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(54) **Title:** TREATMENT FOR NEUROINFLAMMATORY DISORDERS

(57) **Abstract:** The present invention relates to the development of therapeutic compound for the treatment of brain psychiatric diseases. Specifically, the present invention provides a NLRP3 inhibitors or its pharmaceutically acceptable salt or suitable composition useful in the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases. These severe and persistent illnesses include Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

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TREATMENT FOR NEUROINFLAMMATORY DISORDERS

FIELD OF THE INVENTION

The present invention relates to the development of therapeutic compound for the treatment of brain psychiatric diseases. Specifically, the present invention provides a NLRP3 inhibitors or its pharmaceutically acceptable salt or suitable composition useful in the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases. These severe and persistent illnesses include Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

BACKGROUND OF THE INVENTION

The nucleotide-binding oligomerization domain (NOD)-like receptor family, pyrin domain-containing 3 (NLRP3 or NALP3) inflammasome are a major source of mucosal interleukin (IL)-1β and the inflammasomes are mostly subject to activation by multiple aspects of inflammation-associated stress. NLRP3 is a cytosolic pattern recognition receptor (PRR) that senses exogenous and endogenous danger signals. The NLRP3 protein is made up of three domains: a leucine-rich repeat domain (LRR), a NOD containing a caspase activation and recruitment domain (CARD) (NACHT), and a pyrin domain (PYD). Upon activation, NLRP3 oligomerizes and triggers assembly of the adapter apoptosis-associated speck-like protein containing a CARD (ASC) via PYD–PYD interactions. ASC fibrils assemble into large structures, called ASC specks, and recruit pro-caspase-1, leading to its autoproteolytic activation. The activated caspase-1 is able to cleave pro-IL-1β and pro-IL-18 to generate the inflammatory cytokines IL-1β and IL-18 (Guo et al., 2015; Dinarello et al., 2012).

Involvement of the NLRP3 inflammasome in different kinds of diseases provides new avenues to design drugs targeting NLRP3 inflammasome. To date, clinical treatment of NLRP3-related diseases targets IL-1β with IL-1β antibodies or recombinant IL-1β receptor antagonist, such as canakinumab and anakinra, respectively. In addition, a few small-molecule compounds have shown anti-inflammatory effects on NLRP3 inflammasome activation in vitro, including MCC950, β-hydroxybutyrate (BHB), Bay 11-7082, dimethyl sulfoxide (DMSO), and type I interferon. However, most of these inhibitors are relatively nonspecific and have low efficacy.

For inhibitors targeting IL-1β, it should be noted that IL-1β secretion is not the only product of NLRP3 inflammasome activation; instead, other proinflammatory cytokines, including high-mobility group box 1 (HMGB1) and IL-18 may participate in the pathogenesis of these diseases. Moreover, IL-1β can be produced by inflammasome-independent pathways or other inflammasomes. Therefore, inhibitors targeting IL-1β may lead to unintended immunosuppressive effects besides preventing NLRP3 inflammasome activation itself. Pharmacological inhibitors specific to NLRP3 inflammasome may be the best choice for treatment of NLRP3-related diseases. (Yang et al., 2019).

Parkinson's disease (PD) is the most prevalent synucleinopathy and the second most common neurodegenerative disorder worldwide, affecting about 2% of the population over the age of 60 (Nat. Rev. Dis. Primers 3, 17013 (2017)).

Inflammasomes are multiprotein complexes that function as intracellular sensors of environmental and cellular stress (Nat. Rev. Neurosci. 15, 84–97 (2014).). The NLR family pyrin domain containing 3 (NLRP3) inflammasome is composed of the NLRP3 sensor, the signaling adapter apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and the caspase-1 protease. Assembly of the NLRP3 complex in immune cells upon cellular stress triggers caspase-1 activation and caspase-1–mediated release of interleukin-1β (IL-1β) and IL-18, there by initiating inflammatory responses. In neurodegenerative conditions such as Alzheimer's disease (AD), persistent accumulation of misfolded protein aggregates can trigger and sustain inflammasome activation and thereby drive central nervous system (CNS) inflammation and neuropathology (19). Recent findings in AD models have demonstrated that microglia-derived inflammasome components such as ASC specks can cross-seed pathogenic amyloid fibrils (20). In the brains of patients with PD, the inflammasome pathway can potentially be activated by oxidative stress and insoluble α-synuclein aggregates (PLOS ONE 8, e55375 (2013)).

The NLRP3 inflammasome plays a key role in PD-like pathophysiology in rodents and might represent a feasible therapeutic target to mitigate neurotoxic α-synuclein pathology and the resulting nigrostriatal dopaminergic neuron loss in PD (Sci. Transl. Med. 10, eaah4066 (2018)).

Previously demonstrated that nanomolar doses of a small-molecule NLRP3 inhibitor, MCC950, abolished fibrillar α-synuclein–mediated inflammasome activation in mouse microglial cells and extracellular ASC release. Furthermore, oral administration of MCC950 in multiple rodent PD models inhibited inflammasome activation and effectively mitigated motor deficits, nigrostriatal dopaminergic degeneration, and accumulation of α-synuclein aggregates. These findings suggest that microglial NLRP3 may be a sustained source of neuroinflammation that could drive progressive dopaminergic neuropathology and highlight NLRP3 as a potential target for disease-modifying treatments for PD (Sci. Transl. Med. 10, eaah4066 (2018)).

MCC950 inhibited NLRP3 activation in a mouse model of MWS. Peripheral blood mononuclear cells (PBMC) from patients with low penetrance NLRP3 variants (Q703K and V198M) have been shown to display enhanced IL-1β levels following inflammasome activation compared to healthy controls. Furthermore, release of IL-1β has been shown to be NLRP3-dependent as it was blocked by MCC950 (Schuh et al., 2019). The IL-1 receptor antagonist anakinra is conventionally used to control the symptoms of the syndrome, but patients relapse when treatment is withdrawn.

There are various agents in various stages of Phase 1 and Phase II development that target the NLRP3 inflammasome. (Freeman et al., 2020). Agents like MCC950, CY-09, OLT1177, Tranilast, Oridonin, NT-0167 displayed the good therapeutic properties, as they directly target NLRP3 itself, but not other components (NEK7, ASC, caspase-1, or IL-1β) up-/downstream of NLRP3 inflammasome activation. Furthermore, these inhibitors are being used in clinical practice or are being investigated at phase II clinical trials having shown relatively high safety (Yang et al., 2019).

