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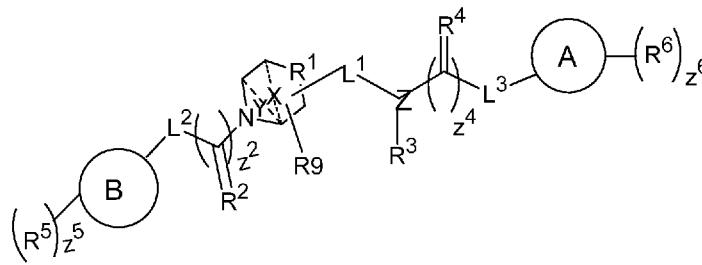
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(54) Title: CHEMICAL COMPOUNDS AS ATF4 PATHWAY INHIBITORS



(57) Abstract: The invention is directed to substituted piperidine derivatives. Specifically, the invention is directed to compounds according to Formula III: wherein A, B, X, Y, L¹, L², L³, R¹, R², R³, R⁴, R⁵, R⁶, R⁹, z², z⁴, z⁵, and z⁶ are as defined herein, and salts thereof. The compounds of the invention are inhibitors of the ATF4 pathway and can be useful in the treatment of cancer, pre-cancerous syndromes and diseases 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, 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, cognitive impairment, atherosclerosis, ocular diseases, arrhythmias, in organ transplantation and in the transportation of organs for transplantation. Accordingly, 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.

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CHEMICAL COMPOUNDS AS ATF4 PATHWAY INHIBITORS

FIELD OF THE INVENTION

The present invention relates to substituted piperidine derivatives that are inhibitors of the ATF4 pathway. 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, cognitive impairment, atherosclerosis, ocular diseases, arrhythmias, in organ transplantation and in the transportation of organs for transplantation.

BACKGROUND OF THE INVENTION

In metazoa, diverse stress signals converge at a single phosphorylation event at serine 51 of a common effector, the translation initiation factor eIF2 α . This step is carried out by four eIF2 α 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. eIF2 α phosphorylation results in an attenuation of translation with consequences that allow cells to cope with the varied stresses (1).

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 α -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 blocking 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 dramatic impact on eIF2B activity in cells.

Paradoxically, under conditions of reduced protein synthesis, a small 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 eIF2 α thus leads to preferential translation of key regulatory molecules and directs diverse changes in the transcriptome of cells upon cellular stress.

One of the eIF2 α 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 luminal 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, eIF2 α . 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).

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).

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.

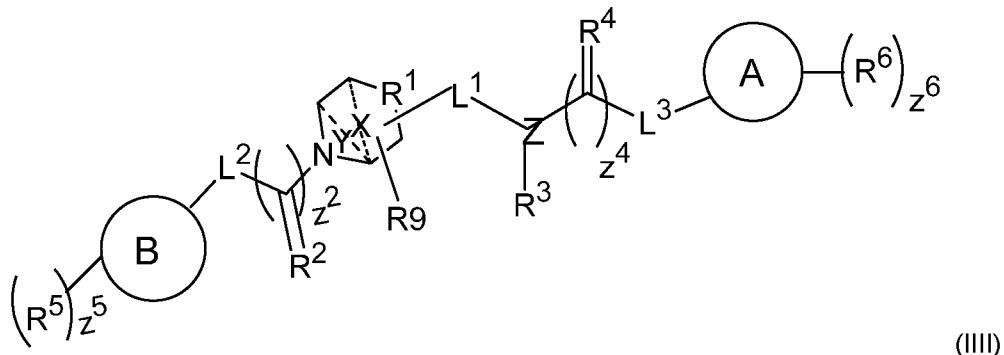
It is an object of the instant invention to provide novel compounds that prevent the translation of ATF4 or are inhibitors of the ATF4 pathway.

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

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 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, 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

The invention is directed to substituted piperidine derivatives. Specifically, the invention is directed to compounds according to Formula III:



wherein A, B, X, Y, L¹, L², L³, R¹, R², R³, R⁴, R⁵, R⁶, R⁹, z², z⁴, z⁵, and z⁶ are as defined below; or a salt thereof including a pharmaceutically acceptable salt thereof.

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

The present invention also relates to the discovery that the compounds of Formula (III) prevent the translation of ATF4.

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 (III) or a pharmaceutically acceptable salt thereof.

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 (III) or a pharmaceutically acceptable salt thereof.

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 (III) or a pharmaceutically acceptable salt thereof.

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 (III) or a pharmaceutically acceptable salt thereof.

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 (III) or a pharmaceutically acceptable salt thereof.

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 (III) or a pharmaceutically acceptable salt thereof.

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 (III) or a pharmaceutically acceptable salt thereof.

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 (III) or a pharmaceutically acceptable salt thereof.

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 (III) or a pharmaceutically acceptable salt thereof.

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 (III) or a pharmaceutically acceptable salt thereof.

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 (III) or a pharmaceutically acceptable salt thereof.

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 (III) or a pharmaceutically acceptable salt thereof.

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 (III) or a pharmaceutically acceptable salt thereof, to the patient.

This invention also relates to a method of treating a disease associated with phosphorylation of eIF2 α in a patient in need of such treatment, the method including administering a therapeutically effective amount of a compound of Formula (III), or a pharmaceutically acceptable salt thereof, to the patient.

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 (III) 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.

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 (III) or a pharmaceutically acceptable salt thereof, to the patient.

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 (III) or a pharmaceutically acceptable salt thereof, to the cell or expression system.

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 (III), or a pharmaceutically acceptable salt thereof, to the patient.

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

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

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, atherosclerosis, ocular diseases, arrhythmias, in organ transplantation and in the transportation of organs for transplantation that comprises administering the compounds of Formula (III).

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

The invention also relates to a compound of Formula (III) or a pharmaceutically

acceptable salt thereof for use in the treatment of Alzheimer's disease.

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

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

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

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

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

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

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

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

The invention also relates to a compound of Formula (III) or a pharmaceutically

acceptable salt thereof for use in the treatment of ischemic stroke.

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

The invention also relates to a compound of Formula (III) 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.

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

The invention also relates to the use of a compound of Formula (III) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease associated with phosphorylation of eIF2a.

The invention also relates to the use of a compound of Formula (III) 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.

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

The invention also relates to the use of a compound of Formula (III) or a

pharmaceutically acceptable salt thereof in the manufacture of a medicament for increasing protein expression of a cell or in vitro expression system.

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

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

The invention also relates to the use of a compound of Formula (III) 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, atherosclerosis, ocular diseases, arrhythmias, in organ transplantation and in the transportation of organs for transplantation.

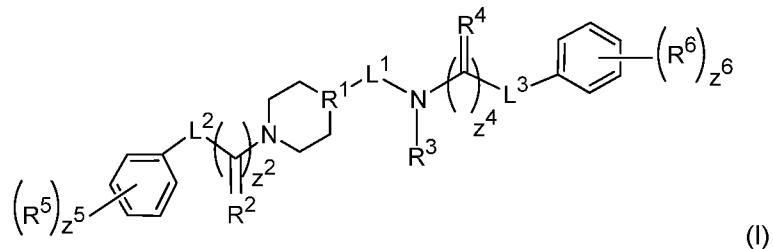
Included in the present invention are pharmaceutical compositions that comprise a pharmaceutical excipient and a compound of Formula (III) or a pharmaceutically acceptable salt thereof.

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

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

DETAILED DESCRIPTION OF THE INVENTION

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



wherein:

L^2 and L^3 are independently a bond, -NH-, -O-, -S-, -S(O)-, -S(O)2-, substituted or unsubstituted C1-6alkylene or substituted or unsubstituted C1-6heteroalkylene;

L^1 is selected from: a bond, -NH-, -C(R^7)-, -O-, -S-, -S(O)-, -S(O)2-, substituted or unsubstituted C1-6alkylene and substituted or unsubstituted C1-6heteroalkylene;

R^1 is CH-, or R^1 is C- and taken together with R^3 and the nitrogen to which R^3 is attached, and optionally from 1 to 3 additional heteroatoms, to form a heterocycloalkyl, which is optionally substituted with from 1 to 5 substituents independently selected from:

fluoro, chloro, C1-6alkyl, C1-6alkyl substituted 1 to 6 times by

fluoro, C1-4alkoxy, C1-4alkoxy substituted 1 to 6 times by fluoro, oxo, and -NH₂;

R^3 , R^5 and R^6 are independently hydrogen, fluoro, chloro, bromo, iodo,

-OCH₃, -OCH₂Ph, -C(O)Ph, -CH₃, -CF₃, -CN, -S(O)CH₃, -OH, -NH₂,
 -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH(CH₃)₂, -CCH, -CH₂CCH,
 -SO₃H, -SO₂NH₂, —NHC(O)NH₂, -NHC(O)H, -NHOH, -OCF₃, -OCHF₂,
 substituted or unsubstituted C₁-6alkyl, substituted or
 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
 substituted or unsubstituted heterocycloalkyl, substituted or
 unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R² and R⁴ are independently NR⁸, O, or S;

R⁷ is selected from: =NR⁸, =O, and =S;

R⁸ is selected from: hydrogen, C₁-6alkyl and C₁-6alkyl substituted 1 to 6 times by
 fluoro;

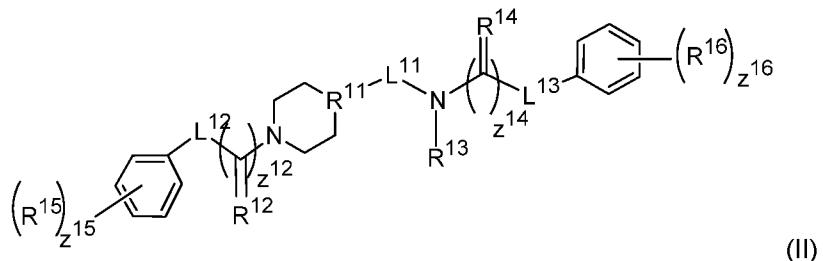
z² and z⁴ are independently 0 or 1; and

z⁵ and z⁶ are independently an integer from 0 to 5;

and salts thereof.

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

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



wherein:

L^{12} and L^{13} are independently: $-\text{CH}_2\text{O}-$, $-\text{OCH}_2-$, $-\text{CH}_2\text{CH}_2\text{O}-$, $-\text{OCH}_2\text{CH}_2-$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{O}-$, and $-\text{OCH}_2\text{CH}_2\text{CH}_2-$;

L^{11} is selected from: a bond, $-\text{CH}_2-$ and $-\text{C}(\text{O})-$;

R^{11} is $\text{CH}-$ and R^{13} is hydrogen, or R^{11} is $\text{C}-$ and taken together with R^{13} and
the nitrogen to which R^{13} is attached form an oxazolidine, which is
optionally substituted by oxo;

R^{15} and R^{16} are independently hydrogen or chloro;

R^{12} and R^{14} are O ;

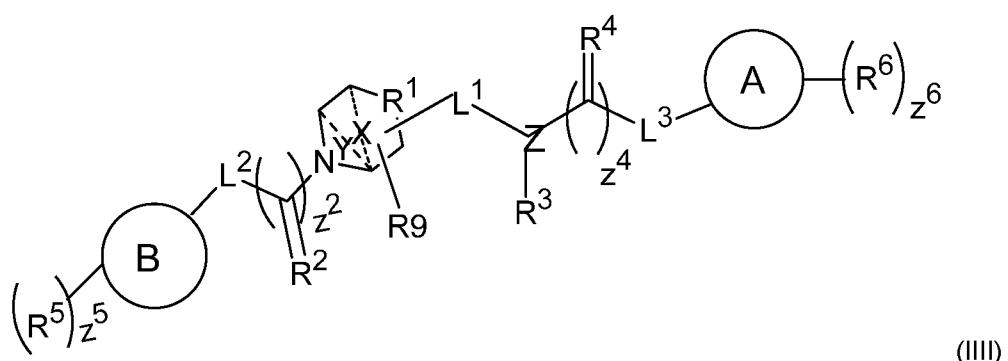
z^{12} and z^{14} are independently 0 or 1; and

z^{15} and z^{16} are independently an integer from 0 to 5;

and salts thereof.

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

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



wherein:

L^2 is selected from: a bond, -NH-, -O-, -S-, -S(O)-, -S(O)2-, substituted or

unsubstituted C1-6alkylene or substituted or unsubstituted

C1-6heteroalkylene, or L^2 is further taken together with B to form

heterocycloalkyl;

L^3 is selected from: a bond, -NH-, -O-, -S-, -S(O)-, -S(O)2-, substituted or

unsubstituted C1-6alkylene or substituted or unsubstituted

C1-6heteroalkylene, or L^3 is further taken together with A to form

heterocycloalkyl;

L^1 is selected from: a bond, -NH-, -C(R^7)-, -O-, -S-, -S(O)-, -S(O)2-, substituted or

unsubstituted C1-6alkylene and substituted or unsubstituted

C1-6heteroalkylene;

R^1 is CH-, or R^1 is C- and taken together with R^3 and the nitrogen to which R^3 is

attached, and optionally from 1 to 3 additional heteroatoms, to form a

heterocycloalkyl, which is optionally substituted with from 1 to 5

substituents independently selected from:

fluoro, chloro, C1-6alkyl, C1-6alkyl substituted 1 to 6 times by

fluoro, C1-4alkoxy, C1-4alkoxy substituted 1 to 6 times by fluoro,

oxo, and -NH₂;

R^3 , R^5 and R^6 and are independently hydrogen, fluoro, chloro, bromo, iodo,

-OCH₃, -OCH₂Ph, -C(O)Ph, -CH₃, -CF₃, -CN, -S(O)CH₃, -OH, -NH₂,

-COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH(CH₃)₂, -CCH, -CH₂CCH,

-SO₃H, -SO₂NH₂, —NHC(O)NH₂, -NHC(O)H, -NHOH, -OCF₃, -OCHF₂,

substituted or unsubstituted C1-6alkylene, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, provided R³ is absent when Z is a nitrogen linked heteroaryl;

R² and R⁴ are independently NR⁸, O, or S;

R⁷ is selected from: =NR⁸, =O, and =S;

R⁸ is selected from: hydrogen, C1-6alkyl and C1-6alkyl substituted 1 to 6 times by fluoro;

R⁹ is selected from: hydrogen, fluoro, chloro, bromo, iodo, -OH, C1-3alkyl and C1-3alkyl substituted with from 1 to 3 substituents independently selected from: fluoro, oxo, -OH, and -NH₂;

A and B are independently aryl or heteroaryl;

z₂ and z₄ are independently 0 or 1;

z₅ and z₆ are independently an integer from 0 to 5;

X is absent or present as C1-2alkyl or C1-2alkyl substituted 1 to 2 times by fluoro, where the dotted lines represent optional bonds of the alkyl chain of X;

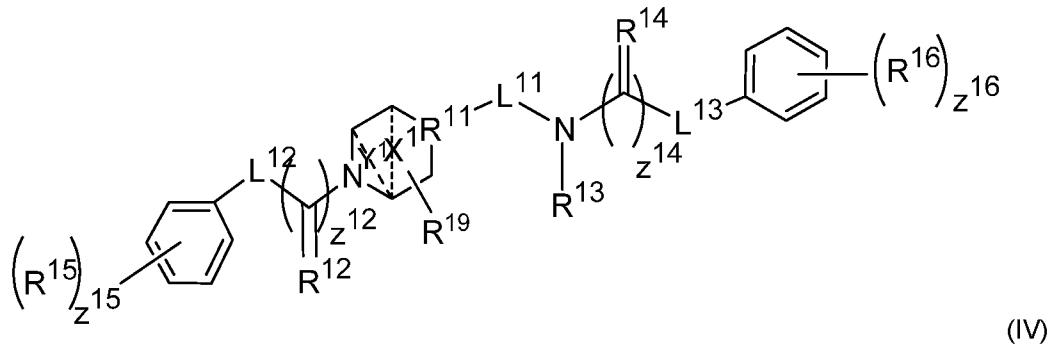
Y is absent or present as C1-2alkyl or C1-2alkyl substituted 1 to 2 times by fluoro, where the dotted lines represent optional bonds of the alkyl chain of Y; and

Z is nitrogen or a nitrogen linked heteroaryl;

and salts thereof.

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

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



wherein:

L^{12} and L^{13} are independently: $-CH_2-O-$, $-O-CH_2-$, $-CH_2-CH_2-O-$, $-O-CH_2-CH_2-$,

$-CH_2-CH_2-CH_2-O-$ and $-O-CH_2-CH_2-CH_2-$;

L^{11} is selected from: a bond, $-CH_2-$ and $-C(O)-$;

R^{11} is $CH-$ and R^{13} is hydrogen, or R^{11} is $C-$ and taken together with R^{13} and the nitrogen to which R^{13} is attached form an oxazolidine, which is optionally substituted by oxo;

R^{15} and R^{16} are independently hydrogen or chloro;

R^{12} and R^{14} are O;

R^{19} is selected from: hydrogen, fluoro, chloro, $-OH$, C1-3alkyl and

C1-3alkyl substituted with from 1 to 3 substituents independently selected from: fluoro, oxo, and $-OH$;

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

z^{15} and z^{16} are independently an integer from 0 to 5;

X^1 is absent or present as C1-2alkyl or C1-2alkyl substituted 1 to 2 times by fluoro, where the dotted lines represent optional bonds of the alkyl chain of X ; and

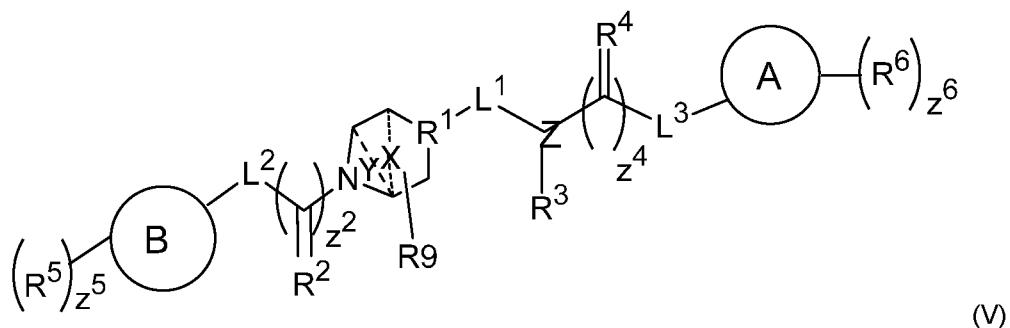
Y^1 is absent or present as C1-2alkyl or C1-2alkyl substituted 1 to 2 times by fluoro,

where the dotted lines represent optional bonds of the alkyl chain of Y ;

and salts thereof.

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

Included in the compounds of the invention and used in the methods of the invention are compounds of Formula (V):



wherein:

L^2 is selected from: a bond, -NH-, -O-, -S-, -S(O)-, -S(O)2-, substituted or

unsubstituted C1-6alkylene or substituted or unsubstituted

C1-6heteroalkylene, or L^2 is further taken together with B to form

heterocycloalkyl;

L^3 is selected from: a bond, -NH-, -O-, -S-, -S(O)-, -S(O)2-, substituted or

unsubstituted C1-6alkylene or substituted or unsubstituted

C1-6heteroalkylene, or L^3 is further taken together with A to form

heterocycloalkyl;

L^1 is selected from: a bond, -NH-, -C(R^7)-, -O-, -S-, -S(O)-, -S(O)2-, substituted or

unsubstituted C1-6alkylene and substituted or unsubstituted

C1-6heteroalkylene;

R^1 is CH-, or R^1 is C- and taken together with R^3 and the nitrogen to which R^3 is attached, and optionally from 1 to 3 additional heteroatoms, to form a heterocycloalkyl, which is optionally substituted with from 1 to 5 substituents independently selected from:

fluoro, chloro, C1-6alkyl, C1-6alkyl substituted 1 to 6 times by

fluoro, C1-4alkoxy, C1-4alkoxy substituted 1 to 6 times by fluoro,

oxo, and -NH₂;

R^3 , R^5 and R^6 and are independently hydrogen, fluoro, chloro, bromo, iodo, -OCH₃, -OCH₂Ph, -C(O)Ph, -CH₃, -CF₃, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH(CH₃)₂, -CCH, -CH₂CCH, -SO₃H, -SO₂NH₂, —NHC(O)NH₂, -NHC(O)H, -NHOH, -OCF₃, -OCHF₂, substituted or unsubstituted C1-6alkylene, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, provided R^3 is absent when Z is a nitrogen linked heteroaryl;

R^2 and R^4 are independently NR⁸, O, or S;

R^7 is selected from: =NR⁸, =O, and =S;

R^8 is selected from: hydrogen, C1-6alkyl and C1-6alkyl substituted 1 to 6 times by fluoro;

R^9 is selected from: hydrogen, fluoro, chloro, bromo, iodo, -OH, C1-3alkyl and

C1-3alkyl substituted with from 1 to 3 substituents independently selected

from: fluoro, oxo, -OH, and -NH₂;

A and B are independently aryl or heteroaryl;

z₂ and z₄ are independently 0 or 1;

z₅ and z₆ are independently an integer from 0 to 5;

X is absent or present as C1-2alkyl or C1-2alkyl substituted 1 to 2 times by fluoro,

where the dotted lines represent optional bonds of the alkyl chain of X;

Y is absent or present as C1-2alkyl or C1-2alkyl substituted 1 to 2 times by fluoro,

where the dotted lines represent optional bonds of the alkyl chain of Y; and

Z is nitrogen or a nitrogen linked heteroaryl;

and salts thereof.

This invention also relates to pharmaceutically acceptable salts of the compounds of Formula (V).

Included in the compounds of Formula (III) are:

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)piperidin-4-yl)acetamide;

8-(2-(4-chlorophenoxy)acetyl)-3-(2-(4-chlorophenoxy)ethyl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one;

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)piperidin-3-yl)acetamide;

N-(2-(4-chlorophenoxy)ethyl)-1-(3-(4-chlorophenoxy)propanoyl)piperidine-4-carboxamide;

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propanoyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)ethyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-((1-(2-(4-chlorophenoxy)acetyl)piperidin-4-yl)methyl)acetamide;

N-(1-(2-((5-chloroisothiazol-3-yl)oxy)ethyl)piperidin-4-yl)-2-(4-chlorophenoxy)acetamide;

N-(1-(3-((5-chloroisothiazol-3-yl)oxy)propyl)piperidin-4-yl)-2-(4-chlorophenoxy)acetamide;

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-hydroxypropyl)piperidin-4-yl)acetamide;

(R)-2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-hydroxypropyl)piperidin-4-yl)acetamide;

(S)-2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-hydroxypropyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-fluoropropyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(2-(3-(4-chlorophenoxy)-2-hydroxypropyl)-2-azabicyclo[2.2.1]heptan-5-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-methoxypropyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(3-((6-chloropyridin-3-yl)oxy)propyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(2-(3-(4-chlorophenoxy)propyl)-2-azabicyclo[2.2.1]heptan-5-yl)acetamide;

N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-((5-chloropyridin-2-yl)oxy)acetamide;

2-(4-chlorophenoxy)-N-(1-(3-((5-chloropyridin-2-yl)oxy)propyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(3-(3,4-dichlorophenoxy)propyl)piperidin-4-yl)acetamide;

4-(2-((4-chlorophenoxy)methyl)-1H-imidazol-1-yl)-1-(3-(4-chlorophenoxy)propyl)piperidine;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)-3-methylpiperidin-4-yl)acetamide;

N-(4-chlorophenethyl)-1-(2-(4-chlorophenoxy)acetyl)piperidine-4-carboxamide;

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propanoyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(4-(4-chlorophenyl)butanoyl)-3-fluoropiperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)piperidin-3-yl)acetamide;

2-(4-chlorophenoxy)-N-(2-(1-(2-(4-chlorophenoxy)acetyl)piperidin-3-yl)ethyl)acetamide;

N-((1-(2-(4-chlorophenoxy)acetyl)piperidin-3-yl)methyl)-2-((6-chloropyridin-3-yl)oxy)acetamide;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)-3-fluoropiperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(2-(2-(4-chlorophenoxy)acetyl)-2-azabicyclo[2.2.1]heptan-5-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-((1R,2R)-2-(4-chlorophenoxy)cyclopropane-1-carbonyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-((1R,2S)-2-(4-chlorophenoxy)cyclopropane-1-carbonyl)piperidin-4-yl)acetamide;

N-((1S,2R)-2-(4-chlorobenzyl)cyclopropane-1-carbonyl)piperidin-4-yl)-2-(4-chlorophenoxy)acetamide;

N-((1R,2R)-2-(4-chlorobenzyl)cyclopropane-1-carbonyl)piperidin-4-yl)-2-(4-chlorophenoxy)acetamide;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenyl)cyclopropane-1-carbonyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(4-(4-chlorophenyl)butanoyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)ethyl)-3-methylpiperidin-4-yl)acetamide;

N,1-bis(2-(4-chlorophenoxy)ethyl)piperidine-4-carboxamide;

N-(2-(4-chlorophenoxy)ethyl)-1-(3-(4-chlorophenoxy)propyl)piperidine-4-carboxamide;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)ethyl)-3-hydroxypiperidin-4-yl)acetamide;

6-chloro-N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)chromane-2-carboxamide;

N-((1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-((6-chloropyridin-3-yl)oxy)acetamide;

N-((1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-(3,4-dichlorophenoxy)acetamide;

N-((1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-(2,4-dichlorophenoxy)acetamide;

2-(4-chlorophenoxy)-N-((1R,5S)-8-(3-(4-chlorophenoxy)propyl)-8-azabicyclo[3.2.1]octan-3-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(2-(3,4-dichlorophenoxy)ethyl)-3-fluoropiperidin-4-yl)acetamide;

N-(1-(2-(4-chlorophenoxy)ethyl)-3-fluoropiperidin-4-yl)-2-(3,4-dichlorophenoxy)acetamide;

2-(4-chlorophenoxy)-N-((1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)methyl)acetamide;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)ethyl)-3-fluoropiperidin-4-yl)acetamide;

4-(4-chlorophenoxy)-2-(4-(2-(4-chlorophenoxy)acetamido)piperidin-1-yl)butanoic acid;

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propyl)-2-oxopiperidin-4-yl)acetamide;

4-(4-chlorophenoxy)-2-(4-(2-(3,4-dichlorophenoxy)acetamido)piperidin-1-yl)butanoic acid;

2-(4-(2-(4-chlorophenoxy)acetamido)piperidin-1-yl)-4-(3,4-dichlorophenoxy)butanoic acid;

N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-(4-(difluoromethoxy)phenoxy)acetamide;

N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-(4-cyclopropylphenoxy)acetamide;

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-N-methylacetamide;

4-(2-(4-chlorophenoxy)acetamido)-1-(3-(4-chlorophenoxy)propyl)piperidine-2-carboxylic acid; and

4-(2-(4-chlorophenoxy)acetamido)-1-(3-(4-chlorophenoxy)propyl)piperidine-2-carboxylic acid;

and salts thereof including pharmaceutically acceptable salts thereof.

L^1 may be a bond or substituted or unsubstituted C₁-C₆ alkylene alkylene. L^1 may be substituted or unsubstituted C₁-C₅ alkylene. L^1 may be substituted or unsubstituted C₁-C₃ alkylene. L^1 may be substituted or unsubstituted methylene. L^1 may be a bond. L^1 may be an unsubstituted alkylene. L^1 may be an unsubstituted methylene. L^1 may be an unsubstituted ethylene. L^1 may be a methylene substituted with an unsubstituted alkyl. L^1 may be a methylene substituted with an unsubstituted C₁-C₄ alkyl. L^1 may be a

methylene substituted with an unsubstituted C₁-C₃ alkyl.

Suitably, R³ is hydrogen. Suitably, R³ is -CH₂CCH.

Suitably, R³ is substituted or unsubstituted C₁₋₆alkylene, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. Suitably, R³ is substituted or unsubstituted C₁₋₆alkylene.

Suitably, R³ is substituted or unsubstituted C₁-C₅ alkyl. Suitably, R³ is substituted or unsubstituted C₁-C₄ alkyl. Suitably, R³ is substituted or unsubstituted C₁-C₃ alkyl.

Suitably, R³ is unsubstituted C₁₋₆alkylene. Suitably, R³ is unsubstituted C₁-C₅ alkyl.

Suitably, R³ is unsubstituted C₁-C₄ alkyl. Suitably, R³ is unsubstituted C₁-C₃ alkyl.

Suitably, R³ is substituted or unsubstituted heteroalkyl. Suitably, R³ is substituted or unsubstituted 2 to 8 membered heteroalkyl. Suitably, R³ is unsubstituted 2 to 8 membered heteroalkyl.

In embodiments, R⁵ is independently hydrogen, fluoro, chloro, bromo, iodo, -OCH₃, -OCH₂Ph, -C(O)Ph, -CH₃, -CF₃, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH(CH₃)₂, -CCH, -CH₂CCH, -SO₃H, -SO₂NH₂, —NHC(O)NH₂, -NHC(O)H, -NHOH, -OCH₃, -OCF₃, -OCHF₂, substituted or unsubstituted C₁₋₆alkylene, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In embodiments, R⁵ is independently hydrogen, fluoro, chloro, bromo, iodo, -OCH₃, -OCH₂Ph, -CH₃, -OH, -CF₃, -CN, -S(O)CH₃, -NO₂, -C(O)CH₃, -C(O)Ph, -CH(CH₃)₂, or —CCH. In embodiments, R⁵ is —F. In embodiments, R⁵ is —Cl. In embodiments, R⁵ is —Br. In embodiments, R⁵ is —I. In embodiments, R⁵ is substituted or unsubstituted C₁₋₆alkylene, substituted or unsubstituted heteroalkyl,

substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In embodiments, R^5 is unsubstituted C_{1-6} alkylene, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl. In embodiments, R^5 is -OCH₃. In embodiments, R^5 is -OCH₂Ph. In embodiments, R^5 is -CH₃. In embodiments, R^5 is -OH. In embodiments, R^5 is -CF₃. In embodiments, R^5 is -CN. In embodiments, R^5 is -S(O)CH₃. In embodiments, R^5 is -NO₂. In embodiments, R^5 is -C(O)CH₃. In embodiments, R^5 is -C(O)Ph. In embodiments, R^5 is -CH(CH₃)₂. In embodiments, R^5 is -CCH. In embodiments, R^5 is -CH₂CCH. In embodiments, R^5 is -SO₃H. In embodiments, R^5 is -SO₂NH₂. In embodiments, R^5 is —NHC(O)NH₂. In embodiments, R^5 is -NHC(O)H. In embodiments, R^5 is -NHOH. In embodiments, R^5 is -OCH₃. In embodiments, R is -OCF₃. In embodiments, R^5 is -OCHF₂.

In embodiments, R^6 is independently hydrogen, fluoro, chloro, bromo, iodo, -OCH₃, -OCH₂Ph, -C(O)Ph, -CH₃, -CF₃, -CN, -S(O)CH₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH(CH₃)₂, -CCH, -CH₂CCH, -SO₃H, -SO₂NH₂, —NHC(O)NH₂, -NHC(O)H, -NHOH, -OCH₃, -OCF₃, -OCHF₂, substituted or unsubstituted C_{1-6} alkylene, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In embodiments, R^6 is independently hydrogen, fluoro, chloro, bromo, iodo, -OCH₃, -OCH₂Ph, -CH₃, -OH, -CF₃, -CN, -S(O)CH₃, -NO₂, -C(O)CH₃, -C(O)Ph, -CH(CH₃)₂, or —CCH. In embodiments, R^6 is —F. In embodiments, R^6 is —Cl. In embodiments, R^6 is —Br. In embodiments, R^6 is —I. In embodiments, R^6 is substituted or unsubstituted C_{1-6} alkylene, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In embodiments, R^6 is unsubstituted C_{1-6} alkylene, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted 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^2 is NR^8 . In embodiments, R^2 is NH . In embodiments, R^2 is O . In embodiments, R^2 is S . In embodiments, R^4 is NR^8 . In embodiments, R^4 is NH . In embodiments, R^4 is O . In embodiments, R^4 is S . In embodiments, R^2 and R^4 are NH . In embodiments, R^2 and R^4 are O . In embodiments, R^2 and R^4 are S . In embodiments, R^2 and R^4 are NR^8 .

In embodiments, L^2 is a bond. In embodiments, L^2 is a substituted or unsubstituted C_{1-6} alkylene. In embodiments, L^2 is a substituted or unsubstituted C_{1-6} heteroalkylene. In embodiments, L^2 is $L^{2A}-L^{2B}-L^{2C}$ and L^{2A} is bonded to the substituted or unsubstituted phenyl, which may be substituted with R^5 . L^{2A} is a bond, $-O-$, $-S-$, $-NH-$, $-S(O)-$, or $-S(O)_2-$. L^{2B} is a bond or substituted or unsubstituted C_{1-6} alkylene. L^{2C} is a bond, $-O-$, or $-NH-$. In embodiments, L^{2A} is a bond. In embodiments, L^{2A} is $-O-$. In embodiments, L^{2A} is $-S-$. In embodiments, L^{2A} is $-NH-$. In embodiments, L^{2A} is $-S(O)-$. In embodiments, L^{2A} is $-S(O)_2-$. In embodiments, L^{2B} is a bond. In embodiments, L^{2B} is a substituted or unsubstituted C_{1-6} alkylene. In embodiments, L^{2B} is an unsubstituted C_{1-6} alkylene. In embodiments, L^{2B} is a substituted or unsubstituted C_{1-C_5} alkylene. In embodiments, L^{2B} is an unsubstituted C_{1-C_5} alkylene. In embodiments, L^{2B} is a

substituted or unsubstituted C₁-C₄ alkylene. In embodiments, L^{2B} is an unsubstituted C₁-C₄ alkylene. In embodiments, L^{2B} is a substituted or unsubstituted C₁-C₃ alkylene. In embodiments, L^{2B} is an unsubstituted C₁-C₃ alkylene. In embodiments, L^{2B} is a substituted C₁-C₅ alkylene. In embodiments, L^{2B} is a substituted C₁-C₆ alkylene. In embodiments, L^{2B} is a substituted C₁-C₄ alkylene. In embodiments, L^{2B} is a C₁-C₆ alkylene substituted with —CF₃. In embodiments, L^{2C} is a bond. In embodiments, L^{2C} is -O-. In embodiments, L^{2C} is —NH-. In embodiments, L^{2A} is a bond; L^{2B} is unsubstituted methylene; and L^{2C} is -O-.

