustrating the principle methods and compositions of the invention, and not by way of limitation. Various other examples will be apparent to the person skilled in the art after reading the present disclosure without departing from the spirit and scope of the invention. It is intended that all such other examples be included within the scope of the appended claims.

General Materials and Methods

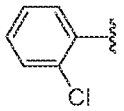
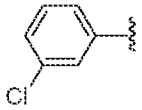
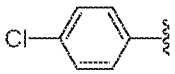
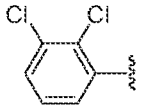
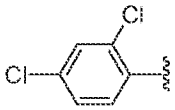
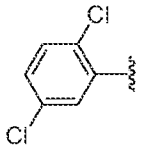
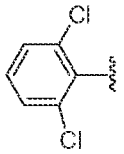
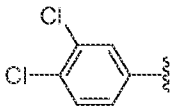
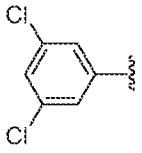
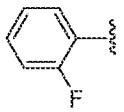
All parts are by weight (e.g., % w/w), and temperatures are in degrees centigrade (°C), unless otherwise indicated.

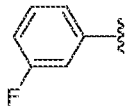
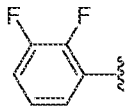
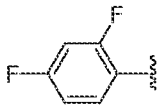
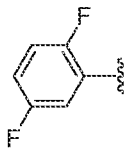
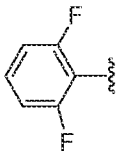
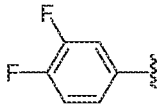
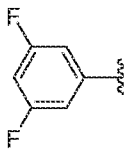
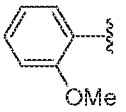
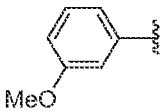
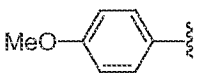
General Chemical Procedures

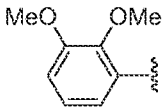
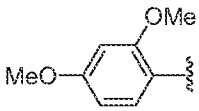
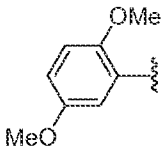
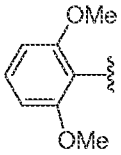
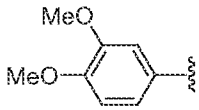
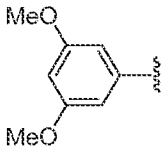
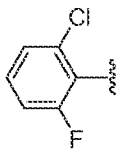
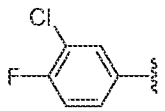
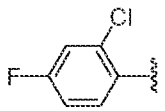
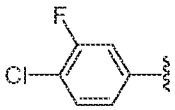
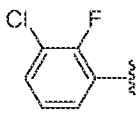
Melting points were determined with a Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra for the compounds were recorded in KBr discs on a Mattson Satellite FTIR in cm^{-1}. ^{1}H and ^{13}C spectra were recorded in DMSO-d_6 on a Bruker Avance III DPX 300 MHz instrument. ^{19}F spectra were recorded in DMSO d_6 on a Bruker Avance III 600 (564.6 mHz). Chemical shifts were expressed in parts per million (δ) with tetramethylsilane as internal standard. Mass spectrometry was performed on a Thermo Scientific LTQ-FT at the University of Cincinnati Mass Spectrometry facility. The purity of the compounds was monitored by HPLC using a Waters 2695 separation module and a 2487 dual λ absorbance detector with a NovaPak C18 4μm 3.9x150mm column. The mobile phases consisted of acetonitrile/H_2O using a 30 minute gradient. All compounds were ≥95%. Microanalysis was performed by Atlantic Microlab Inc., and all compounds were found to be ±0.4%. All reagents were from Sigma-Aldrich. LogS, LogP, Log BBB, human intestinal absorption, p-glycoprotein category, CYP 2C9 pKi, hERG pIC50, CYP 2D6 affinity category, oral CNS score, IV CNS score, MW, flexibility, and total polar surface area were calculated using StarDrop 5.1.1 release Build 178.

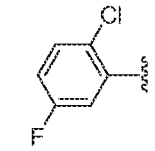
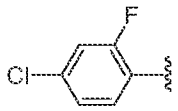
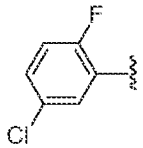
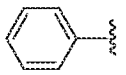
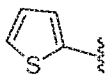
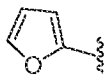
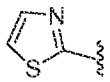
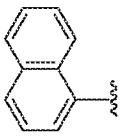
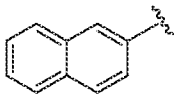
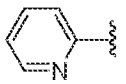
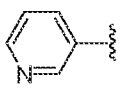
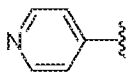
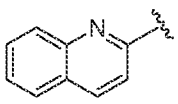
Figures 1-5 illustrate the synthetic reactions used to summarize these reactions. **Table 1** is a non-limiting list of aryl compounds that can be incorporated as "A" from **Formula I**. **Table 2** illustrates the structures, names, and numbers of a variety of key compounds disclosed in in this application.

Table 1
List of Aryl Groups

Compound	Structure	Ar
a		2-chlorophenyl
b		3-chlorophenyl
c		4-chlorophenyl
d		2,3-dichlorophenyl
e		2,4-dichlorophenyl
f		2,5-dichlorophenyl
g		2,6-dichlorophenyl
h		3,4-dichlorophenyl
i		3,5-dichlorophenyl
j		2-fluorophenyl

Compound	Structure	Ar
k		3-fluorophenyl
l		4-fluorophenyl
m		2,3-difluorophenyl
n		2,4-difluorophenyl
o		2,5-difluorophenyl
p		2,6-difluorophenyl
q		3,4-difluorophenyl
r		3,5-difluorophenyl
s		2-methoxyphenyl
t		3-methoxyphenyl
u		4-methoxyphenyl

Compound	Structure	Ar
v		2,3-dimethoxyphenyl
w		2,4-dimethoxyphenyl
x		2,5-dimethoxyphenyl
y		2,6-dimethoxyphenyl
z		3,4-dimethoxyphenyl
aa		3-5-dimethoxyphenyl
ab		2-chloro-6-fluorophenyl
ac		3-chloro-4-fluorophenyl
ad		2-chloro-4-fluorophenyl
ae		4-chloro-3-fluorophenyl
af		3-chloro-2-fluorophenyl

Compound	Structure	Ar
ag		2-chloro-5-fluorophenyl
ah		4-chloro-2-fluorophenyl
ai		5-chloro-2-fluorophenyl
aj		Ph
ak		2-thiophene
al		2-furan
am		2-thiazole
an		1-naphthyl
ao		2-napthyl
ap		2-pyridyl
aq		3-pyridyl
ar		4-pyridyl
as		2-quinolinyl

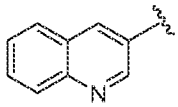
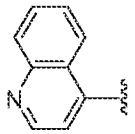
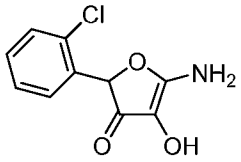
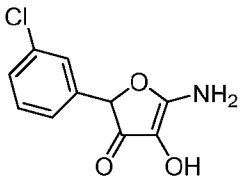
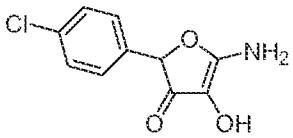
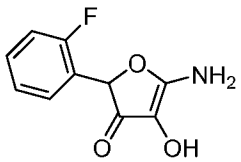
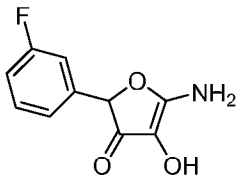
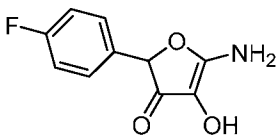
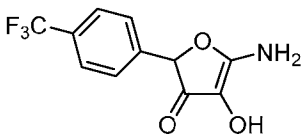
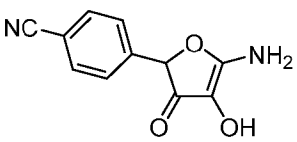
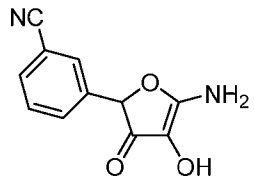
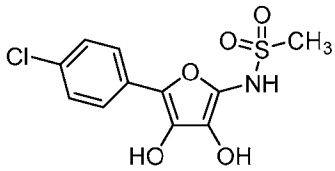
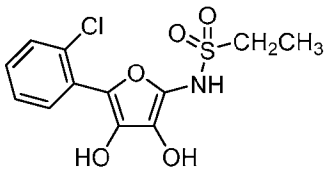
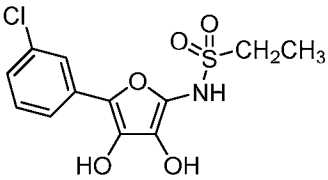
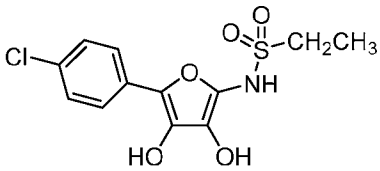
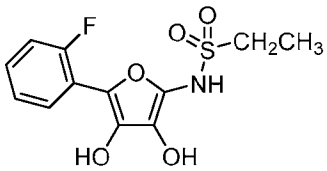
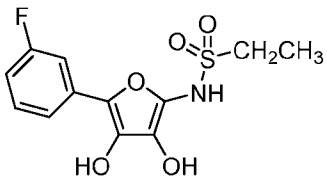
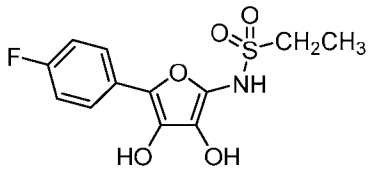
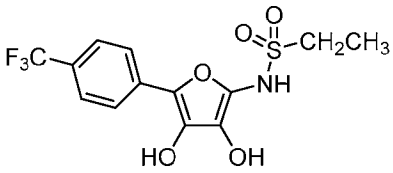
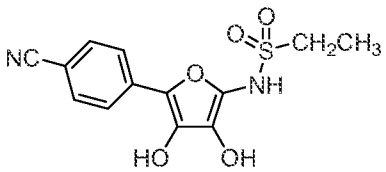
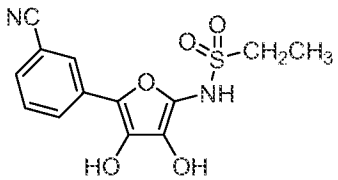
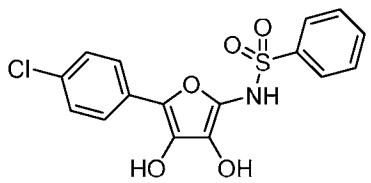
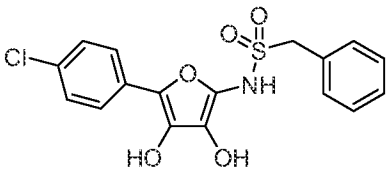
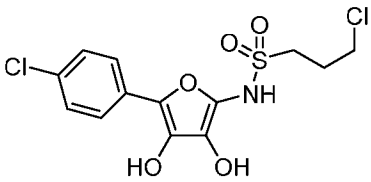
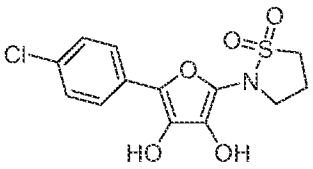
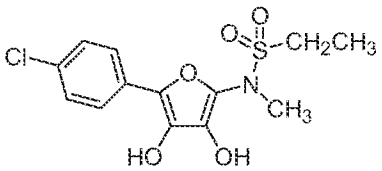
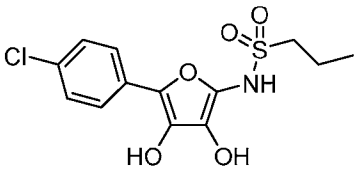
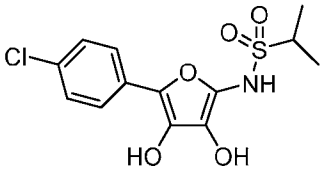
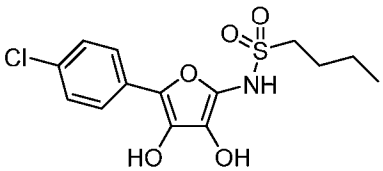
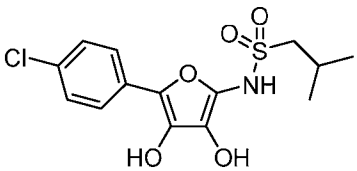
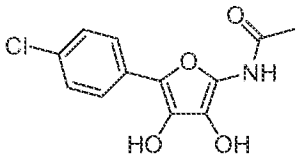
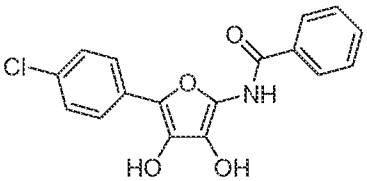
Compound	Structure	Ar
at		3-quinolinyl
au		4-quinolinyl

