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(54) **N-(3-(2-(4-CHLOROPHENOXY) ACETAMIDO)BICYCLO[1.1.1] PENTAN-1-YL)-2-CYCLOBUTANE-1-CARBOXAMIDE DERIVATIVES AND RELATED COMPOUNDS AS ATF4 INHIBITORS FOR TREATING CANCER AND OTHER DISEASES**

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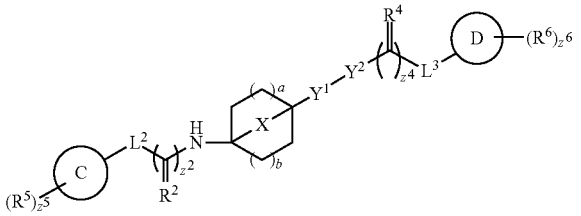
(57) **ABSTRACT**

The invention is directed to substituted bridged cycloalkane derivatives. Specifically, the invention is directed to compounds according to Formula I:

(I)



wherein X, a, b, C, D, L^2, L^3, Y^1, Y^2, R^2, R^4, R^5, R^6, z^2, z^4, z^5, and z^6 are as defined herein, and salts thereof.

The invention is further directed to pharmaceutical compositions comprising a compound of the invention. The invention is still further directed to methods of inhibiting the ATF4 pathway and treatment of disorders associated therewith using a compound of the invention or a pharmaceutical composition comprising a compound of the invention.

N-(3-(2-(4-CHLOROPHENOXY)ACETAMIDO) BICYCLO[1.1.1] PENTAN-1-YL)-2-CYCLOBUTANE-1-CARBOXAMIDE DERIVATIVES AND RELATED COMPOUNDS AS ATF4 INHIBITORS FOR TREATING CANCER AND OTHER DISEASES

FIELD OF THE INVENTION

[0001] The present invention relates to substituted bridged cycloalkane derivatives. The present invention also relates to pharmaceutical compositions comprising such compounds and methods of using such compounds in the treatment of diseases/injuries associated with activated unfolded protein response pathways, such as cancer, pre-cancerous syndromes, Alzheimer's disease, spinal cord injury, traumatic brain injury, ischemic stroke, stroke, diabetes, Parkinson disease, Huntington's disease, Creutzfeldt-Jakob Disease, and related prion diseases, progressive supranuclear palsy, amyotrophic lateral sclerosis, myocardial infarction, cardiovascular disease, inflammation, fibrosis, chronic and acute diseases of the liver, chronic and acute diseases of the lung, chronic and acute diseases of the kidney, chronic traumatic encephalopathy (CTE), neurodegeneration, dementia, traumatic brain injury, cognitive impairment, atherosclerosis, ocular diseases, arrhythmias, in organ transplantation and in the transportation of organs for transplantation.

BACKGROUND OF THE INVENTION

[0002] In metazoa, diverse stress signals converge at a single phosphorylation event at serine 51 of a common effector, the translation initiation factor eIF2α. This step is carried out by four eIF2a kinases in mammalian cells: PERK, which responds to an accumulation of unfolded proteins in the endoplasmic reticulum (ER), GCN2 to amino acid starvation and UV light, PKR to viral infection, and HRI to heme deficiency. This collection of signaling pathways has been termed the "integrated stress response" (ISR), as they converge on the same molecular event. eIF2a phosphorylation results in an attenuation of translation with consequences that allow cells to cope with the varied stresses (1).

[0003] eIF2 (which is comprised of three subunits, α, β, and γ) binds GTP and the initiator Met-tRNA to form the ternary complex (eIF2-GTP-Met-tRNAi), which, in turn, associates with the 40S ribosomal subunit scanning the 5'UTR of mRNAs to select the initiating AUG codon. Upon phosphorylation of its a-subunit, eIF2 becomes a competitive inhibitor of its GTP-exchange factor (GEF), eIF2B (2). The tight and nonproductive binding of phosphorylated eIF2 to eIF2B prevents loading of the eIF2 complex with GTP thus preventing ternary complex formation and reducing translation initiation (3). Because eIF2B is less abundant than eIF2, phosphorylation of only a small fraction of the total eIF2 has a significant impact on eIF2B activity in cells.

[0004] Paradoxically, under conditions of reduced protein synthesis, a select group of mRNAs that contain upstream open reading frames (uORFs) in their 5'UTR are translationally up-regulated (4,5). These include mammalian ATF4 (a cAMP element binding (CREB) transcription factor) and CHOP (a pro-apoptotic transcription factor) (6-8). ATF4 regulates the expression of many genes involved in metabolism and nutrient uptake and additional transcription factors, such as CHOP, which is under both translational and transcriptional control (9). Phosphorylation of eIF2a thus leads to preferential translation of key regulatory molecules and directs diverse changes in the transcriptome of cells upon cellular stress.

[0005] One of the eIF2a kinases, PERK, lies at the intersection of the ISR and the unfolded protein response (UPR) that maintains homeostasis of protein folding rates in the ER (10). The UPR is activated by unfolded or misfolded proteins that accumulate in the ER lumen because of an imbalance between protein folding load and protein folding capacity, a condition known as "ER stress". In mammals, the UPR is comprised of three signaling branches mediated by ER-localized transmembrane sensors, PERK, IRE1, and ATF6. These sensor proteins detect the accumulation of unfolded protein in the ER and transmit the information across the ER membrane, initiating unique signaling pathways that converge in the activation of an extensive transcriptional response, which ultimately results in ER expansion (11). The lumenal stress-sensing domains of PERK and IRE1 are homologous and likely activated in analogous ways by direct binding to unfolded peptides (12). This binding event leads to oligomerization and trans-autophosphorylation of their cytosolic kinase domains, and, for PERK, phosphorylation of its only known substrate, eIF2α. In this way, PERK activation results in a quick reduction in the load of newly synthesized proteins that are translocated into the ER-lumen (13).

[0006] Upon ER stress, both the transcription factor XBP1s, produced as the consequence of a non-conventional mRNA splicing reaction initiated by IRE1, and the transcription factor ATF6, produced by proteolysis and release from the ER membrane, collaborate with ATF4 to induce the vast UPR transcriptional response. Transcriptional targets of the UPR include the ER protein folding machinery, the ER-associated degradation machinery, and many other components functioning in the secretory pathway (14). Although the UPR initially mitigates ER stress and as such confers cytoprotection, persistent and severe ER stress leads to activation of apoptosis that eliminates damaged cells (15, 16).

[0007] Small-molecule therapeutics that inhibit the UPR and/or the Integrated Stress Response could be used in cancer as a single agent or in combination with other chemotherapeutics (17, 18, 19), for enhancement of long-term memory (24,25), in neurodegenerative and prion associated diseases (20), in white matter disease (VWM) (23) and in biotechnology applications that would benefit from increased protein translation.

[0008] It is an object of the instant invention to provide novel compounds that prevent the translation of ATF4 or are inhibitors of the ATF4 pathway.

[0009] It is also an object of the present invention to provide pharmaceutical compositions that comprise a pharmaceutically acceptable excipient and compounds of Formula (I).

[0010] It is also an object of the present invention to provide a method for treating neurodegenerative diseases, cancer, and other diseases/injuries associated with activated unfolded protein response pathways such as: Alzheimer's disease, spinal cord injury, traumatic brain injury, ischemic stroke, stroke, diabetes, Parkinson disease, Huntington's disease, Creutzfeldt-Jakob Disease, and related prion diseases, amyotrophic lateral sclerosis, progressive supra-

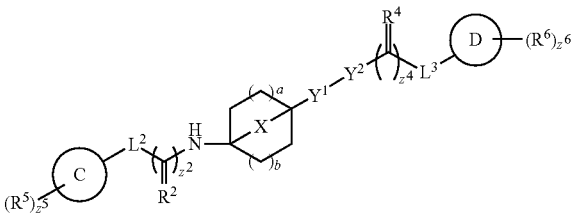
nuclear palsy, myocardial infarction, cardiovascular disease, inflammation, fibrosis, chronic and acute diseases of the liver, chronic and acute diseases of the lung, chronic and acute diseases of the kidney, chronic traumatic encephalopathy (CTE), neurodegeneration, dementias, traumatic brain injuries, atherosclerosis, ocular diseases, arrhythmias, in organ transplantation and in the transportation of organs for transplantation that comprises administering novel inhibitors of the ATF4 pathway.

SUMMARY OF THE INVENTION

[0011] The invention is directed to substituted bridged cycloalkane derivatives.

[0012] Specifically, the invention is directed to compounds according to Formula I:

(I)



wherein X, a, b, C, D, L^2, L^3, Y^1, Y^2, R^2, R^4, R^5, R^6, z^2, z^4, z^5, and z^6 are as defined below; or a salt thereof including a pharmaceutically acceptable salt thereof.

[0013] The present invention also relates to the discovery that the compounds of Formula (I) are active as inhibitors of the ATF4 pathway.

[0014] The present invention also relates to the discovery that the compounds of Formula (I) prevent the translation of ATF4.

[0015] This invention also relates to a method of treating Alzheimer's disease, which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0016] This invention also relates to a method of treating Parkinson's disease, which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0017] This invention also relates to a method of treating amyotrophic lateral sclerosis, which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0018] This invention also relates to a method of treating Huntington's disease, which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0019] This invention also relates to a method of treating Creutzfeldt-Jakob Disease, which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0020] This invention also relates to a method of treating progressive supranuclear palsy (PSP), which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0021] This invention also relates to a method of treating dementia, which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0022] This invention also relates to a method of treating spinal cord injury, which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0023] This invention also relates to a method of treating traumatic brain injury, which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0024] This invention also relates to a method of treating ischemic stroke, which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0025] This invention also relates to a method of treating diabetes, which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0026] This invention also relates to a method of treating a disease state selected from: myocardial infarction, cardiovascular disease, atherosclerosis, ocular diseases, and arrhythmias, which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0027] This invention also relates to a method of treating an integrated stress response-associated disease in a patient in need of such treatment, the method including administering a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, to the patient.

[0028] This invention also relates to a method of treating a disease associated with phosphorylation of eIF2α in a patient in need of such treatment, the method including administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the patient.

[0029] This invention also relates to a method of treating a disease in a patient in need of such treatment, the method including administering a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, to the patient, wherein the disease is selected from the group consisting of cancer, a neurodegenerative disease, vanishing white matter disease, childhood ataxia with CNS hypomyelination, and an intellectual disability syndrome.

[0030] This invention also relates to a method of improving long-term memory in a patient, the method including administering a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, to the patient.

[0031] This invention also relates to a method of increasing protein expression of a cell or in vitro expression system, the method including administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, to the cell or expression system.

[0032] This invention also relates to a method of treating an inflammatory disease in a patient in need of such treatment, the method including administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the patient.

[0033] This invention also relates to a method of using the compounds of Formula (I) in organ transplantation and in the transportation of organs for transplantation.

[0034] Also included in the present invention are methods of co-administering the presently invented compounds with further active ingredients.

[0035] Included in the present invention is a method for treating neurodegenerative diseases, cancer, and other diseases/injuries associated with activated unfolded protein response pathways such as: Alzheimer's disease, spinal cord injury, traumatic brain injury, ischemic stroke, stroke, diabetes, Parkinson disease, Huntington's disease, Creutzfeldt-Jakob Disease, and related prion diseases, amyotrophic lateral sclerosis, progressive supranuclear palsy, myocardial infarction, cardiovascular disease, inflammation, fibrosis, chronic and acute diseases of the liver, chronic and acute diseases of the lung, chronic and acute diseases of the kidney, chronic traumatic encephalopathy (CTE), neurodegeneration, dementias, traumatic brain injuries, atherosclerosis, ocular diseases, arrhythmias, in organ transplantation and in the transportation of organs for transplantation that comprises administering the compounds of Formula (I).

[0036] The invention also relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in therapy.

[0037] The invention also relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of Alzheimer's disease.

[0038] The invention also relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of Parkinson's disease syndromes.

[0039] The invention also relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of amyotrophic lateral sclerosis.

[0040] The invention also relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of Huntington's disease.

[0041] The invention also relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of Creutzfeldt-Jakob Disease.

[0042] The invention also relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of progressive supranuclear palsy (PSP).

[0043] The invention also relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of dementia.

[0044] The invention also relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of spinal cord injury.

[0045] The invention also relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of traumatic brain injury.

[0046] The invention also relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of ischemic stroke.

[0047] The invention also relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of diabetes.

[0048] The invention also relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of a disease state selected from: myocardial infarction, cardiovascular disease, atherosclerosis, ocular diseases, and arrhythmias.

[0049] The invention also relates to the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of an integrated stress response-associated disease.

[0050] The invention also relates to the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease associated with phosphorylation of eIF2α.

[0051] The invention also relates to the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease selected from the group consisting of: cancer, a neurodegenerative disease, vanishing white matter disease, childhood ataxia with CNS hypomyelination, and an intellectual disability syndrome.

[0052] The invention also relates to the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for improving long-term memory.

[0053] The invention also relates to the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for increasing protein expression of a cell or in vitro expression system.

[0054] The invention also relates to the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of inflammatory disease.

[0055] The invention also relates to the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament in organ transplantation and in the transportation of organs for transplantation.

[0056] The invention also relates to the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease state selected from: neurodegenerative diseases, cancer, and other diseases/injuries associated with activated unfolded protein response pathways such as: Alzheimer's disease, spinal cord injury, traumatic brain injury, ischemic stroke, stroke, diabetes, Parkinson disease, Huntington's disease, Creutzfeldt-Jakob Disease, and related prion diseases, amyotrophic lateral sclerosis, progressive supranuclear palsy, myocardial infarction, cardiovascular disease, inflammation, fibrosis, chronic and acute diseases of the liver, chronic and acute diseases of the lung, chronic and acute diseases of the kidney, chronic traumatic encephalopathy (CTE), neurodegeneration, dementias, traumatic brain injuries, atherosclerosis, ocular diseases, arrhythmias, in organ transplantation and in the transportation of organs for transplantation.

[0057] Included in the present invention are pharmaceutical compositions that comprise a pharmaceutical excipient and a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

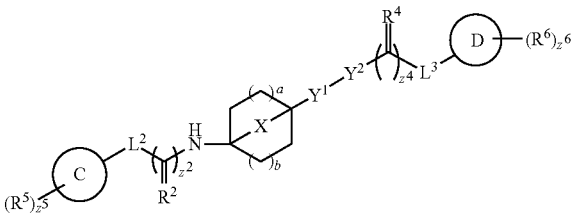
[0058] The invention also relates to a pharmaceutical composition as defined above for use in therapy.

[0059] The invention also relates to a combination for use in therapy which comprises a therapeutically effective amount of (i) a compound of Formula (I) or a pharmaceutically acceptable salt thereof; and (ii) further active ingredients.

DETAILED DESCRIPTION OF THE INVENTION

[0060] Included in the compounds of the invention and used in the methods of the invention are compounds of Formula (I):

(I)



[0061] wherein:

[0062] L^2 is a bond or selected from: —NR^9—, —O—, —S—, —S(O)—, —$S(O)_2$—, C_{1-8}alkylene, substituted C_{1-8}alkylene, C_{1-8}alkyl, substituted C_{1-8}alkyl, C_{1-8}heteroalkylene, substituted C_{1-8}heteroalkylene, C_{1-8}heteroalkyl, and substituted C_{1-8}heteroalkyl;

[0063] L^3 is absent, a bond or selected from: —NR^9—, —O—, —S—, —S(O)—, —$S(O)_2$—, C_{1-8}alkylene, substituted C_{1-8}alkylene, C_{1-8}alkyl, substituted C_{1-8}alkyl, C_{1-8}heteroalkyl, substituted C_{1-8}heteroalkyl, C_{1-8}heteroalkylene and substituted C_{1-8}heteroalkylene;

[0064] Y^1 is selected from: NH—, NH_2, a nitrogen linked heterocycloalkyl, and a substituted nitrogen linked heterocycloalkyl;

[0065] Y^2 is absent, a bond or selected from: C_{1-2}alkylene and C_{1-2}alkylene substituted from 1 to 4 times by fluoro;

[0066] R^5 and R^6, when present, are independently selected from: fluoro, chloro, bromo, iodo, oxo, —OCH_3, —OCH_2Ph, —C(O)Ph, —CH_3, —CF_3, —CHF_2, —CH_2F, —CN, —S(O)CH_3, —$S(O)_2CH_3$, —OH, —NH_2, —$NHCH_3$, —$N(CH_3)_2$, —COOH, —$CONH_2$, —NO_2, —$C(O)CH_3$, —$CH(CH_3)_2$, —$C(CF_3)_3$, —$C(CH_3)_3$, —CH_2—CF_3, —CH_2—CH_3, —CCH, —CH_2CCH, —SO_3H, —SO_2NH_2, —NHC(O)NH_2, —NHC(O)H, —NHOH, —OCF_3, —$OCHF_2$, C_{1-6}alkyl, substituted C_{1-6}alkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

[0067] R^2 and R^4, when present, are independently selected from: NR^8, O, CH_2, and S;

[0068] R^8 is selected from: hydrogen, —OH, C_{1-6}alkyl and C_{1-6}alkyl substituted 1 to 6 times By fluoro;

[0069] R^9 is selected from: hydrogen, C_{1-6}alkyl and C_{1-6}alkyl substituted 1 to 6 times by fluoro;

[0070] a and b are independently 0 or 1;

[0071] C is absent or selected from: phenyl, pyridyl, and cycloalkyl;

[0072] D is absent or selected from: cycloalkyl, and substituted cycloalkyl, heterocycloalkyl, and substituted heterocycloalkyl;

[0073] X is C_{1-3}alkyl or C_{1-3}alkyl substituted 1 to 3 times by fluoro;

[0074] z^2 and z^4 are independently 0 or 1; and

[0075] z^5 and z^6 are independently an integer from 0 to 5;

[0076] provided:

[0077] when Y^1 is NH_2, heterocycloalkyl, or substituted heterocycloalkyl; Y^2, L^3, and D are absent and z^6 is 0;

[0078] when L^2 is monovalent; C is absent and z^5 is 0; and

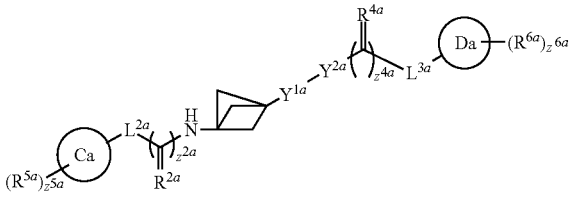
[0079] when L^3 is monovalent; D is absent and z^6 is 0;

and salts thereof.

[0080] This invention also relates to pharmaceutically acceptable salts of the compounds of Formula (I).

[0081] Included in the compounds of the invention and used in the methods of the invention are compounds of Formula (IA):

(IA)



wherein:

[0082] L^{2a} is a bond or selected from: —NR^9—, —O—, —S—, —S(O)—, —$S(O)_2$—, C_{1-8}alkylene, substituted C_{1-8}alkylene, C_{1-8}alkyl, substituted C_{1-8}alkyl, C_{1-8}heteroalkylene, substituted C_{1-8}heteroalkylene, C_{1-8}heteroalkyl, and substituted C_{1-8}heteroalkyl;

[0083] L^{3a} is absent, a bond or selected from: —NR^9—, —O—, —S—, —S(O)—, —$S(O)_2$—, C_{1-8}alkylene, substituted C_{1-8}alkylene, C_{1-8}alkyl, substituted C_{1-8}alkyl, C_{1-8}heteroalkyl, substituted C_{1-8}heteroalkyl, C_{1-8}heteroalkylene and substituted C_{1-8}heteroalkylene;

[0084] Y^{1a} is selected from: NH—, NH_2, a nitrogen linked heterocycloalkyl, and a substituted nitrogen linked heterocycloalkyl;

[0085] Y^{2a} is absent, a bond or selected from: C_{1-2}alkylene and C_{1-2}alkylene substituted from 1 to 4 times by fluoro;

[0086] R^{5a} and R^{6a}, when present, are independently selected from: fluoro, chloro, bromo, iodo, oxo, —OCH_3, —OCH_2Ph, —C(O)Ph, —CH_3, —CF_3, —CHF_2, —CH_2F, —CN, —S(O)CH_3, —$S(O)_2CH_3$, —OH, —NH_2, —$NHCH_3$, —$N(CH_3)_2$, —COOH, —$CONH_2$, —NO_2, —$C(O)CH_3$, —$CH(CH_3)_2$, —$C(CF_3)_3$, —$C(CH_3)_3$, —CH_2—CF_3, —CH_2—CH_3, —CCH, —CH_2CCH, —SO_3H, —SO_2NH_2, —NHC(O)NH_2, —NHC(O)H, —NHOH, —OCF_3, —$OCHF_2$, C_{1-6}alkyl, substituted C_{1-6}alkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

[0087] R^{2a} and R^{4a}, when present, are independently selected from: NR^{8a}, O, CH2, and S;

[0088] R^{8a} is selected from: hydrogen, —OH, C_{1-6}alkyl and C_{1-6}alkyl substituted 1 to 6 times by fluoro;

[0089] R^{9a} is selected from: hydrogen, C_{1-6}alkyl and C_{1-6}alkyl substituted 1 to 6 times by fluoro;

[0090] Ca is absent or selected from: phenyl, pyridyl, and cycloalkyl;

[0091] Da is absent or selected from: cycloalkyl, and substituted cycloalkyl, heterocycloalkyl, and substituted heterocycloalkyl;

[0092] z^{2a} and z^{4a} are independently 0 or 1; and

[0093] z^{5a} and z^{6a} are independently an integer from 0 to 5;

[0094] provided:

[0095] when Y^{1a} is NH_2, heterocycloalkyl, or substituted heterocycloalkyl; Y^{2a}, L^{3a}, and Da are absent and z^{6a} is 0;

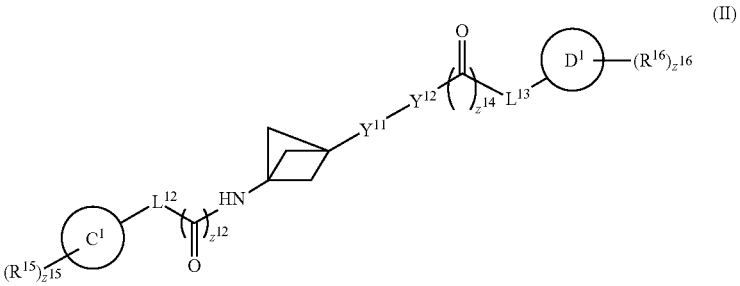
[0096] when L^{2a} is monovalent; Ca is absent and z^{5a} is 0; and

[0097] when L^{3a} is monovalent; Da is absent and z^{6a} is 0;

and salts thereof.

[0098] This invention also relates to pharmaceutically acceptable salts of the compounds of Formula (IA).

[0099] Included in the compounds of the invention and used in the methods of the invention are compounds of Formula (II):



(II)

wherein:

[0100] L^{12} is a bond or selected from: $—CH_2—O—$, and $—CH_2—CH_2—O—$;

[0101] L^{13} is a bond or selected from: $—CH_2—$, $—CH_2—O—CH_3$, $—CH_2—O—$, $—CH_2—O—CH_2—CH_3$, $—CH_2—O—CH_2—CH_2—CH_2—CH_3$, $—CH_2—O—CH_2—$, $—CH_2—O—CH_2—CH_2—CH_3$, $—CH_2—CH_2—CH_3$, $—CH_2—O—CH_2—CH(CH_3)_2$, $—CH_2—O—CH(CH_3)_2$, $—CH_2—O—C(CH_3)_3$, $—CH_2—O—CH_2—CF_3$, $—CH_2—O—C(CH_3)_2—CF_3$, $—CH_2—C(CH_3)_3$, $—CH_2—O—CH_2—(CH_3)_3$, $—CH_2—O—C(CH_3)H—CF_3$, $—CH_2—CH_2—C(CH_3)_3$, $—CH_2—CF_3$, $—CH_2—O—C(CH_3)H—$, $—CH_2—O—C(CH_3)H—CH_2—CH_3$, $—CH_3$, $—CH_2—CH_3$, $—CH_2—O—C(CH_3)H—CH_2—CH_2—CH_3$, $—CH_2—O—CH_2—CH_2—O—CH_3$, $—CH_2—O—C(CH_3)H—CH(CH_3)_2$, $—CH_2—O—C(CH_3)H—CH_2—$, $—CH_2—O—C(CH_3)_2—$, $—CH_2—O—C(CH_3)H—CH_2—O—CH_3$, $—C(CH_3)H—O—CH_3$, $—CH_2—CH_2—$, $—CH_2—CH_2—O—C(CH_3)H—$, $—CH_2—CH_2—O—$, $—CH_2—N(CH_3)_2$, $—CH_2—NH(CH_3)$, $—CH_2—N(CH_3)—CH(CH_3)—$, $—CH_2—N(CH_3)—CH_2—CH_2—CH_3$, $—CH_2—NH—CH_2—CH_2—CH_3$, $—N(CH_3)_2$, $—CH_2—NH—CH_2—CH_2—O—CH_3$, $—CH_2—NH—CH_2—CH_3$, $—NH(CH_3)$, $—CH_2—N(CH_3)—CH_2—CH_3$, $—CH_2—N(CH_3)—CH(CH_3)_2$, $—CH(CF_3)—N(CH_3)_2$, $—CH(N(CH_3)_2)—CH(CH_3)_2$, $—CH(CH_3)—N(CH_3)_2$, and $—C(CH_3)_2—N(CH_3)_2$;

[0102] Y^{11} is selected from: NH—, NH_2, a nitrogen linked heterocycloalkyl, and a nitrogen linked heterocycloalkyl substituted from 1 to 3 times by a substituent selected from: fluoro, chloro, bromo, iodo, oxo, $—OCH_3$, $—OCF_3$, $—CH_3$, and $—CF_3$;

[0103] Y^{12} is absent, a bond or selected from: $—CH_2—$, and $—CH_2—$, substituted once or twice by fluoro;

[0104] R^{15}, when present, is selected from chloro, $—C(CF_3)_3$, and $—C(CH_3)_3$;

[0105] R^{16}, when present, is selected from: fluoro, chloro, bromo, $—C(CF_3)_3$, $—C(CH_3)_3$, $—CH_2—CF_3$, $—CH_2—CH_3$, $—CH_3$, $—CF_3$, and $—N(CH_3)_2$;

[0106] C^1 is absent or selected from: phenyl, and cyclopropyl;

[0107] D^1 is absent or selected from: piperidinyl, cyclohexyl, cyclopropyl, cyclopentyl, cyclobutyl, pyrrolidinyl, tetrahydrofuranyl, and tetrahydropyranyl;

[0108] z^{12} and z^{14} are independently 0 or 1; and

[0109] z^{15} and z^{16} are independently an integer from 0 to 4;

[0110] provided:

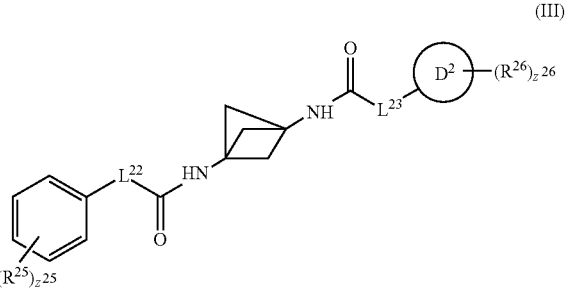
[0111] when Y^{11} is NH_2, heterocycloalkyl, or substituted heterocycloalkyl; Y^{12}, L^{13}, and D^1 are absent and z^{16} is 0; and

[0112] when L^{13} is monovalent; D^1 is absent;

and salts thereof.

[0113] This invention also relates to pharmaceutically acceptable salts of the compounds of Formula (II).

[0114] Included in the compounds of the invention and used in the methods of the invention are compounds of Formula (III):



(III)

wherein:

[0115] L^{22} is a bond or selected from: —CH_2—O—, and —CH_2—CH_2—O—;

[0116] L^{23} is a bond or selected from: —CH_2—, —CH_2—O—CH_3, —CH_2—O—, —CH_2—O—CH_2—CH_3, —CH_2—O—CH_2—CH_2—CH_2—CH_3, —CH_2—O—CH_2—, —CH_2—O—CH_2—CH_2—CH_3, —CH_2—CH_2—CH_3, —CH_2—O—CH_2—$CH(CH_3)_2$, —CH_2—O—$CH(CH_3)_2$, —CH_2—O—$C(CH_3)_3$, —CH_2—O—CH_2—CF_3, —CH_2—O—$C(CH_3)_2$—CF_3, —CH_2—$C(CH_3)_3$, —CH_2—O—CH_2—$(CH_3)_3$, —CH_2—O—$C(CH_3)H$—CF_3, —CH_2—CH_2—$C(CH_3)_3$, —CH_2—CF_3, —CH_2—O—$C(CH_3)H$—, —CH_2—O—$C(CH_3)H$—CH_2—CH_3, —CH_3, —CH_2—CH_3, —CH_2—O—$C(CH_3)H$—CH_2—CH_2—CH_3, —CH_2—O—CH_2—CH_2—O—CH_3, —CH_2—O—$C(CH_3)H$—$CH(CH_3)_2$, —CH_2—O—$C(CH_3)H$—CH_2—, —CH_2—O—$C(CH_3)_2$—, —CH_2—O—$C(CH_3)H$—CH_2—O—CH_3, —$C(CH_3)H$—O—CH_3, —CH_2—CH_2—, —CH_2—CH_2—O—$C(CH_3)H$—, —CH_2—CH_2—O—, —CH_2—$N(CH_3)_2$, —CH_2—NH(CH_3), —CH_2—$N(CH_3)$—$CH(CH_3)$—, —CH_2—N(CH_3)—CH_2—CH_2—CH_3, —CH_2—NH—CH_2—CH_2—CH_3, —$N(CH_3)_2$, —CH_2—NH—CH_2—CH_2—O—CH_3, —CH_2—NH—CH_2—CH_3, —NH(CH_3), —CH_2—$N(CH_3)$—CH_2—CH_3, —CH_2—$N(CH_3)$—$CH(CH_3)_2$, —$CH(CF_3)$—$N(CH_3)_2$, —$CH(N(CH_3)_2)$—$CH(CH_3)_2$, —$CH(CH_3)$—$N(CH_3)_2$, and —$C(CH_3)_2$—$N(CH_3)_2$;

[0117] R^{25}, when present, is selected from chloro, —$C(CF_3)_3$, and —$C(CH_3)_3$;

[0118] R^{26}, when present, is selected from: fluoro, chloro, bromo, —$C(CF_3)_3$, —$C(CH_3)_3$, —CH_2—CF_3, —CH_2—CH_3, —CH_3, —CF_3, and —$N(CH_3)_2$;

[0119] D^2 is absent or selected from: piperidinyl, cyclohexyl, cyclopropyl, cyclopentyl, cyclobutyl, pyrrolidinyl, tetrahydrofuranyl, and tetrahydropyranyl; and

[0120] z^{25} and z^{26} are independently an integer from 0 to 4;

[0121] provided:

[0122] when L^{23} is monovalent, D^2 is absent and z^{26} is 0; and

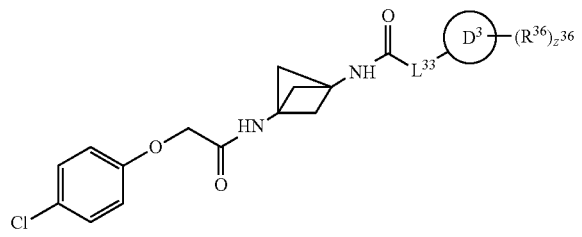
[0123] when D^2 is absent L^{23} is not a bond;

and salts thereof.

[0124] This invention also relates to pharmaceutically acceptable salts of the compounds of Formula (III).

[0125] Included in the compounds of the invention and used in the methods of the invention are compounds of Formula (IV):

(IV)



wherein:

[0126] L^{33} is a bond or selected from: —CH_2—, —CH_2—O—CH_3, —CH_2—O—, —CH_2—O—CH_2—CH_3, —CH_2—O—CH_2—CH_2—CH_2—CH_3, —CH_2—O—CH_2—, —CH_2—O—CH_2—CH_2—CH_3, —CH_2—CH_2—CH_3, —CH_2—O—CH_2—$CH(CH_3)_2$, —CH_2—O—$CH(CH_3)_2$, —CH_2—O—$C(CH_3)_3$, —CH_2—O—CH_2—CF_3, —CH_2—O—$C(CH_3)_2$—CF_3, —CH_2—$C(CH_3)_3$, —CH_2—O—CH_2—$(CH_3)_3$, —CH_2—O—$C(CH_3)H$—CF_3, —CH_2—CH_2—$C(CH_3)_3$, —CH_2—CF_3, —CH_2—O—$C(CH_3)H$—, —CH_2—O—$C(CH_3)H$—CH_2—CH_3, —CH_3, —CH_2—CH_3, —CH_2—O—$C(CH_3)H$—CH_2—CH_2—CH_3, —CH_2—O—CH_2—CH_2—O—CH_3, —CH_2—O—$C(CH_3)H$—$CH(CH_3)_2$, —CH_2—O—$C(CH_3)H$—CH_2—, —CH_2—O—$C(CH_3)_2$—, —CH_2—O—$C(CH_3)H$—CH_2—O—CH_3, —$C(CH_3)H$—O—CH_3, —CH_2—CH_2—, —CH_2—CH_2—O—$C(CH_3)H$—, —CH_2—CH_2—O—, —CH_2—$N(CH_3)_2$, —CH_2—NH(CH_3), —CH_2—$N(CH_3)$—$CH(CH_3)$—, —CH_2—N(CH_3)—CH_2—CH_2—CH_3, —CH_2—NH—CH_2—CH_2—CH_3, —$N(CH_3)_2$, —CH_2—NH—CH_2—CH_2—O—CH_3, —CH_2—NH—CH_2—CH_3, —NH(CH_3), —CH_2—$N(CH_3)$—CH_2—CH_3, —CH_2—$N(CH_3)$—$CH(CH_3)_2$, —$CH(CF_3)$—$N(CH_3)_2$, —$CH(N(CH_3)_2)$—$CH(CH_3)_2$, —$C(CH_3)H$—$N(CH_3)_2$, and —$C(CH_3)_2$—$N(CH_3)_2$;

[0127] R^{36}, when present, is selected from: fluoro, chloro, bromo, —$C(CF_3)_3$, —$C(CH_3)_3$, —CH_2—CF_3, —CH_2—CH_3, —CH_3, —CF_3, and —$N(CH_3)_2$;

[0128] D^3 is absent or selected from: piperidinyl, cyclohexyl, cyclopropyl, cyclopentyl, cyclobutyl, pyrrolidinyl, tetrahydrofuranyl, and tetrahydropyranyl; and

[0129] z^{36} is an integer from 0 to 2;

[0130] provided:

[0131] when L^{33} is monovalent, D^3 is absent and z^{36} is 0; and

[0132] when D^3 is absent L^{33} is not a bond;

and salts thereof.

[0133] This invention also relates to pharmaceutically acceptable salts of the compounds of Formula (IV).

[0134] Included in the compounds of Formula (I) are:

[0135] 2-(4-chlorophenoxy)-N-(3-(2-(cyclohexyloxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0136] 2-(4-chlorophenoxy)-N-(3-(2-(2,2,2-trifluoroethoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0137] 2-(4-chlorophenoxy)-N-(3-(2-(1-methylcyclobutoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0138] 2-(4-chlorophenoxy)-N-(3-(2-(pentan-2-yloxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0139] 2-(4-chlorophenoxy)-N-(3-(2-((1,1,1-trifluoro-2-methylpropan-2-yl)oxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0140] 2-(4-chlorophenoxy)-N-(3-(2-((1-methylcyclopropyl)methoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0141] 2-(4-chlorophenoxy)-N-(3-(2-((1-cyclopropylpropan-2-yl)oxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0142] 2-(4-chlorophenoxy)-N-(3-(2-(cyclopropylmethoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0143] 2-(tert-butoxy)-N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0144] 2-(4-chlorophenoxy)-N-(3-(2-isobutoxyacetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0145] 2-(4-chlorophenoxy)-N-(3-(2-(1-methylcyclopropoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0146] 2-(4-chlorophenoxy)-N-(3-(2-(neopentyloxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0147] 2-(4-chlorophenoxy)-N-(3-(2-(cyclopentyloxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0148] 2-(sec-butoxy)-N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0149] 2-(4-chlorophenoxy)-N-(3-(2-cyclopropoxyacetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0150] 2-(4-chlorophenoxy)-N-(3-(2-(1-cyclopropylethoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0151] 2-(4-chlorophenoxy)-N-(3-(2-(2-methoxyethoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0152] 2-(4-chlorophenoxy)-N-(3-(2-(1,2-dimethylcyclopropoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0153] 2-(4-chlorophenoxy)-N-(3-(2-((1-methoxypropan-2-yl)oxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0154] 2-(1-methylcyclopropoxy)-N-(3-(2-(p-tolyloxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0155] 2-(4-chlorophenoxy)-N-(3-(2-((1,1,1-trifluoropropan-2-yl)oxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0156] 2-butoxy-N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0157] 2-(4-chlorophenoxy)-N-(3-(2-isopropoxyacetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0158] 2-(4-chlorophenoxy)-N-(3-(2-ethoxyacetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0159] 2-(4-chlorophenoxy)-N-(3-(2-((3-methylbutan-2-yl)oxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0160] 2-(4-chlorophenoxy)-N-(3-(2-propoxyacetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0161] 2-(4-chlorophenoxy)-N-(3-(2-methoxyacetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0162] 2-(4-chlorophenoxy)-N-(3-(2-(4,4-difluoropiperidin-1-yl)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0163] 2-(4-chlorophenoxy)-N-(3-((2-(1-methylcyclopropoxy)ethyl)amino)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0164] 2-(4-chlorophenoxy)-N-(3-((2-(1-cyclopropylethoxy)ethyl)amino)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0165] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-methylcyclopropane-1-carboxamide;

[0166] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)tetrahydrofuranyl-2-carboxamide;

[0167] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)tetrahydro-2H-pyran-2-carboxamide;

[0168] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)cyclobutanecarboxamide;

[0169] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-1-(trifluoromethyl)cyclopropane-1-carboxamide;

[0170] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)cyclopropanecarboxamide;

[0171] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-1-methylcyclopropane-1-carboxamide;

[0172] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylpentanamide;

[0173] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)propionamide;

[0174] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-3,3,3-trifluoropropanamide;

[0175] 2-(4-chlorophenoxy)-N-(3-(2-cyclopropylacetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0176] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2,2-dimethylcyclopropane-1-carboxamide;

[0177] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)butyramide;

[0178] N-(3-acetamidobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide;

[0179] 2-(4-chlorophenoxy)-N-(3-(2-(dimethylamino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0180] (R)—N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-(dimethylamino)-3-methylbutanamide;

[0181] (S)—N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-(dimethylamino)-3-methylbutanamide;

[0182] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-3,3-dimethylbutanamide;

[0183] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2,2-difluorocyclopropane-1-carboxamide;

[0184] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-methoxypropanamide;

[0185] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-(dimethylamino)-2-methylpropanamide;

[0186] 2-(4-chlorophenoxy)-N-(3-(2-(methylamino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide hydrochloride;

[0187] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)pyrrolidinyl-2-carboxamide hydrochloride;

[0188] (S)—N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-(dimethylamino)propanamide;

[0189] (R)—N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-(dimethylamino)propanamide;

[0190] 2-(4-chlorophenoxy)-N-(3-(2-(propylamino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0191] 2-(4-chlorophenoxy)-N-(3-(2-(ethylamino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0192] 2-(4-chlorophenoxy)-N-(3-(2-(isopropyl(methyl)amino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0193] 2-(4-chlorophenoxy)-N-(3-((2-(methylamino)-2-oxoethyl)amino)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0194] 2-((3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)amino)-N,N-dimethylacetamide;

[0195] (R)-2-(4-chlorophenoxy)-N-(3-(2-((1-cyclopropylethyl)(methyl)amino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0196] 2-(4-chlorophenoxy)-N-(3-(2-((2-methoxyethyl)-l3-chloranyl)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0197] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-1-(dimethylamino)cyclopropanecarboxamide;

[0198] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-(dimethylamino)-3,3,3-trifluoropropanamide;

[0199] 2-(4-chlorophenoxy)-N-(3-(2-(methyl(propyl)amino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0200] 2-(4-chlorophenoxy)-N-(3-(2-(ethyl(methyl) amino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

[0201] N,N'-(bicyclo[1.1.1]pentane-1,3-diyl)bis(2-(tert-butoxy)acetamide);

[0202] N,N'-(bicyclo[1.1.1]pentane-1,3-diyl)bis(2-(1-methylcyclopropoxy)acetamide);

[0203] (1-methylcyclopropyl)methyl (3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)carbamate;

[0204] N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide;

[0205] 2-(4-chlorophenoxy)-N-(3-(2-oxopiperidin-1-yl) bicyclo[1.1.1]pentan-1-yl)acetamide; and

[0206] N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-1-fluorocyclopropane-1-carboxamide;

[0207] and salts thereof including pharmaceutically acceptable salts thereof.

[0208] In embodiments, R^5 is selected from: fluoro, chloro, bromo, iodo, oxo, —OCH_3, —OCH_2Ph, —C(O)Ph, —CH_3, —CF_3, —CHF_2, —CH_2F, —CN, —S(O)CH_3, —$S(O)_2CH_3$, —OH, —NH_2, —$NHCH_3$, —$N(CH_3)_2$, —COOH, —$CONH_2$, —NO_2, —$C(O)CH_3$, —$CH(CH_3)_2$, —$C(CF_3)_3$, —$C(CH_3)_3$, —CH_2—CF_3, —CH_2—CH_3, —CCH, —CH_2CCH, —SO_3H, —SO_2NH_2, —$NHC(O)NH_2$, —NHC(O)H, —NHOH, —OCF_3, —$OCHF_2$, C_{1-6}alkyl, substituted C_{1-6}alkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl. In embodiments, R^5 is selected from: fluoro, chloro, bromo, iodo, —OCH_3, —OCH_2Ph, —CH_3, —OH, —CF_3, —CN, —S(O)CH_3, —NO_2, —$C(O)CH_3$, —C(O)Ph, —$CH(CH_3)_2$, or —CCH. In embodiments, R^5 is selected from: C_{1-6}alkyl, substituted C_{1-6}alkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl. In embodiments, R^5 is selected from: C_{1-6}alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl. In embodiments, R^5 is —OCH_3. In embodiments, R^5 is —OCH_2Ph. In embodiments, R^5 is —CH_3. In embodiments, R^5 is —OH. In embodiments, R^5 is —CF_3. In embodiments, R^5 is —CN. In embodiments, R^5 is —S(O)CH_3. In embodiments, R^5 is —NO_2. In embodiments, R^5 is —$C(O)CH_3$. In embodiments, R^5 is —C(O)Ph. In embodiments, R^5 is —$CH(CH_3)_2$. In embodiments, R^5 is —CCH. In embodiments, R^5 is —CH_2CCH. In embodiments, R^5 is —SO_3H. In embodiments, R^5 is —SO_2NH_2. In embodiments, R^5 is —$NHC(O)NH_2$. In embodiments, R^5 is —NHC(O)H. In embodiments, R^5 is —NHOH. In embodiments, R^5 is —OCH_3. In embodiments, R^5 is —OCF_3. In embodiments, R^5 is —$OCHF_2$. In embodiments, R^5 is fluoro. In embodiments, R^5 is chloro. In embodiments, R^5 is bromo. In embodiments, R^5 is iodo. In embodiments, R^5 is —$C(CF_3)_3$. In embodiments, R^5 is —$C(CH_3)_3$. In embodiments, R^5 is —CH_2—CF_3. In embodiments, R^5 is —CH_2—CH_3. In embodiments, R^5 is —CH_3. In embodiments, R^5 is —CF_3. In embodiments, R^5 is —$N(CH_3)_2$. In embodiments, R^5 is —CHF_2. In embodiments, R^5 is —CH_2F. In embodiments, R^5 is —$S(O)_2CH_3$.