NLRP3 in innate immune cells are activated by Pathogen Associated Molecular Patterns and Death Associated Molecular Patterns. The resultant NLRP3 inflammasome activates Caspase-1 and in-turn cleave and releases IL-1β and IL-18. NLRP3 inflammasome inhibitors have potential to negate IL-1 mediated neurodegenerative disorder including Parkinson's disease.

All current therapies are limited to injectable biologics that often have limited central nervous system (CNS) penetration, which is particularly important in NOMID patients with severe CNS

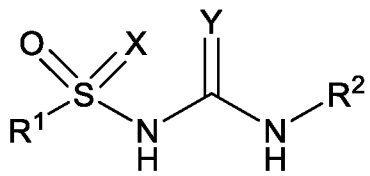
disease. Therefore, there remains an unmet clinical need for more targeted and preferably small molecule, compounds as an alternative to IL-1 targeted biologics.

SUMMARY OF THE INVENTION

The present invention provides a therapeutic compound of formula (I) and their pharmaceutically acceptable salts for the prevention and treatment of treatment of neuroinflammatory disorders or neurodegenerative disorder diseases such as Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

EMBODIMENTS OF THE INVENTION

In an embodiment the present invention provides a therapeutic compound of formula (I)



Formula (I)

suitable for the treatment and prevention of neuroinflammatory disorders or neurodegenerative disorder diseases. These severe and persistent illnesses include Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

In an embodiment, the present invention provides a compound of formula (I) and their pharmaceutically acceptable salts suitable for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases such as Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

In yet another embodiment, the present invention provides the administration of therapeutic compound of formula (I) and their pharmaceutically acceptable salts alone or in combination with suitable for the treatment and prevention of neuroinflammatory disorders or

neurodegenerative disorder diseases such as Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

In a further embodiment, the present invention provides use of compound of formula (I) or its pharmaceutically acceptable salts for the treatment and prevention of neuroinflammatory disorders or neurodegenerative disorder diseases such as Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

In another embodiment, the present invention provides a method of treating neuroinflammatory disorders or neurodegenerative disorder diseases such as Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders using pharmaceutical composition of compound of formula (I) or its pharmaceutically acceptable salts.

In yet another embodiment, the present invention provides a suitable composition comprising the compound of formula (I) or their suitable pharmaceutical compositions for the treatment and prevention of neuroinflammatory disorders or neurodegenerative disorder diseases such as Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

DETAIL DESCRIPTION OF THE INVENTION

Definition:

The terms 'treatment' or 'treat' refer to slowing, stopping, or delaying the progression of the disease or clinical symptoms in a patient, as evidenced by a decrease or elimination of a clinical or diagnostic symptom of the disease, disorder or condition.

"Patient" includes both human and animals. "Mammal" means humans and other mammalian animals.

The term "preventing" refers to barring a subject from acquiring a disorder or disease in the first place.

A "subject" is a mammal, preferably a human, but can also be an animal in need of veterinary treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

As used herein "treating" includes achieving, partially or substantially, one or more of the following results: partially or totally reducing the extent of the disease, disorder or syndrome. Delaying, inhibiting or preventing the progression of the disease, disorder or syndrome includes for example, delaying, inhibiting or preventing the progression of neuroinflammatory disorders or neurodegenerative disorder diseases such as Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

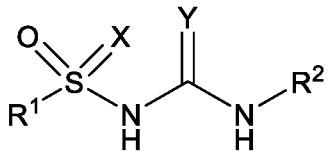
The present invention describes a method of treating a subject suffering from neuroinflammatory disorders or neurodegenerative disorder diseases such as Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

In an embodiment the present invention provides a compound of formula (I) and their pharmaceutically acceptable salts suitable for the treatment or prevention of neuroinflammatory disorders or neurodegenerative disorder diseases such as Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

In a further embodiment the present invention provides use of the compound of formula (I) or their suitable pharmaceutical compositions for the treatment or prevention of neuroinflammatory disorders or neurodegenerative disorder diseases such as Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

In a preferred embodiment, neuroinflammatory disorders or neurodegenerative disorders disease is Parkinson's disease (PD).

The method comprises administering to a subject an effective amount of a compound according to Formula (I),



Formula (I)

their tautomeric forms, their stereoisomers, their enantiomers, their metabolites, their deuterium analogs, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them or their mixtures thereof,

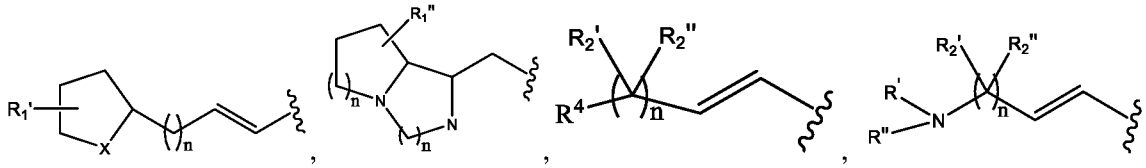
wherein

X is O, NH or N-R^3 wherein R^3 at each occurrence independently represents hydrogen, hydroxyl, halogen, nitro, cyano, haloalkyl, amine, optionally substituted groups selected from (C_1-C_{10})alkyl, (C_1-C_{10})alkoxy, (C_3-C_{10})cycloalkyl, (C_2-C_{10})alkenyl, (C_2-C_{10})alkynyl, SO_2(C_1-C_6)alkyl, thiol, thioalkyl, thio-alkoxy, SO(C_1-C_6)alkyl, benzyl, aryl, heteroaryl, heterocyclyl;

Y is O, S;

R^1 at each occurrence independently represents hydrogen, halogen, haloalkyl, cyano, optionally substituted groups selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkoxy, (C_3-C_7)cycloalkyl, (C_1-C_6)alkylSO_2(C_1-C_6)alkyl, (C_1-C_6)alkylN(C_1-C_6)alkyl, (C_1-C_6)alkylN(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocyclyl, benzyl, tert-butyloxycarbonyl, NH(C_1-C_6)alkyl, N((C_1-C_6)alkyl)$_2$, NH(C_2-C_6)alkenyl, N((C_2-C_6)alkenyl)$_2$, -N-heterocyclyl, N(C_1-C_6)alkyl-heterocyclyl, NR'R'', thiol, mercaptoalkyl, SO_2(C_1-C_6)alkyl, SO_2(C_3-C_7)cycloalkyl, SO_2-aryl, SO_2-heterocyclyl, (C_1-C_6)thioalkyl, (C_1-C_6)thioalkoxy, (C_1-C_6)alkylSO_2NH_2, -$CONH_2$, -CO(C_1-C_6)alkyl, -CO(C_1-C_6)haloalkyl, -CO-aryl, -CO-heteroaryl, -CO-heterocyclyl, 4- to 7-membered heterocyclic ring, 7- to 14-membered bicyclic heterocyclic ring system, bridged or spiro ring system having optionally one or more than one heteroatoms;