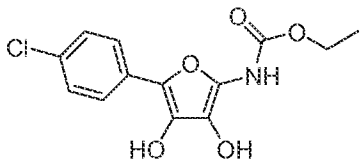
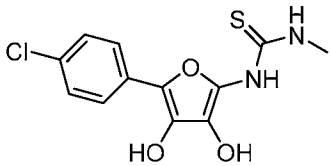
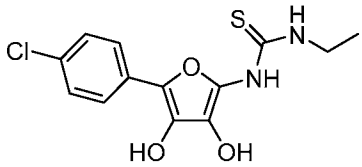
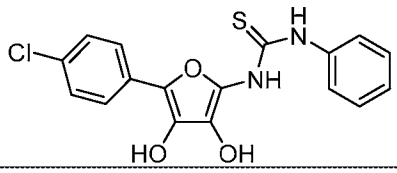
Table 2
Structures of Key Compounds

Structure	Name	Compound
	5-amino-4-hydroxy-2-(2-chlorophenyl)-furan-3-one	1a
	5-amino-4-hydroxy-2-(3-chlorophenyl)-furan-3-one	1b
	5-amino-4-hydroxy-2-(4-chlorophenyl)-furan-3-one	1c
	5-amino-4-hydroxy-2-(2-fluorophenyl)-furan-3-one	1j
	5-amino-4-hydroxy-2-(3-fluorophenyl)-furan-3-one	1k
	5-amino-4-hydroxy-2-(4-fluorophenyl)-furan-3-one	1l
	5-amino-4-hydroxy-2-(4-trifluoromethylphenyl)-furan-3-one	1av
	5-amino-4-hydroxy-2-(4-nitrilephenyl)-furan-3-one	1ay

Structure	Name	Compound
	5-amino-4-hydroxy-2-(3-nitrilephenyl)-furan-3-one	1az
	N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)methanesulfonamide	2c
	N-(3,4-dihydroxy-5-(2-chlorophenyl)-2-furanyl)ethanesulfonamide	3a
	N-(3,4-dihydroxy-5-(3-chlorophenyl)-2-furanyl)ethanesulfonamide	3b
	N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)ethanesulfonamide	3c
	N-(3,4-dihydroxy-5-(2-fluorophenyl)-2-furanyl)ethanesulfonamide	3j
	N-(3,4-dihydroxy-5-(3-fluorophenyl)-2-furanyl)ethanesulfonamide	3k

Structure	Name	Compound
	N-(3,4-dihydroxy-5-(4-fluorophenyl)-2-furanyl)ethanesulfonamide	3l
	N-(3,4-dihydroxy-5-(4-trifluoromethylphenyl)-2-furanyl)ethanesulfonamide	3av
	N-(3,4-dihydroxy-5-(4-nitrilephenyl)-2-furanyl)ethanesulfonamide	3ay
	N-(3,4-dihydroxy-5-(3-nitrilephenyl)-2-furanyl)ethanesulfonamide	3az
	N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)benzenesulfonamide	4c
	N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)benzylsulfonamide	5c
	N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-3-chloropropylsulfonamide	6c

Structure	Name	Compound
	N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-1,1-dioxide-isothiazolidine	7c
	N-methyl-N'-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)ethanesulfonamide	8c
	N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-1-propylsulfonamide	9c
	N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-2-propylsulfonamide	10c
	N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-1-butylsulfonamide	11c
	N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-1-propyl-2-methylsulfonamide	12c
	N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)acetamide	13c
	N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)benzamide	14c

Structure	Name	Compound
	N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-carbamic acid ethyl ester	15c
	N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)- N'-methyl-thiourea	16c
	N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)- N'-ethyl-thiourea	17c
	N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)- N'-phenyl-thiourea	18c

Example 1

Synthesis and characterization of FTO modulating compounds

General Procedures

Potassium cyanide (0.91g) was added to sodium carbonate (1.7g) in deionized water (30 mL) in a 3-Neck Glass Round Flask and placed in an ice bath. The system was repeatedly purged using a vacuum pump and nitrogen gas. Glyoxal (3.72g) was then added to the system without the introduction of O_2 and the reactants were allowed to dissolve with stirring. In a stoppered tube, the appropriate arylaldehyde (7.11 mmoles) was added to 1,4-dioxane (5 mL), purged, and then added drop-wise to the system. The system was then removed from the ice bath and allowed to stir at room temperature for 1 hour. After 1 hour, acetic acid (5 mL) was added drop-wise until gas bubbles were no longer visible from the addition of acetic acid, or until the solution was at a pH of less than 6. The solution was vacuum filtered and washed with ice cold water (5 mL), methanol (5 mL) and ether (5 mL) and then was allowed to air dry. Crude material was recrystallized with methanol, collected by vacuum filtration and rinsed with diethyl ether and dried under vacuum.

Example 1c

5-amino-4-hydroxy-2-(4-chlorophenyl)-furan-3-one

Yield = 70%. mp 221-2°C; FTIR 3079, 1638; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 7.82 (s, 2H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.30 (s, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 5.43 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 182.6, 173.1, 135.7, 133.2, 128.9, 128.6, 111.7, 82.2. HRMS Calc: 248.00849, Found: 248.00852 MNa^+ = $C_{10}H_6NO_3ClNa^+$; Elemental Analysis Calc: C 53.23, H 3.57, N 6.21, Cl 15.71; Found: C 53.35, H 3.61, N 6.24, Cl 15.83 $C_{10}H_8ClNO_3$; HPLC retention time: 16.7 min.

Example 1j

5-amino-4-hydroxy-2-(2-fluorophenyl)-furan-3-one

Yield = 84%. mp 160-3°C; FTIR 3079, 1638; ^{1}H NMR (DMSO d_6) 5.60 (1H, s), 7.22-7.78 (4H, m); HRMS Calc: 210.05610, Found: 210.05609 $MH^+ = C_{10}H_9 F NO_3^+$; Elemental Analysis Calc: C 57.42, H 3.85, N 6.70, F 9.08; Found: C 57.50, H 3.92, N 6.61, F 8.99 $C_{10}H_8FNO_3$; HPLC retention time: 11.42 min.

Example 1k

5-amino-4-hydroxy-2-(3-fluorophenyl)-furan-3-one

Yield = 60%. mp 168°C; FTIR 3356, 3129; ^{1}H NMR (DMSO d_6) 5.44 (1H, s), 7.05-7.27 (4H, m); HRMS Calc: 210.05610, Found: 210.05609 $MH^+ = C_{10}H_9 F NO_3^+$; Elemental Analysis Calc: C 57.42, H 3.85, N 6.70, F 9.08; Found: C 57.41, H 3.87, N 6.61, F 8.97 $C_{10}H_8FNO_3$; HPLC retention time: 12.63 min.

Example 1l

5-amino-4-hydroxy-2-(4-fluorophenyl)-furan-3-one

Yield = 68%. mp 160°C; FTIR 3351, 3138; ^{1}H NMR (DMSO d_6) 5.41 (1H, s), 7.22-7.78 (4H, m); HRMS Calc: 210.05610, Found: 210.05609 $MH^+ = C_{10}H_9 F NO_3^+$; Elemental Analysis Calc: C 57.42, H 3.85, N 6.70, F 9.08; Found: C 57.42, H 3.97, N 6.66, F 8.90 $C_{10}H_8FNO_3$; HPLC retention time: 11.88 min.

Example 1m

5-amino-4-hydroxy-2-(2,3-difluorophenyl)-furan-3-one

Yield = 76%. mp 193°C; FTIR 3391, 3277, 1539; ^{1}H NMR (DMSO d_6) 5.68 (1H, s), 7.05-7.85 (3H, m); HRMS Calc: 228.04668, Found: 228.04669 $MH^+ = C_{10}H_8 F_2NO_3^+$; Elemental Analysis Calc: C 52.87, H 3.11, N 6.17, F 16.73; Found: C 53.10, H 3.11, N 6.17, F 16.57 $C_{10}H_7F_2NO_3$; HPLC retention time: 13.02 min.

Example 1n

5-amino-4-hydroxy-2-(2,4-difluorophenyl)-furan-3-one

Yield = 67%. mp 182-3°C; FTIR 3252, 1608; ^{1}H NMR (DMSO d_6) 5.59 (1H, s), 7.13-7.79 (3H, m); HRMS Calc: 228.04668, Found: 228.04671 $MH^+ = C_{10}H_8 F_2NO_3^+$; Elemental Analysis Calc: C 52.87, H 3.11, N 6.17, F 16.73; Found: C 52.84, H 3.00, N 6.16, F 16.59 $C_{10}H_7F_2NO_3$; HPLC retention time: 12.63 min.

Example 1o

5-amino-4-hydroxy-2-(2,5-difluorophenyl)-furan-3-one

Yield = 80%. mp 196°C; FTIR 3391, 3267; ^{1}H NMR (DMSO d_6) 5.61 (1H, s), 7.03-7.84 (3H, m); HRMS Calc: 228.04668, Found: 228.04670 $MH^+ = C_{10}H_8 F_2NO_3^+$; Elemental Analysis Calc: C 52.87, H 3.11, N 6.17, F 16.73; Found: C 52.79, H 3.11, N 6.15, F 16.57 $C_{10}H_7F_2NO_3$; HPLC retention time: 12.09 min.