[0209] In embodiments, R^6 is selected from: fluoro, chloro, bromo, iodo, oxo, —OCH_3, —OCH_2Ph, —C(O)Ph, —CH_3, —CF_3, —CHF_2, —CH_2F, —CN, —S(O)CH_3, —$S(O)_2CH_3$, —OH, —NH_2, —$NHCH_3$, —$N(CH_3)_2$, —COOH, —$CONH_2$, —NO_2, —$C(O)CH_3$, —$CH(CH_3)_2$, —$C(CF_3)_3$, —$C(CH_3)_3$, —CH_2—CF_3, —CH_2—CH_3, —CCH, —CH_2CCH, —SO_3H, —SO_2NH_2, —$NHC(O)NH_2$, —NHC(O)H, —NHOH, —OCF_3, —$OCHF_2$, C_{1-6}alkyl, substituted C_{1-6}alkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl. In embodiments, R^6 is selected from: fluoro, chloro, bromo, iodo, —OCH_3, —OCH_2Ph, —CH_3, —OH, —CF_3, —CN, —S(O)CH_3, —NO_2, —$C(O)CH_3$, —C(O)Ph, —$CH(CH_3)_2$, or —CCH. In embodiments, R^6 is selected from: C_{1-6}alkyl, substituted C_{1-6}alkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted ary, heteroaryl, and substituted heteroaryl. In embodiments, R^6 is selected from: C_{1-6}alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl. In embodiments, R^6 is —OCH_3. In embodiments, R^6 is —OCH_2Ph. In embodiments, R^6 is —CH_3. In embodiments, R^6 is —OH. In embodiments, R^6 is —CF_3. In embodiments, R^6 is —CN. In embodiments, R^6 is —S(O)CH_3. In embodiments, R^6 is —NO_2. In embodiments, R^6 is —$C(O)CH_3$. In embodiments, R^6 is —C(O)Ph. In embodiments, R^6 is —$CH(CH_3)_2$. In embodiments, R^6 is —CCH. In embodiments, R^6 is —CH_2CCH. In embodiments, R^6 is —SO_3H. In embodiments, R^6 is —SO_2NH_2. In embodiments, R^6 is —$NHC(O)NH_2$. In embodiments, R^6 is —NHC(O)H. In embodiments, R^6 is —NHOH. In embodiments, R^6 is —OCH_3. In embodiments, R^6 is —OCF_3. In embodiments, R^6 is —$OCHF_2$. In embodiments, R^6 is fluoro. In embodiments, R^6 is chloro. In embodiments, R^6 is bromo. In embodiments, R^6 is iodo. In embodiments, R^6 is —$C(CF_3)_3$. In embodiments, R^6 is —$C(CH_3)_3$. In embodiments, R^6 is —CH_2—CF_3. In embodiments, R^6 is —CH_2—CH_3. In embodiments, R^6 is —CH_3. In embodiments, R^6 is —CF_3. In embodiments, R^6 is —$N(CH_3)_2$. In embodiments, R^6 is —CHF_2. In embodiments, R^6 is —CH_2F. In embodiments, R^6 is —$S(O)_2CH_3$.

[0210] In embodiments, R^2 is NR^8. In embodiments, R^2 is NH. In embodiments, R^2 is 0. In embodiments, R^2 is S. In embodiments, R^2 is CH_2. In embodiments, R^4 is NR^8. In embodiments, R^4 is NH. In embodiments, R^4 is 0. In embodiments, R^4 is S. In embodiments, R^4 is CH_2. In embodiments, R^2 and R^4 are NH. In embodiments, R^2 and R^4 are 0. In embodiments, R^2 and R^4 are S. In embodiments, R^2 and R^4 are NR^8.

[0211] In embodiments, R^8 is C_{1-6}alkyl.

[0212] In embodiments, L^2 is a bond. In embodiments, L^2 is C_{1-8}alkylene. In embodiments, L^2 is substituted C_{1-8}alkylene. In embodiments, L^2 is C_{1-8}heteroalkylene. In embodiments, L^2 is substituted C_{1-8}heteroalkylene. In embodiments, L^2 is C_{1-8}alkyl. In embodiments, L^2 is substituted C_{1-8}alkyl. In embodiments, L^2 is C_{1-8}heteroalkyl. In embodiments, L^2 is substituted C_{1-8}heteroalkyl. In embodiments, L^2 is selected from: —O—, —S—, —NH—, —S(O)—, or —$S(O)_2$—. In embodiments, L^2 is —O—. In embodiments, L^2 is —S—. In embodiments, L^2 is —NH—. In embodiments, L^2 is —S(O)—. In embodiments, L^2 is —$S(O)_2$—. In embodiments, L^2 is selected from: —CH_2—, —CH_2—O—CH_3, —CH_2—O—, —CH_2—O—CH_2—CH_3, —CH_2—O—CH_2—CH_2—CH_2—CH_3, —CH_2—O—CH_2—, —CH_2—O—CH_2—CH_2—CH_3, —CH_2—CH_2—CH_3, —CH_2—O—CH_2—$CH(CH_3)_2$, —CH_2O—$CH(CH_3)_2$, —CH_2—O—$C(CH_3)H$—, —CH_2—O—$C(CH_3)_3$, —CH_2—O—CH_2—CF_3, —CH_2—O—$C(CH_3)_2$—CF_3, —CH_2—$C(CH_3)_3$, —CH_2—O—CH_2—$(CH_3)_3$, —CH_2—

O—C(CH_3)H—CF_3, —CH_2—CH_2—C(CH_3)$_3$, —CH_2—CF_3, —CH_2—O—C(CH_3)H—CH_2—CH_3, —CH_3, —CH_2—CH_3, —CH_2—O—C(CH_3)H—CH_2—CH_2—CH_3, —CH_2—O—CH_2—CH_2—O—CH_3, —CH_2—O—C(CH_3)H—CH(CH_3)$_2$, —CH_2—O—C(CH_3)H—CH_2—, —CH_2—O—C(CH_3)$_2$—, —CH_2—O—C(CH_3)H—CH_2—O—CH_3, —C(CH_3)H—O—CH_3, —CH_2—CH_2—, —CH_2—CH_2—O—C(CH_3)H—, —CH_2—CH_2—O—, —CH_2—N(CH_3)$_2$, —CH_2—NH(CH_3), —CH_2—N(CH_3)—CH(CH_3)—, —CH_2—N(CH_3)—CH_2—CH_2—CH_3, —CH_2—NH—CH_2—CH_2—CH_3, —N(CH_3)$_2$, —CH_2—NH—CH_2—CH_2—O—CH_3, —CH_2—NH—CH_2—CH_3, —NH(CH_3), —CH_2—N(CH_3)—CH_2—CH_3, —CH_2—N(CH_3)—CH(CH_3)$_2$, —CH(CF_3)—N(CH_3)$_2$, —CH(N(CH_3)$_2$)—CH(CH_3)$_2$, —CH(CH_3)—N(CH_3)$_2$, and —C(CH_3)$_2$—N(CH_3)$_2$. In embodiments, L^2 is —CH_2—O—.

[0213] In embodiments, L^3 is a bond. In embodiments, L^3 is absent. In embodiments, L^3 is $C_{1\text{-}8}$alkylene. In embodiments, L^3 is substituted $C_{1\text{-}8}$alkylene. In embodiments, L^3 is $C_{1\text{-}8}$heteroalkylene. In embodiments, L^3 is substituted $C_{1\text{-}8}$heteroalkylene. In embodiments, L^3 is $C_{1\text{-}8}$alkyl. In embodiments, L^3 is substituted $C_{1\text{-}8}$alkyl. In embodiments, L^3 is $C_{1\text{-}8}$heteroalkyl. In embodiments, L^3 is substituted $C_{1\text{-}8}$heteroalkyl. In embodiments, L^3 is selected from: —O—, —S—, —NH—, —S(O)—, or —S(O)$_2$—. In embodiments, L^3 is —O—. In embodiments, L^3 is —S—. In embodiments, L^3 is —NH—. In embodiments, L^3 is —S(O)—. In embodiments, L^3 is —S(O)$_2$—. In embodiments, L^3 is selected from: —CH_2—, —CH_2—O—CH_3, —CH_2—O—, —CH_2—O—CH_2—CH_3, —CH_2—O—CH_2—CH_2—CH_2—CH_3, —CH_2—O—CH_2—, —CH_2—O—CH_2—CH_2—CH_2—CH_3, —CH_2—CH_2—CH_2—CH_3, —CH_2—O—CH_2—CH(CH_3)$_2$, —CH_2O—CH(CH_3)$_2$, —CH_2—O—C(CH_3)H—, —CH_2—O—C(CH_3)H—CH_2—CH_3, —CH_3, —CH_2—CH_3, —CH_2—O—C(CH_3)H—CH_2—CH_2—CH_3, —CH_2—O—CH_2—CH_2—O—CH_3, —CH_2—O—C(CH_3)H—CH(CH_3)$_2$, —CH_2—O—C(CH_3)H—CH_2—, —CH_2—O—C(CH_3)$_2$—, —CH_2—O—C(CH_3)H—CH_2—O—CH_3, —C(CH_3)H—O—CH_3, —CH_2—CH_2—, —CH_2—O—C(CH_3)$_3$, —CH_2—O—CH_2—CF_3, —CH_2—O—C(CH_3)$_2$—CF_3, —CH_2—C(CH_3)$_3$, —CH_2—O—CH_2—(CH_3)$_3$, —CH_2—O—C(CH_3)H—CF_3, —CH_2—CH_2—C(CH_3)$_3$, —CH_2—CF_3, —CH_2—CH_2—O—C(CH_3)H—, —CH_2—CH_2—O—, —CH_2—N(CH_3)$_2$, —CH_2—NH(CH_3), —CH_2—N(CH_3)—CH(CH_3)—, —CH_2—N(CH_3)—CH_2—CH_2—CH_3, —CH_2—NH—CH_2—CH_2—CH_3, —N(CH_3)$_2$, —CH_2—NH—CH_2—CH_2—O—CH_3, —CH_2—NH—CH_2—CH_3, —NH(CH_3), —CH_2—N(CH_3)—CH_2—CH_3, —CH_2—N(CH_3)—CH(CH_3)$_2$, —CH(CF_3)—N(CH_3)$_2$, —CH(N(CH_3)$_2$)—CH(CH_3)$_2$, —CH(CH_3)—N(CH_3)$_2$, and —C(CH_3)$_2$—N(CH_3)$_2$.

[0214] In embodiments, z^2 is 0. In embodiments, z^2 is 1. In embodiments, z^4 is 0. In embodiments, z^4 is 1. In embodiments, z^2 and z^4 are 0. In embodiments, z^2 and z^4 are 1. In embodiments, z^5 is 0. In embodiments, z^5 is 1. In embodiments, z^5 is 2. In embodiments, z^5 is 3. In embodiments, z^5 is 4. In embodiments, z^6 is 0. In embodiments, z^6 is 1. In embodiments, z^6 is 2. In embodiments, z^6 is 3. In embodiments, z^6 is 4.

[0215] In embodiments, a is 0. In embodiments, a is 1. In embodiments, b is 0. In embodiments, b is 1. In embodiments, a and b are 0. In embodiments, a and b are 1.

[0216] In embodiments, X is —CH_2—CH_2—CH_2—. In embodiments, X is —CH_2—CH_2—. In embodiments, X is —CH_2—. In embodiments, X is —CH_2—CH_2—CH_2— substituted 1 to 4 times by fluoro. In embodiments, X is —CH_2—CH_2— substituted 1 to 3 times by fluoro. In embodiments, X is —CH_2— substituted 1 or 2 times by fluoro.

[0217] In embodiments, Y^1 is NH—. In embodiments, Y^1 is NH_2. In embodiments, Y^1 is a nitrogen linked heterocycloalkyl. In embodiments, Y^1 is a substituted nitrogen linked heterocycloalkyl. In embodiments, Y^1 is a nitrogen linked heterocycloalkyl substituted from 1 to 3 times by a substituent selected from: fluoro, chloro, bromo, iodo, oxo, —OCH_3, —OCF_3, —CH_3, and —CF_3. In embodiments, Y^1 is a nitrogen linked piperidinyl. In embodiments, Y^1 is a nitrogen linked piperidinyl substituted by oxo.

[0218] In embodiments, Y^2 is absent. In embodiments, Y^2 is a bond. In embodiments, Y^2 is —CH_2—CH_2—. In embodiments, Y^2 is —CH_2—. In embodiments, Y^2 is —CH_2—CH_2— substituted 1 to 4 times by fluoro. In embodiments, Y^2 is —CH_2— substituted 1 or 2 times by fluoro.

[0219] In embodiments, L^{33} is absent or selected from: —CH_2—O—C(CH_3)$_3$, —CH_2—O—CH_2—CF_3, —CH_2—O—C(CH_3)$_2$—CF_3, —CH_2—C(CH_3)$_3$, —CH_2—NH(CH_3), —CH_2—O—, —CH_2—CH_3; D^3 is absent or cyclopropyl; R^{36} is selected from: fluoro, —CH_3, and CF_3; and z^{36} is 0 or 1.

[0220] In embodiments, C is absent. In embodiments, C is phenyl. In embodiments, C is pyridyl. In embodiments, C is cycloalkyl. In embodiments, C is cyclopropyl.

[0221] In embodiments, D is absent. In embodiments, D is cycloalkyl. In embodiments, D is substituted cycloalkyl. In embodiments, D is heterocycloalkyl. In embodiments, D is substituted heterocycloalkyl. In embodiments, D is cyclopropyl. In embodiments, D is piperidinyl. In embodiments, D is cyclohexyl. In embodiments, D is cyclopentyl. In embodiments, D is cyclobutyl. In embodiments, D is pyrrolidinyl. In embodiments, D is tetrahydrofuranyl. In embodiments, D is tetrahydropyranyl.

[0222] The skilled artisan will appreciate that salts, including pharmaceutically acceptable salts, of the compounds according to Formula (I) may be prepared. Indeed, in certain embodiments of the invention, salts including pharmaceutically-acceptable salts of the compounds according to Formula (I) may be preferred over the respective free or unsalted compound. Accordingly, the invention is further directed to salts, including pharmaceutically-acceptable salts, of the compounds according to Formula (I).

[0223] The salts, including pharmaceutically acceptable salts, of the compounds of the invention are readily prepared by those of skill in the art.

[0224] Typically, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention.

[0225] Representative pharmaceutically acceptable acid addition salts include, but are not limited to, 4-acetamidobenzoate, acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate (besylate), benzoate, bisulfate, bitartrate, butyrate, calcium edetate, camphorate, camphorsulfonate (camsylate), caprate (decanoate), caproate (hexanoate), caprylate (octanoate), cinnamate, citrate, cyclamate, digluconate, 2,5-dihydroxybenzoate, disuccinate, dodecylsulfate (estolate), edetate (ethylenediaminetetraacetate), estolate (lauryl sulfate), ethane-1,2-disulfonate (edisylate), ethane-

sulfonate (esylate), formate, fumarate, galactarate (mucate), gentisate (2,5-dihydroxybenzoate), glucoheptonate (gluceptate), gluconate, glucuronate, glutamate, glutarate, glycerophosphorate, glycolate, hexylresorcinate, hippurate, hydrabamine (N,N'-di(dehydroabietyl)-ethylenediamine), hydrobromide, hydrochloride, hydroiodide, hydroxynaphthoate, isobutyrate, lactate, lactobionate, laurate, malate, maleate, malonate, mandelate, methanesulfonate (mesylate), methylsulfate, mucate, naphthalene-1,5-disulfonate (napadisylate), naphthalene-2-sulfonate (napsylate), nicotinate, nitrate, oleate, palmitate, p-aminobenzenesulfonate, p-aminosalicyclate, pamoate (embonate), pantothenate, pectinate, persulfate, phenylacetate, phenylethylbarbiturate, phosphate, polygalacturonate, propionate, p-toluenesulfonate (tosylate), pyroglutamate, pyruvate, salicylate, sebacate, stearate, subacetate, succinate, sulfamate, sulfate, tannate, tartrate, teoclate (8-chlorotheophyllinate), thiocyanate, triethiodide, undecanoate, undecylenate, and valerate.

[0226] Representative pharmaceutically acceptable base addition salts include, but are not limited to, aluminium, 2-amino-2-(hydroxymethyl)-1,3-propanediol (TRIS, tromethamine), arginine, benethamine (N-benzylphenethylamine), benzathine (N,N'-dibenzylethylenediamine), bis-(2-hydroxyethyl)amine, bismuth, calcium, chloroprocaine, choline, clemizole (1-p chlorobenzyl-2-pyrrolildine-1'-ylmethylbenzimidazole), cyclohexylamine, dibenzylethylenediamine, diethylamine, diethyltriamine, dimethylamine, dimethylethanolamine, dopamine, ethanolamine, ethylenediamine, L-histidine, iron, isoquinoline, lepidine, lithium, lysine, magnesium, meglumine (N-methylglucamine), piperazine, piperidinyl, potassium, procaine, quinine, quinoline, sodium, strontium, t-butylamine, and zinc.

[0227] The compounds according to Formula (I) may contain one or more asymmetric centers (also referred to as a chiral center) and may, therefore, exist as individual enantiomers, diastereomers, or other stereoisomeric forms, or as mixtures thereof. Chiral centers, such as chiral carbon atoms, may be present in a substituent such as an alkyl group. Where the stereochemistry of a chiral center present in a compound of Formula (I), or in any chemical structure illustrated herein, if not specified the structure is intended to encompass all individual stereoisomers and all mixtures thereof. Thus, compounds according to Formula (I) containing one or more chiral centers may be used as racemic mixtures, enantiomerically or diastereomerically enriched mixtures, or as enantiomerically or diastereomerically pure individual stereoisomers.

[0228] The compounds according to Formula (I) and pharmaceutically acceptable salts thereof may contain isotopically-labelled compounds, which are identical to those recited in Formula (I) and following, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of such isotopes include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulphur, fluorine, iodine, and chlorine, such as 2H, 3H, 11C, 13C, 14C, 15N, 17O, 18O, 31P, 32P, 35S, 18F, 36Cl, 123I and 125I.

[0229] Isotopically-labelled compounds, for example those into which radioactive isotopes such as 3H or 14C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., 3H, and carbon-14, i.e., 14C, isotopes are particularly preferred for their ease of preparation and detectability. 11C and 18F isotopes are particularly useful in PET (positron emission tomography), and 125I isotopes are particularly useful in SPECT (single photon emission computerized tomography), both are useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., 2H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds can generally be prepared by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

[0230] The compounds according to Formula (I) may also contain double bonds or other centers of geometric asymmetry. Where the stereochemistry of a center of geometric asymmetry present in Formula (I), or in any chemical structure illustrated herein, is not specified, the structure is intended to encompass the trans (E) geometric isomer, the cis (Z) geometric isomer, and all mixtures thereof. Likewise, all tautomeric forms are also included in Formula (I) whether such tautomers exist in equilibrium or predominately in one form.

[0231] The compounds of the invention may exist in solid or liquid form. In solid form, compound of the invention may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon the temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterized by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterized by a phase change, typically first order ('melting point').

[0232] The compounds of the invention may have the ability to crystallize in more than one form, a characteristic, which is known as polymorphism ("polymorphs"). Polymorphism generally can occur as a response to changes in temperature or pressure or both and can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility and melting point.

[0233] The compounds of Formula (I) may exist in solvated and unsolvated forms. As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of Formula (I) or a salt) and a solvent. Such solvents, for the purpose of the invention, may not interfere with the biological activity of the solute. The skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed for crystalline compounds wherein solvent molecules are incorporated into the crystalline lattice during crystallization. The incorporated solvent molecules may be water molecules or non-aqueous such as ethanol, isopropanol, DMSO, acetic acid, ethanolamine, and ethyl acetate molecules. Crystalline lattice incorporated with water molecules are typically referred to as "hydrates". Hydrates

include stoichiometric hydrates as well as compositions containing variable amounts of water.

[0234] It is also noted that the compounds of Formula (I) may form tautomers. 'Tautomers' refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of –π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. It is understood that all tautomers and mixtures of tautomers of the compounds of the present invention are included within the scope of the compounds of the present invention.

[0235] While aspects for each variable have generally been listed above separately for each variable this invention includes those compounds in which several or each aspect in Formula (I) is selected from each of the aspects listed above. Therefore, this invention is intended to include all combinations of aspects for each variable.

Definitions

[0236] "Alkyl" and "alkylene", and derivatives thereof, refer to a hydrocarbon chain having the specified number of "carbon atoms". Alkyl being monovalent and alkylene being bivalent. For example, C_1-C_6 alkyl refers to an alkyl group having from 1 to 6 carbon atoms. Alkyl and alkylene groups may be saturated or unsaturated, straight or branched. Representative branched alkyl groups have one, two, or three branches. Alkyl and alkylene include: methyl, methylene, ethyl, ethylene, propyl (n-propyl and isopropyl), butene, butyl (n-butyl, isobutyl, and t-butyl), pentyl and hexyl.

[0237] "Alkoxy" refers to an —O-alkyl group wherein "alkyl" is as defined herein. For example, C_1-C_4alkoxy refers to an alkoxy group having from 1 to 4 carbon atoms. Representative branched alkoxy groups have one, two, or three branches. Examples of such groups include methoxy, ethoxy, propoxy, and butoxy.

[0238] "Aryl" refers to an aromatic hydrocarbon ring. Aryl groups are monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring member atoms, wherein at least one ring system is aromatic and wherein each ring in the system contains 3 to 7 member atoms, such as phenyl, naphthalene, tetrahydronaphthalene and biphenyl. Suitably aryl is phenyl.

[0239] "Cycloalkyl", unless otherwise defined, refers to a saturated or unsaturated non aromatic hydrocarbon ring having from three to seven carbon atoms. Cycloalkyl groups are monocyclic ring systems. For example, C_3-C_7 cycloalkyl refers to a cycloalkyl group having from 3 to 7 carbon ring atoms. Examples of cycloalkyl as used herein include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptyl. Suitably cycloalkyl is selected from: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

[0240] "Halo" refers to fluoro, chloro, bromo, and iodo.

[0241] "Heteroaryl" refers to a monocyclic aromatic 4 to 8 member ring containing 1 to 7 carbon atoms and containing 1 to 4 heteroatoms, provided that when the number of carbon atoms is 3, the aromatic ring contains at least two heteroatoms, or to such aromatic ring fused to one or more rings, such as heteroaryl rings, aryl rings, heterocyclic rings, cycloalkyl rings. Heteroaryl groups containing more than one heteroatom may contain different heteroatoms. Heteroaryl includes but is not limited to: benzoimidazolyl, benzothiazolyl, benzothiophenyl, benzopyrazinyl, benzotriazolyl, benzotriazinyl, benzo[1,4]dioxanyl, benzofuranyl, 9H-a-carbolinyl, cinnolinyl, furanyl, pyrazolyl, imidazolyl, indolizinyl, naphthyridinyl, oxazolyl, oxothiadiazolyl, oxadiazolyl, phthalazinyl, pyridyl, pyrrolyl, purinyl, pteridinyl, phenazinyl, pyrazolopyrimidinyl, pyrazolopyridinyl, pyrrolizinyl, pyrimidyl, isothiazolyl, furazanyl, pyrimidinyl, tetrazinyl, isoxazolyl, quinoxalinyl, quinazolinyl, quinolinyl, quinolizinyl, thienyl, thiophenyl, triazolyl, triazinyl, tetrazolopyrimidinyl, triazolopyrimidinyl, tetrazolyl, thiazolyl and thiazolidinyl. Suitably heteroaryl is selected from: pyrazolyl, imidazolyl, oxazolyl and thienyl. Suitably heteroaryl is a pyridyl group or an imidazolyl group. Suitably heteroaryl is a pyridyl.

[0242] "Heterocycloalkyl" refers to a saturated or unsaturated non-aromatic ring containing 4 to 12 member atoms, of which 1 to 11 are carbon atoms and from 1 to 6 are heteroatoms. Heterocycloalkyl groups containing more than one heteroatom may contain different heteroatoms. Heterocycloalkyl groups are monocyclic ring systems or a monocyclic ring fused with an aryl ring or to a heteroaryl ring having from 3 to 6 member atoms. Heterocycloalkyl includes: pyrrolidinyl, tetrahydrofuranylyl, dihydrofuranyl, pyranyl, tetrahydropyranylyl, dihydropyranyl, tetrahydrothienyl, pyrazolidinyl, oxazolidinyl, oxetanyl, thiazolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl, 1,3oxazolidin-2-one, hexahydro-1H-azepin, 4,5,6,7,tetrahydro-1H-benzimidazol, piperidinyl, benzotetrahydropyranylyl, 1,2,3,6-tetrahydro-pyridinyl and azetidinyl. Suitably, "heterocycloalkyl" includes: piperidinyl, tetrahydrofuranyl, tetrahydropyranyl and pyrrolidinyl.

[0243] "Heteroatom" refers to a nitrogen, sulphur or oxygen atom.

[0244] "Heteroalkyl" and "heteroalkylene" by itself or in combination with another term, means, unless otherwise stated, a non-cyclic stable saturated or unsaturated, straight or branched chain, having the specified number of "member atoms" in the chain, including at least one carbon atom and at least one heteroatom selected from the group consisting of O, N, P, Si, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. Heteroalkyl being monovalent and heteroalkylene being bivalent. The heteroatom(s) O, N, P, S, and Si may be placed at any interior position of the heteroalkyl or heteroalkylene group or at the position at which the alkyl group is attached to the remainder of the molecule. Up to two or three heteroatoms may be consecutive, such as, for example, —CH_2—NH—OCH_3 and —CH_2—O—$Si(CH_3)_3$. Bivalent substituents can be rotated for attachment. For example "—O—CH_2—" refers to "—O—CH_2—" and "—CH_2—O—". Examples of heteroalkyl and heteroalkylene include, but are not limited to:

[0245] —CH_2—CH_2—O—CH_3, —CH_2—CH_2—NH—CH_3, —CH_2—O—CH_2—CH_2—O—CH_3, —O—CH_3, —CH_2O—$CH(CH_3)$—CH_2—O—CH_3, —CH_2—NH—CH_2—CH_2—O—CH_3, —CH_2—CH_2—$N(CH_3)_2$, —CH_2—NH_2, —CH_2—$NH(CH_3)$, —$NH(CH_3)$, —$N(CH_3)_2$, —CH_2—$N(CH_3)$—CH_2—CH_3, —CH_2—$N(CH_3)$—$CH(CH_3)_2$, —$CH(CH_3)$—O—CH_3, —CH_2—$N(CH_3)_2$, —$CH(N(CH_3)_2)$—$CH(CH_3)_2$, —$C(CH_3)_2$—$N(CH_3)_2$, —CH_2—S—CH_2—CH_3, —CH_2—CH_3, —S(O)—CH_3, —CH_2—

CH_2—$S(O)_2$—CH_3, —CH═CH—O—CH_3, —$Si(CH_3)_3$, —CH_2—CH═N—OCH_3, —CH═$CHN(CH_3)_2$, —CN, —CH_2—O—CH_2—CH_2—O—, —CH_2—O—$CH(CH_3)$—CH_2—O—, —CH_2—NH—, —CH_2—$N(CH_3)$—, —$N(CH_3)$—, —CH_2—CH_2—$N(CH_3)CH_2$—, —CH_2—S—CH_2—CH_2—, —CH_2—CH_2—, —S(O)—CH_2—, —CH_2—CH_2—$S(O)_2$—CH_2—, —CH═CH—O—CH_2—, —Si$(CH_3)_2CH_2$—, —CH_2—CH═N—OCH_2—, —CH_2—NH—CH_2—CH_2—O—, —CH_2—$N(CH_3)$—CH_2—CH_2—, —CH_2—$N(CH_3)$—$CH(CH_3)$—CH_2—, —$CH(CH_3)$—O—CH_2—, —CH_2—$N(CH_3)$—CH_2—, —$CH(N(CH_3)_2)$—$CH(CH_3)$—, —$CH(CH_3)$—$N(CH_3)$—, —$C(CH_3)_2$—$N(CH_3)$—, —CH═CH—$N(CH_3)$—CH_2—, —O—CH_2—, and —O—CH_2—CH_2—. In one embodiment, heteroalkyl and heteroalkylene are selected from: —CH_2—, —CH_2—O—CH_3, —CH_2—O—, —CH_2—O—CH_2—CH_3, —CH_2—O—CH_2—CH_2—CH_2—CH_3, —CH_2—O—CH_2—, —CH_2—O—CH_2—CH_2—CH_3, —CH_2—CH_2—CH_3, —CH_2—O—CH_2—$CH(CH_3)_2$, —CH_2—O—$CH(CH_3)_2$, —CH_2—O—$C(CH_3)_3$, —CH_2—O—CH_2—CF_3, —CH_2—O—$C(CH_3)_2$—CF_3, —CH_2—$C(CH_3)_3$, —CH_2—O—CH_2—$(CH_3)_3$, —CH_2—O—$C(CH_3)H$—CF_3, —CH_2—CH_2—$C(CH_3)_3$, —CH_2—CF_3, —CH_2—O—$C(CH_3)H$—, —CH_2—O—$C(CH_3)H$—CH_2—CH_3, —CH_3, —CH_2—CH_3, —CH_2—O—$C(CH_3)H$—CH_2—CH_2—CH_3, —CH_2—O—CH_2—CH_2—O—CH_3, —CH_2—O—$C(CH_3)H$—CH—$(CH_3)_2$, —CH_2—O—$C(CH_3)H$—CH_2—, —CH_2—O—$C(CH_3)_2$—, —CH_2—O—$C(CH_3)H$—CH_2—O—CH_3, —$C(CH_3)H$—O—CH_3, —CH_2—CH_2—, —CH_2—CH_2—O—$C(CH_3)H$—, —CH_2—CH_2—O—, —CH_2—$N(CH_3)_2$, —CH_2—$NH(CH_3)$, —CH_2—$N(CH_3)$—$CH(CH_3)$—, —CH_2—$N(CH_3)$—CH_2—CH_2—CH_3, —CH_2—NH—CH_2—CH_2—CH_3, —$N(CH_3)_2$, —CH_2—NH—CH_2—CH_2—O—CH_3, —CH_2—NH—CH_2—CH_3, —$NH(CH_3)$, —CH_2—$N(CH_3)$—CH_2—CH_3, —CH_2—$N(CH_3)$—$CH(CH_3)_2$, —$CH(CF_3)$—$N(CH_3)_2$, —$CH(N(CH_3)_2)$—$CH(CH_3)_2$, —$CH(CH_3)$—$N(CH_3)_2$, and —$C(CH_3)_2$—$N(CH_3)_2$.

[0246] "Substituted" as used herein, unless otherwise defined, is meant that the subject chemical moiety has from one to nine substituents, suitably from one to five substituents, selected from the group consisting of:

[0247] fluoro,

[0248] chloro,

[0249] bromo,

[0250] iodo,

[0251] $C_{1\text{-}6}$alkyl,

[0252] $C_{1\text{-}6}$alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,

[0253] —$OC_{1\text{-}6}$alkyl,

[0254] —$OC_{1\text{-}6}$alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,

[0255] cycloalkyl,

[0256] cycloalkyl substituted with from 1 to 4 substituents independently selected from: —CH_3, and fluoro,

[0257] mercapto,

[0258] —SR^x,

[0259] where R^x is selected from $C_{1\text{-}6}$alkyl, and $C_{1\text{-}6}$alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, —OH,

[0260] —COOH, —NH_2, and —CN,

[0261] —$S(O)R^x$,

[0262] where R^x is selected from $C_{1\text{-}6}$alkyl, and $C_{1\text{-}6}$alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,

[0263] —$S(O)_2H$,

[0264] —$S(O)_2R^x$,

[0265] where R^x is selected from $C_{1\text{-}6}$alkyl, and $C_{1\text{-}6}$alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,

[0266] oxo,

[0267] hydroxy,

[0268] amino,

[0269] NHR^x,

[0270] where R^x is selected from $C_{1\text{-}6}$alkyl, and $C_{1\text{-}6}$alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,

[0271] —$NR^{x1}R^{x2}$,

[0272] where R^{x1} and R^{x2} are each independently selected from $C_{1\text{-}6}$alkyl, and $C_{1\text{-}6}$alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,

[0273] guanidino,

[0274] hydroxyguanidino,

[0275] oxyguanidino;

[0276] —C(O)OH,

[0277] —$C(O)OR^x$,

[0278] where R^x is selected from $C_{1\text{-}6}$alkyl, and $C_{1\text{-}6}$alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,

[0279] —$C(O)NH_2$,

[0280] —$C(O)NHR^x$,

[0281] where R^x is selected from $C_{1\text{-}6}$alkyl, and $C_{1\text{-}6}$alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,

[0282] —$C(O)NR^{x1}R^{x2}$,

[0283] where R^{x1} and R^{x2} are each independently selected from $C_{1\text{-}6}$alkyl, and $C_{1\text{-}6}$alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,

[0284] —$S(O)_2NH_2$,

[0285] —$S(O)_2NHR^x$,

[0286] where R^x is selected from $C_{1\text{-}6}$alkyl, and $C_{1\text{-}6}$alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,

[0287] —$S(O)_2NR^{x1}R^{x2}$,

[0288] where R^{x1} and R^{x2} are each independently selected from $C_{1\text{-}6}$alkyl, and $C_{1\text{-}6}$alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,

[0289] —$NHS(O)_2H$,

[0290] —$NHS(O)_2R^x$,

[0291] where R^x is selected from $C_{1\text{-}6}$alkyl, and $C_{1\text{-}6}$alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,

[0292] —NHC(O)H,
[0293] —NHC(O)R^x,
[0294] where R^x is selected from C_{1-6}alkyl, and C_{1-6}alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,
[0295] —NHC(O)NH_2,
[0296] —NHC(O)NHR^x,
[0297] where R^x is selected from C_{1-6}alkyl, and C_{1-6}alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,
[0298] —NHC(O)$NR^{x1}R^{x2}$,
[0299] where R^{x1} and R^{x2} are each independently selected from C_{1-6}alkyl, and C_{1-6}alkyl substituted with from 1 to 6 substituents independently selected from:
[0300] fluoro, oxo, —OH, —COOH, —NH_2, and —CN,
[0301] nitro, and
[0302] cyano.

[0303] Suitably "substituted" means the subject chemical moiety has from one to five substituents selected from the group consisting of:
[0304] fluoro,
[0305] chloro,
[0306] bromo,
[0307] iodo,
[0308] C_{1-4}alkyl,
[0309] C_{1-4}alkyl substituted with from 1 to 4 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN, —OC_{1-4}alkyl,
[0310] —OC_{1-4}alkyl substituted with from 1 to 4 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,
[0311] cycloalkyl,
[0312] cycloalkyl substituted with from 1 to 4 substituents independently selected from: —CH_3, and fluoro,
[0313] —SH,
[0314] —$S(O)_2H$,
[0315] oxo,
[0316] hydroxy,
[0317] amino,
[0318] —NHR^x,
[0319] where R^x is selected from C_{1-4}alkyl, and C_{1-6}alkyl substituted one to 4 times by fluoro,
[0320] —$NR^{x1}R^{x2}$,
[0321] where R^{x1} and R^{x2} are each independently selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted one to four times by fluoro,
[0322] guanidino,
[0323] hydroxyguanidino,
[0324] oxyguanidino;
[0325] —C(O)OH,
[0326] —C(O)OR^x,
[0327] where R^x is selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted one to four times by fluoro,
[0328] —C(O)NH_2,
[0329] —C(O)NHR^x,
[0330] where R^x is selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted one to four times by fluoro,
[0331] —C(O)$NR^{x1}R^{x2}$,
[0332] where R^{x1} and R^{x2} are each independently selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted one to four times by fluoro,
[0333] —$S(O)_2NH_2$,
[0334] —$NHS(O)_2H$,
[0335] —NHC(O)H,
[0336] —NHC(O)NH_2,
[0337] nitro, and
[0338] cyano.

[0339] In one embodiment, "substituted" means the subject chemical moiety has from one to five substituents selected from the group consisting of:
[0340] fluoro,
[0341] chloro,
[0342] bromo,
[0343] C_{1-4}alkyl,
[0344] C_{1-4}alkyl substituted with from 1 to 4 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,
[0345] —OC_{1-4}alkyl,
[0346] —OC_{1-4}alkyl substituted with from 1 to 4 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,
[0347] cycloalkyl,
[0348] cycloalkyl substituted with from 1 to 4 substituents independently selected from: —CH_3, and fluoro,
[0349] oxo,
[0350] hydroxy,
[0351] amino,
[0352] —NHR^x,
[0353] where R^x is selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted one to 4 times by fluoro,
[0354] —$NR^{x1}R^{x2}$,
[0355] where R^{x1} and R^{x2} are each independently selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted one to four times by fluoro,
[0356] —C(O)OH,
[0357] —C(O)OR^x,
[0358] where R^x is selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted one to four times by fluoro,
[0359] —C(O)NH_2,
[0360] —$NHS(O)_2H$,
[0361] —NHC(O)H,
[0362] —NHC(O)NH_2,
[0363] nitro, and
[0364] cyano.

[0365] In another embodiment, "substituted" means the subject chemical moiety has from one to three substituents selected from the group consisting of:
[0366] fluoro,
[0367] chloro,
[0368] bromo,
[0369] C_{1-4}alkyl,
[0370] C_{1-4}alkyl substituted with from 1 to 4 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,
[0371] —OC_{1-4}alkyl,
[0372] —OC_{1-4}alkyl substituted with from 1 to 4 substituents independently selected from: fluoro, oxo, —OH, —COOH, —NH_2, and —CN,
[0373] hydroxy,
[0374] amino,
[0375] —NHR^x,

[0376] where R^x is selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted one to 4 times by fluoro,

[0377] —$NR^{x1}R^{x2}$,

[0378] where R^{x1} and R^{x2} are each independently selected from C_{1-4}alkyl, and C_{1-4}alkyl substituted one to four times by fluoro,

[0379] —$C(O)NH_2$,

[0380] nitro, and

[0381] cyano.

[0382] In another embodiment, "substituted" means the subject chemical moiety has from one to three substituents selected from the group consisting of:

[0383] fluoro,

[0384] chloro,

[0385] —CH_3,

[0386] —OCH_3,

[0387] hydroxy,

[0388] amino,

[0389] —$C(O)NH_2$,

[0390] nitro, and

[0391] cyano.

[0392] As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

[0393] Ac (acetyl);

[0394] Ac_2O (acetic anhydride);

[0395] ACN (acetonitrile);

[0396] AIBN (azobis(isobutyronitrile));

[0397] BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl);

[0398] BMS (borane-dimethyl sulphide complex);

[0399] Bn (benzyl);

[0400] Boc (tert-Butoxycarbonyl);

[0401] Boc_2O (di-tert-butyl dicarbonate);

[0402] BOP (Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate);

[0403] CAN (cerric ammonium nitrate);

[0404] Cbz (benzyloxycarbonyl);

[0405] CSI (chlorosulfonyl isocyanate);

[0406] CSF (cesium fluoride);

[0407] DABCO (1,4-Diazabicyclo[2.2.2]octane);

[0408] DAST (Diethylamino)sulfur trifluoride);

[0409] DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene);

[0410] DCC (Dicyclohexyl Carbodiimide);

[0411] DCE (1,2-dichloroethane);

[0412] DCM (dichloromethane);

[0413] DDQ (2,3-Dichloro-5,6-dicyano-1,4-benzoquinone);

[0414] ATP (adenosine triphosphate);

[0415] Bis-pinacolatodiboron (4,4,4',4',5,5,5',5'-Octamethyl-2,2'-bi-1,3,2-dioxaborolane);

[0416] BSA (bovine serum albumin);

[0417] C18 (refers to 18-carbon alkyl groups on silicon in HPLC stationary phase);

[0418] CH_3CN (acetonitrile);

[0419] Cy (cyclohexyl);

[0420] DCM (dichloromethane);

[0421] DIPEA (Hünig's base, N-ethyl-N-(1-methylethyl)-2-propanamine);

[0422] Dioxane (1,4-dioxane);

[0423] DMAP (4-dimethylaminopyridine);

[0424] DME (1,2-dimethoxyethane);

[0425] DMEDA (N,N'-dimethylethylenediamine);

[0426] DMF (N,N-dimethylformamide);

[0427] DMSO (dimethylsulfoxide);

[0428] DPPA (diphenyl phosphoryl azide);

[0429] EDC (N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide);

[0430] EDTA (ethylenediaminetetraacetic acid);

[0431] EtOAc (ethyl acetate);

[0432] EtOH (ethanol);

[0433] Et_2O (diethyl ether);

[0434] HEPES (4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid);

[0435] HATU (O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate);

[0436] HOAt (1-hydroxy-7-azabenzotriazole);

[0437] HOBt (1-hydroxybenzotriazole);

[0438] HOAc (acetic acid);

[0439] HPLC (high pressure liquid chromatography);

[0440] HMDS (hexamethyldisilazide);

[0441] Hunig's Base (N,N-Diisopropylethylamine);

[0442] IPA (isopropyl alcohol);

[0443] Indoline (2,3-dihydro-1H-indole);

[0444] KHMDS (potassium hexamethyldisilazide);

[0445] LAH (lithium aluminum hydride);

[0446] LDA (lithium diisopropylamide);

[0447] LHMDS (lithium hexamethyldisilazide);

[0448] MeOH (methanol);

[0449] MTBE (methyl tert-butyl ether);

[0450] mCPBA (m-chloroperbezoic acid);

[0451] NaHMDS (sodium hexamethyldisilazide);

[0452] NBS (N-bromosuccinimide);

[0453] PE (petroleum ether);

[0454] $Pd_2(dba)_3$ (Tris(dibenzylideneacetone)dipalladium (0);

[0455] Pd(dppf)Cl_2.DCM Complex ([1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II).dichloromethane complex);

[0456] PyBOP (benzotriazo-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate);

[0457] PyBrOP (bromotripyrrolidinophosphonium hexafluorophosphate);

[0458] RPHPLC (reverse phase high pressure liquid chromatography);

[0459] RT (room temperature);

[0460] Sat. (saturated);

[0461] SFC (supercritical fluid chromatography);

[0462] SGC (silica gel chromatography);

[0463] SM (starting material);

[0464] TLC (thin layer chromatography);

[0465] TEA (triethylamine);

[0466] TEMPO (2,2,6,6-Tetramethylpiperidinyl 1-oxyl, free radical);

[0467] TFA (trifluoroacetic acid); and

[0468] THF (tetrahydrofuranyl).

[0469] All references to ether are to diethyl ether and brine refers to a saturated aqueous solution of NaCl.

Compound Preparation

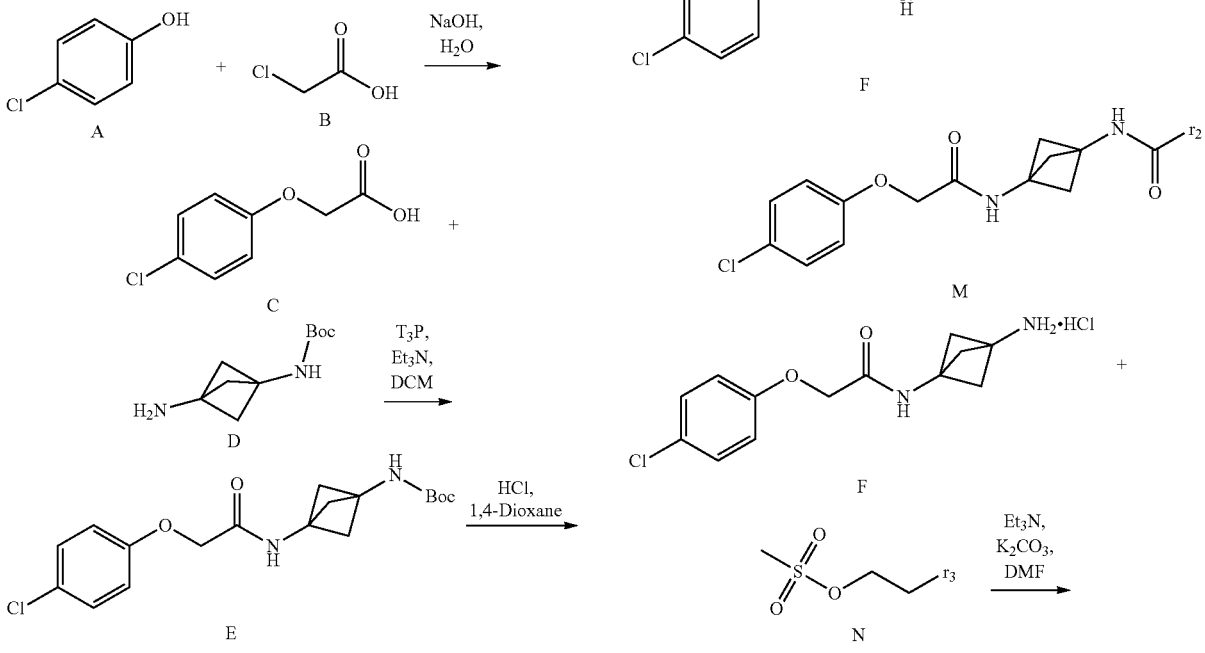
[0470] The compounds according to Formula (I) are prepared using conventional organic synthetic methods. A suitable synthetic route is depicted below in the following general reaction schemes. All of the starting materials are commercially available or are readily prepared from commercially available starting materials by those of skill in the art.