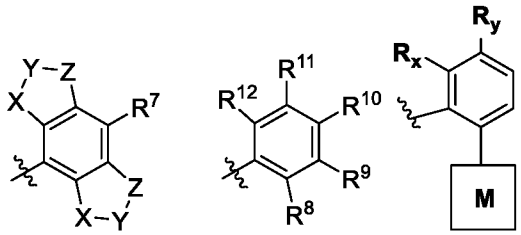
In an embodiment R^1 represents:



n independently represents from integer 0-3;

each of R', R", R_1', R_1'', R_2' and R_2" at each occurrence independently represents hydrogen, halogen, haloalkyl, cyano, optionally substituted groups selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkoxy, (C_3-C_7)cycloalkyl, (C_1-C_6)alkylSO_2(C_1-C_6)alkyl, (C_1-C_6)alkylN(C_1-C_6)alkyl, (C_1-C_6)alkylN(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocyclyl, benzyl, tert-butyloxycarbonyl, thiol, mercaptoalkyl, SO_2(C_1-C_6)alkyl, SO_2(C_3-C_7)cycloalkyl, SO_2-aryl, SO_2-heterocyclyl, (C_1-C_6)thioalkyl, (C_1-C_6)thioalkoxy, (C_1-C_6)alkylSO_2NH_2, -$CONH_2$, -CO(C_1-C_6)alkyl, -CO(C_1-C_6)haloalkyl, -CO-aryl, -CO-heteroaryl, -CO-heterocyclyl, 4- to 7-membered heterocyclic ring, 7- to 14-membered bicyclic heterocyclic ring system, bridged or spiro ring system having optionally one or more than one heteroatoms; In an embodiment R' and R" optionally forms 4- to 7-membered heterocyclic ring system;

R^2 is selected from the following ring system



wherein X, Y, Z at each occurrence independently represents C, N, S, SO_2, and O, which may be optionally substituted;

R^4 at each occurrence independently represents hydrogen, halogen, haloalkyl, cyano, optionally substituted groups selected from (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_1-C_6)alkoxy, (C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocyclyl, benzyl, bicyclic heterocyclic ring system, substituted amines, thiol, mercapto alkyl, (C_1-C_6)thio-alkoxy groups;

each of R^7, R^8, R^9, R^{10}, $R^{11}$and R^{12} at each occurrence are independently selected from hydrogen, halogen, cyano, amide, sulphonamide, acyl, hydroxyl, optionally substituted groups selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy, benzyl, aryl, heteroaryl,

heterocyclyl; In one embodiment each of R^8 and R^9, R^9 and R^{10}, R^{10} and $R^{11}$and R^{11} and R^{12} wherever possible, together may form a 4 to 7 membered saturated or partially saturated ring containing from 0-2 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$; p = 1-2.

R_x and R_y at each occurrence are independently selected from hydrogen, halogen, optionally substituted groups selected from $(C_1$-$C_6)$alkyl; alternatively R_x and R_y together may form a 4- to 7-membered heterocyclic ring system;

'M' is selected from aryl, heteroaryl, heterocyclyl;

When any of above defined group is substituted the substitutions on them may be selected from those described above or may be selected from hydrogen, hydroxy, cyano, halo, haloalkyl, haloalkyloxy, alkylthio, optionally substituted group selected from $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_{10})$cycloalkyl, C_1-C_6 alkoxy, aryl, heterocyclyl, heteroaryl, -COR_{11},-CSR_{11}, $C(O)OR_{11}$, $C(O)$-R_{11}, -$C(O)$-$NR_{11}R_{12}$, -$C(S)$-$NR_{11}R_{12}$, -SO_2R_{11}group, wherein each of, R_{11} and R_{12} is independently selected from hydrogen, optionally substituted group selected from $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_7)$cycloalkyl, aryl, heteroaryl, heterocyclyl groups;

In a preferred embodiment, the groups, radicals described above may be selected from:

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy and alkanoyl, means a carbon chain which may further be substituted with an oxygen atom as is well understood by a skilled artisan, which may further be either linear or branched, and combinations thereof, unless the carbon chain is defined otherwise. Examples of alkyl group include but not limited to methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert. -butyl, pentyl, hexyl etc. Where the specified number of carbon atoms permits e.g. from C_{3-10}, the term alkyl also includes cycloalkyl groups, and combinations of linear or branched alkyl chains combined with cycloalkyl structures. When no number of carbon atoms is specified, C_{1-6} is intended. Substituted alkyl includes alkyl substituted with one or more moieties selected from the group consisting of halo {e.g., CI, F, Br, and I); halogenated alkyl {e.g., CF_3, 2-Br-ethyl, CH_2F, CH_2CI, CH_2CF_3, or CF_2CF_3); hydroxyl; amino; carboxylate; carboxamido; alkylamino; arylamino; alkoxy; aryloxy; nitro; azido; cyano;

thio; sulfonic acid; sulfate; phosphonic acid; phosphate; and phosphonate as well as those described under the definition of 'Optionally substituted'.

"Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof, unless the carbon chain is defined otherwise. Examples of alkenyl include but not limited to vinyl, allyl, isopropenyl, hexenyl, pentenyl, heptenyl, 1 -propenyl, 2-butenyl, 2-methyl -2-butenyl etc. Where the specified number of carbon atoms permits, e.g., from C_{5-10}, the term alkenyl also includes cycloalkenyl groups and combinations of linear, branched and cyclic structures. When no number of carbon atoms is specified, C_{2-6}) is intended.

"Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl- 1 -pentynyl etc. When no number of carbon atoms is specified, is intended.

the "thioalkyl" group used either alone or in combination with other radicals, denotes an alkyl group, as defined above, attached to a group of formula –SR', (sulfur and its oxidized forms) where R' represents hydrogen, alkyl or aryl group, e.g. thiomethyl, methylthiomethyl, phenylthiomethyl and the like, which may be optionally substituted.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable monocyclic or bicyclic or tricyclic ring, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin). In a broader perspective, the term carbocycle is intended to include, wherever applicable, the groups representing cycloalkyl, phenyl and other saturated, partially saturated or aromatic residues;

The terms "cycloalkyl" and "cycloalkenyl" refers to optionally substituted, saturated and unsaturated mono-cyclic, bicyclic or tricyclic carbon groups. Where appropriate, the cycloalkyl or cycloalkenyl group may have a specified number of carbon atoms, for example, C_3-C_6 cycloalkyl or cycloalkenyl includes within its scope a carbocyclic group having 3, 4, 5 or 6 carbon atoms. Examples of such substituents may be selected from the group consisting of

cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and the like. Substituted cycloalkyl or cycloalkenyl includes substitutions with one or more moieties selected from the group consisting of halo (e.g. , CI, F, Br, and I); halogenated alkyl (e.g. , CF_3, 2-Br-ethyl, CH_2F, CH_2CI, CH_2CF_3, or CF_2CF_3); hydroxyl; amino; carboxylate; carboxamido; alkylamino; arylamino; alkoxy; aryloxy; nitro; azido; cyano; thio; sulfonic acid; sulfate; phosphonic acid; phosphate; and phosphonate as well as those described under the definition of 'Optionally substituted'.

The "alkoxy" refers to the straight or branched chain alkoxides of the number of carbon atoms specified.

"Aryl" means a mono- or polycyclic aromatic ring system containing carbon ring atoms. The preferred aryls are monocyclic or bicyclic 6-10 membered aromatic ring systems. Phenyl and naphthyl are preferred aryls.

"Heterocyclyl" means a saturated, partially saturated or unsaturated aromatic or non-aromatic mono, bi or tricyclic radicals, containing one or more heteroatoms selected from nitrogen, sulfur and oxygen, further optionally including the oxidized forms of sulfur, namely SO & SO_2 Heterocyclyl systems may be attached to another moiety via any number of carbon atoms or heteroatoms of the radical and may be both saturated and unsaturated. Examples of heterocycles include tetrahydrofuran (THF), dihydrofuran, 1,4-dioxane, morpholine, 1 ,4-dithiane, piperazine, piperidine, 1 ,3-dioxolane, imidazoline, imidazolidine, pyrrolidine, pyrroline, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1 ,3-dioxane, 1 ,3-dithiane, oxathiane, thiomorpholine, etc. The term "heterocycloalkyl" refers to a heterocyclic group as defined above connected to an alkyl group as defined above;

"Heteroaryl" means an aromatic or partially aromatic heterocycle that contains at least one ring heteroatom selected from O, S and N. Heteroaryls thus include heteroaryls fused to other kinds of rings, such as aryls, cycloalkyls, and heterocycles that are not aromatic. Examples of heteroaryl groups include; pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, triazinyl, thienyl, pyrimidyl, benzisoxazolyl, benzoxazolyl, benzthiazolyl, benzothiadiazolyl, dihydrobenzofuranyl, indolinyl, pyridazinyl, indazolyl, isoindolyl, dihydrobenzothienyl, indolinyl, pyridazinyl,

indazolyl, isoindolyl, dihydrobenzothienyl, indolizinyl, cinnolinyl, phthalazinyl, quinazolinyl, napthyridinyl, carbazolyl, benzodioxolyl, quinoxalinyl, purinyl, furazanyl, isobenzylfuranyl, benzimidazolyl, benzofuranyt, benzothienyl, quinolyl, indolyl, isoquinolyl, dibenzofuranyl etc. For heterocyclyl; and heteroaryl groups, rings and ring systems containing from 3-15 carbon atoms are included, forming 1-3 rings.

The term "haloalkyl "means an alkyl structure in which at least one hydrogen is replaced with a halogen atom. In certain embodiments in which two or more hydrogen atoms are replaced with halogen atoms, the halogen atoms are all the same as one another.

the “haloalkoxy” group is selected from suitable haloalkyl, as defined above, directly attached to an oxygen atom, more preferably groups selected from fluoromethoxy, chloromethoxy, fluoroethoxy, chloroethoxy and the like;
In certain other embodiment in which two or more hydrogen atoms are replaced with halogen atoms, the halogen atoms are not all the same as one another.

"Aryloxyalkyl" means an alkyl radical substituted with aryloxy group as defined herein.

"Aryloxyaryl" means an aryl radical substituted with aryloxy group as defined herein.

"Aryloxyheteroaryl" means a heteroaryl radical substituted with aryloxy group as defined herein.

"Halo/ Halogen" refers to fluorine, chlorine, bromine, iodine. Chlorine and fluorine are generally preferred.

Suitable groups and substituents on the groups may be selected from those described anywhere in the specification.

The term "substituted," as used herein, means that any one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound.

"Pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of the basic residues. Such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 1 , 2-ethanedisulfonic, 2-acetoxybenzoic, 2-hydroxyethanesulfonic, acetic, ascorbic, benzenesulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromie, hydrochloric, hydroiodide, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, -lauryl sulfonic, maleic, malic, mandelic, methanesulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicyclic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluenesulfonic.

The term 'optional' or ‘optionally' means that the subsequent described event or circumstance may or may not occur, and the description includes instances where the event or circumstance occur and instances in which it does not. For example, optionally substituted alkyl' means either 'alkyl' or 'substituted alkyl'. Further an optionally substituted group includes an unsubstituted group.

Unless otherwise stated in the specification, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms.

Particularly useful compounds may be selected from but not limited to the following:

N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide;

N'-cyano-4-fluoro-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide;

N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)furan-2-sulfonimidamide;

(E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(thiazol-2-yl)ethenesulfonamide;

(E)-2-(1-ethyl-1H-imidazol-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethenesulfonamide;

(E)-2-(1-ethyl-4-methyl-1H-imidazol-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethenesulfonamide;

(R,E)-2-(1-ethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-ethanesulfonamide;

(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(pyrrolidin-2-yl)ethene-1-sulfonamide;

(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(1-methylpyrrolidin-2-yl)ethene-1-sulfonamide;

(S,E)-2-(1-ethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-ethanesulfonamide;

(R,E)-2-(1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide;

(S,E)-2-(1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide;

sodium(S,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide;

potassium (R,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide;

Sodium(R,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide;

(E)-N'-cyano-2-((S)-1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonimidamide;

(E)-N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-((R)-1-methylpyrrolidin-2-yl)ethene-1-sulfonimidamide;

(E)-N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-((R)-1-methylpyrrolidin-2-yl)ethene-1-sulfonimidamide;

(E)-N'-cyano-2-((R)-1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonimidamide;

N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-1-((1S,8aR)-3,3,8a-trimethyloctahydropyrrolo[1,2-a]pyrazin-1-yl)methanesulfonamide;