Example 1p

5-amino-4-hydroxy-2-(2,6-difluorophenyl)-furan-3-one

Yield = 70%. mp 159-60°C; FTIR 3535, 3406; ^{1}H NMR (DMSO d_6) 5.68 (1H, s), 7.14-7.73 (3H, m); HRMS Calc: 228.04668, Found: 228.04670 $MH^+ = C_{10}H_8 F_2NO_3^+$; Elemental Analysis Calc: C 52.87, H 3.11, N 6.17, F 16.73; Found: C 52.62, H 3.10, N 5.94, F 16.57 $C_{10}H_7F_2NO_3$; HPLC retention time: 11.30 min.

Example 1q

5-amino-4-hydroxy-2-(3,4-difluorophenyl)-furan-3-one

Yield = 76%. mp 190-4°C; FTIR 3322, 3124; ^{1}H NMR (DMSO d_6) 5.44 (1H, s), 7.13-7.85 (3H, m); HRMS Calc: 228.04668, Found: 228.04670 $MH^+ = C_{10}H_8 F_2NO_3^+$; Elemental Analysis Calc: C 52.87, H 3.11, N 6.17, F 16.73; Found: C 53.13, H 3.16, N 6.15, F 16.61 $C_{10}H_7F_2NO_3$; HPLC retention time: 13.79 min.

Example 1r

5-amino-4-hydroxy-2-(3,5-difluorophenyl)-furan-3-one

Yield = 58%. mp 190-1°C; FTIR 3346, 3143; ^{1}H NMR (DMSO d_6) 5.68 (1H, s), 7.05-7.85 (3H, m); HRMS Calc: 228.04668, Found: 228.04670 $MH^+ = C_{10}H_8F_2NO_3^+$; Elemental Analysis Calc: C 52.87, H 3.11, N 6.17, F 16.73; Found: C 52.88, H 3.06, N 6.15, F 16.70 $C_{10}H_7F_2NO_3$; HPLC retention time: 14.00 min.

Example 2c

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)methanesulfonamide

5g of 5-amino-4-hydroxy-2-(4-chlorophenyl)-furan-3-one was stirred in 50 mL of dry THF under nitrogen gas for 16 hours with 4.6 g K_2CO_3 and 1.5 mL of methanesulfonyl chloride. The reaction was filtered, and the filtrate was acidified with 24 mL 1N HCl, and extracted 5 times with 20 mL of diethyl ether. The combined ether extracts were washed with brine, and dried with Na_2SO_4. After filtration, 100 mL of hexanes was added to the solution, resulting in a precipitate, which was collected using vacuum filtration and recrystallized with MeOH. The material was further purified by column chromatography. Yield = 18%. mp 175°C; FTIR 3169, 1616; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 8.41 (s, 1H), 8.09 (s, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.85 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 3.55 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 185.7, 165.1, 140.7, 136.9, 135.9, 133.5, 130.0, 129.7, 40.7. Elemental Analysis Calc: C 43.50, H 3.32, Cl 11.67, N 4.61; Found: C 43.66, H 3.40, Cl 11.54, N 4.55; $C_{11}H_{10}ClNO_5S$; HPLC retention time: 25.2 min.

Example 3a

N-(3,4-dihydroxy-5-(2-chlorophenyl)-2-furanyl)ethanesulfonamide

5g of 5-amino-4-hydroxy-2-(2-chlorophenyl)-furan-3-one is stirring in 50 mL of dry THF under nitrogen gas for 16 hours with 1eq dimethylaminopyridine, 0.5 mL of DMF and 1 eq of ethanesulfonyl chloride. The reaction is filtered, and the filtrate is acidified with saturated ammonium chloride solution, and is extracted 5 times with 20 mL of diethyl ether. The combined ether extracts are washed with brine, and dried with Na_2SO_4. After filtering, the solution is concentrated under reduced pressure and recrystallized with methanol or ethyl acetate.

Example 3b

N-(3,4-dihydroxy-5-(3-chlorophenyl)-2-furanyl)ethanesulfonamide

5g of 5-amino-4-hydroxy-2-(3-chlorophenyl)-furan-3-one is stirring in 50 mL of dry THF under nitrogen gas for 16 hours with 1eq dimethylaminopyridine, 0.5 mL of DMF and 1 eq of ethanesulfonyl chloride. The reaction is filtered, and the filtrate is acidified with saturated ammonium chloride solution, and is extracted 5 times with 20 mL of diethyl ether. The combined ether extracts are washed with brine, and dried with Na_2SO_4. After filtering, the solution is concentrated under reduced pressure and recrystallized with methanol or ethyl acetate.

Example 3c

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)ethanesulfonamide

5g of 5-amino-4-hydroxy-2-(4-chlorophenyl)-furan-3-one was stirred in 50 mL of dry THF under nitrogen gas for 16 hours with 1eq dimethylaminopyridine, 0.5 mL of DMF and 1 eq of ethanesulfonyl chloride. The reaction was filtered, and the filtrate was acidified with 24 mL 1N HCl, and extracted 5 times with 20 mL of diethyl ether. The combined ether extracts were washed with brine, and dried with Na_2SO_4. After filtration, the solution was concentrated under reduced pressure and recrystallized with methanol. Yield = 31%. mp 183-185°C; FTIR 3181, 1616; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 8.41 (s, 1H), 8.08 (s, 1H), 7.95 (d, *J* = 9.3 Hz, 2H), 7.85 (s, 1H), 7.59 (d, *J* = 9.0 Hz, 2H), 3.68 (q, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm) δ 185.8, 165.1, 140.7, 136.8, 136.1, 133.5, 130.0, 129.7, 48.0, 8.6. Elemental Analysis Calc: C 45.36, H 3.81, Cl 11.16, N 4.41; Found: C 45.42, H 3.85, Cl 11.06, N 4.37; $C_{12}H_{12}ClNO_5S$; HPLC retention time: 29.9 min.

Example 3j

N-(3,4-dihydroxy-5-(2-fluorophenyl)-2-furanyl)ethanesulfonamide

5g of 5-amino-4-hydroxy-2-(2-fluorophenyl)-furan-3-one is stirring in 50 mL of dry THF under nitrogen gas for 16 hours with 1eq dimethylaminopyridine, 0.5 mL of DMF and 1 eq of ethanesulfonyl chloride. The reaction is filtered, and the filtrate is acidified with saturated ammonium chloride solution, and is extracted 5 times with 20 mL of diethyl ether. The combined ether extracts are washed with brine, and dried with Na_2SO_4. After filtering, the solution is concentrated under reduced pressure and recrystallized with methanol or ethyl acetate.

Example 3k

N-(3,4-dihydroxy-5-(3-fluorophenyl)-2-furanyl)ethanesulfonamide

5g of 5-amino-4-hydroxy-2-(3-fluorophenyl)-furan-3-one is stirring in 50 mL of dry THF under nitrogen gas for 16 hours with 1eq dimethylaminopyridine, 0.5 mL of DMF and 1 eq of ethanesulfonyl chloride. The reaction is filtered, and the filtrate is acidified with saturated ammonium chloride solution, and is extracted 5 times with 20 mL of diethyl ether. The combined ether extracts are washed with brine, and dried with Na_2SO_4. After filtering, the solution is concentrated under reduced pressure and recrystallized with methanol or ethyl acetate.

Example 3l

N-(3,4-dihydroxy-5-(4-fluorophenyl)-2-furanyl)ethanesulfonamide

5g of 5-amino-4-hydroxy-2-(4-fluorophenyl)-furan-3-one is stirring in 50 mL of dry THF under nitrogen gas for 16 hours with 1eq dimethylaminopyridine, 0.5 mL of DMF and 1 eq of ethanesulfonyl chloride. The reaction is filtered, and the filtrate is acidified with saturated ammonium chloride solution,

and is extracted 5 times with 20 mL of diethyl ether. The combined ether extracts are washed with brine, and dried with Na_2SO_4. After filtering, the solution is concentrated under reduced pressure and recrystallized with methanol or ethyl acetate.

Example 3av

N-(3,4-dihydroxy-5-(4-trifluoromethylphenyl)-2-furanyl)ethanesulfonamide

5g of 5-amino-4-hydroxy-2-(4-trifluoromethylphenyl)-furan-3-one is stirring in 50 mL of dry THF under nitrogen gas for 16 hours with 1eq dimethylaminopyridine, 0.5 mL of DMF and 1 eq of ethanesulfonyl chloride. The reaction is filtered, and the filtrate is acidified with saturated ammonium chloride solution, and is extracted 5 times with 20 mL of diethyl ether. The combined ether extracts are washed with brine, and dried with Na_2SO_4. After filtering, the solution is concentrated under reduced pressure and recrystallized with methanol or ethyl acetate.

Example 3ay

N-(3,4-dihydroxy-5-(4-nitrilephenyl)-2-furanyl)ethanesulfonamide

5g of 5-amino-4-hydroxy-2-(4-nitrilephenyl)-furan-3-one is stirring in 50 mL of dry THF under nitrogen gas for 16 hours with 1eq dimethylaminopyridine, 0.5 mL of DMF and 1 eq of ethanesulfonyl chloride. The reaction is filtered, and the filtrate is acidified with saturated ammonium chloride solution, and is extracted 5 times with 20 mL of diethyl ether. The combined ether extracts are washed with brine, and dried with Na_2SO_4. After filtering, the solution is concentrated under reduced pressure and recrystallized with methanol or ethyl acetate.

Example 3az

N-(3,4-dihydroxy-5-(3-nitrilephenyl)-2-furanyl)ethanesulfonamide

5g of 5-amino-4-hydroxy-2-(3-nitrilephenyl)-furan-3-one is stirring in 50 mL of dry THF under nitrogen gas for 16 hours with 1eq dimethylaminopyridine, 0.5 mL of DMF and 1 eq of ethanesulfonyl chloride. The reaction is filtered, and the filtrate is acidified with saturated ammonium chloride solution, and is extracted 5 times with 20 mL of diethyl ether. The combined ether extracts are washed with brine, and dried with Na_2SO_4. After filtering, the solution is concentrated under reduced pressure and recrystallized with methanol or ethyl acetate.

Example 4c

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)benzenesulfonamide

5g of 5-amino-4-hydroxy-2-(4-chlorophenyl)-furan-3-one is stirring in 50 mL of dry THF under nitrogen gas for 16 hours with 1eq dimethylaminopyridine, 0.5 mL of DMF and 1 eq of benzenesulfonyl chloride. The reaction is filtered, and the filtrate is acidified with saturated ammonium chloride solution,

and is extracted 5 times with 20 mL of diethyl ether. The combined ether extracts are washed with brine, and dried with Na_2SO_4. After filtering, the solution is concentrated under reduced pressure and recrystallized with methanol or ethyl acetate.

Example 5c

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)benzylsulfonamide

5g of 5-amino-4-hydroxy-2-(4-chlorophenyl)-furan-3-one is stirring in 50 mL of dry THF under nitrogen gas for 16 hours with 1eq dimethylaminopyridine, 0.5 mL of DMF and 1 eq of phenylmethylsulfonyl chloride. The reaction is filtered, and the filtrate is acidified with saturated ammonium chloride solution, and is extracted 5 times with 20 mL of diethyl ether. The combined ether extracts are washed with brine, and dried with Na_2SO_4. After filtering, the solution is concentrated under reduced pressure and recrystallized with methanol or ethyl acetate.