[0471] The skilled artisan will appreciate that if a substituent described herein is not compatible with the synthetic methods described herein, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions. The protecting group may be removed at a suitable point in the reaction sequence to provide a desired intermediate or target compound. Suitable protecting groups and the methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, *Protecting Groups in Organic Synthesis* (4th ed.), John Wiley & Sons, NY (2006). In some instances, a substituent may be specifically selected to be reactive under the reaction conditions used. Under these circumstances, the reaction conditions convert the selected substituent into another substituent that is either useful as an intermediate compound or is a desired substituent in a target compound.

[0472] As used in the Schemes, "r" groups represent corresponding positional groups on Formulas I and II. The compounds of Formulas I to II can be prepared generally as described in the Schemes using appropriate substitutions for starting materials.

General Schemes

[0473]



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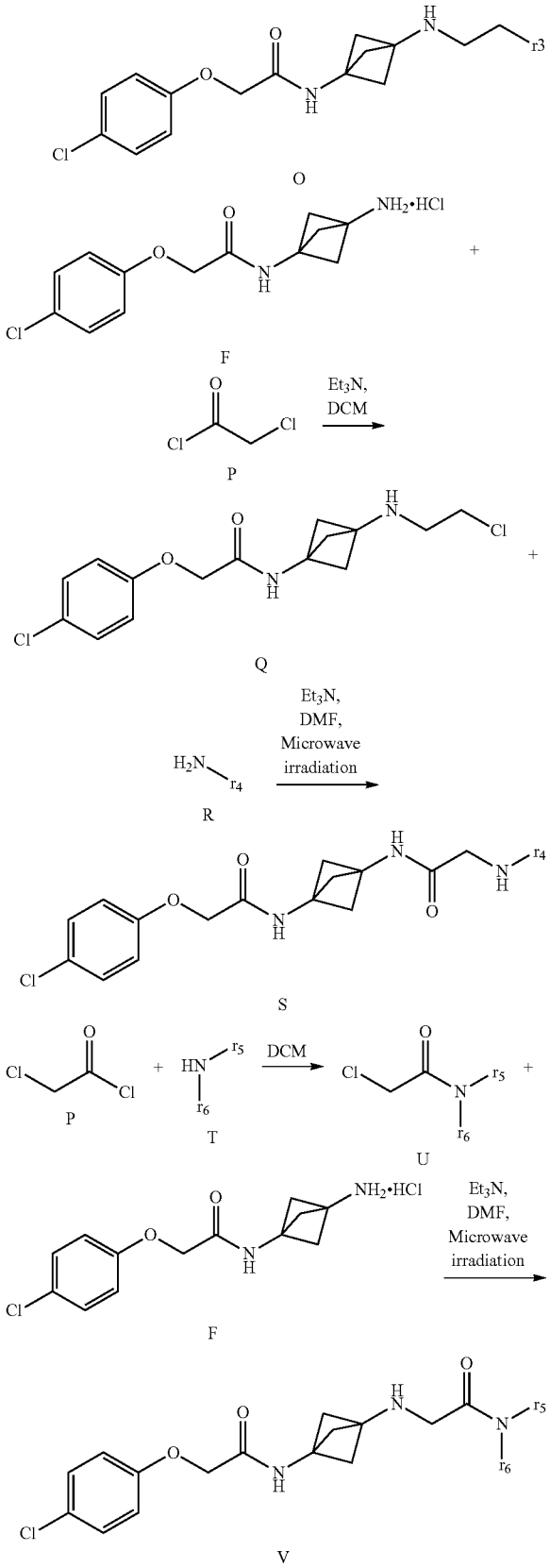

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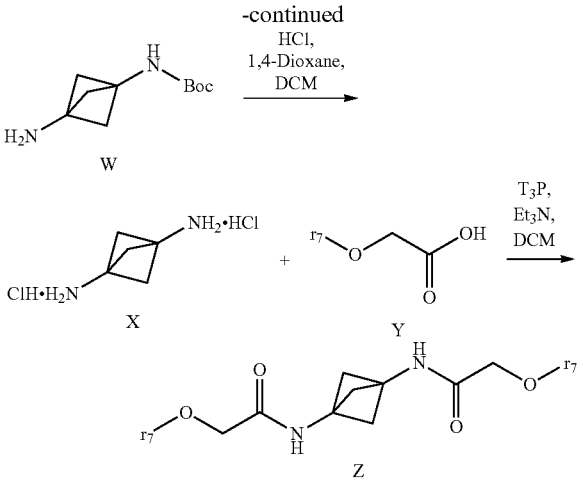


Methods of Use

[0474] The compounds according to Formula (I) and pharmaceutically acceptable salts thereof are inhibitors of the ATF4 pathway. Compounds which are inhibitors of the ATF4 pathway are readily identified by exhibiting activity in the ATF4 Cell Based Assay below. These compounds are potentially useful in the treatment of conditions wherein the underlying pathology is attributable to (but not limited to) modulation of the eIF2alpha pathway, for example, neurodegenerative disorders, cancer, cardiovascular and metabolic diseases. Accordingly, in another aspect the invention is directed to methods of treating such conditions.

[0475] The Integrated Stress Response (ISR) is a collection of cellular stress response pathways that converge in phosphorylation of the translation initiation factor eIF2α resulting in a reduction in overall translation in cells. Mammalian cells have four eIF2α kinases that phosphorylate this initiation factor in the same residue (serine 51); PERK is activated by the accumulation of unfolded proteins in the endoplasmic reticulum (ER), GCN2 is activated by amino acid starvation, PKR by viral infection and HRI by heme deficiency. Activation of these kinases decreases bulk protein synthesis but it also culminates in increased expression of specific mRNAs that contain uORFs. Two examples of these mRNAs are the transcription factor ATF4 and the pro-apoptotic gene CHOP. Phosphorylation of eIF2α upon stress and the concomitant reduction in protein translation has been shown to both have cytoprotective and cytotoxic effects depending on the cellular context and duration and severity of the stress. An integrated stress response-associated disease is a disease characterized by increased activity in the integrated stress response (e.g. increased phosphorylation of eIF2α by an eIF2α kinase compared to a control such as a subject without the disease). A disease associated with phosphorylation of eIF2α is disease characterized by an increase in phosphorylation of eIF2α relative to a control, such as a subject without the disease.

[0476] Activation of PERK occurs upon ER stress and hypoxic conditions and its activation and effect on translation has been shown to be cytoprotective for tumor cells (17). Adaptation to hypoxia in the tumor microenvironment is critical for survival and metastatic potential. PERK has also been shown to promote cancer proliferation by limiting

oxidative DNA damage and death (18, 19). Moreover, a newly identified PERK inhibitor has been shown to have antitumor activity in a human pancreatic tumor xenograft model (20). Compounds disclosed herein decrease the viability of cells that are subjected to ER-stress. Thus, pharmacological and acute inhibition of the PERK branch with the compounds disclosed herein results in reduced cellular fitness. During tumor growth, compounds disclosed herein, that block the cytoprotective effects of eIF2α phosphorylation upon stress may prove to be potent anti-proliferative agents.

[0477] It is known that under certain stress conditions several eIF2α kinases can be simultaneously activated. For example, during tumor growth, the lack of nutrients and hypoxic conditions are known to both activate GCN2 and PERK. Like PERK, GCN2 and their common target, ATF4, have been proposed to play a cytoprotective role (21). By blocking signaling by both kinases, compounds disclosed herein may bypass the ability of the ISR to protect cancer cells against the effects of low nutrients and oxygen levels encountered during the growth of the tumor.

[0478] Prolonged ER stress leads to the accumulation of CHOP, a pro-apoptotic molecule. In a prion mouse model, overexpression of the phosphatase of eIF2α increased survival of prion-infected mice whereas sustained eIF2α phosphorylation decreased survival (22). The restoration of protein translation rates during prion disease was shown to rescue synaptic deficits and neuronal loss. The compounds disclosed herein that make cells insensitive to eIF2α phosphorylation sustain protein translation. Compounds disclosed herein could prove potent inhibitors of neuronal cell death in prion disease by blocking the deleterious effects of prolonged eIF2α phosphorylation. Given the prevalence of protein misfolding and activation on the UPR in several neurodegenerative diseases (e.g. Alzheimer's (AD) and Parkinson's (PD)), manipulation of the PERK-eIF2α branch could prevent synaptic failure and neuronal death across the spectrum of these disorders.

[0479] Another example of tissue-specific pathology that is linked to heightened eIF2α phosphorylation is the fatal brain disorder, vanishing white matter disease (VWM) or childhood ataxia with CNS hypo-myelination (CACH). This disease has been linked to mutation in eIF2B, the GTP exchange factor that is necessary for eIF2 function in translation (23). eIF2α phosphorylation inhibits the activity of eIF2B and mutations in this exchange factor that reduce its exchange activity exacerbate the effects of eIF2α phosphorylation. The severe consequences of the CACH mutations point to the dangers of UPR hyper-activation, especially as it pertains to the myelin-producing oligodendrocyte. Small molecules, such as compounds disclosed herein, that block signaling through eIF2α phosphorylation may reduce the deleterious effects of its hyperactivation in VWM.

[0480] In another aspect is provided a method of improving long-term memory in a patient, the method including administering a therapeutically effective amount of a compound of Formula (I) to the patient. In embodiments, the patient is human. In embodiments, the patient is a mammal.

[0481] In embodiments, the compounds set forth herein are provided as pharmaceutical compositions including the compound and a pharmaceutically acceptable excipient. In embodiments of the method, the compound, or a pharmaceutically acceptable salt thereof, is co-administered with a second agent (e.g. therapeutic agent). In embodiments of the method, the compound, or a pharmaceutically acceptable salt thereof, is co-administered with a second agent (e.g. therapeutic agent), which is administered in a therapeutically effective amount. In embodiments, the second agent is an agent for improving memory.

[0482] Induction of long-term memory (LTM) has been shown to be facilitated by decreased and impaired by increased eIF2α phosphorylation. The data strongly support the notion that under physiological conditions, a decrease in eIF2α phosphorylation constitutes a critical step for the long term synaptic changes required for memory formation and ATF4 has been shown to be an important regulator of these processes (24) (25) (26). It is not known what the contributions of the different eIF2α kinases to learning are or whether each plays a differential role in the different parts of the brain. Regardless of the eIF2α kinase/s responsible for phosphorylation of eIF2α in the brain, compounds disclosed herein that block translation and ATF4 production make them ideal molecules to block the effects of this phosphorylation event on memory. Pharmacological treatment with compounds disclosed herein may increase spatial memory and enhance auditory and contextual fear conditioning.

[0483] Regulators of translation, such as the compounds of Formula (I), could serve as therapeutic agents that improve memory in human disorders associated with memory loss such as Alzheimer's disease and in other neurological disorders that activate the UPR in neurons and thus could have negative effects on memory consolidation such as Parkinson's disease, Amyotrophic lateral sclerosis and prion diseases. In addition, a mutation in eIF2γ, that disrupts complex integrity linked intellectual disability (intellectual disability syndrome or ID) to impaired translation initiation in humans (27). Hence, two diseases with impaired eIF2 function, ID and VWM, display distinct phenotypes but both affect mainly the brain and impair learning.

[0484] The compounds of Formula (I) are also useful in applications where increasing protein production output is desirable, such as in vitro cell free systems for protein production. In vitro systems have basal levels of eIF2α phosphorylation that reduce translational output (28, 29). Similarly production of antibodies by hybridomas may also be improved by addition of compounds disclosed herein.

[0485] In another aspect of the invention, regulators of translation, such as the compounds of Formula (I), could serve as therapeutic agents that improve lung function impaired in patients with asthma, emphesyma, or lung fibrosis in general. It has been shown that the PERK-ATF4 pathway is activated in models of lung diseases and intervention reduces the severity of the dysfunction [Guo Q, et al., Tunicamycin aggravates endoplasmic reticulum stress and airway inflammation via PERK-ATF4-CHOP signaling in a murine model of neutrophilic asthma. J Asthma. 2017 March; 54(2):125-133. Makhija L, et al., Chemical chaperones mitigate experimental asthma by attenuating endoplasmic reticulum stress. Am J Respir Cell Mol Biol. 2014 May; 50(5):923-31. Lin L, et al., Ursolic acid attenuates cigarette smoke-induced emphysema in rats by regulating PERK and Nrf2 pathways. Pulm Pharmacol Ther. 2017 June; 44:111-121.]

[0486] In another aspect is provided a method of increasing protein expression of a cell or in vitro expression system, the method including administering an effective amount of a compound of Formula (I) to the cell or expression system.

In embodiments, the method is a method of increasing protein expression by a cell and includes administering an effective amount of a compound of Formula (I) to the cell. In embodiments, the method is a method of increasing protein expression by an in vitro protein expression system and includes administering an effective amount of a compound of Formula (I) to the in vitro (e.g. cell free) protein expression system.

[0487] In embodiments, the compounds set forth herein are provided as pharmaceutical compositions including the compound and a pharmaceutically acceptable excipient. In embodiments of the method, the compound, or a pharmaceutically acceptable salt thereof, is co-administered with a second agent. In embodiments of the method, the compound, or a pharmaceutically acceptable salt thereof, is co-administered with a second agent, which is administered in a therapeutically effective amount. In embodiments, the second agent is an agent for improving protein expression.

[0488] Suitably, the present invention relates to a method for treating or lessening the severity of breast cancer, including inflammatory breast cancer, ductal carcinoma, and lobular carcinoma.

[0489] Suitably the present invention relates to a method for treating or lessening the severity of colon cancer.

[0490] Suitably the present invention relates to a method for treating or lessening the severity of pancreatic cancer, including insulinomas, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, and glucagonoma.

[0491] Suitably the present invention relates to a method for treating or lessening the severity of skin cancer, including melanoma, including metastatic melanoma.

[0492] Suitably the present invention relates to a method for treating or lessening the severity of lung cancer including small cell lung cancer, non-small cell lung cancer, squamous cell carcinoma, adenocarcinoma, and large cell carcinoma.

[0493] Suitably the present invention relates to a method for treating or lessening the severity of cancers selected from the group consisting of brain (gliomas), glioblastomas, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, head and neck, kidney, liver, melanoma, ovarian, pancreatic, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma, insulinoma, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid, lymphoblastic T cell leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic neutrophilic leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, Immunoblastic large cellleukemia, mantle cell leukemia, multiple myeloma, megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, erythroleukemia, malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor), neuroendocrine cancers and testicular cancer.

[0494] Suitably the present invention relates to a method for treating or lessening the severity of pre-cancerous syndromes in a mammal, including a human, wherein the pre-cancerous syndrome is selected from: cervical intraepithelial neoplasia, monoclonal gammapathy of unknown significance (MGUS), myelodysplastic syndrome, aplastic anemia, cervical lesions, skin nevi (pre-melanoma), prostatic intraepithelial (intraductal) neoplasia (PIN), Ductal Carcinoma in situ (DCIS), colon polyps and severe hepatitis or cirrhosis.

[0495] Suitably the present invention relates to a method for treating or lessening the severity of neurodegenerative diseases/injury, such as Alzheimer's disease, spinal cord injury, traumatic brain injury, ischemic stroke, stroke, diabetes, Parkinson disease, Huntington's disease, Creutzfeldt-Jakob Disease, and related prion diseases, progressive supranuclear palsy, amyotrophic lateral sclerosis, myocardial infarction, cardiovascular disease, inflammation, fibrosis, chronic and acute diseases of the liver, chronic and acute diseases of the lung, chronic and acute diseases of the kidney, chronic traumatic encephalopathy (CTE), neurodegeneration, dementia, traumatic brain injury, cognitive impairment, atherosclerosis, ocular diseases, arrhythmias, in organ transplantation and in the transportation of organs for transplantation.

[0496] Suitably the present invention relates to a method for preventing organ damage during and after organ transplantation and in the transportation of organs for transplantation. The method of preventing organ damage during and after organ transplantation will comprise the in vivo administration of a compound of Formula (I). The method of preventing organ damage during the transportation of organs for transplantation will comprise adding a compound of Formula (I) to the solution housing the organ during transportation.

[0497] Suitably the present invention relates to a method for treating or lessening the severity of ocular diseases/angiogenesis. The method of treating or lessening the severity of ocular diseases/angiogenesis will comprise the in vivo administration of a compound of Formula (I). In embodiments of methods according to the invention, the disorder of ocular diseases, including vascular leakage can be: edema or neovascularization for any occlusive or inflammatory retinal vascular disease, such as rubeosis irides, neovascular glaucoma, pterygium, vascularized glaucoma filtering blebs, conjunctival papilloma; choroidal neovascularization, such as neovascular age-related macular degeneration (AMD), myopia, prior uveitis, trauma, or idiopathic; macular edema, such as post surgical macular edema, macular edema secondary to uveitis including retinal and/or choroidal inflammation, macular edema secondary to diabetes, and macular edema secondary to retinovascular occlusive disease (i.e. branch and central retinal vein occlusion); retinal neovascularization due to diabetes, such as retinal vein occlusion, uveitis, ocular ischemic syndrome from carotid artery disease, ophthalmic or retinal artery occlusion, sickle cell retinopathy, other ischemic or occlusive neovascular retinopathies, retinopathy of prematurity, or Eale's Disease; and genetic disorders, such as VonHippel-Lindau syndrome.

[0498] In some embodiments, the neovascular age-related macular degeneration is wet age-related macular degeneration. In other embodiments, the neovascular age-related macular degeneration is dry age-related macular degenera-

tion and the patient is characterized as being at increased risk of developing wet age-related macular degeneration.

[0499] The methods of treatment of the invention comprise administering an effective amount of a compound according to Formula (I) or a pharmaceutically acceptable salt, thereof to a patient in need thereof.

[0500] The invention also provides a compound according to Formula (I) or a pharmaceutically-acceptable salt thereof for use in medical therapy, and particularly in therapy for: cancer, pre-cancerous syndromes, Alzheimer's disease, spinal cord injury, traumatic brain injury, ischemic stroke, stroke, diabetes, Parkinson disease, Huntington's disease, Creutzfeldt-Jakob Disease, and related prion diseases, progressive supranuclear palsy, amyotrophic lateral sclerosis, myocardial infarction, cardiovascular disease, inflammation, fibrosis, chronic and acute diseases of the liver, chronic and acute diseases of the lung, chronic and acute diseases of the kidney, chronic traumatic encephalopathy (CTE), neurodegeneration, dementia, traumatic brain injury, cognitive impairment, atherosclerosis, ocular diseases, in organ transplantation and arrhythmias. The invention also provides a compound according to Formula (I) or a pharmaceutically-acceptable salt thereof for use in preventing organ damage during the transportation of organs for transplantation. Thus, in further aspect, the invention is directed to the use of a compound according to Formula (I) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a disorder characterized by activation of the UPR, such as cancer.

[0501] The methods of treatment of the invention comprise administering a safe and effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof to a mammal, suitably a human, in need thereof.

[0502] As used herein, "treat", and derivatives thereof, in reference to a condition means: (1) to ameliorate the condition or one or more of the biological manifestations of the condition, (2) to interfere with (a) one or more points in the biological cascade that leads to or is responsible for the condition or (b) one or more of the biological manifestations of the condition, (3) to alleviate one or more of the symptoms or effects associated with the condition, or (4) to slow the progression of the condition or one or more of the biological manifestations of the condition.

[0503] The term "treating" and derivatives thereof refers to therapeutic therapy. Therapeutic therapy is appropriate to alleviate symptoms or to treat at early signs of disease or its progression.

[0504] Prophylactic therapy is appropriate when a subject has, for example, a strong family history of neurodegenerative diseases. Prophylactic therapy is appropriate when a subject has, for example, a strong family history of cancer or is otherwise considered at high risk for developing cancer, or when a subject has been exposed to a carcinogen.

[0505] The skilled artisan will appreciate that "prevention" is not an absolute term. In medicine, "prevention" is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or severity of a condition or biological manifestation thereof, or to delay the onset of such condition or biological manifestation thereof.

[0506] As used herein, "safe and effective amount" in reference to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, means an amount of the compound sufficient to treat the patient's condition but low enough to avoid serious side effects (at a reasonable benefit/risk ratio) within the scope of sound medical judgment. A safe and effective amount of the compound will vary with the particular route of administration chosen; the condition being treated; the severity of the condition being treated; the age, size, weight, and physical condition of the patient being treated; the medical history of the patient to be treated; the duration of the treatment; the nature of concurrent therapy; the desired therapeutic effect; and like factors, but can nevertheless be determined by the skilled artisan.

[0507] As used herein, "subject", "patient", and derivatives thereof refers to a human or other mammal, suitably a human.

[0508] As used herein, "patient", and derivatives thereof refers to a human or other mammal, suitably a human.

[0509] The subject to be treated in the methods of the invention is typically a mammal in need of such treatment, preferably a human in need of such treatment.

[0510] The compounds of Formula (I) or pharmaceutically acceptable salts thereof may be administered by any suitable route of administration, including systemic administration.

[0511] Systemic administration includes oral administration, and parenteral administration.

[0512] Parenteral administration refers to routes of administration other than enteral, transdermal, or by inhalation, and is typically by injection or infusion. Parenteral administration includes intravenous, intramuscular, and subcutaneous injection or infusion.

[0513] The compounds of Formula (I) or pharmaceutically acceptable salts thereof may be administered once or according to a dosing regimen wherein a number of doses are administered at varying intervals of time for a given period of time. For example, doses may be administered one, two, three, or four times per day. Doses may be administered until the desired therapeutic effect is achieved or indefinitely to maintain the desired therapeutic effect. Suitable dosing regimens for a compound of the invention depend on the pharmacokinetic properties of that compound, such as absorption, distribution, and half-life, which can be determined by the skilled artisan. In addition, suitable dosing regimens, including the duration such regimens are administered, for a compound of the invention depend on the condition being treated, the severity of the condition being treated, the age and physical condition of the patient being treated, the medical history of the patient to be treated, the nature of concurrent therapy, the desired therapeutic effect, and like factors within the knowledge and expertise of the skilled artisan. It will be further understood by such skilled artisans that suitable dosing regimens may require adjustment given an individual patient's response to the dosing regimen or overtime as individual patient needs change.

[0514] Typical daily dosages may vary depending upon the particular route of administration chosen. Typical dosages for oral administration range from 1 mg to 1000 mg per person per dose. Preferred dosages are 1-500 mg once daily or twice a day per person.

[0515] Additionally, the compounds of Formula (I) or pharmaceutically-acceptable salts thereof may be administered as prodrugs. As used herein, a "prodrug" of a compound of the invention is a functional derivative of the compound which, upon administration to a patient, eventually liberates the compound of the invention in vivo. Administration of a compound of the invention as a prodrug may enable the skilled artisan to do one or more of the following: (a) modify the onset of the compound in vivo; (b) modify the

duration of action of the compound in vivo; (c) modify the transportation or distribution of the compound in vivo; (d) modify the solubility of the compound in vivo; and (e) overcome a side effect or other difficulty encountered with the compound. Typical functional derivatives used to prepare prodrugs include modifications of the compound that are chemically or enzymatically cleaved in vivo. Such modifications, which include the preparation of phosphates, ethers, esters, carbonates, and carbamates, are well known to those skilled in the art. Where a —COOH or —OH group is present, pharmaceutically acceptable esters can be employed, for example methyl, ethyl, and the like for —COOH, and acetate maleate and the like for —OH, and those esters known in the art for modifying solubility or hydrolysis characteristics.

[0516] The compounds of Formula (I) and pharmaceutically acceptable salts thereof may be co-administered with at least one other active agent known to be useful in the treatment of cancer or pre-cancerous syndromes.

[0517] By the term "co-administration" as used herein is meant either simultaneous administration or any manner of separate sequential administration of an ATF4 pathway inhibiting compound, as described herein, and a further active agent or agents, known to be useful in the treatment of cancer, including chemotherapy and radiation treatment. The term further active agent or agents, as used herein, includes any compound or therapeutic agent known to or that demonstrates advantageous properties when administered to a patient in need of treatment for cancer. Preferably, if the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered by injection and another compound may be administered orally.

[0518] Typically, any anti-neoplastic agent that has activity versus a susceptible tumor being treated may be co-administered in the treatment of cancer in the present invention. Examples of such agents can be found in Cancer Principles and Practice of Oncology by V. T. Devita and S. Hellman (editors), 6^{th} edition (Feb. 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Typical anti-neoplastic agents useful in the present invention include, but are not limited to, anti-microtubule agents such as diterpenoids and *vinca* alkaloids; platinum coordination complexes; alkylating agents such as nitrogen mustards, oxazaphosphorines, alkylsulfonates, nitrosoureas, and triazenes; antibiotic agents such as anthracyclins, actinomycins and bleomycins; topoisomerase II inhibitors such as epipodophyllotoxins; antimetabolites such as purine and pyrimidine analogues and anti-folate compounds; topoisomerase I inhibitors such as camptothecins; hormones and hormonal analogues; signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; cell cycle signaling inhibitors; proteasome inhibitors; and inhibitors of cancer metabolism.

[0519] Examples of a further active ingredient or ingredients (anti-neoplastic agent) for use in combination or co-administered with the presently invented ATF4 pathway inhibiting compounds are chemotherapeutic agents.

[0520] Suitably, the pharmaceutically active compounds of the invention are used in combination with a VEGFR inhibitor, suitably 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl) methylamino]-2-pyrimidinyl]amino]-2-methylbenzene-sulfonamide, or a pharmaceutically acceptable salt, suitably the monohydrochloride salt thereof, which is disclosed and claimed in International Application No. PCT/US01/49367, having an International filing date of Dec. 19, 2001, International Publication Number WO02/059110 and an International Publication date of Aug. 1, 2002, the entire disclosure of which is hereby incorporated by reference, and which is the compound of Example 69. 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl] amino]-2-methylbenzenesulfonamide can be prepared as described in International Application No. PCT/US01/49367.

[0521] In one embodiment, the cancer treatment method of the claimed invention includes the co-administration a compound of Formula (I) and/or a pharmaceutically acceptable salt thereof and at least one anti-neoplastic agent, such as one selected from the group consisting of anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, cell cycle signaling inhibitors; proteasome inhibitors; and inhibitors of cancer metabolism.

[0522] In one embodiment, a compound of Formula (I) is used as a chemosensitizer to enhance tumor cell killing.

[0523] In one embodiment, a compound of Formula (I) is used in combination as a chemosensitizer to enhance tumor cell killing.

[0524] In one embodiment, a compound of Formula (I) is used in combination with a compound that inhibits the activity of protein kinase R (PKR)-like ER kinase, PERK (PERK inhibitor).

[0525] In one embodiment, a compound of Formula (I) is used in combination with a PERK inhibitor to treat diseases/injuries associated with activated unfolded protein response pathways.

[0526] In one embodiment, a compound of Formula (I) is used in combination with a PERK inhibitor to treat neurodegenerative diseases.

[0527] In one embodiment, a compound of Formula (I) is used in combination with a PERK inhibitor to treat cancer.

[0528] Suitably, the compounds of Formula (I) and pharmaceutically acceptable salts thereof may be co-administered with at least one other active agent known to be inhibitors or PERK kinase (EIF2K3) for treating or lessening the severity of neurodegenerative diseases/injury, such as Alzheimer's disease, spinal cord injury, traumatic brain injury, ischemic stroke, stroke, diabetes, Parkinson disease, Huntington's disease, Creutzfeldt-Jakob Disease, and related prion diseases, progressive supranuclear palsy, amyotrophic lateral sclerosis, myocardial infarction, cardiovascular disease, inflammation, fibrosis, chronic and acute diseases of the liver, chronic and acute diseases of the lung, chronic and acute diseases of the kidney, chronic traumatic encephalopathy (CTE), neurodegeneration, dementia, traumatic brain injury, cognitive impairment, atherosclerosis, ocular diseases, arrhythmias, in organ transplantation and in the transportation of organs for transplantation. "Chemo-

therapeutic" or "chemotherapeutic agent" is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

[0529] Additionally, the compounds described herein can be co-administered with conventional immunotherapeutic agents including, but not limited to, immunostimulants (e.g., *Bacillus* Calmette-Guerin (BCG), levamisole, interleukin-2, alpha-interferon, etc.), monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-*pseudomonas* exotoxin conjugate, etc.), and radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to ^{111}In, ^{90}Y, or ^{131}I, etc.).

[0530] In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as ^{47}Sc, ^{64}C ^{67}C, ^{89}Sr, ^{86}Y, ^{87}Y, and ^{212}Bi, optionally conjugated to antibodies directed against tumor antigens.

[0531] Additional examples of a further active ingredient or ingredients (anti-neoplastic agent) for use in combination or co-administered with the presently invented ATF4 pathway inhibiting compounds are anti-PD-1 agents.

[0532] Anti-PD-1 antibodies and methods of making the same are known in the art.

[0533] Such antibodies to PD-L1 may be polyclonal or monoclonal, and/or recombinant, and/or humanized.

[0534] Exemplary PD-L1 antibodies are disclosed in:

[0535] U.S. Pat. No. 8,217,149; Ser. No. 12/633,339;

[0536] U.S. Pat. No. 8,383,796; Ser. No. 13/091,936;

[0537] U.S. Pat. No. 8,552,154; Ser. No. 13/120,406;

[0538] US patent publication No. 20110280877; Ser. No. 13/068,337;

[0539] US Patent Publication No. 20130309250; Ser. No. 13/892,671;

[0540] WO2013019906;

[0541] WO2013079174;

[0542] U.S. application Ser. No. 13/511,538 (filed Aug. 7, 2012), which is the US National Phase of International Application No. PCT/US10/58007 (filed 2010);

[0543] and

[0544] U.S. application Ser. No. 13/478,511 (filed May 23, 2012).

[0545] Additional exemplary antibodies to PD-L1 (also referred to as CD274 or B7-H1) and methods for use are disclosed in U.S. Pat. No. 7,943,743; US20130034559, WO2014055897, U.S. Pat. Nos. 8,168,179; and 7,595,048. PD-L1 antibodies are in development as immuno-modulatory agents for the treatment of cancer.

[0546] In one embodiment, the antibody to PD-L1 is an antibody disclosed in U.S. Pat. No. 8,217,149. In another embodiment, the anti-PD-L1 antibody comprises the CDRs of an antibody disclosed in U.S. Pat. No. 8,217,149.

[0547] In another embodiment, the antibody to PD-L1 is an antibody disclosed in US application Ser. No. 13/511,538. In another embodiment, the anti-PD-L1 antibody comprises the CDRs of an antibody disclosed in U.S. application Ser. No. 13/511,538.

[0548] In another embodiment, the antibody to PD-L1 is an antibody disclosed in application Ser. No. 13/478,511. In another embodiment, the anti-PD-L1 antibody comprises the CDRs of an antibody disclosed in U.S. application Ser. No. 13/478,511.

[0549] In one embodiment, the anti-PD-L1 antibody is BMS-936559 (MDX-1105). In another embodiment, the anti-PD-L1 antibody is MPDL3280A (RG7446). In another embodiment, the anti-PD-L1 antibody is MEDI4736.

[0550] Additional examples of a further active ingredient or ingredients (anti-neoplastic agent) for use in combination or co-administered with the presently invented ATF4 pathway inhibiting compounds are PD-1 antagonist. "PD-1 antagonist" means any chemical compound or biological molecule that blocks binding of PD-L1 expressed on a cancer cell to PD-1 expressed on an immune cell (T cell, B cell or NKT cell) and preferably also blocks binding of PD-L2 expressed on a cancer cell to the immune-cell expressed PD-1. Alternative names or synonyms for PD-1 and its ligands include: PDCD1, PD1, CD279 and SLEB2 for PD-1; PDCD1L1, PDL1, B7H1, B7-4, CD274 and B7-H for PD-L1; and PDCD1L2, PDL2, B7-DC, Btdc and CD273 for PD-L2. In any embodiments of the aspects or embodiments of the present invention in which a human individual is to be treated, the PD-1 antagonist blocks binding of human PD-L1 to human PD-1, and preferably blocks binding of both human PD-L1 and PD-L2 to human PD-1. Human PD-1 amino acid sequences can be found in NCBI Locus No.: NP_005009. Human PD-L1 and PD-L2 amino acid sequences can be found in NCBI Locus No.: NP_054862 and NP_079515, respectively.

[0551] PD-1 antagonists useful in the any of the aspects of the present invention include a monoclonal antibody (mAb), or antigen binding fragment thereof, which specifically binds to PD-1 or PD-L1, and preferably specifically binds to human PD-1 or human PD-L1. The mAb may be a human antibody, a humanized antibody or a chimeric antibody, and may include a human constant region. In some embodiments, the human constant region is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4 constant regions, and in preferred embodiments, the human constant region is an IgG1 or IgG4 constant region. In some embodiments, the antigen binding fragment is selected from the group consisting of Fab, Fab'-SH, F(ab')2, scFv and Fv fragments.

[0552] Examples of mAbs that bind to human PD-1, and useful in the various aspects and embodiments of the present invention, are described in U.S. Pat. Nos. 7,488,802, 7,521,051, 8,008,449, 8,354,509, 8,168,757, WO2004/004771, WO2004/072286, WO2004/056875, and US2011/0271358.

[0553] Specific anti-human PD-1 mAbs useful as the PD-1 antagonist in any of the aspects and embodiments of the present invention include: MK-3475, a humanized IgG4 mAb with the structure described in *WHO Drug Information*, Vol. 27, No. 2, pages 161-162 (2013) and which comprises the heavy and light chain amino acid sequences shown in FIG. 6; nivolumab, a human IgG4 mAb with the structure described in *WHO Drug Information*, Vol. 27, No. 1, pages 68-69 (2013) and which comprises the heavy and light chain amino acid sequences shown in FIG. 7; the humanized antibodies h409A11, h409A16 and h409A17, which are described in WO2008/156712, and AMP-514, which is being developed by Medimmune.

[0554] Other PD-1 antagonists useful in the any of the aspects and embodiments of the present invention include an immunoadhesin that specifically binds to PD-1, and preferably specifically binds to human PD-1, e.g., a fusion protein

containing the extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region such as an Fc region of an immunoglobulin molecule. Examples of immunoadhesion molecules that specifically bind to PD-1 are described in WO2010/027827 and WO2011/066342. Specific fusion proteins useful as the PD-1 antagonist in the treatment method, medicaments and uses of the present invention include AMP-224 (also known as B7-DCIg), which is a PD-L2-FC fusion protein and binds to human PD-1.

[0555] Other examples of mAbs that bind to human PD-L1, and useful in the treatment method, medicaments and uses of the present invention, are described in WO2013/019906, WO2010/077634 A1 and U.S. Pat. No. 8,383,796. Specific anti-human PD-L1 mAbs useful as the PD-1 antagonist in the treatment method, medicaments and uses of the present invention include MPDL3280A, BMS-936559, MEDI4736, MSB0010718C.

[0556] KEYTRUDA/pembrolizumab is an anti-PD-1 antibody marketed for the treatment of lung cancer by Merck. The amino acid sequence of pembrolizumab and methods of using are disclosed in U.S. Pat. No. 8,168,757.

[0557] Opdivo/nivolumab is a fully human monoclonal antibody marketed by Bristol Myers Squibb directed against the negative immunoregulatory human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1/PCD-1) with immunopotentiation activity. Nivolumab binds to and blocks the activation of PD-1, an Ig superfamily transmembrane protein, by its ligands PD-L1 and PD-L2, resulting in the activation of T-cells and cell-mediated immune responses against tumor cells or pathogens. Activated PD-1 negatively regulates T-cell activation and effector function through the suppression of P13k/Akt pathway activation. Other names for nivolumab include: BMS-936558, MDX-1106, and ONO-4538. The amino acid sequence for nivolumab and methods of using and making are disclosed in U.S. Pat. No. 8,008,449.

[0558] Additional examples of a further active ingredient or ingredients (anti-neoplastic agent) for use in combination or co-administered with the presently invented ATF4 pathway inhibiting compounds are immuno-modulators.

[0559] As used herein "immuno-modulators" refer to any substance including monoclonal antibodies that affects the immune system. The ICOS binding proteins of the present invention can be considered immune-modulators. Immuno-modulators can be used as anti-neoplastic agents for the treatment of cancer. For example, immune-modulators include, but are not limited to, anti-CTLA-4 antibodies such as ipilimumab (YERVOY) and anti-PD-1 antibodies (Opdivo/nivolumab and Keytruda/pembrolizumab). Other immuno-modulators include, but are not limited to, OX-40 antibodies, PD-L1 antibodies, LAG3 antibodies, TIM-3 antibodies, 41BB antibodies and GITR antibodies.

[0560] Yervoy (ipilimumab) is a fully human CTLA-4 antibody marketed by Bristol Myers Squibb. The protein structure of ipilimumab and methods are using are described in U.S. Pat. Nos. 6,984,720 and 7,605,238.

[0561] Suitably, the compounds of Formula (I) and pharmaceutically acceptable salts thereof may be co-administered with at least one other active agent known to be useful in the treatment of neurodegenerative diseases/injury.

[0562] Suitably, the compounds of Formula (I) and pharmaceutically acceptable salts thereof may be co-administered with at least one other active agent known to be useful in the treatment of diabetes.

[0563] Suitably, the compounds of Formula (I) and pharmaceutically acceptable salts thereof may be co-administered with at least one other active agent known to be useful in the treatment of cardiovascular disease.

[0564] Suitably, the compounds of Formula (I) and pharmaceutically acceptable salts thereof may be co-administered with at least one other active agent known to be useful in the treatment of ocular diseases.

[0565] The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer (e.g. pancreatic cancer, breast cancer, multiple myeloma, or cancers of secretory cells), neurodegenerative diseases, vanishing white matter disease, childhood ataxia with CNS hypo-myelination, and/or intellectual disability syndromes (e.g. associated with impaired function of eIF2 or components in a signal transduction pathway including eIF2), or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

[0566] In embodiments, the compounds set forth herein are provided as pharmaceutical compositions including the compound and a pharmaceutically acceptable excipient. In embodiments of the method, the compound, or a pharmaceutically acceptable salt thereof, is co-administered with a second agent (e.g. therapeutic agent). In embodiments of the method, the compound, or a pharmaceutically acceptable salt thereof, is co-administered with a second agent (e.g. therapeutic agent), which is administered in a therapeutically effective amount. In embodiments of the method, the second agent is an agent for treating cancer (e.g. pancreatic cancer, breast cancer, multiple myeloma, or cancers of secretory cells), neurodegenerative diseases, vanishing white matter disease, childhood ataxia with CNS hypo-myelination, and/or intellectual disability syndromes (e.g. associated with impaired function of eIF2 or components in a signal transduction pathway including eIF2), or an inflammatory disease (e.g. POCD or TBI). In embodiments, the second agent is an anti-cancer agent. In embodiments, the second agent is a chemotherapeutic. In embodiments, the second agent is an agent for improving memory. In embodiments, the second agent is an agent for treating a neurodegenerative disease. In embodiments, the second agent is an agent for treating vanishing white matter disease. In embodiments, the second agent is an agent for treating childhood ataxia with CNS hypo-myelination. In embodiments, the second agent is an agent for treating an intellectual disability syndrome. In embodiments, the second agent is an agent for treating pancreatic cancer. In embodiments, the second agent is an agent for treating breast cancer. In embodiments, the second agent is an agent for treating multiple myeloma. In embodiments, the second agent is an agent for treating myeloma. In embodiments, the second agent is an agent for treating a cancer of a secretory cell. In embodiments, the second agent is an agent for reducing eIF2α phosphorylation. In embodiments, the second agent is an agent for inhibiting a pathway activated by eIF2α phosphorylation. In embodiments, the second agent is an agent for inhibiting the integrated stress response. In embodiments, the second agent is an anti-inflammatory agent.

[0567] The term "eIF2alpha" or "eIF2α" refers to the protein "Eukaryotic translation initiation factor 2A". In embodiments, "eIF2alpha" or "eIF2α" refers to the human protein. Included in the term "eIF2alpha" or "eIF2α" are the wildtype and mutant forms of the protein. In embodiments, "eIF2alpha" or "eIF2α" refers to the protein associated with Entrez Gene 83939, OMIM 609234, UniProt Q9BY44, and/or RefSeq (protein) NP 114414.

[0568] Suitably, the present invention relates to a method for treating an integrated stress response associated disease in a patient in need of such treatment, the method including administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the patient.

[0569] Suitably, the integrated stress response-associated disease is cancer. Suitably, the integrated stress response-associated disease is a neurodegenerative disease. Suitably, the integrated stress response-associated disease is vanishing white matter disease. Suitably, the integrated stress response-associated disease is childhood ataxia with CNS hypo-myelination. Suitably, the integrated stress response-associated disease is an intellectual disability syndrome.

[0570] Suitably, the present invention relates to a method for treating a disease associated with phosphorylation of eIF2α in a patient in need of such treatment, the method including administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the patient.

[0571] Suitably, the disease associated with phosphorylation of eIF2 α is cancer. Suitably, the disease associated with phosphorylation of eIF2 α is a neurodegenerative disease. Suitably, the disease associated with phosphorylation of eIF2 α is vanishing white matter disease. Suitably, the disease associated with phosphorylation of eIF2 α is childhood ataxia with CNS hypo-myelination. Suitably, the disease associated with phosphorylation of eIF2 α is an intellectual disability syndrome.

[0572] Suitably, the present invention relates to a method for treating a disease selected from the group consisting of cancer, a neurodegenerative disease, vanishing white matter disease, childhood ataxia with CNS hypomyelination, and an intellectual disability syndrome.

[0573] Suitably, the present invention relates to a method for treating an inflammatory disease in a patient in need of such treatment, the method including administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the patient.

[0574] Suitably, the inflammatory disease is associated with neurological inflammation. Suitably, the inflammatory disease is postoperative cognitive dysfunction. Suitably, the inflammatory disease is traumatic brain injury or chronic traumatic encephalopathy (CTE).

[0575] In embodiments of the method of treating a disease, the disease is selected from the group consisting of cancer, a neurodegenerative disease, vanishing white matter disease, childhood ataxia with CNS hypo-myelination, and an intellectual disability syndrome. In embodiments of the method of treating a disease, the disease is cancer.

[0576] In embodiments of the method of treating a disease, the disease is a neurodegenerative disease. In embodiments of the method of treating a disease, the disease is vanishing white matter disease. In embodiments of the method of treating a disease, the disease is childhood ataxia with CNS hypo-myelination. In embodiments of the method of treating a disease, the disease is an intellectual disability syndrome. In embodiments of the method of treating a disease, the disease is associated with phosphorylation of eIF2α. In embodiments of the method of treating a disease, the disease is associated with an eIF2α signaling pathway. In embodiments of the method of treating a disease, the disease is a cancer of a secretory cell type. In embodiments of the method of treating a disease, the disease is pancreatic cancer. In embodiments of the method of treating a disease, the disease is breast cancer. In embodiments of the method of treating a disease, the disease is multiple myeloma. In embodiments of the method of treating a disease, the disease is lymphoma. In embodiments of the method of treating a disease, the disease is leukemia. In embodiments of the method of treating a disease, the disease is a hematopoietic cell cancer.

[0577] In embodiments of the method of treating a disease, the disease is Alzheimer's disease. In embodiments of the method of treating a disease, the disease is Amyotrophic lateral sclerosis. In embodiments of the method of treating a disease, the disease is Creutzfeldt-Jakob disease. In embodiments of the method of treating a disease, the disease is frontotemporal dementia. In embodiments of the method of treating a disease, the disease is Gerstmann-Straussler-Scheinker syndrome. In embodiments of the method of treating a disease, the disease is Huntington's disease. In embodiments of the method of treating a disease, the disease is HIV-associated dementia. In embodiments of the method of treating a disease, the disease is kuru. In embodiments of the method of treating a disease, the disease is Lewy body dementia. In embodiments of the method of treating a disease, the disease is Multiple sclerosis. In embodiments of the method of treating a disease, the disease is Parkinson's disease. In embodiments of the method of treating a disease, the disease is a Prion disease. In embodiments of the method of treating a disease, the disease is a traumatic brain injury.