N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-1-((4S,8aS)-2,3,3,8a-tetramethyloctahydropyrrolo[1,2-a]pyrazin-4-yl)methanesulfonamide;

(E)-3-(dimethylamino)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)prop-1-ene-1-sulfonamide;

sodium (E)-((3-(dimethylamino)-3-methylbut-1-en-1-yl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide;

(S,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-methyl-1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide;

(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-methyl-1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide

(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide;

(E)-3-(bis(methyl-d)amino)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-3-methylbut-1-ene-1-sulfonamide;

Sodium (R,E)-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)((2-(2-methyl-1-(methyl-d)pyrrolidin-2-yl)vinyl)sulfonyl)amide;

N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-1-((1S,8aR)-3,3,8a-trimethyl-2-(methyl-d)octahydropyrrolo[1,2-a]pyrazin-1-yl)methanesulfonamide;

(R,E)-2-(1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5-tetrahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide;

(E)-2-((R)-1,2-dimethylpyrrolidin-2-yl)-N-((2-hydroxy-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide;

(E)-2-((R)-1,2-dimethylpyrrolidin-2-yl)-N-((3-hydroxy-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide;

(E)-2-((R)-1,2-dimethylpyrrolidin-2-yl)-N-((1-hydroxy-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide;

or pharmaceutically acceptable salts of any of the compounds above.

Following is a list of abbreviations used in the description of the preparation of the compounds of the present invention:

µg: microgram

^{1}H NMR : Proton nuclear magnetic resonance

bs: broad singlet

$CDCl_3$: Deuterated chloroform

$CHCl_3$: Chloroform

d: doublet

DAMP: damage-associated molecular pattern;

DBU: 1,8-Diazabicyclo(5.4.0)undec-7-ene

DCM: Dichloromethane

dd: doublet of doublet

DMAC: N,N-(Dimethylacetamide)

DMAP: 4-(Dimethylamino) pyridine

DMF: N,N-Dimethyl formamide

DMSO: Dimethyl sulfoxide

dt: doublet of triplet

EDTA: Ethylenediaminetertraacetic acid

EtOAc: Ethyl acetate

EtOH: Ethanol

HCl(g): Hydrogen chloride (gas)

IL1β: Interleukin 1 beta

K_2CO_3: Potassium carbonate

m: multiplet

MeOH: Methanol

mmol: millimoles

MS: Mass spectrum

N_2: Nitrogen

Na_2CO_3: Sodium carbonate

ng: nanogram

NIS: Niodosuccinimide

PAMP: pathogen-associated molecular pattern;

PMA: Phorbol 12-myristate 13-acetate

$POCl_3$: Phosphorylchloride

RM: reaction mixture

r.t., RT: room temperature

s: singlet

t: Triplet

td: triplet of doublet

THF: Tetrahydrofuran

TLC: Thin layer chromatography

TLR: Toll-like receptor.

TNF α: Tumor necrosis factor alpha

In one embodiment, the present invention provides a suitable composition comprising the compound of formula (I) or their suitable pharmaceutical compositions for the treatment and prevention of neuroinflammatory disorders or neurodegenerative disorder diseases such as Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

The term "pharmaceutical composition" refers to a mixture of an NLRP3 antagonist or other compound described herein with other chemical components (referred to collectively herein as "excipients") such as carriers, stabilizers, diluents, dispersing agents, suspending agents, and/or thickening agents. The pharmaceutical composition facilitates administration of the NLRP3 antagonist or other compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to rectal, oral, and intravenous, aerosol, and parenteral, ophthalmic, pulmonary, and topical administration.

In an embodiment, the present invention provides effective amount of compound of formula (I) or its pharmaceutically acceptable salts may be selected from 1 mg to 500 mg; preferably 1 mg to 250 mg and more preferably 1 mg to 150 mg for the treatment and prevention of neuroinflammatory disorders or neurodegenerative disorder diseases.

In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 150 mg on each day the compound is administered to the subject. For example, in certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1mg to about 25 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 25 mg to about 50 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 50 mg to about 75 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an

amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 75 mg to about 100 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 100 mg to about 125 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 125 mg to about 150 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 150 mg to about 175 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 175 mg to about 200 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 200 mg to about 225 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 225 mg to about 250 mg on each day the compound is administered to the subject.

In certain other embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 25 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 50 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 75 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 100 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an

amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 125 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 150 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 175 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 200 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 225 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (I) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 250 mg on each day the compound is administered to the subject.

In an embodiment, the present invention provides effective amount of compound of formula (I) or its pharmaceutically acceptable salt may be administered by oral, topical, parenteral, intravenous or intramuscular route of administration. In a preferred embodiment, the present invention provides effective amount of formula (I) or its pharmaceutically acceptable salts is administered by oral route of administration.

The compound of formula (I) or its pharmaceutically acceptable salts may be provided to the subject daily, weekly, as prescribed by physician to the person in need thereof.

In another embodiment, the present invention provides a method of treating a subject suffering from neuroinflammatory disorders or neurodegenerative disorder diseases such as Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders preferably Parkinson's disease (PD) which comprises treatment of a patient in need of such therapy, with compound of formula (I) or its pharmaceutically acceptable salts or suitable pharmaceutical compositions containing them.

In an embodiment, the present invention provides the combination of compound of formula (I) or its pharmaceutically acceptable salts with other suitable agents as therapeutic agent for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases.

In an embodiment, the additional therapeutic agent used is selected from Inhibitors of interleukin-1β (e.g. Rilonacept, Canakinumab, and Anakinra); immune-suppressants (e.g., Methotrexate, Mercaptopurine, Cyclophosphamide), metabolic disorders drugs, glucocorticoids, non-steroidal anti-inflammatory drugs, Gasdermin D inhibitors (e.g., Necrosulfonamide); Cox-2 specific inhibitors, TNF-α binding proteins (e.g.,Infliximab, Etanercept), Interferon-13, Interferon, Interleukin-2, antihistamines, beta-agonist, BTK inhibitors, anticolinergics, anti-cancer agents; anti-viral drugs, for example: Remdesivir, Lopinavir/Ritonavir, Favipiravir, Molnupiravir,Tamiflu; anti-malarial agents, for example: Choloroquinone, Hydroxyl Chloroquinone; or their suitable pharmaceutically acceptable salts. Further examples for use in combination with Non-Alcoholic Steato- Hepatitis (NASH) and fibrosis drugs; anticancer; antibiotics, for example Azithromycin; hormones, Aromatase inhibitors, Colchicine, Anticoagulants, antibodies, cytokines, anti-IL6 drugs; Antiparasitics; vaccines; Interferons; drug conjugates; Drugs originally developed for SARS (ACE2 protein decoy); Intravenous vitamin C; inhibitors of mitogen-activated protein kinase signaling (ex: BAY 43-9006); Syk inhibitors; mTOR inhibitors; antibodies (Rituxan); and BCR/ABL antagonist.