Example 6c

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-3-chloropropylsulfonamide

5g of 5-amino-4-hydroxy-2-(4-chlorophenyl)-furan-3-one is stirring in 50 mL of dry THF under nitrogen gas for 16 hours with 1eq dimethylaminopyridine, 0.5 mL of DMF and 1 eq of 3-chloropropylsulfonyl chloride. The reaction is filtered, and the filtrate is acidified with saturated ammonium chloride solution, and is extracted 5 times with 20 mL of diethyl ether. The combined ether extracts are washed with brine, and dried with Na_2SO_4. After filtering, the solution is concentrated under reduced pressure and recrystallized with methanol or ethyl acetate.

Example 7c

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-1,1-dioxide-isothiazolidine

1 g of 5-amino-4-hydroxy-2-(4-fluorophenyl)-furan-3-one is stirring in 50mL dry THF under dry nitrogen. The reaction is cooling in an ice bath, and 1 equivalent of sodium hydride is added. The reaction is warmed to room temperature, and is stirring for 2 hours. Methanol followed by a saturated ammonium chloride solution is added to quench the reaction, and the reaction is extracted 3 times with 20mL diethyl ether. The combined ether extracts are washed with water and brine, the ether is dried with sodium sulfate, is filtered, and evaporates to yield a solid which is recrystallized with methanol.

Example 8c

N-methyl-N'-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)ethanesulfonamide

1 g of N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)ethanesulfonamide is stirring in 25mL diethyl ether. The reaction is cooling in an ice bath, and 1 equivalent of diazomethane solution is carefully added dropwise. The reaction is stirred at room temperature for 2 hours. The ether solution is washed

with water and brine, the ether is dried with sodium sulfate, is filtered, and evaporates to yield a solid which is recrystallized with methanol.

Example 9c

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-1-propylsulfonamide

5g of 5-amino-4-hydroxy-2-(2-chlorophenyl)-furan-3-one is stirring in 50 mL of dry THF under nitrogen gas for 16 hours with 1eq dimethylaminopyridine, 0.5 mL of DMF and 1 eq of n-propanesulfonyl chloride. The reaction is filtered, and the filtrate is acidified with saturated ammonium chloride solution, and is extracted 5 times with 20 mL of diethyl ether. The combined ether extracts are washed with brine, and dried with Na_2SO_4. After filtering, the solution is concentrated under reduced pressure and recrystallized with methanol or ethyl acetate.

Example 10c

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-2-propylsulfonamide

5g of 5-amino-4-hydroxy-2-(2-chlorophenyl)-furan-3-one is stirring in 50 mL of dry THF under nitrogen gas for 16 hours with 1eq dimethylaminopyridine, 0.5 mL of DMF and 1 eq of i-propanesulfonyl chloride. The reaction is filtered, and the filtrate is acidified with saturated ammonium chloride solution, and is extracted 5 times with 20 mL of diethyl ether. The combined ether extracts are washed with brine, and dried with Na_2SO_4. After filtering, the solution is concentrated under reduced pressure and recrystallized with methanol or ethyl acetate.

Example 11c

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-1-butylsulfonamide

5g of 5-amino-4-hydroxy-2-(2-chlorophenyl)-furan-3-one is stirring in 50 mL of dry THF under nitrogen gas for 16 hours with 1eq dimethylaminopyridine, 0.5 mL of DMF and 1 eq of n-butanesulfonyl chloride. The reaction is filtered, and the filtrate is acidified with saturated ammonium chloride solution, and is extracted 5 times with 20 mL of diethyl ether. The combined ether extracts are washed with brine, and dried with Na_2SO_4. After filtering, the solution is concentrated under reduced pressure and recrystallized with methanol or ethyl acetate.

Example 12c

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-1-propyl-2-methylsulfonamide

5g of 5-amino-4-hydroxy-2-(2-chlorophenyl)-furan-3-one is stirring in 50 mL of dry THF under nitrogen gas for 16 hours with 1eq dimethylaminopyridine, 0.5 mL of DMF and 1 eq of i-butanesulfonyl chloride. The reaction is filtered, and the filtrate is acidified with saturated ammonium chloride solution, and is extracted 5 times with 20 mL of diethyl ether. The combined ether extracts are washed with brine,

and dried with Na_2SO_4. After filtering, the solution is concentrated under reduced pressure and recrystallized with methanol or ethyl acetate.

Example 13c

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)acetamide

5 g of 5-amino-4-hydroxy-2-(4-fluorophenyl)2-methyl-furan-3-one is stirring in 50mL dry THF under dry nitrogen. The reaction is cooling in an ice bath, and 1 equivalent of triethylamine is added dropwise in dry THF. The reaction is warmed to room temperature, chlorotertbutyldimethylsilane is added dropwise and the reaction is refluxing gently with a water bath for 30 minutes. The reaction is cooled down with an ice bath, and 1 equivalent of acetyl chloride is added dropwise in dry THF. 1 equivalent of dimethylaminopyridine is added dropwise in dry THF, and the reaction is stirring for 6 hours under argon. The reaction is cooling in an ice bath and 1 equivalent of tetrabutylammonium fluoride is added and stirs for 30 minutes. A saturated ammonium chloride solution is added to quench the reaction, and the reaction is extracted 3 times with 20mL diethyl ether. The combined ether extracts are washed with water and brine, the ether is dried with sodium sulfate, is filtered, and evaporates to yield a solid which is recrystallized with methanol.

Example 14c

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)benzamide

5 g of 5-amino-4-hydroxy-2-(4-fluorophenyl)2-methyl-furan-3-one is stirring in 50mL dry THF under dry nitrogen. The reaction is cooling in an ice bath, and 1 equivalent of triethylamine is added dropwise in dry THF. The reaction is warmed to room temperature, chlorotertbutyldimethylsilane is added dropwise and the reaction is refluxing gently with a water bath for 30 minutes. The reaction is cooled down with an ice bath, and 1 equivalent of benzoyl chloride is added dropwise in dry THF. 1 equivalent of dimethylaminopyridine is added dropwise in dry THF, and the reaction is stirring for 6 hours under argon. The reaction is cooling in an ice bath and 1 equivalent of tetrabutylammonium fluoride is added and stirs for 30 minutes. A saturated ammonium chloride solution is added to quench the reaction, and the reaction is extracted 3 times with 20mL diethyl ether. The combined ether extracts are washed with water and brine, the ether is dried with sodium sulfate, is filtered, and evaporates to yield a solid which is recrystallized with methanol.

Example 15c

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)- carbamic acid ethyl ester

5 g of 5-amino-4-hydroxy-2-(4-fluorophenyl)2-methyl-furan-3-one is stirring in 50mL dry THF under dry nitrogen. The reaction is cooling in an ice bath, and 1 equivalent of triethylamine is added dropwise in dry THF. The reaction is warmed to room temperature, chlorotertbutyldimethylsilane is

added dropwise and the reaction is refluxing gently with a water bath for 30 minutes. The reaction is cooled down with an ice bath, and 1 equivalent of ethylchloroformate is added dropwise in dry THF. 1 equivalent of dimethylaminopyridine is added dropwise in dry THF, and the reaction is stirring for 6 hours under argon. The reaction is cooling in an ice bath and 1 equivalent of tetrabutylammonium fluoride is added and stirs for 30 minutes. A saturated ammonium chloride solution is added to quench the reaction, and the reaction is extracted 3 times with 20mL diethyl ether. The combined ether extracts are washed with water and brine, the ether is dried with sodium sulfate, is filtered, and evaporates to yield a solid which is recrystallized with ethyl acetate.

Example 16c

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)- N'-methyl-thiourea

5 g of 5-amino-4-hydroxy-2-(4-fluorophenyl)2-methyl-furan-3-one is stirring in 50mL methanol under argon. 1 eq of methylisothiocyanate is added in methanol dropwise. The reaction is refluxing gently with a water bath for 30 minutes. The reaction is cooled down to room temperature. A saturated ammonium chloride solution is added, and the reaction is extracted 3 times with 20mL diethyl ether. The combined ether extracts are washed with water and brine, the ether is dried with sodium sulfate, is filtered, and evaporates to yield a solid which is recrystallized with methanol.

Example 17c

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)- N'-ethyl-thiourea

5 g of 5-amino-4-hydroxy-2-(4-fluorophenyl)2-methyl-furan-3-one is stirring in 50mL methanol under argon. 1 eq of ethylisothiocyanate is added in methanol dropwise. The reaction is refluxing gently with a water bath for 30 minutes. The reaction is cooled down to room temperature. A saturated ammonium chloride solution is added, and the reaction is extracted 3 times with 20mL diethyl ether. The combined ether extracts are washed with water and brine, the ether is dried with sodium sulfate, is filtered, and evaporates to yield a solid which is recrystallized with methanol.

Example 18c

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)- N'-phenyl-thiourea

5 g of 5-amino-4-hydroxy-2-(4-fluorophenyl)2-methyl-furan-3-one is stirring in 50mL methanol under argon. 1 eq of phenylisothiocyanate is added in methanol dropwise. The reaction is refluxing gently with a water bath for 30 minutes. The reaction is cooled down to room temperature. A saturated ammonium chloride solution is added, and the reaction is extracted 3 times with 20mL diethyl ether. The combined ether extracts are washed with water and brine, the ether is dried with sodium sulfate, is filtered, and evaporates to yield a solid which is recrystallized with methanol.

Example 2

Biological Activity and Toxicity of Selected Compounds

In this example, the biological activity and toxicity of selected compounds disclosed in Example 1 are measured by various assays described below.

Maximal Electroshock (MES) Model Assays

In the MES test, an electrical stimulus of 0.2 s in duration (50 mA in mice and 150 mA in rat at 60Hz) is delivered via corneal electrodes primed with an electrolyte solution containing an anesthetic agent. Mice are tested at 30 minutes and 4 hours following doses of 100 mg/kg of test compound. Abolition of the hindlimb tonic extensor component indicates the test compound's ability to inhibit MES-induced seizure spread (White *et al.,* 1995a; White *et* al., 1995b; Swinyard *et al.,* 1989).

PTZ Model Assays

The scPTZ test utilizes a dose of pentylenetetrazol (85 mg/kg in Carworth Farms No. 1 mice). This produces clonic seizures lasting for a period of at least five seconds in 97 per cent (CD97) of animals tested. At the anticipated time of testing the convulsant is administered subcutaneously. The test compound is administered intraperitoneally in mice. Animals are observed over a 30 minute period. Absence of clonic spasms in the observed time period indicates a compound's ability to abolish the effect of pentylenetetrazol on seizure threshold (Swinyard et al., 1989).

6Hz Model Qualitative Assays

Test compounds are pre-administered to mice via i.p. injection. At varying times, individual mice (four per time point) are challenged with sufficient current delivered through corneal electrodes to elicit a psychomotor seizure in 97% of animals (32 mA for 3s) (Toman et al., 1952). Untreated mice will display seizures characterized by a minimal clonic phase followed by stereotyped, automatistic behaviors described originally as being similar to the aura of human patients with partial seizures. Animals not displaying this behavior are considered protected. Toxicity is observed using the rotorod test.