[0578] In embodiments of the method of treating a disease, the disease is an inflammatory disease. In embodiments, the inflammatory disease is postoperative cognitive dysfunction. In embodiments, the inflammatory disease is traumatic brain injury. In embodiments, the inflammatory disease is arthritis. In embodiments, the inflammatory disease is rheumatoid arthritis. In embodiments, the inflammatory disease is psoriatic arthritis. In embodiments, the inflammatory disease is juvenile idiopathic arthritis. In embodiments, the inflammatory disease is multiple sclerosis. In embodiments, the inflammatory disease is systemic lupus erythematosus (SLE). In embodiments, the inflammatory disease is myasthenia gravis. In embodiments, the inflammatory disease is juvenile onset diabetes. In embodiments, the inflammatory disease is diabetes mellitus type 1. In embodiments, the inflammatory disease is Guillain-Barre syndrome. In embodiments, the inflammatory disease is Hashimoto's encephalitis. In embodiments, the inflammatory disease is Hashimoto's thyroiditis. In embodiments, the inflammatory disease is ankylosing spondylitis. In embodiments, the inflammatory disease is psoriasis. In embodiments, the inflammatory disease is Sjogren's syndrome. In embodiments, the inflammatory disease is vasculitis. In embodiments, the inflammatory disease is glomerulonephritis. In embodiments, the inflammatory disease is autoimmune thyroiditis. In embodiments, the inflammatory disease is Behcet's disease. In embodiments, the inflammatory disease is Crohn's disease. In embodiments, the inflamma-

tory disease is ulcerative colitis. In embodiments, the inflammatory disease is bullous pemphigoid. In embodiments, the inflammatory disease is sarcoidosis. In embodiments, the inflammatory disease is ichthyosis. In embodiments, the inflammatory disease is Graves ophthalmopathy. In embodiments, the inflammatory disease is inflammatory bowel disease. In embodiments, the inflammatory disease is Addison's disease. In embodiments, the inflammatory disease is Vitiligo. In embodiments, the inflammatory disease is asthma. In embodiments, the inflammatory disease is allergic asthma. In embodiments, the inflammatory disease is acne vulgaris. In embodiments, the inflammatory disease is celiac disease. In embodiments, the inflammatory disease is chronic prostatitis. In embodiments, the inflammatory disease is inflammatory bowel disease. In embodiments, the inflammatory disease is pelvic inflammatory disease. In embodiments, the inflammatory disease is reperfusion injury. In embodiments, the inflammatory disease is sarcoidosis. In embodiments, the inflammatory disease is transplant rejection. In embodiments, the inflammatory disease is interstitial cystitis. In embodiments, the inflammatory disease is atherosclerosis. In embodiments, the inflammatory disease is atopic dermatitis.

[0579] In embodiments, the method of treatment is a method of prevention. For example, a method of treating postsurgical cognitive dysfunction may include preventing postsurgical cognitive dysfunction or a symptom of postsurgical cognitive dysfunction or reducing the severity of a symptom of postsurgical cognitive dysfunction by administering a compound described herein prior to surgery.

[0580] In an embodiment, this invention provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease selected from the group consisting of cancer, a neurodegenerative disease, vanishing white matter disease, childhood ataxia with CNS hypomyelination, and an intellectual disability syndrome.

[0581] In an embodiment, this invention provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of an integrated stress response associated disease.

[0582] In an embodiment, this invention provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease associated with phosphorylation of eIF2α.

[0583] In an embodiment, this invention provides for the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease selected from the group consisting of cancer, a neurodegenerative disease, vanishing white matter disease, childhood ataxia with CNS hypomyelination, and an intellectual disability syndrome.

[0584] In an embodiment, this invention provides for the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment an integrated stress response associated disease.

[0585] In an embodiment, this invention provides for the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease associated with phosphorylation of eIF2α.

Compositions

[0586] The pharmaceutically active compounds within the scope of this invention are useful as ATF4 pathway inhibitors in mammals, particularly humans, in need thereof.

[0587] The present invention therefore provides a method of treating cancer, neurodegeneration and other conditions requiring ATF4 pathway inhibition, which comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. The compounds of Formula (I) also provide for a method of treating the above indicated disease states because of their demonstrated ability to act as ATF4 pathway inhibitors. The drug may be administered to a patient in need thereof by any conventional route of administration, including, but not limited to, intravenous, intramuscular, oral, topical, subcutaneous, intradermal, intraocular and parenteral. Suitably, a ATF4 pathway inhibitor may be delivered directly to the brain by intrathecal or intraventricular route, or implanted at an appropriate anatomical location within a device or pump that continuously releases the ATF4 pathway inhibiting drug.

[0588] The pharmaceutically active compounds of the present invention are incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers are employed. Solid carriers include, starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampoule, or an aqueous or nonaqueous liquid suspension.

[0589] When referring to a pharmaceutical compositions, the term carrier and excipient are used interchangeably herein.

[0590] As used herein the terms "disease" and "disease state" are considered to refer to the same condition. These terms are used interchangeably herein.

[0591] The pharmaceutical compositions are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

[0592] Doses of the presently invented pharmaceutically active compounds in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity preferably selected from the range of 0.001-100 mg/kg of active compound, preferably 0.001-50 mg/kg. When treating a human patient in need of a ATF4 pathway inhibitor, the selected dose is administered preferably from 1-6 times daily, orally or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermally, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 0.05 to 3500 mg of active compound. Oral administration, which uses lower dosages, is preferred. Parenteral administration, at high dosages, however, also can be used when safe and convenient for the patient.

[0593] Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular ATF4 pathway inhibitor in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular patient being treated will result in a need to adjust dosages, including patient age, weight, diet, and time of administration.

[0594] When administered to prevent organ damage in the transportation of organs for transplantation, a compound of Formula (I) is added to the solution housing the organ during transportation, suitably in a buffered solution.

[0595] The method of this invention of inducing ATF4 pathway inhibitory activity in mammals, including humans, comprises administering to a subject in need of such activity an effective ATF4 pathway inhibiting amount of a pharmaceutically active compound of the present invention.

[0596] The invention also provides for the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use as an ATF4 pathway inhibitor.

[0597] The invention also provides for the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in therapy.

[0598] The invention also provides for the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in treating cancer, pre-cancerous syndromes, Alzheimer's disease, spinal cord injury, traumatic brain injury, ischemic stroke, stroke, diabetes, Parkinson disease, Huntington's disease, Creutzfeldt-Jakob Disease, and related prion diseases, progressive supranuclear palsy, amyotrophic lateral sclerosis, myocardial infarction, cardiovascular disease, inflammation, fibrosis, chronic and acute diseases of the liver, chronic and acute diseases of the lung, chronic and acute diseases of the kidney, chronic traumatic encephalopathy (CTE), neurodegeneration, dementia, traumatic brain injury, cognitive impairment, atherosclerosis, ocular diseases, arrhythmias, in organ transplantation and in the transportation of organs for transplantation.

[0599] The invention also provides for the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in preventing organ damage during the transportation of organs for transplantation.

[0600] The invention also provides for a pharmaceutical composition for use as a ATF4 pathway inhibitor which comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[0601] The invention also provides for a pharmaceutical composition for use in the treatment of cancer which comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[0602] In addition, the pharmaceutically active compounds of the present invention can be co-administered with further active ingredients, such as other compounds known to treat cancer, or compounds known to have utility when used in combination with a ATF4 pathway inhibitor.

[0603] The invention also provides novel processes and novel intermediates useful in preparing the presently invented compounds.

[0604] The invention also provides a pharmaceutical composition comprising from 0.5 to 1,000 mg of a compound of Formula (I) or pharmaceutically acceptable salt thereof and from 0.5 to 1,000 mg of a pharmaceutically acceptable excipient.

[0605] Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

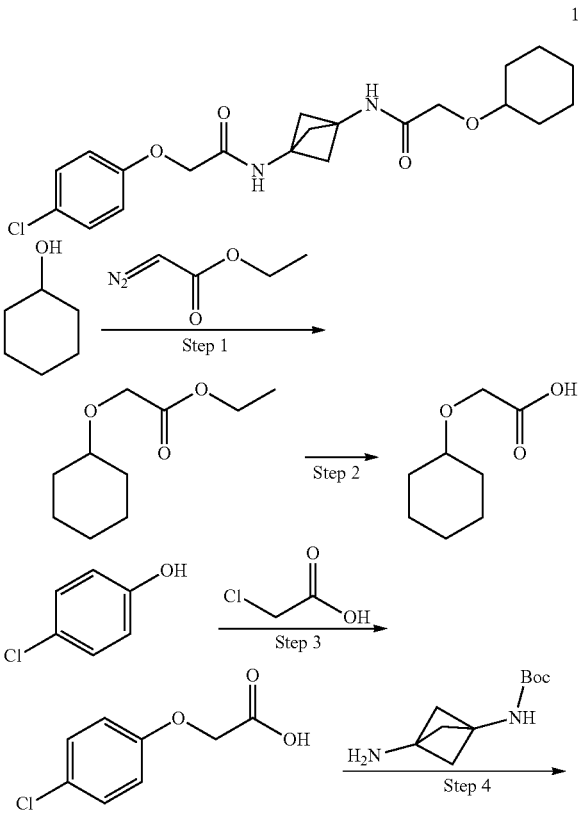
EXAMPLES

[0606] The following examples illustrate the invention. These examples are not intended to limit the scope of the present invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the present invention. While particular embodiments of the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention.

Example 1

2-(4-chlorophenoxy)-N-(3-(2-(cyclohexyloxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide

[0607]



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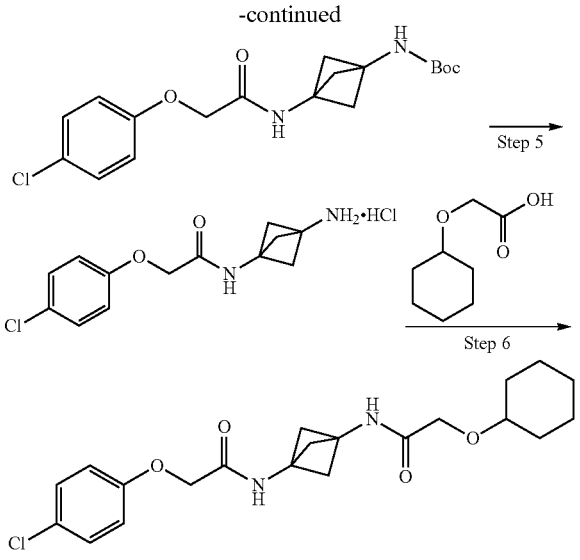

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[0608] Step 1: To a solution of cyclohexanol (0.5 g, 5 mmol, 1 equiv) indichloromethane (10 mL) was added rhodium (II) acetate dimer (0.022 g, 0.05 mmol, 0.01 equiv) followed by ethyl diazoacetate (0.57 g, 5 mmol, 1 equiv) at 00° C. The reaction mixture was stirred at room temperature for 1 h at which time the starting materials were completely consumed. Then the reaction mixture was diluted with DCM (20 mL), filtered through a celite bed and the filtrate was concentrated under vacuum to get the crude product (0.91 g). The crude product was carried to next step without any further purification. LCMS (ES) m/z=187.1 $[M+H]^+$.

[0609] Step 2: To a solution of ethyl 2-(cyclohexyloxy) acetate (0.9 g, 4.83 mmol, 1 equiv) in methanol (10 mL) was added 1 N NaOH (9.5 mL, 9.67 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 16 h at which time the starting material was completely consumed. Then the reaction mixture was concentrated under vacuum and the crude obtained was re-dissolved in water (7 mL). The aqueous layer was extracted with ethylacetate (2×15 mL). The aqueous layer was then acidified with 2 N HCl (to pH=2) and extracted with ethyl acetate (25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under vacuum to afford 2-(cyclohexyloxy)acetic acid (0.35 g, 44.30% yield) as pale yellow oil. LCMS (ES) m/z=157.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.14-1.24 (m, 5H), 1.43-1.45 (m, 1H), 1.62-1.63 (m, 2H), 1.81-1.83 (m, 2H), 3.28-3.29 (m, 1H), 3.97 (s, 2H), 12.41 (bs, 1H).

[0610] Step 3: To a solution of 4-chlorophenol (30.0 g, 233.3 mmol, 1 equiv) in water (100 mL) at 0° C. was added a solution of sodium hydroxide (14 g, 350.0 mmol, 1.5 equiv) and 4-chloroacetic acid (30.87 g, 326.6 mmol, 1.4 equiv) was added. After stirring for 10 minutes at 0° C., the reaction mixture was allowed to warm to room temperature and the reaction mixture was heated at 100° C. for 6 h. After consumption of the starting material (TLC, 5% Methanol in DCM), the reaction mixture was allowed to cool down to room temperature. The reaction mixture was diluted with water (50 mL). The aqueous layer was acidified with 1 N HCl up to pH 3 and the precipitated product was filtered through a sintered funnel, washed with ice-cold water (10 mL) and dried under high vacuum to give 2-(4-chlorophenoxy)acetic acid (31 g, 72% yield) as white solid. LCMS (ES) m/z=186.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 4.64 (s, 2H), 6.91 (d, J=9.2 Hz, 2H), 7.30 (d, J=8.8 Hz, 2H), 13.0 (bs, 1H).

[0611] Step 4: To a solution of tert-butyl (3-aminobicyclo [1.1.1]pentan-1-yl)carbamate (5.0 g, 25.2 mmol, 1 equiv) in DCM (30 mL) at 0° C. was added triethylamine (13.9 mL, 100.8 mmol, 4 equiv) and 2-(4-chlorophenoxy)acetic acid (5.6 g, 2.4 mmol, 1.2 equiv). After the reaction mixture was stirred for 5 minutes at 0° C., T_3P (50 wt. % in ethyl acetate) (22.3 g, 3.0 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 12 h. After consumption of tert-butyl (3-aminobicyclo[1.1.1]pentan-1-yl)carbamate (TLC, 5% methanol in DCM), the reaction mixture was concentrated under vacuum then washed with saturated aqueous $NaHCO_3$ solution (40 mL) and water (40 mL), and stirred it for 30 minutes. The precipitated product was filtered through a sintered funnel, and washed the solid with n-pentane (50 mL) and dried under vacuum to give tert-butyl (3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1] pentan-1-yl)carbamate (9.2 g, 100% yield) as off white solid. LCMS (ES) m/z=311.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 9H), 2.11 (s, 6H), 4.39 (s, 2H), 6.94 (d, J=8.8 Hz, 2H), 7.31 (d, J=8.8 Hz, 2H), 7.45 (bs, 1H), 8.60 (bs, 1H).

[0612] Step 5: To a solution of tert-butyl (3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)carbamate (9.2 g, 250.68 mmol, 1 equiv) in 1,4-Dioxane (70 mL) was added 4.0 M HCl in dioxane (20 mL) at rt and was stirred for 12 h. After consumption of the starting material (TLC, 5% Methanol in DCM), 1,4-dioxane was evaporated under reduced pressure. The solid obtained was triturated with n-pentane (50 mL) and dried under high vacuum to give N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy) acetamide hydrochloride. (6.7 g, 90% yield) as off white solid. LCMS (ES) m/z=267.1 $[M+H]^+$ ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.20-2.22 (m, 6H), 4.43 (s, 2H), 6.95 (d, J=8.0 Hz, 2H), 7.32 (d, J=8.0 Hz, 2H), 8.85 (s, 1H), 8.97 (bs, 3H).

[0613] Step 6: To a solution of N-(3-aminobicyclo[1.1.1] pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.05 g, 0.16 mmol, 1 equiv) in DCM (7.0 mL) at 0° C. was added triethylamine (0.06 g, 0.64 mmol, 4 equiv) and 2-(cyclohexyloxy)acetic acid (0.04 g, 0.24 mmol, 1.5 equiv). After stirring for 5 minutes at 0° C., T_3P (50 wt. % in ethyl acetate, 0.08 g, 0.24 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 16 h at which time the starting materials were completely consumed. The reaction mixture was diluted with water (5 mL) and extracted with DCM (2×10 mL). The combined organic extract was washed sequentially with a saturated solution of aqueous $NaHCO_3$ (8.0 mL), water (5.0 mL), brine (5.0 mL) and dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated under vacuum to give the crude product. The crude product was purified by flash column chromatography using a silica gel column and the product was eluted at 2.5% methanol in dichloromethane. Fractions containing the product were concentrated to give 2-(4-chlorophenoxy)-N-(3-(2-(cyclohexyloxy)acetamido) bicyclo[1.1.1]pentan-1-yl)acetamide (26 mg, 38.8% yield) as white solid. LCMS (ES) m/z=407.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.15-1.25 (m, 5H), 1.44-1.46 (m, 1H), 1.63-1.65 (m, 2H), 1.80-1.83 (m, 2H), 2.22 (s, 6H),

3.23-3.25 (m, 1H), 3.77 (s, 2H), 4.40 (s, 2H), 6.95 (d, J=9.2 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 8.05 (s, 1H), 8.63 (s, 1H).

[0614] The compounds 2 to 20 were prepared generally according to the procedures described above for Example 1.

TABLE 1

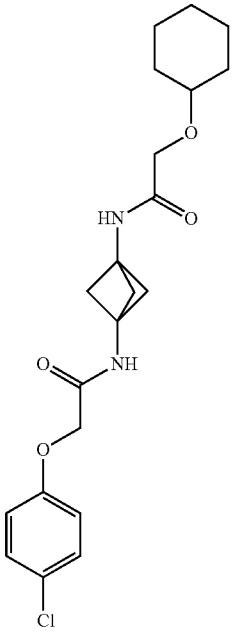
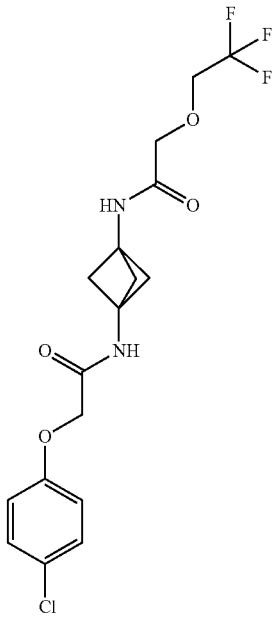
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
1		2-(4-chloro-phenoxy)-N-(3-(2-cyclohexyloxy)-acetamido)bicyclo-[1.1.1]pentan-1-yl)-acetamide	407.2	1.15-1.25 (m, 5 H), 1.44-1.46 (m, 1 H), 1.63-1.65 (m, 2 H), 1.80-1.83 (m, 2 H), 2.22 (s, 6 H), 3.23-3.25 (m, 1 H), 3.77 (s, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 9.2 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.05 (s, 1 H), 8.63 (s, 1 H).
2		2-(4-chloro phenoxy)-N-(3-(2-(2,2,2-trifluoro-ethoxy)acetamido)-bicyclo[1.1.1]-pentan-1-yl)-acetamide	407.0	2.24 (s, 6 H), 4.00 (s, 2 H), 4.12 (q, J = 9.2 Hz, 2 H), 4.41 (s, 2 H), 6.95 (d, J = 9.2 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.42 (s, 1 H), 8.65 (s, 1 H).

TABLE 1-continued

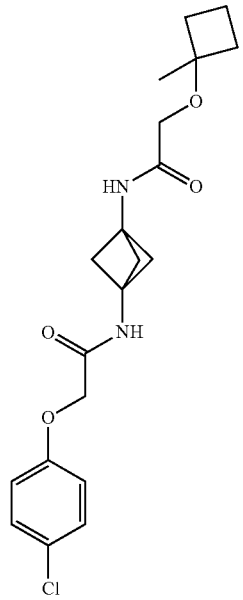
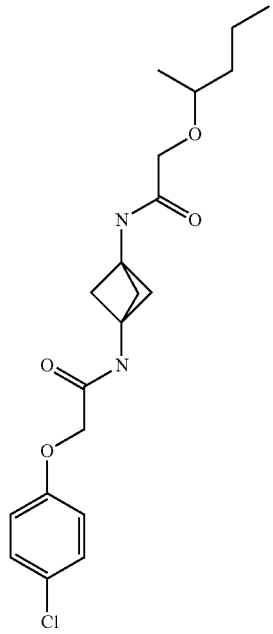
Cmpd #	Structure	Name	LCMS m/z [M + H]+	^{1}H-NMR (400 MHz, DMSO-d_6)
3		2-(4-chloro-phenoxy)-N-(3-(2-(1-methylcyclo-butoxy)acetamido)-bicyclo[1.1.1]-pentan-1-yl)-acetamide	393.2	1.22 (s, 3 H), 1.48-1.67 (m, 2 H), 1.73-1.91 (m, 2 H), 2.05-2.18 (m, 2 H), 2.23 (s, 6 H), 3.62 (s, 2 H), 4.41 (s, 2 H), 6.95 (d, J = 9.2 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.08 (s, 1 H), 8.63 (s, 1 H).
4		2-(4-chloro-phenoxy)-N-(3-(2-(pentan-2-yloxy)-acetamido)bicyclo-[1.1.1]pentan-1-yl)acetamide	395.1	0.85 (t, J = 6.8 Hz, 3 H), 1.06 (d, J = 5.6 Hz, 3 H), 1.22-1.35 (m, 3 H), 1.48 (t, J = 6.8 Hz, 1 H), 2.22 (s, 6 H), 3.39-3.43 (m, 1 H), 3.75 (dd, J = 26.0, 14.4 Hz, 2 H), 4.41 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.02 (s, 1 H), 8.64 (s, 1 H).

TABLE 1-continued

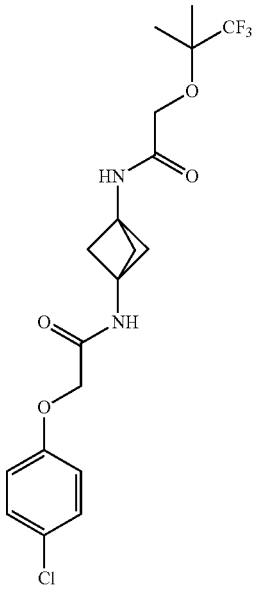
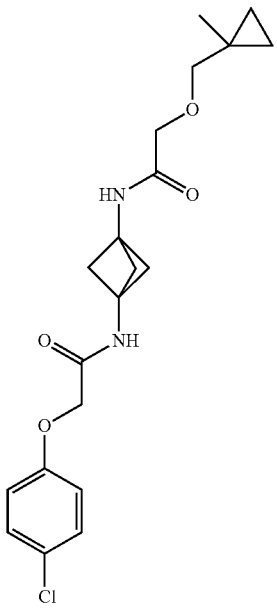
Cmpd #	Structure	Name	LCMS m/z [M + H]$^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
5		2-(4-chloro-phenoxy)-N-(3-(2-((1,1,1-trifluoro-2-methylpropan-2-yl)oxy)acetamido)-bicyclo[1.1.1]-pentan-1-yl)-acetamide	435.1	1.33 (s, 6 H), 2.23 (s, 6 H), 3.90 (s, 2 H), 4.41 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.11 (s, 1 H), 8.65 (s, 1 H).
6		2-(4-chloro-phenoxy)-N-(3-(2-((1-methylcyclo-propyl)methoxy)-acetamido)bicyclo-[1.1.1]pentan-1-yl)acetamide	393.1	0.24-0.27 (m, 2 H), 0.35-0.37 (m, 2 H), 1.06 (s, 3 H), 2.22 (s, 6 H), 3.21 (s, 2 H), 3.78 (s, 2 H), 4.41 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.13 (s, 1 H), 8.64 (s, 1 H).

TABLE 1-continued

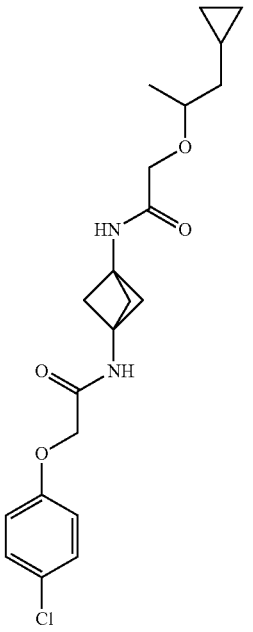
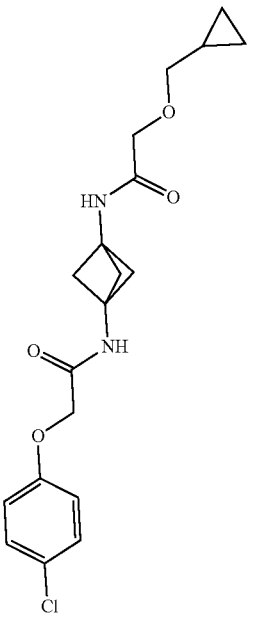
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
7		2-(4-chloro-phenoxy)-N-(3-(2-((1-cyclopropyl-propan-2-yl)oxy)-acetamido)bicyclo-[1.1.1]pentan-1-yl)acetamide	407.2	0.02 (bs, 2 H), 0.38-0.40 (m, 2 H), 0.69-0.72 (m, 1 H), 1.14 (d, J = 10.8 Hz, 3 H), 1.20-1.27 (m, 1 H), 1.41-1.48 (m, 1 H), 2.22 (s, 6 H), 3.45-3.49 (m, 1 H), 3.72-3.82 (m, 2 H), 4.41 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.00 (s, 1 H), 8.64 (s, 1 H).
8		2-(4-chloro-phenoxy)-N-(3-(2-(cyclopropylmeth-oxy)acetamido)-bicyclo[1.1.1]-pentan-1-yl)-acetamide	379.2	0.14-0.17 (m, 2 H), 0.43-0.47 (m, 2 H), 0.97-1.03 (m, 1 H), 2.21 (s, 6 H), 3.26 (t, J = 5.6 Hz, 2 H), 3.78 (s, 2 H), 4.41 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.18 (s, 1 H), 8.63 (s, 1 H).

TABLE 1-continued

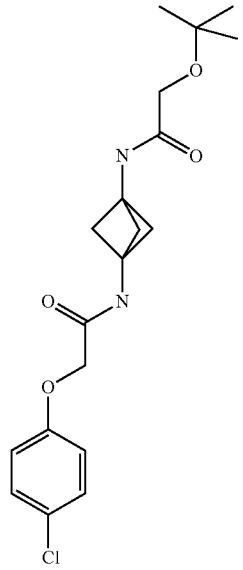
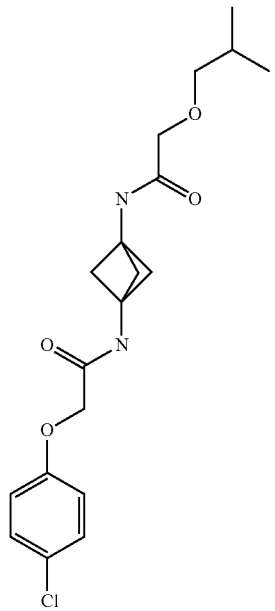
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
9		2-(tert-butoxy)-N-(3-(2-(4-chlorophenoxy)-acetamido)bicyclo-[1.1.1]pentan-1-yl)acetamide	381.1	1.14 (s, 9 H), 2.23 (s, 6 H), 3.68 (s, 2 H), 4.4 (s, 2 H), 6.95 (d, J = 9.2 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 7.94 (s, 1 H), 8.63 (s, 1 H).
10		2-(4-chloro-phenoxy)-N-(3-(2-isobutoxy-acetamido)bicyclo-[1.1.1]pentan-1-yl)acetamide	381.2	0.84 (s, 6 H), 1.79-1.8 (m, 1 H), 2.22 (s, 6 H), 3.16 (d, J = 7.2 Hz, 2 H), 3.75 (s, 2 H), 4.41 (s, 2 H), 6.95 (d, J = 9.2 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.14 (s, 1 H), 8.64 (s, 1 H).

TABLE 1-continued

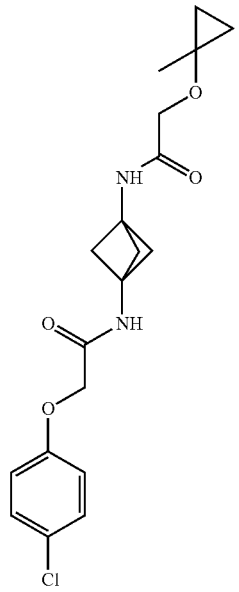
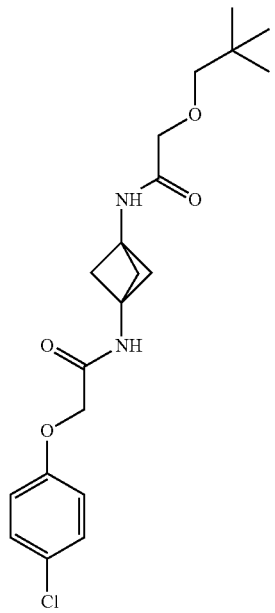
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
11		2-(4-chloro-phenoxy)-N-(3-(2-(1-methyl-cyclopropoxy)-acetamido)bicyclo-[1.1.1]pentan-1-yl)acetamide	379.1	0.35-0.38 (m, 2 H), 0.75-0.95 (m, 2 H), 1.29 (s, 3 H), 2.24 (s, 6 H), 3.76 (s, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.33 (d, J = 8.8 Hz, 2 H), 8.08 (s, 1 H), 8.62 (s, 1 H).
12		2-(4-chloro-phenoxy)-N-(3-(2-(neopentyloxy)-acetamido)bicyclo-[1.1.1]pentan-1-yl)acetamide	395.2	0.86 (s, 9 H), 2.22 (s, 6 H), 3.07 (s, 2 H), 3.77 (s, 2 H), 4.40 (s, 2 H), 6.96 (d, J = 9.2 Hz, 2 H), 7.33 (d, J = 8.8 Hz, 2 H), 8.04 (bs, 1 H), 8.65 (bs, 1 H).

TABLE 1-continued

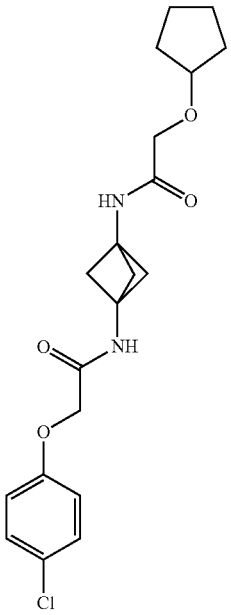
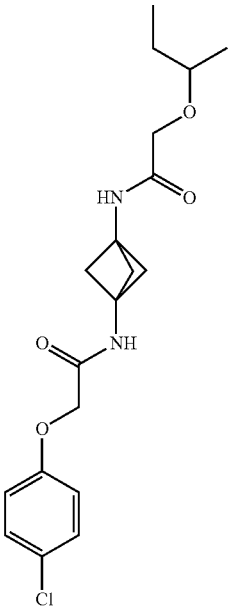
Cmpd #	Structure	Name	LCMS m/z [M + H]$^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
13		2-(4-chloro-phenoxy)-N-(3-(2-(cyclopentyloxy)-acetamido)bicyclo-[1.1.1]pentan-1-yl)acetamide	393.1	1.45 (bs, 2 H), 1.60-1.61 (m, 6 H), 2.22 (s, 6 H), 3.70 (s, 2 H), 3.88 (bs, 1 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.07 (s, 1 H), 8.63 (s, 1 H).
14		2-(sec-butoxy)-N-(3-(2-(4-chlorophenoxy)-acetamido)bicyclo-[1.1.1]pentan-1-yl)acetamide	381.1	0.82 (t, J = 8.0 Hz, 3 H), 1.06 (d, J = 6.0 Hz, 3 H), 1.34-1.40 (m, 1 H), 1.47-1.52 (m, 1 H), 2.22 (s, 6 H), 3.37-3.27 (m, 1 H), 3.70-3.79 (m, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 8.0 Hz, 2 H), 7.31 (d, J = 8.8 Hz, 2 H), 8.02 (bs, 1 H), 8.63 (bs, 1 H).

TABLE 1-continued

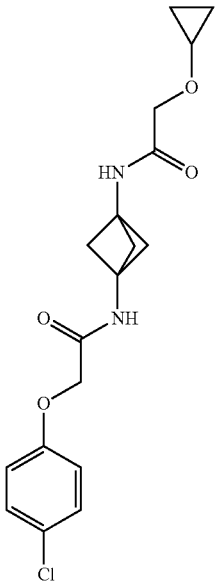
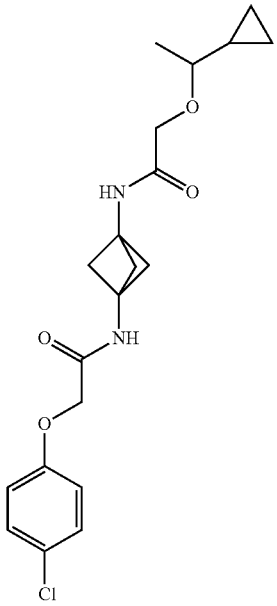
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
15		2-(4-chloro-phenoxy)-N-(3-(2-cyclopropoxy-acetamido)bicyclo-[1.1.1]pentan-1-yl)acetamide	365.1	0.38-0.43 (m, 2 H), 0.49-0.52 (m, 2 H), 2.21 (s, 6 H), 3.34-3.37 (m, 1 H), 3.79 (s, 2 H), 4.40 (s, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 9.2 Hz, 2 H), 8.24 (s, 1 H), 8.63 (s, 1 H).
16		2-(4-chloro-phenoxy)-N-(3-(2-(1-cyclopropyl-ethoxy)acetamido)-bicyclo[1.1.1]-pentan-1-yl)-acetamide	393.1	0.03-0.04 (m, 1 H), 0.31-0.39 (m, 2 H), 0.46-0.48 (m, 1 H), 0.76-0.79 (m, 1 H), 1.16 (d, J = 6.0 Hz, 3 H), 2.22 (s, 6 H), 2.78-2.81 (m, 1 H), 3.83 (q, J = 14.5 Hz, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.4 Hz, 2 H), 8.03 (s, 1 H), 8.63 (s, 1 H).

TABLE 1-continued

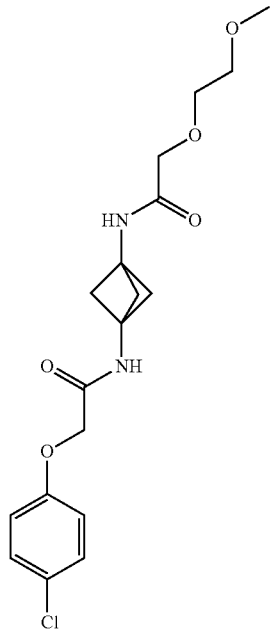
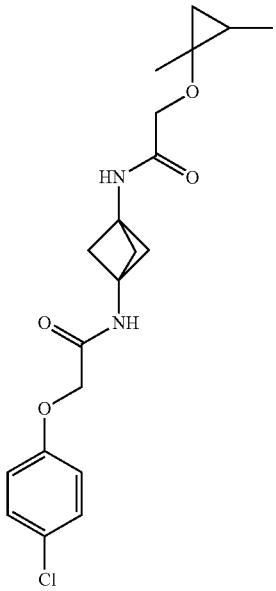
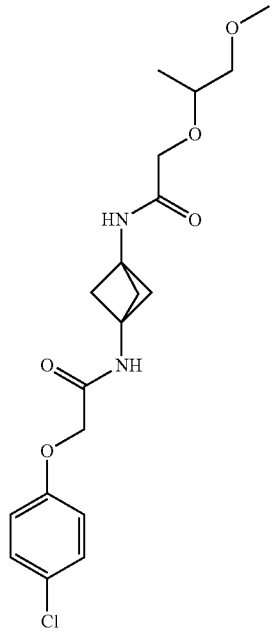
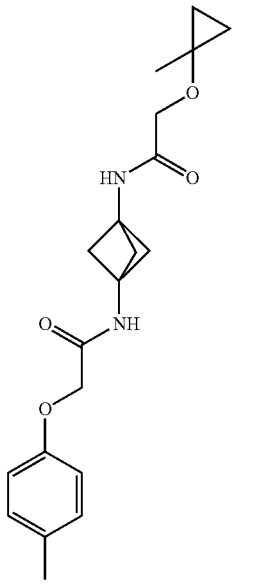
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
17		2-(4-chloro-phenoxy)-N-(3-(2-(2-methoxyethoxy)-acetamido)bicyclo-[1.1.1]pentan-1-yl)acetamide	383.1	2.22 (s, 6 H), 3.24 (s, 3 H), 3.44 (t, J = 4.4 Hz, 2 H), 3.54 (t, J = 4.4 Hz, 2 H), 3.80 (s, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.19 (s, 1 H), 8.64 (s, 1 H).
18		2-(4-chloro-phenoxy)-N-(3-(2-(1,2-dimethyl-cyclopropoxy)-acetamido)bicyclo-[1.1.1]pentan-1-yl)acetamide	393.2	0.83-0.87 (m, 2 H), 0.94 (d, J = 6.0 Hz, 3 H), 0.99-1.00 (m, 1 H), 1.25 (s, 3 H), 2.22 (s, 6 H), 3.70-3.77 (m, 2 H), 4.40 (s, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 7.31 (d, J = 8.8 Hz, 2 H), 7.96-8.10 (m, 1 H), 8.62 (s, 1 H).

TABLE 1-continued

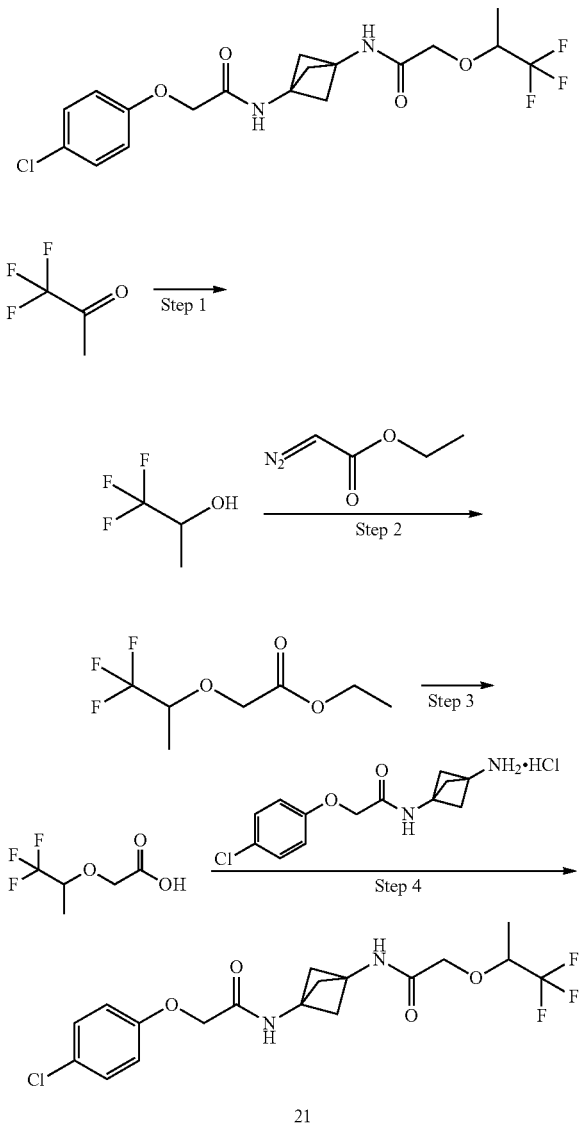
Cmpd #	Structure	Name	LCMS m/z [M + H]$^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
19		2-(4-chloro-phenoxy)-N-(3-(2-((1-methoxy-propan-2-yl)oxy)-acetamido)bicyclo-[1.1.1]pentan-1-yl)acetamide	397.1	1.03 (d, J = 6.4 Hz, 3 H), 2.22 (s, 6 H), 3.27 (d, J = 2.8 Hz, 3 H), 3.28-3.33 (m, 2 H), 3.54-3.58 (m, 1 H), 3.82 (q, J = 14.8 Hz, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 9.2 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.17 (s, 1 H), 8.65 (s, 1 H).
20		2-(1-methyl-cyclopropoxy)-N-(3-(2-(p-tolyloxy)-acetamido)bicyclo-[1.1.1]pentan-1-yl)acetamide	359.2	0.36 (t, J = 5.4 Hz, 2 H), 0.75-0.77 (m, 2 H), 1.29 (s, 3 H), 2.20 (s, 9 H), 3.76 (s, 2 H), 4.33 (s, 2 H), 6.81 (d, J = 8.4 Hz, 2 H), 7.06 (d, J = 8.4 Hz, 2 H), 8.07 (s, 1 H), 8.56 (s, 1 H).

Example 21

2-(4-chlorophenoxy)-N-(3-(2-((1,1,1-trifluoropropan-2-yl)oxy)acetamido)bicyclo[1.1.1]pentan-1-yl) acetamide

[0615]

21



21

[0616] Step 1: To a solution of 1,1,1-trifluoropropan-2-one (1.0 g, 8.9 mmol, 1 equiv) in diethyl ether (20 mL) was added 2 M solution of lithium aluminium hydride in THF (8.92 mL, 17.8 mmol, 2 equiv) at 0° C. The reaction mixture was stirred at room temperature for 2 h. After consumption of the starting material (TLC, 10% EtOAc in hexane), the reaction mixture was quenched with saturated ammonium chloride solution (5 mL), filtered through celite bed, rinsing the celite bed with diethyl ether (2×50 mL), and the filtrate was concentrated to obtain 1,1,1-trifluoropropan-2-ol as gum which was forwarded to the next step without further purification (1.0 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.17 (t, J=6.4 Hz, 3H), 4.01-4.06 (m, 1H), 5.97 (d, J=6.0 Hz, 1H).

[0617] Step 2: To a solution of 1,1,1-trifluoropropan-2-ol (1.0 g, 8.7 mmol, 1 equiv) in DCM (50 mL) was added $Rh_2(OAc)_4$ (0.038 g, 0.087 mmol, 0.01 equiv) and ethyl 2-diazoacetate (0.92 mL, 8.7 mmol, 1 equiv) at 0° C. The reaction mixture was stirred at room temperature for 3 h. After consumption of the starting material (TLC, 20% EtOAc in hexane), the reaction mixture was filtered through celite bed, rinsing the celite bed with DCM (2×25 mL); the filtrate was extracted with cold water (2×25 mL) and the DCM extract was dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated to obtain ethyl 2-((1,1,1-trifluoropropan-2-yl)oxy)acetate (1.0 g, crude) as viscous liquid which was taken to the next step without further purification.

[0618] Step 3: To a solution of ethyl 2-((1,1,1-trifluoropropan-2-yl)oxy)acetate (1.0 g, 4.9 mmol, 1 equiv) in methanol (10.0 mL) was added 2 N NaOH (3.0 mL) at 0° C. Reaction mixture was allowed to stir at room temperature (27° C.) for 6 h. After consumption of the starting material, methanol was evaporated and the crude product was diluted with water (20 mL), acidified with 1 N HCl (up to pH~2) at 0° C. and extracted with DCM (2×50 mL). The combined organic layer was washed with cold water (2×20 mL), dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated to obtain 2-((1,1,1-trifluoropropan-2-yl)oxy)acetic acid (0.5 g, crude) as viscous liquid which was directly used in the next step. LCMS (ES) m/z=171.0 $[M-H]^+$.

[0619] Step 4: To a solution of N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.05 g, 0.16 mmol, 1 equiv) in DCM (50.0 mL) were added triethylamine (0.056 mL, 4.0 mmol, 2.5 equiv), 2-((1,1,1-trifluoropropan-2-yl)oxy)acetic acid (0.034 g, 0.19 mmol, 1.2 equiv) and T_3P (50 wt. % in ethyl acetate) (0.24 mL, 0.40 mmol, 2.5 equiv) at 0° C. The reaction mixture was stirred at room temperature for 18 h, after completion of the starting material, the reaction mixture was concentrated under vacuum, diluted with saturated aqueous $NaHCO_3$ solution (50 mL) and stirred for 30 minutes where the product was precipitated as white solid. The solid was filtered through a Buchner funnel, washed with cold water (2×25 mL) followed by n-pentane (10 mL) and then dried under vacuum to obtain the crude product. It was purified by preparative HPLC (analytical conditions: column: Inertsil ODS 3V (250 mm×4.6 mm×5 micron, Mobile phase (A): 0.1% Ammonia in water, Mobile phase (B): Acetonitrile) to obtain 2-(4-chlorophenoxy)-N-(3-(2-((1,1,1-trifluoropropan-2-yl)oxy) acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide as white solid (0.035 g, 52.23%). LCMS (ES) m/z=421.4 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27 (t, J=6.0 Hz 3H), 2.22 (s, 6H), 4.00 (s, 2H), 4.15-4.18 (m, 1H), 4.40 (s, 2H), 6.95 (d, J=9.2 Hz, 2H), 7.32 (d, J=8.4 Hz, 2H), 8.28 (s, 1H), 8.64 (s, 1H).