In embodiments, L³ is a bond. In embodiments, L³ is a substituted or unsubstituted C₁-₆alkylene. In embodiments, L³ is a substituted or unsubstituted C₁-₆heteroalkylene. In embodiments, L³ is L^{3A}-L^{3B}-L^{3C} and L^{3A} is bonded to the substituted or unsubstituted phenyl, which may be substituted with R⁵. L^{3A} is a bond, —O-, -S-, -NH-, -S(O)-, or —S(O)₂-. L^{3B} is a bond or substituted or unsubstituted C₁-₆alkylene. L^{3C} is a bond, -O-, or —NH-. In embodiments, L^{3A} is a bond. In embodiments, L^{3A} is —O-. In embodiments, L^{3A} is -S-. In embodiments, L^{3A} is -NH-. In embodiments, L^{3A} is -S(O)-. In embodiments, L^{3A} is —S(O)₂- . In embodiments, L^{3B} is a bond. In embodiments, L^{3B} is a substituted or unsubstituted C₁-₆alkylene. In embodiments, L^{3B} is an unsubstituted C₁-₆alkylene. In embodiments, L^{3B} is a substituted or unsubstituted C₁-C₅ alkylene. In embodiments, L^{3B} is a substituted or unsubstituted C₁-C₄ alkylene. In embodiments, L^{3B} is a substituted or unsubstituted C₁-C₃ alkylene. In embodiments, L^{3B} is a substituted C₁-C₅ alkylene. In embodiments, L^{3B} is a substituted C₁-C₆ alkylene. In embodiments, L^{3B} is a substituted C₁-C₄ alkylene. In embodiments, L^{3B} is a substituted or unsubstituted C₁-C₃alkylene. In embodiments, L^{3B} is an unsubstituted C₁-C₃ alkylene. In embodiments, L^{3B} is a substituted C₁-C₅ alkylene. In embodiments, L^{3B} is a substituted C₁-C₆ alkylene. In embodiments, L^{3B} is a substituted C₁-C₄ alkylene. In embodiments, L^{3B} is a C₁-C₆ alkylene substituted with —CF₃. In embodiments, L^{3C} is a bond. In embodiments, L^{3C} is -O-. In embodiments, L^{3C} is —NH-. In embodiments, L^{3A} is a bond; L^{3B} is unsubstituted methylene; and L^{3C} is -O-.

In embodiments, the symbol z^2 is 0. In embodiments, the symbol z^2 is 1. In embodiments, the symbol z^4 is 0. In embodiments, the symbol z^4 is 1. In embodiments, the symbols z^2 and z^4 are 0. In embodiments, the symbols z^2 and z^4 are 1. In embodiments, the symbol z^5 is 0. In embodiments, the symbol z^5 is 1. In embodiments, the symbol z^5 is 2. In embodiments, the symbol z^5 is 3. In embodiments, the symbol z^5 is 4. In embodiments, the symbol z^6 is 0. In embodiments, the symbol z^6 is 1. In embodiments, the symbol z^6 is 2. In embodiments, the symbol z^6 is 3. In embodiments, the symbol z^6 is 4.

The skilled artisan will appreciate that salts, including pharmaceutically acceptable salts, of the compounds according to Formula (III) may be prepared. Indeed, in certain embodiments of the invention, salts including pharmaceutically-acceptable salts of the compounds according to Formula (III) 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 (III).

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

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.

Representative pharmaceutically acceptable acid addition salts include, but are not limited to, 4-acetamidobenzoate, acetate, adipate, alginic acid, 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), ethanesulfonate (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*-aminosalicylate, pamoate (embonate), pantothenate, pectinate, persulfate, phenylacetate, phenylethylbarbiturate, phosphate, polygalacturonate, propionate, *p*-toluenesulfonate (tosylate), pyroglutamate, pyruvate, salicylate, sebacate, stearate, subacetate, succinate, sulfamate, sulfate, tannate, tartrate, teoclolate (8-chlorotheophyllinate), thiocyanate, triethiodide, undecanoate, undecylenate, and valerate.

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-pyrrolidine-1'-ylmethylbenzimidazole), cyclohexylamine, dibenzylethylenediamine, diethylamine, diethyltriamine, dimethylamine, dimethylethanolamine, dopamine, ethanolamine, ethylenediamine, L-histidine, iron, isoquinoline, lepidine, lithium, lysine, magnesium, meglumine (*N*-methylglucamine), piperazine, piperidine, potassium, procaine, quinine, quinoline, sodium, strontium, *t*-butylamine, and zinc.

The compounds according to Formula (III) 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 (III), 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 (III) 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.

The compounds according to Formula (III) and pharmaceutically acceptable salts thereof may contain isotopically-labelled compounds, which are identical to those recited in Formula (III) 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 .

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.

The compounds according to Formula (III) may also contain double bonds or other centers of geometric asymmetry. Where the stereochemistry of a center of geometric asymmetry present in Formula (III), 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 (III) whether such tautomers exist in equilibrium or predominately in one form.

The compounds of Formula (III) or salts, including pharmaceutically acceptable salts, thereof may exist in solid or liquid form. In the solid state, the compounds of the invention may exist in crystalline or noncrystalline form, or as a mixture thereof. For compounds of the invention that are in crystalline form, the skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed wherein solvent molecules are

incorporated into the crystalline lattice during crystallization. Solvates wherein water is the solvent that is incorporated into the crystalline lattice are typically referred to as "hydrates." Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water.

The skilled artisan will further appreciate that certain compounds of Formula (III) or salts, including pharmaceutically acceptable salts thereof that exist in crystalline form, including the various solvates thereof, may exhibit polymorphism (i.e. the capacity to occur in different crystalline structures). These different crystalline forms are typically known as "polymorphs." Polymorphs have the same chemical composition but differ in packing, geometrical arrangement, and other descriptive properties of the crystalline solid state. Polymorphs, therefore, may have different physical properties such as shape, density, hardness, deformability, stability, and dissolution properties. Polymorphs typically exhibit different melting points, IR spectra, and X-ray powder diffraction patterns, which may be used for identification. The skilled artisan will appreciate that different polymorphs may be produced, for example, by changing or adjusting the reaction conditions or reagents, used in making the compound. For example, changes in temperature, pressure, or solvent may result in polymorphs. In addition, one polymorph may spontaneously convert to another polymorph under certain conditions.

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 (III) is selected from each of the aspects listed above. Therefore, this invention is intended to include all combinations of aspects for each variable.

Definitions

“Alkyl” and “alkylene”, and derivatives thereof, refer to a hydrocarbon chain having the specified number of “member atoms”. Alkyl being monovalent and alkylene being bivalent. For example, C₁-C₆ alkyl refers to an alkyl group having from 1 to 6 member atoms. Alkyl groups may be saturated, unsaturated, straight or branched. Representative branched alkyl groups have one, two, or three branches. Alkyl and alkylene includes methyl, ethyl, ethylene, propyl (n-propyl and isopropyl), butene, butyl (n-butyl, isobutyl, and t-butyl), pentyl, methylcyclopropane, and hexyl.

In an embodiment, “**alkyl**” and “**alkylene**” further includes cycloalkyl in the carbon chain, for example –CH₃cyclopropane-.

“**Alkoxy**” refers to an -O-alkyl group wherein “alkyl” is as defined herein. For example, C₁-C₄alkoxy refers to an alkoxy group having from 1 to 4 member atoms.

Representative branched alkoxy groups have one, two, or three branches. Examples of such groups include methoxy, ethoxy, propoxy, and butoxy.

“**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.

“**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, C₃-C₇ cycloalkyl refers to a cycloalkyl group having from 3 to 7 member atoms. Examples of cycloalkyl as used herein include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptyl.

“**Halo**” refers to the halogen radicals fluoro, chloro, bromo, and iodo.

“**Heteroaryl**” refers to a monocyclic aromatic 4 to 8 member ring containing 1 to 7 carbon atoms and 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.

“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, tetrahydrofuranyl, dihydrofuranyl, pyranyl, tetrahydropyranyl, 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, 1,3-oxazolidin-2-one, hexahydro-1H-azepin, 4,5,6,7-tetrahydro-1H-benzimidazol, piperidinyl, 1,2,3,6-tetrahydro-pyridinyl and azetidinyl. Suitably, “heterocycloalkyl” includes: piperidine, tetrahydrofuran, tetrahydropyran and pyrrolidine.

“Heteroatom” refers to a nitrogen, sulphur or oxygen atom.

“Heteroalkyl” and **“heteroalkylene”** by itself or in combination with another term, means, unless otherwise stated, a non-cyclic stable straight or branched chain, or combinations thereof, 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 heteroalkyl and heteroalkylene groups may be taken together with another substituent to form a heterocycloalkyl group. 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. Examples include, but are not limited to:

-CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)₂, -CH₂-S-CH₂-CH₃, -CH₂-CH₃, -S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃, -CH₂-CH=N-OCH₃,

-CH=CHN(CH₃)₂, -O-CH₃, -O-CH₂-CH₃, and -CN. Examples include, but are not limited to: -CH₃, -CH₂-, -CH₂-CH₂-O-CH₂-, CH₂-CH₂-NH-CH₂-, -CH₂-CH₂-N(CH₃)CH₂-, -CH₂-S-CH₂-CH₂-, -CH₂-CH₂-, -S(O)-CH₂-, -CH₂-CH₂-S(O)₂-CH₂-, -CH=CH-O-CH₂-, -Si(CH₃)₂CH₂-, -N(CH₃)CH₂-, -O-CH₂-CH₂-CH₂-, -CH₂-CH=N-OCH₂-, -CH=CHN(CH₃)CH₂-, -O-CH₂-, and -O-CH₂-CH₂-. Up to two or three heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and —CH₂-O-Si(CH₃)₃.

“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:

fluoro,

chloro,

bromo,

iodo,

C₁-6alkyl,

C₁-6alkyl substituted with from 1 to 6 substituents

independently selected from: fluoro, oxo, -OH,

-COOH, -NH₂, and -CN,

-OC₁-6alkyl,

-OC₁-6alkyl substituted with from 1 to 6 substituents

independently selected from: fluoro, oxo, -OH,

-COOH, -NH₂, and -CN,

mercapto,

-SR^X,

where R^X is selected from C₁-6alkyl, and C₁-6alkyl substituted with from 1 to 6 substituents

independently selected from: fluoro, oxo, -OH,
-COOH, -NH₂, and -CN,
-S(O)R^X,
where R^X is selected from C1-6alkyl, and C1-6alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, -OH,
-COOH, -NH₂, and -CN,
-S(O)₂H,
-S(O)₂R^X,
where R^X is selected from C1-6alkyl, and C1-6alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, -OH,
-COOH, -NH₂, and -CN,
oxo,
hydroxy,
amino,
-NHR^X,
where R^X is selected from C1-6alkyl, and C1-6alkyl substituted with from 1 to 6 substituents independently selected from: fluoro, oxo, -OH,
-COOH, -NH₂, and -CN,
-NR^{X1}R^{X2},
where R^{X1} and R^{X2} are each independently selected from C1-6alkyl, and C1-6alkyl substituted with from 1 to 6

substituents independently selected from: fluoro,

oxo, -OH, -COOH, -NH₂, and -CN,

guanidino,

-C(O)OH,

-C(O)OR^X,

where R^X is selected from C1-6alkyl, and C1-6alkyl

substituted with from 1 to 6 substituents

independently selected from: fluoro, oxo, -OH,

-COOH, -NH₂, and -CN,

-C(O)NH₂,

-C(O)NHR^X,

where R^X is selected from C1-6alkyl, and C1-6alkyl

substituted with from 1 to 6 substituents

independently selected from: fluoro, oxo, -OH,

-COOH, -NH₂, and -CN,

-C(O)NR^{X1}R^{X2},

where R^{X1} and R^{X2} are each independently selected

from C1-6alkyl, and C1-6alkyl substituted with from 1 to 6

substituents independently selected from: fluoro,

oxo, -OH, -COOH, -NH₂, and -CN,

-S(O)₂NH₂,

-S(O)₂NHR^X,

where R^X is selected from C1-6alkyl, and C1-6alkyl

substituted with from 1 to 6 substituents

independently selected from: fluoro, oxo, -OH,
-COOH, -NH₂, and -CN,
-S(O)₂NR^{X1}R^{X2},
where R^{X1} and R^{X2} are each independently selected
from C1-6alkyl, and C1-6alkyl substituted with from 1
to 6
substituents independently selected from: fluoro,
oxo, -OH, -COOH, -NH₂, and -CN,
-NHS(O)H₂,
-NHS(O)₂R^X,
where R^X is selected from C1-6alkyl, and C1-6alkyl
substituted with from 1 to 6 substituents
independently selected from: fluoro, oxo, -OH,
-COOH, -NH₂, and -CN,
-NHC(O)H,
-NHC(O)R^X,
where R^X is selected from C1-6alkyl, and C1-6alkyl
substituted with from 1 to 6 substituents
independently selected from: fluoro, oxo, -OH,
-COOH, -NH₂, and -CN,
-NHC(O)NH₂,
-NHC(O)NHR^X,
where R^X is selected from C1-6alkyl, and C1-6alkyl
substituted with from 1 to 6 substituents
independently selected from: fluoro, oxo, -OH,

-COOH, -NH₂, and -CN,

-NHC(O)NR^{x1}R^{x2},

where R^{x1} and R^{x2} are each independently selected

from C1-6alkyl, and C1-6alkyl substituted with from 1 to 6

Substituents independently selected from: fluoro,

oxo, -OH, -COOH, -NH₂, and -CN,

nitro, and

cyano.

Suitably "substituted" means the subject chemical moiety has from one to four substituents selected from the group consisting of:

fluoro,

chloro,

bromo,

iodo,

C1-4alkyl,

C1-4alkyl substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, -OH,

-COOH, -NH₂, and -CN,

-OC1-4alkyl,

-OC1-4alkyl substituted with from 1 to 4 substituents

independently selected from: fluoro, oxo, -OH,

-COOH, -NH₂, and -CN,

-SH,

S(O)2H,

oxo,

hydroxy,

amino,

$-\text{NHR}^X$,

where R^X is selected from C1-4alkyl, and C1-6alkyl substituted one to 4 times by fluoro,

$-\text{NR}^{x1}\text{R}^{x2}$,

where R^{x1} and R^{x2} are each independently selected from C1-4alkyl, and C1-4alkyl substituted one to four times by fluoro,

guanidino,

$-\text{C}(\text{O})\text{OH}$,

$-\text{C}(\text{O})\text{OR}^X$,

where R^X is selected from C1-4alkyl, and C1-4alkyl substituted one to four times by fluoro,

$-\text{C}(\text{O})\text{NH}_2$,

$-\text{C}(\text{O})\text{NHR}^X$,

where R^X is selected from C1-4alkyl, and C1-4alkyl substituted one to four times by fluoro,

$-\text{C}(\text{O})\text{NR}^{x1}\text{R}^{x2}$,

where R^{x1} and R^{x2} are each independently selected from C1-4alkyl, and C1-4alkyl substituted one to four times by fluoro,

$-\text{S}(\text{O})_2\text{NH}_2$,

$-\text{NHS}(\text{O})_2\text{H}$,

-NHC(O)H,
-NHC(O)NH₂,
nitro, and
cyano.

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:

Ac (acetyl);
Ac₂O (acetic anhydride);
ACN (acetonitrile);
AIBN (azobis(isobutyronitrile));
BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl);
BMS (borane - dimethyl sulphide complex);
Bn (benzyl);
Boc (tert-Butoxycarbonyl);
Boc₂O (di-*tert*-butyl dicarbonate);
BOP (Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate);
CAN (ceric ammonium nitrate);
Cbz (benzyloxycarbonyl);
CSI (chlorosulfonyl isocyanate);
CSF (cesium fluoride);
DABCO (1,4-Diazabicyclo[2.2.2]octane);
DAST (Diethylamino)sulfur trifluoride);

DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene);
DCC (Dicyclohexyl Carbodiimide);
DCE (1,2-dichloroethane);
DCM (dichloromethane);
DDQ (2,3-Dichloro-5,6-dicyano-1,4-benzoquinone);
ATP (adenosine triphosphate);
Bis-pinacolatodiboron (4,4,4',4',5,5,5',5'-Octamethyl-2,2'-bi-1,3,2-dioxaborolane);
BSA (bovine serum albumin);
C18 (refers to 18-carbon alkyl groups on silicon in HPLC stationary phase);
CH₃CN (acetonitrile);
Cy (cyclohexyl);
DCM (dichloromethane);
DIPEA (Hünig's base, *N*-ethyl-*N*-(1-methylethyl)-2-propanamine);
Dioxane (1,4-dioxane);
DMAP (4-dimethylaminopyridine);
DME (1,2-dimethoxyethane);
DMEDA (*N,N*'-dimethylethylenediamine);
DMF (*N,N*-dimethylformamide);
DMSO (dimethylsulfoxide);
DPPA (diphenyl phosphoryl azide);
EDC (*N*-(3-dimethylaminopropyl)-*N*'ethylcarbodiimide);
EDTA (ethylenediaminetetraacetic acid);
EtOAc (ethyl acetate);
EtOH (ethanol);
Et₂O (diethyl ether);
HEPES (4-(2-hydroxyethyl)-1-piperazine ethane sulfonic acid);
HATU (O-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate);
HOAt (1-hydroxy-7-azabenzotriazole);

HOBt (1-hydroxybenzotriazole);

HOAc (acetic acid);

HPLC (high pressure liquid chromatography);

HMDS (hexamethyldisilazide);

Hunig's Base (*N,N*-Diisopropylethylamine);

IPA (isopropyl alcohol);

Indoline (2,3-dihydro-1*H*-indole);

KHMDS (potassium hexamethyldisilazide);

LAH (lithium aluminum hydride);

LDA (lithium diisopropylamide);

LHMDS (lithium hexamethyldisilazide);

MeOH (methanol);

MTBE (methyl tert-butyl ether);

mCPBA (m-chloroperbezoic acid);

NaHMDS (sodium hexamethyldisilazide);

NBS (*N*-bromosuccinimide);

PE (petroleum ether);

Pd₂(dba)₃ (Tris(dibenzylideneacetone)dipalladium(0);

Pd(dppf)Cl₂.DCM Complex ([1,1'-

Bis(diphenylphosphino)ferrocene]dichloropalladium(II).dichloromethane complex);

PyBOP (benzotriazol-1-yl-oxytritypyrrolidinophosphonium hexafluorophosphate);

PyBrOP (bromotripyrrolidinophosphonium hexafluorophosphate);

RPHPLC (reverse phase high pressure liquid chromatography);

RT (room temperature);

Sat. (saturated);

SFC (supercritical fluid chromatography);

SGC (silica gel chromatography);

SM (starting material);

TLC (thin layer chromatography);
TEA (triethylamine);
TEMPO (2,2,6,6-Tetramethylpiperidine 1-oxyl, free radical);
TFA (trifluoroacetic acid); and
THF (tetrahydrofuran).

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

Methods of Use

The compounds according to Formula (III) 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.

The Integrated Stress Response (ISR) is a collection of cellular stress response pathways that converge in phosphorylation of the translation initiation factor eIF2 α resulting in a reduction in overall translation in cells. Mammalian cells have four eIF2 α 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 eIF2 α 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 eIF2 α by an eIF2 α kinase compared to a control such as a subject without the disease). A disease associated with

phosphorylation of eIF2 α is disease characterized by an increase in phosphorylation of eIF2 α relative to a control, such as a subject without the disease.

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 eIF2 α phosphorylation upon stress may prove to be potent anti-proliferative agents.

It is known that under certain stress conditions several eIF2 α 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.

Prolonged ER stress leads to the accumulation of CHOP, a pro-apoptotic molecule. In a prion mouse model, overexpression of the phosphatase of eIF2 α increased survival of prion- infected mice whereas sustained eIF2 α 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 eIF2 α 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 eIF2 α 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-eIF2 α branch could prevent synaptic failure and neuronal death across the spectrum of these disorders.

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 hyper-activation in VWM.

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 (III) to the patient. In embodiments, the patient is human. In embodiments, the patient is a mammal.

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.

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 is or whether each play 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 increase spatial memory and enhance auditory and contextual fear conditioning.

Regulators of translation, such as the compounds of Formula (III), 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 eIF2 γ , 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.

The compounds of Formula (III) 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 eIF2 α phosphorylation that reduce translational output [28, 29]. Similarly production of antibodies by hybridomas may also be improved by addition of compounds disclosed herein.

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 (III) 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 (III) 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 (III) to the in vitro (e.g. cell free) protein expression system.

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.

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.

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

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.

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

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.

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 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.

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 gammopathy 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.

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, cognitive impairment, atherosclerosis, ocular diseases, arrhythmias, in organ transplantation and in the transportation of organs for transplantation.

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 (III). The method of preventing organ damage during the transportation of organs for transplantation will comprise adding a compound of Formula (III) to the solution housing the organ during transportation.

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 (III). 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.

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

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

The invention also provides a compound according to Formula (III) 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, cognitive impairment, atherosclerosis, ocular diseases, in organ transplantation and arrhythmias. The invention also provides a compound according to Formula (III) 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 (III) 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.

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

As used herein, "treating", and derivatives thereof, in reference to a condition means: (1) to ameliorate or prevent 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.

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. 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.

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.

As used herein, "safe and effective amount" in reference to a compound of Formula (III), 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 routinely determined by the skilled artisan.

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

The compounds of Formula (III) or pharmaceutically acceptable salts thereof may be administered by any suitable route of administration, including systemic administration. Systemic administration includes oral administration, and parenteral administration. 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.

The compounds of Formula (III) 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 over time as individual patient needs change.

Additionally, the compounds of Formula (III) 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. 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.

The compounds of Formula (III) 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.

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.

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), 6th edition (February 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 anthracyclines, 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.

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.

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-methylbenzenesulfonamide, 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 December 19, 2001, International Publication Number WO02/059110 and an International Publication date of August 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.

In one embodiment, the cancer treatment method of the claimed invention includes the co-administration a compound of Formula (III) 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.

"Chemotherapeutic" 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.

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 ¹¹¹In, ⁹⁰Y, or ¹³¹I, etc.).

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

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-L1 agents.

Anti-PD-L1 antibodies and methods of making the same are known in the art. Such antibodies to PD-L1 may be polyclonal or monoclonal, and/or recombinant, and/or humanized.

Exemplary PD-L1 antibodies are disclosed in:

US Patent No. 8,217,149; 12/633,339;

US Patent No. 8,383,796; 13/091,936;

US Patent No 8,552,154; 13/120,406;

US patent publication No. 20110280877; 13/068337;

US Patent Publication No. 20130309250; 13/892671;

WO2013019906;

WO2013079174;

US Application No. 13/511,538 (filed August 7, 2012), which is the US National Phase of International Application No. PCT/US10/58007 (filed 2010);
and
US Application No. 13/478,511 (filed May 23, 2012).

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

In one embodiment, the antibody to PD-L1 is an antibody disclosed in US Patent No. 8,217,149. In another embodiment, the anti-PD-L1 antibody comprises the CDRs of an antibody disclosed in US Patent No. 8,217,149.

In another embodiment, the antibody to PD-L1 is an antibody disclosed in US Application No. 13/511,538. In another embodiment, the anti-PD-L1 antibody comprises the CDRs of an antibody disclosed in US Application No. 13/511,538.

In another embodiment, the antibody to PD-L1 is an antibody disclosed in Application No. 13/478,511. In another embodiment, the anti-PD-L1 antibody comprises the CDRs of an antibody disclosed in US Application No. 13/478,511.

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.

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.

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.

Examples of mAbs that bind to human PD-1, and useful in the various aspects and embodiments of the present invention, are described in US7488802, US7521051, US8008449, US8354509, US8168757, WO2004/004771, WO2004/072286, WO2004/056875, and US2011/0271358.

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 Figure 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 Figure 7; the humanized antibodies h409A11, h409A16 and h409A17, which are described in WO2008/156712, and AMP-514, which is being developed by Medimmune.

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.

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, W02010/077634 A1 and US8383796. 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.

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 US Patent No. 8,168,757.

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 US Patent No. US 8,008,449.

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.

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.

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 US Patent Nos. 6,984,720 and 7,605,238.

Suitably, the compounds of the invention are combined with an inhibitor of the activity of the protein kinase R (PKR)-like ER kinase, PERK.

Suitably, the compounds of Formula (III) 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.

Suitably, the compounds of Formula (III) 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.

Suitably, the compounds of Formula (III) 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.

Suitably, the compounds of Formula (III) 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.

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.

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 reducing eIF2a phosphorylation. In embodiments, the second agent is an agent for inhibiting a pathway activated by eIF2a 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.

The term "eIF2alpha" or "eIF2 α " refers to the protein "Eukaryotic translation initiation factor 2A". In embodiments, "eIF2alpha" or "eIF2 α " refers to the human protein. Included in the term "eIF2alpha" or "eIF2 α " are the wildtype and mutant forms of the protein. In embodiments, "eIF2alpha" or "eIF2 α " refers to the protein associated with Entrez Gene 83939, OMIM 609234, UniProt Q9BY44, and/or RefSeq (protein) NP 114414.

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 (III), or a pharmaceutically acceptable salt thereof, to the patient.

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.

Suitably, the present invention relates to a method for treating a disease associated with phosphorylation of eIF2 α in a patient in need of such treatment, the method including administering a therapeutically effective amount of a compound of Formula (III), or a pharmaceutically acceptable salt thereof, to the patient.

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.

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.

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 (III), or a pharmaceutically acceptable salt thereof, to the patient.

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).

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. 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.

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 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 auto-immune thyroiditis. In embodiments, the inflammatory disease is Behcet's disease. In embodiments, the inflammatory disease is Crohn's disease. In embodiments, the inflammatory 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.

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.

In an embodiment, this invention provides a compound of Formula (III), 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.

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

In an embodiment, this invention provides a compound of Formula (III), or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease associated with phosphorylation of eIF2 α .

In an embodiment, this invention provides for the use of a compound of Formula (III), 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..

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

In an embodiment, this invention provides for the use of a compound of Formula (III), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease associated with phosphorylation of eIF2a.

Compositions

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

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 (III) or a pharmaceutically acceptable salt thereof. The compounds of Formula (III) 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.

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.

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.

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.

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.

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

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.

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

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

The invention also provides for the use of a compound of Formula (III) 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, cognitive impairment, atherosclerosis, ocular diseases, arrhythmias, in organ transplantation and in the transportation of organs for transplantation. .

The invention also provides for the use of a compound of Formula (III) 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.

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

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

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.

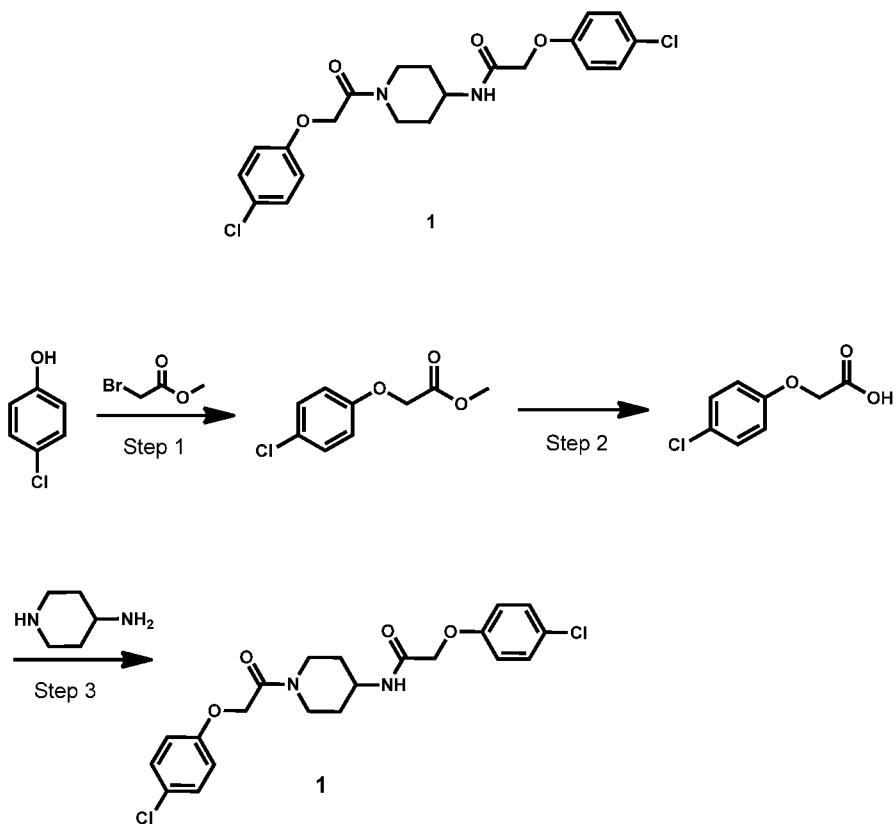
The invention also provides novel processes and novel intermedites useful in preparing the presently invented compounds.

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.

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

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 12-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)piperidin-4-yl)acetamide

Step 1: To a solution of 4-chlorophenol (15 g, 116.67 mmol, 1 equiv) in DMF (100 mL) at room temperature was added anhydrous potassium carbonate (24.15 g, 175.01 mmol, 1.5 equiv) portionwise. After stirring for 2 minutes, methyl-2-bromoacetate (13.3 mL, 140.01 mmol, 1.2 equiv) was added. The reaction mixture was heated at 80 °C for 4 h. After consumption of the starting material (TLC, 5 % EtOAc in hexane), the reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulphate, filtered and concentrated en vacuo 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 15% ethyl acetate in hexane. Fractions containing product were concentrated to give methyl 2-(4-chlorophenoxy)acetate (22.5 g, 96.5% yield)

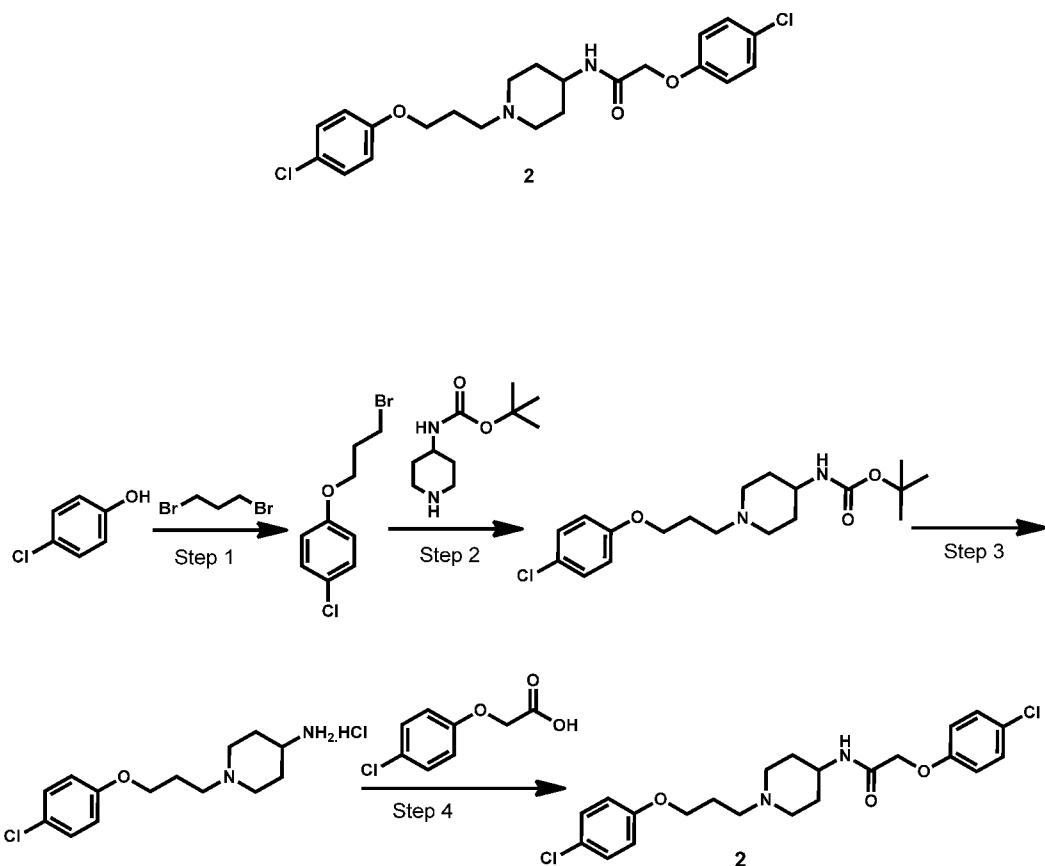
as pale yellow liquid. ^1H NMR (400 MHz, CDCl_3): δ ppm 3.67 (s, 3 H), 4.78 (s, 2 H), 6.91 – 6.95 (m, 2 H), 7.28 – 7.32 (m, 2 H).

Step 2: To a solution of methyl 2-(4-chlorophenoxy)acetate (22.5 g, 112.15 mmol, 1 equiv) in ethanol (100 mL) at 0 °C was added a solution of sodium hydroxide (5.38 g, 134.58 mmol) in water (10 mL). After stirring for 5 minutes at 0 °C, the reaction mixture was allowed to warm to room temperature and then refluxed for 2.5 h during which the starting material was completely consumed. Heating was removed and the reaction mixture was allowed to cool down to room temperature. Ethanol was evaporated removed en vacuo and the reaction mixture was diluted with water (50 mL) followed by extraction with Et_2O (50 mL). The aqueous layer was acidified with 1 N HCl up to pH 3 and the precipitated product was filtered through a cintered funnel, washed with ice-cold water (10 mL) and dried under high vacuum to give 2-(4-chlorophenoxy)acetic acid (20 g, 95.6% yield) as white solid. LCMS (ES) m/z = 186.1 [M+H] $^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 4.65 (s, 2 H), 6.91 (d, J = 9.2 Hz, 2 H), 7.29 (d, J = 8.8 Hz, 2 H), 12.98 (bs, 1 H).