6Hz Model Quantitative Assays

Test compounds are pre-administered to rats via i.p. injection. At varying times and doses, individual rats (several per time point) are challenged with sufficient current delivered through corneal electrodes to elicit a psychomotor seizure in 97% of animals (32 mA for 3s) (Toman et al., 1952). Untreated mice will display seizures characterized by a minimal clonic phase followed by stereotyped, automatistic behaviors described originally as being similar to the aura of human patients with partial seizures. Animals not displaying this behavior are considered protected. Toxicity is observed using the rotorod test.

Neuroprotection Assay

Primary cortical neurons were pretreated with Mesyl (compound 4c) 0.1-2uM, Ethyl (compound 5c) 0.1-2uM for 18h and then exposed to glutamate analog homocysteate (HCA; 5mM) for 24h, after which cell viability was assessed by MTT assay (A and B) and LIVE-DEAD assay. Panel (C)shows the live dead assay, live cells were shown in green, while dead cells were seen in red. *Live cells are detected by uptake and* trapping of calcein AM (green fluorescence). Dead cells fail to trap calcein but are freely permeable to the highly charged DNA-intercalating dye ethidium homodimer (red fluorescence).

FTO Enzyme Inhibition Assays

The activity assay was performed as previously described (Fu, Dai et al. 2010, Jia, Fu et al. 2011). The reaction mixture contained the following components:

DNA containing m^6A (5'-ATTGTCA(m^6A)CAGCAGC-3') (SEQ ID NO: 1)

(100 μM), FTO protein (30 μM), KCl (100 mM), $MgCl_2$ (2 mM), L-ascorbic acid (2 mM), α-ketoglutarate (300 μM), $(NH_4)_2Fe(SO_4)_2 \cdot 6H_2O$ (150 μM) and 50 mM of HEPES buffer (pH 7.5). The reaction was incubated with the inhibitor at room temperature for 15 min, then quenched by adding 5 mM EDTA followed by heating at 95°C for 10 min. DNA was digested by nuclease P1 and alkaline phosphatase, and then analyzed on a HPLC system equipped with an Acclaim 120, C18, 5 μm Analytical column (4.6×150 mm) (Thermo Scientific, Sunnyvale, CA) eluted with buffer A (5 mM ammonia acetate) and buffer B (60% acetonitrile, 0.01% TFA, 5 mM ammonia acetate) with a flow rate of 1 ml min^{-1} at room temperature. The detection wave length was set at 260 nm.

Quantification of Cellular m6A

The activity assay was performed as described (Fu, Dai et al. 2010, Jia, Fu et al. 2011). Total RNA was isolated from HeLa cells with TRAZOL Reagent (Life Technologies, Carlsbad, CA). The mRNA was extracted using PolyATtract® mRNA Isolation Systems (Promega, Madison, Wi), followed by further removing of contaminated rRNA using RiboMinus Transcriptome Isolation Kit (Life Technologies, Carlsbad, CA). The concentration of mRNA samples was measured by NanoDrop. The quality of mRNA samples was analyzed using Agilent 2100 bioanalyzer with an RNA NanoChip. 1 μg of mRNA was digested by nuclease P1 (2 U) in 40 μl of buffer containing 25 mM of NaCl, and 2.5 mM of $ZnCl_2$ at 37 ºC for 1 h, followed by the addition of NH_4HCO_3 (1 M, 3 μl) and alkaline phosphatase (0.5 U). After an additional incubation at 37°C for 1 h, the solution was diluted 5 times, and 10 μl of the solution was injected into LC-MS/MS. The nucleosides were separated by reverse phase ultra-performance liquid chromatography on a C18 column, with online mass spectrometry detection using Agilent 6410 QQQ triple-quadrupole LC mass spectrometer in positive electrospray ionization mode. The nucleosides were quantified using the nucleoside to base ion mass transitions of 282 to 150 (m6A), and 268 to 136 (A). Quantification was performed by

comparison with the standard curve obtained from pure nucleoside standards running at the same batch of samples. The ratio of m6A to A was calculated based on the calculated concentrations. Statistical analysis performed included the t-test and calculation of the p-value.

Micro RNA methods

HeLa cells were grown at 37°C with 5% CO_2 in Dulbecco's Modification of Eagle's Medium (DMEM) supplemented with 5% fetal bovine serum (FBS) and 0.1 mM non-essential amino acid (Life Technologies, Carlsbad, CA). Cells were seeded into 100 mm culture dishes. When cell layers reached ~80% confluence, the medium was replaced with OPTI-MEM (Life Technologies, Carlsbad, CA) and incubated for 24 hours. The mRNA was isolated from cells using miRvana kits (Life Technologies, Carlsbad, CA), and submitted to LC Sciences (Houston, TX) for analysis using a proprietary microRNA (miR Base version 19) microarray.

Table 3
6 Hz Assay Results for Selected Compounds

Compound	Time (Hours)	Activity 0.25 (N/F)	Activity 0.5 (N/F)	Activity 1.0 (N/F)	Activity 2.0 (N/F)	Activity 4.0 (N/F)	Toxicity 0.25 (N/F)	Toxicity 0.5 (N/F)	Toxicity 1.0 (N/F)	Toxicity 2.0 (N/F)	Toxicity 4.0 (N/F)
1c		1/4	0/4	1/4	1/4	0/4	0/4	0/4	0/4	0/4	0/4
1j		1/4	1/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
1k		0/4	2/4	0/4	0/4	1/4	0/4	0/4	0/4	0/4	0/4
1l		0/4	0/4	1/4	1/4	0/4	0/4	0/4	0/4	0/4	0/4
1m		0/4	0/4	2/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
1n		1/4	1/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
1o		1/4	3/4	1/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
2c		1/4	4/4	4/4	3/4	4/4	0/4	1/4	2/4	0/4	3/4
3c		1/4	3/4	2/4	3/4	3/4	0/4	0/4	0/4	1/4	0/4

All compounds in **Table 3** were tested at 100 mg/kg. As noted in the Table 3, compounds 4c and 5c have the most significant activity, but compound 5c has decreased toxicity relative to compound 4c. Taken together, these compounds demonstrate significant activity in the 6Hz model of pharmacoresistant epilepsy.

Table 4
MES Assay Results For Selected Compounds

Compound	Time (Hours)	Activity 0.25 (N/F)	Activity 0.5 (N/F)	Activity 1.0 (N/F)	Activity 2.0 (N/F)	Activity 4.0 (N/F)	Toxicity 0.25 (N/F)	Toxicity 0.5 (N/F)	Toxicity 1.0 (N/F)	Toxicity 2.0 (N/F)	Toxicity 4.0 (N/F)
1c		0/4	0/4	0/4	0/4	0/4	0/8	0/8	0/8	0/8	0/8
1j		ND	0/3	ND	ND	0/3	ND	0/8	ND	ND	0/4
1k		ND	0/3	ND	ND	0/3	ND	0/8	ND	ND	0/4
1l		ND	0/3	ND	ND	0/3	ND	0/8	ND	ND	0/4
1m		ND	0/3	ND	ND	0/3	ND	0/8	ND	ND	0/4
1n		ND	0/3	ND	ND	0/3	ND	0/8	ND	ND	0/4
1o		ND	0/3	ND	ND	0/3	ND	0/8	ND	ND	0/4
2c		0/4	0/4	0/4	0/4	0/4	0/8	0/8	1/8	1/8	4/8
3c		0/4	1/4	0/4	0/4	1/4	0/8	0/8	0/8	0/8	0/8

All compounds in Table 4 were tested at 100 mg/kg. As noted in the Table 3, these compounds have little to no activity in the well-known MES model.

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Table 5
scPTZ Assay Results For Selected Compounds

Compound	Time (Hours)	Activity 0.25 (N/F)	Activity 0.5 (N/F)	Activity 1.0 (N/F)	Activity 2.0 (N/F)	Activity 4.0 (N/F)	Toxicity 0.25 (N/F)	Toxicity 0.5 (N/F)	Toxicity 1.0 (N/F)	Toxicity 2.0 (N/F)	Toxicity 4.0 (N/F)
1c		ND	0/1	ND	ND	0/1	ND	0/8	ND	ND	0/4
1j		ND	0/1	ND	ND	0/1	ND	0/8	ND	ND	0/4
1k		ND	0/1	ND	ND	0/1	ND	0/8	ND	ND	0/4
1l		ND	0/1	ND	ND	0/1	ND	0/8	ND	ND	0/4
1m		ND	0/1	ND	ND	0/1	ND	0/8	ND	ND	0/4
1n		ND	0/1	ND	ND	0/1	ND	0/8	ND	ND	0/4
1o		ND	0/1	ND	ND	0/1	ND	0/8	ND	ND	0/4
2c		0/4	1/4	0/4	0/4	2/3	0/8	0/8	1/8	1/8	4/8
3c		0/4	0/4	0/4	1/4	1/4	0/8	0/8	0/8	0/8	0/8

All compounds in Table 5 were tested at 100mg/kg. As noted in the Table 3, these compounds have little to no activity in the well-known MES model.

5

Table 6
6Hz Quantitative Assay Results For Compound 3c

Test	Time (Hours)	Dose (mg/kg)	N/F
6Hz	1.0	1.0	0/8
6Hz	1.0	2.5	1/8
6Hz	1.0	5.0	5/8
6Hz	1.0	10.0	5/8
6Hz	1.0	25.0	11/16
6Hz	1.0	50.0	4/8
6Hz	1.0	100.0	10/16
6Hz	1.0	200.0	6/8
Toxicity	8.0	100.0	0/8
Toxicity	8.0	200.0	2/8
Toxicity	8.0	300.0	3/8
Toxicity	8.0	500.0	5/8
Toxicity	8.0	750.0	7/7

Compound 5c possesses significant activity in the 6Hz quantitative model, with a seizure suppressive ED_{50} of 18 mg/kg, a toxic ED_{50} of 347 mg/kg, giving a safety ratio of toxic ED_{50}/seizure suppressive ED_{50} of 19. Taken together, these results indicate that compound 5c has both potent seizure suppressive activity in the pharmacoresistant 6Hz model, as well as a very good safety ratio, implying that this compound possesses a clinically useful therapeutic window.

Table 7
Modulation of microRNA by 25 μM 3c.

microRNA	P-Value	Log2(G2/G1)[a]
miR-6509-3p	1.94E-02	-2.73
miR-4444	4.06E-02	0.60
miR-671-5p	4.20E-02	0.35
miR-6722-5p	4.40E-02	-1.05
miR-4713-5p	5.99E-02	-1.39
miR-4638-5p	6.21E-02	1.47
miR-4717-5p	6.62E-02	-1.70
miR-6514	7.06E-02	-1.44
miR-4329	7.18E-02	-1.62
miR-4485	7.52E-02	-0.60
miR-486-3p	8.61E-02	-1.81
miR-34b-3p	8.91E-02	-1.66

[a] G2 is the signal from **3c** treated (25uM) HeLa cells, G1 is the signal from untreated control HeLa cells.

While the preferred embodiments of the invention have been illustrated and described in detail, it will be appreciated by those skilled in the art that that various changes can be made therein without departing from the spirit and scope of the invention. Accordingly, the particular arrangements disclosed are meant to be illustrative only and not limiting as to the scope of the invention, which is to be given the full breadth of the appended claims and any equivalent thereof.