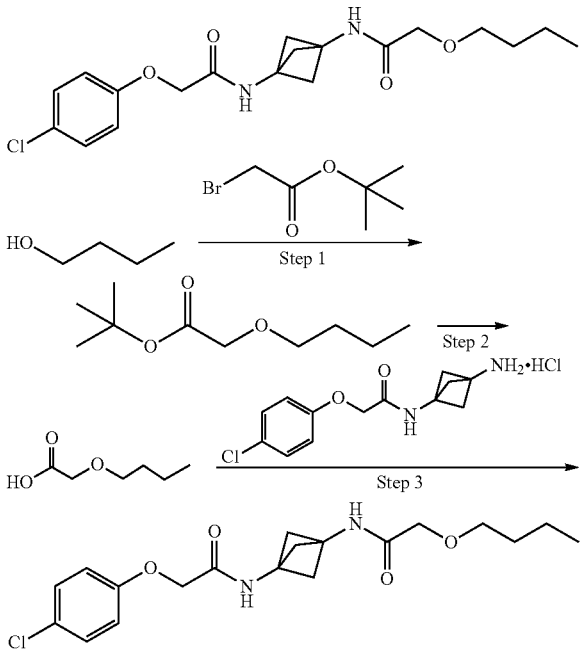
[0620] The compound of Example 22 was prepared generally according to the procedure described above for Example 21.

Example 23

2-butoxy-N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide

[0621]

23



23

[0622] Step 1: To a solution of butan-1-ol (0.5 g, 6.75 mmol, 1 equiv) in Toluene (5 mL) was added tert-butyl 2-bromoacetate (1.9 mL, 13.51 mmol, 2 equiv), tetrabutylammonium chloride (0.18, 13.51 mmol, 0.1 equiv) and 50% aq NaOH (5 mL). The reaction mixture was stirred at room temperature for 16 h. Reaction mixture was diluted with water (10 mL) and extracted with EtOAc (15 mL). The combined organic extract was washed with cold water (100 mL) followed by a saturated brine solution (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude product (0.3 g crude product). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 0.97-1.01 (m, 3H), 1.32-1.36 (m, 2H), 1.41-1.43 (m, 9H), 1.63-1.71 (m, 2H), 3.34-3.38 (m, 2H), 3.91 (s, 1H), 4.06 (s, 1H).

[0623] Step 2: To a solution of tert-butyl 2-butoxyacetate (0.3 g, 1.59 mmol, 1 equiv) in DCM (10 mL) at 0° C. was added 4 M HCl in dioxane (10 mL) and the reaction mixture allowed to stir at room temperature for 12 hours. After consumption of the starting material, the solvent was evaporated under reduced pressure to get the crude product, which was then triturated with Et_2O (10 mL). The ether was decanted and the solid was dried under high vacuum to give 2-butoxyacetic acid (0.1 g, crude) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 0.84-0.91 (m, 3H), 1.29-1.34 (m, 2H), 1.40-1.48 (m, 2H), 3.41 (t, J=6.6 Hz, 2H), 3.93 (s, 2H), 12.10-12.90 (m, 1H).

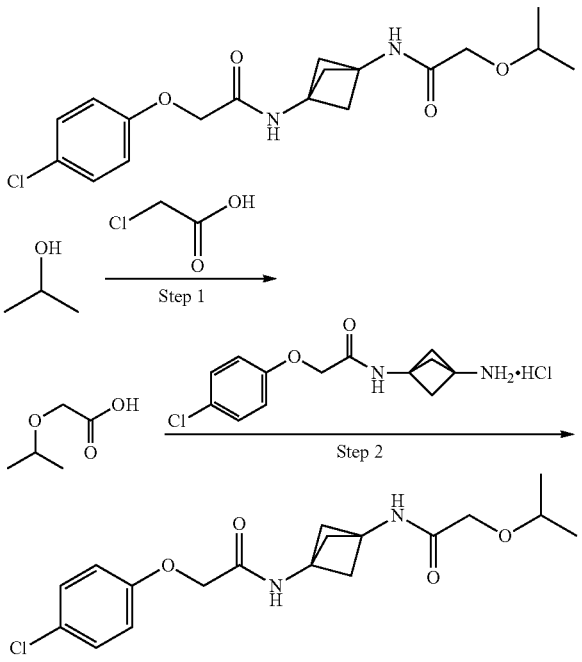
[0624] Step 3: To N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.050 g, 0.165 mmol, 1 equiv) in DCM (10 mL) at 0° C. was added triethylamine (0.07 mL, 0.495 mmol, 3 equiv) and 2-butoxyacetic acid (0.032 g, 0.247 mmol, 1.5 equiv). After the reaction mixture was stirred for 5 minutes at 0° C., T_3P (50 wt. % in ethyl acetate) (0.20 mL, 0.33 mmol, 2 equiv) was added and the reaction mixture was stirred at room temperature for 14 h. The reaction mixture was then diluted with water (15 mL) and extracted with DCM (2×10 mL). The combined organic extract was washed with a saturated aqueous $NaHCO_3$ solution (5 mL) and water (5 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude product which was purified by flash column chromatography using a silica gel column and methanol in DCM as eluent. The product was eluted at 2-3% methanol. Fractions containing product were concentrated to give 2-butoxy-N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide (0.0037 g, 6% yield) as an off white solid. LCMS (ES) m/z=381.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 0.84-0.88 (m, 3H), 1.25-1.34 (m, 2H), 1.45-1.52 (m, 2H), 2.21 (s, 6H), 3.37-3.40 (m, 2H), 3.74 (s, 2H), 4.40 (s, 2H), 6.96 (d, J=8.8 Hz, 2H), 7.33 (d, J=8.8 Hz, 2H), 8.16 (bs, 1H), 8.63 (bs, 1H).

Example 24

2-(4-chlorophenoxy)-N-(3-(2-isopropoxyacetamido) bicyclo[1.1.1]pentan-1-yl)acetamide

[0625]

24



24

[0626] Step 1: Sodium hydride (0.21 g, 5.29 mmol, 1 equiv, 60% in mineral oil) was added to a round bottom flask connected to a water condenser under N_2 atmosphere. THF (10 mL) was added dropwise at 0° C. and then stirred for 10

min. 2-chloroacetic acid (0.5 g, 5.29 mmol 1 equiv) was added dropwise followed by propan-2-ol (0.6 g, 7.93 mmol, 1.5 equiv) dissolved in THF also added dropwise to the mixture of NaH in THF at 0° C. and then stirred for 30 mins. Then the reaction mixture was heated at 60° C. for 16 h. After consumption of the starting material (TLC, 5% methanol in DCM), the reaction mixture was cooled to room temperature, and quenched the reaction. THF was concentrated under vacuum and the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (15 mL). The aqueous layer was acidified with 1 N HCl up to pH 1.5 and was extracted with DCM (2×10 mL). The organic phase was separated and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2-isopropoxyacetic acid (0.015 g, 45% yield) as light brown colour solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.07-1.06 (m, 6H), 3.61-3.53 (m, 1H), 3.93-3.63 (m, 2H), 12.4 (m, 1H).

[0627] Step 2: To a solution of N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.05 g, 0.16 mmol, 1 equiv) in DCM (10 mL) at 0° C. was added triethylamine (0.05 mL, 0.64 mmol, 4 equiv) and 2-isopropoxyacetic acid (0.01 mL, 0.19 mmol, 1.2 equiv). After stirring the reaction mixture for 5 minutes at 0° C., T_3P (50 wt. % in ethyl acetate) (0.1 mL, 0.24 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then diluted with water (10 mL) and extracted with EtOAc (2×10 mL). The combined organic extract was washed with saturated aqueous $NaHCO_3$ solution (10 mL) and water (10 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude product which was purified by flash column chromatography using a silica gel column where the product was eluted at 2-2.5% methanol in DCM. Fractions containing the product were concentrated under reduced pressure and dried under high vacuum to give 2-(4-chlorophenoxy)-N-(3-(2-isopropoxyacetamido)bicyclo[1.1.1]pentan-1-yl)acetamide (0.008 g, 13% yield) as off white solid. LCMS (ES) m/z=367.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 (d, J=5.6 Hz, 6H), 2.22 (s, 6H), 3.59-3.53 (m, 1H), 3.73 (s, 2H), 4.40 (s, 2H), 6.95 (d, J=8.0 Hz, 2H), 7.32 (d, J=8.0 Hz, 2H), 8.05 (bs, 1H), 8.63 (bs, 1H).

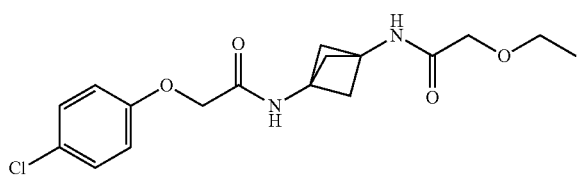
[0628] The Compound of Example 25 was prepared generally according to the procedures described above for Example 24.

Example 26

2-(4-chlorophenoxy)-N-(3-(2-ethoxyacetamido)bicyclo[1.1.1]pentan-1-yl)acetamide

[0629]

26



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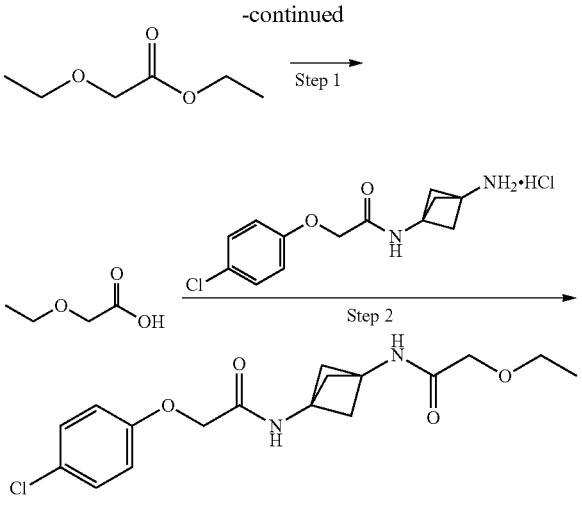


26

[0630] Step 1: To a solution of ethyl 2-ethoxyacetate (1 g, 7.57 mmol, 1 equiv) in THF (10 mL) was added Lithium hydroxide monohydrate (0.37 g, 9.08 mmol, 1.2 equiv) and water (1 mL). The reaction mixture was stirred at room temperature for 12 h. After consumption of the starting material (TLC, 5% Methanol in DCM), THF was concentrated under vacuum and the reaction mixture was diluted with water (10 mL) followed by extraction with EtOAc (20 mL). The aqueous layer was acidified with 1 N HCl (up to pH=2) and then extracted with DCM (20 mL) The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to give 2-ethoxyacetic acid (0.04 g, 5% yield) as a gum. LCMS (ES) m/z=104.0 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.11-1.07 (m, 3H), 3.48-3.43 (m, 2H), 3.93 (s, 2H), 12.48 (bs, 1H).

[0631] Step 2: To a solution of N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.05 g, 0.16 mmol, 1 equiv) in DCM (10 mL) at 0° C. was added triethylamine (0.09 mL, 0.64 mmol, 4 equiv) and 2-ethoxyacetic acid (0.02 g, 0.19 mmol, 1.2 equiv). After the reaction mixture was stirred for 5 minutes at 0° C., T_3P (50 wt. % in ethyl acetate) (0.14 mL, 0.24 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 12 h. After consumption of the starting material (TLC, 5% Methanol in DCM), the reaction mixture was concentrated under vacuum, then washed with saturated aqueous $NaHCO_3$ solution (20 mL) and water (10 mL) and stirred it for 30 mins. Then obtained solid was filtered through sintered funnel and washed the solid with n-pentane (20 mL) and dried under vacuum to give 2-(4-chlorophenoxy)-N-(3-(2-ethoxyacetamido)bicyclo[1.1.1]pentan-1-yl) acetamide. 0.008 g, 13% yield) as off white solid. LCMS (ES) m/z=353.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.13-1.09 (m, 3H), 2.21 (s, 6H), 3.47-3.41 (m, 2H), 3.74 (s, 2H), 4.40 (s, 2H), 6.95 (d, J=8.0 Hz, 2H), 7.32 (d, J=8.0 Hz, 2H), 8.20 (bs, 1H), 8.63 (bs, 1H).

[0632] The Compound of Example 27 was prepared generally according to the procedures described above for Example 26.

TABLE 2

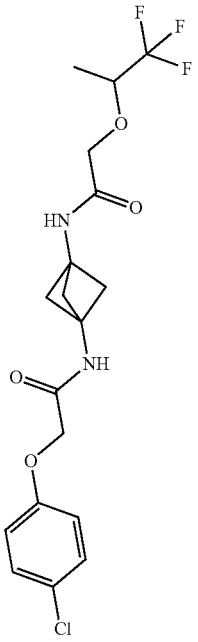
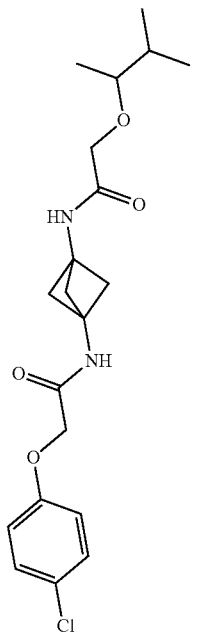
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
21		2-(4-chlorophenoxy)-N-(3-(2-((1,1,1-trifluoropropan-2-yl)-oxy)acetamido)bicyclo-[1.1.1]pentan-1-yl)-acetamide	421.4	1.27 (t, J = 6.0 Hz 3 H), 2.22 (s, 6 H), 4.00(s, 2 H), 4.15-4.18 (m, 1 H), 4.40 (s, 2 H), 6.95 (d, J = 9.2 Hz, 2 H), 7.32 (d, J = 8.4 Hz, 2 H), 8.28 (s, 1 H), 8.64 (s, 1 H)
22		2-(4-chlorophenoxy)-N-(3-(2-((3-methyl-butan-2-yl)oxy)-acetamido)bicyclo-[1.1.1]pentan-1-yl)-acetamide	395.1	0.80-0.84 (m, 6 H), 0.98-1.00 (m, 3 H), 1.70-1.75 (m, 1 H), 2.22 (s, 6 H), 3.18-3.22 (m, 1 H), 3.75 (q, J = 14.8 Hz, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 7.98 (bs, 1 H), 8.64 (bs, 1 H)

TABLE 2-continued

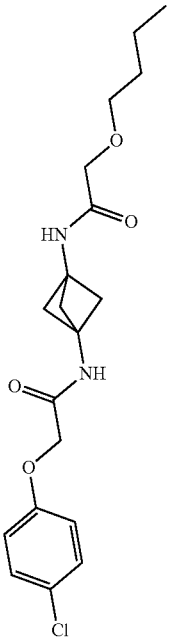
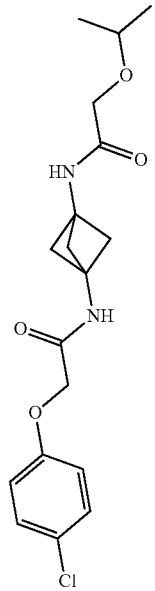
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
23		2-butoxy-N-(3-(2-(4-chlorophenoxy)-acetamido)bicyclo-[1.1.1]pentan-1-yl)-acetamide	381.1	0.84-0.88 (m, 3 H), 1.25-1.34 (m, 2 H), 1.45-1.52 (m, 2 H), 2.21 (s, 6 H), 3.37-3.40 (m, 2 H), 3.74 (s, 2 H), 4.40 (s, 2 H), 6.96 (d, J = 8.8 Hz, 2 H), 7.33 (d, J = 8.8 Hz, 2 H), 8.16 (bs, 1 H), 8.63 (bs, 1 H).
24		2-(4-chlorophenoxy)-N-(3-(2-isopropoxy-acetamido)bicyclo-[1.1.1]pentan-1-yl)-acetamide	367.1	1.09 (d, J = 5.6 Hz, 6 H), 2.22 (s, 6 H), 3.59-3.53 (m, 1 H), 3.73 (s, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 8.05 (bs, 1 H), 8.63 (bs, 1 H)

TABLE 2-continued

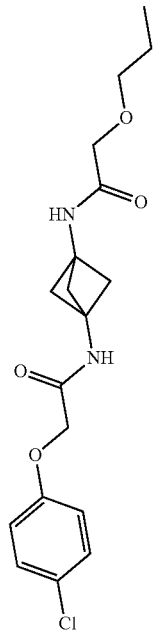
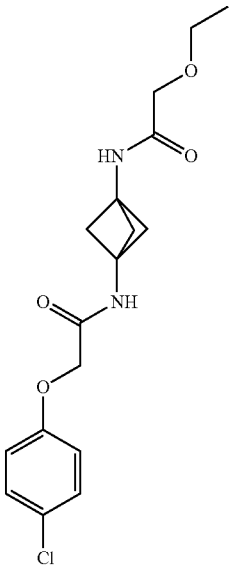
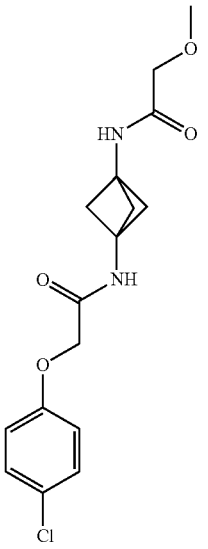
Cmpd #	Structure	Name	LCMS m/z [M + H]$^+$	^{1}H-NMR (400 MHz, DMSO-d$_6$)
25		2-(4-chlorophenoxy)-N-(3-(2-propoxy-acetamido)bicyclo-[1.1.1]pentan-1-yl)-acetamide	367.1	0.83-0.86 (m, 3 H), 1.47-1.56 (m, 2 H), 2.22 (s, 6 H), 3.33-3.36 (m, 2 H), 3.75 (s, 2 H), 4.40 (s, 2 H), 6.96 (d, J = 8.8 Hz, 2 H), 7.33 (d, J = 8.8 Hz, 2 H), 8.16 (bs, 1 H), 8.62 (bs, 1 H)
26		2-(4-chlorophenoxy)-N-(3-(2-ethoxy-acetamido)bicyclo-[1.1.1]pentan-1-yl)-acetamide	353.1	1.13-1.09 (m, 3 H), 2.21 (s, 6 H), 3.47-3.41 (m, 2 H), 3.74 (s, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 8.20 (bs, 1 H), 8.63 (bs, 1 H)

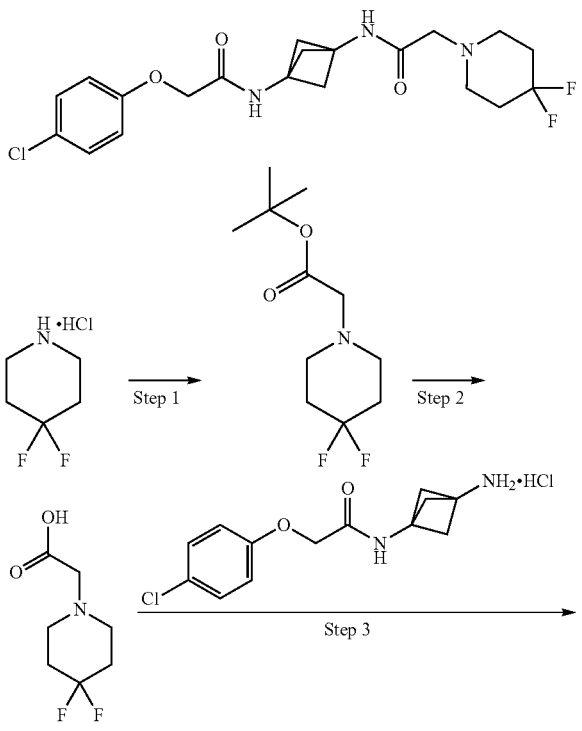
TABLE 2-continued

Cmpd #	Structure	Name	LCMS m/z [M + H]+	^{1}H-NMR (400 MHz, DMSO-d_6)
27		2-(4-chlorophenoxy)-N-(3-(2-methoxy-acetamido)bicyclo-[1.1.1]pentan-1-yl)-acetamide	339.1	2.21 (s, 6 H), 3.26 (s, 3 H), 3.71 (s, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.29 (s, 1 H), 8.63 (s, 1 H).

Example 28

2-(4-chlorophenoxy)-N-(3-(2-(4,4-difluoropiperidin-1-yl)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide

[0633]



28

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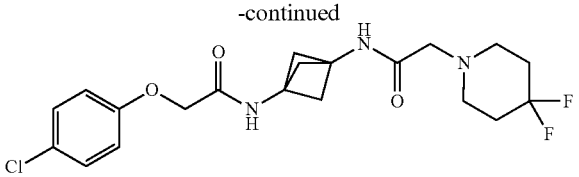


28

[0634] Step 1: To a solution of 4,4-difluoropiperidinyl hydrochloride (2.0 g, 12.68 mmol) in THF (20 mL) at 0° C. was added TEA (4.45 mL, 31.72 mmol) and tert-butyl 2-bromoacetate (2.28 mL, 15.22 mmol). Then, the reaction mixture was refluxed for 4 h. The Reaction mixture was cool to room temperature, diluted with water (15 mL) and extracted with (2×20 mL) ethyl acetate. The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give tert-butyl 2-(4,4-difluoropiperidin-1-yl)acetate (2.6 g, 87.24% yield) as a colorless liquid. LCMS (ES) m/z=236.2 [M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.48 (s, 9H), 2.03-2.07 (m, 4H), 2.66-2.69 (m, 4H), 3.15 (s, 2H),

[0635] Step 2: To a solution of compound tert-butyl 2-(4,4-difluoropiperidin-1-yl)acetate (2.6 g, 11.05 mmol) in 1,4-dioxane (30 mL) at 0° C. was added 4 M HCl in 1,4-dioxane (12 mL). Then the reaction mixture was allowed to stir at room temperature for 16 h. The solvent was evaporated from the reaction mixture. The obtained solid was triturated with diethyl ether (15 mL) and dried under vacuum to give 2-(4,4-difluoropiperidin-1-yl)acetic acid (2.4 g, crude) as an off white solid. LCMS (ES) m/z=180.1 [M+H]$^+$.

[0636] Step 3: To N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.050 g, 0.164 mmol, 1 equiv) in DCM (10 mL) at 0° C. was added

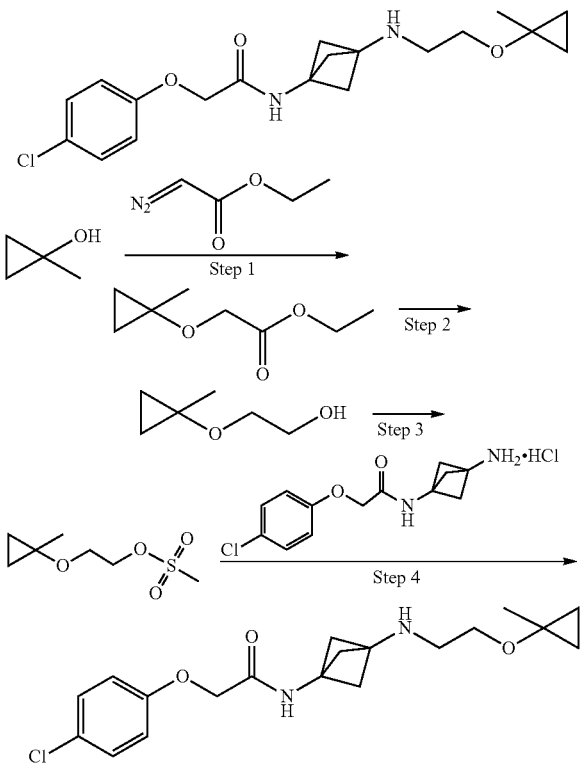
triethylamine (0.05 mL, 0.494 mmol, 3 equiv) and 2-(4,4-difluoropiperidin-1-yl)acetic acid (0.038 g, 0.214 mmol, 1.3 equiv). After the reaction mixture was stirred for 5 minutes at 0° C., T_3P (50 wt. % in ethyl acetate) (0.2 mL, 0.329 mmol, 2 equiv) was added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then diluted with water (15 mL) and extracted with DCM (2×10 mL). The combined organic extract was washed with saturated aqueous $NaHCO_3$ solution (15 mL) and water (15 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude product which was purified by flash column chromatography using a silica gel column and methanol in DCM as the eluent. The product was eluted at 3-4% MeOH. Fractions containing the product were concentrated to give 2-(4-chlorophenoxy)-N-(3-(2-(4,4-difluoropiperidin-1-yl)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide (0.03 g, 42% yield) as an off white solid. LCMS (ES) m/z=428.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ ppm 1.93-2.00 (m, 4H), 2.21-2.25 (m, 6H), 2.48-2.51 (m, 4H), 2.93 (s, 2H), 4.40 (s, 2H), 6.96 (d, J=9.2 Hz, 2H), 7.33 (d, J=8.8 Hz, 2H), 8.26 (s, 1H), 8.63 (s, 1H).

Example 29

2-(4-chlorophenoxy-N-(3-((2-(1-methylcyclopropoxy)ethyl)amino)bicyclo[1.1.1]pentan-1-yl) acetamide

[0637]

29



29

[0638] Step 1: To a solution of 1-methylcyclopropan-1-ol (0.5 g, 6.93 mmol, 1.0 equiv) in DCM (5 mL) was added rhodium (II) acetate dimer (0.011 g, 0.025 mmol, 0.01 equiv) and ethyl 2-diazoacetate (0.26 mL, 2.49 mmol, 1.0 equiv) at 0° C. The reaction mixture was stirred at room temperature for 4 h at which time the starting materials were completely consumed. Then the reaction mixture was diluted with DCM (20 mL), filtered through a celite bed and the filtrate was concentrated under vacuum to obtain the crude product (0.75 g). This crude product was carried to next step without further purification.

[0639] Step 2: To a stirred solution ethyl 2-(1-methylcyclopropoxy)acetate (0.3 g, 1.896 mmol, 1.0 equivalent) in THF (5 mL) was added lithium aluminium hydride 1M solution in THF (3.8 mL, 3.79 mmol, 2.0 equiv) at 0° C. The reaction mixture was then stirred at room temperature for 6 h, at which time the starting materials were completely consumed. Then the reaction mixture was cooled to 0° C. and quenched with brine (0.14 mL). Diethyl ether was then added (30 mL) and the resulting mixture was stirred at room temperature for 30 min. This mixture was filtered through a celite bed, washed with diethyl ether (20 mL) and the filtrate was evaporated to obtain 2-(1-methylcyclopropoxy)ethan-1-ol (0.3 g, crude) as a colourless liquid and as such taken to the next step.

[0640] Step 3: To a stirred solution of 2-(1-methylcyclopropoxy)ethan-1-ol (0.3 g, 2.58 mmol, 1.0 equiv) in DCM (30 mL) was added triethylamine (1.1 mL, 7.74 mmol, 3 equiv) and methanesulfonyl chloride (0.4 mL, 5.16 mmol, 2 equiv) at 0° C. The reaction mixture was stirred at room temperature for 16 h at which time the starting materials were completely consumed. The reaction mixture was quenched with saturated solution of aqueous $NaHCO_3$ (5 mL) and water (10 mL) was added. The resulting mixture was extracted with dichloromethane (3×30 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under vacuum to get crude product, which was purified by flash column chromatography (Combiflash) using a silica gel column and the product was eluted at 20% ethyl acetate in hexane. Fractions containing the product were concentrated to give 2-(1-methylcyclopropoxy)ethyl methanesulfonate (0.13 g, crude product) as pale yellow liquid. LCMS (ES) m/z=195.0 $[M+H]^+$.

[0641] Step 4: To the stirred solution of N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.1 g, 0.33 mmol, 1.0 equiv) in DMF (2 mL) was added triethylamine (2 mL), potassium carbonate (0.092 g, 0.66 mmol, 2.0 equiv) and 2-(1-methylcyclopropoxy) ethyl methanesulfonate (0.077 g, 0.40 mmol, 1.2 equiv) at room temperature. The reaction mixture was stirred at 100° C. for 16 h at which time the starting materials were completely consumed. The reaction mixture was cooled to room temperature and diluted with water (20 mL). The resulting mixture was extracted with ethyl acetate (3×30 mL) and the combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under vacuum to get crude product. The crude material was purified by flash column chromatography (Combiflash) using a silica gel column and the product eluted at 3% methanol in dichloromethane. The material was further purified by preparative HPLC (analytical conditions: Column: Inertsil ODS

3V (250 mm×4.6 mm×5 micron), Mobile phase (A): 0.1% ammonia in water, Mobile phase (B): acetonitrile), to afford the 2-(4-chlorophenoxy)-N-(3-((2-(1-methylcyclopropoxy) ethyl)amino)bicyclo[1.1.1]pentan-1-yl)acetamide (0.02 g, 16.6% yield) as an brown liquid. LCMS (ES) m/z=365.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.33-0.35 (m, 2H), 0.63 (s, 2H), 1.28 (s, 3H), 1.91 (s, 6H), 2.15 (bs, 1H), 2.52-2.53 (m, 2H), 3.38 (t, J=6.4 Hz, 2H), 4.39 (s, 2H), 6.94 (d, J=8.8 Hz, 2H), 7.31 (d, J=8.8 Hz, 2H), 8.53 (s, 1H).

[0642] The compound of Examples 30 was prepared generally according to the procedure described above for Example 29.

TABLE 3

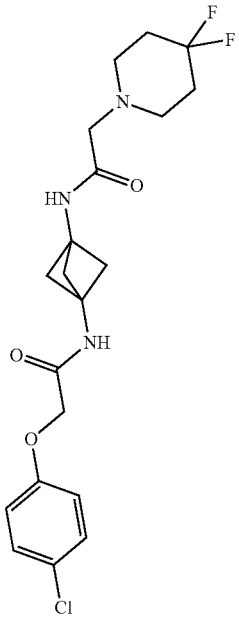
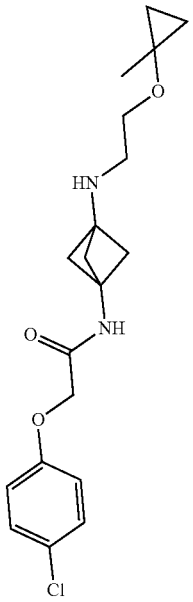
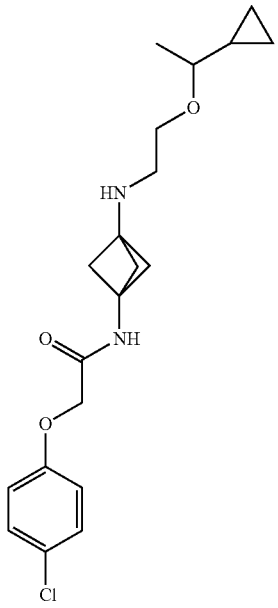
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^1H-NMR (400 MHz, DMSO-d_6)
28		2-(4-chloro-phenoxy)-N-(3-(2-(4,4-difluoro-piperidin-1-yl)-acetamido)bicyclo-[1.1.1]pentan-1-yl)-acetamide	428.1	1.93-2.00 (m, 4 H), 2.21-2.25 (m, 6 H), 2.48-2.51 (m, 4 H), 2.93 (s, 2 H), 4.40 (s, 2 H), 6.96 (d, J = 9.2 Hz, 2 H), 7.33 (d, J = 8.8 Hz, 2 H), 8.26 (s, 1 H), 8.63 (s, 1 H)
29		2-(4-chloro-phenoxy)-N-(3-((2-(1-methylcyclo-propoxy)ethyl)-amino)bicyclo-[1.1.1]pentan-1-yl)acetamide	365.1	0.33-0.35 (m, 2 H), 0.63 (s, 2 H), 1.28 (s, 3 H), 1.91 (s, 6 H), 2.15 (bs, 1 H), 2.52-2.53 (m, 2 H), 3.38 (t, J = 6.4 Hz, 2 H), 4.39 (s, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 7.31 (d, J = 8.8 Hz, 2 H), 8.53 (s, 1 H)

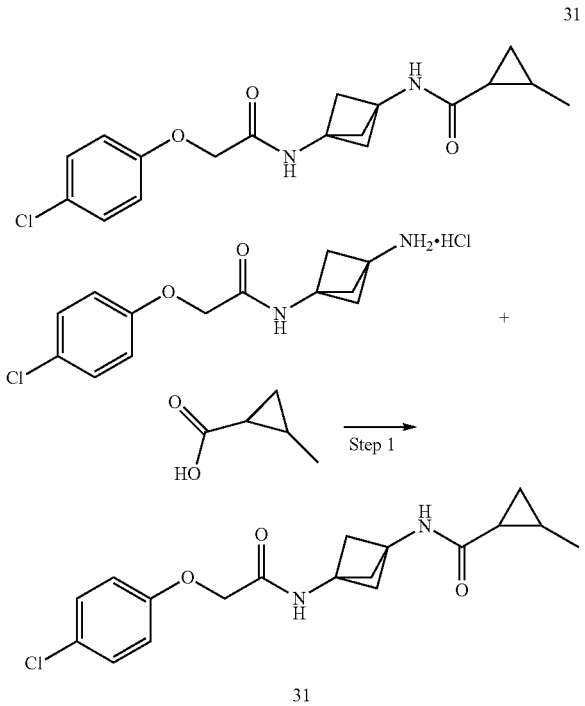
TABLE 3-continued

Cmpd #	Structure	Name	LCMS m/z [M + H]+	^{1}H-NMR (400 MHz, DMSO-d_6)
30		2-(4-chloro-phenoxy)-N-(3-((2-(1-cyclopropyl-ethoxy)ethyl)-amino)bicyclo-[1.1.1]pentan-1-yl)acetamide	379.1	0.03-0.05 (m, 2 H), 0.27-0.35 (m, 1 H), 0.36-0.46 (m, 1 H), 0.47-0.74 (m, 1 H), 1.09-1.11 (m, 3 H), 1.92 (s, 6 H), 2.17-2.48 (m, 1 H), 2.56-2.65 (m, 2 H), 2.72-2.75 (m, 1 H), 3.35-3.38 (m, 1 H), 3.49-3.52 (m, 1 H), 4.39 (s, 2 H), 6.94 (d, J = 8.0 Hz, 2 H), 7.31 (d, J = 8.0 Hz, 2 H), 8.53 (bs, 1 H).

Example 31

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-methylcyclopropane-1-carboxamide

[0643]



[0644] Step 1: To a solution of N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.03 g, 0.09 mmol, 1 equiv) in DCM (5.0 mL) at 0° C. was added triethylamine (0.04 g, 0.39 mmol, 4 equiv) and 2-methylcyclopropane-1-carboxylic acid (0.011 g, 0.1 mmol, 1.1 equiv). After stirring for 5 minutes at 0° C., T_3P (50 wt. % in ethyl acetate) (0.047 g, 0.14 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 16 h at which time the starting materials were completely consumed. The reaction mixture was diluted with water (5 mL) and extracted with DCM (2×10 mL). The combined organic extract was washed with a saturated solution of aqueous $NaHCO_3$ (5.0 mL), water (5.0 mL) and brine (5.0 mL) and was then dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated to give the crude product. The crude product was purified by flash column chromatography (Combiflash) using a silica gel column and the product was eluted at 5% methanol in dichloromethane. The fractions containing product were concentrated to give N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-methylcyclopropane-1-carboxamide (16 mg, 47% yield) as white solid. LCMS (ES) m/z=349.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.43-0.58 (m, 1H), 0.75-0.82 (m, 1H),

0.98-1.03 (m, 4H), 1.17-1.47 (m, 1H), 2.18 (s, 6H), 4.39 (s, 2H), 6.94 (d, J=9.2 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 8.48-8.52 (m, 1H), 8.62-8.68 (m, 1H).

[0645] The Compounds of Examples 32 to 51 were prepared generally according to the procedure described above for Example 31.

TABLE 4

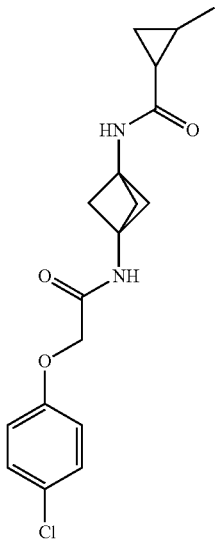
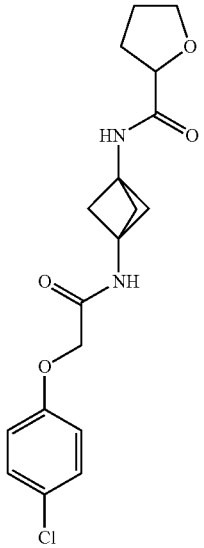
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
31		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)-2-methylcyclopropane-1-carboxamide	349.1	0.43-0.58 (m, 1 H), 0.75-0.82 (m, 1 H), 0.98-1.03 (m, 4 H), 1.17-1.47 (m, 1 H), 2.18 (s, 6 H), 4.39 (s, 2 H), 6.94 (d, J = 9.2 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.48-8.52 (m, 1 H), 8.62-8.68 (m, 1 H).
32		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)tetrahydrofuranyl-2-carboxamide	365.1	1.74-1.78 (m, 3 H), 2.00-2.09 (m, 1 H), 2.20 (s, 6 H), 3.70-3.71 (m, 1 H), 3.83-3.84 (m, 1 H), 4.09-4.10 (m, 1 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.25 (s, 1 H), 8.62 (s, 1 H).

TABLE 4-continued

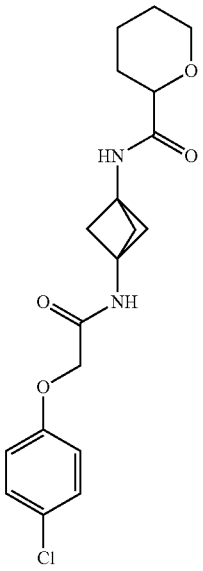
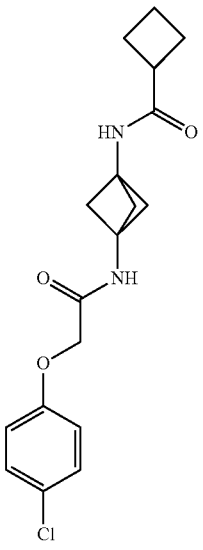
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
33		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl) tetrahydro-2H-pyran-2-carboxamide	379.1	1.24-1.27 (m, 1 H), 1.45 (bs, 3 H), 1.75-1.81 (m, 2 H), 2.19 (s, 6 H), 3.36-3.38 (m, 1 H), 3.61-3.64 (m, 1 H), 3.89-3.91 (m, 1 H), 4.39 (s, 2 H), 6.94 (d, J = 8.4 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.04 (s, 1 H), 8.61 (s, 1 H).
34		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)cyclobutane-carboxamide	349.1	1.69-1.73 (m, 1 H), 1.81-1.84 (m, 1 H), 1.93-1.95 (m, 2 H), 2.04-2.09 (m, 2 H), 2.18 (s, 6 H), 2.88-2.92 (m, 1 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.17 (s, 1 H), 8.62 (s, 1 H).

TABLE 4-continued

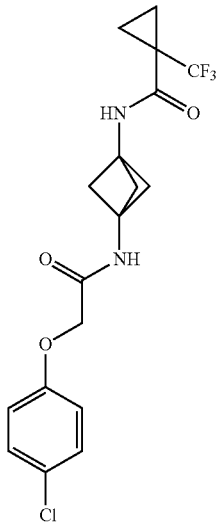
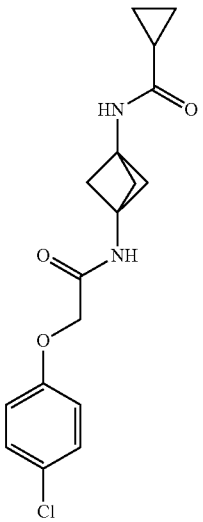
Cmpd #	Structure	Name	LCMS m/z [M + H]+	^{1}H-NMR (400 MHz, DMSO-d_6)
35		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)-1-(trifluoromethyl) cyclopropane-1-carboxamide	403.1	1.15-1.18 (m, 2 H), 1.22-1.26 (m, 2 H), 2.20 (s, 6 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.23 (s, 1 H), 8.64 (s, 1 H).
36		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)cyclopropane-carboxamide	335.2	0.59-0.62 (m, 4 H), 1.43-1.44 (m, 1 H), 2.19 (s, 6 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.60 (s, 1 H), 8.63 (s, 1 H).

TABLE 4-continued

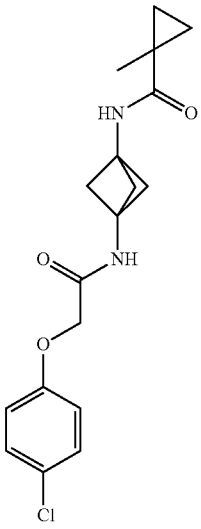
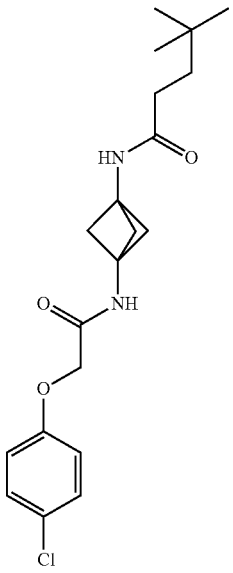
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
37		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)-1-methylcyclopropane-1-carboxamide	349.1	0.44 (d, J = 2.4 Hz, 2 H), 0.9 (d, J = 2.4 Hz, 2 H), 1.19 (s, 3 H), 2.19 (s, 6 H), 4.39 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 7.94 (s, 1 H), 8.60 (s, 1 H).
38		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)-4,4-dimethyl-pentanamide	379.2	0.81 (s, 9 H), 1.35 (t, J = 8.0 Hz, 2 H), 1.96 (t, J = 8.0 Hz, 2 H), 2.17 (s, 6 H), 4.39 (s, 2 H), 6.94 (d, J = 8.4 Hz, 2 H), 7.31 (d, J = 8.8 Hz, 2 H), 8.31 (s, 1 H), 8.61 (s, 1 H).

TABLE 4-continued

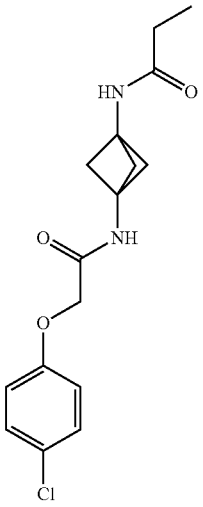
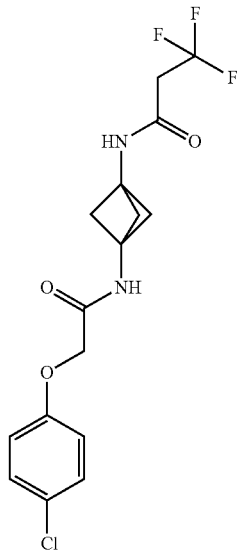
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
39		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)propionamide	323.1	0.93 (t, J = 7.4 Hz, 3 H), 2.00 (q, J = 7.6 Hz, 2 H), 2.18 (s, 6 H), 4.40 (s, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.27 (s, 1 H), 8.62 (s, 1 H).
40		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)-3,3,3-trifluoro-propanamide	377.1	2.22 (s, 6 H), 3.17 (q, J = 11.3 Hz, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.67 (s, 1 H), 8.80 (s, 1 H).