Step 3: To a solution of piperidin-4-amine (0.075 g, 0.74 mmol, 1 equiv) in DCM (7.0 mL) at 0 °C was added triethylamine (0.52 mL, 3.74 mmol, 5 equiv) and 2-(4-chlorophenoxy)acetic acid (0.3 g, 1.64 mmol, 2.2 equiv). After stirring for 5 minutes, T_3P (50 wt. % in ethyl acetate) (2.84 mL, 4.48 mmol, 6 equiv) was added to the reaction mixture. Then reaction mixture was allowed to stir at room temperature for 16 h. After consumption of piperidin-4-amine, the reaction mixture was diluted with water (5 mL) and extracted with DCM (2 x 15 mL). The combined organic extract was washed with a saturated solution of aqueous NaHCO_3 (8.0 mL), water (5.0 mL) and dried over anhydrous sodium sulphate. The organic layer was filtered and concentrated at rotavapor to give 2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)piperidin-4-yl)acetamide (0.18 g, 55.04 % yield) as white solid. LCMS (ES) m/z = 437.1 [M+H] $^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 – 1.33 (m, 1 H), 1.43 – 1.46 (m, 1 H), 1.71 – 1.74 (m, 2 H), 2.70 – 2.79 (m, 1 H), 3.09 – 3.16 (m, 1 H), 3.76 – 3.79 (m, 1 H), 3.88 – 3.90 (m, 1 H), 4.18 – 4.21 (m, 1 H), 4.46 (s, 2 H), 4.80 – 4.83 (m, 2 H), 6.95 (dd, J = 9.2 Hz, 4 H), 7.32 (t, J = 9.2 Hz, 4 H), 8.02 (d, J = 7.6 Hz, 1 H).

Example 2

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)acetamide



Step 1: To a solution of 4-chlorophenol (5 g, 38.89 mmol, 1 equiv) in DMF (60 mL) was added anhydrous potassium carbonate (6.44 g, 46.67 mmol, 1.2 equiv) and 1,3-dibromopropane (5.94 mL, 58.34 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 16 h. Reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 150 mL). The combined organic extract was washed with cold water (100 mL) followed by a saturated brine solution (50 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography using a silica gel column and a mixture of ethyl acetate and hexane as eluent and the product was eluted at 2 – 3% EtOAc in hexane. Fractions containing product were concentrated to give 1-(3-bromopropoxy)-4-chlorobenzene (3.8 g, 39.25 % yield) as colorless liquid. LCMS (ES) m/z = 248.0, 250.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 2.27 – 2.33 (m, 2 H), 3.59 (t, J = 6.4 Hz, 2 H), 4.07 (t, J = 5.6 Hz, 2 H), 6.83 (d, J = 8.8 Hz, 2 H), 7.22 – 7.24 (m, 2 H).

Step 2: To a solution of *tert*-butyl piperidin-4-ylcarbamate (0.5 g, 2.49 mmol, 1 equiv) in DMF (10 mL) was added cesium carbonate (0.976 g, 2.99 mmol, 1.2 equiv) and 1-(3-bromopropoxy)-4-chlorobenzene (0.747 g, 2.99 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 13 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extract was washed with a saturated brine solution (10 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography using a silica gel column and mixture of ethyl acetate in hexane as eluent. The product was eluted at 58 – 62 % ethylacetate in hexane. Fractions containing product were concentrated under reduced pressure to give *tert*-butyl (1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)carbamate (0.510 g, 55.43 % yield) as color less liquid. LCMS (ES) m/z = 369.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.31 – 1.34 (m, 11 H), 1.62 – 1.65 (m, 2 H), 1.78 – 1.89 (m, 4 H), 2.34 (t, J = 7.2 Hz, 2 H), 2.75 – 2.78 (m, 2 H), 3.15 (s, 1 H), 3.94 (t, J = 6.0 Hz, 2 H), 6.73 (d, 7.6 Hz, 1 H), 6.92 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H).

Step 3: To a solution of *tert*-butyl (1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)carbamate (0.510 g, 1.38 mmol, 1 equiv) in DCM (12 mL) at 0 °C was added 4 M HCl in dioxane (8 mL) and the reaction mixture allowed to stir at room temperature for 12 h. After consumption of the starting material, solvent was evaporated under reduced pressure. The solid obtained was triturated with Et₂O (10 mL). The ether layer was decanted and the solid was dried under high vacuum to give 1-(3-(4-chlorophenoxy)propyl)piperidin-4-amine hydrochloride (0.380 g, 89.8% yield) as white solid. LCMS (ES) m/z = 269.3 [M+H]⁺.

Step 4: To 1-(3-(4-chlorophenoxy)propyl)piperidin-4-amine hydrochloride (0.120 g, 0.393 mmol, 1 equiv) in DCM (10 mL) at 0 °C was added triethylamine (0.165 mL, 1.179 mmol, 3 equiv) and 2-(4-chlorophenoxy)acetic acid (0.088 g, 0.471 mmol, 1.2 equiv). After the reaction mixture was stirred for 5 minutes at 0 °C, T₃P (50 wt. % in ethyl acetate) (0.374 mL, 0.587 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 14 h. The reaction mixture was then diluted with water (8 mL) and extracted with DCM (2 x 10 mL). The combined organic extract was washed with saturated aqueous NaHCO₃ solution (10 mL) and water (10 mL). The organic phase was dried over anhydrous sodium sulphate, 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 3 – 4 % methanol in DCM. Fractions containing the product were concentrated under reduced pressure and dried under high vacuum to give 2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)acetamide (0.072 g, 42.1 % yield) as off white solid. LCMS (ES) m/z = 437.0 [M+H]⁺. ¹H

NMR (400 MHz, DMSO-d₆) δ ppm 1.41 – 1.48 (m, 2 H), 1.64 – 1.67 (m, 2 H), 1.79 – 1.83 (m, 2 H), 1.90 – 1.95 (m, 2 H), 2.36 (t, *J* = 6.4 Hz, 2 H), 2.76 – 2.79 (m, 2 H), 3.57 – 3.59 (m, 1 H), 3.95 (t, *J* = 6.0 Hz, 2 H), 4.43 (s, 2 H), 6.91 – 6.95 (m, 4 H), 7.27 – 7.32 (m, 4 H), 7.93 (d, *J* = 8.0 Hz, 1 H).

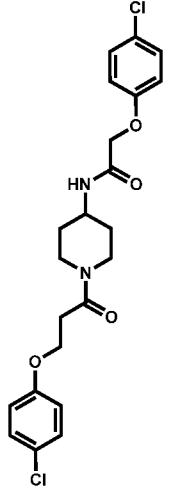
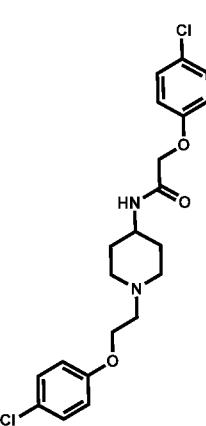
Examples 3 to 8

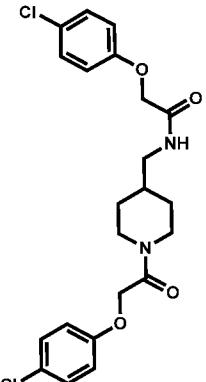
The Compounds of Examples 3 to 8 were prepared generally according to the procedures described above for Examples 1 and 2.

Table 1

Cmpd #	Structure	Name	LCMS <i>m/z</i> [M+H] ⁺	¹ H-NMR (400 MHz, DMSO-d ₆)
3		8-(2-(4-chlorophenoxy)acetyl)-3-(2-(4-chlorophenoxy)ethyl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one	479.1	1.64 – 1.70 (m, 2H), 1.74 – 1.79 (m, 2H), 3.21 – 3.26 (m, 1H), 3.38 – 3.39 (m, 1H), 3.44 (s, 2H), 3.50 – 3.53 (m, 3H), 3.77 – 3.80 (m, 1H), 4.11 (t, <i>J</i> = 10 Hz, 2H), 4.83 (s, 2H), 6.92 – 6.98 (m, 4H), 7.28 – 7.33 (m, 4H).

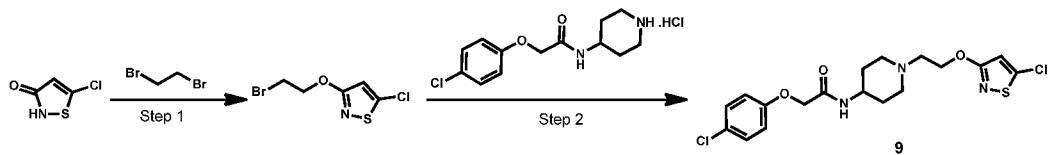
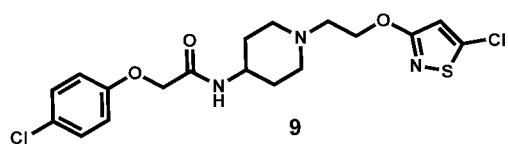
4		2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)piperidin-3-yl)acetamide	451.0	1.31 – 1.37 (m, 1H), 1.52 – 1.55 (m, 1H), 1.66 (bs, 2H), 2.30 – 2.38 (m, 1H), 2.58 – 2.64 (m, 1H), 2.98 – 3.04 (m, 1H), 3.37 – 3.39 (m, 2H), 3.77 – 3.80 (m, 1H), 3.94 – 3.97 (m, 2H), 4.22 – 4.26 (m, 1H), 4.75 – 4.84 (m, 2H), 6.90 – 6.95 (m, 4H), 7.28 – 7.30 (m, 4H), 8.02 (s, 1H).
5		N-(2-(4-chlorophenoxy)ethyl)-1-(3-(4-chlorophenoxy)propanoyl)piperidine-4-carboxamide	465.3	1.33 – 1.39 (m, 1H), 1.48 – 1.54 (m, 1H), 1.63 – 1.66 (m, 2H), 2.37 – 2.48 (m, 1H), 2.54 – 2.64 (m, 1H), 2.71 – 2.81 (m, 2H), 2.97 – 3.00 (m, 1H), 3.37 – 3.39 (m, 2H), 3.87 – 3.96 (m, 3H), 4.16 (s, 2H), 4.31 – 4.36 (m, 1H), 6.91 – 6.94 (m, 4H), 7.27 – 7.30 (m, 4H), 8.01 (s, 1H).

6		<p>2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propanoyl)piperidin-4-yl)acetamide</p>	451.1	<p>1.28 – 1.34 (m, 1H), 1.38 – 1.41 (m, 1H), 1.68 – 1.76 (m, 2H), 2.65 – 2.70 (m, 1H), 2.73 – 2.78 (m, 2H), 3.07 – 3.13 (m, 1H), 3.84 – 3.87 (m, 2H), 4.15 – 4.17 (m, 2H), 4.26 – 4.27 (m, 1H), 4.45 (s, 2H), 6.93 (t, J = 9.2 Hz, 4H), 7.30 (t, J = 12 Hz, 4H), 7.98 – 8.0 (m, 1H).</p>
7		<p>2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)ethyl)piperidin-4-yl)acetamide</p>	423.3	<p>1.42 – 1.50 (m, 2H), 1.65 (d, J = 10.4 Hz, 2H), 2.07 (t, J = 10.8 Hz, 2H), 2.63 (d, J = 5.6 Hz, 2H), 2.83 (d, J = 11.6 Hz, 2H), 3.57 (br. s., 1H), 4.02 (t, J = 5.6 Hz, 2H), 4.43 (s, 2H), 6.94 (d, J = 7.6 Hz, 4H), 7.27 – 7.32 (m, 4H), 7.90 (d, J = 7.6 Hz, 1H).</p>

8		2-(4-chlorophenoxy)-N-((1-(4-chlorophenoxy)acetyl)piperidin-4-yl)methylacetamide	451.1	0.90 – 0.93 (m, 1H), 1.06 – 1.09 (m, 1H), 1.55 – 1.67 (m, 3H), 2.47 – 2.52 (m, 1H), 2.91 – 3.01 (m, 3H), 3.76 (d, <i>J</i> = 13.2 Hz, 1H), 4.23 (q, <i>J</i> = 12.4 Hz, 1H), 4.46 (s, 2H), 4.77 (q, <i>J</i> = 11.4 Hz, 2H), 6.90 (d, <i>J</i> = 8.8 Hz, 2H), 6.95 (d, <i>J</i> = 9.2 Hz, 2H), 7.27 – 7.33 (m, 4H), 8.09 (br. s., 1H).
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Example 9

N-(1-(2-((5-chloroisothiazol-3-yl)oxy)ethyl)piperidin-4-yl)-2-(4-chlorophenoxy)acetamide



Step 1: To a stirred solution of 5-chloroisothiazol-3(2H)-one (0.3 g, 2.21 mmol, 1 equiv) in THF was added DBU (0.6 mL, 4.42 mmol, 2 equiv) drop wise under cooling condition, it was stirred for 5 mins at 0 °C, after that 1,2-dibromoethane (0.4 mL, 4.42 mmol, 2 equiv) was added drop wise under cooling condition, reaction mixture was stirred at room

temperature for 3 hours, reaction mixture was quenched with saturated NH₄Cl solution, aqueous layer was extracted with (2 X 15 mL) of ethyl acetate, combined organic layers were dried over under anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to get crude product, crude product which was purified by silicagel column chromatography using 7 – 8 % ethyl acetate in hexane as an eluent to get afford titled compound 3-(2-bromoethoxy)-5-chloroisothiazole (0.06 g, 11.21 %, Brown solid).¹H NMR (400 MHz, CDCl₃-d6): δ 3.63 – 3.66 (m, 2 H), 4.61 – 4.64 (m, 2 H), 6.56 (s, 1 H).

Step 2: To a stirred solution of 3-(2-bromoethoxy)-5-chloroisothiazole (0.059 g, 0.24 mmol, 1.5 equiv) in ACN (10 mL) was added Cesium carbonate (0.13 g, 0.4 mmol, 2.5 equiv), TEA (0.06 mL, 0.40, 2.5 equiv) and 2-(4-chlorophenoxy)-N-(piperidin-4-yl)acetamide hydrochloride (0.05 g, 0.16 mmol, 2.5 equiv) portion wise at 0 °C. Then reaction mixture was stirred at 85 °C for 4 hours. Reaction mixture was diluted with ice cold water (20 mL), extracted with (2 X 25 mL) ethyl acetate. Combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure, Crude product which was purified by Prep TLC using 5 % MeOH in DCM as an eluent to get afford titled compound N-(1-(2-((5-chloroisothiazol-3-yl)oxy)ethyl)piperidin-4-yl)-2-(4-chlorophenoxy)acetamide (0.0051 g, 7.2 %, Light yellow solid), LCMS (ES) *m/z* = 430 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d6): δ 1.40 – 1.48 (m, 2 H), 1.63 – 1.66 (m, 2 H), 2.02 – 2.08 (m, 2 H), 2.64 – 2.65 (m, 2 H), 2.81 – 2.84 (m, 2 H), 3.57 – 3.59 (m, 1 H), 4.32 – 4.35 (m, 2 H), 4.43 (s, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 7.04 (s, 1 H), 7.32 (d, *J* = 8.8 Hz, 2 H), 7.90 (d, *J* = 7.6 Hz, 1 H).

The Compounds of Example 10 was prepared generally according to the procedures described above for Example 9.

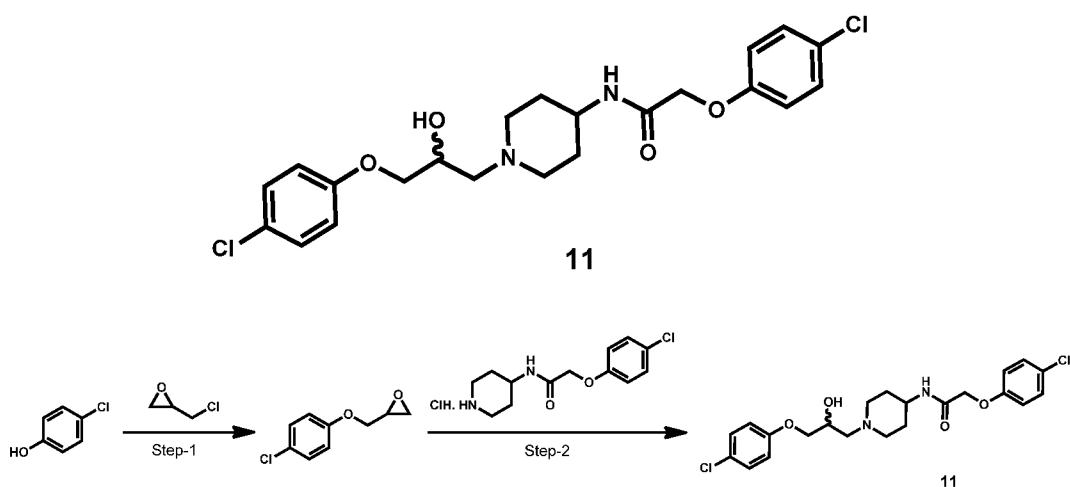
Table 2

Cmpd #	Structure	Name	LCMS <i>m/z</i> [M+H] ⁺	¹ H-NMR (400 MHz, DMSO-d ₆)
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9		N-(1-(2-((5-chloroisothiazol-3-yl)oxy)ethyl)piperidin-4-yl)-2-(4-chlorophenoxy)acetamide	430	1.40 – 1.48 (m, 2 H), 1.63 – 1.66 (m, 2 H), 2.02 – 2.08 (m, 2 H), 2.64 – 2.65 (m, 2 H), 2.81 – 2.84 (m, 2 H), 3.57 – 3.59 (m, 1 H), 4.32 – 4.35 (m, 2 H), 4.43 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.04 (s, 1 H), 7.32 (d, J = 8.8 Hz, 2 H), 7.90 (d, J = 7.6 Hz, 1 H).
10		N-(1-(3-((5-chloroisothiazol-3-yl)oxy)propyl)piperidin-4-yl)-2-(4-chlorophenoxy)acetamide	441.1	1.44 – 1.46 (m, 2 H), 1.65 – 1.67 (m, 2 H), 1.78 – 1.85 (m, 2 H), 1.93 (bs, 2 H), 2.30 – 2.40 (m, 2 H), 2.77 (bs, 2 H), 3.58 (bs, 1 H), 4.28 (t, J = 6.2 Hz, 2 H), 4.43 (s, 2 H), 6.94 (d, J = 8.4 Hz, 2 H), 7.01 (s, 1 H), 7.31 (d, J = 8.8 Hz, 2 H), 7.90 (d, J = 6.8 Hz, 1 H).

Example 11

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-hydroxypropyl)piperidin-4-yl)acetamide



Step 1: To a stirred solution of 4-chlorophenol (1.0 g, 7.78 mmol) in acetone (50 mL) was added potassium carbonate (3.2 g, 23.33 mmol) followed by 2-(chloromethyl)oxirane (2.4 mL, 31.11 mmol) drop wise and the reaction mixture was refluxed for 16h. After completion of the reaction, reaction mixture was filtered by sintered funnel and concentrated under reduced pressure and the crude was purified by silica-gel column chromatography by using 8% EA: Hex Yield: 1.3 g (85.71%) as pale yellow liquid. ^1H NMR (400 MHz, CDCl_3): δ ppm: 2.74 – 2.75 (m, 1 H), 2.89 – 2.91 (m, 1H), 3.32 – 3.35 (m, 1H), 3.9 – 3.94 (m, 1H), 4.21 (dd, $J_1=10.8$ Hz, $J_2= 2.8$ Hz, 1H), 6.83 – 6.87 (m, 2H), 7.19 – 7.24 (m, 2H).

Step 2: To a stirred solution of 2-(4-chlorophenoxy)-N-(piperidin-4-yl)acetamide hydrochloride (1.0 g, 3.27 mmol) in ethanol (20 mL) was added triethylamine (0.91 mL, 6.55 mmol) followed by 2-((4-chlorophenoxy)methyl)oxirane (0.91 g, 4.91 mmol) and the reaction mixture was stirred at rt (29 °C) for 16 h. After completion of the reaction, reaction mixture was concentrated under reduced pressure and the crude product was purified by silica-gel column chromatography by using 4% MeOH: DCM as an eluent to get the product and the position of the hydroxyl group was confirmed by ^{13}NMR , COSY, HSQC and HMBC NMR. Yield: 0.9 g (60.8%) as a white solid. LC-MS (ES) m/z : 453.6 [$\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ ppm: 1.42 – 1.5 (m, 2 H), 1.63 – 1.66 (m, 2 H), 2.01 – 2.09 (m, 2 H), 2.29 – 2.48 (m, 2 H), 2.77 – 2.85 (m, 2 H), 3.57 – 3.59 (m, 1 H), 3.81 – 3.85 (m, 1 H), 3.88 – 3.89 (m, 1 H), 3.94 – 3.96 (m, 1 H), 4.43 (s, 2 H), 4.78 (d, $J= 4.0$ Hz, 1 H), 6.94 (d, $J= 8.0$ Hz, 4 H), 7.30 (t, $J= 8.8$ Hz, 4 H), 7.89 (d, $J= 8.0$ Hz, 1H).

The Compounds of Examples 12 and 13 were prepared generally according to the procedures described above for Example 11.

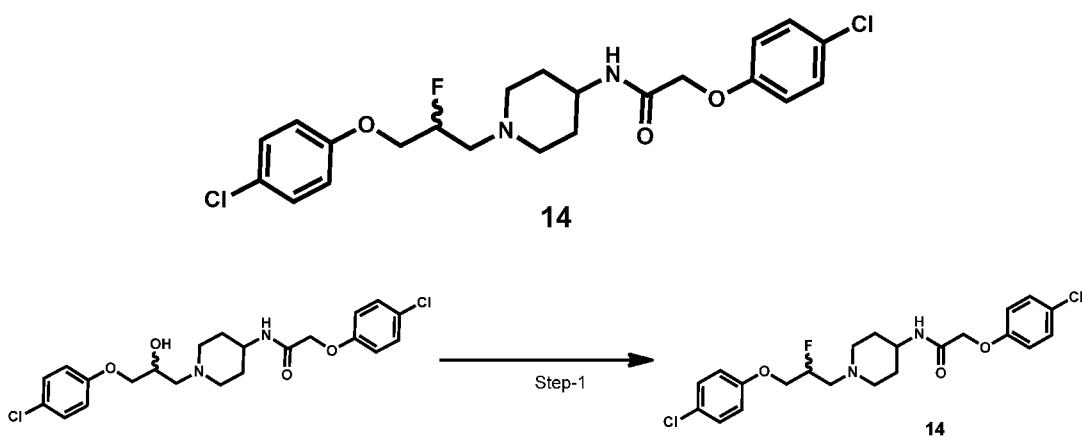
Table 3

Cmpd #	Structure	Name	LCMS <i>m/z</i> [M+H] ⁺	¹ H-NMR (400 MHz, DMSO-d ₆)
11		2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-hydroxypropyl)peridin-4-yl)acetamide	453.6	1.42 – 1.50 (m, 2 H), 1.63 – 1.66 (m, 2 H), 2.01 – 2.09 (m, 2 H), 2.29 – 2.48 (m, 2 H), 2.77 – 2.85 (m, 2 H), 3.57 – 3.59 (m, 1 H), 3.81 – 3.85 (m, 1 H), 3.88 – 3.89 (m, 1 H), 3.94 – 3.96 (m, 1 H), 4.43 (s, 2 H), 4.78 (d, <i>J</i> = 4.0 Hz, 1 H), 6.94 (d, <i>J</i> = 8.0 Hz, 4 H), 7.30 (t, <i>J</i> = 8.8 Hz, 4 H), 7.89 (d, <i>J</i> = 8.0 Hz, 1 H).
12		(R)-2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-hydroxypropyl)peridin-4-yl)acetamide	453.1	1.42 – 1.49 (m, 2 H), 1.63 (bs, 2 H), 2.09 – 2.01 (m, 2 H), 2.31 – 2.42 (m, 2 H), 2.77 – 2.85 (m, 2 H), 3.57 – 3.59 (m, 1 H), 3.81 – 3.96 (m, 3 H), 4.43 (s, 2 H), 4.78 (d, <i>J</i> = 4.4 Hz, 1 H), 6.94 (d, <i>J</i> = 8.8 Hz, 4 H), 7.3 (t, <i>J</i> = 8.8 Hz, 4 H), 7.89 (d, <i>J</i> = 7.6 Hz, 1 H).

13	 Isomer 2	(S)-2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-hydroxypropyl)piperidin-4-yl)acetamide	453.1	1.42 – 1.49 (m, 2 H), 1.63 (bs, 2 H), 2.09 – 2.01 (m, 2 H), 2.31 – 2.42 (m, 2 H), 2.77 – 2.85 (m, 2 H), 3.57 – 3.59 (m, 1 H), 3.81 – 3.96 (m, 3 H), 4.43 (s, 2 H), 4.78 (d, J = 4.4 Hz, 1 H), 6.94 (d, J = 8.8 Hz, 4 H), 7.32 – 7.28 (m, 4 H), 7.89 (d, J = 7.6 Hz, 1 H).
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Example 14

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-fluoropropyl)piperidin-4-yl)acetamide



Step 1: To a stirred solution of 2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-hydroxypropyl)piperidin-4-yl)acetamide (0.05 g, 0.11 mmol) in DCM, DAST (0.03 mL, 0.22 mmol) was added at 0°C and followed by ethanol 0.1 mL was added and stirred the reaction mixture was stirred at rt(29°) for 16h. After completion of the reaction, reaction mixture was quenched with DCM 5 mL, and diluted with water 50 mL and extracted with

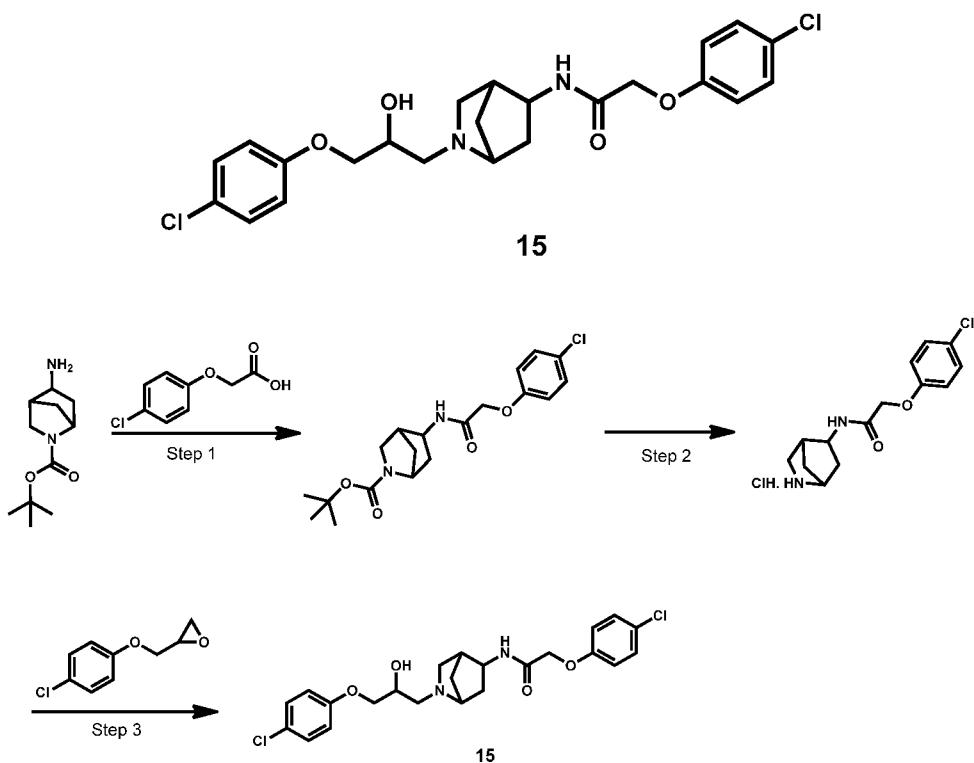
DCM 50 mL X 2, the combined organic layer was washed with sodium bicarbonate solution and dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure and the crude product was purified by prep.TLC by using 50% EA: Hex as an eluent to get the product. Yield: 0.0119 g (11.9%) as a white solid. LC-MS (ES) m/z: 455.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO- d_6): δ ppm 1.43 – 1.51 (m, 2 H), 1.64 – 1.67 (m, 2 H), 2.11 – 2.13 (m, 2 H), 2.58 – 2.58 (m, 2 H), 2.81 – 2.84 (m, 2 H), 3.58 – 3.6(m, 1H), 4.06 – 4.23 (m, 2 H), 4.44 (s, 2 H), 4.88 – 5.0 (m, 1 H), 6.96 (t, J = 10.0 Hz, 4 H), 7.31 (d, J = 8.8 Hz, 4 H), 7.90 (d, J = 7.2 Hz, 1 H).

Table 4

Cm pd #	Structure	Name	LCMS m/z [M+H] ⁺	^1H -NMR (400 MHz, DMSO- d_6)
14		2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-fluoropropyl)pyridin-4-yl)acetamide	455.1	1.43 – 1.51 (m, 2 H), 1.64 – 1.67 (m, 2 H), 2.11 – 2.13 (m, 2 H), 2.58 – 2.58 (m, 2 H), 2.81 – 2.84 (m, 2 H), 3.58 – 3.6(m, 1H), 4.06 – 4.23 (m, 2 H), 4.44 (s, 2 H), 4.88 – 5.0 (m, 1 H), 6.96 (t, J = 10.0 Hz, 4 H), 7.31 (d, J = 8.8 Hz, 4 H), 7.90 (d, J = 7.2 Hz, 1 H).

Example 15

2-(4-chlorophenoxy)-N-(2-(3-(4-chlorophenoxy)-2-hydroxypropyl)-2-azabicyclo[2.2.1]heptan-5-yl)acetamide



Step 1: To 2-(4-chlorophenoxy)acetic acid (0.52 g, 1.81 mmol, 2.83 equiv) in DCM (15 mL) at 0 °C was added triethylamine (0.78 mL, 5.66 mmol, 3.0 equiv) and was stirred for 5 minutes at 0 °C, T3P (50 wt % in ethyl acetate) (2.4 mL, 3.77 mmol, 2 equiv) was added and the reaction mixture was stirred at 0 ° for 10 mins. After that tert-butyl 5-amino-2-azabicyclo[2.2.1]heptane-2-carboxylate (0.4 g, 1.88 mmol, 1.0 equiv.) was added to the reaction mixture, reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was then diluted with water (15 mL) and extracted with DCM (2 x 10 mL). The combined organic extract was washed with saturated aqueous NaHCO₃ solution (10 mL) and water (15 mL), precipitated the solid, precipitated was filtered through a sintered funnel, washed with ice-cold water (10 mL), finally washed with n-pentane (100 mL) dried under high vacuum to give to give tert-butyl 5-(2-(4-chlorophenoxy)acetamido)-2-azabicyclo[2.2.1]heptane-2-carboxylate (0.7 g, 98 %, as a Brown liquid) LC-MS: 381 [M+H]⁺, ¹H NMR (400 MHz, DMSO-d₆): δ 1.30 – 1.36 (m, 9 H), 1.50 – 1.51 (m, 2 H), 1.52 – 1.53 (m, 1 H), 1.96 – 2.10 (m, 2 H), 3.00 – 3.32 (m, 2 H), 4.00 – 4.03 (m, 2 H), 4.45 – 4.50 (m, 2 H), 6.92 – 6.95 (m, 2 H), 7.32 (d, *J* = 6.4 Hz, 2 H), 8.03 – 8.21 (m, 1 H).

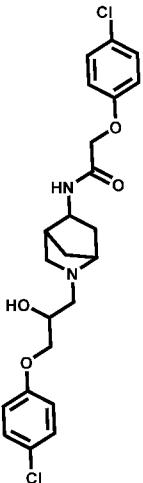
Step 2: To a solution of tert-butyl 5-(2-(4-chlorophenoxy)acetamido)-2-azabicyclo[2.2.1]heptane-2-carboxylate (0.7 g, 1.84 mmol, 1.0 equiv) in DCM (15 mL)

was added and 4.0 M in dioxane.HCl (10 mL) was added and stirred it for 12 h. After consumption of the starting material (TLC, 5 % Methanol in DCM), DCM was evaporated under reduced pressure. The solid obtained was triturated with n-pentane (10 mL) , diethyl ether (10 mL), dried under high vacuum to give N-(2-azabicyclo[2.2.1]heptan-5-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.55 g , crude). LC-MS: 281 [M+H]⁺ (free base) ¹H NMR (400 MHz, DMSO-d₆): δ 1.53 – 1.61 (m, 1 H), 1.66 – 1.69 (m, 1 H), 1.78 – 1.83 (m, 1 H), 2.03 – 2.17 (m, 1 H), 2.65 – 2.69 (m, 1 H), 2.85 – 2.90 (m, 1 H), 2.91 – 2.98 (m, 1 H), 3.00 – 3.19 (m, 0.5 H), 3.20 – 3.32 (m, 0.5 H), 3.81 – 3.90 (m, 0.5 H), 3.94 – 4.00 (m, 1 H), 4.15 – 4.16 (m, 0.5 H), 4.47 – 4.51 (m, 2 H), 6.95 (d, *J* = 8.8 Hz, 1 H), 7.03 (d, *J* = 8.8 Hz, 1 H), 7.31 – 7.34 (m, 2 H), 8.17 – 8.21 (m, 1 H), 8.36 (bs, 1 H), 8.79 (bs, 1 H).

Step 3: To a stirred solution of compound N-(2-azabicyclo[2.2.1]heptan-5-yl)-2-(4-chlorophenoxy)acetamide hydrochloride (0.15 g, 0.47 mmol, 1 equiv) in ethanol was added TEA (0.2 mL , 1.41 mmol, 3 equiv) drop wise under cooling condition , reaction mixture was stirred for 5 mins, after that 2-((4-chlorophenoxy)methyl)oxirane (0.10 g, 0.56 mmol, 1.2 equiv) was added to reaction mixture drop wise under cooling condition ,reaction mixture was stirred at room temperature (29 °C) for 12 hours, after completion of the reaction , reaction mass was evaporated under reduced pressure to get the crude product, obtained crude was quenched with 10 mL of water, extracted with (2 X 15 mL) of DCM, combined organic layers were washed with 10 mL of brine , organic layer was dried over under anhydrous Na₂SO₄ , filtered and concentrated under reduced pressure to get the crude product. The crude product which was purified by silicagel column chromatography using 5 % MeOH in DCM as an eluent to give the 2-(4-chlorophenoxy)-N-(2-(3-(4-chlorophenoxy)-2-hydroxypropyl)-2-azabicyclo[2.2.1]heptan-5-yl)acetamid ,0.05 g (22.72 %, as gummy solid),LC-MS: 465.1 [M+H]⁺,¹H NMR (400 MHz, DMSO-d₆): δ 1.27 – 1.30 (m, 0.5 H), 1.40 – 1.47 (m, 2 H), 1.62 – 1.64 (m, 1 H), 1.79 – 1.88 (m, 1 H), 2.07 – 2.17 (m, 1 H), 2.47 (s, 1 H), 2.48 (s, 1 H), 2.65 (s, 0.5 H), 2.20 – 2.30 (m, 0.5 H), 3.12 – 3.32 (m, 1 H), 3.60 – 3.70 (m, 0.5 H), 3.80 – 3.86 (m, 2 H), 3.94 – 4.00 (m, 2 H), 4.43 – 4.49 (m, 2 H), 4.60 – 4.90 (m, 1 H), 6.92 – 6.95 (m, 4 H), 7.28 – 7.32 (m, 4 H), 7.91 – 8.04 (m, 1 H).