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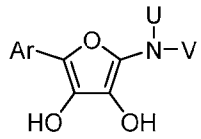
CLAIMS

1. A compound of **Formula I**, a pharmaceutically-acceptable salt thereof, and mixtures of any of the forgoing:



(I)

wherein Ar is a substituted or unsubstituted aryl or heteroaryl ring;

wherein said aryl ring comprises at least one R group selected from the group consisting of -H, -OH, -SH, -CN, -F, -Cl, -Br, -CN, NO_2 -NO, $-NH_2$, -NHR, -NRR, -C(O)R, -C(O)OH, -C(O)OR, $-C(O)NH_2$, -C(O)NHR, and -C(O)NRR, -SOR, $-SO_2R$, $-SO_2NH_2$, $-SO_2NHR$, $-SO_2NRR$;

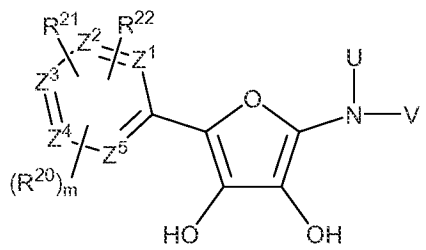
wherein each R is independently selected from the group consisting of $(C_1\text{-}C_5)$ alkyl, substituted $(C_1\text{-}C_6)$ alkyl, $(C_2\text{-}C_6)$ alkenyl, substituted $(C_2\text{-}C_6)$ alkenyl, $(C_2\text{-}C_6)$ alkynyl, substituted $(C_2\text{-}C_6)$ alkynyl, $(C_5\text{-}C_{20})$ aryl, substituted $(C_5\text{-}C_{20})$ aryl, $(C_6\text{-}C_{26})$ arylalkyl, substituted $(C_6\text{-}C_{26})$ arylalkyl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, 6-26 membered heteroarylalkyl, and substituted 6-26 membered heteroarylalkyl; and

wherein V is selected from the group consisting of $-SO_2R$, - SO_2R, -C(O)R, -C(O)OR, -C(S)R, and -C(S)NHR;

wherein both U and V are not hydrogen; and

wherein U and V can join together to form an unsubstituted or substituted ring.

2. A compound of Claim 1, represented by the structure of **Formula II**:



(II)

wherein R^{20}, R^{21}, and R^{22} are independently selected from the group consisting of H, -F, -Cl, -Br, -I, -OH, -SH, -CN, NO_2 -NO, $-NH_2$, -NHR, -NRR, -C(O)R, -C(O)OH, -C(O)OR, -C(O)NH2, -C(O)NHR, -C(O)NRR, -SOR, $-SO_2R$, $-SO_2NH_2$, $-SO_2NHR$, and $-SO_2NRR$;

wherein Z^1, Z^2, Z^3, Z^4, Z^5 are independently selected from C, N;

wherein each R is independently selected from the group consisting of (C_1-C_5) alkyl, substituted (C_1-C_6) alkyl, (C_2-C_6) alkenyl, substituted (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, substituted (C_2-C_6) alkynyl, (C_5-C_{20}) aryl, substituted (C_5-C_{20}) aryl, (C_6-C_{26}) arylalkyl, substituted (C6-C26) arylalkyl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, 6-26 membered heteroarylalkyl, and substituted 6-26 membered heteroarylalkyl; and

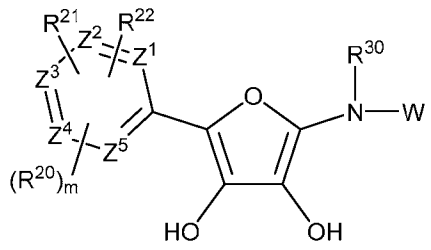
wherein U is selected from the group consisting of hydrogen, (C_1-C_5) alkyl, substituted (C_1-C_6) alkyl, (C_2-C_6) alkenyl, substituted (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, substituted (C_2-C_6) alkynyl, (C_5-C_{20}) aryl, substituted (C_5-C_{20}) aryl, (C_6-C_{26}) arylalkyl, substituted (C_6-C_{26}) arylalkyl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, 6-26 membered heteroarylalkyl, and substituted 6-26 membered heteroarylalkyl;

wherein V is selected from the group consisting of $-SO_2R$, - SO_2R, -C(O)R, -C(O)OR, -C(S)R, and -C(S)NHR;

wherein both U and V are not hydrogen; and

wherein U and V can join together to form an unsubstituted or substituted ring.

3. A compound of Claim 2, represented by the structure of **Formula III**:



(III)

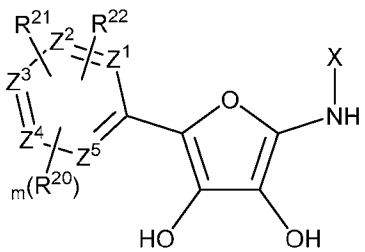
wherein R^{20}, R^{21}, and R^{22} are independently selected from the group consisting of H, -F, -Cl, -Br, -I, -OH, -SH, -CN, NO_2 -NO, $-NH_2$, -NHR, -NRR, -C(O)R, -C(O)OH, -C(O)OR, -C(O)NH2, -C(O)NHR, -C(O)NRR, -SOR, $-SO_2R$, $-SO_2NH_2$, $-SO_2NHR$, and $-SO_2NRR$;

wherein R^{30} is selected from the group consisting of hydrogen, (C_1-C_5) alkyl, substituted (C_1-C_6) alkyl, (C_2-C_6) alkenyl, substituted (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, substituted (C_2-C_6) alkynyl, (C_5-C_{20}) aryl, substituted (C_5-C_{20}) aryl, (C_6-C_{26}) arylalkyl, substituted (C_6-C_{26}) arylalkyl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, 6-26 membered heteroarylalkyl or substituted 6-26 membered heteroarylalkyl ;

wherein Z^1, Z^2, Z^3, Z^4, Z^5 are independently selected from C, N;

wherein W is selected from the group consisting of hydrogen, alkyl, haloalkyl, -C(O)R, -C(O)OR, -SOR, $-SO_2R$, -C(O)NHR, -C(O)NRR where each R is independently (C_1-C_5) alkyl, substituted (C_1-C_6) alkyl, (C_2-C_6) alkenyl, substituted (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, substituted (C_2-C_6) alkynyl, (C_5-C_{20}) aryl, substituted (C_5-C_{20}) aryl, (C_6-C_{26}) arylalkyl, substituted (C6-C26) arylalkyl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, 6-26 membered heteroarylalkyl or substituted 6-26 membered heteroarylalkyl.

4. A compound of Claim 3, represented by the structure of **Formula IV**:



(IV)

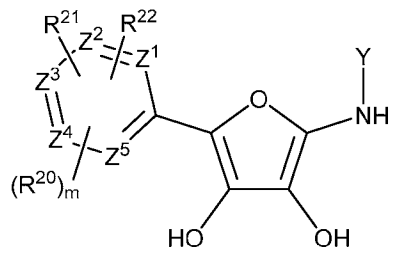
wherein R^{20}, R^{21}, and R^{22} are independently selected from the group consisting of H, -F, -Cl, -Br, -I, -OH, -SH, -CN, NO_2 -NO, $-NH_2$, -NHR, -NRR, -C(O)R, -C(O)OH, -C(O)OR, -C(O)NH2, -C(O)NHR, -C(O)NRR, -SOR, $-SO_2R$, $-SO_2NH_2$, $-SO_2NHR$, and $-SO_2NRR$;

wherein Z^1, Z^2, Z^3, Z^4, Z^5 are independently selected from C, N;

wherein X is selected from the group consisting of SO_2R,

where each R is independently (C_1-C_5) alkyl, substituted (C_1-C_6) alkyl, (C_2-C_6) alkenyl, substituted (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, substituted (C_2-C_6) alkynyl, (C_5-C_{20}) aryl, substituted (C_5-C_{20}) aryl, (C_6-C_{26}) arylalkyl, substituted (C_6-C_{26}) arylalkyl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, 6-26 membered heteroarylalkyl or substituted 6-26 membered heteroarylalkyl.

5. A compound of Claim 4, represented by the structure of **Formula V**:



(V)

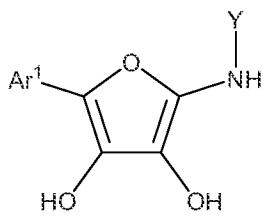
wherein R^{20}, R^{21}, and R^{22} are independently selected from the group consisting of H, -F, -Cl, -Br, -I, -OH, -SH, -CN, NO_2 -NO, $-NH_2$. -NHR, -NRR, -C(O)R, -C(O)OH, -C(O)OR, $-C(O)NH_2$, -C(O)NHR, -C(O)NRR, -SOR, $-SO_2R$, $-SO_2NH_2$, $-SO_2NHR$, and $-SO_2NRR$; and

wherein Z^1, Z^2, Z^3, Z^4, Z^5 are independently selected from C, N;

wherein Y is selected from the group consisting of SO_2R,

where each R is independently (C_1-C_5) alkyl, substituted (C_1-C_6) alkyl, (C_2-C_6) alkenyl, substituted (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, and substituted (C_2-C_6) alkynyl.

6. A compound of Claim 5, represented by the structure of **Formula VI**:

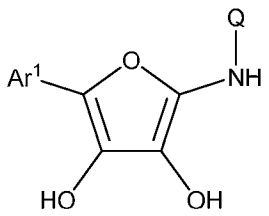


(VI)

wherein Ar^1 is selected from the group consisting of phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-thiophene, 2-furan, 2-thiazole, 1-naphthyl, 2-napthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3-cyanophenyl, and 4-cyanophenyl; and

wherein Y is selected from the group consisting of SO_2R, where R is independently $(C_1\text{-}C_5)$ alkyl, substituted $(C_1\text{-}C_6)$ alkyl, $(C_2\text{-}C_6)$ alkenyl, substituted $(C_2\text{-}C_6)$ alkenyl, $(C_2\text{-}C_6)$ alkynyl, and substituted $(C_2\text{-}C_6)$ alkynyl.

7. A compound of Claim 6, represented by the structure of **Formula VII**:



(VII)

wherein Ar^1 is selected from the group consisting of phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 3-cyanophenyl; and

wherein Q is selected from the group consisting of SO_2R, where R is independently $(C_1\text{-}C_5)$ alkyl, substituted $(C_1\text{-}C_6)$ alkyl.

8. A compound of claim 1, selected from the group consisting of the following named compounds:

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)methanesulfonamide;

N-(3,4-dihydroxy-5-(2-chlorophenyl)-2-furanyl)ethanesulfonamide;

N-(3,4-dihydroxy-5-(3-chlorophenyl)-2-furanyl)ethanesulfonamide;

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)ethanesulfonamide;

N-(3,4-dihydroxy-5-(2-fluorophenyl)-2-furanyl)ethanesulfonamide;

N-(3,4-dihydroxy-5-(3-fluorophenyl)-2-furanyl)ethanesulfonamide;

N-(3,4-dihydroxy-5-(4-fluorophenyl)-2-furanyl)ethanesulfonamide;

N-(3,4-dihydroxy-5-(4-trifluoromethylphenyl)-2-furanyl)ethanesulfonamide;

N-(3,4-dihydroxy-5-(4-nitrilephenyl)-2-furanyl)ethanesulfonamide;

N-(3,4-dihydroxy-5-(3-nitrilephenyl)-2-furanyl)ethanesulfonamide;

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-1-propylsulfonamide;

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-2-propylsulfonamide;

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-1-butylsulfonamide;

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-1-propyl-2-methylsulfonamide;

N-methyl-N'-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)ethanesulfonamide;

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)benzenesulfonamide;

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)benzylsulfonamide;

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)-1,1-dioxide-isothiazolidine;

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)acetamide;

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)benzamide;

N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)- carbamic acid ethyl ester;

Thiourea, N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)- N'-methyl;

Thiourea, N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)- N'-ethyl; and

Thiourea, N-(3,4-dihydroxy-5-(4-chlorophenyl)-2-furanyl)- N'-phenyl.