TABLE 4-continued

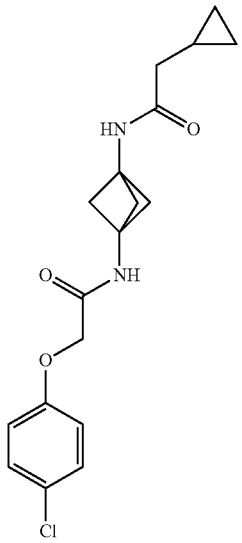
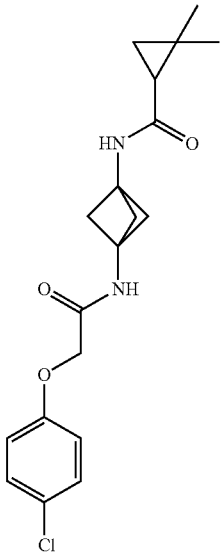
Cmpd #	Structure	Name	LCMS m/z [M + H]+	^{1}H-NMR (400 MHz, DMSO-d_6)
41		2-(4-chlorophenoxy)-N-(3-(2-cyclopropylacetamido) bicyclo[1.1.1]pentan-1-yl)acetamide	349.2	0.04-0.07 (m, 2 H), 0.37-0.41 (m, 2 H), 0.86-0.91 (m, 1 H), 1.90 (d, J = 6.8 Hz, 2 H), 2.19 (s, 6 H), 4.40 (s, 2 H), 6.95 (d, J = 9.2 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.23 (s, 1 H), 8.62 (s, 1 H).
42		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)-2,2-dimethylcyclo-propane-1-carboxamide	363.1	0.58-0.61 (m, 1 H), 0.77-0.79 (m, 1 H), 1.05 (d, J = 5.6 Hz, 6 H), 1.30-1.33 (m, 1 H), 2.18 (s, 6 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.31 (d, J = 8.8 Hz, 2 H), 8.44 (s, 1 H), 8.61 (s, 1 H).

TABLE 4-continued

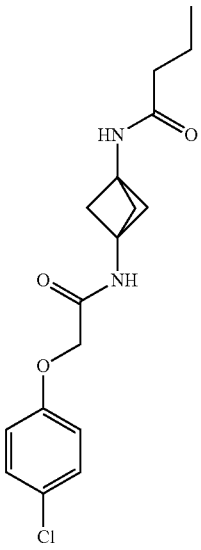
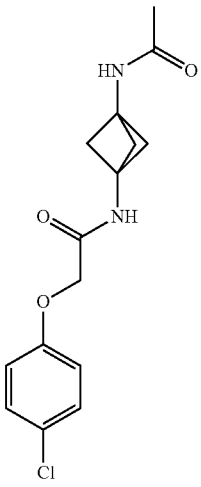
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
43		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl) butyramide	337.1	0.79-0.83 (m, 3 H), 1.40-1.50 (m, 2 H), 1.95-1.98 (m, 2 H), 2.18 (s, 6 H), 4.40 (s, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 8.28 (bs, 1 H), 8.62 (bs, 1 H).
44		N-(3-acetamidobicyclo [1.1.1]pentan-1-yl)-2-(4-chlorophenoxy) acetamide	309.1	1.73 (s, 3 H), 2.17 (s, 6 H), 4.40 (s, 2 H), 6.94 (d, J = 8.0 Hz, 2 H), 7.31 (d, J = 8.8 Hz, 2 H), 8.36 (bs, 1 H), 8.62 (bs, 1 H).

TABLE 4-continued

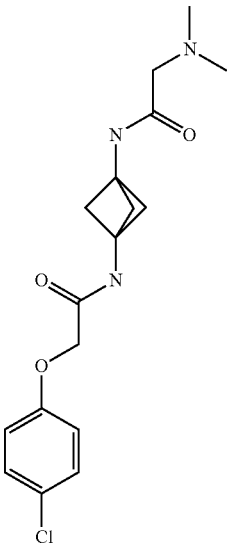
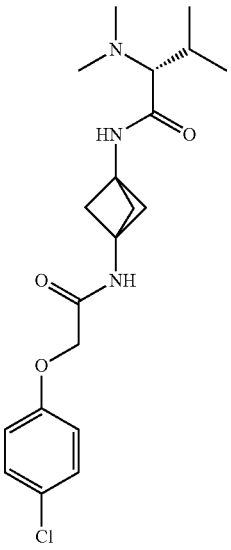
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
45		2-(4-chlorophenoxy)-N-(3-(2-(dimethylamino) acetamido)bicyclo [1.1.1]pentan-1-yl) acetamide	352.1	2.15 (s, 6 H), 2.20 (s, 6 H), 2.78 (s, 2 H), 4.4 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.18 (s, 1 H), 8.62 (s, 1 H).
46		(R)-N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)-2-(dimethylamino)-3-methylbutanamide	394.2	0.73 (d, J = 6.4 Hz, 3 H), 0.8 (d, J = 6.4 Hz, 3 H), 1.88 (m, 1 H), 2.15 (s, 6 H), 2.2 (s, 6 H), 2.37 (d, J = 10.0 Hz, 1 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.4 Hz, 2 H), 8.27 (s, 1 H), 8.63 (s, 1 H).

TABLE 4-continued

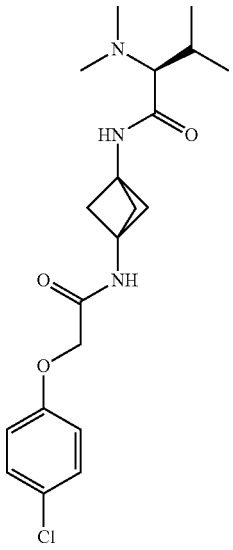
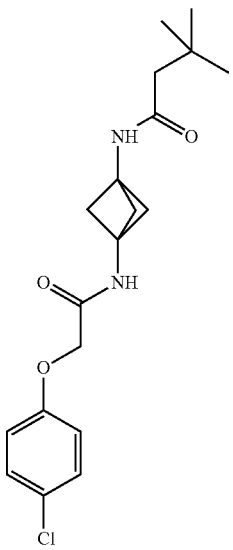
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
47		(S)-N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)-2-(dimethylamino)-3-methylbutanamide	394.4	0.74 (d, J = 6.4 Hz, 3 H), 0.84 (d, J = 6.8 Hz, 3 H), 1.9 (bs, 1 H), 2.16 (s, 6 H), 2.2 (s, 6 H), 2.38 (m, 1 H), 4.4 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.4 Hz, 2 H), 8.28 (s, 1 H), 8.63 (s, 1 H).
48		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)-3,3-dimethyl-butanamide	365.2	0.91 (s, 9 H), 1.87 (s, 2 H), 2.18 (s, 6 H), 4.40 (s, 2 H), 6.96 (d, J = 8.8 Hz, 2 H), 7.33 (d, J = 8.8 Hz, 2 H), 8.22 (bs, 1 H), 8.62 (bs, 1 H).

TABLE 4-continued

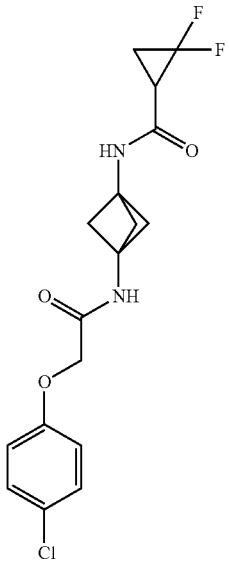
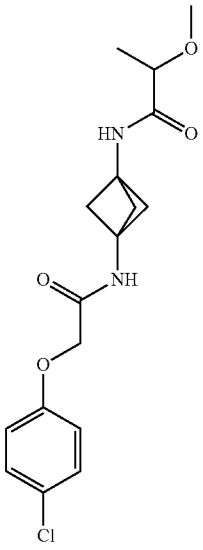
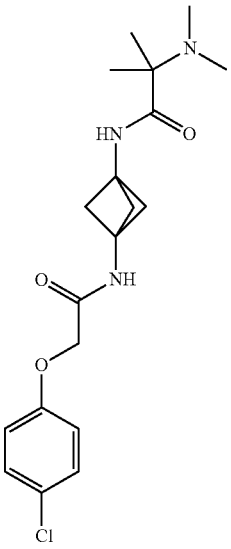
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
49		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)-2,2-difluorocyclo-propane-1-carboxamide	371.2	1.74-1.88 (m, 2 H), 2.16 (s, 6 H), 2.41-2.43 (m, 1 H), 4.41 (s, 2 H), 6.96 (d, J = 8.8 Hz, 2 H), 7.33 (d, J = 8.8 Hz, 2 H), 8.66 (s, 1 H), 8.87 (s, 1 H).
50		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)-2-methoxy-propanamide	353.1	1.16-1.15 (m, 3 H), 2.21 (s, 6 H), 3.22 (s, 3 H), 3.55-3.60 (m, 1 H), 4.40 (s, 2 H), 6.96 (d, J = 9.6 Hz, 2 H), 7.33 (d, J = 8.8 Hz, 2 H), 8.32 (s, 1 H), 8.63 (s, 1 H).

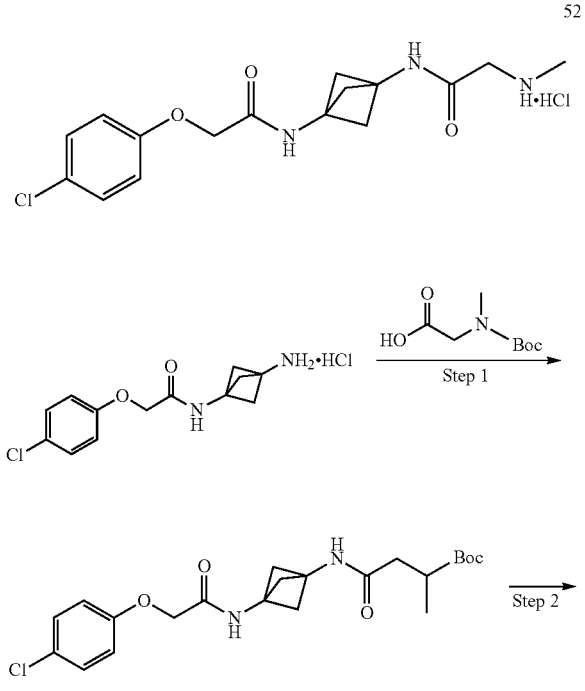
TABLE 4-continued

Cmpd #	Structure	Name	LCMS m/z [M + H]+	1H-NMR (400 MHz, DMSO-d6)
51		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)-2-(dimethylamino)-2-methylpropanamide	380.2	1.00 (s, 6 H), 2.06 (s, 6 H), 2.19 (s, 6 H), 4.39 (s, 2 H), 6.96 (d, J = 8.8 Hz, 2 H), 7.33 (d, J = 8.8 Hz, 2 H), 8.06 (bs, 1 H), 8.61 (bs, 1 H).

Example 52

2-(4-chlorophenoxy)-N-(3-(2-(methylamino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide hydrochloride

[0646]



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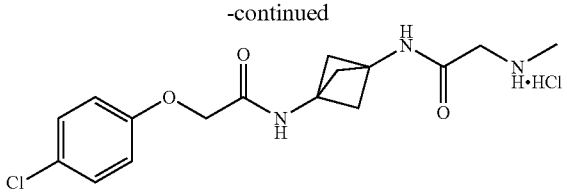


52

[0647] Step 1: To a solution of N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.15 g, 0.49 mmol, 1 equiv) in DCM (10.0 mL) at 0° C. was added triethylamine (0.27 mL, 1.96 mmol, 4 equiv). The mixture was stirred for 10 minutes and then N-(tert-butoxycarbonyl)-N-methylglycine (0.19 g, 0.99 mmol, 2.0 equiv) and T_3P (50 wt. % in ethyl acetate) (0.44 mL, 0.49 mmol, 1.5 equiv) were added to the reaction mixture. The reaction mixture was allowed to stir at room temperature (26° C.) for 1 h. After consumption of the starting material (TLC, 5% MeOH in DCM), the reaction mixture was concentrated under reduced pressure and to the crude mixture was added saturated solution of aqueous $NaHCO_3$ (10 mL). After stirring for 15 mins, the precipitate was filtered and dried under high vacuum to give tert-butyl (2-((3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)amino)-2-oxoethyl)(methyl)carbamate (0.21 g, 97.2% yield) as off white solid. LCMS (ES) m/z=338.3 $[M-Boc+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.31-1.37 (m, 9H), 2.20 (s, 6H), 2.76 (s, 3H), 3.62-3.69 (m, 2H), 4.40 (s, 2H), 6.95 (d, J=8.8 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 8.41 (s, 1H), 8.64 (s, 1H).

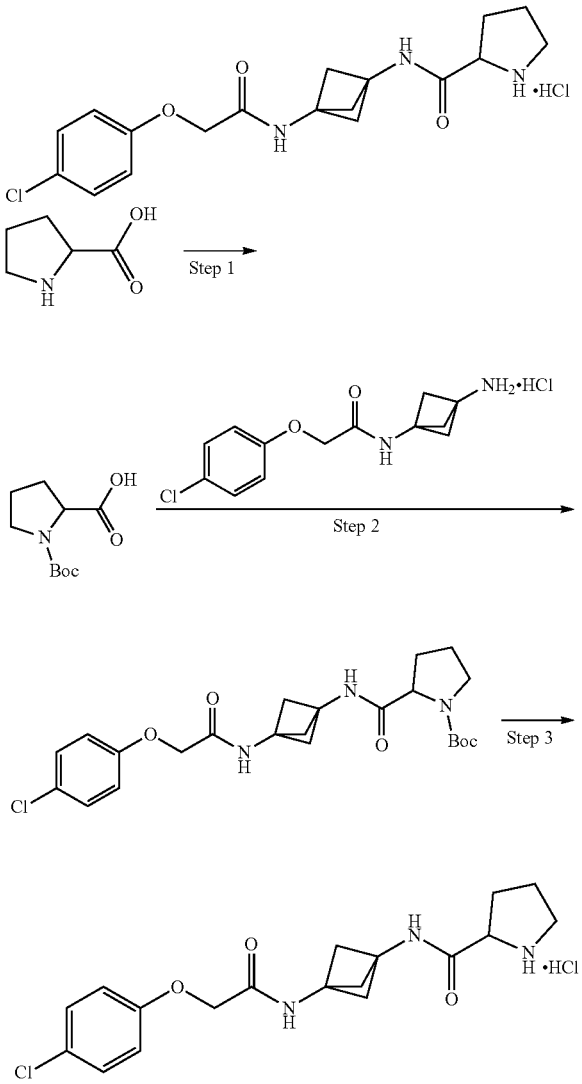
[0648] Step 2: To a stirred solution of tert-butyl (2-((3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)amino)-2-oxoethyl)(methyl)carbamate (0.21 g, 1.0 equiv.) in DCM (5.0 mL) was added 4M HCl in dioxane (2.0 mL)

dropwise at 0° C. Then reaction mixture was stirred at room temperature for 1 h. After consumption of the starting material (TLC, 5% MeOH in DCM), reaction mixture was concentrated under reduced pressure and the solid obtained was washed with n-pentane (2×10 mL), dried under high vacuum to afford 2-(4-chlorophenoxy)-N-(3-(2-(methylamino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide hydrochloride (0.152 g, 93.8% yield) as off-white solid. LCMS (ES) m/z=338.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.24 (s, 6H), 2.52 (t, J=5.2 Hz, 3H), 3.61 (t, J=5.6 Hz, 2H), 4.42 (s, 2H), 6.95 (d, J=8.8 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 8.72 (s, 1H), 8.80 (bs, 2H), 9.10 (s, 1H).

Example 53

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)pyrrolidinyl-2-carboxamide hydrochloride

[0649]



53

[0650] Step 1: To a solution of DL-Proline (0.3 g, 2.60 mmol, 1 equiv) in a saturated solution of aqueous $NaHCO_3$ (3.9 mL) was added di-tert-butyl dicarbonate (0.65 mL, 2.86 mmol, 1.1 equiv) with THF (3.0 mL) at 0° C. The reaction mixture was stirred at room temperature for 16 h at which time the starting materials were completely consumed. After this time, the reaction mixture was concentrated under vacuum and the crude material was redissolved in water (5 mL). The aqueous layer was then acidified with 3 N HCl (to pH=2) and extracted with ethyl acetate (30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under vacuum to afford (tert-butoxycarbonyl) proline (0.55 g, 98% yield) as colorless oil. LCMS (ES) m/z=214 $[M-H]^-$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 (s, 9H), 1.90-1.95 (m, 2H), 2.26-2.44 (m, 2H), 3.35-3.42 (m, 2H), 4.34 (bs, 1H).

[0651] Step 2: To a solution of N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.05 g, 0.16 mmol, 1 equiv) in DCM (7.0 mL) at 0° C. was added triethylamine (0.06 g, 0.64 mmol, 4 equiv) and (tert-butoxycarbonyl)proline (0.04 g, 0.18 mmol, 1.1 equiv). After stirring for 5 minutes at 0° C., T_3P (50 wt. % in ethyl acetate) (0.076 g, 0.24 mmol, 1.5 equiv) was added. The reaction mixture was stirred at room temperature for 16 h at which time the starting materials were completely consumed. The reaction mixture was diluted with water (7 mL) and extracted with DCM (2×15 mL). The combined organic layer was washed with a saturated solution of aqueous $NaHCO_3$ (6.0 mL), water (5.0 mL) and brine (5.0 mL), and then dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated to give the crude product. The crude product was purified by flash column chromatography (Combiflash) using a silica gel column and the product was eluted at 2.5% methanol in dichloromethane. Fractions containing product were concentrated to give tert-butyl 2-((3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)carbamoyl)pyrrolidinyl-1-carboxylate (77 mg, 100% yield) as colorless syrup. LCMS (ES) m/z=364 $[M-Boc+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.31-1.37 (m, 9H), 1.68-1.71 (m, 3H), 2.10 (bs, 1H), 2.20 (s, 6H), 3.22-3.25 (m, 1H), 3.31 (bs, 1H), 3.86-3.98 (m, 1H), 4.40 (s, 2H), 6.95 (d, J=8.8 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 8.33 (s, 0.3H), 8.42 (s, 0.7H), 8.63 (s, 1H).

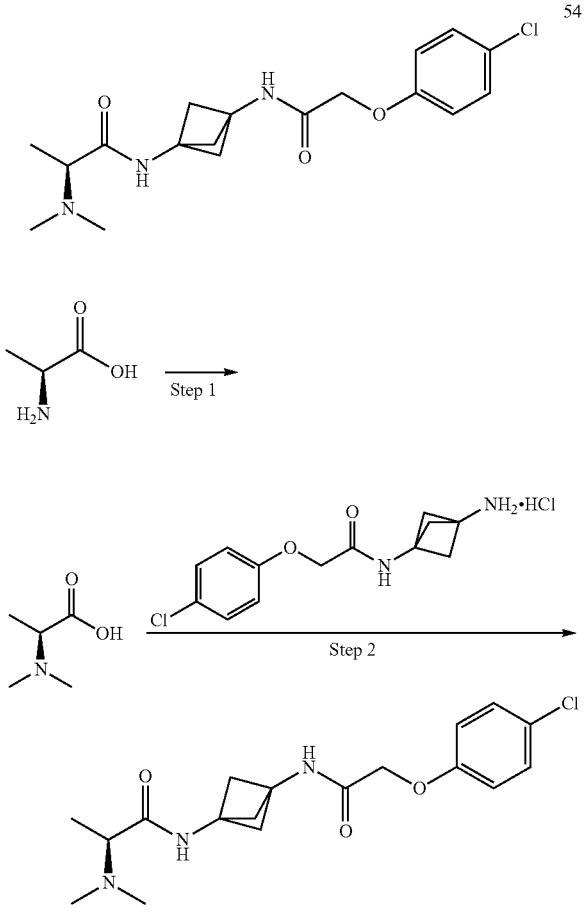
[0652] Step 3: To a solution of tert-butyl 2-((3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)carbamoyl)pyrrolidinyl-1-carboxylate (0.075 g, 0.16 mmol, 1 equiv) in 1,4-dioxane (4 mL) was added and 4N HCl in

dioxane (1 mL). This reaction mixture was stirred at room temperature for 16 hours at which time starting materials were completely consumed. The solvent was then evaporated under reduced pressure from the reaction mixture and the resulting solid was triturated with n-pentane (30 mL) to give N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)pyrrolidinyl-2-carboxamide hydrochloride (0.065 g, 100% yield) as white solid. LCMS (ES) m/z=364.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.72-1.79 (m, 1H), 1.82-1.89 (m, 2H), 2.25 (s, 7H), 3.10-3.40 (m, 2H), 4.03 (bs, 1H), 4.41 (s, 2H), 6.95 (d, J=8.8 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 8.49 (bs, 1H), 8.70 (s, 1H), 9.13 (s, 1H), 9.43 (bs, 1H).

Example 54

(S)—N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-v)-2-(dimethylamino)propanamide

[0653]



[0654] Step 1: To a suspension of L-alanine (0.35 g, 3.92 mmol, 1.0 equiv) in methanol (15 mL) was added formaldehyde solution, 37 wt. % in H_2O (1.7 mL, 14.9 mmol, 3.8 equiv), and Pd/C (10%) (0.1 g). The flask was purged with argon and then the reaction mixture was saturated with hydrogen under passive vacuum. After purging and backfilling with hydrogen three times, the reaction mixture was stirred under hydrogen at room temperature and atmospheric pressure for 24 h. After consumption of the starting material (TLC, 5% methanol in DCM), the reaction mixture was filtered through a celite bed using sintered funnel. The filtrate was concentrated under vacuum to give dimethyl-L-alanine (0.4 g, 86% crude product) as colorless liquid. LCMS (ES) m/z=118.1 $[M+H]^+$.

[0655] Step 2: To a solution of N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.1 g, 0.33 mmol, 1 equiv) in DMF (20.0 mL) at 0° C. was added DIPEA (0.12 mL, 0.66 mmol, 2 equiv), and HATU (0.18 g, 0.49 mmol, 1.5 equiv). The reaction was stirred for 10 minutes and then dimethyl-L-alanine (0.046 g, 0.39 mmol, 1.2 equiv) was added to the reaction mixture. Then reaction mixture was allowed to stir at room temperature for 10 mins. The reaction mixture was heated 80° C. for 16 h. After consumption of the starting material (TLC, 5% methanol in DCM), the reaction mixture was diluted with water (2×20 mL) and extracted by EtOAc (2×15 mL). The combined organic extract was separated and dried over anhydrous sodium sulfate and concentrated under vacuum to give (S)—N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-(dimethylamino)propanamide (0.037 g, 21% yield) as off white solid. LCMS (ES) m/z=366.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 (d, J=7.2 Hz, 3H), 2.12 (s, 6H), 2.19 (s, 6H), 2.84-2.86 (m, 1H), 4.40 (s, 2H), 6.95 (d, =8.0 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 8.19 (bs, 1H), 8.62 (bs, 1H).

[0656] The Compound of Example 55 was prepared generally according to the procedure described above for Example 54.

TABLE 5

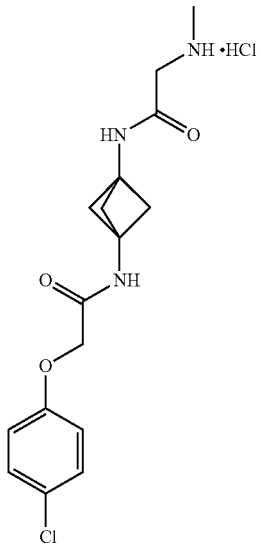
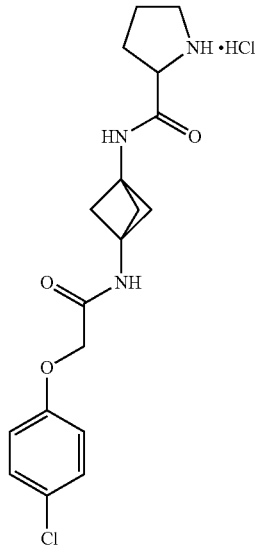
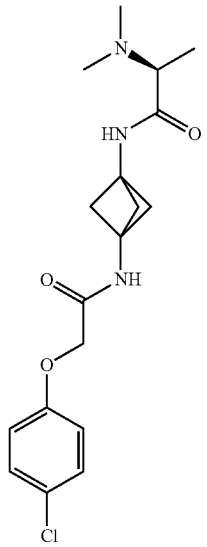
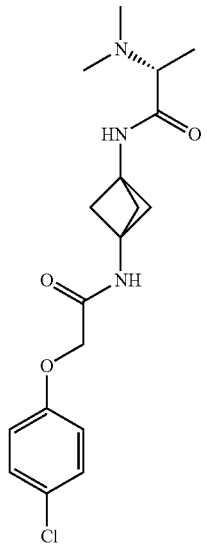
Cmpd #	Structure	Name	LCMS m/z [M + H]+	^{1}H-NMR (400 MHz, DMSO-d_6)
52		2-(4-chlorophenoxy)-N-(3-(2-(methylamino) acetamido)bicyclo [1.1.1]pentan-1-yl) acetamide hydrochloride	338.1	2.24 (s, 6 H), 2.52 (t, J = 5.2 Hz, 3 H), 3.61 (t, J = 5.6 Hz, 2 H), 4.42 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.72 (s, 1 H), 8.80 (bs, 2 H), 9.10 (s, 1 H)
53		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo[1.1.1] pentan-1-yl)pyrrolidinyl-2-carboxamide hydrochloride	364.1	1.72-1.79 (m, 1 H), 1.82-1.89 (m, 2 H), 2.25 (s, 7 H), 3.10-3.40 (m, 2 H), 4.03 (bs, 1 H), 4.41 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.49 (bs, 1 H), 8.70 (s, 1 H), 9.13 (s, 1 H), 9.43 (bs, 1 H).

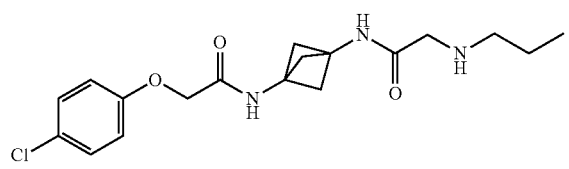
TABLE 5-continued

Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
54		(S)-N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo[1.1.1] pentan-1-yl)-2-(dimethylamino) propanamide	366.1	1.00 (d, J = 7.2 Hz, 3 H), 2.12 (s, 6 H), 2.19 (s, 6 H), 2.84-2.86 (m, 1 H), 4.40 (s, 2 H), 6.95 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.19 (bs, 1 H), 8.62 (bs, 1 H)
55		(R)-N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)-2-(dimethylamino) propanamide	366.1	1.00 (d, J = 7.2 Hz, 3 H), 2.12 (s, 6 H), 2.19 (s, 6 H), 2.82-2.87 (m, 1 H), 4.40 (s, 2 H), 6.95 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.19 (bs, 1 H), 8.62 (bs, 1 H).

Example 56

2-(4-chlorophenoxy)-N-(3-(2-(propylamino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide

[0657]



56

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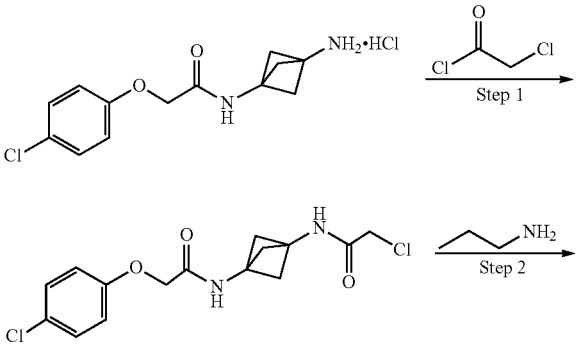

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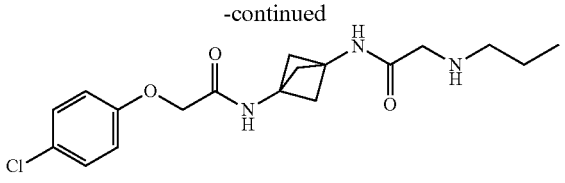


56

[0658] Step 1: To a solution of N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.075 g, 0.24 mmol, 1 equiv) in DCM (15 mL) was added triethylamine (0.08 mL, 0.6 mmol, 2.5 equiv) and the reaction mixture was stirred at room temperature for 10 mins. 2-chloroacetyl chloride (0.04 mL, 0.37 mmol, 1.5 equiv) was added at 0° C., and the solution was then stirred at room temperature for 12 h. After consumption of the starting material (TLC, 5% Methanol in DCM), the reaction mixture was diluted with water (5 mL) and extracted with DCM (2×15 mL). The combined organic extract was washed with saturated aqueous $NaHCO_3$ solution (8 mL) and water (5 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2-chloro-N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide (0.18 g, 97% yield) as brownish colour solid. LCMS (ES) m/z=343.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 2.50 (s, 6H), 4.00 (s, 2H), 4.40 (s, 2H), 6.84-6.89 (m, 2H), 6.92-6.99 (m, 2H), 7.25-7.28 (m, 2H).

[0659] Step 2: To a solution of 2-chloro-N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide (0.08 g, 0.23 mmol, 1 equiv) in DMF (8 mL) were added triethylamine (0.12 mL, 0.92 mmol, 4 equiv) and propylamine (0.54 mL, 0.94 mmol, 4 equiv) and the reaction mixture was stirred at 0° C. for 10 mins. After stirring for 0° C., the reaction mixture was allowed to warm to room temperature and then refluxed at 80° C. for 2.0 h under microwave conditions, during which the starting material was completely consumed. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (2×15 mL). The combined organic extract was washed with brine and the organic phase was separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography (Combiflash) using a silica gel column and the product was eluted at 2.5% methanol in DCM. Fractions containing product were concentrated to give 2-(4-chlorophenoxy)-N-(3-(2-(propylamino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide (0.03 g, 35% yield) as an off brown solid. LCMS (ES) m/z=366.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ ppm 0.83 (t, J=7.6 Hz, 3H), 1.37 (q, J=7.2 Hz, 2H), 2.21 (s, 6H), 2.38-2.42 (m, 2H), 3.01 (s, 2H), 4.40 (s, 2H), 6.95 (d, J=8.8 Hz, 2H), 7.32 (d, J=8.0 Hz, 2H), 8.27 (bs, 1H), 8.64 (bs, 1H).

[0660] The Compound of Example 57 was prepared generally according to the procedures described above for Example 56.

TABLE 6

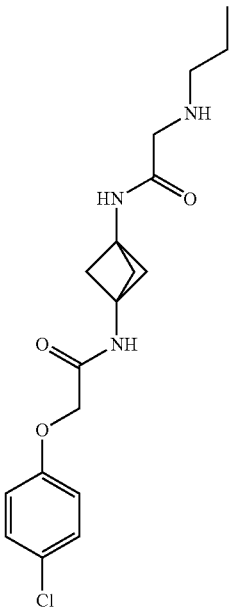
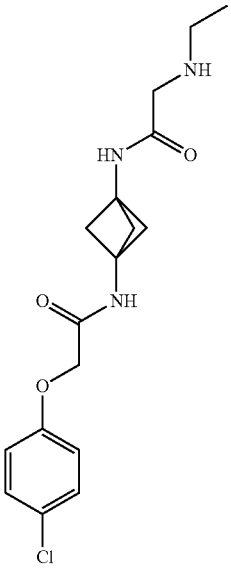
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^1H-NMR (400 MHz, DMSO-d_6)
56		2-(4-chlorophenoxy)-N-(3-(2-(propylamino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide	366.1	0.83 (t, J = 7.6 Hz, 3 H), 1.37 (q, J = 7.2 Hz, 2 H), 2.21 (s, 6 H), 2.38-2.42 (m, 2 H), 3.01 (s, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 8.27 (bs, 1 H), 8.64 (bs, 1 H).

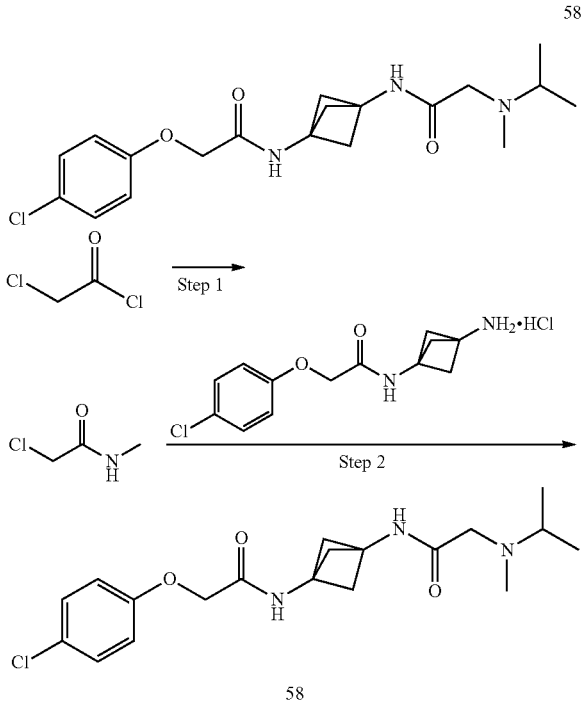
TABLE 6-continued

Cmpd #	Structure	Name	LCMS m/z [M + H]+	1H-NMR (400 MHz, DMSO-d6)
57		2-(4-chlorophenoxy)-N-(3-(2-(ethylamino) acetamido)bicyclo [1.1.1]pentan-1-yl)acetamide	352.3	0.96 (t, J = 6.8 Hz, 3 H), 2.03 (bs, 1 H), 2.21 (s, 6 H), 2.42-2.44 (m, 2 H), 2.98 (s, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 8.27 (bs, 1 H), 8.63 (bs, 1 H).

Example 58

2-(4-chlorophenoxy-N-(3-(2-(isopropyl(methyl) amino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide

[0661]



[0662] Step 1: To a solution of propan-2-amine (3.5 g, 59.21 mmol, 1 equiv) and triethylamine (9.9 mL, 71.05 mmol, 1.2 equiv) in THF (150 mL) was added a solution of tert-butyl 2-bromoacetate (8.8 mL, 65.13 mmol, 1.1 equiv) in THF (50 mL) at 0° C. The reaction mixture was allowed to warm to room temperature and stirred for 8 h. The solid was filtered and the filtrate was concentrated under vacuum to give the crude product. The crude product was purified by flash column chromatography (Combiflash) using a silica gel column and the product was eluted at 50% ethyl acetate in hexane. Fractions containing product were concentrated to obtain tert-butyl isopropylglycinate (2.5 g, 23% yield) as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.08 (d, J=6.0 Hz, 6H), 1.46 (s, 9H), 2.83 (m, 1H), 3.32 (s, 2H).

[0663] Step 2: To a solution of tert-butyl isopropylglycinate (0.5 g, 2.88 mmol, 1 equiv) in THF (10 mL) at 0° C. was added 37 wt % formaldehyde solution in water (0.46 mL, 5.77 mmol, 2.0 equiv), the reaction mixture was allowed to warm to 25° C. and stirred for 2 h. Sodium cyanoborohydride was added to above mixture at 0° C., the reaction mixture was allowed to warm to 25° C. and stirred for 16 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was quenched with 10% sodium bicarbonate solution (50 mL) and extracted with ethyl acetate (3×50 mL). The combined organic extract was washed with water (50 mL) and brine (50 mL), then dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to get the crude product. The crude product was purified by flash column chromatography (Combiflash) using a silica gel column and the product eluted at 50% ethyl acetate in hexane. Fractions containing product were concentrated to obtain tert-butyl N-isopropyl-N-methylglycinate (0.5 g, 92% yield) as colourless oil. LCMS (ES) m/z=188.2 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.04 (d, J=6.4 Hz, 6H), 1.46 (s, 9H), 2.35 (s, 3H), 2.93-2.96 (m, 1H), 3.17 (s, 2H).

[0664] Step 3: 4 M HCl in 1,4-dioxane (2 mL) was added to tert-butyl N-isopropyl-N-methylglycinate (0.25 g, 1.33 mmol, 1 equiv) at 0° C. The resulting mixture was allowed to warm to 27° C. and stirred for 16 h. The progress of the reaction was monitored by TLC. After completion of reaction, the mixture was concentrated under reduced pressure to obtain the title compound N-isopropyl-N-methylglycine hydrochloride (0.3 g, crude) as colourless gum. LCMS (ES) m/z=132.2 $[M+H]^+$. The crude product was taken as such to next step without purification.

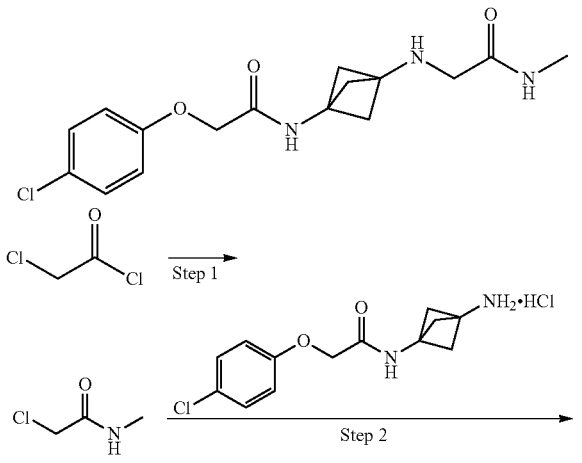
[0665] Step 4: To a mixture of N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.07 g, 0.23 mmol, 1 equiv), N-isopropyl-N-methylglycine hydrochloride (0.05 g, 0.30 mmol, 1.3 equiv) and triethylamine (0.25 mL, 1.84 mmol, 8.0 equiv) in dichloromethane (10 mL) was added T_3P (50 wt. % in ethyl acetate) (0.3 g, 0.46 mmol, 2.0 equiv) 0° C. The reaction mixture was allowed to warm to 27° C. and was stirred for 16 h. The progress of the reaction was monitored by TLC. After completion of reaction, the mixture was diluted with ethyl acetate (90 mL), washed with 10% sodium bicarbonate solution (50 mL), water (25 mL) and brine (25 mL). The mixture was then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography (Combiflash) using a silica gel column and the product was eluted at 5% methanol in DCM as the eluent to obtain 2-(4-chlorophenoxy)-N-(3-(2-(isopropyl(methyl)amino)acetamido)bicyclo[1.1.1]pentan-1-yl) acetamide (0.04 g, 47.5% yield) as white solid. LCMS (ES) m/z=380.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.92 (d, J=6.8 Hz, 6H), 2.10 (s, 3H), 2.21 (s, 6H), 2.72-2.75 (m, 1H), 2.81 (s, 2H), 4.40 (s, 2H), 6.95 (d, J=8.8 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 8.06 (s, 1H), 8.63 (s, 1H).

Example 59

2-(4-chlorophenoxy)-N-(3-((2-(methylamino)-2-oxoethyl)amino)bicyclo[1.1.1]pentan-1-yl)acetamide

[0666]

59



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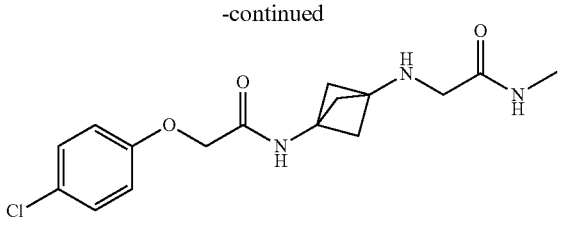


59

[0667] Step 1: To a solution of 2-chloroacetyl chloride (1.0 g, 8.85 mmol, 1.0 equiv) in DCM (100 mL) was added a 2 M solution of methyl amine in THF (5.32 mL, 10.62 mmol, 1.2 equiv) at 0° C. and the mixture was stirred for 2 h. The reaction mixture was washed with saturated solution of sodium bicarbonate (50 mL), water (20 mL) and brine (20 mL), then dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to give 2-chloro-N-methylacetamide (0.2 g, crude) as off white solid. The crude product was taken as such to next step without purification. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.60 (d, J=4.8 Hz, 3H), 4.01 (s, 2H), 8.09 (bs, 1H).

[0668] Step 2: A mixture of N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.05 g, 0.16 mmol, 1 equiv), 2-chloro-N-methylacetamide (0.035 g, 0.32 mmol, 2.0 equiv) and triethylamine (0.046 mL, 0.32 mmol, 2.0 equiv) in DMF (2 mL) was subjected to microwave irradiation at 80° C. for 2 h. The progress of the reaction was monitored by TLC. The reaction mixture was concentrated under vacuum to obtain the crude product. The crude product was purified by flash column chromatography (Combiflash) using a silica gel column and the product was eluted at 6% methanol in dichloromethane. Fractions containing product were combined and concentrated to give impure product, which was purified again by preparative HPLC (analytical conditions, column: Inertsil ODS 3V (250 mm×4.6 mm×5 micron), mobile phase (A): 0.1% ammonia in water, mobile phase (B): acetonitrile) to obtain the title compound 2-(4-chlorophenoxy)-N-(3-((2-(methylamino)-2-oxoethyl)amino)bicyclo[1.1.1]pentan-1-yl)acetamide (0.03 g, 54% yield) as white gum. LCMS (ES) m/z=338.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.90 (s, 6H), 2.58 (d, J=4.8 Hz, 3H), 2.89 (s, 1H), 3.00 (s, 2H), 4.38 (s, 2H), 6.94 (d, J=8.8 Hz, 2H), 7.31 (d, J=8.8 Hz, 2H), 7.62 (bs, 1H), 8.53 (s, 1H).

[0669] The Compound of Example 60 was prepared generally according to the procedure described above for Example 59.

TABLE 7

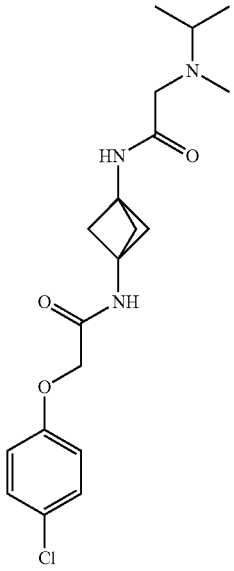
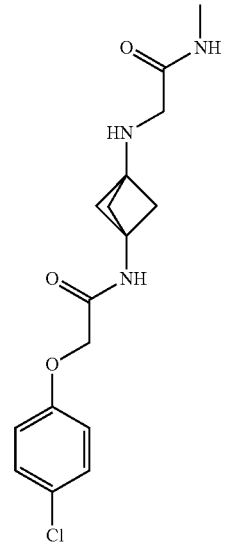
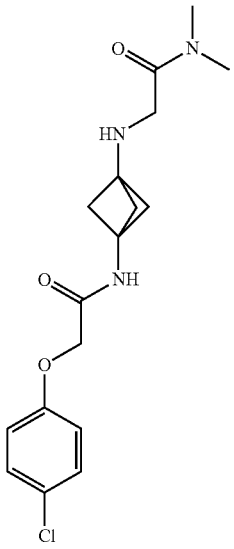
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
58		2-(4-chlorophenoxy)-N-(3-(2-(isopropyl(methyl)amino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide	380.2	0.92 (d, J = 6.8 Hz, 6 H), 2.10 (s, 3 H), 2.21 (s, 6 H), 2.72-2.75 (m, 1 H), 2.81 (s, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.06 (s, 1 H), 8.63 (s, 1 H)
59		2-(4-chlorophenoxy)-N-(3-((2-(methylamino)-2-oxoethyl)amino)bicyclo[1.1.1]pentan-1-yl)acetamide	338.1	1.90 (s, 6 H), 2.58 (d, J = 4.8 Hz, 3 H), 2.89 (s, 1 H), 3.00 (s, 2 H), 4.38 (s, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 7.31 (d, J = 8.8 Hz, 2 H), 7.62 (bs, 1 H), 8.53 (s, 1 H)

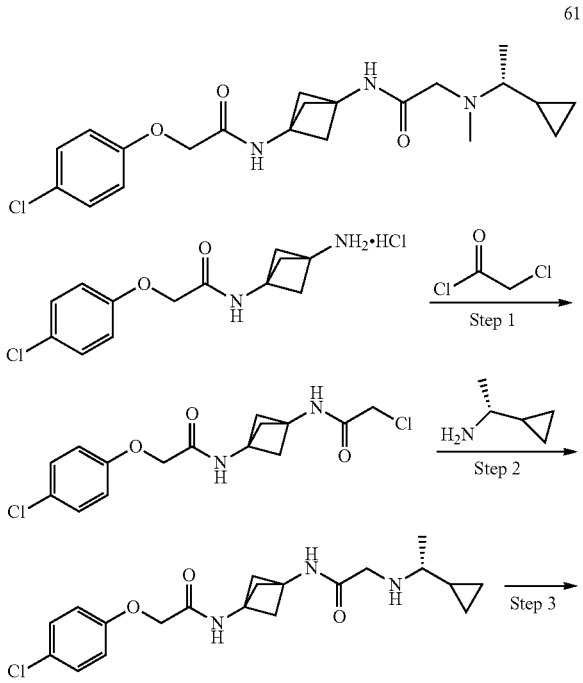
TABLE 7-continued

Cmpd #	Structure	Name	LCMS m/z [M + H]+	^{1}H-NMR (400 MHz, DMSO-d_6)
60		2-((3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)amino)-N,N-dimethylacetamide	352.1	2.15 (s, 6 H), 2.2 (s, 6 H), 2.77 (s, 2 H), 4.4 (s, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.18 (s, 1 H), 8.62 (s, 1 H).