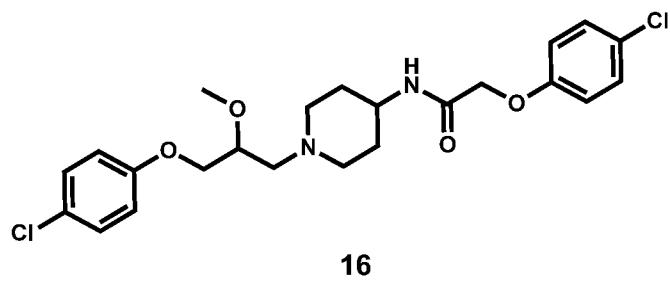
Table 5

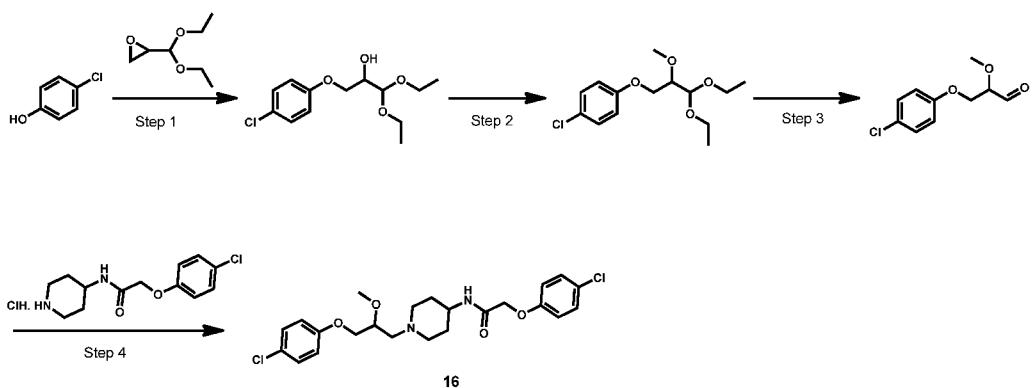
Cmpd #	Structure	Name	LCMS <i>m/z</i> [M+H] ⁺	¹ H-NMR (400 MHz, DMSO-d ₆)
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15	 <p>2-(4-chlorophenoxy)-N-(2-(3-(4-chlorophenoxy)-2-hydroxypropyl)-2-azabicyclo[2.2.1]heptan-5-yl)acetamide</p>	465.1	1.27 – 1.30 (m, 0.5 H), 1.40 – 1.47 (m, 2 H), 1.62 – 1.64 (m, 1 H), 1.79 – 1.88 (m, 1 H), 2.07 – 2.17 (m, 1 H), 2.47 (s, 1 H), 2.48 (s, 1 H), 2.65 (s, 0.5 H), 2.20 – 2.30 (m, 0.5 H), 3.12 – 3.32 (m, 1 H), 3.60 – 3.70 (m, 0.5 H), 3.80 – 3.86 (m, 2 H), 3.94 – 4.00 (m, 2 H), 4.43 – 4.49 (m, 2 H), 4.60 – 4.90 (m, 1 H), 6.92 – 6.95 (m, 4 H), 7.28 – 7.32 (m, 4 H), 7.91 – 8.04 (m, 1 H).
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Example 16

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-methoxypropyl)piperidin-4-yl)acetamide





Step 1: To a stirred solution of 24-chlorophenol (2.0 g, 15.56 mmol, 1equiv) in water (20mL), triethylamine (6.5 mL, 46.67 mmol, 3equiv) was added the reaction mixture was stirred at rt(27°) for 16h. After completion of the reaction, reaction mixture was extracted with DCM 50 mL x 2, the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product. The crude product was purified by silica gel column chromatography by using 8% EA: Hex. Yield: 1.5 g (34.88%) as colorless liquid. ^1H NMR (400 MHz, CDCl_3): δ ppm: 1.21 (t, J = 6.8 Hz, 3 H), 1.25 (t, J = 7.2 Hz, 3 H), 3.57 – 3.65 (m, 2 H), 3.75 - 3.84 (m, 2 H), 3.96 (bs, 1 H), 4.00 - 4.04 (m, 1 H), 4.11 – 4.15 (m, 1 H), 4.60 (d, J = 5.6 Hz, 1 H), 6.87 (d, J = 9.2 Hz, 2 H), 7.22 (d, J = 8.8 Hz, 2 H).

Step 2: To a stirred solution of 3-(4-chlorophenoxy)-1,1-diethoxypropan-2-ol(1.5 g, 5.45 mmol, 1 equiv) in THF (10 mL), 60% NaH (0.44 g, 21.82 mmol, 4 equiv) was added at 0°C and stirred the reaction mixture at rt(27°) for 30 min. Finally methyl iodide was added to the reaction mixture at 0°C and allowed the reaction mixture to stir at rt (27 °C) for 2 h. After completion of the reaction, reaction mixture was quenched with ice and extracted with ethyl acetate 100 mL, the organic layer was separated and dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product. The crude product was purified by silica gel column chromatography by using 9% EA;Hex. Yield: 1.3 g (82.80%) as colorless liquid. ^1H NMR (400 MHz, CDCl_3): δ ppm: 1.19 (t, J = 7.2 Hz, 3 H), 1.25 (t, J = 6.8 Hz, 3 H), 3.53 – 3.55 (m, 5 H), 3.58 – 3.67 (m, 1 H), 3.71 – 3.78 (m, 2 H), 4.02 - 4.06 (m, 1 H), 4.19 (dd, J = 2.4, 10.4 Hz, 1 H), 4.57 (d, J = 5.2 Hz, 1 H), 6.86 (d, J = 8.8 Hz, 2 H), 7.21 (d, J = 8.8 Hz, 2H).

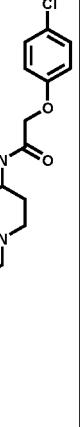
Step 3: To a stirred solution of 1-chloro-4-(3,3-diethoxy-2-methoxypropoxy)benzene(1.0 g, 3.46 mmol, 1.0 equiv) in acetone (10 mL), 2N HCl (10 mL) was added drop wise at rt (27 °C) and heated the reaction mixture at 50 °C for 16 h. After completion of the reaction, reaction mixture was concentrated under reduced pressure and diluted the crude with 10

mL of water and extracted with DCM (50 mL x 2), the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated to get the crude product and the crude product was carried to next step without any purification. Weight: 0.7 g crude as brown liquid. ^1H NMR (400 MHz, CDCl_3): δ ppm: 3.59 (s, 1 H), 3.95 (s, 1 H), 4.17 – 4.26 (m, 1 H), 4.26 – 4.29 (m, 1 H), 6.84 (d, J = 8.4 Hz, 2 H), 7.23 (d, J = 8.4 Hz, 2 H), 9.81 (s, 1H).

Step 4: 2-(4-chlorophenoxy)-N-(piperidin-4-yl)acetamide hydrochloride was taken in 20mL of DCM and cooled to 0 °C and added saturated solution of sodium bicarbonate solution to pH = 7 and then extracted with DCM, organic layer was dried over anhydrous sodium sulphate, filtered and concentrated to get the pre base amine. To a solution of 2-(4-chlorophenoxy)-N-(piperidin-4-yl)acetamide (0.15 g, 0.491 mmol, 1 equiv) in dichloroethane, 3-(4-chlorophenoxy)-2-methoxypropanal (0.21 g, 0.982 mmol, 2 equiv) was added followed by 3 drops of acetic acid were added and stirred at rt (27 °C) for 30 min. Finally to the suspension sodium cyanoborohydride was added and stirred the reaction mixture at rt (27 °C) for 16 h. After completion of the reaction, reaction mixture was diluted with 50 mL of water and extracted with DCM (50 mL x 2), the combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated to get the crude product and the crude product was purified by prep TLC by using 5% MeOH:DCM as an eluent to get the pure product. Yield: 0.021 g (9.5%), as white solid. LC-MS (ES) m/z : 467.1 [M+H] $^+$. ^1H NMR (400 MHz, DMSO-d_6): δ ppm: 1.41 – 1.49 (m, 2 H), 1.63 – 1.70 (m, 2 H), 2.42 – 2.43 (m, 2 H), 2.81 (t, J = 10.8 Hz, 2 H), 3.33 (s, 3 H), 2.6 – 3.59 (m, 2 H), 3.96 – 3.92 (m, 1 H), 4.07 (dd, J = 3.2, 10.4 Hz, 1 H), 4.43 (s, 2 H), 6.94 – 6.97 (m, 4 H), 7.29 – 7.33 (m, 4 H), 7.88 (d, J = 7.6 Hz, 1 H).

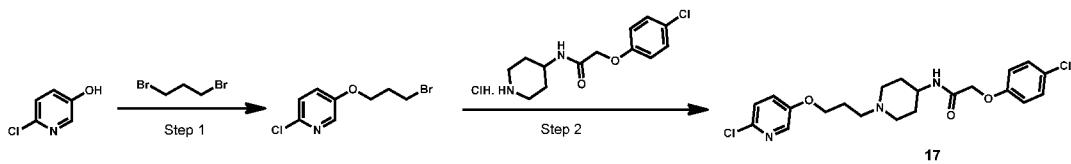
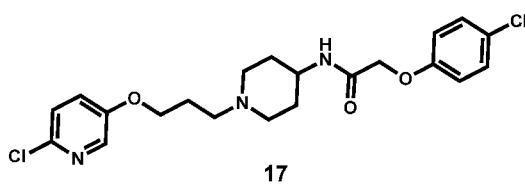
Table 6

Cmpd #	Structure	Name	LCMS m/z [M+H] $^+$	$^1\text{H-NMR}$ (400 MHz, DMSO-d_6)
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16		2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-methoxypropyl)piperidin-4-yl)acetamide	467.1	1.41 – 1.49 (m, 2 H), 1.63 – 1.70 (m, 2 H), 2.42 – 2.43 (m, 2 H), 2.81 (t, J = 10.8 Hz, 2 H), 3.33 (s, 3 H), 2.60 – 3.59 (m, 2 H), 3.96 – 3.92 (m, 1 H), 4.07 (dd, J = 3.2, 10.4 Hz, 1 H), 4.43 (s, 2 H), 6.94 – 6.97 (m, 4 H), 7.29 – 7.33 (m, 4 H), 7.88 (d, J = 7.6 Hz, 1 H).
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Example 17

2-(4-chlorophenoxy)-N-(1-(3-((6-chloropyridin-3-yl)oxy)propyl)piperidin-4-yl)acetamide



Step 1: To a solution of 6-chloropyridin-3-ol (0.3 g, 2.315 mmol, 1.0 equiv) in *N,N*-dimethylformamide (5 mL) was added potassium carbonate (0.48 g, 3.473 mmol, 1.5 equiv) and 1,3-dibromopropane (0.48 g, 3.473 mmol, 1.5 equiv) at 27 °C. The resulting mixture was stirred at 27 °C for 16 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with

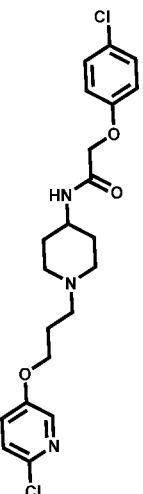
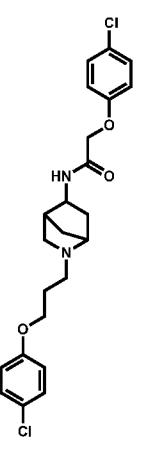
cold water (50 mL), brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get the crude product. The crude product was purified by silicagel column chromatography using 10% ethyl acetate in hexane as eluent to obtain the title compound 5-(3-bromopropoxy)-2-chloropyridine (0.3 g, crude) as white solid. LCMS (ES) m/z = 250 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ ppm 2.30 – 2.36 (m, 2 H), 3.59 (t, J = 1.7 Hz, 2 H), 4.14 (t, J = 6.0 Hz, 2 H), 7.18 – 7.22 (m, 2 H), 8.07 (d, J = 1.6 Hz, 1 H).

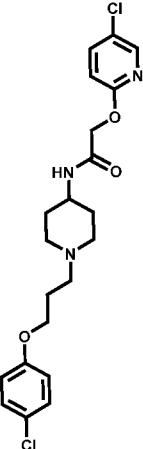
Step 2: To a stirred solution of 2-(4-chlorophenoxy)-N-(piperidin-4-yl)acetamide hydrochloride (0.1 g, 0.327 mmol, 1.0 equiv) in *N,N*-dimethylmethanamide (10 mL) was added cesium carbonate (0.16 g, 0.491 mmol, 1.5 equiv), triethyl amine (0.09 mL, 0.655 mmol, 2.0 equiv) and 5-(3-bromopropoxy)-2-chloropyridine (0.098 g, 0.393 mmol, 1.2 equiv) at 27 °C. The resulting mixture was stirred at 27 °C for 16 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (50 mL), the product was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with cold water (25 mL), brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get the crude product. The crude product was purified by silicagel column chromatography using 5% methanol in dichloromethane as eluent to obtain the title compound 2-(4-chlorophenoxy)-N-(1-(3-((6-chloropyridin-3-yl)oxy)propyl)piperidin-4-yl)acetamide (0.07 g, 48.9 % yield) as white solid. LCMS (ES) m/z = 438.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ ppm 1.41 – 1.49 (m, 2 H), 1.65 – 1.67 (m, 2 H), 1.82 – 1.85 (m, 2 H), 1.91 – 1.97 (m, 2 H), 2.38 (t, J = 6.4 Hz, 2 H), 2.78 (d, J = 11.2 Hz, 2 H), 3.58 – 3.59 (m, 1 H), 4.06 (t, J = 6.4 Hz, 2 H), 4.43 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.31 (d, J = 8.8 Hz, 2 H), 7.39 (d, J = 8.8 Hz, 1 H), 7.44 – 7.47 (m, 1 H), 7.90 (d, J = 8.0 Hz, 1 H), 8.08 (d, J = 2.4 Hz, 1 H).

The Compounds of Examples 18 and 19 were prepared generally according to the procedures described above for Example 17.

Table 7

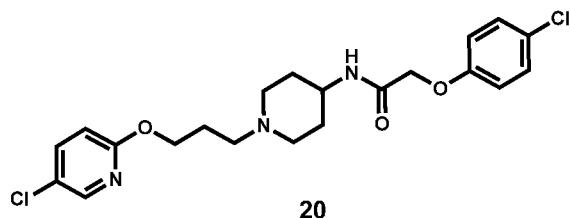
Cmpd #	Structure	Name	LCMS m/z [M+H] ⁺	¹ H-NMR (400 MHz, DMSO-d ₆)
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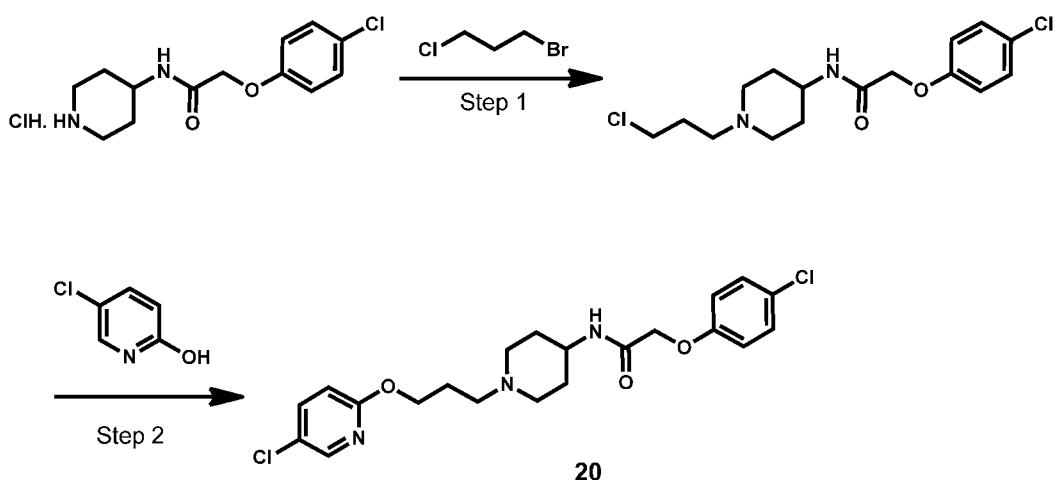
17		2-(4-chlorophenoxy)-N-(1-(3-((6-chloropyridin-3-yl)oxy)propyl)peridin-4-yl)acetamide	438.3	1.41 – 1.49 (m, 2 H), 1.65 – 1.67 (m, 2 H), 1.82 – 1.85 (m, 2 H), 1.91 – 1.97 (m, 2 H), 2.38 (t, J = 6.4 Hz, 2 H), 2.78 (d, J = 11.2 Hz, 2 H), 3.58 – 3.59 (m, 1 H), 4.06 (t, J = 6.4 Hz, 2 H), 4.43 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.31 (d, J = 8.8 Hz, 2 H), 7.39 (d, J = 8.8 Hz, 1 H), 7.44 – 7.47 (m, 1 H), 7.90 (d, J = 8.0 Hz, 1 H), 8.08 (d, J = 2.4 Hz, 1 H).
18		2-(4-chlorophenoxy)-N-(2-(3-(4-chlorophenoxy)propyl)-2-azabicyclo[2.2.1]heptan-5-yl)acetamide	449.1	1.23 – 1.54 (m, 2 H), 1.55 – 1.64 (m, 1 H), 1.65 – 1.90 (m, 3 H), 1.92 – 2.15 (m, 2 H), 2.34 – 2.42 (m, 2 H), 2.50 – 2.62 (m, 1 H), 2.90 – 3.12 (m, 1 H), 3.60 – 3.70 (m, 0.5 H), 3.88 – 3.95 (m, 0.5 H), 3.98 (d, J = 4.4 Hz, 2 H), 4.47 (d, J = 22.8 Hz, 2 H), 6.92 – 6.94 (m, 4 H), 7.28 – 7.32 (m, 4 H), 7.97 (bs, 1 H), 8.82 (bs, 0.2 H).

19		N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-((5-chloropyridin-2-yl)oxy)acetamide	438.1	1.36 – 1.44 (m, 2 H), 1.63 – 1.66 (m, 2 H), 1.81 (t, J = 6.8 Hz, 2 H), 1.92 (t, J = 11.2 Hz, 2 H), 2.36 (t, J = 6.8 Hz, 2 H), 2.75 – 2.78 (m, 2 H), 3.53 – 3.55 (m, 1 H), 3.96 (t, J = 6.0 Hz, 2 H), 4.65 (s, 2 H), 6.91 – 6.94 (m, 3 H), 7.28 (d, J = 8.8 Hz, 2 H), 7.79 – 7.85 (m, 2 H), 8.14 (s, 1 H).
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Example 20

2-(4-chlorophenoxy)-N-(1-(3-((5-chloropyridin-2-yl)oxy)propyl)piperidin-4-yl)acetamide





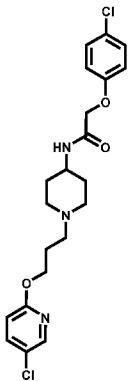
Step 1: To a mixture of 2-(4-chlorophenoxy)-*N*-(piperidin-4-yl)acetamide hydrochloride (0.5 g, 1.638 mmol, 1.0 equiv) in dichloromethane (20 mL) was added potassium carbonate (0.45 g, 3.276 mmol, 2.0 equiv) and 1-bromo-3-chloropropane (0.51 g, 3.276 mmol, 2.0 equiv) at 27 °C, the resulting mixture was stirred for 24 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (50 mL), the product was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get the crude product. The crude product was purified by silicagel column chromatography using 4% methanol in dichloromethane as eluent to obtain the title compound 2-(4-chlorophenoxy)-*N*-(1-(3-chloropropyl)piperidin-4-yl)acetamide (0.21 g, 37 % yield) as off white solid. LCMS (ES) *m/z* = 345.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ ppm 1.41 – 1.48 (m, 2 H), 1.64 – 1.67 (m, 2 H), 1.81 – 1.84 (m, 2 H), 1.91 – 1.96 (m, 2 H), 2.30 – 2.36 (m, 2 H), 2.65 – 2.73 (m, 2 H), 3.61 – 3.64 (m, 3 H), 4.43 (s, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 7.32 (d, *J* = 8.8 Hz, 2 H), 7.90 (d, *J* = 8.0 Hz, 1 H).

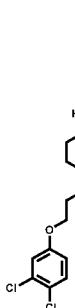
Step 2: In microwave vial, to a stirred solution of 2-(4-chlorophenoxy)-*N*-(1-(3-chloropropyl)piperidin-4-yl)acetamide (0.15 g, 0.434 mmol, 1.0 equiv) in *N,N*-dimethylmethanamide (3 mL) was added silver carbonate (0.24 g, 0.868 mmol, 2.0 equiv) and 5-chloropyridin-2-ol (0.056 g, 0.434 mmol, 1.0 equiv) at 27 °C. The resulting mixture was subjected to microwave irradiation at 80 °C for 1 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was filtered through celite pad, washed the celite pad with ethyl acetate (20 mL). The filtrate was washed with

water (20 mL), brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get the crude product. The crude product was purified by silicagel column chromatography using 6% methanol in dichloromethane as eluent to obtain the title compound 2-(4-chlorophenoxy)-N-(1-(3-((5-chloropyridin-2-yl)oxy)propyl)piperidin-4-yl)acetamide (0.02 g, 10 % yield), as white solid. LCMS (ES) m/z = 438.1 [M+H]⁺. ^1H NMR (400 MHz, DMSO-d₆): δ ppm 1.43 – 1.49 (m, 2 H), 1.64 – 1.67 (m, 2 H), 1.81 – 1.84 (m, 2 H), 1.90 – 1.95 (m, 2 H), 2.36 (bs, 2 H), 2.78 (d, J = 10.0 Hz, 2 H), 3.57 (bs, 1 H), 4.23 (t, J = 6.0 Hz, 2 H), 4.43 (s, 2 H), 6.83 (d, J = 8.8 Hz, 1 H), 6.94 (d, J = 8.8 Hz, 2 H), 7.31 (d, J = 8.4 Hz, 2 H), 7.74 – 7.77 (m, 1 H), 7.90 (d, J = 7.6 Hz, 1 H), 8.16 (s, 1 H).

The Compound of Example 21 was prepared generally according to the procedure described above for Example 20.

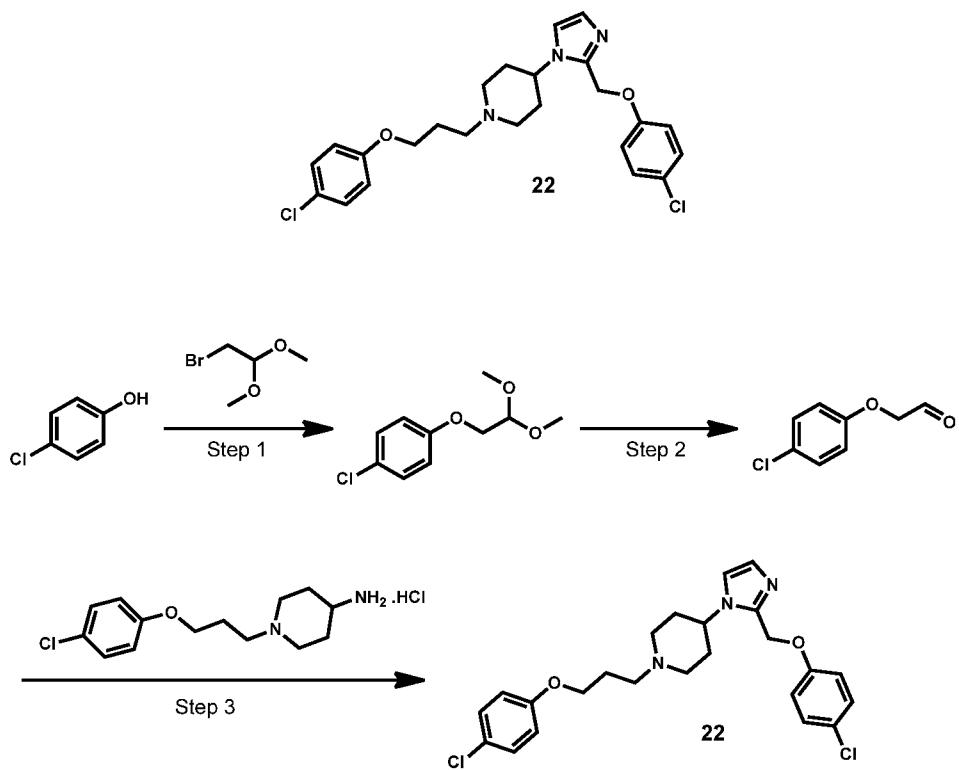
Table 8

Cmpd #	Structure	Name	LCMS m/z [M+H] ⁺	^1H -NMR (400 MHz, DMSO-d ₆)
20		2-(4-chlorophenoxy)-N-(1-(3-((5-chloropyridin-2-yl)oxy)propyl)piperidin-4-yl)acetamide	438.1	1.43 – 1.49 (m, 2 H), 1.64 – 1.67 (m, 2 H), 1.81 – 1.84 (m, 2 H), 1.90 – 1.95 (m, 2 H), 2.36 (bs, 2 H), 2.78 (d, J = 10.0 Hz, 2 H), 3.57 (bs, 1 H), 4.23 (t, J = 6.0 Hz, 2 H), 4.43 (s, 2 H), 6.83 (d, J = 8.8 Hz, 1 H), 6.94 (d, J = 8.8 Hz, 2 H), 7.31 (d, J = 8.4 Hz, 2 H), 7.74 – 7.77 (m, 1 H), 7.90 (d, J = 7.6 Hz, 1 H), 8.16 (s, 1 H).

21		2-(4-chlorophenoxy)-N-(1-(3-(3,4-dichlorophenoxy)propyl)piperidin-4-yl)acetamide	471.1	<p>1.41 – 1.49 (m, 2 H), 1.66 (d, J = 10.8 Hz, 2 H), 1.80 – 1.84 (m, 2 H), 1.94 (t, J = 11.0 Hz, 2 H), 2.36 (t, J = 6.8 Hz, 2 H), 2.78 (d, J = 10.8 Hz, 2 H), 3.58 – 3.59 (m, 1 H), 4.00 (t, J = 6.0 Hz, 2 H), 4.43 (s, 2 H), 6.91 – 6.96 (m, 3 H), 7.19 (d, J = 2.4 Hz, 1 H), 7.31 (d, J = 8.8 Hz, 2 H), 7.48 (d, J = 8.8 Hz, 1 H), δ 7.89 (d, J = 8.0 Hz, 1 H).</p>
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Example 22

4-((2-((4-chlorophenoxy)methyl)-1H-imidazol-1-yl)-1-(3-(4-chlorophenoxy)propyl)piperidine



Step 1: To a mixture of 4-chlorophenol (5.0 g, 38.892 mmol, 1.0 equiv) in *N,N*-dimethylmethanamide (10 mL) was added potassium carbonate (10.74 g, 138.2 mmol, 3.5 equiv), sodium iodide (0.58 g, 3.889 mmol, 0.1 equiv) and 2-bromo-1,1-dimethoxyethane (6.8 mL, 58.338 mmol, 1.5 equiv) at 27 °C. The resulting mixture was heated to 120 °C and stirred for 40 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (100 mL), the product was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with cold water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get the crude product. The crude product was purified by silicagel column chromatography using 20% ethyl acetate in hexane as eluent to obtain the title compound 1-chloro-4-(2,2-dimethoxyethoxy)benzene (3.2 g, 38 % yield) as colourless oil. ^1H NMR (400 MHz, CDCl₃): δ ppm 3.45 (s, 6 H), 3.97 (d, *J* = 5.2 Hz, 2 H), 4.69 (t, *J* = 4.8 Hz, 1 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 7.23 (d, *J* = 8.8 Hz, 2 H).

Step 2: To a stirred solution of 1-chloro-4-(2,2-dimethoxyethoxy)benzene (3.2 g, 14.81 mmol, 1.0 equiv) in acetone (40 mL) was added 2M hydrochloric acid (4 mL). The resulting mixture was heated to 60 °C and stirred for 6 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was concentrated under reduced pressure, the residue was diluted with water (100 mL), the product was extracted with ethyl acetate (3 x 75 mL), and the combined organics were washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get the crude product. The crude product was purified by silicagel column chromatography using 20% ethyl acetate in hexane as eluent to obtain the title compounds 2-(4-chlorophenoxy)acetaldehyde (1.8 g, crude) as colourless oil. ^1H NMR (400 MHz, CDCl₃): δ ppm 4.55 (s, 2 H), 6.76 – 6.88 (m, 2 H), 7.18 – 7.28 (m, 2 H), 9.84 (s, 1 H).

Step 3: To a stirred solution of 1-(3-(4-chlorophenoxy)propyl)piperidin-4-amine hydrochloride (0.3 g, 0.982 mmol, 1.0 equiv), 2-(4-chlorophenoxy)acetaldehyde (0.25 g, 1.474 mmol, 1.5 equiv) and glyoxal (40% in water) (0.21 g, 1.474 mmol, 1.5 equiv) in methanol (10 mL) was added ammonium acetate (0.12 g, 1.474 mmol, 1.5 equiv). The resulting mixture was heated to 80 °C and stirred for 24 h. The progress of the reaction

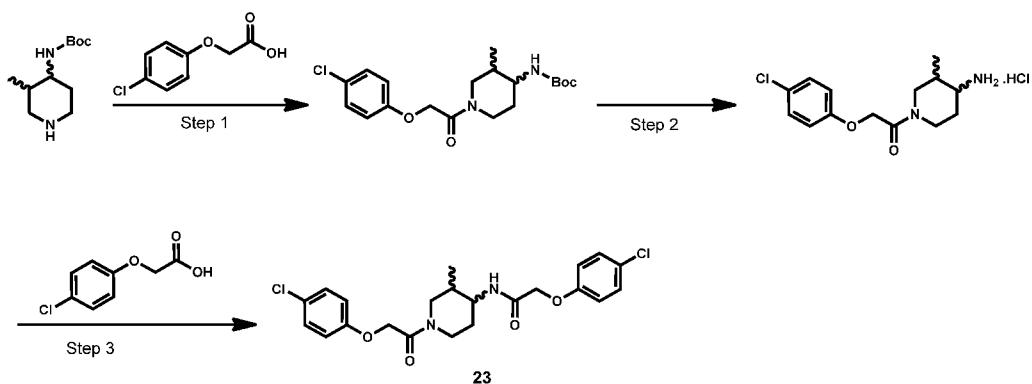
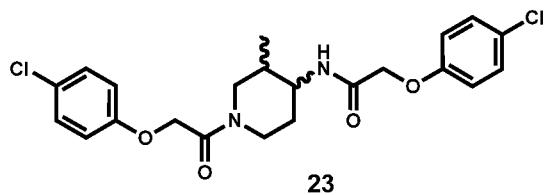
was monitored by TLC. After completion of reaction, the reaction mixture was concentrated under reduced pressure. The obtained residue was dissolved with ethyl acetate (250 mL), washed with water (100 mL), brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get the crude product. The crude product was purified by silicagel column chromatography using 6% methanol in dichloromethane as eluent to get the impure compound and it was purified by preparative HPLC [HPLC Method: Column :Inertsil ODS 3V(250mm X 4.6mm X 5mic), mobile phase(A): 0.1% NH₃ in water, mobile phase(B): acetonitrile, flow rate : 1.0 mL/min, T/%B: 0/20,10/80, 25/90,27/20,30/20] to obtain the title compound 4-(2-((4-chlorophenoxy)methyl)-1H-imidazol-1-yl)-1-(3-(4-chlorophenoxy)propyl)piperidine (0.035 g, 7.7 % yield) as white solid. LCMS (ES) *m/z* = 460.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ ppm 1.96 (bs, 6 H), 2.09 – 2.12 (m, 2 H), 2.54 – 2.57 (m, 2 H), 3.07 (d, *J* = 10.4 Hz, 2 H), 3.99 (bs, 2 H), 4.12 – 4.14 (m, 1 H), 5.15 (s, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 7.35 (d, *J* = 4.8 Hz, 2 H), 7.21 – 7.25 (m, 4 H).

Table 9

Cmpd #	Structure	Name	LCMS <i>m/z</i> [M+H] ⁺	¹ H-NMR (400 MHz, CDCl ₃)
22		4-(2-((4-chlorophenoxy)methyl)-1H-imidazol-1-yl)-1-(3-(4-chlorophenoxy)propyl)piperidine e	460.1	1.96 (bs, 6 H), 2.09 – 2.12 (m, 2 H), 2.54 – 2.57 (m, 2 H), 3.07 (d, <i>J</i> = 10.4 Hz, 2 H), 3.99 (bs, 2 H), 4.12 – 4.14 (m, 1 H), 5.15 (s, 2 H), 6.82 (d, <i>J</i> = 8.8 Hz, 2 H), 6.95 (d, <i>J</i> = 8.8 Hz, 2 H), 7.35 (d, <i>J</i> = 4.8 Hz, 2 H), 7.21 – 7.25 (m, 4 H).

Example 23

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)-3-methylpiperidin-4-

yl)acetamide

Step 1: To a stirred solution of *tert*-butyl (3-methylpiperidin-4-yl)carbamate (0.2 g, 0.933 mmol, 1.0 equiv), 2-(4-chlorophenoxy)acetic acid (0.2 g, 1.119 mmol, 1.2 equiv) and triethyl amine (1.04 mL, 7.466 mmol, 8.0 equiv) in dichloromethane (10 mL) was added propylphosphonic anhydride solution (\geq 50 wt. % in ethyl acetate) (1.18 g, 1.866 mmol, 2.0 equiv) at 0 °C. The resulting mixture was allowed to warm to 25 °C and stirred for 3 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with dichloromethane (100 mL), washed with water (2 x 30 mL), brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get the crude product. The crude product was purified by silicagel column chromatography using 5% methanol in dichloromethane as eluent to obtain the title compound *tert*-butyl (1-(2-(4-chlorophenoxy)acetyl)-3-methylpiperidin-4-yl)carbamate (0.21 g, 80 % yield) as off white solid. LCMS (ES) *m/z* = 327.0 [(M+H)⁺ - (t-butyl group)].