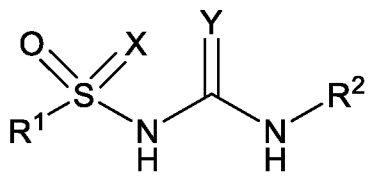
The compound of formula (I) of the present invention or its pharmaceutically acceptable salts may be used further in combination with one or more suitable pharmaceutically active agents selected from following therapeutic agents in any combinations. MAO B inhibitors, selegiline (Zelapar), rasagiline (Azilect) and safinamide (Xadago); Catechol O-methyltransferase (COMT) inhibitors, Entacapone (Comtan) and opicapone (Ongentys); benztropine (Cogentin), trihexyphenidyl, Amantadine; cholinesterase inhibitors, donepezil (Aricept), galantamine (Razadyne) and rivastigmine (Exelon), Memantine (Namenda), aducanumab (Aduhelm); Riluzole (Rilutek), Edaravone (Radicava); ocrelizumab (Ocrevus), prednisone and methylprednisolone; tetrabenazine (Xenazine) and deutetrabenazine (Austedo), haloperidol (Haldol) and fluphenazine, risperidone (Risperdal), olanzapine (Zyprexa) and quetiapine (Seroquel), levetiracetam (Keppra, Elepsia XR, Spritam) and clonazepam (Klonopin); citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac, Sarafem) and sertraline (Zoloft),

quetiapine (Seroquel), risperidone (Risperdal) and olanzapine (Zyprexa), divalproex (Depakote), carbamazepine (Carbatrol, Epitol) and lamotrigine (Lamictal).

The compounds and compositions of the present invention are also intended for use with general care provided patients with Arenaviridae viral infections, including parenteral fluids (including dextrose saline and Ringer's lactate) and nutrition, antibiotic (including Metronidazole and Cephalosporin antibiotics, such as Ceftriaxone and Cefuroxime) and/or antifungal prophylaxis, fever and pain medication, antiemetic (such as Metoclopramide) and/or antidiarrheal agents, vitamin and mineral supplements (including Vitamin C or/and K and zinc sulfate), anti-inflammatory agents (such as Ibuprofen), pain medications, and medications for other common diseases in the patient population, such anti-malarial agents (including Artemether and Artesunate-lumefantrine combination therapy), typhoid (including quinolone antibiotics, such as Ciprofloxacin, macrolide antibiotics, such as Azithromycin, cephalosporin antibiotics, such as Ceftriaxone, or aminopenicillins, such as Ampicillin), or shigellosis.

In yet another embodiment, compound of formula (I) or its pharmaceutically acceptable salts is provided in the form of pharmaceutical composition.

In an embodiment, present invention provides a pharmaceutical composition comprising compound of formula (I) or its pharmaceutically acceptable salts for treatment of neuroinflammatory disorders or neurodegenerative disorder diseases such as Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders preferably Parkinson's disease (PD) wherein compound of formula (I) is



Formula (I)

In an embodiment, the present invention provides pharmaceutical composition comprising compound of formula (I) and suitable pharmaceutically acceptable excipients for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases such as Traumatic brain

injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders preferably Parkinson's disease (PD).

The pharmaceutically acceptable excipients may be selected at least one from diluents, carriers, binders, disintegrating agents, lubricating agents, surface active agents and the like.

In an embodiment, the present invention provides a pharmaceutical composition comprising compound of formula (I) or its pharmaceutically acceptable salts wherein effective amount of compound of formula (I) or its pharmaceutically acceptable salt may be selected from 1 mg to 500 mg; preferably 1 mg to 250 mg and more preferably 1 mg to 150 mg for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases.

In an embodiment, the present invention provides pharmaceutical composition comprising compound of formula (I) or its pharmaceutically acceptable salts may be administered by oral, topical, parenteral, intravenous or intramuscular route of administration. In a preferred embodiment, the pharmaceutical composition may be administered by oral route of administration.

In another embodiment of the present invention provides a process for the preparation of a stable pharmaceutical composition of compounds of formula (1) or its pharmaceutically acceptable salts.

The stable pharmaceutical composition may be made by dry mixing, wet granulation or dry granulation methods by techniques known to persons skilled in the art. Thus, for example,

In wet granulation process, the drug is mixed with one or more pharmaceutical excipients and granulated with suitable binding solution as described earlier, to form wet granules, the wet granules are dried and optionally sieved. The dried granules are mixed with one or more suitable excipients from those described elsewhere and then compressed into tablets or filled into capsules.

In dry mixing process, the drug is mixed with all the pharmaceutical excipients required. The blend is mixed with one or more suitable excipients from those described elsewhere and then final blend is either compressed into tablets or filled in capsules.

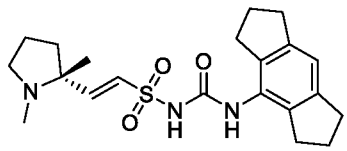
In dry granulation process, the drug is mixed with one or more pharmaceutical excipients and compressed into slugs and these slugs are passed through required sieve. The sieved granules are mixed with one or more suitable excipients from those described elsewhere and then compressed into tablets or filled into capsules.

One or more solvents or vehicle used in the formulation are selected from water, acetone, chloroform, dichloromethane, ethyl alcohol, ethyl acetate, methyl alcohol, isopropyl alcohol and combinations thereof and other such materials known to those of ordinary skill in the art.

The present invention further discloses use of said compound of formula (I) or their suitable pharmaceutical compositions for the treatment of neuroinflammatory or neurodegenerative disorder diseases such as Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders preferably Parkinson's disease (PD).

In another embodiment, the present invention provides a method of treating neuroinflammatory disorders or neurodegenerative disorder diseases using pharmaceutical composition of compound of formula (I) or its pharmaceutically acceptable salts. In a preferred embodiment, a method of treating neuroinflammatory disorders or neurodegenerative disorder diseases using compound of formula (I) or its pharmaceutical composition.