8. A pharmaceutical composition comprising at least one pharmaceutically-acceptable excipient and a therapeutically effective amount of the compound or salt according to any one of claims 1-7.

9. A method of modulating the level or activity of at least one polypeptide having Fe(II) and 2-oxoglutarate (2OG) dependent oxygenase activity in a cell or tissue comprising

(a) contacting the cell with the compound of claim 1; and

(b) measuring the level or activity of said polypeptide.

10. The method of claim 9, wherein at least one of said polypeptides is an Fe(II) and 2-oxoglutarate (2OG)-dependent selected from the group consisting of

(a) polypeptide hydroxylases;

(b) polypeptide demethylases; and

(c) nucleic acid hydroxylases.

11. The method of claim 10, wherein at least one of said polypeptides is a polypeptide hydroxylase selected from the group consisting of FIH, ASPH, PHD, C-P4H, C-P3H, and PLODs.

12. The method of claim 10, wherein at least one of said polypeptides is a polypeptide demethylase selected from the group consisting of lysine demethylases (KDM) and PHF8.

13. The method of claim 10, wherein at least one of said polypeptides is a nucleic acid hydrolase hydroxylase selected from the group consisting of FTO, TET1-3, and AlkBH1-8.

14. The method of claim 13, wherein at least one of said polypeptides is FTO.

15. The method of claim 9, wherein said cell or tissue is a vertebrate cell or tissue.

16. The method of claim 15, wherein said vertebrate cell or tissue is a mammalian cell or tissue.

17. The method of claim 16, wherein said mammalian cell or tissue is a mammalian cell or tissue.

18. The method of claim 17, wherein said mammalian cell or tissue is a human cell or tissue.

19. A method of modulating the level or activity of at least one polypeptide having Fe(II) and 2-oxoglutarate (2OG)-dependent oxygenase activity in a subject, which comprises:

(a) administering a therapeutically-effective amount of a compound of claim 1 to said subject;

(b) measuring the level or activity of said polypeptide.

20. The method of claim 19, wherein at least one of said polypeptides is an Fe(II) and 2-oxoglutarate (2OG) dependent selected from the group consisting of

(a) polypeptide hydroxylases;

(b) polypeptide demethylases; and

(c) nucleic acid hydroxylases.

21. The method of claim 20, wherein at least one of said polypeptides is a polypeptide hydroxylase selected from the group consisting of FIH, ASPH, PHD, C-P4H, C-P3H, and PLODs.

22. The method of claim 20, wherein at least one of said polypeptides is a polypeptide demethylase selected from the group consisting of lysine demethylase (KDM) and PHF8.

23. The method of claim 20, wherein at least one of said polypeptides is a nucleic acid hydrolase hydroxylase selected from the group consisting of FTO, TET1-3, and AlkBH1-8.

24. The method of claim 23, wherein at least one of said polypeptides is FTO.

25. The method of claim 19, wherein said cell or tissue is a vertebrate cell or tissue.

26. The method of claim 25, wherein said vertebrate cell or tissue is a mammalian cell or tissue.

27. The method of claim 26, wherein said mammalian cell or tissue is a mammalian cell or tissue.

28. The method of claim 27, wherein said mammalian cell or tissue is a human cell or tissue.

29. A method of preventing, ameliorating, or treating at least one FTO-mediated condition or disease in a subject, comprising administering to said subject a therapeutically-effective amount of the compound or salt according to claim 1, wherein said condition or disease is selected from the group consisting of neurological disorders, degenerative central nervous system disorders, metabolic disorders, and drug abuse.

30. The method of claim 29, wherein said condition or disease is a neurological disorder.

31. The method of claim 30, wherein said neurological disorder is selected from the group consisting of epilepsy, epileptogenesis, depression, and stroke.

32. The method of claim 29, wherein said condition or disease is a degenerative disorder selected from the group consisting of Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, traumatic brain injury, and multiple sclerosis.

33. The method of claim 29, wherein said condition or disease is a metabolic disorder.

34. The method of claim 33, wherein said metabolic disorder is selected from the group consisting of diabetes, anemia, renal failure-associated anemia, and obesity.