Step 2: To a solution of *tert*-butyl (1-(2-(4-chlorophenoxy)acetyl)-3-methylpiperidin-4-yl)carbamate (0.21 g, 0.548 mmol, 1.0 equiv) in dichloromethane (5 mL) was added 4M

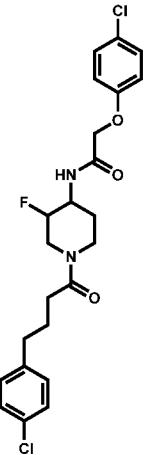
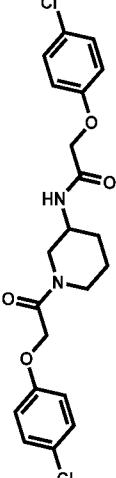
hydrochloric acid in 1, 4-dioxane (5 mL) at 0 °C. The reaction mixture was allowed to warm to 27 °C and stirred for 4 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was concentrated under reduced pressure to get the crude product. The crude product was triturated with *n*-pentane to obtain the title compound 1-(4-amino-3-methylpiperidin-1-yl)-2-(4-chlorophenoxy)ethan-1-one hydrochloride (0.23 g, crude) as off white gum, which was taken as such to next step without further purification. LCMS (ES) *m/z* = 283.1 [M+H]⁺.

Step 3: To a stirred solution of 1-(4-amino-3-methylpiperidin-1-yl)-2-(4-chlorophenoxy)ethan-1-one hydrochloride (0.12 g, 0.375 mmol, 1.0 equiv), 2-(4-chlorophenoxy)acetic acid (0.084 g, 0.451 mmol, 1.2 equiv) and triethyl amine (0.42 mL, 3.006 mmol, 8.0 equiv) in dichloromethane (10 mL) was added propylphosphonic anhydride solution (≥50 wt. % in ethyl acetate) (0.5 g, 0.751 mmol, 2.0 equiv) at 0 °C. The resulting mixture was allowed to warm to 25 °C and stirred for 3 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with dichloromethane (50 mL), washed with water (2 x 30 mL), brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get the crude product. The crude product was purified by silicagel column chromatography using 6% methanol in dichloromethane as eluent to obtain the title compound 2-(4-chlorophenoxy)-*N*-(1-(2-(4-chlorophenoxy)acetyl)-3-methylpiperidin-4-yl)acetamide (0.095 g, 59 % yield) as pale green solid. LCMS (ES) *m/z* = 451.1 [M+H]⁺.
¹H NMR (400 MHz, , DMSO-d₆): δ ppm 0.68 – 0.70, 0.77, 1.31 – 1.33 (m, 3 H), 1.57 – 1.69, 1.89 – 1.97 (m, 3 H), 2.48, 2.65 – 2.74 (m, 1 H), 3.06 – 3.09, 3.28 (m, 1 H), 3.49 – 3.59, 3.73 – 3.81 (m, 2 H), 4.02, 4.48 – 4.52 (m, 1 H), 4.48 – 4.52 (m, 2 H), 4.78 – 4.89 (m, 2 H), 6.90 – 6.96 (m, 4 H), 7.28 – 7.32 (m, 4 H), 7.92 (bs, 1 H). (Due to diasteromeric mixture the peaks were split). VT NMR at 90 °C ¹H NMR (400 MHz, , DMSO-d₆): δ ppm 0.75 – 0.81 (m, 3 H), 1.59 – 1.73 (m, 2 H), 1.97 (bs, 1 H), 3.33 – 3.42 (m, 3 H), 3.59 – 3.62 (m, 1 H), 4.04 – 4.06 (m, 1 H), 4.47 – 4.51 (m, 2 H), 4.72 – 4.77 (m, 2 H), 6.92 – 6.97 (m, 4 H), 7.27 – 7.31 (m, 4 H), 7.60 – 7.67 (m, 1 H).

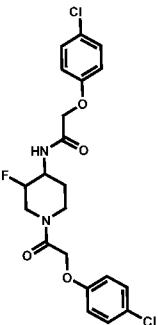
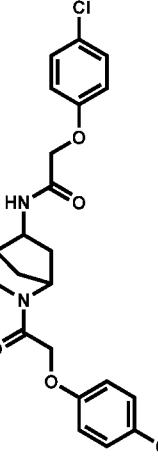
The Compounds of Examples from 24 to 37 were prepared generally according to the procedure described above for Example 23.

Table 10

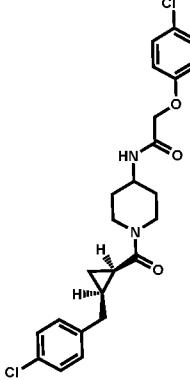
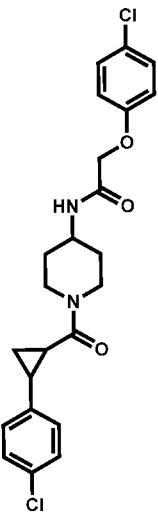
Cmpd #	Structure	Name	LCMS <i>m/z</i> [M+H] ⁺	¹ H-NMR (400 MHz, DMSO-d ₆)
23		2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)-3-methylpiperidin-4-yl)acetamide	451.1	0.75 – 0.81 (m, 3 H), 1.59 – 1.73 (m, 2 H), 1.97 (bs, 1 H), 3.33 – 3.42 (m, 3 H), 3.59 – 3.62 (m, 1 H), 4.04 – 4.06 (m, 1 H), 4.47 – 4.51 (m, 2 H), 4.72 – 4.77 (m, 2 H), 6.92 – 6.97 (m, 4 H), 7.27 – 7.31 (m, 4 H), 7.60 – 7.67 (m, 1 H).
24		N-(4-chlorophenethyl)-1-(2-(4-chlorophenoxy)acetyl)piperidine-4-carboxamide	435.1	1.31 – 1.33 (m, 1 H), 1.49 – 1.54 (m, 1 H), 1.61 (bs, 2 H), 2.27 – 2.33 (m, 1 H), 2.57 – 2.60 (m, 1 H), 2.66 – 2.69 (m, 2 H), 2.96 – 3.02 (m, 1 H), 3.21 – 3.24 (m, 2 H), 3.76 – 3.79 (m, 1 H), 4.21 – 4.24 (m, 1 H), 4.74 – 4.84 (m, 2 H), 6.91 (d, J = 8.8 Hz, 2 H), 7.19 (d, J = 8.4 Hz, 2 H), 7.30 (t, J = 8.0 Hz, 4 H), 7.78 – 7.86 (m, 1 H).
25		2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propanoyl)piperidin-4-yl)acetamide	451	1.28 – 1.34 (m, 1 H), 1.38 – 1.41 (m, 1 H), 1.68 – 1.76 (m, 2 H), 2.65 – 2.78 (m, 3 H), 3.07 – 3.13 (m, 1 H), 3.84 – 3.87 (m, 2 H), 4.15 – 4.17 (m, 2 H), 4.26 – 4.27 (m, 1 H), 4.45 (s, 2 H), 6.93 (t, J = 9.2 Hz, 4 H), 7.30 (t, J = 12 Hz, 4 H).

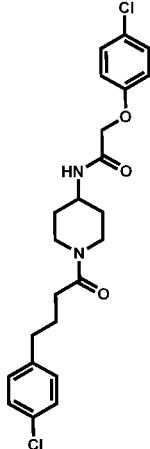
				H), 7.98 – 8.00 (m, 1 H).
26		2-(4-chlorophenoxy)-N-(1-(4-(4-chlorophenyl)butanoyl)-3-fluoropiperidin-4-yl)acetamide	467.3	1.33 – 1.50 (m, 1 H), 1.72 – 1.78 (m, 3 H), 2.31 – 2.33 (m, 2 H), 2.56 (t, J = 7.4 Hz, 2 H), 2.85 – 2.95 (m, 1 H), 3.08 – 3.17 (m, 0.6 H), 3.20 – 3.25 (m, 0.4 H), 3.65 – 3.72 (m, 0.5 H), 3.91 – 4.12 (m, 2 H), 4.26 – 4.33 (m, 0.3 H), 4.40 (brs, 1 H), 4.49 (s, 2 H), 6.96 (d, J = 8.8 Hz, 2 H), 7.20 (d, J = 8.0 Hz, 2 H), 7.31 (t, J = 7.4 Hz, 4 H), 8.17 (d, J = 8.4 Hz, 1 H).
27		2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)piperidin-3-yl)acetamide	437.4	1.33 – 1.37 (m, 0.5 H), 1.50 (s, 1.5 H), 1.69 (s, 1 H), 1.79 (s, 1 H), 2.73 – 2.78 (m, 0.5 H), 2.98 – 3.12 (m, 1.5 H), 3.58 – 3.62 (m, 1.5 H), 3.76 (s, 1 H), 4.00 – 4.02 (m, 0.5 H), 4.41 – 4.48 (m, 2 H), 4.73 – 4.85 (m, 2 H), 6.92 (s, 4 H), 7.26 – 7.30 (m, 4 H), 7.95 – 7.99 (m, 0.5 H), 8.10 – 8.12 (m, 0.46 H).

28		2-(4-chlorophenoxy)-N-(2-(2-(4-chlorophenoxy)acetyl)piperidin-3-yl)acetamide	465.1	1.10 – 1.24 (m, 2 H), 1.26 – 1.35 (m, 4 H), 1.57 – 1.60 (m, 1 H), 1.71 – 1.79 (m, 1 H), 2.58 – 2.69 (m, 1 H), 2.99 – 3.12 (2 H), 3.61 – 3.64 (m, 0.5 H), 3.72 – 3.75 (m, 0.5 H), 3.98 – 4.02 (m, 0.5 H), 4.11 – 4.15 (m, 0.5 H), 4.43 – 4.46 (m, 2 H), 4.76 – 4.87 (m, 2 H), 6.90 – 6.95 (m, 4 H), 7.26 – 7.31 (m, 4 H), 8.04 – 8.09 (m, 1 H).
29		N-((1-(2-(4-chlorophenoxy)acetyl)piperidin-3-yl)methyl)-2-(6-chloropyridin-3-yl)oxyacetamide	452.1	1.21 – 1.26 (m, 1 H), 1.36 – 1.39 (m, 0.5 H), 1.52 – 1.58 (m, 0.5 H), 1.70 – 1.81 (m, 2 H), 2.38 – 2.44 (m, 1 H), 2.69 – 2.80 (m, 1 H), 2.95 – 3.10 (m, 3 H), 3.62 – 3.68 (m, 1 H), 3.98 – 4.01 (m, 0.5 H), 4.11 – 4.14 (m, 0.5 H), 4.56 – 4.58 (m, 2 H), 4.68 – 4.84 (m, 2 H), 6.90 – 6.91 (m, 2 H), 7.24 – 7.29 (m, 2 H), 7.39 – 7.45 (m, 2 H), 8.11 (s, 1 H), 8.18 (s, 1 H).

30	 <p>2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)-3-fluoropiperidin-4-yl)acetamide</p>	455.0	<p>1.40 – 1.43 (m, 0.5 H), 1.54 – 1.56 (m, 0.5 H), 1.75 – 1.88 (m, 1 H), 2.90 – 2.99 (m, 0.5 H), 3.01 (bs, 0.5 H), 3.20 – 3.37 (m, 1 H), 3.69 (d, J = 12.0 Hz, 0.5 H), 4.01 – 4.09 (m, 2 H), 4.31 (bs, 0.7 H), 4.50 – 4.58 (m, 2.5 H), 4.63 (bs, 0.3 H), 4.79 – 4.96 (m, 2 H), 6.91 – 6.97 (m, 4 H), 7.29 – 7.34 (m, 4 H), 8.22 (d, J = 7.6 Hz, 1 H).</p>
31	 <p>2-(4-chlorophenoxy)-N-(2-(2-(4-chlorophenoxy)acetyl)-2-azabicyclo[2.2.1]heptan-5-yl)acetamide</p>	449.0	<p>1.40 – 1.58 (m, 2 H), 1.65 – 1.72 (m, 1 H), 1.88 – 2.10 (m, 1 H), 2.41 – 2.48 (m, 0.5 H), 2.67 (d, J = 12.8 Hz, 0.5 H), 2.92 (d, J = 11.2 Hz, 0.25 H), 3.09 – 3.11 (m, 0.25 H), 3.17 – 3.27 (m, 1 H), 3.31 – 3.36 (m, 0.5 H), 3.76 (bs, 0.25 H), 3.89 (bs, 0.25 H), 4.10 – 4.20 (m, 0.5 H), 4.26 – 4.38 (m, 1 H), 4.42 – 4.67 (m, 3.5 H), 4.72 – 4.79 (m, 0.5 H), 6.88 – 6.95 (m, 4 H), 7.27 – 7.33 (m, 4 H), 8.06 (d, J = 6.4 Hz, 0.5 H), 8.23 – 8.28 (m, 0.5 H).</p>

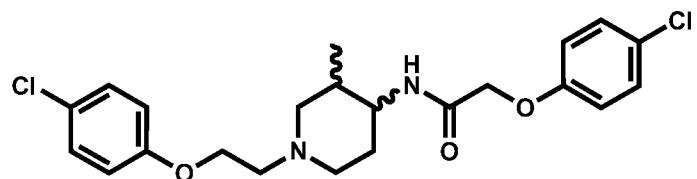
32	<p>2-(4-chlorophenoxy)-N-(1-((1R,2R)-2-(4-chlorophenoxy)cyclopropane-1-carbonyl)piperidin-4-yl)acetamide (Racemate)</p>	463.4	1.29 – 1.37 (m, 4 H), 1.72 (bs, 2 H), 2.31 – 2.33 (m, 1 H), 2.65 – 2.73 (m, 1 H), 3.15 – 3.19 (m, 1 H), 3.95 (bs, 2 H), 4.09 (d, J = 13.2 Hz, 1 H), 4.26 (bs, 1 H), 4.46 (d, J = 8.0 Hz, 2 H), 6.96 – 6.98 (m, 4 H), 7.31 – 7.33 (m, 4 H), 8.01 (bs, 1 H).
33	<p>2-(4-chlorophenoxy)-N-(1-((1R,2S)-2-(4-chlorophenoxy)cyclopropane-1-carbonyl)piperidin-4-yl)acetamide (Racemate)</p>	463.1	1.11 – 1.17 (m, 1 H), 1.27 – 1.46 (m, 3 H), 1.61 – 1.76 (m, 2 H), 2.22 – 2.28 (m, 1 H), 2.48 (bs, 0.5 H), 2.73 (t, J = 9.0 Hz, 0.5 H), 2.97 (t, J = 9.0 Hz, 0.5 H), 3.22 – 3.27 (m, 0.5 H), 3.82 (bs, 1 H), 4.08 – 4.19 (m, 3 H), 4.46 (s, 2 H), 6.94 – 7.02 (m, 4 H), 7.32 (d, J = 8.0 Hz, 4 H), 7.95 – 8.01 (m, 1 H).
34	<p>N-(1-((1S,2R)-2-(4-chlorobenzyl)cyclopropane-1-carbonyl)piperidin-4-yl)-2-(4-chlorophenoxy)acetamide (racemate)</p>	461.1	0.71 (bs, 1 H), 0.98 (bs, 1 H), 1.32 (bs, 3 H), 1.65 (bs, 2 H), 1.94 (bs, 1 H), 2.48 (bs, 1 H), 2.65 – 2.67 (m, 2 H), 3.08 – 3.11 (m, 1 H), 3.86 (bs, 1 H), 4.06 (bs, 1 H), 4.18 (bs, 1 H), 4.45 (s, 2 H), 6.95 (d, J = 8.4 Hz, 2 H), 7.27 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.4 Hz, 4 H),

				7.97 (bs, 1 H).
35	 <p>N-((1R,2R)-2-(4-chlorobenzyl)cyclopropane-1-carbonyl)piperidin-4-yl)-2-(4-chlorophenoxy)acetamide (Racemate)</p>	461.4	0.85 (bs, 1 H), 0.95 (bs, 1 H), 1.09 (bs, 0.5 H), 1.28 – 1.47 (m, 3 H), 1.60 – 1.69 (m, 2.5 H), 2.01 (d, J = 5.6 Hz, 1 H), 2.60 – 2.65 (m, 2 H), 3.16 – 3.20 (m, 1 H), 3.82 (bs, 1 H), 3.92 – 3.96 (m, 1 H), 4.22 – 4.31 (m, 1 H), 4.45 (s, 2 H), 6.96 (bs, 2 H), 7.13 (d, J = 7.6 Hz, 1 H), 7.20 (d, J = 7.2 Hz, 1 H), 7.32 (d, J = 8.0 Hz, 4 H), 7.89 – 7.98 (m, 1 H).	
36	 <p>2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenyl)cyclopropane-1-carbonyl)piperidin-4-yl)acetamide</p>	447.1	1.14 – 1.19 (m, 1 H), 1.29 – 1.39 (m, 3 H), 1.69 – 1.72 (m, 2 H), 2.24 – 2.31 (m, 2 H), 2.72 (bs, 1 H), 3.10 – 3.19 (m, 1 H), 3.88 – 3.90 (m, 1 H), 4.10 (bs, 1 H), 4.25 (bs, 1 H), 4.44 (s, 2 H), 6.95 (d, J = 8.4 Hz, 2 H), 7.19 (d, J = 8.8 Hz, 2 H), 7.31 (t, J = 8.4 Hz, 4 H), 7.95 – 8.01 (m, 1 H).	

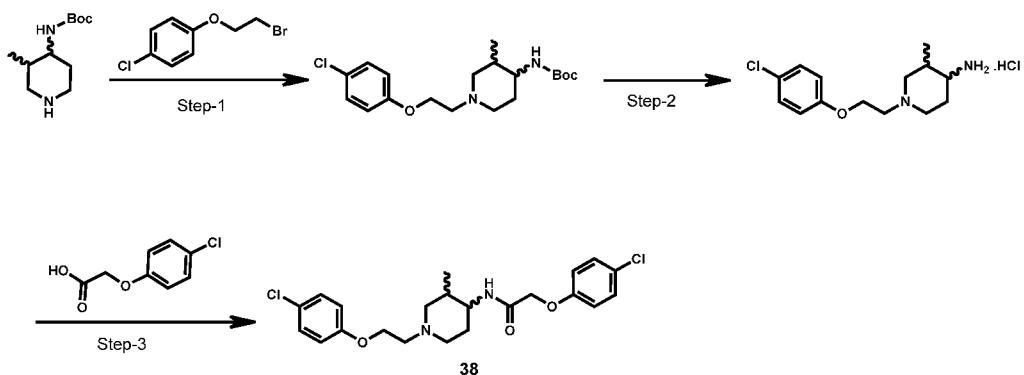
37		2-(4-chlorophenoxy)-N-(1-(4-(4-chlorophenyl)butanoyl)piperidin-4-yl)acetamide	449.1	1.26 – 1.34 (m, 2 H), 1.66 – 1.78 (m, 4 H), 2.28 (t, J = 7.2 Hz, 2 H), 2.67-2.54 (m, 3H), 3.04 (t, J = 12.0 Hz, 1 H), 3.75 (d, J = 12.8 Hz, 1 H), 3.85 (d, J = 8.0 Hz, 1 H), 4.26 (d, J = 12.8 Hz, 2 H), 4.44 (s, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 7.2 (d, J = 8.4 Hz, 2 H), 7.3 – 7.33 (m, 4 H), 7.97 (d, J = 8.0 Hz, 1 H).
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Example 38

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)ethyl)-3-methylpiperidin-4-yl)acetamide



38



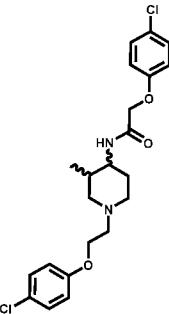
Step 1: To a stirred solution of *tert*-butyl (3-methylpiperidin-4-yl)carbamate (0.2 g, 0.933 mmol, 1.0 equiv) in *N,N*-dimethylmethanamide (10 mL) was added cesium carbonate (0.45 g, 1.399 mmol, 1.5 equiv), triethyl amine (0.26 mL, 1.866 mmol, 2.0 equiv) and 1-(3-bromopropoxy)-4-chlorobenzene (0.33 g, 1.399 mmol, 1.5 equiv) at 25 °C. The resulting mixture was stirred at 25 °C for 16 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (50 mL), the product was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with cold water (50 mL), brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get the crude product. The crude product was purified by silicagel column chromatography using 4% methanol in dichloromethane as eluent to obtain the title compound *tert*-butyl (1-(2-(4-chlorophenoxy)ethyl)-3-methylpiperidin-4-yl)carbamate (0.21 g, 61 % yield) as off white gum. LCMS (ES) *m/z* = 369.2 [M+H]⁺.

Step 2: To a solution of *tert*-butyl (1-(2-(4-chlorophenoxy)ethyl)-3-methylpiperidin-4-yl)carbamate (0.21 g, 0.569 mmol, 1.0 equiv) in dichloromethane (5 mL), was added 4M hydrochloric acid in 1, 4-dioxane (5 mL) at 0 °C. The reaction mixture was allowed to warm to 25 °C and stirred for 4 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was concentrated under reduced pressure to get the crude product. The crude product was triturated with *n*-pentane to obtain the title compound 1-(2-(4-chlorophenoxy)ethyl)-3-methylpiperidin-4-amine hydrochloride (0.2 g, crude) as off white gum, which was taken as such to next step without further purification. LCMS (ES) *m/z* = 269.2 [M+H]⁺.

Step 3: To a stirred solution of 1-(2-(4-chlorophenoxy)ethyl)-3-methylpiperidin-4-amine hydrochloride (0.15 g, 0.491 mmol, 1.0 equiv), 2-(4-chlorophenoxy)acetic acid (0.11 g, 0.589 mmol, 1.2 equiv) and triethyl amine (0.55 mL, 3.931 mmol, 8.0 equiv) in dichloromethane (10 mL) was added propylphosphonic anhydride solution (≥ 50 wt. % in ethyl acetate) (0.62 g, 0.982 mmol, 2.0 equiv) at 0 °C. The resulting mixture was allowed to warm to 25 °C and stirred for 6 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with dichloromethane (70 mL), washed with water (2 x 30 mL), brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get the crude product. The crude product was purified by silicagel column chromatography using 4% methanol in dichloromethane as eluent to obtain the title compound 2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)ethyl)-3-methylpiperidin-4-yl)acetamide (0.11 g, 21 % crude yield) as colourless gum. LCMS (ES) m/z = 437.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ ppm 0.71 (d, J = 6.8 Hz, 1 H), 0.78 (d, J = 6.4 Hz, 2 H), 1.59, 1.71 – 1.76, (m, 2.5 H, 0.41 H), 1.89, 1.99 – 2.04 (m, 0.75 H, 0.45 H), 2.30 – 2.36 (m, 2 H), 2.64 – 2.65 (m, 2 H), 2.88 (bs, 1 H), 3.84 (bs, 1 H), 4.03 (bs, 2 H), 4.46 – 4.56 (m, 2 H), 6.92 – 6.96 (m, 4 H), 7.27 – 7.32 (m, 4 H), 7.66 – 7.68, 7.83 – 7.85 (m, 0.63 H, 0.32 H).

The Compounds of Examples 39 to 50 were prepared generally according to the procedure described above for Example 38.

Table 11

Cmpd #	Structure	Name	LCMS m/z [M+H] ⁺	¹ H-NMR (400 MHz, DMSO-d ₆)
38		2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)ethyl)-3-methylpiperidin-4-yl)acetamide	437.1	0.71 (d, J = 6.8 Hz, 1 H), 0.78 (d, J = 6.4 Hz, 2 H), 1.59, 1.71 – 1.76, (m, 2.5 H, 0.41 H), 1.89, 1.99 – 2.04 (m, 0.75 H, 0.45 H), 2.30 – 2.36 (m, 2 H), 2.64 – 2.65 (m, 2 H), 2.88 (bs, 1 H), 3.84 (bs, 1 H), 4.03 (bs, 2 H), 4.46 – 4.56 (m, 2 H), 6.92 – 6.96 (m, 4 H), 7.27 – 7.32 (m, 4 H), 7.66 – 7.68, 7.83 – 7.85 (m, 0.63 H, 0.32 H)

				7.85 (m, 0.63 H, 0.32 H).
39		N,1-bis(2-(4-chlorophenoxy)ethyl)piperidine-4-carboxamide	437.1	1.49 – 1.58 (m, 4 H), 1.97 (t, J = 10.6 Hz, 2 H), 2.04 – 2.09 (m, 1 H), 2.62 – 2.64 (m, 2 H), 2.88 – 2.90 (m, 2 H), 3.34 – 3.38 (m, 2 H), 3.94 (t, J = 5.6 Hz, 2 H), 4.02 (t, J = 5.6 Hz, 2 H), 6.93 (d, J = 8.4 Hz, 4 H), 7.27 – 7.30 (m, 4 H), 7.92 (bs, 1 H).
40		N-(2-(4-chlorophenoxy)ethyl)-1-(3-(4-chlorophenoxy)propyl)piperidine-4-carboxamide	451.1	1.51 – 1.61 (m, 4 H), 1.80 – 1.83 (m, 4 H), 2.04 – 2.07 (m, 1 H), 2.30 – 2.35 (m, 2 H), 2.82 – 2.84 (m, 2 H), 3.36 – 3.37 (m, 2 H), 3.92 – 3.95 (m, 4 H), 6.91 – 6.94 (m, 4 H), 7.27 – 7.30 (m, 4 H), 7.92 (bs, 1 H).
41		2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)ethyl)-3-hydroxypiperidin-4-yl)acetamide	439	1.39 – 1.41 (m, 1 H), 1.68 – 1.71 (m, 1 H), 1.86 – 1.91 (m, 1 H), 1.98 – 2.04 (m, 1 H), 2.69 (t, J = 5.4 Hz, 2 H), 2.80 – 2.82 (m, 1 H), 2.98 – 3.00 (m, 1 H), 3.43 (bs, 2 H), 4.03 (t, J = 5.4 Hz, 2 H), 4.44 (s, 2 H), 4.71 – 4.72 (m, 1 H), 6.95 (t, J = 9.4 Hz, 4 H), 7.30 (t, J = 9.0 Hz, 4 H), 7.82 – 7.83 (m, 1 H).

42		6-chloro-N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)chromane-2-carboxamide	463.1	1.43 – 1.52 (m, 2 H), 1.68 – 1.72 (m, 2 H), 1.78 – 1.88 (m, 3 H), 1.90 – 1.99 (m, 2 H), 2.07 – 2.15 (m, 1 H), 2.33 – 2.41 (m, 2 H), 2.67 (d, J = 10.4 Hz, 1 H), 2.71 – 2.82 (m, 3 H), 3.57 (bs, 1 H), 3.96 (d, J = 6.0 Hz, 2 H), 4.49 (d, J = 6.8 Hz, 1 H), 6.87 (d, J = 8.4 Hz, 1 H), 6.93 (d, J = 8.0 Hz, 2 H), 7.11 (d, J = 7.6 Hz, 2 H), 7.29 (d, J = 8.4 Hz, 2 H), 7.77 (d, J = 7.6 Hz, 1 H).
43		N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-((6-chloropyridin-3-yl)oxy)acetamide	440.0	1.40 – 1.52 (m, 2 H), 1.64 – 1.72 (m, 2 H), 1.79 – 1.88 (m, 2 H), 1.90 – 2.00 (m, 2 H), 2.35 – 2.42 (m, 2 H), 2.79 (bs, 2 H), 3.60 (bs, 1 H), 3.97 (s, 2 H), 4.56 (s, 2 H), 6.93 (d, J = 8.4 Hz, 2 H), 7.29 (d, J = 8.4 Hz, 2 H), 7.43 (s, 2 H), 7.98 (bs, 1 H), 8.11 (bs, 1 H).
44		N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-(3,4-dichlorophenoxy)acetamide	473.1	1.41 – 1.49 (m, 2 H), 1.65 – 1.68 (m, 2 H), 1.82 (t, J = 6.6 Hz, 2 H), 1.94 (t, J = 10.6 Hz, 2 H), 2.36 – 2.37 (m, 2 H), 2.78 (d, J = 10.8 Hz, 2 H), 3.58 – 3.60 (m, 1 H), 3.96 (t, J = 6.2 Hz, 2 H), 4.49 (s, 2 H), 6.91 – 6.97 (m, 3 H), 7.23 (d, J = 2.4 Hz, 1 H), 7.28 (d, J = 8.8 Hz, 2 H), 7.52 (d, J = 8.8 Hz, 1 H),

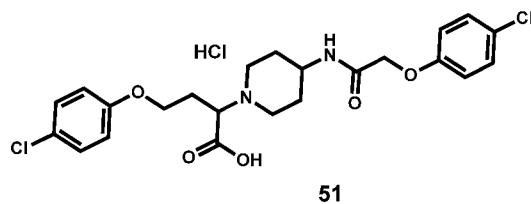
				7.93 (d, J = 7.6 Hz, 1 H).
45		N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-(2,4-dichlorophenoxy)acetamide	473.1	1.38 – 1.45 (m, 2 H), 1.69 – 1.71 (m, 2 H), 1.81 (t, J = 6.6 Hz, 2 H), 1.97 (t, J = 10.2 Hz, 2 H), 2.37 (t, J = 7.0 Hz, 2 H), 2.73 – 2.76 (m, 2 H), 3.57 – 3.59 (m, 1 H), 3.96 (t, J = 6.4 Hz, 2 H), 4.57 (s, 2 H), 6.92 (d, J = 8.8 Hz, 2 H), 7.01 (d, J = 8.8 Hz, 1 H), 7.28 (d, J = 8.8 Hz, 2 H), 7.33 – 7.35 (m, 1 H), 7.56 (d, J = 2.0 Hz, 1 H), 7.82 (d, J = 7.6 Hz, 1 H).
46		2-(4-chlorophenoxy)-N-((1R,5S)-8-(3-(4-chlorophenoxy)propyl)-8-azabicyclo[3.2.1]octan-3-yl)acetamide	463.3	1.49 – 1.58 (m, 6 H), 1.77 – 1.83 (m, 4 H), 2.42 – 2.48 (m, 2 H), 3.17 (s, 2 H), 4.01 (t, J = 6.2 Hz, 3 H), 4.39 (s, 2 H), 6.91 – 6.94 (m, 4 H), 7.29 (t, J = 7.8 Hz, 4 H), 7.86 (d, J = 8.4 Hz, 1 H).

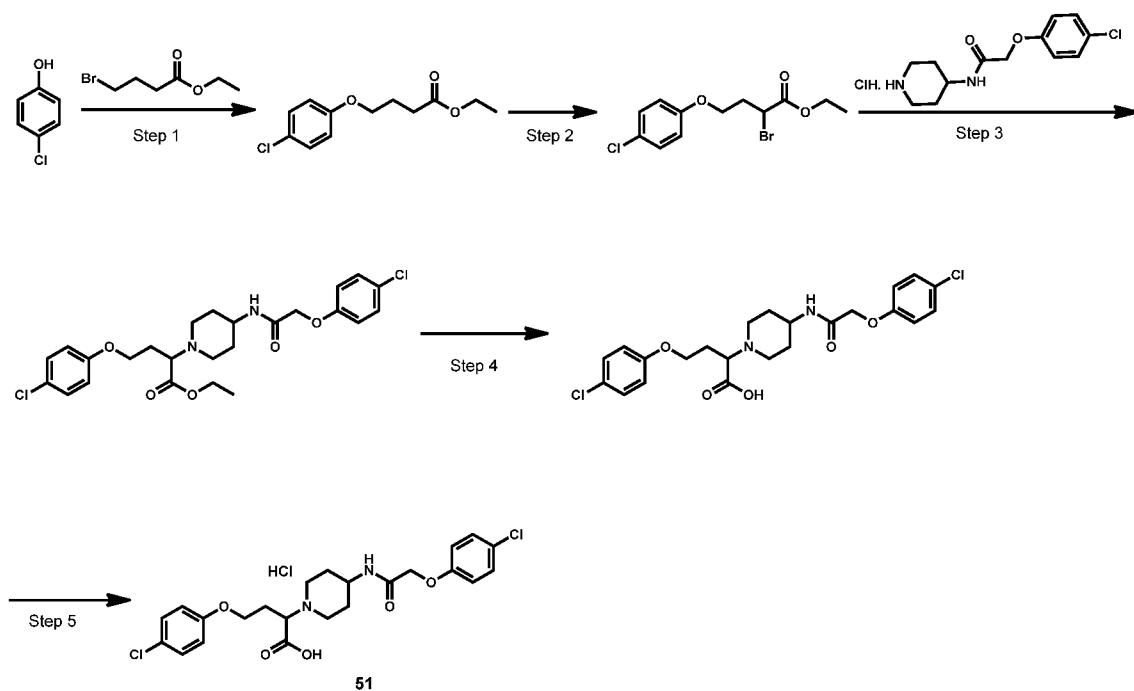
47		2-(4-chlorophenoxy)-N-(1-(2-(3,4-dichlorophenoxy)ethyl)-3-fluoropiperidin-4-yl)acetamide	475.1	1.45 – 1.53 (m, 1 H), 1.70 (bs, 1 H), 2.11 – 2.19 (m, 2 H), 2.75 (bs, 2 H), 2.81 (d, $J = 11.2$ Hz, 1 H), 3.20 – 3.25 (m, 1 H), 3.72 – 3.85 (m, 1 H), 4.09 (t, $J = 5.2$ Hz, 2 H), 4.38 – 4.43 (m, 0.5 H), 4.47 (s, 2 H), 4.52 – 4.57 (m, 0.5 H), 6.93 – 6.97 (m, 3 H), 7.23 (d, $J = 2.0$ Hz, 1 H), 7.32 (d, $J = 8.8$ Hz, 2 H), 7.48 (d, $J = 8.8$ Hz, 1 H), 8.17 (d, $J = 8.4$ Hz, 1 H).
48		N-(1-(2-(4-chlorophenoxy)ethyl)-3-fluoropiperidin-4-yl)-2-(3,4-dichlorophenoxy)acetamide	477.1	1.45 – 1.53 (m, 1 H), 1.71 (bs, 1 H), 2.11 – 2.17 (m, 2 H), 2.75 (s, 2 H), 2.82 (d, $J = 10.8$ Hz, 1 H), 3.20 – 3.25 (m, 1 H), 3.78 (bs, 1 H), 4.05 (t, $J = 5.6$ Hz, 2 H), 4.40 – 4.41 (m, 0.5 H), 4.53 (s, 2.5 H), 6.93 – 6.99 (m, 3 H), 7.23 (d, $J = 2.8$ Hz, 1 H), 7.29 (d, $J = 9.2$ Hz, 2 H), 7.52 (d, $J = 8.8$ Hz, 1 H), 8.18 (d, $J = 8.8$ Hz, 1 H).
49		2-(4-chlorophenoxy)-N-((1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)methyl)acetamide	451.1	1.11 – 1.20 (m, 2 H), 1.31 (bs, 1 H), 1.55 (bs, 2 H), 1.83 – 2.15 (m, 4 H), 2.35 – 2.48 (m, 2 H), 2.75 – 2.81 (m, 2 H), 2.99 (bs, 2 H), 3.97 (s, 2 H), 4.46 (s, 2 H), 6.93 (t, $J = 10$ Hz, 4 H), 7.30 (t, $J = 9.2$ Hz, 4 H), 8.06 (bs, 1 H).