In a preferred embodiment, the present invention provides compound of formula (11)



Formula (11)

or its pharmaceutically acceptable salts suitable for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases. These severe and persistent illnesses include Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

In a preferred embodiment neuroinflammatory disorders or neurodegenerative disorder diseases is Parkinson's disease (PD).

In a further preferred embodiment, the present invention provides use of the compound of formula (11) or their suitable pharmaceutical compositions for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases such as Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders preferably Parkinson's disease (PD).

In another preferred embodiment, the present invention provides effective amount of compound of formula (11) or its pharmaceutically acceptable salt may be selected from 1 mg to 500 mg; preferably 1 mg to 250 mg and more preferably 1 mg to 150 mg for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases.

In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 250 mg on each day the compound is administered to the subject. For example, in certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 25 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 25 mg to about 50 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 50 mg to about 75 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 75 mg to about 100 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 100 mg to about 125 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a

pharmaceutically acceptable salt thereof in the range of about 125 mg to about 150 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 150 mg to about 175 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 175 mg to about 200 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 200 mg to about 225 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 225 mg to about 250 mg on each day the compound is administered to the subject.

In certain other embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 25 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 50 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 75 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 100 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 125 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 150 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a

pharmaceutically acceptable salt thereof in the range of about 1 mg to about 175 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 200 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 225 mg on each day the compound is administered to the subject. In certain embodiments, the compound is administered orally in an amount to provide compound of formula (11) or a pharmaceutically acceptable salt thereof in the range of about 1 mg to about 250 mg on each day the compound is administered to the subject.

In another preferred embodiment, the present invention provides effective amount of compound of formula (11) or its pharmaceutically acceptable salt may be administered by oral, topical, parenteral, intravenous or intramuscular route of administration. In a preferred embodiment, the present invention provides effective amount of formula (11) or its pharmaceutically acceptable salt is administered by oral route of administration.

The compound of formula (11) or its pharmaceutically acceptable salts may be provided to the subject daily, weekly, as prescribed by physician to the person in need thereof.

In one of the preferred embodiment, the present invention provides the combination of compound of formula (11) and their pharmaceutically acceptable salts with other suitable agents as therapeutic agent for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases.

Wherein other suitable therapeutic agents may be selected from Inhibitors of interleukin-1β (e.g. Rilonacept, Canakinumab, and Anakinra); immune-suppressants (e.g., Methotrexate, Mercaptopurine, Cyclophosphamide), metabolic disorders drugs, glucocorticoids, non-steroidal anti-inflammatory drugs, Gasdermin D inhibitors (e.g., Necrosulfonamide); Cox-2 specific inhibitors, TNF-α binding proteins (e.g.,Infliximab, Etanercept), Interferon-13, Interferon, Interleukin-2, antihistamines, beta-agonist, BTK inhibitors, anticolinergics, anti-cancer agents; anti-viral drugs, for example: Remdesivir, Lopinavir/Ritonavir, Favipiravir, Molnupiravir, Tamiflu; anti-malarial agents, for example: Choloroquinone, Hydroxyl Chloroquinone; or their

suitable pharmaceutically acceptable salts. Further examples for use in combination with Non-Alcoholic Steato- Hepatitis (NASH) and fibrosis drugs; anticancer; antibiotics, for example Azithromycin; hormones, Aromatase inhibitors, Colchicine, Anticoagulants, antibodies, cytokines, anti-IL6 drugs; Antiparasitics; vaccines; Interferons; drug conjugates; Drugs originally developed for SARS (ACE2 protein decoy); Intravenous vitamin C; inhibitors of mitogen-activated protein kinase signaling (ex: BAY 43-9006); Syk inhibitors; mTOR inhibitors; antibodies (Rituxan); and BCR/ABL antagonist may also be used in combination with compound of formula (11) for treatment of neuroinflammatory disorders or neurodegenerative disorder diseases.

The compound of formula (11) of the present invention or its pharmaceutically acceptable salts may be used further in combination with one or more suitable pharmaceutically active agents selected from following therapeutic agents in any combinations. MAO B inhibitors, selegiline (Zelapar), rasagiline (Azilect) and safinamide (Xadago); Catechol O-methyltransferase (COMT) inhibitors, Entacapone (Comtan) and opicapone (Ongentys); benztropine (Cogentin), trihexyphenidyl, Amantadine; cholinesterase inhibitors, donepezil (Aricept), galantamine (Razadyne) and rivastigmine (Exelon), Memantine (Namenda), aducanumab (Aduhelm); Riluzole (Rilutek), Edaravone (Radicava); ocrelizumab (Ocrevus), prednisone and methylprednisolone; tetrabenazine (Xenazine) and deutetrabenazine (Austedo), haloperidol (Haldol) and fluphenazine, risperidone (Risperdal), olanzapine (Zyprexa) and quetiapine (Seroquel), levetiracetam (Keppra, Elepsia XR, Spritam) and clonazepam (Klonopin); citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac, Sarafem) and sertraline (Zoloft), quetiapine (Seroquel), risperidone (Risperdal) and olanzapine (Zyprexa), divalproex (Depakote), carbamazepine (Carbatrol, Epitol) and lamotrigine (Lamictal).

The compounds of formula (11) and its compositions of the present invention are also intended for use with general care provided patients with Arenaviridae viral infections, including parenteral fluids (including dextrose saline and Ringer's lactate) and nutrition, antibiotic (including Metronidazole and Cephalosporin antibiotics, such as Ceftriaxone and Cefuroxime) and/or antifungal prophylaxis, fever and pain medication, antiemetic (such as Metoclopramide) and/or antidiarrheal agents, vitamin and mineral supplements (including Vitamin C or/and K and zinc sulfate), anti-inflammatory agents (such as Ibuprofen), pain medications, and medications

for other common diseases in the patient population, such anti-malarial agents (including Artemether and Artesunate-lumefantrine combination therapy), typhoid (including quinolone antibiotics, such as Ciprofloxacin, macrolide antibiotics, such as Azithromycin, cephalosporin antibiotics, such as Ceftriaxone, or aminopenicillins, such as Ampicillin), or shigellosis.

In a preferred embodiment, present invention provides a pharmaceutical composition comprising compound of formula (11) or its pharmaceutically acceptable salts for treatment of neuroinflammatory disorders or neurodegenerative disorder diseases. These severe and persistent illnesses include Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

In a preferred embodiment, neuroinflammatory disorders or neurodegenerative disorder diseases is Parkinson's disease.

In another preferred embodiment, the present invention provides pharmaceutical composition comprising compound of formula (11) and suitable pharmaceutically acceptable excipients for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases.