35. The method of claim 34, wherein said metabolic disorder is obesity.

36. The method of claim 29, wherein said condition or disease is drug abuse.

37. The method of claim 29, wherein said subject is a mammal.

38. The method of claim 37, wherein said mammal is a human.

Mechanism of Action of FTO Modulators

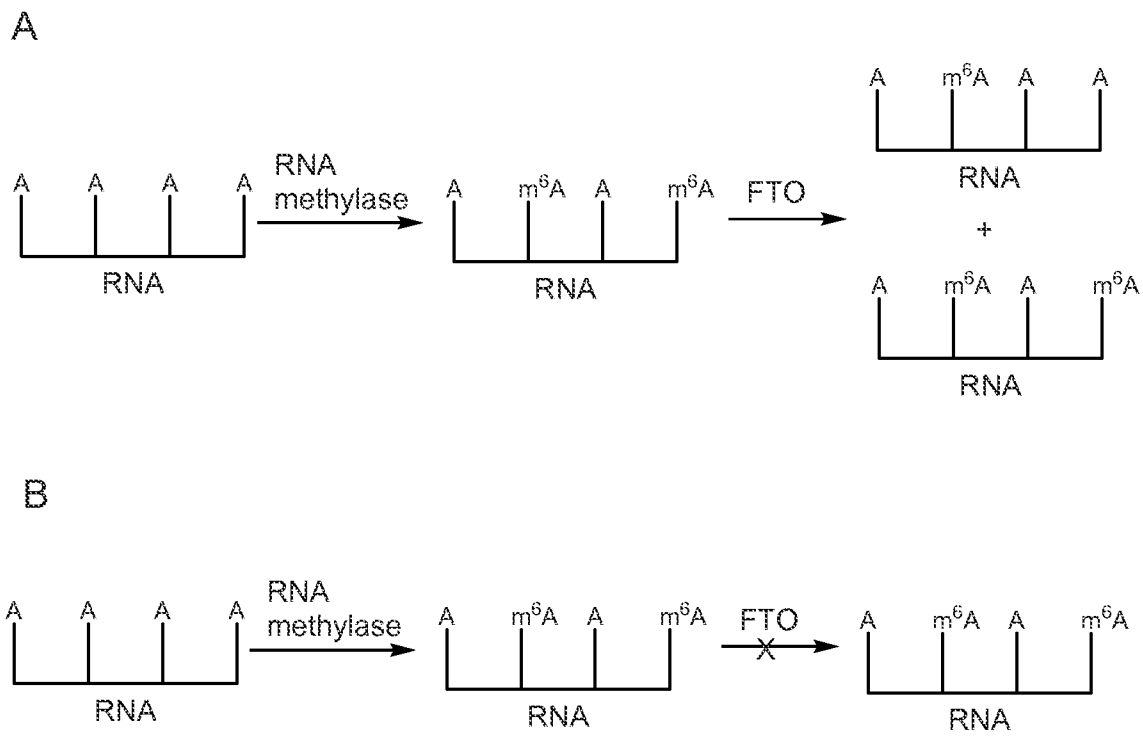


Figure 1

FTO Modulator Synthesis

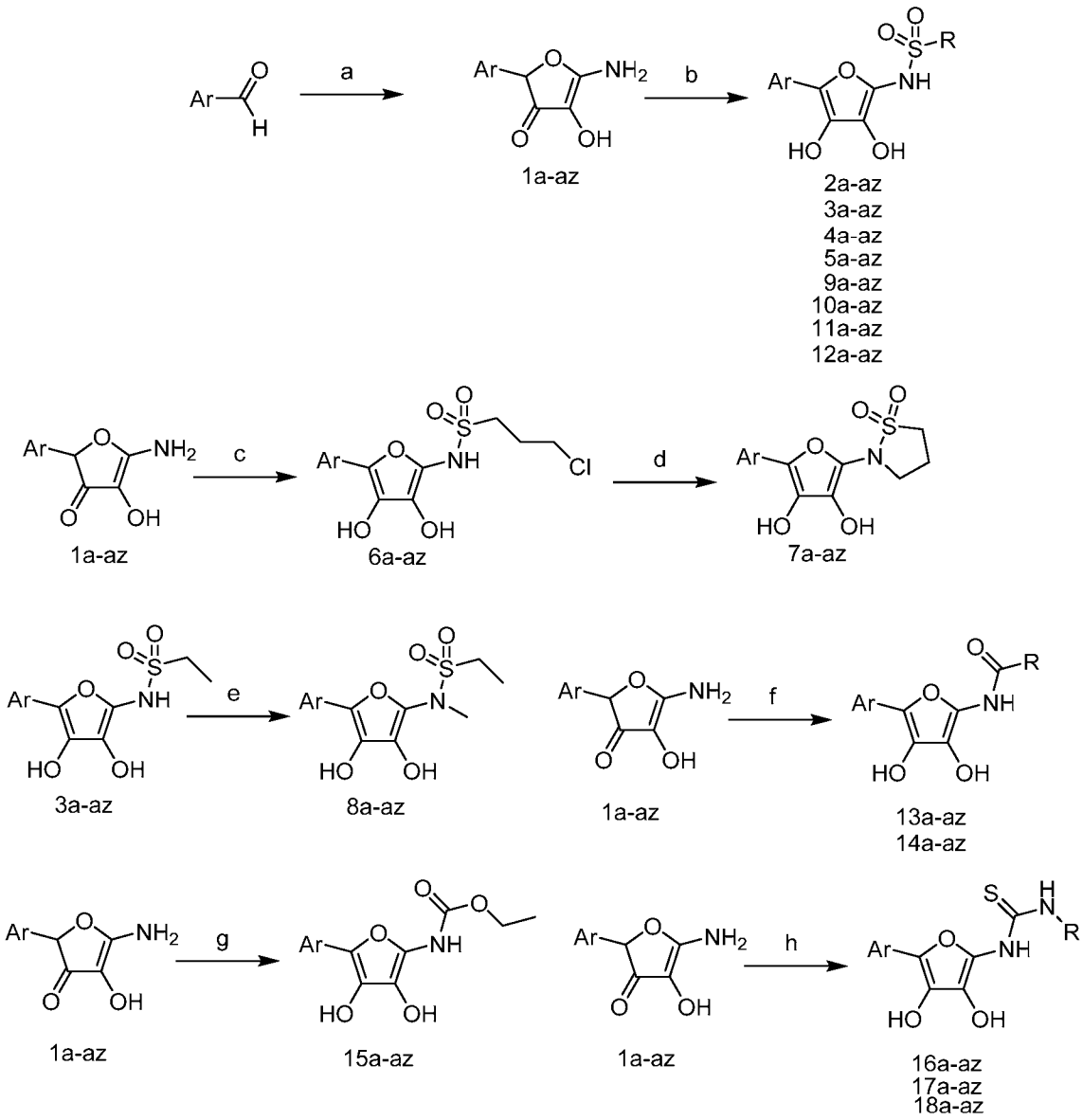


Figure 2

Neuroprotective Effects of FTO modulators

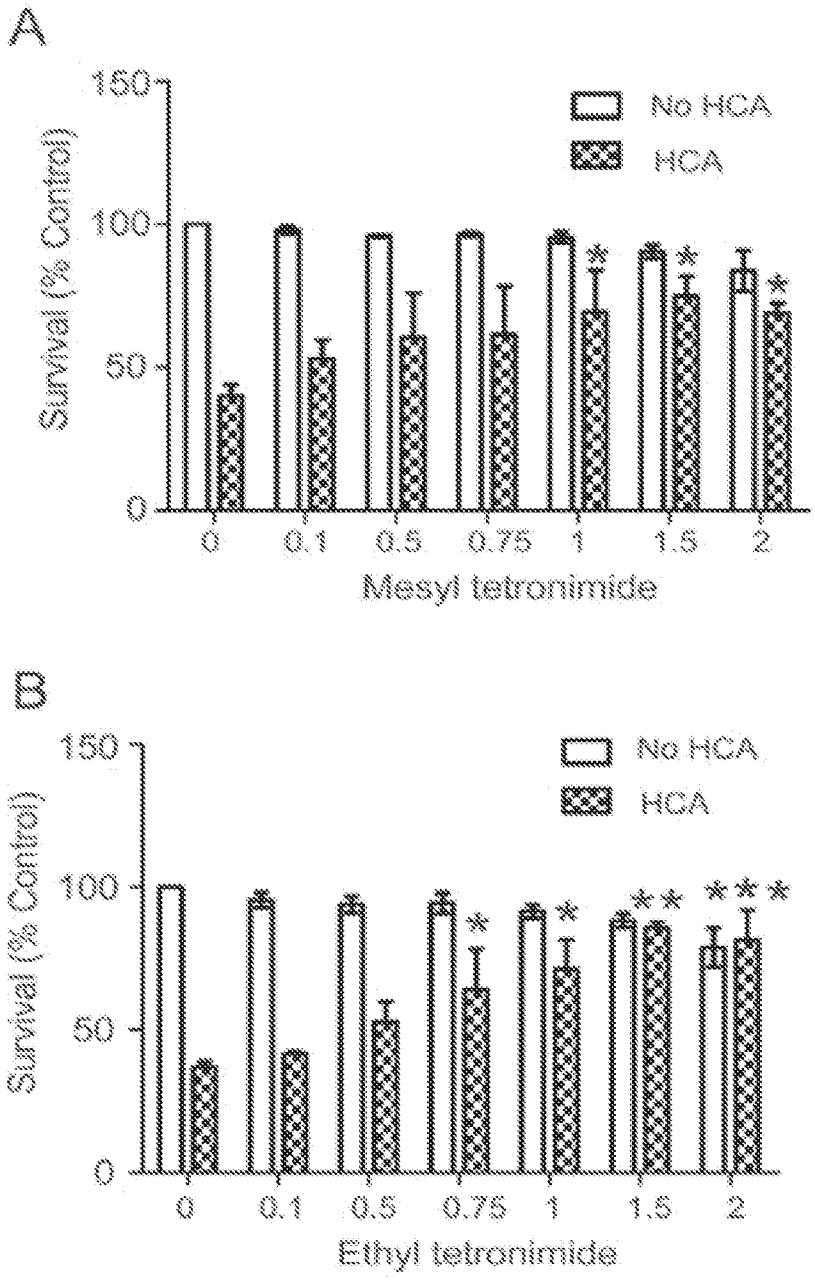


Figure 3 (Panels 3A and 3B)

Neuroprotective Effects of FTO modulators (Continued)

C

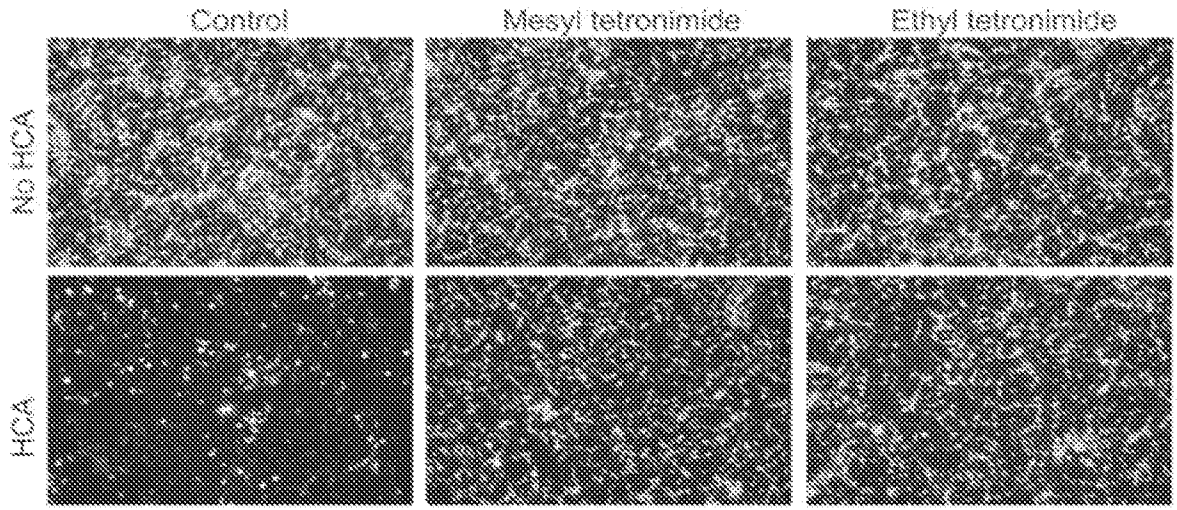


Figure 3 (Panel 3C)

Modulation of FTO Enzyme Activity

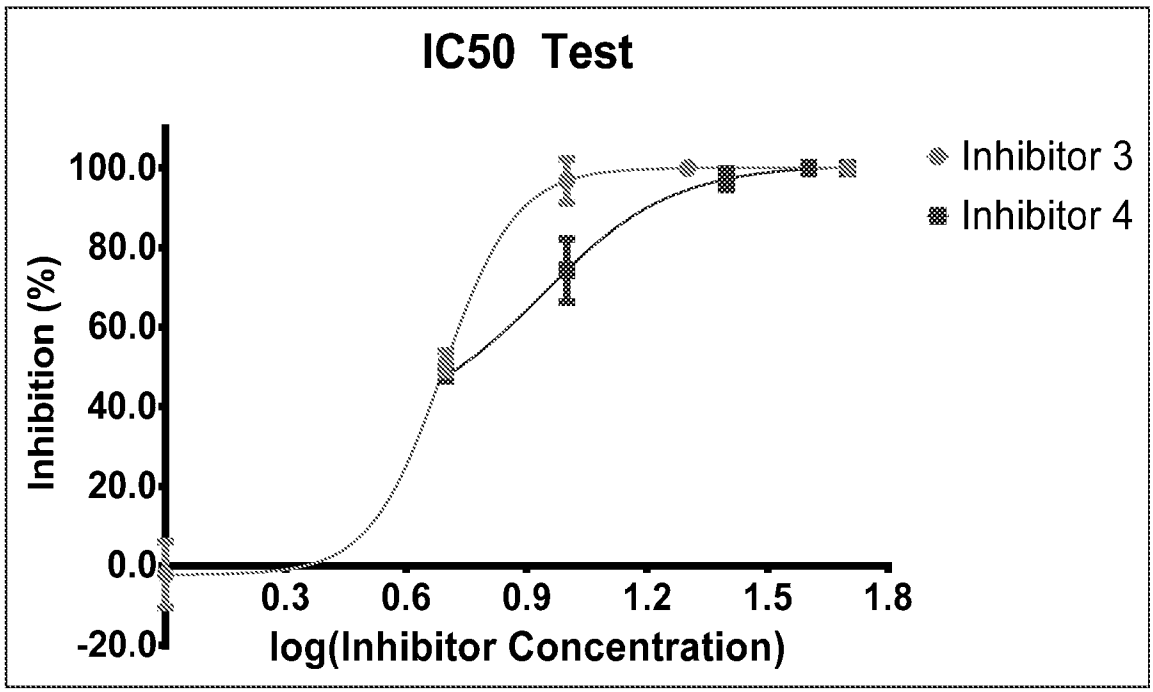


Figure 4

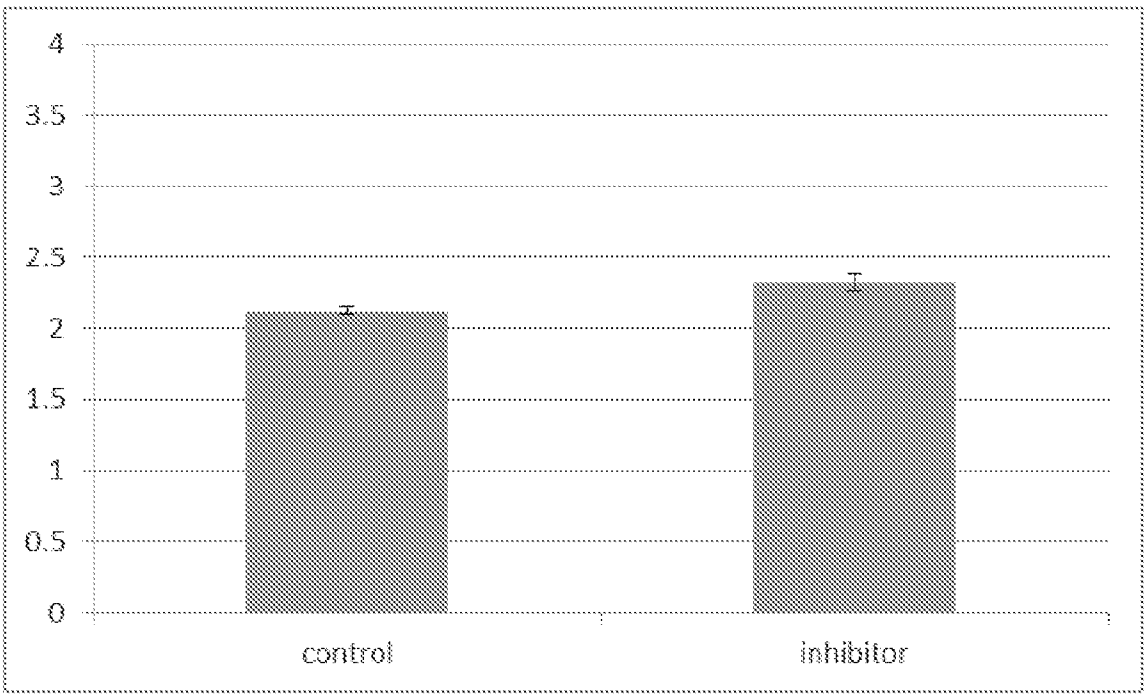

Modulation of Cellular m6A
4
3.5
3
2.5
2
1.5
1
0.5
0
control
inhibitor

Figure 5