50		2-(4-chlorophenoxy)- -N-(1-(2-(4-chlorophenoxy) -ethyl)-3- -fluoropiperidin- -4-yl)acetamide	442.1	1.45 – 1.54 (m, 1 H), 1.65 – 1.75 (m, 1 H), 2.11 – 2.19 (m, 2 H), 2.76 (t, J = 5.6 Hz, 2 H), 2.81 (d, J = 11.2 Hz, 1 H), 3.21 – 3.27 (m, 1 H), 3.75 – 3.85 (m, 1 H), 4.05 (t, J = 5.2 Hz, 2 H), 4.39 – 4.44 (m, 0.5 H), 4.47 (s, 2 H), 4.51 – 4.57 (m, 0.5 H), 6.95 (t, J = 8.4 Hz, 4 H), 7.28 – 7.33 (m, 4 H), 8.16 (d, J = 8.4 Hz, 1 H).
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Example 51

**4-(4-chlorophenoxy)-2-(4-(2-(4-chlorophenoxy)acetamido)piperidin-1-yl)butanoic
acid hydrochloride**





Step 1: To a solution of 4-chlorophenol (2.0 g, 15.556 mmol, 1 equiv) in acetonitrile (60 mL) was added anhydrous potassium carbonate (4.3 g, 31.113 mmol, 2 equiv) and ethyl 4-bromobutanoate (3.56 mL, 24.891 mmol, 1.6 equiv). The reaction mixture was heated to reflux and stirred for 8 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was allowed to cool to 27 °C, filtered the solid and washed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure to give the crude product. The crude product was purified by silica gel column chromatography using 10% ethyl acetate in hexane as eluent to obtain the title compound ethyl 4-(4-chlorophenoxy)butanoate (3.5 g, 92 % yield) as colourless liquid. LCMS (ES) *m/z* = 242.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ ppm 1.25 (t, *J* = 6.8 Hz, 3 H), 2.06 – 2.06 (m, 2 H), 2.49 (t, *J* = 6.8 Hz, 2 H), 3.97 (t, *J* = 6.0 Hz, 2 H), 4.11 – 4.17 (m, 2 H), 6.80 (d, *J* = 8.4 Hz, 2 H), 7.21 (d, *J* = 8.8 Hz, 2 H).

Step 2: To a solution of ethyl 4-(4-chlorophenoxy)butanoate (1.0 g, 4.120 mmol, 1.0 equiv) in dry tetrahydrofuran (10 mL) was added lithium diisopropylamide solution (2.0 M in THF/heptane/ethylbenzene) (2.47 mL, 4.944 mmol, 1.2 equiv) slowly at –78 °C. The reaction mixture was stirred for another 1 h at –78 °C. After 1 h, a solution of carbon tetrabromide (2.0 g, 6.198 mmol, 1.5 equiv) in dry tetrahydrofuran (15 mL) was added at –78 °C, the mixture was gradually allowed to warm to 27 °C and stirred for 2 h. The

mixture was quenched with saturated aqueous solution of ammonium chloride (20 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by silica gel column chromatography using 10% ethyl acetate in hexane as eluent to obtain the title compound ethyl 2-bromo-4-(4-chlorophenoxy)butanoate (0.45 g, crude) as pale brown liquid. ¹H NMR (400 MHz, CDCl₃): δ ppm 1.30 (t, *J* = 7.2 Hz, 3 H), 2.35 – 2.43 (m, 1 H), 2.52 – 2.60 (m, 1 H), 4.04 – 4.13 (m, 2 H), 4.22 – 4.27 (m, 2 H), 4.52 – 4.55 (m, 1 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 7.23 (d, *J* = 8.8 Hz, 2 H).

Step 3: To a solution of ethyl 2-bromo-4-(4-chlorophenoxy)butanoate (0.16 g, 0.491 mmol, 1 equiv) in *N,N*-dimethylformamide (10 mL) were added a 2-(4-chlorophenoxy)-N-(piperidin-4-yl)acetamide hydrochloride (0.15 g, 0.491 mmol, 1 equiv), cesium carbonate (0.32 g, 0.982 mmol, 2.0 equiv) and triethyl amine (0.14 mL, 0.982 mmol, 2.0 equiv). The resulting mixture was stirred for 16 h at 27 °C. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (3 x 30 mL), the combined organics were washed with water (30 mL), brine (20 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product. The crude product was purified by silica gel column chromatography (Combiflash) using 50% ethyl acetate in hexane as eluent. The product was again purified with preparative HPLC (analytical Conditions: column: inertsil ODS 3V(250mm X 4.6mm X 5mic), mobile phase(A) : 0.1% Ammonia in water, mobile phase(B) : acetonitrile, flow rate : 1.0 mL/min, T/%B: 0/20, 10/80, 25/90, 27/20, 30/20) to obtain the title compound ethyl 4-(4-chlorophenoxy)-2-(4-(2-(4-chlorophenoxy)acetamido)piperidin-1-yl)butanoate (0.08 g, 40% yield) as off white solid. LCMS (ES) *m/z* = 509.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ ppm 1.21 – 1.31 (m, 3 H), 1.31 – 1.47 (m, 3 H), 1.66 (bs, 2 H), 1.96 – 2.18 (m, 2 H), 2.24 – 2.28 (m, 1 H), 2.73 (d, *J* = 11.2 Hz, 1 H), 2.82 (d, *J* = 11.6 Hz, 1 H), 3.38 (t, *J* = 6.8 Hz, 1 H) 3.55 – 3.57 (m, 1 H), 3.93 – 4.13 (m, 4 H), 4.42 (s, 2 H), 6.90 – 6.95 (m, 4 H), 7.28 – 7.32 (m, 4 H), 7.90 (d, *J* = 8.0 Hz, 1 H).

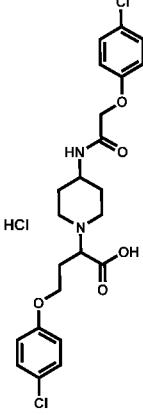
Step 4: To a solution of ethyl 4-(4-chlorophenoxy)-2-(4-(2-(4-chlorophenoxy)acetamido)piperidin-1-yl)butanoate (0.04 g, 0.078 mmol, 1 equiv) in ethanol (5 mL) was added sodium hydroxide (0.3 g, 0.785 mmol, 10 equiv) in 1 mL of water, the resulting mixture was heated to 50 °C and stirred for 4 h. The progress of the reaction was monitored by TLC. After completion of reaction, the ethanol was removed by evaporation, the residue was diluted with water (2 mL), acidified with 1.5 M hydrochloric acid to pH ~ 3 to 4. The aqueous was extracted with ethyl acetate (3 x 30 mL). The

combined organic layers were washed with water (10 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. The crude product triturated with *n*-pentane and dried to obtain the title compound 4-(4-chlorophenoxy)-2-(4-(2-(4-chlorophenoxy)acetamido)piperidin-1-yl)butanoic acid (0.025 g, 67% yield) as off white solid. LCMS (ES) m/z = 481.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ ppm 1.41 – 1.47 (m, 2 H), 1.94 (bs, 2 H), 2.05 – 2.19 (m, 2 H), 2.25 – 2.30 (m, 1 H), 2.56 – 2.59 (m, 1 H), 2.75 – 2.78 (m, 1 H), 2.83 – 2.86 (m, 1 H), 3.32 – 3.34 (m, 1 H), 3.57 (bs, 1 H), 3.95 – 3.99 (m, 1 H), 4.02 – 4.05 (m, 1 H), 4.42 (s, 2 H), 6.91 – 6.95 (m, 4 H), 7.28 – 7.32 (m, 4 H), 7.93 (d, J = 8.0 Hz, 1 H).

Step 5: To mixture of 4-(4-chlorophenoxy)-2-(4-(2-(4-chlorophenoxy)acetamido)piperidin-1-yl)butanoic acid (0.02 g, 0.041 mmol, 1 equiv) in tetrahydrofuran (1 mL) was added 1 M aqueous hydrochloric acid (2 mL) at 27 °C and the resulting mixture was stirred for 10 min (up to clear solution). The reaction mixture was concentrated under reduced pressure to get the crude product, which was triturated with *n*-pentane and dried to obtain the title compound 4-(4-chlorophenoxy)-2-(4-(2-(4-chlorophenoxy)acetamido)piperidin-1-yl)butanoic acid hydrochloride (0.015 g, 71% yield) as off white solid. LCMS (ES) m/z = 481.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.79 (bs, 2 H), 1.91 (bs, 2 H), 2.25 (bs, 1 H), 3.20 (bs, 2 H), 3.86 (bs, 1 H), 4.04 – 4.12 (m, 3 H), 4.47 (s, 2 H), 6.92 – 6.96 (m, 4 H), 7.32 (d, J = 7.6 Hz, 4 H), 8.19 (d, J = 6.8 Hz, 1 H), 10.2 (bs, 1 H). (Note: Protons are merged with water residual peak). ¹H NMR-D₂O (400 MHz, DMSO-d₆) δ ppm 1.76 – 1.84 (m, 2 H), 1.94 (bs, 2 H), 2.23 – 2.30 (m, 1 H), 2.39 (bs, 1 H), 3.09 – 3.14 (m, 1 H), 3.20 – 3.25 (m, 1 H), 3.35 – 3.38 (m, 1 H), 3.49 – 3.52 (m, 1 H), 3.84 – 3.86 (m, 1 H), 4.00 – 4.10 (m, 3 H), 4.45 (s, 2 H), 6.90 – 6.95 (m, 4 H), 7.29 (d, J = 8.4 Hz, 4 H).

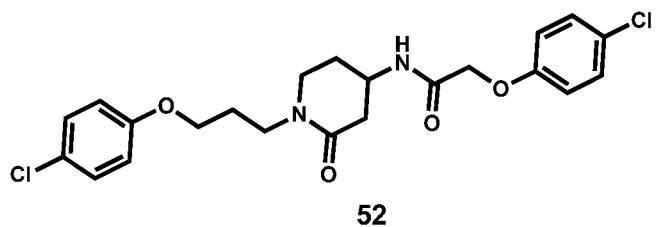
Table 12

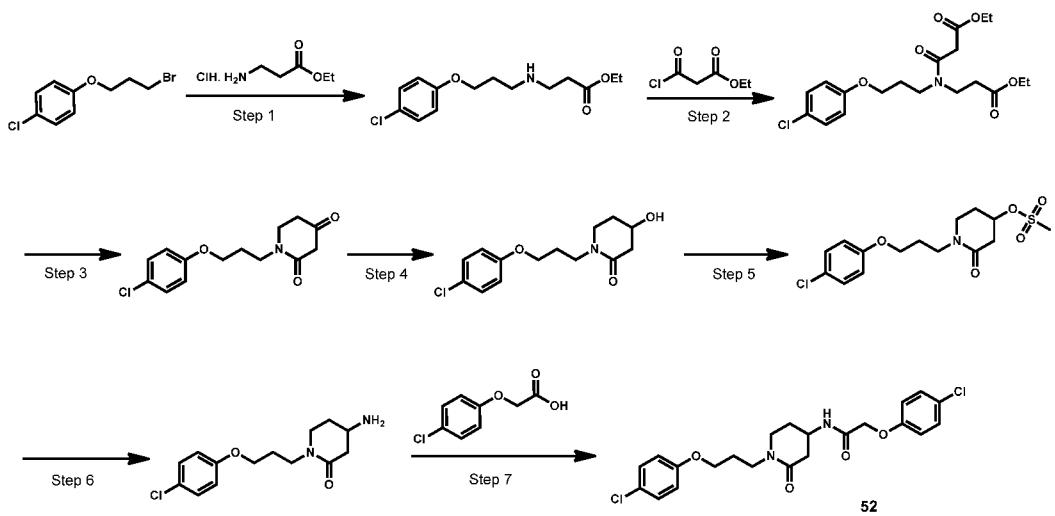
Cmpd #	Structure	Name	LCMS m/z [M+H] ⁺	¹ H-NMR (400 MHz, DMSO-d ₆)
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51	 HCl	4-(4-chlorophenoxy)-2-(2-(4-chlorophenoxy)acetamido)propyl eridin-1-yl butanoic acid hydrochloride	481.1	1.76 – 1.84 (m, 2 H), 1.94 (bs, 2 H), 2.23 – 2.30 (m, 1 H), 2.39 (bs, 1 H), 3.09 – 3.14 (m, 1 H), 3.20 – 3.25 (m, 1 H), 3.35 – 3.38 (m, 1 H), 3.49 – 3.52 (m, 1 H), 3.84 – 3.86 (m, 1 H), 4.00 – 4.10 (m, 3 H), 4.45 (s, 2 H), 6.90 – 6.95 (m, 4 H), 7.29 (d, J = 8.4 Hz, 4 H).
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Example 52

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propyl)-2-oxopiperidin-4-yl)acetamide





Step 1: To a solution of 1-(3-bromopropoxy)-4-chlorobenzene (1.0 g, 6.509 mmol, 1 equiv) in dichloromethane (15 mL) were added ethyl 3-aminopropanoate hydrochloride (1.62 g, 6.509 mmol, 1.0 equiv) and triethyl amine (1.82 mL, 13.019 mmol, 2.0 equiv). The resulting mixture was subjected to microwave irradiation at 80 °C for 1h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with dichloromethane (100 mL), washed with water (2 x 30 mL), brine (30 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product. The crude product was purified by silicagel column chromatography using 4% methanol in dichloromethane as eluent to obtain the title compound ethyl 3-((3-(4-chlorophenoxy)propyl)amino)propanoate (0.3 g, crude) as pale brown gum. LCMS (ES) *m/z* = 286.1 [M+H]⁺

Step 2: To a solution of ethyl 3-((3-(4-chlorophenoxy)propyl)amino)propanoate (0.8 g, 2.799 mmol, 1.0 equiv) in dichloromethane (20 mL) were added ethyl 3-chloro-3-oxopropanoate (0.36 mL, 2.799 mmol, 1.0 equiv) and triethylamine (0.78 mL, 5.598 mmol, 2.0 equiv) at 0 °C. The resulting mixture was allowed to warm to 27 °C and stirred for 2 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with dichloromethane (100 mL), washed with water (2 x 30 mL), brine (30 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product. The crude product was purified by silicagel column chromatography using 70% ethyl acetate in hexane as eluent to obtain the title compound ethyl 3-((3-(4-chlorophenoxy)propyl)(3-ethoxy-3-oxopropyl)amino)-3-

oxopropanoate (1.1 g, crude) as pale brown liquid. LCMS (ES) m/z = 400.1 [M+H]⁺

Step 3: To a stirred solution of ethyl 3-((3-(4-chlorophenoxy)propyl)(3-ethoxy-3-oxopropyl)amino)-3-oxopropanoate (1.1 g crude, 2.750 mmol, 1.1 equiv) was added sodium ethoxide solution (21% in ethanol) (1.016 mL, 3.301 mmol, 1.2 equiv) at 0 °C. The reaction mixture was allowed to warm to 27 °C and stirred for 16 h. The reaction mixture was concentrated under reduced pressure; the residue was triturated with *n*-pentane and diethyl ether to obtain solid crude intermediate. The obtained solid was dissolved with dichloromethane (10 mL) and 2M hydrochloric acid (20 mL) and stirred for 30 minutes at 27 °C. The organic phases were separated out and the aqueous layer was extracted with dichloromethane (20 mL). The combined organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude intermediate. The crude intermediate was dissolved with acetonitrile (10 mL) and water (0.5 mL) and the mixture was heated to 70 °C and stirred for 1 h. After 1 h, the reaction mixture was concentrated under reduced pressure to obtain the crude product, which was purified by silicagel column chromatography using 50 % ethyl acetate in hexane as eluent to obtain the title compound 1-(3-(4-chlorophenoxy)propyl)piperidine-2,4-dione (0.2 g) as off white gum. LCMS (ES) m/z = 282.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ ppm 2.04 – 2.11 (m, 2 H), 2.60 – 2.65 (m, 2 H), 3.34 (s, 2 H), 3.58 – 3.63 (m, 2 H), 3.65 – 3.70 (m, 2 H), 3.98 (t, J = 6.4 Hz, 2 H), 6.79 – 6.82 (m, 2 H), 7.23 (d, J = 9.6 Hz, 2 H).

Step 4: To a stirred solution of 1-(3-(4-chlorophenoxy)propyl)piperidine-2,4-dione (0.09 g, 0.319, 1.0 equiv) in methanol (5 mL) was added sodium borohydride (0.12 g, 3.194 mmol, 10 equiv) at 26 °C. The progress of the reaction was monitored by TLC. The reaction was quenched with cold water (10 mL), the product was extracted by ethyl acetate (3 x 30 mL). The combined organics were washed with brine (30 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by silicagel column chromatography using 5 % methanol in dichloromethane as eluent to obtain the title compound 1-(3-(4-chlorophenoxy)propyl)-4-hydroxypiperidin-2-one (0.08 g, crude) as pale brown gum. LCMS (ES) m/z = 284.1 [M+H]⁺

Step 5: To a stirred mixture of 1-(3-(4-chlorophenoxy)propyl)-4-hydroxypiperidin-2-one (0.085 g crude, 0.299 mmol, 1.0 equiv), 4-dimethylaminopyridine (0.11 g, 0.898 mmol, 3.0 equiv) in dichloromethane (5 mL) was added methane sulfonylchloride (0.07 mL, 0.898

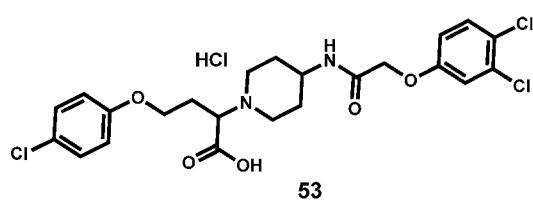
mmol, 3.0 equiv) at 0 °C. The reaction mixture was heated slowly to 50 °C and stirred for 12 h. The progress of the reaction was monitored by TLC. The reaction mixture was allowed to cool to 26 °C, diluted with dichloromethane (50 mL), washed with water (2 x 30 mL), brine (20 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by silicagel column chromatography using 10% methanol in dichloromethane as eluent to obtain the title compound 1-(3-(4-chlorophenoxy)propyl)-2-oxopiperidin-4-yl methanesulfonate (0.08 g, crude) as pale brown oil. LCMS (ES) m/z = 362.1 [M+H]⁺

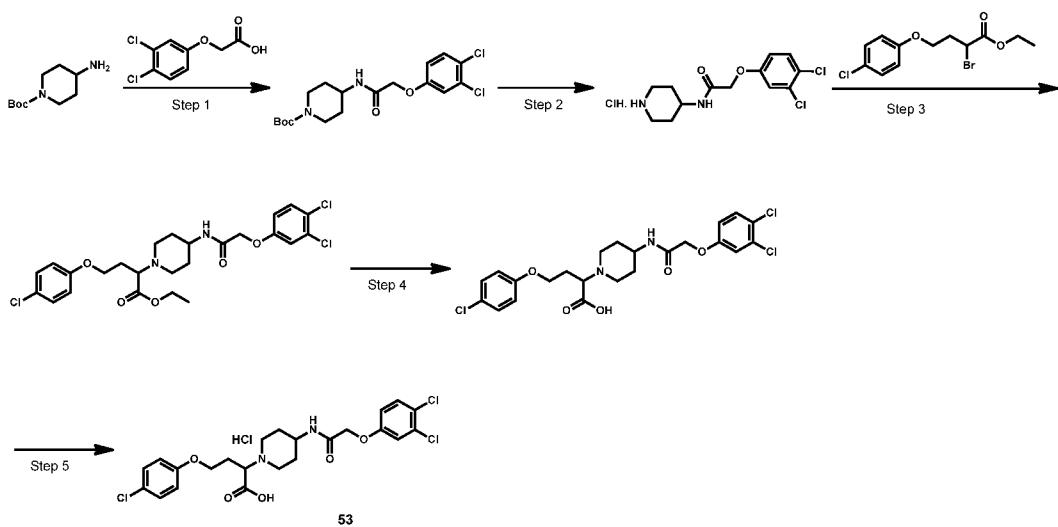
Step 6: In autoclave, a mixture of 1-(3-(4-chlorophenoxy)propyl)-2-oxopiperidin-4-yl methanesulfonate (0.085 g crude, 0.234 mmol, 1.0 equiv) and methanolic ammonia (10 mL) were heated to 65 °C and stirred for 12 h. After 12 h, the reaction was allowed to cool to 27 °C and reaction mixture was concentrated under reduced pressure to obtain the crude product 4-amino-1-(3-(4-chlorophenoxy)propyl)piperidin-2-one (0.1 g, crude) as brown oil. The crude product was taken as such next step without purification. LCMS (ES) m/z = 283.1 [M+H]⁺

Step 7: To a mixture of 4-amino-1-(3-(4-chlorophenoxy)propyl)piperidin-2-one (0.1 g crude, 0.353 mmol, 1.0 equiv), 2-(4-chlorophenoxy)acetic acid (0.065 g, 0.353 mmol, 1.0 equiv) and triethyl amine (0.25 mL, 1.768 mmol, 5.0 equiv) in dichloromethane (10 mL) was added T3P (50 wt. % in ethyl acetate) (0.44 mL, 0.707 mmol, 2.0 equiv) at 0 °C. The reaction mixture was allowed to warm to 27 °C, stirred for 16 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with dichloromethane (30 mL), washed with water (30 mL), brine (25 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by silica gel column chromatography (CombiFlash) using 6% methanol in dichloromethane as eluent to obtain the title compound 2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propyl)-2-oxopiperidin-4-yl)acetamide (0.0031 g) as pale brown gum. LCMS (ES) m/z = 451.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ ppm 1.64 (m, 1 H), 1.80 – 2.03 (m, 2 H), 2.16 – 2.23 (m, 1 H), 2.27 – 2.33 (m, 1 H), 2.73 – 2.78 (m, 1 H), 3.30 – 3.38 (m, 1 H), 3.40 – 3.45 (m, 1 H), 3.55 (t, J = 14.4 Hz, 2 H), 3.98 (t, J = 12 Hz, 2 H), 4.32 (bs, 1 H), 4.45 (s, 2 H), 6.43 (d, J = 7.6 Hz, 1 H), 6.79 – 6.85 (m, 4 H), 7.20 – 7.28 (m, 4 H).

Table 13

Cmpd #	Structure	Name	LCMS <i>m/z</i> [M+H] ⁺	¹ H-NMR (400 MHz, CDCl ₃)
52		2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propyl)-2-oxopiperidin-4-yl)acetamide	451.1	1.64 (m, 1 H), 1.80 – 2.03 (m, 2 H), 2.16 – 2.23 (m, 1 H), 2.27 – 2.33 (m, 1 H), 2.73 – 2.78 (m, 1 H), 3.30 – 3.38 (m, 1 H), 3.40 – 3.45 (m, 1 H), 3.55 (t, <i>J</i> = 14.4 Hz, 2 H), 3.98 (t, <i>J</i> = 12 Hz, 2 H), 4.32 (bs, 1 H), 4.45 (s, 2 H), 6.43 (d, <i>J</i> = 7.6 Hz, 1 H), 6.79 – 6.85 (m, 4 H), 7.20 – 7.28 (m, 4 H).

Example 53**4-(4-chlorophenoxy)-2-(4-(2-(3,4-dichlorophenoxy)acetamido)piperidin-1-yl)butanoic acid hydrochloride**



Step 1: To a mixture of *tert*-butyl 4-aminopiperidine-1-carboxylate (0.25 g, 1.248 mmol, 1 equiv), 2-(3,4-dichlorophenoxy)acetic acid (0.3 g, 1.373 mmol, 1.1 equiv) and triethyl amine (1.4 mL, 9.986 mmol, 8.0 equiv) in dichloromethane (10 mL) was added T3P (50 wt. % in ethyl acetate) (1.58 mL, 2.496 mmol, 2.0 equiv) at 0 °C. The reaction mixture was allowed to warm to 27 °C and stirred for 12 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with dichloromethane (50 mL), washed with water (2 x 30 mL), brine (30 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by silicagel column chromatography (Combiflash) using 5% methanol in dichloromethane as eluent to obtain the title compound *tert*-butyl 4-(2-(3,4-dichlorophenoxy)acetamido)piperidine-1-carboxylate (0.42 g, 84% yield) as off white gum. LCMS (ES) m/z = 303.1 [(M+H)-(Boc group)]⁺. ¹H NMR (400 MHz, CDCl₃): δ ppm 1.35 – 1.38 (m, 2 H), 1.45 (s, 9 H), 1.90 – 1.93 (m, 2 H), 2.87 (bs, 2 H), 4.03 – 4.04 (m, 3 H), 4.44 (s, 2 H), 6.30 (d, J = 7.6 Hz, 1 H), 6.76 – 6.79 (m, 1 H), 7.04 (d, J = 2.4 Hz, 1 H), 7.37 (d, J = 8.8 Hz, 1 H).

Step 2: To a solution of *tert*-butyl 4-(2-(3,4-dichlorophenoxy)acetamido)piperidine-1-carboxylate (0.42 g, 1.044 mmol, 1 equiv) in dichloromethane (5 mL) was added 4M hydrochloric acid solution in 1, 4- dioxane (5 mL) at 0 °C. The resulting mixture was allowed to warm to 27 °C and stirred for 4 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 2-(3,4-dichlorophenoxy)-N-(piperidin-4-yl)acetamide hydrochloride (0.38 g, crude) as off white solid. LCMS (ES) m/z = 303.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ ppm 1.63 – 1.66 (m, 2 H), 1.84 – 1.87 (m, 2 H), 2.94 (bs, 2 H), 3.22 (s, 2 H), 3.89 (bs, 1 H), 4.53 (s, 2 H), 6.94 – 6.97 (m, 1 H), 7.22 (d, J = 2.8 Hz, 1 H),

7.52 (d, J = 8.8 Hz, 1 H), 8.26 (d, J = 8.0 Hz, 1 H), 8.62 – 8.70 (m, 2 H), 11.0 (bs 1 H).

The crude product was taken as such to next step without purification.

Step 3: To a solution of 2-(3,4-dichlorophenoxy)-N-(piperidin-4-yl)acetamide hydrochloride (0.2 g, 0.588 mmol, 1 equiv) in dichloromethane (10 mL) were added ethyl 2-bromo-4-(4-chlorophenoxy)butanoate (0.22 g, 0.706 mmol, 1.2 equiv) and triethyl amine (0.25 mL, 1.766 mmol, 3.0 equiv). The resulting mixture was subjected to microwave irradiation at 80 °C for 2 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with ethyl acetate (100 mL), washed with water (2 x 30 mL), brine (30 mL), dried over anhydrous sodium sulphate, 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 dichloromethane as eluent to obtain the title compound ethyl 4-(4-chlorophenoxy)-2-(4-(2-(3,4-dichlorophenoxy)acetamido)piperidin-1-yl)butanoate (0.07 g) as pale brown gum. LCMS (ES) m/z = 543.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ ppm 1.25 – 1.29 (m, 3 H), 1.42 (bs, 2 H), 1.92 (bs, 2 H), 2.06 (bs, 1 H), 2.16 (bs, 1 H), 2.34 (bs, 1 H), 2.69 – 2.89 (m, 3 H), 3.47 (bs, 1 H), 3.88 – 3.96 (m, 2 H), 4.04 (bs, 1 H), 4.18 (bs, 2 H), 4.42 (s, 2 H), 6.30 (bs, 1 H), 6.76 – 6.81 (m, 3 H), 7.04 (bs, 1 H), 7.21 – 7.25 (m, 3 H), 7.37 (d, J = 8.0 Hz, 1 H).

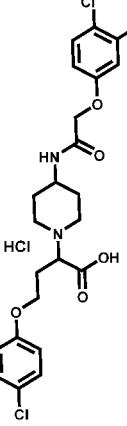
Step 4: To a solution of ethyl 4-(4-chlorophenoxy)-2-(4-(2-(3,4-dichlorophenoxy)acetamido)piperidin-1-yl)butanoate (0.07 g, 0.128 mmol, 1 equiv) in ethanol (5 mL) was added sodium hydroxide (0.05 g, 1.287 mmol, 10 equiv) in 2 mL of water, the mixture stirred for 4h. The progress of the reaction was monitored by TLC. After completion of reaction, the ethanol was removed by evaporation, the residue was diluted with water (5 mL), acidified with 1.5M hydrochloric acid to pH ~ 2 to 3. The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with water (10 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. Which was triturated with diethyl ether and *n*-pentane to obtain the title compound 4-(4-chlorophenoxy)-2-(4-(2-(3,4-dichlorophenoxy)acetamido)piperidin-1-yl)butanoic acid (0.048 g, 72% yield) as off white solid. LCMS (ES) m/z = 515.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ ppm 1.68 (bs, 2 H), 1.84 (bs, 2 H), 2.20 (bs, 2 H), 2.91 (bs, 2 H), 3.77 (bs, 2 H), 4.03 (bs, 1 H), 4.08 (bs, 1 H), 4.52 (s, 2 H), 6.92 – 6.97 (m, 3 H), 7.22 (d, J = 2.8 Hz, 1 H), 7.32 (d, J = 8.8 Hz, 2 H), 7.49 – 7.52 (m, 1 H), 8.14 (bs, 1 H). (two protons are merged with water peak. ¹H NMR-D₂O (400 MHz, DMSO-d₆): δ ppm 1.76 – 1.79 (m, 2 H), 1.93 – 1.97 (m, 2 H), 2.24 – 2.32 (m, 2 H), 3.01 – 3.11 (m, 2 H), 3.30 – 3.33 (m, 1 H), 3.38 – 3.42 (m, 1 H), 3.83 (bs, 2 H),

4.08 – 4.12 (m, 2 H), 4.54 (s, 2 H), 6.95 – 7.00 (m, 3 H), 7.24 (bs, 1 H), 7.34 (d, J = 8.0 Hz, 2 H), 7.54 (d, J = 8.8 Hz, 1 H).

Step 5: To a mixture of 4-(4-chlorophenoxy)-2-(4-(2-(3,4-dichlorophenoxy)acetamido)piperidin-1-yl)butanoic acid (0.045 g, 0.087 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added 1 M aqueous hydrochloric acid (2 mL) at 27 °C and the resulting mixture was stirred for 10 min (up to clear solution). The reaction mixture was concentrated under reduced pressure to give the crude product, which was triturated with *n*-pentane and dried to obtain the title compound 4-(4-chlorophenoxy)-2-(4-(2-(3,4-dichlorophenoxy)acetamido)piperidin-1-yl)butanoic acid hydrochloride (0.045 g, 95% yield) as off white solid.. LCMS (ES) m/z = 515.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.81 – 1.83 (m, 2 H), 1.93 (bs, 2 H), 2.26 – 2.27 (m, 1 H), 3.13 (bs, 2 H), 3.50 (bs, 2 H), 3.87 (bs, 1 H), 4.05 (bs, 2 H), 4.10 – 4.14 (m, 1 H), 4.54 (s, 2 H), 6.93 – 6.97 (m, 3 H), 7.22 (d, J = 3.2 Hz, 1 H), 7.33 (d, J = 8.8 Hz, 2 H), 7.52 (d, J = 8.8 Hz, 1 H). 8.27 (d, J = 7.2 Hz, 1 H). 10.3 (bs, 1 H). (Note: Protons are merged with water residual peak). ¹H NMR-D2O (400 MHz, DMSO-d₆) δ ppm 1.76 – 1.81(m, 2 H), 1.93 (bs, 2 H), 2.23 – 2.27 (m, 1 H), 2.36 (bs, 1 H), 3.06 – 3.12 (m, 1 H), 3.15 – 3.21 (m, 1 H), 3.32 – 3.35 (m, 1 H), 3.49 – 3.71 (m, 1 H), 3.82 (bs, 1 H), 3.95 – 3.97 (m, 1 H), 4.02 – 4.10 (m, 2 H), 4.49 (s, 2 H), 6.90 – 6.95 (m, 3 H), 7.19 (d, J = 2.4 Hz, 1 H), 7.30 (d, J = 8.8 Hz, 2 H), 7.49 (d, J = 8.8 Hz, 1 H).