Example 61

(R)-2-(4-chlorophenoxy)-N-(3-(2-((1-cyclopropylethyl)(methyl)amino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide

[0670]



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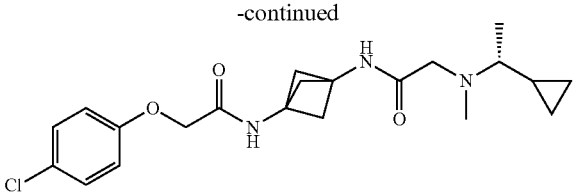


61

[0671] Step 1: To a solution of N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.4 g, 1.31 mmol, 1.0 equiv) in DCM (10 mL) was added triethylamine (0.37 mL, 2.63 mmol, 2.0 equiv) and 2-chloroacetyl chloride (0.12 mL, 1.58 mmol, 1.2 equiv) at 0° C. The resulting mixture was allowed to warm to 27° C. and was stirred for 2 h. The progress of the reaction was monitored by TLC. Upon completion the solid was filtered, washed with water (25 mL), n-pentane (25 mL) and then dried under vacuum to give 2-chloro-N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide (0.32 g, 71% yield) as off white solid. LCMS (ES) m/z=343.0 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.22 (s, 6H), 3.97 (s, 2H), 4.41 (s, 2H), 6.95 (d, J=8.8 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 8.66 (s, 1H), 8.78 (s, 1H).

[0672] Step 2: A mixture of 2-chloro-N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide (0.06 g, 0.17 mmol, 1 equiv), (R)-1-cyclopropylethan-1-amine (0.03 g, 0.34 mmol, 2.0 equiv) and triethylamine (0.05 mL, 0.34 mmol, 2.0 equiv) in DMF (1 mL) was subjected to microwave irradiation at 80° C. for 2 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated under vacuum, the residue was diluted with DCM (40 mL) washed with water (20 mL) and brine (20 mL), then dried over anhydrous sodium sulfate, filtered and concentrated under

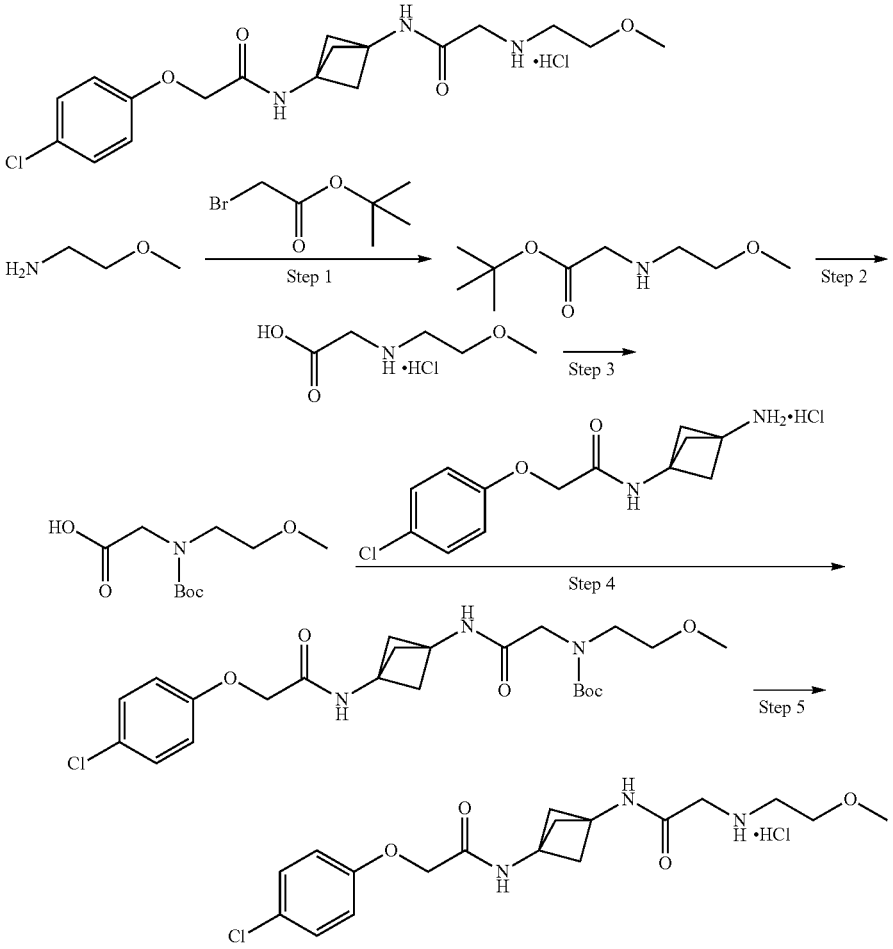
vacuum to obtain the crude product. The crude product was purified by flash column chromatography (Combiflash) using a silica gel column and the product was eluted at 8% methanol in dichloromethane. Fractions containing product were combined and concentrated to obtain the title product (R)-2-(4-chlorophenoxy)-N-(3-(2-((1-cyclopropylethyl) amino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide (0.04 g, crude product) as gum. LCMS (ES) m/z=392.2 $[M+H]^+$.

[0673] Step 3: To a solution of (R)-2-(4-chlorophenoxy)-N-(3-(2-((1-cyclopropylethyl)amino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide (0.04 g, 0.10 mmol, 1 equiv) in THF (10 mL) at 0° C. was added 37 wt % formaldehyde in water (0.02 mL, 0.20 mmol, 2.0 equiv) and catalytic amount of acetic acid. The reaction mixture was allowed to warm to 25° C. and stirred for 1 h. Sodium cyanoborohydride was added to the mixture at 0° C. and the reaction mixture was allowed to warm to 25° C. and stirred for 2 h. The reaction was monitored by TLC. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3×30 mL). The combined organics were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to obtain the crude product. The crude product was purified by flash column chromatography (Combiflash) using a silica gel column. It was then repurified by preparative HPLC (analytical conditions; column: Inertsil ODS 3V (250 mm×4.6 mm×5 micron), mobile phase (A): 0.1% ammonia in water, mobile phase (B): acetonitrile) to obtain the title product (R)-2-(4-chlorophenoxy)-N-(3-(2-((1-cyclopropylethyl)(methyl)amino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide (0.035 g) as white solid. LCMS (ES) m/z=406.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.01-0.01 (m, 1H), 0.21-0.26 (m, 1H), 0.33-0.39 (m, 1H), 0.42-0.44 (m, 1H), 0.70-0.74 (m, 1H), 0.98 (d, J=6.4 Hz, 3H), 1.84-1.91 (m, 1H), 2.21 (s, 9H), 2.95 (s, 2H), 4.40 (s, 2H), 6.93 (d, J=9.6 Hz, 2H), 7.32 (d, J=8.4 Hz, 2H), 8.05 (s, 1H), 8.63 (s, 1H).

Example 62

2-(4-chlorophenoxy-N-(3-(2-((2-methoxyethyl-l3-chloranyl)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide

[0674]



62

[0675] Step 1: To a stirred solution of 2-methoxyethan-1-amine (0.1 g, 1.33 mmol, 1.0 equiv.) in THF (5 mL) at 0° C.

were added compound tert-butyl 2-bromoacetate (0.19 mL, 1.33 mmol, 1.0 equiv.) and triethylamine (0.28 mL, 1.99 mmol, 1.5 equiv.). Then reaction mixture was stirred at room temperature (26° C.) for 16 h. After the starting material was consumed (TLC, 70% EtOAc in hexane), the solvent was removed under reduced pressure, the mixture diluted with DCM (50 mL) and washed with water (2×20 mL). Combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to obtain tert-butyl (2-methoxyethyl) glycinate (0.23 g, crude) as pale yellow liquid. LCMS (ES) m/z=190.2 $[M+H]^+$.

[0676] Step 2: To tert-butyl (2-methoxyethyl) glycinate (0.23 g, 1.21 mmol, 1.0 equiv.) was added 4M HCl in dioxane (3.0 mL) dropwise at 0° C. Then reaction mixture was stirred at room temperature (25° C.) for 16 h. After the starting material was consumed (TLC, 5% MeOH in DCM), the reaction mixture was concentrated under reduced pressure, washed with n-pentane (50 mL), dried under high vacuum to afford (2-methoxyethyl)glycine (0.2 g, crude) as off white solid. LCMS (ES) m/z=134.1 $[M+H]^+$.

[0677] Step 3: To a stirred solution of (2-methoxyethyl) glycine (0.2 g, 1.50 mmol, 1.0 equiv.) in THF (10 mL) was added a saturated aqueous sodium bicarbonate solution (2.0 mL, 4.50 mmol, 3.0 equiv.) at 0° C. Then Boc anhydride (0.38 mL, 1.65 mmol, 1.1 equiv.) was added and the reaction mixture was allowed to stir at room temperature (24° C.) for 16 h. After the starting material was consumed (TLC, 5% MeOH in DCM), the THF was evaporated and the crude mixture was cooled to 0° C., acidified with 3N HCl solution (adjusted to pH=2), extracted with ethyl acetate (2×50 mL). The combined organic extract was dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated under vacuum to provide the crude product which was purified by silica gel column chromatography using 7-8% methanol in dichloromethane to obtain N-(tert-butoxycarbonyl)-N-(2-methoxyethyl)glycine (0.18 g, 51.4% yield) as off white solid. LCMS (ES) m/z=134.2 $[M+H]^+-100$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (d, J=18.8 Hz, 9H), 3.20 (d, J=6.0 Hz, 3H), 3.31-3.34 (m, 2H), 3.35-3.39 (m, 2H), 3.82 (d, J=8.8 Hz, 2H), 12.5 (bs, 1H).

[0678] Step 4: To a solution N-(3-aminobicyclo[1.1.1] pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.2 g, 0.66 mmol, 1 equiv) in DCM (10.0 mL) at 0° C. was added triethylamine (0.37 mL, 2.64 mmol, 4 equiv). The mixture was stirred for 10 minutes and then N-(tert-butoxycarbonyl)-N-(2-methoxyethyl) glycine (0.185 g, 0.79 mmol, 1.2 equiv) and T_3P (50 wt. % in ethyl acetate) (0.79 mL, 1.32 mmol, 2.0 equiv) were added to the reaction mixture. Then reaction mixture was allowed to stir at room temperature (26° C.) for 16 h. After the stating material was consumed (TLC, 5% MeOH in DCM), the reaction mixture was concentrated under reduced pressure. A saturated aqueous sodium bicarbonate solution was added and the mixture was stirred for 20 mins. The solid was filtered and washed with water (50 mL) and n-pentane (50 mL) and then dried under high vacuum to obtain tert-butyl (2-((3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)amino)-2-oxoethyl)(2-methoxyethyl)carbamate (0.23 g, 72.3% yield) as off white solid. LCMS (ES) m/z=382.1 $[M+H]^+-100$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.31-1.37 (m, 9H). 2.20 (s, 6H), 3.20 (s, 3H), 3.29-3.31 (m, 2H), 3.36-3.37 (m, 2H), 3.63 (s, 1H), 3.72 (s, 1H), 4.40 (s, 2H), 6.94 (d, J=8.8 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 8.33 (d, J=14.0 Hz, 1H), 8.64 (s, 1H).

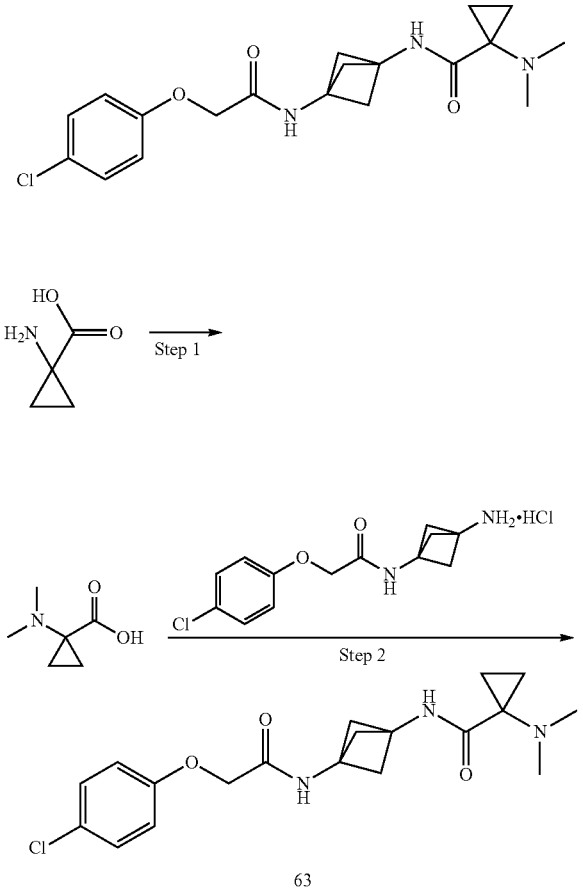
[0679] Step 5: To a stirred solution of tert-butyl (2-((3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl) amino)-2-oxoethyl)(2-methoxyethyl) carbamate (0.23 g, 0.55 mmol, 1.0 equiv.) in DCM (10.0 mL) was added 4M HCl in dioxane (2.0 mL) dropwise at 0° C. Then reaction mixture was stirred at room temperature for 16 h. After the starting material was consumed (TLC, 5% MeOH in DCM), the reaction mixture was concentrated under reduced pressure and washed with n-pentane (2×10 mL). The resulting solid was dried under high vacuum to afford 2-(4-chlorophenoxy)-N-(3-(2-((2-methoxyethyl)-l3-chloranyl)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide (0.15 g, 75.3%, yield) as off white solid. LCMS (ES) m/z=382.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.24 (s, 6H), 3.09 (t, J=5.0 Hz, 2H), 3.26 (s, 3H), 3.54 (d, J=5.2 Hz, 2H), 3.63 (s, 2H), 4.41 (s, 2H), 6.95 (d, J=9.2 Hz, 2H), 7.32 (d, J=9.6 Hz, 2H), 8.60-8.69 (m, 3H), 8.99 (s, 1H).

Example 63

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1] pentan-1-yl)-1-(dimethylamino)cyclopropanecarboxamide

[0680]

63



63

[0681] Step 1: To the stirred suspension of 1-aminocyclopropane-1-carboxylic acid (0.2 g, 1.97 mmol, 1.0 equiv) in methanol (20 mL), 37 wt % formaldehyde in water (0.64 mL, 7.91 mmol, 4 equiv) and 10% Pd/C (50% wet) (0.1 g) were added at room temperature (25° C.). The reaction mixture was hydrogenated under hydrogen bladder at room temperature (25° C.) for 16 h. After consumption of the starting material (TLC, 5% MeOH in DCM), reaction mixture was filtered through a celite bed and filtrate was evaporated to afford 1-(dimethylamino)cyclopropane-1-carboxylic acid (0.16 g, 61.5% yield) as off white solid. LCMS (ES) m/z: 130.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.80-0.81 (m, 2H), 1.08-1.09 (m, 2H), 2.42 (s, 6H), 12.10 (bs, 1H).

[0682] Step 2: To a stirred solution of 1-(dimethylamino) cyclopropane-1-carboxylic acid (0.031 g, 0.24 mmol, 1.2 equiv) in dichloromethane (10 mL), triethylamine (0.11 mL, 0.79 mmol, 4.0 equiv) and N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.06 g, 0.19 mmol, 1.0 equiv) were added at room temperature (25° C.) and reaction mixture was cooled to 0° C. T_3P (50 wt. % in ethyl acetate, 0.24 mL, 0.39 mmol, 2.0 equiv) was then added and reaction mixture was stirred at room temperature (25° C.) for 3 h. After the starting material was consumed (TLC, 5% MeOH in DCM), the reaction mixture was diluted with DCM (100 mL) and was washed with saturated sodium bicarbonate solution (2×10 mL) and water (2×20 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated. The resulting crude material was purified by silica gel column chromatography using 2-3% methanol in dichloromethane to afford titled compound N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-1-(dimethylamino)cyclopropanecarboxamide (0.04 g, 54.0% yield) as off-white solid. LCMS (ES) m/z=378.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.88 (d, J=10.0 Hz, 4H), 2.13 (s, 6H), 2.21 (s, 6H), 4.39 (s, 2H), 6.95 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.8 Hz, 2H), 8.31 (s, 1H), 8.62 (s, 1H).

[0683] The Compound of Example 64 was prepared generally according to the procedure described above for Example 63.

TABLE 8

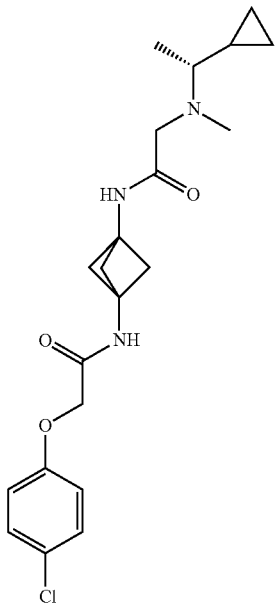
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^1H-NMR (400 MHz, DMSO-d_6)
61		(R)-2-(4-chlorophenoxy)-N-(3-(2-((1-cyclopropylethyl)(methyl)amino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide	406.2	0.01-0.01 (m, 1 H), 0.21-0.26 (m, 1 H), 0.33-0.39 (m, 1 H), 0.42-0.44 (m, 1 H), 0.70-0.74 (m, 1 H), 0.98 (d, J = 6.4 Hz, 3 H), 1.84-1.91 (m, 1 H), 2.21 (s, 9 H), 2.95 (s, 2 H), 4.40 (s, 2 H), 6.93 (d, J = 9.6 Hz, 2 H), 7.32 (d, J = 8.4 Hz, 2 H), 8.05 (s, 1 H), 8.63 (s, 1 H).

TABLE 8-continued

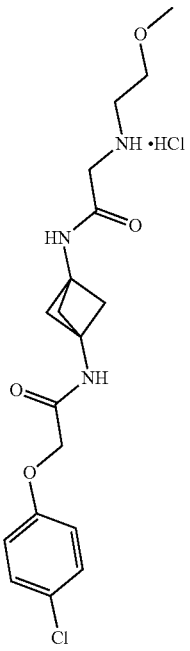
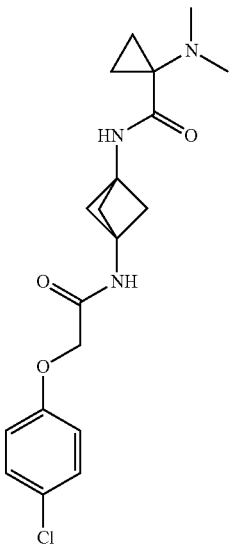
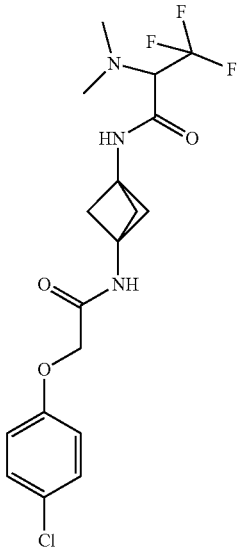
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
62		2-(4-chlorophenoxy)-N-(3-(2-((2-methoxyethyl)-l3-chloranyl)acetamido) bicyclo[1.1.1]pentan-1-yl)acetamide	382.2	2.24 (s, 6 H), 3.09 (t, J = 5.0 Hz, 2 H), 3.26 (s, 3 H), 3.54 (d, J = 5.2 Hz, 2 H), 3.63 (s, 2 H), 4.41 (s, 2 H), 6.95 (d, J = 9.2 Hz, 2 H), 7.32 (d, J = 9.6 Hz, 2 H), 8.60-8.69 (m, 3 H), 8.99 (s, 1 H).
63		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)-1-(dimethylamino) cyclopropane-carboxamide	378.3	0.88 (d, J = 10.0 Hz, 4 H), 2.13 (s, 6 H), 2.21 (s, 6 H), 4.39 (s, 2 H), 6.95 (d, J = 8.0 Hz, 2 H), 7.31 (d, J = 8.8 Hz, 2 H), 8.31 (s, 1 H), 8.62 (s, 1 H).

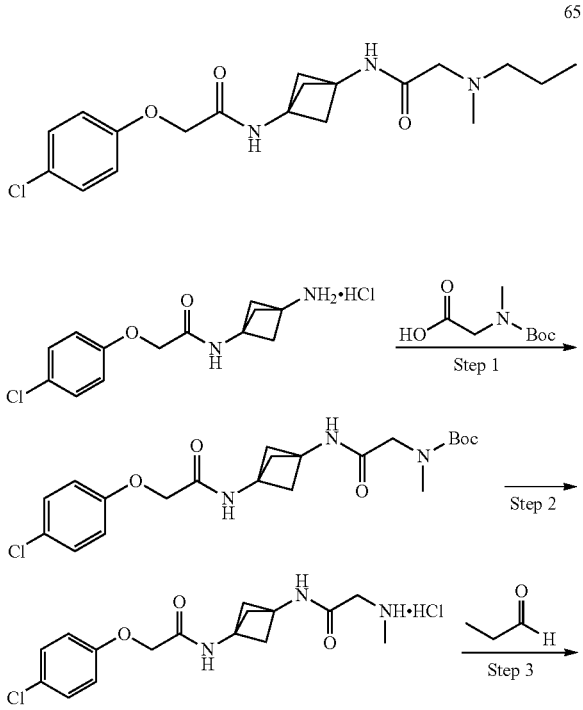
TABLE 8-continued

Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
64		N-(3-(2-(4-chlorophenoxy) acetamido)bicyclo [1.1.1]pentan-1-yl)-2-(dimethylamino)-3,3,3-trifluoro-propanamide	420.1	2.24 (s, 6 H), 2.37 (s, 6 H), 3.93-3.91 (m, 1 H), 4.41 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.67 (s, 1 H), 8.72 (s, 1 H).

Example 65

2-(4-chlorophenoxy)-N-(3-(2-(methyl(propyl)amino) acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide

[0684]



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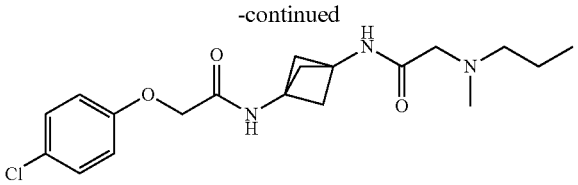


65

[0685] Step 1: To a solution of N-(3-aminobicyclo[1.1.1] pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.3 g, 0.98 mmol, 1 equiv) in DCM (100.0 mL) were added triethylamine (0.33 mL, 2.4 mmol, 2.5 equiv), N-(tert-butoxycarbonyl)-N-methylglycine (0.22 g, 1.18 mmol, 1.2 equiv) and T_3P (50 wt. % in ethyl acetate) (1.47 mL, 2.4 mmol, 2.5 equiv) at 0° C. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated under vacuum, diluted with saturated aqueous $NaHCO_3$ solution (50 mL) and stirred for 30 minutes. A white solid precipitated, which was filtered through Buchner funnel. The solid was washed sequentially with cold water (2×25 mL) and n-pentane (2×50 mL) and dried under vacuum to obtain tert-butyl (2-((3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)amino)-2-oxoethyl) (methyl)carbamate (0.4 g, 93.24% yield) as white solid. LCMS (ES) m/z=383.1 $[M+H]^+$−56. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 5H), 1.37 (s, 4H), 2.20 (s, 6H), 2.76 (s, 3H), 3.62 (s, 1H), 3.69 (s, 1H), 4.40 (s, 2H), 6.95 (d, J=8.8 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 8.41 (s, 1H), 8.64 (s, 1H).

[0686] Step 2: To a solution of tert-butyl (2-((3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl) amino)-2-oxoethyl)(methyl)carbamate (0.4 g, 0.91 mmol, 1 equiv) in DCM (10.0 mL) was added 4 M HCl in dioxane (4.0 mL at 0° C. The reaction mixture was stirred at room

temperature for 12 h. The mixture was then concentrated under vacuum and washed with n-pentane (2×20 mL) to obtain 2-(4-chlorophenoxy)-N-(3-(2-ethylamino)acetamido)bicyclo[1.1.1] pentan-1-yl)acetamide hydrochloride (0.55 g, 88.23% yield) as white solid. LCMS (ES) m/z=338.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.24 (s, 6H), 2.50-2.53 (m, 3H), 3.61 (t, J=5.8 Hz, 2H), 4.42 (s, 2H), 6.95 (d, J=8.8 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 8.72 (s, 1H), 8.78 (s, 1H), 9.06 (s, 1H).

[0687] Step 3: To a solution of 2-(4-chlorophenoxy)-N-(3-(2-ethylamino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide hydrochloride (0.15 g, 0.4 mmol, 1 equiv) in methanol (10 mL) was added propionaldehyde (0.14 mL, 2.0 mmol, 5 equiv) at 0° C. and the mixture was stirred for 1 h at room temperature. Sodium cyanoborohydride (0.10 g, 1.6 mmol, 4 equiv) and acetic acid (0.02 mL, catalytic) were then added at 0° C. The reaction mixture was stirred at room temperature for 24 h. After the starting material was consumed (TLC, 10% Methanol in DCM), the reaction mixture was concentrated, diluted with DCM (100 mL) and washed with 10% aqueous $NaHCO_3$ solution (2×25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was triturated with diethyl ether (2×10 mL) and n-pentane (2×10 mL) and then dried under vacuum obtain 2-(4-chlorophenoxy)-N-(3-(2-(methyl(propyl)amino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide (0.09 g, 59.60% yield) as white solid. LCMS (ES) m/z=380.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.82 (t, J=7.4 Hz, 3H), 1.36-1.41 (m, 2H), 2.15 (s, 3H), 2.24 (s, 6H), 2.25-2.28 (m, 2H), 2.82 (s, 2H), 4.40 (s, 2H), 6.95 (d, J=8.8 Hz, 2H), 7.31 (d, J=9.2 Hz, 2H), 8.06 (s, 1H), 8.63 (s, 1H).

[0688] The Compound of Example 66 was prepared generally according to the procedure described above for Example 65.

TABLE 9

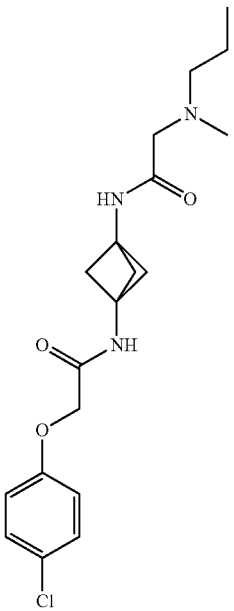
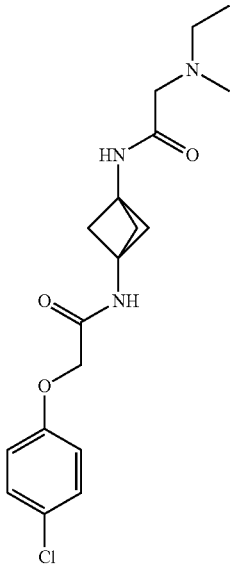
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^1H-NMR (400 MHz, DMSO-d_6)
65		2-(4-chlorophenoxy)-N-(3-(2-(methyl(propyl) amino)acetamido) bicyclo[1.1.1] pentan-1-yl)acetamide	380.2	0.82 (t, J = 7.4 Hz, 3 H), 1.36-1.41 (m, 2 H), 2.15 (s, 3 H), 2.24 (s, 6 H), 2.25-2.28 (m, 2 H), 2.82 (s, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.31 (d, J = 9.2 Hz, 2 H), 8.06 (s, 1 H), 8.63 (s, 1 H).

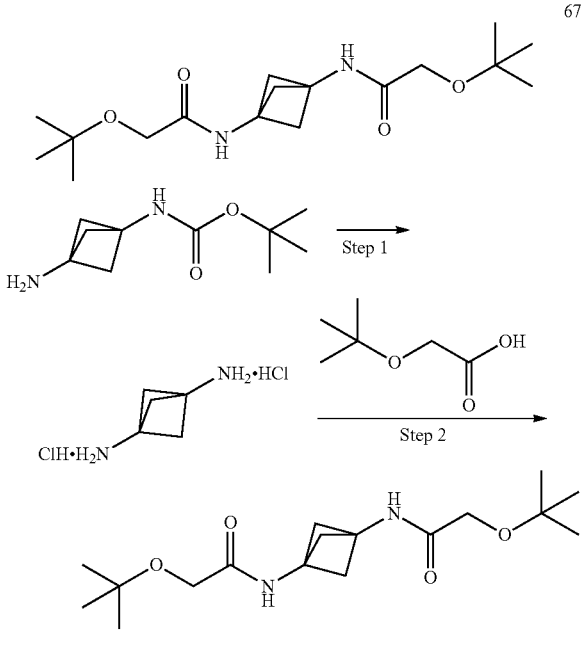
TABLE 9-continued

Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
66		2-(4-chlorophenoxy)-N-(3-(2-(ethyl(methyl)amino) acetamido)bicyclo [1.1.1]pentan-1-yl)acetamide	366.2	0.95 (t, J = 7.2 Hz, 3 H), 2.14 (s, 3 H), 2.21 (s, 6 H), 2.37 (q, J = 7.2 Hz, 2 H), 2.82 (s, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.11 (s, 1 H), 8.63 (s, 1 H).

Example 67

N,N'-(bicyclo[1.1.1]pentane-1,3-diyl)bis(2-(tert-butoxy)acetamide)

[0689]



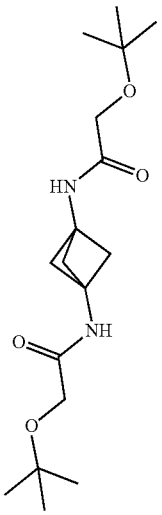
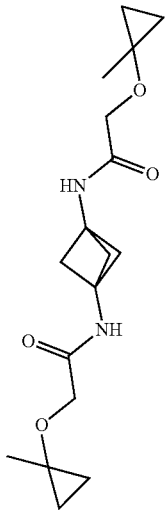
67

[0690] Step 1: To a stirred solution of tert-butyl (3-aminobicyclo[1.1.1]pentan-1-yl)carbamate (0.3 g, 1.51 mmol, 1.0 equiv.) in DCM (8.0 mL) was added 4M HCl in dioxane (3.0 mL) dropwise at 0° C. The reaction mixture was stirred at room temperature for 3 h. After the starting material was consumed (TLC, 5% MeOH in DCM), the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with n-pentane (3×10 mL) and then dried under high vacuum to afford bicyclo[1.1.1]pentane-1,3-diamine dihydrochloride (0.25 g, 96.1% yield) as off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 2.18 (s, 6H), 8.81 (s, 6H).

[0691] Step 2: To a solution of bicyclo[1.1.1]pentane-1,3-diamine dihydrochloride (0.07 g, 0.41 mmol, 1 equiv) in DCM (8.0 mL) at 0° C. was added triethylamine (0.29 mL, 2.04 mmol, 5.0 equiv). The mixture was stirred for 10 minutes and then 2-(tert-butoxy)acetic acid (0.13 g, 1.02 mmol, 2.5 equiv) and T_3P (50 wt. % in ethyl acetate) (0.49 mL, 0.82 mmol, 2.0 equiv) was added to the reaction mixture. Then reaction mixture was allowed to stir at room temperature (27° C.) for 3 h. After the starting material was consumed (TLC, 5% MeOH in DCM), the reaction mixture was concentrated under reduced pressure. Saturated aqueous sodium bicarbonate (25 mL) was added and the mixture was stirred for 20 mins. The resulting solid was filtered, washed with water (20 mL) and n-pentane (20 mL) and dried under high vacuum to give N,N'-(bicyclo[1.1.1]pentane-1,3-diyl) bis(2-(tert-butoxy)acetamide)(0.05 g, 37.6% yield) as off white solid. LCMS (ES) m/z=327.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.19 (s, 18H), 2.21 (s, 6H), 3.67 (s, 4H), 7.91, 2H).

[0692] The Compound of Example 68 was prepared generally according to the procedure described above for Example 67.

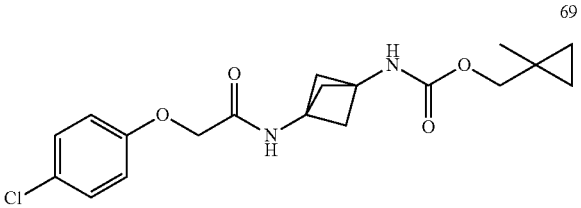
TABLE 10

Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
67		N,N'-(bicyclo[1.1.1]pentane-1,3-diyl)bis(2-(tert-butoxy)acetamide)	327.2	1.19 (s, 18 H), 2.21 (s, 6 H), 3.67 (s, 4 H), 7.91 (s, 2 H).
68		N,N'-(bicyclo[1.1.1]pentane-1,3-diyl)bis(2-(1-methylcyclopropoxy) acetamide	323.2	0.35-0.37 (m, 4 H), 0.75 (m, 4 H), 1.29 (s, 6 H), 2.17 (s, 6 H), 3.75 (s, 4 H), 8.07 (s, 2 H).

Example 69

(1-methylcyclopropyl)methyl (3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)carbamate

[0693]



69

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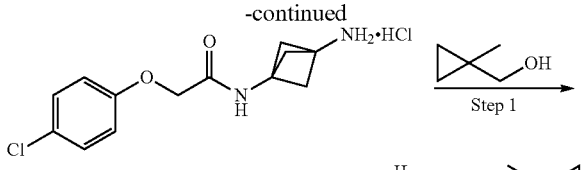
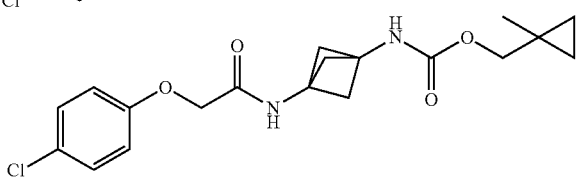




69

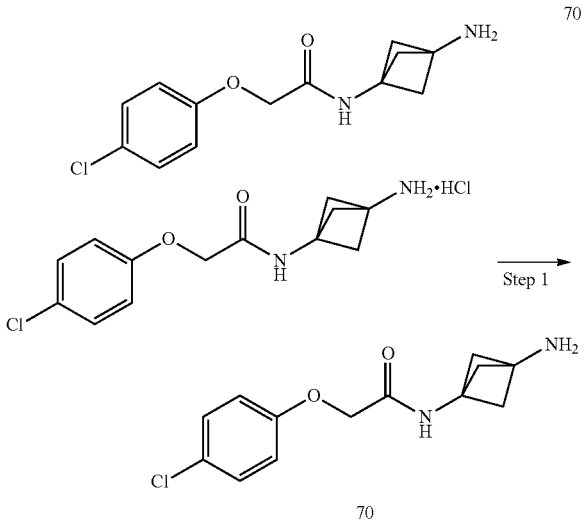
[0694] Step 1: To the stirred solution of (1-methylcyclopropyl)methanol (0.047 g, 0.54 mmol, 2.2 equiv) in dichlo-

romethane (10 mL) was added triethylamine (0.10 mL, 0.74 mmol, 3.0 equiv) and triphosgene (0.073 g, 0.247 mmol, 1.0 equiv) at 0° C. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then cooled to 0° C. and N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.073 g, 0.24 mmol, 1.0 equiv) was added. The mixture was stirred at room temperature for 2 days. Saturated solution of aqueous $NaHCO_3$ (5 mL) and water (10 mL) were added and the product was extracted with dichloromethane (3×30 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude material was purified by flash column chromatography (Combiflash) using a silica gel column and the product was eluted at 3% methanol in dichloromethane. Fractions containing product were combined and concentrated to give (1-methylcyclopropyl)methyl (3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)carbamate (0.02 g, 21.3%) as an off-white solid. LCMS (ES) m/z=379.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.29 (s, 2H), 0.41 (s, 2H), 1.05 (s, 3H), 2.05 (s, 6H), 3.71 (s, 2H), 4.40 (s, 2H), 6.95 (d, J=8.8 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 7.82 (bs, 1H), 8.63 (s, 1H).

Example 70

N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide

[0695]



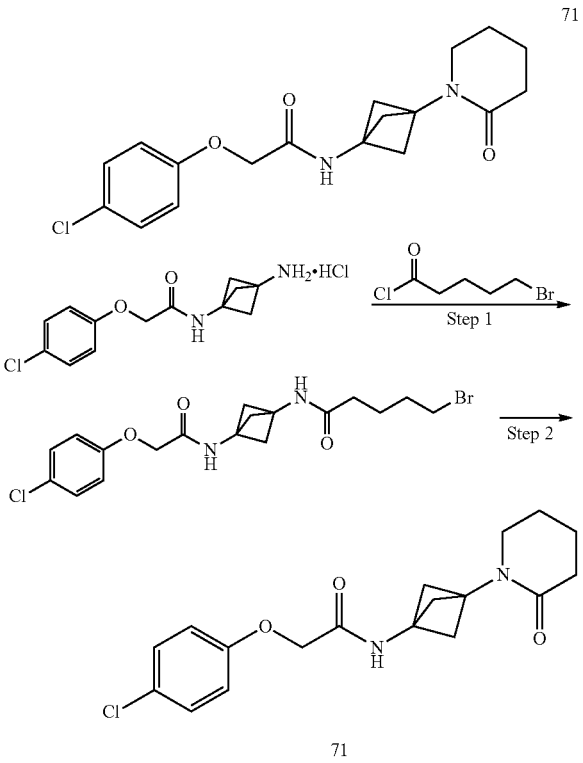
70

[0696] Step 1: To a solution of N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.1 g, 3.2 mmol, 1 equiv) in DCM (20.0 mL) was added 10% $NaHCO_3$ solution (5 mL) at 0° C. and the reaction mixture was allowed to stir at room temperature for 1 h. The organic layer was then separated, dried over anhydrous sodium sulfate, filtered and concentrated to obtain N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide (0.05 g, 58.82% yield) as white solid. LCMS (ES) m/z=267.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm, 1.91 (s, 6H), 2.17 (bs, 2H), 4.37 (s, 2H), 6.94 (d, J=8.8 Hz, 2H), 7.31 (d, J=8.8 Hz, 2H), 8.47 (s, 1H).

Example 71

2-(4-chlorophenoxy)-N-(3-(2-oxopiperidin-1-yl) bicyclo[1.1.1]pentan-1-yl)acetamide

[0697]



71

[0698] Step 1: To a solution of N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.1 g, 0.33 mmol, 1 equiv) in dichloromethane (4 mL) was added triethylamine (0.083 g, 0.82 mmol, 2.5 equiv) followed by 5-bromopentanoyl chloride (0.085 g, 0.42 mmol, 1.3 equiv) at 0° C. The reaction mixture was stirred at room temperature for 4 h at which time starting materials were completely consumed. The reaction mixture was diluted with a saturated solution of aqueous $NaHCO_3$ (5 mL) and DCM (20 mL). The organic layer was separated, washed with water (10 mL) and brine (10 mL), and then dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated to give the crude product, which was carried to next step without purification. LCMS (ES) m/z=429.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.53-1.59 (m, 2H), 1.71-1.78 (m, 2H), 2.03 (t, J=7.4 Hz, 2H), 2.18 (s, 6H), 3.49 (t, J=6.8 Hz, 2H), 4.40 (s, 2H), 6.95 (d, J=8.8 Hz, 2H), 7.31 (d, J=8.8 Hz, 2H), 8.34 (s, 1H), 8.62 (s, 1H).

[0699] Step 2: To a solution of 5-bromo-N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)pentanamide (0.1 g, 0.23 mmol, 1 equiv) in THF (10 mL) was added potassium tert-butoxide (0.34 mL, 0.34 mmol, 1.5 equiv) at 0° C. The reaction mixture was stirred at room temperature for 16 h at which time the starting materials were completely consumed. The reaction mixture was diluted with water (7 mL) and extracted with EtOAc (2×15 mL). The combined organic extract was washed water (5.0 mL) and brine (5.0

mL), and then dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated. The crude material was purified by flash column chromatography (Combiflash) using a silica gel column and the product was eluted at 3% methanol in dichloromethane. Fractions containing product were combined and concentrated to give 2-(4-chlorophenoxy)-N-(3-(2-oxopiperidin-1-yl)bicyclo[1.1.1]pentan-1-yl)acetamide (70 mg, 86% yield) as white solid. LCMS (ES) m/z=349.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.62-1.67 (m, 4H), 2.14 (t, J=6.4 Hz, 2H), 2.29 (s, 6H), 3.18 (t, J=6.0 Hz, 2H), 4.40 (s, 2H), 6.95 (d, J=9.6 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 8.64 (s, 1H).

TABLE 11

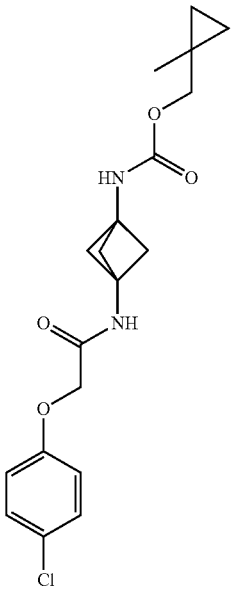
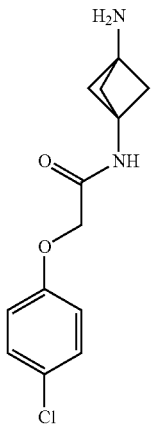
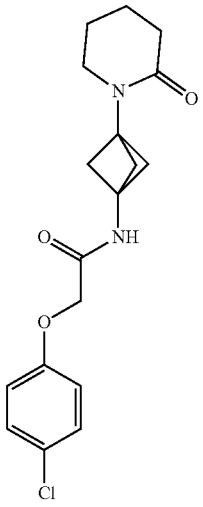
Cmpd #	Structure	Name	LCMS m/z $[M + H]^+$	^1H-NMR (400 MHz, DMSO-d_6)
69		(1-methylcyclopropyl) methyl (3-(2-(4-chlorophenoxy)acetamido) bicyclo[1.1.1]pentan-1-yl) carbamate	379.4	0.29 (s, 2 H), 0.41 (s, 2 H), 1.05 (s, 3 H), 2.05 (s, 6 H), 3.71 (s, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 7.82 (bs, 1 H), 8.63 (s, 1 H).
70		N-(3-aminobicyclo[1.1.1] pentan-1-yl)-2-(4-chlorophenoxy) acetamide	267.0	1.91 (s, 6 H), 2.17 (bs, 2 H), 4.37 (s, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 7.31 (d, J = 8.8 Hz, 2 H), 8.47 (s, 1 H).