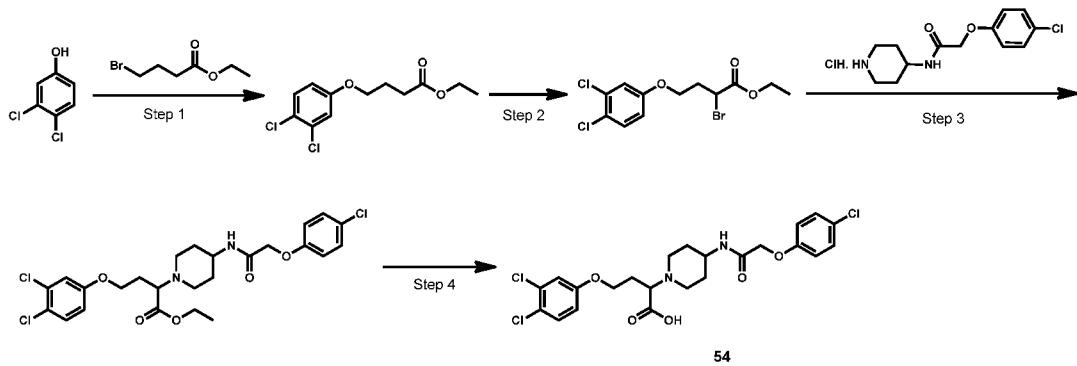
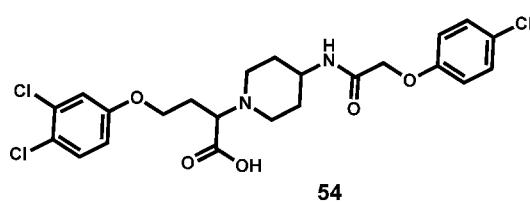
Table 14

Cmpd #	Structure	Name	LCMS m/z [M+H] ⁺	¹ H-NMR (400 MHz, DMSO-d ₆)
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53		4-(4-chlorophenoxy)-2-(4-(2-(3,4-dichlorophenoxy)acetamido)piperidin-1-yl)butanoic acid hydrochloride	515.0	1.81 – 1.83 (m, 2 H), 1.93 (bs, 2 H), 2.26 – 2.27 (m, 1 H), 3.13 (bs, 2 H), 3.50 (bs, 2 H), 3.87 (bs, 1 H), 4.05 (bs, 2 H), 4.10 – 4.14 (m, 1 H), 4.54 (s, 2 H), 6.93 – 6.97 (m, 3 H), 7.22 (d, <i>J</i> = 3.2 Hz, 1 H), 7.33 (d, <i>J</i> = 8.8 Hz, 2 H), 7.52 (d, <i>J</i> = 8.8 Hz, 1 H), 8.27 (d, <i>J</i> = 7.2 Hz, 1 H), 10.3 (bs, 1 H).
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Example 54

2-(4-(2-(4-chlorophenoxy)acetamido)piperidin-1-yl)-4-(3,4-dichlorophenoxy)butanoic acid



Step 1: To a solution of 3, 4-dichlorophenol (1.0 g, 6.134 mmol, 1 equiv) in N, N-dimethylformamide (10 mL) was added anhydrous potassium carbonate (1.69 g, 12.269 mmol, 2.0 equiv) and ethyl 4-bromobutanoate (1.31 mL, 9.202 mmol, 1.5 equiv). The reaction mixture was heated to 140 °C and stirred for 3 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was allowed to cool to 27 °C, the reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the combined organics were washed with brine (50 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by silica gel column chromatography using 10% ethyl acetate in hexane as eluent to obtain the title compound ethyl 4-(3,4-dichlorophenoxy)butanoate (1.5 g, 89 % yield) as colourless liquid. LCMS (ES) *m/z* = 277.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ ppm 1.25 (t, *J* = 7.2 Hz, 3 H), 2.06 – 2.13 (m, 2 H), 2.49 (t, *J* = 7.6 Hz, 2 H), 3.97 (t, *J* = 6.4 Hz, 2 H), 4.12 – 4.17 (m, 2 H), 6.73 (dd, *J* = 8.8 Hz, 2.8 Hz, 1 H), 6.97 (d, *J* = 2.8 Hz, 1 H), 7.30 (d, *J* = 8.8 Hz, 1 H).

Step 2: To a solution of ethyl 4-(3,4-dichlorophenoxy)butanoate (0.5 g, 1.804 mmol, 1.0 equiv) in dry tetrahydrofuran (20 mL) was added lithium diisopropylamide solution (2.0 M in THF/heptane/ethylbenzene) (1.35 mL, 2.706 mmol, 1.5 equiv) slowly at – 78 °C. The reaction mixture was stirred for another 1 h at – 78 °C. After 1 h, a solution of carbon tetrabromide (0.89 g, 2.706 mmol, 1.5 equiv) in dry tetrahydrofuran (15 mL) was added at – 78 °C, the mixture was gradually allowed to warm to 27 °C and stirred for 2 h. The reaction mixture was quenched with saturated aqueous solution of ammonium chloride (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by silica gel column chromatography using 7% ethyl acetate in hexane as eluent to obtain the title compound ethyl 2-bromo-4-(3,4-dichlorophenoxy)butanoate (0.15 g, crude) as pale brown liquid. ¹H NMR (400 MHz, CDCl₃): δ ppm 1.30 (t, *J* = 6.8 Hz, 3 H), 2.35 – 2.43 (m, 1 H), 2.49 – 2.58 (m, 1 H), 4.04 – 4.13 (m, 2 H), 4.20 – 4.28 (m, 2 H), 4.50 – 4.53 (m, 1 H), 6.74 (dd, *J* = 9.2 Hz, 3.2 Hz, 1 H), 6.99 (d, *J* = 2.4 Hz, 1 H), 7.32 (d, *J* = 8.8 Hz, 1 H).

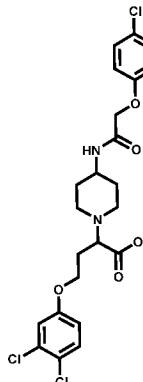
Step 3: To a stirred solution of ethyl 2-bromo-4-(3,4-dichlorophenoxy)butanoate (0.28 g, 0.786 mmol, 1.2 equiv) in *N,N*-dimethylformamide (5 mL) were added a 2-(4-chlorophenoxy)-*N*-(piperidin-4-yl)acetamide hydrochloride (0.2 g, 0.655 mmol, 1 equiv), and triethyl amine (0.27 mL, 1.965 mmol, 3.0 equiv). The resulting mixture was stirred for 16 h at 27 °C. The progress of the reaction was monitored by TLC. After completion of

reaction, the reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (3 x 50 mL), the combined organics were washed with water (30 mL), brine (20 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by silica gel column chromatography (CombiFlash) using 3% methanol in dichloromethane as eluent to obtain the title compound ethyl 2-(4-(2-(4-chlorophenoxy)acetamido)piperidin-1-yl)-4-(3,4-dichlorophenoxy)butanoate (0.18 g, 51% yield) as pale brown gum. LCMS (ES) m/z = 543.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ ppm 1.18 (t, J = 7.2 Hz, 3 H), 1.37 – 1.44 (m, 3 H), 1.66 (bs, 2 H), 1.95 – 2.06 (m, 2 H), 2.11 – 2.17 (m, 1 H), 2.65 – 2.72 (m, 1 H), 2.83 – 2.84 (m, 1 H), 3.39 (t, J = 8.0 Hz, 1 H), 3.55 (bs, 1 H), 3.98 – 4.14 (m, 4 H), 4.42 (s, 2 H), 6.91 – 6.95 (m, 3 H), 7.19 (d, J = 2.8 Hz, 1 H) 7.31 (d, J = 8.8 Hz, 2 H), 7.49 (d, J = 9.2 Hz, 1 H), 7.90 (d, J = 8.0 Hz, 1 H).

Step 4: To a solution of ethyl 2-(4-(2-(4-chlorophenoxy)acetamido)piperidin-1-yl)-4-(3,4-dichlorophenoxy)butanoate (0.17 g, 0.312 mmol, 1 equiv) in ethanol (5 mL) was added sodium hydroxide (0.12 g, 0.3125 mmol, 10 equiv) in 2 ml of water, the mixture was heated to 50 °C and stirred for 3h. The progress of the reaction was monitored by TLC. After completion of reaction, the ethanol was removed by evaporation, the residue was diluted with water (5 mL), acidified with 1.5 M hydrochloric acid to pH ~ 2 to 3. The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with water (2 x 30 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give the crude product. The crude product was triturated with *n*-pentane and dried to obtain the title compound 2-(4-(2-(4-chlorophenoxy)acetamido)piperidin-1-yl)-4-(3,4-dichlorophenoxy)butanoic acid (0.085 g, 53% yield) as off white solid. LCMS (ES) m/z = 515.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ ppm 1.41 – 1.50 (m, 2 H), 1.69 (bs, 2 H), 1.94 – 2.05 (m, 2 H), 2.29 (d, J = 9.6 Hz, 1 H), 2.60 (bs, 1 H), 2.77 (d, J = 10.8 Hz, 1 H), 2.85 (d, J = 11.2 Hz, 1 H) 3.38 (bs, 1 H), 3.58 (bs, 1 H), 4.01 – 4.09 (m, 2 H), 4.43 (s, 2 H), 6.94 (d, J = 8.8 Hz, 3 H), 7.20 (d, J = 2.4 Hz, 1 H), 7.31 (d, J = 8.8 Hz, 2 H), 7.49 (d, J = 8.8 Hz, 1 H) 7.93 (d, J = 7.6 Hz, 1 H), 12.0 (bs, 1 H).

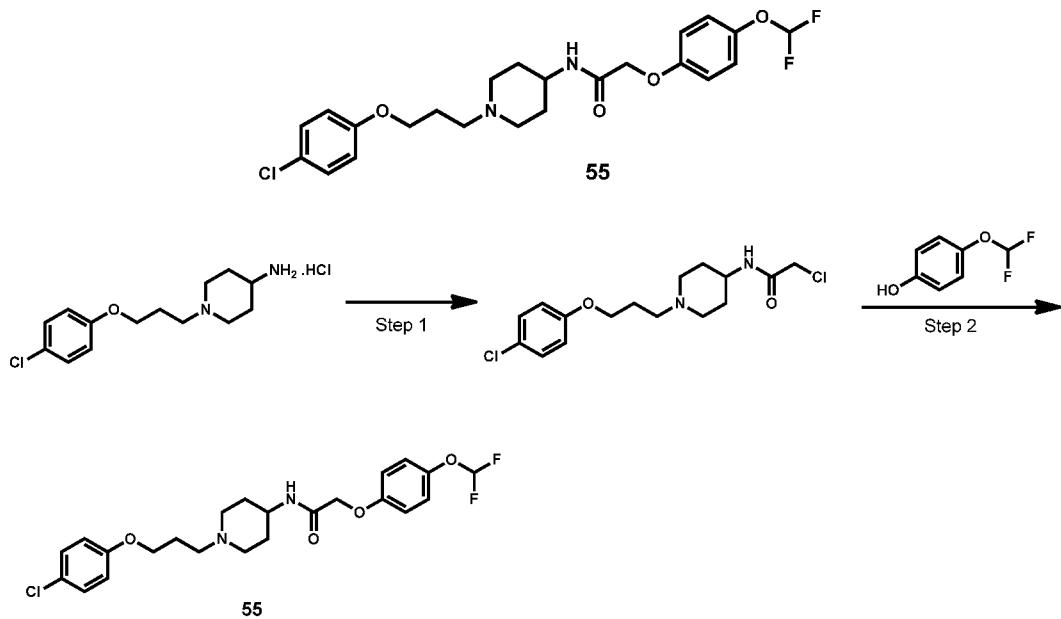
Table 15

Cmpd #	Structure	Name	LCMS m/z [M+H] ⁺	¹ H-NMR (400 MHz, DMSO-d ₆)
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54		2-(4-(2-(4-chlorophenoxy)acetamido)piperidin-1-yl)-4-(3,4-dichlorophenoxy)butanoic acid	515.1	1.41 – 1.50 (m, 2 H), 1.69 (bs, 2 H), 1.94 – 2.05 (m, 2 H), 2.29 (d, J = 9.6 Hz, 1 H), 2.60 (bs, 1 H), 2.77 (d, J = 10.8 Hz, 1 H), 2.85 (d, J = 11.2 Hz, 1 H), 3.38 (bs, 1 H), 3.58 (bs, 1 H), 4.01 – 4.09 (m, 2 H), 4.43 (s, 2 H), 6.94 (d, J = 8.8 Hz, 3 H), 7.20 (d, J = 2.4 Hz, 1 H), 7.31 (d, J = 8.8 Hz, 2 H), 7.49 (d, J = 8.8 Hz, 1 H), 7.93 (d, J = 7.6 Hz, 1 H), 12.00 (bs, 1 H).
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Example 55

N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-(4-(difluoromethoxy)phenoxy)acetamide



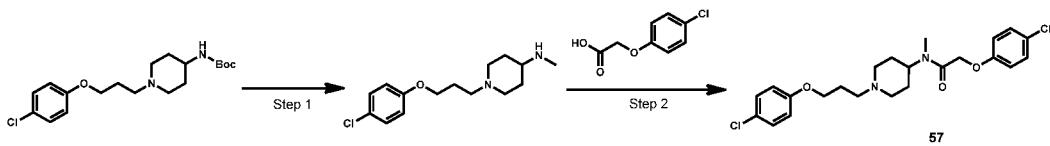
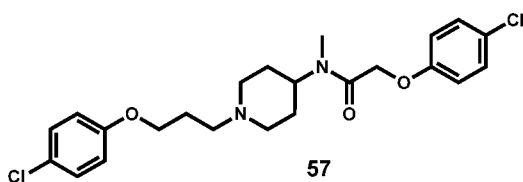
Step 1: To a stirred solution of 1-(3-(4-chlorophenoxy)propyl)piperidin-4-amine hydrochloride (0.5 g, 1.64 mmol, 1.0 equiv.) in DCM (70 mL) was added triethyl amine (0.81 mL, 5.74 mmol, 3.5 equiv.) dropwise at 0 °C and was stirred for 30 mins. Then compound chloro acetyl chloride (0.15 mL, 1.96 mmol, 1.2 equiv.) was added dropwise at 0 °C. Then reaction mixture was stirred at room temperature for 16 h. After consumption of the starting material (TLC, 5 % MeOH in DCM), reaction mixture was diluted with DCM (100 mL), washed with ice cold water (2 × 50 mL), saturated ammonium chloride solution (50 mL) and water (50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Crude was purified by flash column chromatography using 6 % methanol in dichloromethane to give 2-chloro-N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)acetamide (0.15 g, 26.5 % yield) as off white solid. LCMS (ES) m/z = 345.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.35 – 1.43 (m, 2 H), 1.68 – 1.71 (m, 2 H), 1.82 (t, J = 6.6 Hz, 2 H), 1.96 (t, J = 11.0 Hz, 2 H), 2.38 (t, J = 6.4 Hz, 2 H), 2.77 (d, J = 11.2 Hz, 2 H), 3.50 (bs, 1 H), 3.95 – 3.98 (m, 4 H), 6.93 (d, J = 8.8 Hz, 2 H), 7.29 (d, J = 8.8 Hz, 2 H), 8.07 (d, J = 7.2 Hz, 1 H).

Step 2: To a stirred solution of 2-chloro-N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)acetamide (0.15 g, 0.43 mmol, 1.0 equiv.) in acetonitrile (20 mL) was added caesium carbonate (0.35 g, 1.08 mmol, 2.5 equiv.) and compound 4-(difluoromethoxy)phenol (0.08 mL, 0.65 mmol, 1.5 equiv.) at room temperature and then reaction mixture was stirred at 80 °C for 16 h.. After consumption of the starting material (TLC, 5 % MeOH in DCM), reaction mixture was concentrated under reduced pressure and to the residue obtained was added water (5 mL), stirred for 15 - 20 mins and was filtered through sintered funnel. The solid obtained was washed with water (10 mL), diethyl ether (3 × 10 mL) and n-pentane (2 × 10 mL), dried under high vaccum to give N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-(4-(difluoromethoxy)phenoxy)acetamide (0.136 g, 66.9 % yield) as off white solid. LCMS (ES) m/z = 469.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.42 – 1.50 (m, 2 H), 1.65 – 1.68 (m, 2 H), 1.82 (t, J = 6.6 Hz, 2 H), 1.94 (t, J = 11.0 Hz, 2 H), 2.37 (t, J = 6.8 Hz, 2 H), 2.77 – 2.80 (m, 2 H), 3.59 – 3.60 (m, 1 H), 3.97 (t, J = 6.2 Hz, 2 H), 4.43 (s, 2 H), 6.88 (s, 0.25 H), 6.92 – 6.97 (m, 4 H), 7.07 (s, 0.25 H), 7.10 (d, J = 8.8 Hz, 2 H), 7.25 (s, 0.25 H), 7.29 (d, J = 8.8 Hz, 2 H), 7.89 (d, J = 8.0 Hz, 1 H).

The Compound of Example 56 was prepared generally according to the procedure described above for Example 55.

Table 16

Cmpd #	Structure	Name	LCMS <i>m/z</i> [M+H] ⁺	¹ H-NMR (400 MHz, DMSO-d ₆)
55		N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-(4-(difluoromethoxy)phenoxy)acetamide	469.1	1.42 – 1.50 (m, 2 H), 1.65 – 1.68 (m, 2 H), 1.82 (t, <i>J</i> = 6.6 Hz, 2 H), 1.94 (t, <i>J</i> = 11.0 Hz, 2 H), 2.37 (t, <i>J</i> = 6.8 Hz, 2 H), 2.77 – 2.80 (m, 2 H), 3.59 – 3.60 (m, 1 H), 3.97 (t, <i>J</i> = 6.2 Hz, 2 H), 4.43 (s, 2 H), 6.88 (s, 0.25 H), 6.92 – 6.97 (m, 4 H), 7.07 (s, 0.25 H), 7.10 (d, <i>J</i> = 8.8 Hz, 2 H), 7.25 (s, 0.25 H), 7.29 (d, <i>J</i> = 8.8 Hz, 2 H), 7.89 (d, <i>J</i> = 8.0 Hz, 1 H).
56		N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-(4-cyclopropylphenoxy)acetamide	443.2	0.55 (d, <i>J</i> = 4.4 Hz, 2 H), 0.85 (d, <i>J</i> = 7.2 Hz, 2 H), 1.42 – 1.50 (m, 2 H), 1.64 – 1.67 (m, 2 H), 1.82 – 1.83 (m, 3 H), 1.94 (t, <i>J</i> = 11.0 Hz, 2 H), 2.37 (t, <i>J</i> = 6.8 Hz, 2 H), 2.76 – 2.79 (m, 2 H), 3.58 – 3.60 (m, 1 H), 3.96 (t, <i>J</i> = 6.2 Hz, 2 H), 4.37 (s, 2 H), 6.81 (d, <i>J</i> = 8.4 Hz, 2 H), 6.93 (d, <i>J</i> = 8.8 Hz, 2 H), 6.97 (d, <i>J</i> = 8.4 Hz, 2 H), 7.29 (d, <i>J</i> = 8.8 Hz, 2 H), 7.83 (d, <i>J</i> = 8.0 Hz, 1 H).

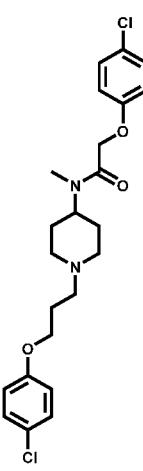
Example 57**2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-N-methylacetamide**

Step 1: To a stirred solution of tert-butyl (1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)carbamate (0.1 g, 0.27 mmol, 1.0 equiv.) in THF (10.0 mL) was added lithium aluminium hydride (1.0 M in THF) (0.81 g, 0.81 mmol, 3.0 equiv.) at 0 °C. The reaction was stirred at 70 °C for 3 h. After consumption of the starting material (TLC, 70 % EtOAc in hexane), the reaction mixture was quenched by ice cold water (3 mL) at 0 °C and was concentrated to give 1-(3-(4-chlorophenoxy)propyl)-N-methylpiperidin-4-amine (0.08 g, crude) as pale yellow liquid. LCMS (ES) m/z = 283.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm – crude

Step 2: To a stirred solution of 1-(3-(4-chlorophenoxy)propyl)-N-methylpiperidin-4-amine (0.08 g, 0.28 mmol, 1.0 equiv.) in DCM (10 mL) was added triethyl amine (0.12 mL, 0.84 mmol, 3.0 equiv.) and compound 2-(4-chlorophenoxy)acetic acid (0.063 g, 0.34 mmol, 1.2 equiv.) and T₃P (50% wt. in ethyl acetate) (0.42 mL, 0.70 mmol, 2.5 equiv.) was added dropwise at 0 °C. The reaction was stirred at room temperature for 16 h. After consumption of the starting material (TLC, 5 % MeOH in DCM), the reaction mixture was diluted with DCM (50 mL), and was washed with saturated sodium bicarbonate solution (2 × 10 mL) and water (2 × 10 mL). Combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to get the crude. Crude was purified by flash

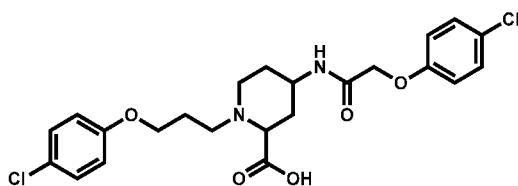
column chromatography using 3 – 4 % methanol in dichloromethane. It was again purified by prep HPLC (Analytical conditions: Column: Inertsil ODS 3V (50mm × 2.1mm × 3mic), Mobile phase (A): 0.1 % Ammonia in water, Mobile phase (B): Acetonitrile Flow rate: 0.7 mL/min, Compound RT: 4.89) to give 2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-N-methylacetamide (0.014 g, 11.0 % yield) as off white solid. LCMS (ES) m/z = 451.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.41 (d, J = 10.8 Hz, 1 H), 1.61 – 1.75 (m, 3 H), 1.82 (t, J = 6.4 Hz, 2 H), 1.89 – 1.96 (m, 2 H), 2.38 – 2.40 (m, 2 H), 2.69 (s, 1 H), 2.81 (s, 2 H), 2.90 (d, J = 10.8 Hz, 2 H), 3.50 – 3.60 (m, 0.5 H), 3.96 (t, J = 6.0 Hz, 2 H), 4.10 – 4.20 (m, 0.6 H), 4.81 (d, J = 22.4 Hz, 2 H), 6.88 – 6.93 (m, 4 H), 7.28 (d, J = 8.8 Hz, 4 H).

Table 17

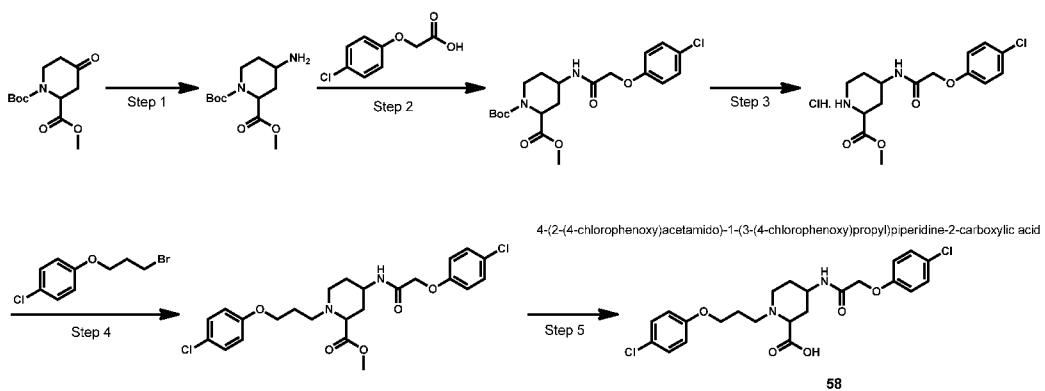
Cmpd #	Structure	Name	LCMS m/z [M+H] ⁺	¹ H-NMR (400 MHz, DMSO-d ₆)
57		2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-N-methylacetamide	451.1	1.41 (d, J = 10.8 Hz, 1 H), 1.61 – 1.75 (m, 3 H), 1.82 (t, J = 6.4 Hz, 2 H), 1.89 – 1.96 (m, 2 H), 2.38 – 2.40 (m, 2 H), 2.69 (s, 1 H), 2.81 (s, 2 H), 2.90 (d, J = 10.8 Hz, 2 H), 3.50 – 3.60 (m, 0.5 H), 3.96 (t, J = 6.0 Hz, 2 H), 4.10 – 4.20 (m, 0.6 H), 4.81 (d, J = 22.4 Hz, 2 H), 6.88 – 6.93 (m, 4 H), 7.28 (d, J = 8.8 Hz, 4 H).

Example 58

4-(2-(4-chlorophenoxy)acetamido)-1-(3-(4-chlorophenoxy)propyl)piperidine-2-carboxylic acid



58



Step 1: To a solution of 1-(tert-butyl) 2-methyl 4-oxopiperidine-1,2-dicarboxylate (0.6 g, 2.3 mmol, 1 equiv) in methanol (60 mL) at 0 °C was added portion wise ammonium acetate (1.79 g, 23.3 mmol, 10 equiv) and maintained for 1 h at room temperature. After that sodium cyanoborohydride (0.57 g, 9.2 mmol, 4 equiv) and acetic acid (2 drops, catalytic) were added and maintained for 48 h at room temperature. After consumption of the starting material (tlc, 50 % EtOAc in hexane), the reaction mixture was concentrated, diluted with 10 % methanol in DCM (150 mL) and washed with 10% aqueous NaHCO₃ solution (20 mL), cold water (20 mL), the organic layer dried over anhydrous sodium sulphate, filtered and concentrated to obtain 1-(tert-butyl) 2-methyl 4-aminopiperidine-1,2-dicarboxylate (0.5 g, crude, 99.6% yield) as off white solid. LCMS (ES) *m/z* = 259.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm – crude.

Step 2: To a solution of 1-(tert-butyl) 2-methyl 4-aminopiperidine-1,2-dicarboxylate (0. 5

g, 1.90 mmol, 1 equiv) in DCM (100.0 mL) at 0 °C was added triethylamine (0.66 mL, 4.7 mmol, 2.5 equiv) and 2-(4-chlorophenoxy)acetic acid (0.43 g, 2.30 mmol, 1.2 equiv). After stirring for 5 minutes, T₃P (50 wt. % in ethyl acetate) (2.85 mL, 4.70 mmol, 2.5 equiv) was added to the reaction mixture. Then reaction mixture was allowed to stir at room temperature for 18 h. After consumption of 1-(tert-butyl) 2-methyl 4-aminopiperidine-1,2-dicarboxylate, the reaction mixture was diluted with DCM (150 mL) and washed with cold water (50 mL). The combined organic extract was washed with 10% aqueous NaHCO₃ solution (2 × 50 mL), water (50 mL) and dried over anhydrous sodium sulphate. The organic layer was filtered and concentrated at rotavapor to give 1-(tert-butyl) 2-methyl 4-(2-(4-chlorophenoxy)acetamido)piperidine-1,2-dicarboxylate (0.70 g, crude) as viscous liquid. LCMS (ES) *m/z* = 327.2 [M+H]⁺ (Deboc mass was observed).. ¹H NMR (400 MHz, DMSO-d₆) δ ppm – crude.

Step 3: To a solution of 1-(tert-butyl) 2-methyl 4-(2-(4-chlorophenoxy)acetamido)piperidine-1,2-dicarboxylate (0.7 g, 1.6 mmol, 1 equiv) in DCM (7.0 mL) at 0 °C was added 4MHCl in dioxane (7.0 mL). Then reaction mixture was allowed to stir at room temperature for 16 h. After consumption of 1-(tert-butyl) 2-methyl 4-(2-(4-chlorophenoxy)acetamido)piperidine-1,2-dicarboxylate, the reaction mixture was concentrated at rotavapor and washed with n-pentane (2 × 10 mL) to give methyl 4-(2-(4-chlorophenoxy)acetamido)piperidine-2-carboxylate hydrochloride (0.55 g, crude, 86.41% yield) as off white solid. LCMS (ES) *m/z* = 327.0 [M+H]⁺ , free amine mass was observed. ¹H NMR (400 MHz, DMSO-d₆) δ ppm – crude.

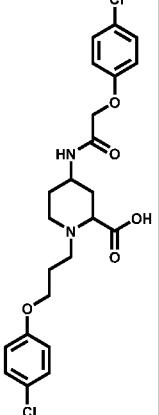
Step 4: To a solution of methyl 4-(2-(4-chlorophenoxy)acetamido)piperidine-2-carboxylate hydrochloride (0.55 g, 1.5 mmol, 1 equiv) in Triethyl amine (0.84 mL, 6.0 mmol, 4.0 equiv) at 0 °C was added 1-(3-bromopropoxy)-4-chlorobenzene (0.45 g, 1.8 mmol, 1.2 equiv). Then reaction mixture was allowed to stir at 100 °C for 4 h. After consumption of methyl 4-(2-(4-chlorophenoxy)acetamido)piperidine-2-carboxylate hydrochloride, the reaction mixture was diluted with 10 % methanol in DCM (150 mL) and washed with cold water (2 × 20 mL). The combined organic extract was dried over anhydrous sodium sulphate. The organic layer was filtered and concentrated at rotavapor to give crude which was purified by flash chromatography using 1 % to 50 % ethyl acetate in hexane as an eluent to afford methyl 4-(2-(4-chlorophenoxy)acetamido)-1-(3-(4-chlorophenoxy)propyl)piperidine-2-carboxylate (0.15 g, 20 % yield) as off white solid.

LCMS (ES) m/z = 495.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.44 – 1.59 (m, 2 H), 1.66 – 1.72 (m, 2 H), 1.79 – 1.96 (m, 2.5 H), 2.02 – 2.20 (m, 1 H), 2.21 – 2.30 (m, 0.5 H), 2.58 – 2.64 (m, 1.5 H), 2.84 – 2.89 (m, 0.5 H), 2.97 – 3.02 (m, 1 H), 3.55 (s, 1 H), 3.58 (s, 2 H), 3.59 – 3.68 (m, 0.5 H), 3.80 – 3.82 (m, 0.5 H), 3.95 – 4.01 (m, 2 H), 4.43 (s, 2 H), 6.89 – 6.95 (m, 4 H), 7.30 (t, J = 9.4 Hz, 4 H), 7.91 (d, J = 8.0 Hz, 0.5 H), 7.97 (d, J = 7.6 Hz, 0.5 H).

Step 5: To a stirred solution of methyl 4-(2-(4-chlorophenoxy)acetamido)-1-(3-(4-chlorophenoxy)propyl)piperidine-2-carboxylate (0.15 g, 0.3 mmol, 1.0 equiv) in tetrahydrofuran (3 mL), water (0.75 mL) and lithium hydroxide monohydrate (0.05 g, 1.2 mmol, 4 equiv) were added at room temperature and stirred for 36 h. Reaction mixture was evaporated, resulting aqueous layer was acidified with 2 N HCl solution at 0 °C and pH was maintained 5-6, obtained precipitate was filtered washed with cold water (2×5 mL), diethyl ether (2x10 mL) pentane (2x10 mL) and dried under vacuum to obtain 4-(2-(4-chlorophenoxy)acetamido)-1-(3-(4-chlorophenoxy)propyl)piperidine-2-carboxylic acid (0.04 g, 27.58% yield) as off white solid. LCMS (ES) m/z = 481.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.49 – 1.54 (m, 0.5 H), 1.57 – 1.60 (m, 0.5 H), 1.68 – 1.77 (m, 1.5 H), 1.84 – 1.94 (m, 3 H), 2.65 – 2.71 (m, 1 H), 2.80 (bs, 0.5 H), 2.90 (bs, 0.5 H), 3.02 (bs, 1 H), 3.16 – 3.19 (m, 1 H), 3.53 (s, 1 H), 3.77 – 3.83 (m, 1.5 H), 3.97 (s, 2 H), 4.44 (s, 2 H), 6.90 – 6.95 (m, 4 H), 7.30 (t, J = 9.0 Hz, 4 H), 7.95 (d, J = 7.2 Hz, 0.6 H), 8.08 (d, J = 7.6 Hz, 0.4 H).

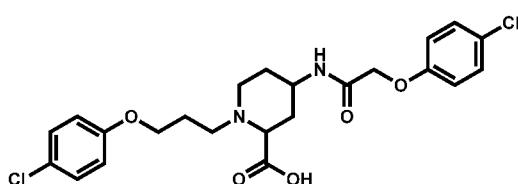
Table 18

Cmpd #	Structure	Name	LCMS m/z [M+H] ⁺	¹ H-NMR (400 MHz, DMSO-d ₆)
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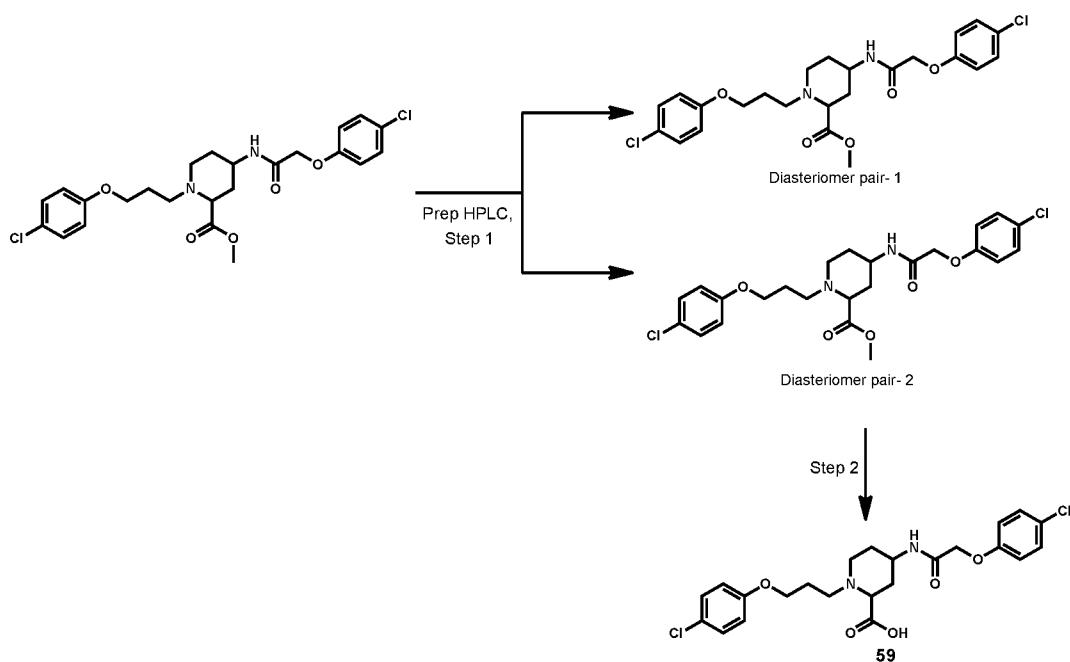
58		4-(2-(4-chlorophenoxy)acetamido)-1-(3-(4-chlorophenoxy)propyl)piperidine-2-carboxylic acid	481.4	1.49 – 1.54 (m, 0.5 H), 1.57 – 1.60 (m, 0.5 H), 1.68 – 1.77 (m, 1.5 H), 1.84 – 1.94 (m, 3 H), 2.65 – 2.71 (m, 1 H), 2.80 (bs, 0.5 H), 2.90 (bs, 0.5 H), 3.02 (bs, 1 H), 3.16 – 3.19 (m, 1 H), 3.53 (s, 1 H), 3.77 – 3.83 (m, 1.5 H), 3.97 (s, 2 H), 4.44 (s, 2 H), 6.90 – 6.95 (m, 4 H), 7.30 (t, J = 9.0 Hz, 4 H), 7.95 (d, J = 7.2 Hz, 0.6 H), 8.08 (d, J = 7.6 Hz, 0.4 H).
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Example 59

4-(2-(4-chlorophenoxy)acetamido)-1-(3-(4-chlorophenoxy)propyl)piperidine-2-carboxylic acid



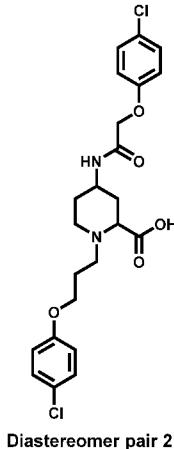
59



Step 1: Methyl 4-(2-(4-chlorophenoxy)acetamido)-1-(3-(4-chlorophenoxy)propyl)piperidine-2-carboxylate was purified by prep HPLC (Analytical conditions: Column: Inertsil ODS 3V (250mm × 4.6mm × 5mic), Mobile phase (A): 0.1 % Ammonia in water, Mobile phase (B): Acetonitrile, Flow rate: 1.0 mL/min, compound RT (pair -1): 14.108 minutes, compound RT (pair -2): 17.987 minutes) to get Z14 (pair -1) and Z15 (pair -2). Z15 is used to next step (Methyl ester hydrolysis).