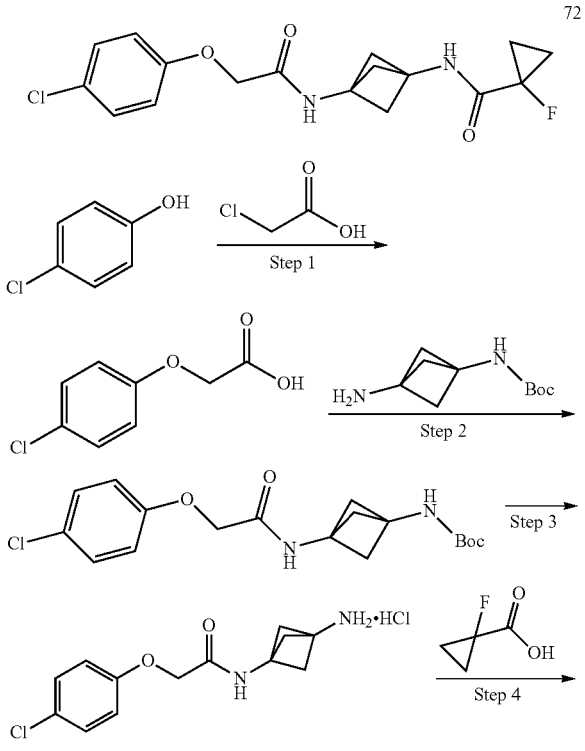
TABLE 11-continued

Cmpd #	Structure	Name	LCMS m/z [M + H]+	1H-NMR (400 MHz, DMSO-d6)
71		2-(4-chlorophenoxy)-N-(3-(2-oxopiperidin-1-yl)bicyclo[1.1.1]pentan-1-yl)acetamide	349.1	1.62-1.67 (m, 4 H), 2.14 (t, J = 6.4 Hz, 2 H), 2.29 (s, 6 H), 3.18 (t, J = 6.0 Hz, 2 H), 4.40 (s, 2 H), 6.95 (d, J = 9.6 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.64 (s, 1 H)

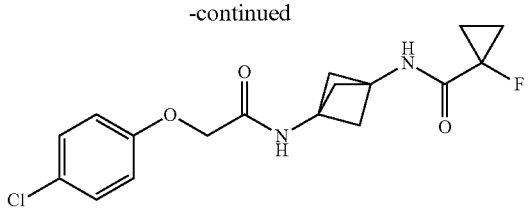
Example 72

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-1-fluorocyclopropane-1-carboxamide

[0700]



-continued



72

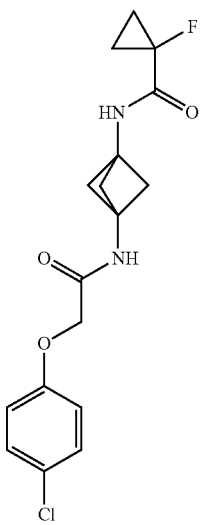
[0701] Step 1: To a stirred solution of 4-chlorophenol (60 g, 466.7 mmol, 1 equiv) in water (200 mL) was added a solution of sodium hydroxide (74.15 g, 1866 mmol, 4 equiv) in water (200 mL) at 0° C. After 15 min, 4-chloroacetic acid (66.15 g, 700.06 mmol, 1.5 equiv) was added to the reaction mixture portionwise at 0° C. and stirred for 10 min at the same temperature. The resulting mixture was then heated to 100° C. and stirred for 12 h. After consumption of the starting material (TLC, 5% Methanol in DCM), the reaction mixture was allowed to cool to 27° C. The reaction mixture was diluted with water (150 mL) and the aqueous layer was washed with ethyl acetate (2×150 mL). The aqueous layer was then acidified with concentrated HCl to pH=1 and the precipitated product was filtered through a sintered funnel, and washed with ice-cold water (100 mL) and n-pentane (100 mL). The solid was dried under high vacuum to give 2-(4-chlorophenoxy)acetic acid (40 g, 45% yield) as a white solid. LCMS (ES) m/z=186.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 4.64 (s, 2H), 6.91 (d, J=9.2 Hz, 2H), 7.30 (d, J=8.8 Hz, 2H), 13.0 (bs, 1H).

[0702] Step 2: To a stirred solution of 2-(4-chlorophenoxy)acetic acid (22.58 g, 121.04 mmol, 1.2 equiv) in dichloromethane (75 mL) at 0° C. was added triethylamine (56 mL, 403.49 mmol, 4 equiv) and the mixture was stirred for 5 minutes at 0° C. T3P (50 wt. % in ethyl acetate) (96.28 mL, 151.30 mmol, 1.5 equiv) was added and the reaction mixture was stirred for 10 min at 0° C. After 10 minutes,

tert-butyl (3-aminobicyclo[1.1.1]pentan-1-yl)carbamate (20 g, 100.87 mmol, 1 equiv) was then added and the reaction mixture was allowed to warm to 27° C. and was stirred for 12 hours. The reaction was monitored by TLC, and upon completion, was diluted with water (200 mL) and extracted with dichloromethane (2×200 mL). The combined organic extract was washed with saturated aqueous $NaHCO_3$ solution (100 mL) and water (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was then triturated with n-pentane to obtain the title compound tert-butyl (3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)carbamate (35 g, 94% yield) as a light brown solid. (Note: Performed multiple batches (20 g, 20 g, 22.5 g, 10 g) following the above procedure and stoichiometry. All batches were combined into a single batch and characterized). LCMS (ES) m/z=311.1 {[M+H]$^+$-(t-butyl)}. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 9H), 2.11 (s, 6H), 4.39 (s, 2H), 6.94 (d, J=8.8 Hz, 2H), 7.31 (d, J=8.8 Hz, 2H), 7.45 (bs, 1H), 8.60 (bs, 1H).

[0703] Step 3: To a solution of tert-butyl (3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)carbamate (18 g, 49.04 mmol, 1 equiv) in dichloromethane (250 mL) was added 4.0 M hydrochloric acid in dioxane (70 mL) at 0° C. The resulting mixture was allowed to warm to 27° C. and stirred for 12 h. After the starting material was consumed (TLC, 5% Methanol in DCM), the dichloromethane was evaporated under reduced pressure. The residue was triturated with n-pentane (50 mL), diethylether (30 mL) and dried under high vacuum to obtain title product N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (13 g, 87% yield), as off white solid. (Note: Performed multiple batches (17 g, 18 g and 17 g) following the above procedure and stoichiometry. All batches were combined into a single batch and characterized). LCMS (ES) m/z=267.1 [M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20-2.22 (m, 6H), 4.43 (s, 2H), 6.95 (d, J=8.0 Hz, 2H), 7.32 (d, J=8.0 Hz, 2H), 8.85 (s, 1H), 8.97 (bs, 3H).

[0704] Step 4: To a stirred solution of 1-fluorocyclopropane-1-carboxylic acid (0.6 g, 5.748 mmol, 1 equiv) and triethylamine (1.61 mL, 11.496 mmol, 2 equiv) in dichloromethane (40 mL) was added T3P (50 wt. % in ethyl acetate) (5.48 mL, 8.62 mmol, 1.5 equiv) at 0° C. and the mixture was stirred for 10 minutes. A stirred solution of N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy) acetamide hydrochloride (1.65 g, 5.460 mmol, 0.95 mmol) and triethylamine (1.61 mL, 11.496 mmol, 2 equiv) in dichloromethane (10 mL) was prepared in another flask and then added to the above reaction mixture at 0° C. The resulting mixture was allowed to warm to 27° C. and stirred for 16 h. The progress of the reaction was monitored by TLC. After completion of reaction, the mixture was diluted with dichloromethane (500 mL), washed with an aqueous 10% sodium bicarbonate solution (200 mL), water (2×100 mL), and brine (100 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography using a silica gel column and the product eluted at 7% methanol in dichloromethane to obtain the title compound N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-1-fluorocyclopropane-1-carboxamide (1.12 g, 59% yield) as a white solid. LCMS (ES) m/z=353.2 [M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12-1.15 (m, 2H), 1.20-1.24 (m, 2H), 2.24 (s, 6H), 4.40 (s, 2H), 6.95 (d, J=9.2 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 8.64 (s, 1H), 8.91 (s, 1H).

Cmpd #	Structure	Name	LCMS m/z [M + H]$^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
72		N-(3-(2-(4-chlorophenoxy) acetamido) bicyclo[1.1.1] pentan-1-yl)-1-fluorocyclopropane-1-carboxamide	353	1.12-1.15 (m, 2 H), 1.20-1.24 (m, 2 H), 2.24 (s, 6 H), 4.40 (s, 2 H), 6.95 (d, J = 9.2 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 8.64 (s, 1 H), 8.91 (s, 1 H).

Example 73

ATF4 Cell Based Assay

[0705] The ATF4 reporter assay measures the effect of Thapsigargin induced cellular stress on ATF4 expression. For this reporter assay, a stable cell line was created by transfecting SH-SY5Y cells with a plasmid containing the

NanoLuc® luciferase gene fused to the 5'-UTR of ATF4, under the control of the CMV promoter. The ATF4 5'-UTR contains two open reading frames which mediate the cellular stress-dependent translation of the reporter gene. Clones stably expressing the reporter construct were isolated and selected based on the luminescence response to thapsigargin and inhibition of this signal by test compounds. Briefly, SH-SY5Y-ATF4-NanoLuc cells were challenged with Thapsigargin for 14-18 hours to determine the stress effect with or without test compounds.

[0706] Cells were propagated in growth media consisting of 90% DMEM F12 (InVitrogen #11320-033), 10% Fetal Bovine Serum (Gibco #10438-026), 5 mM Glutamax (Gibco #35050-061), 5 mM Hepes, (Gibco #15630-080), and 0.5 mg/ml Geneticin (Gibco #10131-027). Cells were prepared for the assay by removing all media from cells, washing the plated cells with phosphate buffered saline, and detached by adding a solution comprised of 10% Tryple express solution (InVitrogen12604-021) and 90% enzyme-free cell dissociation buffer HANKS base (Gibco 13150-016). The trypsin was deactivated by adding assay media comprised of 90% phenol-red free DMEM F12 (InVitrogen, 11039), 10% Fetal Bovine Serum (Gibco #10438-026), (5 mM Glutamax (Gibco #35050-061), 5 mM Hepes, (Gibco #15630-080), and 0.5 mg/ml Geneticin (Gibco #10131-027). Suspended cells were spun down at 300 g for 5 min, the supernatant was removed and the cell pellet was suspended in warm media (30-37° C.) comprised as above but without 10% Fetal Bovine Serum to a concentration of 1e6 cells/ml.

[0707] Assay plates were prepared by adding 250 nL of compound stock solution in 100% DMSO to each well, followed by dispensing 20 microliters/well cell suspension to deliver 15-20 k cell/well. Cells were incubated for 1 hour at 37° C. Then, 5 μL of 1.5 μM or 1 μM of Thapsigargin (final concentration: 200-300 nM) was added to each well of cells. Assay plates containing cells were incubated for 14-18 hours at 37° C.

[0708] The measurement of luciferase produced by the ATF4 constructs was measured as follows. Aliquots of the Nano-Glo reagent (Nano-Glo® Luciferase Assay Substrate, Promega, N113, Nano-Glo® Luciferase Assay Buffer, Promega, N112 (parts of Nano-Glo® Luciferase Assay System, N1150) were brought to room temperature, the substrate and buffer were mixed according to manufacturer's instructions. The cell plates were equilibrated to room temperature. 25 microliters/well of the mixed Nano-Glo reagent were dispensed into assay wells and pulse spun to settle contents and the plate was sealed with film. The plates were incubated at room temperature for 1 hour before detecting luminescence on an EnVision® plate reader.

Example 74

Capsule Composition

[0709] An oral dosage form for administering the present invention is produced by filing a standard two piece hard gelatin capsule with the ingredients in the proportions shown in Table 2, below.

TABLE 2

INGREDIENTS	AMOUNTS
2-(4-chlorophenoxy)-N-(3-(2-(cyclohexyloxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide (Compound of Example 1)	7 mg
Lactose	53 mg
Talc	16 mg
Magnesium Stearate	4 mg

Example 75

Injectable Parenteral Composition

[0710] An injectable form for administering the present invention is produced by stirring 1.7% by weight of 2-(4-chlorophenoxy)-N-(3-(2-(2,2,2-trifluoroethoxy)acetamido) bicyclo[1.1.1]pentan-1-yl)acetamide (Compound of Example 2) in 10% by volume propylene glycol in water.

Example 76

Tablet Composition

[0711] The sucrose, calcium sulfate dihydrate and an ATF4 pathway inhibitor as shown in Table 3 below, are mixed and granulated in the proportions shown with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, screened and compressed into a tablet.

TABLE 3

INGREDIENTS	AMOUNTS
2-(4-chlorophenoxy)-N-(3-(2-(1-methylcyclobutoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide (Compound of Example 3)	12 mg
calcium sulfate dihydrate	30 mg
sucrose	4 mg
starch	2 mg
talc	1 mg
stearic acid	0.5 mg

Biological Activity

[0712] Compounds of the invention are tested for activity against ATF4 translation in the above assay.

[0713] The compound of Example 20 was tested generally according to the above ATF4 cell based assay and in a set of two or more experimental runs exhibited an average ATF4 pathway inhibitory activity (IC_{50}) of 6324 nM.

[0714] The compound of Example 32 was tested generally according to the above ATF4 cell based assay and in a set of two or more experimental runs exhibited an average ATF4 pathway inhibitory activity (IC_{50}) of 4764 nM.

[0715] The compound of Example 34 was tested generally according to the above ATF4 cell based assay and in a set of two or more experimental runs exhibited an average ATF4 pathway inhibitory activity (IC_{50}) of 3267 nM.

[0716] The compound of Example 53 was tested generally according to the above ATF4 cell based assay and in a set of two or more experimental runs exhibited an average ATF4 pathway inhibitory activity (IC_{50}) of 3357 nM.

REFERENCES

[0717] 1. Wek R C, Jiang H-Y, Anthony T G. *Coping with stress: eIF2 kinases and translational control. Biochem. Soc. Trans.* 2006 February; 34(Pt 1):7-11.

[0718] 2. Hinnebusch A G, Lorsch J R. *The mechanism of eukaryotic translation initiation: new insights and challenges. Cold Spring Harb Perspect Biol.* 2012; 4(10).

[0719] 3. Krishnamoorthy T, Pavitt G D, Zhang F, Dever T E, Hinnebusch A G. *Tight binding of the phosphorylated alpha subunit of initiation factor 2 (eIF2alpha) to the regulatory subunits of guanine nucleotide exchange factor e1F2B is required for inhibition of translation initiation. Mol. Cell Biol.* 2001 August; 21(15):5018-30.

[0720] 4. Hinnebusch A G. *Translational regulation of GCN4 and the general amino acid control of yeast. Annu. Rev. Microbiol.* 2005; 59:407-50.

[0721] 5. Jackson R J, Hellen C U T, Pestova T V. *The mechanism of eukaryotic translation initiation and principles of its regulation. Nat. Rev. Mol. Cell Biol.* 2010 February I; I 1(2):113-27.

[0722] 6. Harding H P, Novoa I, Zhang Y, Zeng H, Wek R, Schapira M, et al. *Regulated translation initiation controls stress-induced gene expression in mammalian cells. Mol. Cell.* 2000 November; 6(5):1099-108.

[0723] 7. Palam L R, Baird T D, Wek R C. *Phosphorylation of eIF2 facilitates ribosomal bypass of an inhibitory upstream ORF to enhance CHOP translation. Journal of Biological Chemistry.* 2011 Apr. 1; 286(13):10939-49.

[0724] 8. Vattem K M, Wek R C. *Reinitiation involving upstream ORFs regulates ATF4 mRNA translation in mammalian cells. Proc. Natl. Acad. Sci. USA.* 2004 Aug. 3; 101(31):11269-74.

[0725] 9. Ma Y, Brewer J W, Diehl J A, Hendershot L M. *Two distinct stress signaling pathways converge upon the CHOP promoter during the mammalian unfolded protein response. J. Mol. Biol.* 2002 May 17; 318(5):1351-65.

[0726] 10. Pavitt G D, Ron D. *New insights into translational regulation in the endoplasmic reticulum unfolded protein response. Cold Spring Harb Perspect Biol.* 2012 June; 4(6).

[0727] 11. Ron D, Walter P. *Signal integration in the endoplasmic reticulum unfolded protein response. Nat. Rev. Mol. Cell Biol.* 2007 July; 8(7):519-29.

[0728] 12. Gardner B M, Walter P. *Unfolded proteins are Irel-activating ligands that directly induce the unfolded protein response. Science.* 2011 Sep. 30; 333(6051):1891-4.

[0729] 13. Harding H P, Zhang Y, Bertolotti A, Zeng H, Ron D. *Perk is essential for translational regulation and cell survival during the unfolded protein response. Mol. Cell.* 2000 May; 5(5):897-904.

[0730] 14. Walter P, Ron D. *The unfolded protein response: from stress pathway to homeostatic regulation. Science.* 2011 Nov. 25; 334(6059):1081-6.

[0731] 15. Tabas I, Ron D. *Integrating the mechanisms of apoptosis induced by endoplasmic reticulum stress. Nat. Cell Biol.* 2011 Mar. 1; 13(3):184-90.

[0732] 16. Shore G C G, Papa F R F, Oakes S A S. *Signaling cell death from the endoplasmic reticulum stress response. Current Opinion in Cell Biology.* 2011 Apr. 1; 23(2):143-9.

[0733] 17. Bi M, Naczki C, Koritzinsky M, Fels D, 174 WO 2014/144952 PCT/US2014/029568 Blais J, Hu N, Harking H, Novoa I, Varia M, Raleigh J, Scheuner D, Kaufman R J, Bell J, Ron D, Wouters B G, Koumenis C. 2005. *ER stress-regulated translation increases tolerance to extreme hypoxia and promotes tumor growth. EMBO J.* 24:3470-3481.

[0734] 18. Bobrovnikova-Marjon E, Pytel D, Vaites L P, Singh N, Koretzky G A, Diehl J A. 2010. *PERK promotes cancer cell proliferation and tumor growth by limiting oxidative DNA damage. Oncogene* 29: 3881-3895.

[0735] 19. Avivar-Valderas A, Bobrovnikova-Marjon E, Diehl A, Nagi C, Debnath J, Aguirre-Guiso J A 2011. *PERK integrates autophagy and oxidative stress responses to promote survival during extracellular matrix detachment. Mol. Cell Biol.* 31:3616-3629.

[0736] 20. Axten J M., Medina J. R., Feng Y., Shu A., Romeril S. P. et al. 2012. *Discovery of 7-methy-5(1-{[3[(trifluoromethyl)phenyl]acetyl}-2,3-dihydro-1H-indol-5yl)-7H-pyrrolo [2,3-d]pyrimidin-4 amine (GSK2606414), a potent and selective first-in-class inhibitor of protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK). J. Med. Chem.* 55(16):7193-7207

[0737] 21. Ye J. Kumanova M., Hart L. S., Sloane K., Zhang H. et al. 2010. *The GCN2-ATF4 pathway is critical for tumour cell survival and proliferation in response to nutrient deprivation. EMBO J.* 29: 2082-2096.

[0738] 22. Moreno J A, Radford H, Peretti D, Steinert J R, Verity N, Martin M G, Halliday M, Morgan J, Dinsdale D, Ortori C A, Barrett D A, Tsaytler P, Bertolotti A, Willis A E, Bushell M, Mallucci G R. 2012. *Sustained translational repression by eIF2α-P mediates prion neurodegeneration. Nature* 485:507-511.

[0739] 23. Pavitt G D and Proud C G. 2009. *Protein synthesis and its control in neuronal cells with a focus on vanishing white matter disease. Biochem. Soc. Trans.* 37:1298-20 1310.

[0740] 24. Costa-Mattioli M. Gobert D., Harding H., Herdy B. Azzi M., Bruno M. et al, 2005. *Translational control of hippocampal synaptic plasticity and memory by the eIF2α kinase GCN2. Nature* 436:1166-1173.

[0741] 25. Costa-Mattioli M., Gobert D., Stern E., Garnache K., Colina R I, Cuello C., Sossin W., Kaufman R., Pelletier J., Rosenblum et al. 2007. *eIF2α phosphorylation bidirectionally regulates the switch from short to long term synaptic plasticity and memory. Cell* 25 129: 195-206.

[0742] 26. Zhu P. J, Huan W., Kalikulov D., Yoo J. W., Placzek A. N., Stoica L, Zhou H., Bell J. C., Frielander M. J., Krnjevic K., Noebels J. L., Costa-Mattioli M. 2011. *Suppression of PKR promotes network excitability and enhanced cognition by interferon-7-mediated disinhibition. Cell* 147: 1384-1396.

[0743] 27. Borck G., Shin B. S., Stiller B., et al 2012. *eIF2γ mutation that disrupts eIF2 complex integrity links intellectual disability to impaired translation initiation. Mol Cell* 48:1-6.

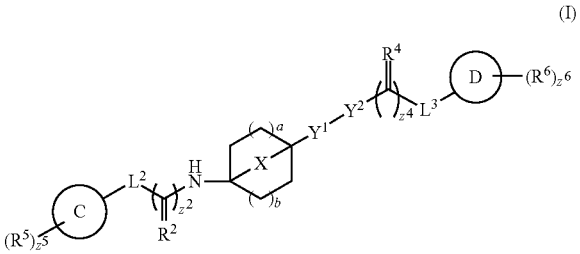
[0744] 28. Zeenko V. V., Wang C, Majumder M, Komar A. A., Snider M. D., Merrick W. C., Kaufman R. J. and Hatzoglou M. (2008). *An efficient in vitro translation system from mammalian cell lacking translational inhibition caused by eIF2 phosphorylation. RNA* 14: 593-602.

[0745] 29. Mikami S., Masutani M., Sonenber N., Yokoyama S. And Imataka H. 175 WO 2014/144952 PCT/US2014/029568 2006. *An efficient mammalian cell-*

free translation system supplemented with translation factors. Protein Expr. Purif. 46:348-357.

[0746] While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

1. A compound according to Formula (I):



(I)

wherein:

L^2 is a bond or selected from: —NR^9—, —O—, —S—, —S(O)—, —$S(O)_2$—, C_{1-8}alkylene, substituted C_{1-8}alkylene, C_{1-8}alkyl, substituted C_{1-8}alkyl, C_{1-8}heteroalkylene, substituted C_{1-8}heteroalkylene, C_{1-8}heteroalkyl, and substituted C_{1-8}heteroalkyl;

L^3 is absent, a bond or selected from: —NR^2—, —O—, —S—, —S(O)—, —$S(O)_2$—, C_{1-8}alkylene, substituted C_{1-8}alkylene, C_{1-8}alkyl, substituted C_{1-8}alkyl, C_{1-8}heteroalkyl, substituted C_{1-8}heteroalkyl, C_{1-8}heteroalkylene and substituted C_{1-8}heteroalkylene;

Y^1 is selected from: NH—, NH_2, a nitrogen linked heterocycloalkyl, and a substituted nitrogen linked heterocycloalkyl;

Y^2 is absent, a bond or selected from: C_{1-2}alkylene and C_{1-2}alkylene substituted from 1 to 4 times by fluoro;

R^5 and R^6, when present, are independently selected from: fluoro, chloro, bromo, iodo, oxo, —OCH_3, —OCH_2Ph, —C(O)Ph, —CH_3, —CF_3, —CHF_2, —CH_2F, —CN, —S(O)CH_3, —$S(O)_2CH_3$, —OH, —NH_2, —$NHCH_3$, —$N(CH_3)_2$, —COOH, —$CONH_2$, —NO_2, —C(O)CH_3, —$CH(CH_3)_2$, —$C(CF_3)_3$, —$C(CH_3)_3$, —CH_2—CF_3, —CH_2—CH_3, —CCH, —CH_2CCH, —SO_3H, —SO_2NH_2, —$NHC(O)NH_2$, —NHC(O)H, —NHOH, —OCF_3, —$OCHF_2$, C_{1-6}alkyl, substituted C_{1-6}alkyl, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^2 and R^4, when present, are independently selected from: NR^8, O, CH_2, and S;

R^8 is selected from: hydrogen, —OH, C_{1-6}alkyl and C_{1-6}alkyl substituted 1 to 6 times by fluoro;

R^9 is selected from: hydrogen, C_{1-6}alkyl and C_{1-6}alkyl substituted 1 to 6 times by fluoro;

a and b are independently 0 or 1;

C is absent or selected from: phenyl, pyridyl, and cycloalkyl;

D is absent or selected from: cycloalkyl, and substituted cycloalkyl, heterocycloalkyl, and substituted heterocycloalkyl;

X is C_{1-3}alkyl or C_{1-3}alkyl substituted 1 to 3 times by fluoro;

z^2 and z^4 are independently 0 or 1; and

z^5 and z^6 are independently an integer from 0 to 5;

provided:

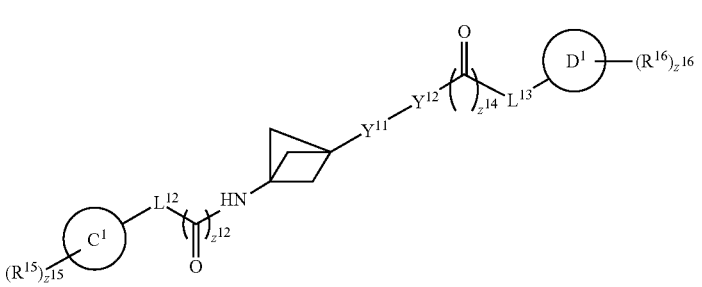
when Y^1 is NH_2, heterocycloalkyl, or substituted heterocycloalkyl; Y^2, L^3, and D are absent and z^6 is 0;

when L^2 is monovalent; C is absent and z^5 is 0; and

when L^3 is monovalent; D is absent and z^6 is 0;

or a salt thereof including a pharmaceutically acceptable salt thereof.

2. The compound of claim **1** represented by the following Formula (II):



(II)

wherein:

L^{12} is a bond or selected from: —CH_2—O—, and —CH_2—CH_2—O—;

L^{13} is a bond or selected from: —CH_2—, —CH_2—O—CH_3, —CH_2—O—, —CH_2—O—CH_2—CH_3, —CH_2—O—CH_2—CH_2—CH_2—CH_3, —CH_2—O—CH_2—, —CH_2—O—CH_2—CH_2—CH_3, —CH_2—CH_2—CH_3, —CH_2—O—CH_2—$CH(CH_3)_2$, —CH_2—O—$CH(CH_3)_2$, —CH_2—O—$C(CH_3)_3$, —CH_2—O—CH_2—CF_3, —CH_2—O—$C(CH_3)_2$—CF_3, —CH_2—$C(CH_3)_3$, —CH_2—O—CH_2—$(CH_3)_3$, —CH_2—O—C(CH$_3$)H—CF_3, —CH_2—CH_2—$C(CH_3)_3$, —CH_2—CF_3, —CH_2—O—C(CH$_3$)H—, —CH_2—O—C(CH$_3$)H—CH_2—CH_3, —CH_3, —CH_2—CH_3, —CH_2—O—C(CH$_3$)H—CH_2—CH_2—CH_3, —CH_2—O—CH_2—CH_2—O—CH_3, —CH_2—O—C(CH$_3$)H—$CH(CH_3)_2$, —CH_2—O—C(CH$_3$)H—CH_2—, —CH_2—O—$C(CH_3)_2$—, —CH_2—O—C(CH$_3$)H—CH_2O—CH_3, —$C(CH_3)$HO—CH_3, —CH_2—CH_2—, —CH_2—CH_2—O—C

$(CH_3)H$—, —CH_2—CH_2—O—, —CH_2—$N(CH_3)_2$, —CH_2—$NH(CH_3)$, —CH_2—$N(CH_3)$—$CH(CH_3)$—, —CH_2—$N(CH_3)$—CH_2—CH_2—CH_3, —CH_2—NH—CH_2—CH_2—CH_3, —$N(CH_3)_2$, —CH_2—NH—CH_2—CH_2—O—CH_3, —CH_2—NH—CH_2—CH_3, —$NH(CH_3)$, —CH_2—$N(CH_3)$—CH_2—CH_3, —CH_2—$N(CH_3)$—$CH(CH_3)_2$, —$CH(CF_3)$—$N(CH_3)_2$, —$CH(N(CH_3)_2)$—$CH(CH_3)_2$, —$CH(CH_3)$—$N(CH_3)_2$, and —$C(CH_3)_2$—$N(CH_3)_2$;

Y^{11} is selected from: NH—, NH_2, a nitrogen linked heterocycloalkyl, and a nitrogen linked heterocycloalkyl substituted from 1 to 3 times by a substituent selected from: fluoro, chloro, bromo, iodo, oxo, —OCH_3, —OCF_3, —CH_3, and —CF_3;

Y^{12} is absent, a bond or selected from: —CH_2—, and —CH_2—, substituted once or twice by fluoro;

R^{15}, when present, is selected from chloro, —$C(CF_3)_3$, and —$C(CH_3)_3$;

R^{16}, when present, is selected from: fluoro, chloro, bromo, —$C(CF_3)_3$, —$C(CH_3)_3$, —CH_2—CF_3, —CH_2—CH_3, —CH_3, —CF_3, and —$N(CH_3)_2$;

C^1 is absent or selected from: phenyl, and cyclopropyl;

D^1 is absent or selected from: piperidinyl, cyclohexyl, cyclopropyl, cyclopentyl, cyclobutyl, pyrrolidinyl, tetrahydrofuranyl, and tetrahydropyranyl;

z^{12} and z^{14} are independently 0 or 1; and

z^{15} and z^{16} are independently an integer from 0 to 4;

provided:

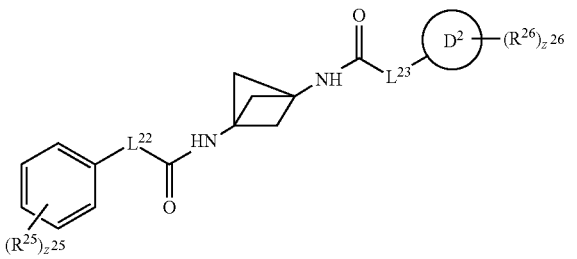
when Y^{11} is NH_2, heterocycloalkyl, or substituted heterocycloalkyl; Y^{12}, L^{13}, and D^1 are absent and z^{16} is 0; and

when L^{13} is monovalent; D^1 is absent;

or a salt thereof including a pharmaceutically acceptable salt thereof.

3. A compound of claim **1** represented by the following Formula (III):

(III)



wherein:

L^{22} is a bond or selected from: —CH_2—O—, and —CH_2—CH_2—O—;

L^{23} is a bond or selected from: —CH_2—, —CH_2—O—CH_3, —CH_2—O—, —CH_2—O—CH_2—CH_3, —CH_2—O—CH_2—CH_2—CH_2—CH_3, —CH_2—O—CH_2—, —CH_2—O—CH_2—CH_2—CH_3, —CH_2—CH_2—CH_3, —CH_2—O—CH_2—$CH(CH_3)_2$, —CH_2—O—$CH(CH_3)_2$, —CH_2—O—$C(CH_3)_3$, —CH_2—O—CH_2—CF_3, —CH_2—O—$C(CH_3)_2$—CF_3, —CH_2—$C(CH_3)_3$, —CH_2—O—CH_2—$(CH_3)_3$, —CH_2—O—$C(CH_3)H$—CF_3, —CH_2—CH_2—$C(CH_3)_3$, —CH_2—CF_3, —CH_2—O—$C(CH_3)H$—, —CH_2—O—$C(CH_3)H$—CH_2—CH_3, —CH_3, —CH_2—CH_3, —CH_2—O—$C(CH_3)H$—CH_2—CH_2—CH_3, —CH_2—O—CH_2—CH_2—O—CH_3, —CH_2—O—$C(CH_3)H$—$CH(CH_3)_2$, —CH_2—O—$C(CH_3)H$—CH_2—, —CH_2—O—$C(CH_3)_2$—, —CH_2—O—$C(CH_3)H$—CH_2—O—CH_3, —$C(CH_3)HO$—CH_3, —CH_2—CH_2—, —CH_2—CH_2—O—$C(CH_3)H$—, —CH_2—CH_2—O—, —CH_2—$N(CH_3)_2$, —CH_2—$NH(CH_3)$, —CH_2—$N(CH_3)$—$CH(CH_3)$—, —CH_2—$N(CH_3)$—CH_2—CH_2—CH_3, —CH_2—NH—CH_2—CH_2—CH_3, —$N(CH_3)_2$, —CH_2—NH—CH_2—CH_2—O—CH_3, —CH_2—NH—CH_2—CH_3, —$NH(CH_3)$, —CH_2—$N(CH_3)$—CH_2—CH_3, —CH_2—$N(CH_3)$—$CH(CH_3)_2$, —$CH(CF_3)$—$N(CH_3)_2$, —$CH(N(CH_3)_2)$—$CH(CH_3)_2$, —$CH(CH_3)$—$N(CH_3)_2$, and —$C(CH_3)_2$—$N(CH_3)_2$;

R^{25}, when present, is selected from chloro, —$C(CF_3)_3$, and —$C(CH_3)_3$;

R^{26}, when present, is selected from: fluoro, chloro, bromo, —$C(CF_3)_3$, —$C(CH_3)_3$, —CH_2—CF_3, —CH_2—CH_3, —CH_3, —CF_3, and —$N(CH_3)_2$;

D^2 is absent or selected from: piperidinyl, cyclohexyl, cyclopropyl, cyclopentyl, cyclobutyl, pyrrolidinyl, tetrahydrofuranyl, and tetrahydropyranyl; and

z^{25} and z^{26} are independently an integer from 0 to 4;

provided:

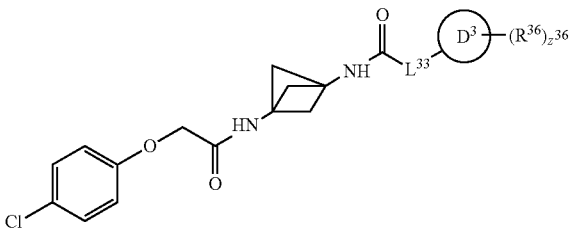
when L^{23} is monovalent, D^2 is absent and z^{26} is 0; and

when D^2 is absent L^{23} is not a bond;

or a salt thereof including a pharmaceutically acceptable salt thereof.

4. A compound of claim **1** represented by the following Formula (IV):

(IV)



wherein:

L^{33} is a bond or selected from: —CH_2—, —CH_2—O—CH_3, —CH_2—O—, —CH_2—O—CH_2—CH_3, —CH_2—O—CH_2—CH_2—CH_2—CH_3, —CH_2—O—CH_2—, —CH_2—O—CH_2—CH_2—CH_3, —CH_2—CH_2—CH_3, —CH_2—O—CH_2—$CH(CH_3)_2$, —CH_2—O—$CH(CH_3)_2$, —CH_2—O—$C(CH_3)_3$, —CH_2—O—CH_2—CF_3, —CH_2—O—$C(CH_3)_2$—CF_3, —CH_2—$C(CH_3)_3$, —CH_2—O—CH_2—$(CH_3)_3$, —CH_2—O—$C(CH_3)H$—CF_3, —CH_2—CH_2—$C(CH_3)_3$, —CH_2—CF_3, —CH_2—O—$C(CH_3)H$—, —CH_2—O—$C(CH_3)H$—CH_2—CH_3, —CH_3, —CH_2—CH_3, —CH_2—O—$C(CH_3)H$—CH_2—CH_2—CH_3, —CH_2—O—CH_2—CH_2—O—CH_3, —CH_2—O—$C(CH_3)H$—$CH(CH_3)_2$, —CH_2—O—$C(CH_3)H$—CH_2—, —CH_2—O—$C(CH_3)_2$—, —CH_2—O—$C(CH_3)H$—CH_2—O—CH_3, —$C(CH_3)HO$—CH_3, —CH_2—CH_2—, —CH_2—CH_2—O—$C(CH_3)H$—, —CH_2—CH_2—O—,

—CH_2—$N(CH_3)_2$, —CH_2—$NH(CH_3)$, —CH_2—$N(CH_3)$—$CH(CH_3)$—, —CH_2—$N(CH_3)$—CH_2—CH_2—CH_3, —CH_2—NH—CH_2—CH_2—CH_3, —$N(CH_3)_2$, —CH_2—NH—CH_2—CH_2—O—CH_3, —CH_2—NH—CH_2—CH_3, —$NH(CH_3)$, —CH_2—$N(CH_3)$—CH_2—CH_3, —CH_2—$N(CH_3)$—$CH(CH_3)_2$, —$CH(CF_3)$—$N(CH_3)_2$, —$CH(N(CH_3)_2)$—$CH(CH_3)_2$, —$CH(CH_3)$—$N(CH_3)_2$, and —$C(CH_3)_2$—$N(CH_3)_2$;

R^{36}, when present, is selected from: fluoro, chloro, bromo, —$C(CF_3)_3$, —$C(CH_3)_3$, —CH_2—CF_3, —CH_2—CH_3, —CH_3, —CF_3, and —$N(CH_3)_2$;

D^3 is absent or selected from: piperidinyl, cyclohexyl, cyclopropyl, cyclopentyl, cyclobutyl, pyrrolidinyl, tetrahydrofuranyl, and tetrahydropyranyl; and

z^{36} is an integer from 0 to 2;

provided:

when L^{33} is monovalent, D^3 is absent and z^{36} is 0; and

when D^3 is absent L^{33} is not a bond;

or a salt thereof including a pharmaceutically acceptable salt thereof.

5. The compound of claim **1** selected from:

2-(4-chlorophenoxy)-N-(3-(2-(cyclohexyloxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-(2,2,2-trifluoroethoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-(1-methylcyclobutoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-(pentan-2-yloxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-((1,1,1-trifluoro-2-methylpropan-2-yl)oxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-((1-methylcyclopropyl)methoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-((1-cyclopropylpropan-2-yl)oxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-(cyclopropylmethoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(tert-butoxy)-N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-isobutoxyacetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-(1-methylcyclopropoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-(neopentyloxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-(cyclopentyloxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(sec-butoxy)-N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-cyclopropoxyacetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-(1-cyclopropylethoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-(2-methoxyethoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-(1,2-dimethylcyclopropoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-((1-methoxypropan-2-yl)oxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(1-methylcyclopropoxy)-N-(3-(2-(p-tolyloxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-((1,1,1-trifluoropropan-2-yl)oxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-butoxy-N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-isopropoxyacetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-ethoxyacetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-((3-methylbutan-2-yl)oxy)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-propoxyacetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-methoxyacetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-(4,4-difluoropiperidin-1-yl)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-((2-(1-methylcyclopropoxy)ethyl)amino)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-((2-(1-cyclopropylethoxy)ethyl)amino)bicyclo[1.1.1]pentan-1-yl)acetamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-methylcyclopropane-1-carboxamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)tetrahydrofuranyl-2-carboxamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)tetrahydro-2H-pyran-2-carboxamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)cyclobutanecarboxamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-1-(trifluoromethyl)cyclopropane-1-carboxamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)cyclopropanecarboxamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-1-methylcyclopropane-1-carboxamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylpentanamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)propionamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-3,3,3-trifluoropropanamide;

2-(4-chlorophenoxy)-N-(3-(2-cyclopropylacetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2,2-dimethylcyclopropane-1-carboxamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)butyramide;

N-(3-acetamidobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-(dimethylamino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

(R)—N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-(dimethylamino)-3-methylbutanamide;

(S)—N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-(dimethylamino)-3-methylbutanamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-3,3-dimethylbutanamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2,2-difluorocyclopropane-1-carboxamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-methoxypropanamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-(dimethylamino)-2-methylpropanamide;

2-(4-chlorophenoxy)-N-(3-(2-(methylamino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide hydrochloride;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)pyrrolidinyl-2-carboxamide hydrochloride;

(S)—N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-(dimethylamino)propanamide;

(R)—N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-(dimethylamino)propanamide;

2-(4-chlorophenoxy)-N-(3-(2-(propylamino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-(ethylamino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-(isopropyl(methyl)amino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-((2-(methylamino)-2-oxoethyl)amino)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-((3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)amino)-N,N-dimethylacetamide;

(R)-2-(4-chlorophenoxy)-N-(3-(2-((1-cyclopropylethyl)(methyl)amino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-((2-methoxyethyl)-l3-chloranyl)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-1-(dimethylamino)cyclopropanecarboxamide;

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-2-(dimethylamino)-3,3,3-trifluoropropanamide;

2-(4-chlorophenoxy)-N-(3-(2-(methyl(propyl)amino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-(ethyl(methyl)amino)acetamido)bicyclo[1.1.1]pentan-1-yl)acetamide;

N,N'-(bicyclo[1.1.1]pentane-1,3-diyl)bis(2-(terf-butoxy)acetamide);

N,N'-(bicyclo[1.1.1]pentane-1,3-diyl)bis(2-(1-methylcyclopropoxy)acetamide);

(1-methylcyclopropyl)methyl (3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)carbamate;

N-(3-aminobicyclo[1.1.1]pentan-1-yl)-2-(4-chlorophenoxy)acetamide;

2-(4-chlorophenoxy)-N-(3-(2-oxopiperidin-1-yl)bicyclo[1.1.1]pentan-1-yl)acetamide; and

N-(3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentan-1-yl)-1-fluorocyclopropane-1-carboxamide;

or a salt thereof including a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition comprising a compound according to claim **1** or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

7. A method of treating a disease selected from: cancer, pre-cancerous syndromes, Alzheimer's disease, spinal cord injury, traumatic brain injury, ischemic stroke, stroke, diabetes, Parkinson disease, Huntington's disease, Creutzfeldt-Jakob Disease, and related prion diseases, progressive supranuclear palsy, amyotrophic lateral sclerosis, myocardial infarction, cardiovascular disease, inflammation, fibrosis, chronic and acute diseases of the liver, chronic and acute diseases of the lung, chronic and acute diseases of the kidney, chronic traumatic encephalopathy (CTE), neurodegeneration, dementia, traumatic brain injury, cognitive impairment, atherosclerosis, ocular diseases, in organ transplantation and arrhythmias, in a human in need thereof, which comprises administering to such human a therapeutically effective amount of a compound as described in claim **1** or a pharmaceutically acceptable salt thereof.

8-13. (canceled)

14. The method of inhibiting the ATF4 pathway in a human in need thereof, which comprises administering to such human a therapeutically effective amount of a compound as described in claim **1** or a pharmaceutically acceptable salt thereof.

15. (canceled)

16. A method of treating cancer in a human in need thereof, which comprises: administering to such human a therapeutically effective amount of

a) a compound as described in claim **1** or a pharmaceutically acceptable salt thereof; and

b) at least one anti-neoplastic agent.

17-19. (canceled)

20. The method according to claim **7** wherein said cancer is selected from: breast cancer, inflammatory breast cancer, ductal carcinoma, lobular carcinoma, colon cancer, pancreatic cancer, insulinomas, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma, skin cancer, melanoma, metastatic melanoma, lung cancer, small cell lung cancer, non-small cell lung cancer, squamous cell carcinoma, adenocarcinoma, large cell carcinoma, brain (gliomas), glioblastomas, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, head and neck, kidney, liver, melanoma, ovarian, pancreatic, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma, insulinoma, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid,

lymphoblastic T cell leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic neutrophilic leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, Immunoblastic large cell leukemia, mantle cell leukemia, multiple myeloma, megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, erythroleukemia,

malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma,

neuroblastoma, bladder cancer, urothelial cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor), neuroendocrine cancers and testicular cancer.

21. (canceled)

22. A process for preparing a pharmaceutical composition containing a pharmaceutically acceptable excipient and an effective amount of a compound as described in claim **1** or a pharmaceutically acceptable salt thereof, which process comprises bringing the compound or a pharmaceutically acceptable salt thereof into association with a pharmaceutically acceptable excipient.

23. The method according to claim **7** wherein said pre-cancerous syndrome is selected from: cervical intraepithelial neoplasia, monoclonal gammapathy of unknown significance (MGUS), myelodysplastic syndrome, aplastic anemia, cervical lesions, skin nevi (pre-melanoma), prostatic intraepithelial (intraductal) neoplasia (PIN), Ductal Carcinoma in situ (DCIS), colon polyps and severe hepatitis or cirrhosis.

24. (canceled)

25. A method of treating ocular diseases in a human in need thereof, which comprises administering to such human a therapeutically effective amount of a compound as described in claim **1** or a pharmaceutically acceptable salt thereof.

26. A method according to claim **25** wherein the ocular disease is selected from: rubeosis irides; neovascular glaucoma; pterygium; vascularized glaucoma filtering blebs; conjunctival papilloma; choroidal neovascularization associated with age-related macular degeneration (AMD), myopia, prior uveitis, trauma, or idiopathic; macular edema; retinal neovascularization due to diabetes; age-related macular degeneration (AMD); macular degeneration; ocular ischemic syndrome from carotid artery disease; ophthalmic or retinal artery occlusion; sickle cell retinopathy; retinopathy of prematurity; Eale's Disease; and VonHippel-Lindau syndrome.

27. A method according to claim **25** wherein the ocular disease is selected form: age-related macular degeneration (AMD) and macular degeneration.

28. A method of treating neurodegeneration in a human in need thereof, which comprises administering to such human a therapeutically effective amount of a compound of Formula (I), as described in claim **1** or a pharmaceutically acceptable salt thereof.

29. A method of preventing organ damage during the transportation of organs for transplantation, which comprises adding a compound as described in claim **1** or a pharmaceutically acceptable salt thereof, to a solution housing the organ during transportation.

30-37. (canceled)

38. A method of treating a disease associated with phosphorylation of eIF2α in a human in need thereof, which comprises administering to such human a therapeutically effective amount of a compound of Formula (I), as described in claim **1** or a pharmaceutically acceptable salt thereof.

39. A method of treating an integrated stress response associated disease in a human in need thereof, which comprises administering to such human a therapeutically effective amount of a compound of Formula (I), as described in claim **1** or a pharmaceutically acceptable salt thereof.

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