Step 2: Compound 6 procedure reference is example of 5. (4-(2-(4-chlorophenoxy)acetamido)-1-(3-(4-chlorophenoxy)propyl)piperidine-2-carboxylic acid) (0.08 g, 83.33 % yield) as white solid. LCMS (ES) $m/z = 481.1 [M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.53 (d, $J = 9.2$ Hz, 1 H), 1.70 – 1.77 (m, 2 H), 1.86 – 1.95 (m, 3 H), 2.63 – 2.70 (m, 2 H), 2.85 (bs, 1 H), 3.05 – 3.09 (m, 1 H), 3.60 (bs, 1 H), 3.82 – 3.86 (m, 1 H), 3.98 (t, $J = 6.2$ Hz, 2 H), 4.45 (s, 2 H), 6.93 (t, $J = 8.2$ Hz, 4 H), 7.30 (t, $J = 8.8$ Hz, 4 H), 7.98 (d, $J = 7.6$ Hz, 1 H).

Table 19

Cmpd #	Structure	Name	LCMS <i>m/z</i> [M+H] ⁺	¹ H-NMR (400 MHz, DMSO-d ₆)
59	 Diastereomer pair 2	4-(2-(4-chlorophenoxy)acetamido)-1-(3-(4-chlorophenoxy)propyl)piperidine-2-carboxylic acid	481.1	1.53 (d, <i>J</i> = 9.2 Hz, 1 H), 1.70 – 1.77 (m, 2 H), 1.86 – 1.95 (m, 3 H), 2.63 – 2.70 (m, 2 H), 2.85 (bs, 1 H), 3.05 – 3.09 (m, 1 H), 3.60 (bs, 1 H), 3.82 – 3.86 (m, 1 H), 3.98 (t, <i>J</i> = 6.2 Hz, 2 H), 4.45 (s, 2 H), 6.93 (t, <i>J</i> = 8.2 Hz, 4 H), 7.30 (t, <i>J</i> = 8.8 Hz, 4 H), 7.98 (d, <i>J</i> = 7.6 Hz, 1 H).

Example 60: ATF4 Cell Based Assay

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.

Cells were propagated in growth media consisting of 90% DMEM F12 (InVitrogen # 11320-033), 10% Fetal Bovine Serum (Gibco # 10438-026), 5mM Glutamax (Gibco #

35050-061), 5mM Hepes, (Gibco # 15630-080), and 0.5mg/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), (5mM Glutamax (Gibco # 35050-061), 5mM Hepes, (Gibco # 15630-080), and 0.5mg/ml Geneticin (Gibco # 10131-027). Suspended cells were spun down at 300g for 5 min, the supernatant was removed and the cell pellet was suspended in warm media (30-37°C) comprised as above at (1e6 cell/ml).

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 15-20k cell/well. Cells were incubated for 1hour at 37°C. Then, 5µL of 1.5µM or 1 µM of Thapsigargin (final concentration: 200-300nM) was added to each well of cells. Assay plates containing cells were incubated for 14-18 hours at 37°C.

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. 25microliters/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 61 - Capsule Composition

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 20

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)piperidin-4-yl)acetamide (Compound of Example 1)	7 mg
Lactose	53 mg
Talc	16 mg
Magnesium Stearate	4 mg

Example 62 - Injectable Parenteral Composition

An injectable form for administering the present invention is produced by stirring 1.7% by weight of 2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)acetamide (Compound of Example 2) in 10% by volume propylene glycol in water.

Example 63 Tablet Composition

The sucrose, calcium sulfate dihydrate and a PERK inhibitor as shown in Table 4 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 21

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
8-(2-(4-chlorophenoxy)acetyl)-3-(2-(4-chlorophenoxy)ethyl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (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

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

The compounds of Examples 1 and 3 to 8 were 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}) < 300 nM.

The compound of Example 1 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 75.86 nM.

The compound of Example 2 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}) < 4000 nM.

The compounds of Examples 9 to 26, 28, 30 to 38, 41 to 48, 50 to 55, and 57 to 59 were 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}) < 1,000 nM.

The compounds of Examples 27, 29, 39, 40, 49, and 56 were 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}) > 1,000 nM.

The compound of Example 11 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 32 nM.

The compound of Example 17 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 76.8 nM.

The compound of Example 24 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 200.6 nM.

The compound of Example 30 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 110.5 nM.

The compound of Example 37 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 98.7 nM.

The compound of Example 43 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 58.4 nM.

The compound of Example 50 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 93.9 nM.

The compound of Example 57 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 61.2 nM.

The compound of Example 59 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 (IC₅₀) of 172.5 nM.

References.

1. Wek RC, Jiang H-Y, Anthony TG. *Coping with stress: eIF2 kinases and translational control.* *Biochem. Soc. Trans.* 2006 Feb;34(Pt 1):7-11.
2. Hinnebusch AG, Lorsch JR. *The mechanism of eukaryotic translation initiation: new insights and challenges.* *Cold Spring Harb Perspect Biol.* 2012;4(10).
3. Krishnamoorthy T, Pavitt GD, Zhang F, Dever TE, Hinnebusch AG. *Tight binding of the phosphorylated alpha subunit of initiation factor 2 (eIF2alpha) to the regulatory subunits of guanine nucleotide exchange factor eIF2B is required for inhibition of translation initiation.* *Mol Cell Biol.* 2001 Aug;21(15):5018-30.
4. Hinnebusch AG. *Translational regulation of GCN4 and the general amino acid control of yeast.* *Annu. Rev. Microbiol.* 2005;59:407-50.
5. Jackson RJ, Hellen CUT, Pestova TV. *The mechanism of eukaryotic translation initiation and principles of its regulation.* *Nat Rev Mol Cell Biol.* 2010 Feb 1;11(2):113-27.
6. Harding HP, 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 Nov;6(5):1099-108.
7. Palam LR, Baird TD, Wek RC. *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.
8. Vattem KM, Wek RC. *Reinitiation involving upstream ORFs regulates ATF4 mRNA translation in mammalian cells.* *Proc Natl Acad Sci USA.* 2004 Aug 3;101(31):11269-74.

9. Ma Y, Brewer JW, Diehl JA, Hendershot LM. *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.
10. Pavitt GD, Ron D. *New insights into translational regulation in the endoplasmic reticulum unfolded protein response.* *Cold Spring Harb Perspect Biol.* 2012 Jun;4(6).
11. Ron D, Walter P. *Signal integration in the endoplasmic reticulum unfolded protein response.* *Nat Rev Mol Cell Biol.* 2007 Jul;8(7):519—29.
12. Gardner BM, Walter P. *Unfolded proteins are Irel-activating ligands that directly induce the unfolded protein response.* *Science.* 2011 Sep 30;333(6051):1891-4.
13. Harding HP, 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.
14. Walter P, Ron D. *The unfolded protein response: from stress pathway to homeostatic regulation.* *Science.* 2011 Nov 25;334(6059):1081-6.
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.
16. Shore GCG, Papa FRF, Oakes SAS. *Signaling cell death from the endoplasmic reticulum stress response.* *Current Opinion in Cell Biology.* 2011 Apr 1;23(2):143-9.
17. Bi M, Naczki C, Koritzinsky M, Fels D, 174 WO 2014/144952 PC T/US2014/029568 Blais J, Hu N, Harking H, Novoa I, Varia M, Raleigh J, Scheuner D, Kaufman RJ, Bell J, Ron D, Wouters BG, Koumenis C. 2005. *ER stress-regulated translation increases tolerance to extreme hypoxia and promotes tumor growth.* *EMBO J.* 24:3470-3481.
18. Bobrovnikova-Marjon E, Pytel D, Vaites LP, Singh N, Koretzky GA, Diehl JA. 2010. *PERK promotes cancer cell proliferation and tumor growth by limiting oxidative DNA damage.* *Oncogene* 29: 3881-3895.

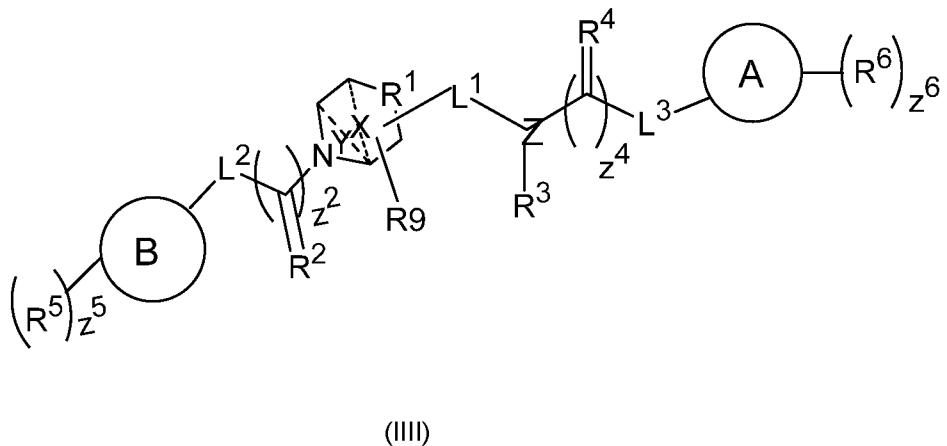
19. Avivar-Valderas A, Bobrovnikova-Marjon E, Diehl A, Nagi C, Debnath J, Aguirre-Guiso JA 2011. *PERK integrates autophagy and oxidative stress responses to promote survival during extracellular matrix detachment.* Mol Cel Biol 31:3616-3629.
20. Axten JM., Medina J. R., Feng Y., Shu A., Romeril S. P. et al. 2012. *Discovery of 7-methoxy-5(I-([3-10 (trifluoromethyl)phenyl]acetyl)-2, 3-dihydro-1H-indo1-5yl)-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
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.
22. Moreno JA, Radford H, Peretti D, Steinert JR, Verity N, Martin MG, Halliday M, Morgan J, Dinsdale D, Ortori CA, Barrett DA, Tsaytler P, Bertolotti A, Willis AE, Bushell M, Mallucci GR. 2012. *Sustained translational repression by eIF2n-P mediates prion neurodegeneration.* Nature 485:507-511.
23. Pavitt GD and Proud CG. 2009. *Protein synthesis and its control in neuronal cells with a focus on vanishing white matter disease.* Biochem Soc Trans 37:1298-201310.
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 eIF2n kinase GCN2.* Nature 436:1166-1173.
25. Costa-Mattioli M., Gobert D., Stern E., Garnache K., Colina RI, Cuello C., Sossin W., Kaufman R., Pelletier J., Rosenblum et al. 2007. *eIF2n phosphorylation bidirectionally regulates the switch from short to long term synaptic plasticity and memory.* Cell 25 129: 195-206.
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.

27. Borck G., Shin B.S., Stiller B., et al 2012. *eIF2y mutation that disrupts eIF2 complex integrity links intellectual disability to impaired translation 30 initiation.* *Mol Cell* 48:1-6.
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.
29. Mikami S., Masutani M., Sonenber N., Yokoyama S. And Imataka H. 175 WO 2014/144952 PC T/US2014/029568 2006. *An efficient mammalian cell-free translation system supplemented with translation factors.* *Protein Expr. Purif.* 46:348-357.

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.

What is claimed is:

1. A compound according to Formula (III):



wherein:

L^2 is selected from: a bond, -NH-, -O-, -S-, -S(O)-, -S(O)2-, substituted or

unsubstituted C1-6alkylene or substituted or unsubstituted

C1-6heteroalkylene, or L^2 is further taken together with B to form

heterocycloalkyl;

L^3 is selected from: a bond, -NH-, -O-, -S-, -S(O)-, -S(O)2-, substituted or

unsubstituted C1-6alkylene or substituted or unsubstituted

C1-6heteroalkylene, or L^3 is further taken together with A to form

heterocycloalkyl;

L^1 is selected from: a bond, -NH-, -C(R^7)-, -O-, -S-, -S(O)-, -S(O)2-, substituted or

unsubstituted C1-6alkylene and substituted or unsubstituted

C1-6heteroalkylene;

R^1 is CH-, or R^1 is C- and taken together with R^3 and the nitrogen to which R^3 is

attached, and optionally from 1 to 3 additional heteroatoms, to form a heterocycloalkyl, which is optionally substituted with from 1 to 5 substituents independently selected from:

fluoro, chloro, C1-6alkyl, C1-6alkyl substituted 1 to 6 times by

fluoro, C1-4alkoxy, C1-4alkoxy substituted 1 to 6 times by fluoro,

oxo, and -NH₂;

R³, R⁵ and R⁶ and are independently hydrogen, fluoro, chloro, bromo, iodo,

-OCH₃, -OCH₂Ph, -C(O)Ph, -CH₃, -CF₃, -CN, -S(O)CH₃, -OH, -NH₂,

-COOH, -CONH₂, -NO₂, -C(O)CH₃, -CH(CH₃)₂, -CCH, -CH₂CCH,

-SO₃H, -SO₂NH₂, —NHC(O)NH₂, -NHC(O)H, -NHOH, -OCF₃, -OCHF₂,

substituted or unsubstituted C1-6alkylene, substituted or

unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,

substituted or unsubstituted heterocycloalkyl, substituted or

unsubstituted aryl, or substituted or unsubstituted heteroaryl,

provided R³ is absent when Z is a nitrogen linked heteroaryl;

R²and R⁴ are independently NR⁸, O, or S;

R⁷ is selected from: =NR⁸, =O, and =S;

R⁸ is selected from: hydrogen, C1-6alkyl and C1-6alkyl substituted 1 to 6 times by

fluoro;

R⁹ is selected from: hydrogen, fluoro, chloro, bromo, iodo, -OH, C1-3alkyl and

C1-3alkyl substituted with from 1 to 3 substituents independently selected

from: fluoro, oxo, -OH, and -NH₂;

A and B are independently aryl or heteroaryl;

z2 and z4 are independently 0 or 1;

z_5 and z_6 are independently an integer from 0 to 5;

X is absent or present as C1-2alkyl or C1-2alkyl substituted 1 to 2 times by fluoro,

where the dotted lines represent optional bonds of the alkyl chain of X ;

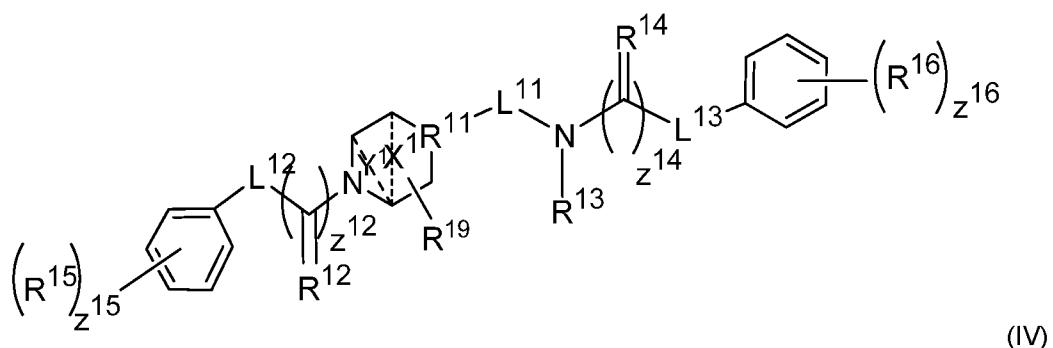
Y is absent or present as C1-2alkyl or C1-2alkyl substituted 1 to 2 times by fluoro,

where the dotted lines represent optional bonds of the alkyl chain of Y ; and

Z is nitrogen or a nitrogen linked heteroaryl;

or a salt thereof including a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 represented by the following Formula (IV):



wherein:

L^{12} and L^{13} are independently: $-\text{CH}_2\text{-O-}$, $-\text{O-CH}_2\text{-}$, $-\text{CH}_2\text{-CH}_2\text{-O-}$, $-\text{O-CH}_2\text{-CH}_2\text{-}$,

$-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-O-}$ and $-\text{O-CH}_2\text{-CH}_2\text{-CH}_2\text{-}$;

L^{11} is selected from: a bond, $-\text{CH}_2\text{-}$ and $-\text{C}(\text{O})\text{-}$;

R^{11} is CH- and R^{13} is hydrogen, or R^{11} is C- and taken together with R^{13} and

the nitrogen to which R^{13} is attached form an oxazolidine, which is

optionally substituted by oxo;

R^{15} and R^{16} are independently hydrogen or chloro;

R^{12} and R^{14} are O;

R^{19} is selected from: hydrogen, fluoro, chloro, -OH, C1-3alkyl and C1-3alkyl substituted with from 1 to 3 substituents independently selected from: fluoro, oxo, and -OH;

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

z^{15} and z^{16} are independently an integer from 0 to 5;

X^1 is absent or present as C1-2alkyl or C1-2alkyl substituted 1 to 2 times by fluoro, where the dotted lines represent optional bonds of the alkyl chain of X ; and

Y^1 is absent or present as C1-2alkyl or C1-2alkyl substituted 1 to 2 times by fluoro, where the dotted lines represent optional bonds of the alkyl chain of Y ;

or a salt thereof including a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 selected from:

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)piperidin-4-yl)acetamide;

8-(2-(4-chlorophenoxy)acetyl)-3-(2-(4-chlorophenoxy)ethyl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one;

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)piperidin-3-yl)acetamide;

N-(2-(4-chlorophenoxy)ethyl)-1-(3-(4-chlorophenoxy)propanoyl)piperidine-4-carboxamide;

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propanoyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)ethyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-((1-(2-(4-chlorophenoxy)acetyl)piperidin-4-yl)methyl)acetamide;

N-(1-(2-((5-chloroisothiazol-3-yl)oxy)ethyl)piperidin-4-yl)-2-(4-chlorophenoxy)acetamide;

N-(1-(3-((5-chloroisothiazol-3-yl)oxy)propyl)piperidin-4-yl)-2-(4-chlorophenoxy)acetamide;

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-hydroxypropyl)piperidin-4-yl)acetamide;

(R)-2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-hydroxypropyl)piperidin-4-yl)acetamide;

(S)-2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-hydroxypropyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-fluoropropyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(2-(3-(4-chlorophenoxy)-2-hydroxypropyl)-2-azabicyclo[2.2.1]heptan-5-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)-2-methoxypropyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(3-((6-chloropyridin-3-yl)oxy)propyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(2-(3-(4-chlorophenoxy)propyl)-2-azabicyclo[2.2.1]heptan-5-yl)acetamide;

N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-((5-chloropyridin-2-yl)oxy)acetamide;

2-(4-chlorophenoxy)-N-(1-(3-((5-chloropyridin-2-yl)oxy)propyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(3-(3,4-dichlorophenoxy)propyl)piperidin-4-yl)acetamide;

4-(2-((4-chlorophenoxy)methyl)-1H-imidazol-1-yl)-1-(3-(4-chlorophenoxy)propyl)piperidine;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)-3-methylpiperidin-4-yl)acetamide;

N-(4-chlorophenethyl)-1-(2-(4-chlorophenoxy)acetyl)piperidine-4-carboxamide;

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propanoyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(4-(4-chlorophenyl)butanoyl)-3-fluoropiperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)piperidin-3-yl)acetamide;

2-(4-chlorophenoxy)-N-(2-(1-(2-(4-chlorophenoxy)acetyl)piperidin-3-yl)ethyl)acetamide;

N-((1-(2-(4-chlorophenoxy)acetyl)piperidin-3-yl)methyl)-2-((6-chloropyridin-3-yl)oxy)acetamide;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)acetyl)-3-fluoropiperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(2-(2-(4-chlorophenoxy)acetyl)-2-azabicyclo[2.2.1]heptan-5-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-((1R,2R)-2-(4-chlorophenoxy)cyclopropane-1-carbonyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-((1R,2S)-2-(4-chlorophenoxy)cyclopropane-1-carbonyl)piperidin-4-yl)acetamide;

N-(1-((1S,2R)-2-(4-chlorobenzyl)cyclopropane-1-carbonyl)piperidin-4-yl)-2-(4-chlorophenoxy)acetamide;

N-(1-((1R,2R)-2-(4-chlorobenzyl)cyclopropane-1-carbonyl)piperidin-4-yl)-2-(4-chlorophenoxy)acetamide;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenyl)cyclopropane-1-carbonyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(4-(4-chlorophenyl)butanoyl)piperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)ethyl)-3-methylpiperidin-4-yl)acetamide;

N,1-bis(2-(4-chlorophenoxy)ethyl)piperidine-4-carboxamide;

N-(2-(4-chlorophenoxy)ethyl)-1-(3-(4-chlorophenoxy)propyl)piperidine-4-carboxamide;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)ethyl)-3-hydroxypiperidin-4-yl)acetamide;

6-chloro-N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)chromane-2-carboxamide;

N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-((6-chloropyridin-3-yl)oxy)acetamide;

N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-(3,4-dichlorophenoxy)acetamide;

N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-(2,4-dichlorophenoxy)acetamide;

2-(4-chlorophenoxy)-N-((1R,5S)-8-(3-(4-chlorophenoxy)propyl)-8-azabicyclo[3.2.1]octan-3-yl)acetamide;

2-(4-chlorophenoxy)-N-(1-(2-(3,4-dichlorophenoxy)ethyl)-3-fluoropiperidin-4-yl)acetamide;

N-(1-(2-(4-chlorophenoxy)ethyl)-3-fluoropiperidin-4-yl)-2-(3,4-dichlorophenoxy)acetamide;

2-(4-chlorophenoxy)-N-((1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)methyl)acetamide;

2-(4-chlorophenoxy)-N-(1-(2-(4-chlorophenoxy)ethyl)-3-fluoropiperidin-4-yl)acetamide;

4-(4-chlorophenoxy)-2-(4-(2-(4-chlorophenoxy)acetamido)piperidin-1-yl)butanoic acid;

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propyl)-2-oxopiperidin-4-yl)acetamide;

4-(4-chlorophenoxy)-2-(4-(2-(3,4-dichlorophenoxy)acetamido)piperidin-1-yl)butanoic acid;

2-(4-(2-(4-chlorophenoxy)acetamido)piperidin-1-yl)-4-(3,4-dichlorophenoxy)butanoic acid;

N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-(4-(difluoromethoxy)phenoxy)acetamide;

N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-2-(4-cyclopropylphenoxy)acetamide;

2-(4-chlorophenoxy)-N-(1-(3-(4-chlorophenoxy)propyl)piperidin-4-yl)-N-methylacetamide;

4-(2-(4-chlorophenoxy)acetamido)-1-(3-(4-chlorophenoxy)propyl)piperidine-2-carboxylic acid; and

4-(2-(4-chlorophenoxy)acetamido)-1-(3-(4-chlorophenoxy)propyl)piperidine-2-carboxylic acid;

or a salt thereof including a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising a compound according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

5. 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, cognitive impairment, atherosclerosis, ocular diseases, in organ transplantation and arrhythmias, in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound as described in any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof.

6. The method of claim 5 wherein the mammal is a human.

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, cognitive impairment, atherosclerosis, ocular diseases, in organ transplantation and arrhythmias in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound of claim 3 or a pharmaceutically acceptable salt thereof.

8. The method of claim 7 wherein the mammal is a human.

9. The method according to claim 5 wherein said cancer is selected from: brain (gliomas), glioblastomas, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma, insulinoma, prostate, sarcoma and thyroid.

10. The method according to claim 7 wherein: said cancer is selected from brain (gliomas), glioblastomas, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, adenocarcinoma, ductal adenocarcinoma, adenosquamous carcinoma, acinar cell carcinoma, glucagonoma,

insulinoma, prostate, sarcoma and thyroid.

11. The use of a compound as described in any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer.

12. The method of inhibiting the ATF4 pathway in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound as described in any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof.

13. The method of claim 12 wherein the mammal is a human.

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

a) a compound as described in any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof; and

b) at least one anti-neoplastic agent.

15. The method of claim 14, wherein the at least one anti-neoplastic agent is 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.

16. A pharmaceutical combination comprising:

a) a compound as described in any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof; and

b) at least one anti-neoplastic agent.

17. A pharmaceutical combination as claimed in claim 16 for use in the treatment of cancer.

18. The method according to claim 5 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.

19. The method of claim 18 wherein the mammal is a human.

20. A process for preparing a pharmaceutical composition containing a pharmaceutically acceptable excipient and an effective amount of a compound as described in any one of claims 1 to 3 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.

21. The method according to claim 5 wherein said pre-cancerous syndrome is selected from: cervical intraepithelial neoplasia, monoclonal gammopathy 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.

22. The method of claim 14, wherein the at least one anti-neoplastic agent is pazopanib.

23. 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 any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof.

24. A method according to claim 23 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 (AMD); 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.

25. A method according to claim 23 wherein the ocular disease is selected from: age-related macular degeneration (AMD) and macular degeneration.

26. 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 any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof.

27. A method of preventing organ damage during the transportation of organs for transplantation, which comprises adding a compound as described in any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, to a solution housing the organ during transportation.

28. A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3, for use in therapy.

29. Use of a compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3, in the manufacture of a medicament for use in treating a disease state 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, cognitive impairment, atherosclerosis, ocular diseases, in organ transplantation and arrhythmias.

30. A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3, for use in treating a disease state 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, cognitive impairment, atherosclerosis, ocular diseases, in organ transplantation and arrhythmias.

31. A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3, for use in the treatment of an integrated stress response associated disease.

32. A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3, for use in the treatment of a disease associated with phosphorylation of eIF2 α .

33. Use of a compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3, in the manufacture of a medicament for use in treating or lessening the severity of an integrated stress response associated disease.

34. Use of a compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3, in the manufacture of a medicament for use in treating a disease associated with phosphorylation of eIF2 α .

35. A pharmaceutical composition comprising from 0.5 to 1,000 mg of a compound or pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 3, and from 0.5 to 1,000 mg of a pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/053372

A. CLASSIFICATION OF SUBJECT MATTER				
INV.	C07D401/04	C07D401/12	C07D405/12	C07D417/12
	C07D498/10	C07D209/52	C07D211/26	C07D211/56
	C07D211/60	C07D211/62	A61K31/4468	A61K31/46
				A61K31/454

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	D SUBHAS BOSE ET AL: "BORON TRIFLUORIDE PROMOTED CLEAVAGE OF BENZYL CARBAHWTES", TETRAHEDRON LETTERS, vol. 31, no. 47, 1 January 1990 (1990-01-01), pages 6903-6906, XP055391816, entry 10; table 1 -----	1,2
X	Pubchem: "AK0S007163870 C23H27ClN2O4 - PubChem", , 25 January 2012 (2012-01-25), XP055391848, Retrieved from the Internet: URL:https://pubchem.ncbi.nlm.nih.gov/compo und/55856026#section=Top [retrieved on 2017-07-18] abstract ----- -/-	1,2

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 July 2017	31/07/2017
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Brandstetter, T

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/053372

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Pubchem: "CID 46411251 C22H25C1N204 - PubChem", , 23 July 2010 (2010-07-23), XP055391861, Retrieved from the Internet: URL: https://pubchem.ncbi.nlm.nih.gov/compound/46411251#section=Top [retrieved on 2017-07-18] abstract -----	1,2
X	Pubchem: "AKOS006914510 C23H28N204 - PubChem", , 25 January 2012 (2012-01-25), XP055391863, Retrieved from the Internet: URL: https://pubchem.ncbi.nlm.nih.gov/compound/55633417#section=Top [retrieved on 2017-07-18] abstract -----	1,2
X	Pubchem: "AKOS008276098 C21H24C12N203 - PubChem", , 18 October 2012 (2012-10-18), XP055391908, Retrieved from the Internet: URL: https://pubchem.ncbi.nlm.nih.gov/compound/60326518#section=Chemical-Vendors [retrieved on 2017-07-18] abstract -----	1,2
X	WO 2016/055935 A1 (GLAXOSMITHKLINE IP NO 2 LTD [GB]) 14 April 2016 (2016-04-14) claims 1, 4, 6, 20 page 32, line 3 page 23, line 11 - page 24, line 3 page 46, line 8 - line 14 page 32, line 18 - page 33, line 4 -----	1,4-6,9, 11-25, 28-35
X	US 2002/160968 A1 (BIEDERMANN ELFI [DE] ET AL) 31 October 2002 (2002-10-31) claims 8-10, 14, 16, 21 -----	1,4-6,9, 11-13, 17-20, 28-34
X	WO 2013/124158 A1 (ACRAF [IT]) 29 August 2013 (2013-08-29) claims 1, 12, 14, 21, 23 page 16, line 25 - line 30 page 52; compound 36 ----- -/-	1,4-6,9, 11-13, 17-20, 26,28-34

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/053372

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/124169 A1 (ACRAF [IT]) 29 August 2013 (2013-08-29) claims 1, 11, 12 page 7, line 3 - line 15 tables 1, 1A -----	1,4-6,9, 11-13, 17-20, 26,28-34
X	US 2005/176764 A1 (MATAKI CHIKAGE [JP] ET AL) 11 August 2005 (2005-08-11) claims 1, 6, 16 paragraph [0093] - paragraph [0094] examples 1, 4 -----	1,4-6,9, 11-13, 17-21, 26,28-35
X	Pubchem: "AKOS029758367 C21H22Cl2N204 - PubChem", , 15 January 2016 (2016-01-15), XP055391404, Retrieved from the Internet: URL: https://pubchem.ncbi.nlm.nih.gov/compound/108554336#section=Top [retrieved on 2017-07-17] abstract -----	1-3
X	Pubchem: "AKOS008275990 C21H24Cl2N203 - PubChem", , 18 October 2012 (2012-10-18), XP055391561, Retrieved from the Internet: URL: https://pubchem.ncbi.nlm.nih.gov/compound/60326410#section=Top [retrieved on 2017-07-18] abstract -----	1-3
X	WO 2015/136463 A1 (GLAXOSMITHKLINE IP NO 2 LTD [GB]) 17 September 2015 (2015-09-17) claims 1, 6-26 -----	1,4-35
A	----- WO 98/22465 A1 (LINK TECHNOLOGY INC [US]; NEELY CONSTANCE F [US]) 28 May 1998 (1998-05-28) claim 1 page 9, line 3 - line 6 -----	2,3
A	----- 27	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2017/053372

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 2016055935	A1	14-04-2016	NONE		
US 2002160968	A1	31-10-2002	AT 374185 T AU 2915800 A DE 60036538 T2 DK 1154998 T3 EP 1031564 A1 EP 1154998 A1 EP 1816124 A2 ES 2293894 T3 JP 2002537380 A JP 2011254820 A PT 1154998 E US 2002160968 A1 WO 0050399 A1		15-10-2007 14-09-2000 19-06-2008 21-01-2008 30-08-2000 21-11-2001 08-08-2007 01-04-2008 05-11-2002 22-12-2011 07-01-2008 31-10-2002 31-08-2000
WO 2013124158	A1	29-08-2013	AR 090086 A1 AU 2013224302 A1 CA 2860250 A1 CN 104093712 A CY 1117469 T1 DK 2817302 T3 EA 201491449 A1 EP 2817302 A1 ES 2564961 T3 GE P20166489 B HK 1203930 A1 HR P20160125 T1 HU E026893 T2 IL 233824 A JP 6141331 B2 JP 2015506993 A KR 20140130124 A SG 10201701649Y A SG 11201403602W A SI 2817302 T1 SM T201600053 B UA 112564 C2 US 2015057294 A1 US 2017157121 A1 US 2017174657 A1 WO 2013124158 A1		15-10-2014 17-07-2014 29-08-2013 08-10-2014 26-04-2017 21-03-2016 28-11-2014 31-12-2014 30-03-2016 10-06-2016 06-11-2015 11-03-2016 28-07-2016 29-09-2016 07-06-2017 05-03-2015 07-11-2014 27-04-2017 30-07-2014 31-03-2016 29-04-2016 26-09-2016 26-02-2015 08-06-2017 22-06-2017 29-08-2013
WO 2013124169	A1	29-08-2013	AR 090085 A1 AU 2013224313 A1 CA 2860466 A1 CN 104080781 A CY 1117467 T1 DK 2817301 T3 EA 201491448 A1 EP 2817301 A1 ES 2564033 T3 GE P201606552 B HK 1203931 A1 HR P20160124 T1 HU E027445 T2 JP 2015506995 A KR 20140122725 A		15-10-2014 17-07-2014 29-08-2013 01-10-2014 26-04-2017 14-03-2016 28-11-2014 31-12-2014 17-03-2016 10-10-2016 06-11-2015 11-03-2016 28-09-2016 05-03-2015 20-10-2014

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2017/053372

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		PT 2817301 E	14-03-2016
		SG 10201701171T A	27-04-2017
		SG 11201403788V A	28-08-2014
		SI 2817301 T1	31-03-2016
		SM T201600054 B	29-04-2016
		UA 113189 C2	26-12-2016
		US 2014378455 A1	25-12-2014
		US 2016045485 A1	18-02-2016
		WO 2013124169 A1	29-08-2013
<hr/>			
US 2005176764	A1 11-08-2005	AU 2003222449 A1	27-10-2003
		EP 1494670 A1	12-01-2005
		JP 2005522492 A	28-07-2005
		MY 134200 A	30-11-2007
		TW 200407141 A	16-05-2004
		US 2005176764 A1	11-08-2005
		WO 03086397 A1	23-10-2003
<hr/>			
WO 2015136463	A1 17-09-2015	EP 3116877 A1	18-01-2017
		JP 2017507967 A	23-03-2017
		WO 2015136463 A1	17-09-2015
<hr/>			
WO 9822465	A1 28-05-1998	AT 315567 T	15-02-2006
		AU 5261598 A	10-06-1998
		CA 2264721 A1	28-05-1998
		EP 0946557 A1	06-10-1999
		EP 1790651 A1	30-05-2007
		JP 2001504491 A	03-04-2001
		US 5786360 A	28-07-1998
		US 6117998 A	12-09-2000
		US 6489332 B1	03-12-2002
		US 6495687 B1	17-12-2002
		US 2002082269 A1	27-06-2002
		WO 9822465 A1	28-05-1998
<hr/>			