The pharmaceutically acceptable excipients may be selected at least one from diluents, carriers, binders, disintegrating agents, lubricating agents, surface active agents and the like.

In another embodiment, the present invention further discloses use of said compound of formula (11) or their suitable pharmaceutical compositions for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases such as Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders preferably Parkinson's disease.

In another preferred embodiment, the present invention provides a method of treating neuroinflammatory disorders or neurodegenerative disorder diseases using pharmaceutical composition of compound of formula (11) or its pharmaceutically acceptable salts. In a preferred embodiment, a method of treating neuroinflammatory disorders or neurodegenerative disorder diseases using compound of formula (11) or its pharmaceutical composition.

In another preferred embodiment of the present invention provides a process for the preparation of a stable pharmaceutical composition of compounds of formula (11).

The stable pharmaceutical composition may be made by dry mixing, wet granulation or dry granulation methods by techniques known to persons skilled in the art. Thus, for example,

In wet granulation process, the drug is mixed with one or more pharmaceutical excipients and granulated with suitable binding solution as described earlier, to form wet granules, the wet granules are dried and optionally sieved. The dried granules are mixed with one or more suitable excipients from those described elsewhere and then compressed into tablets or filled into capsules.

In dry mixing process, the drug is mixed with all the pharmaceutical excipients required. The blend is mixed with one or more suitable excipients from those described elsewhere and then final blend is either compressed into tablets or filled in capsules.

In dry granulation process, the drug is mixed with one or more pharmaceutical excipients and compressed into slugs and these slugs are passed through required sieve. The sieved granules are mixed with one or more suitable excipients from those described elsewhere and then compressed into tablets or filled into capsules.

One or more solvents or vehicle used in the formulation are selected from water, acetone, chloroform, dichloromethane, ethyl alcohol, ethyl acetate, methyl alcohol, isopropyl alcohol and combinations thereof and other such materials known to those of ordinary skill in the art.

In an embodiment, the pharmaceutically acceptable excipients described in the present invention are selected at least one from diluents, carriers, binders, disintegrating agents, lubricating agents, surface active agents and the like.

Diluents include, but are not limited to lactose monohydrate, polymethacrylates selected from Eudragit, potassium chloride, sulfobutylether b-cyclodextrin, sodium chloride and spray dried lactose, combinations thereof and other such materials known to those of ordinary skill in the art.

Carriers include, but are not limited to lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate and kaolin, crystalline cellulose and silicic acid, combinations thereof and other such materials known to those of ordinary skill in the art.

Binders include, but are not limited to carbomers selected from carbopol, gellan, gum Arabic, hydrogenated vegetable oil, polymethacrylates selected from Eudragit, xanthan, lactose and Zein, combinations thereof and other such materials known to those of ordinary skill in the art.

Disintegrating agents include, but are not limited to, bicarbonate salt, chitin, gellan gum, polacrillin potassium and docusate sodium, combinations thereof and other such materials known to those of ordinary skill in the art.

Lubricating agents used include, but are not limited to, glycerin behenate, hydrogenated vegetable oil, sodium stearyl fumarate and myristic acid, combinations thereof and other such materials known to those of ordinary skill in the art.

Surface active agents include but are not limited to, nonionic surfactant selected from alkyl polyglucosides, cocamide DEA, cocamide MBA, cocamide TEA, decyl maltoside and octyl glucoside; anionic surfactant selected from arachnidan acid and arachidonic acid; cationic surfactant selected from cetyl trimethylammonium bromide and cetylpyridinium chloride, combinations thereof and other such materials known to those of ordinary skill in the art.

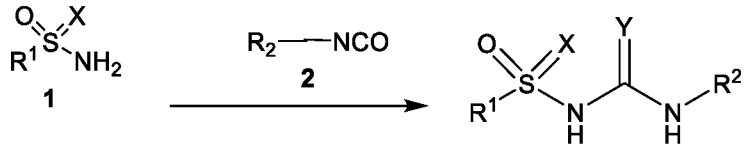
General Process for Preparation

The novel compounds of the present invention can be prepared using the reactions and techniques described below, together with conventional techniques known to those skilled in the art of organic synthesis, or variations thereon as appreciated by those skilled in the art.

The reactions can be performed in solvents appropriate to the reagents and materials employed and suitable for the transformations being affected. Preferred methods include, but not limited to those described below, where all symbols are as defined earlier unless and otherwise defined below.

The compounds of the general formula (I) can be prepared as described in schemes below along with suitable modifications/variations which are well within the scope of a person skilled in the art.

Scheme 1



Formula (I)

Wherein each of R^1, R^2, X, and Y, are as defined earlier. Compound **1** and Compound **2** can be prepared by variety of methods familiar to those skilled in art using reported procedures. Compound (**1**) on treatment with isocyanato derivative (**2**) under suitable conditions in presence of base like sodium hydride and appropriate solvent to afford compound of formula (**I**).

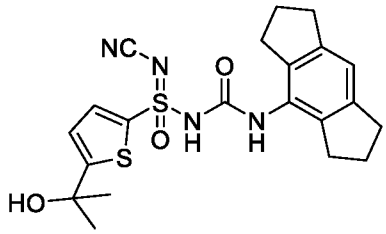
Specific reaction conditions, solvents and other parameters necessary for carrying out the process steps as described above are well within the capabilities of a person skilled in the art.

The invention is further illustrated by the following non-limiting examples which describe the preferred way of carrying out the present invention. These are provided without limiting the scope of the present invention in any way.

^{1}H NMR spectral data given in the examples (vide infra) are recorded using a 400 MHz spectrometer (Bruker AVANCE-400) and reported in δ scale. Until and otherwise mentioned the solvent used for NMR is $CDCl_3$ using TMS as the internal standard.

Example – 1

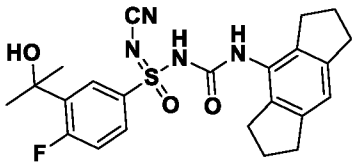
N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.95 (bs, 1H), 7.23 (d, J = 4.0 Hz, 1H), 6.82 (d, J = 4.0 Hz, 1H), 6.81 (s, 1H), 5.63 (s, 2H), 2.77 (t, J = 7.2 Hz, 4H), 2.68 – 2.65 (m, 4H), 1.94 (qui, J = 7.2 Hz, 4H), 1.49 (s, 6H); MS (ESI): *m/z* (%) = 445.10 (100%) $(M+H)^+$, 443.10 (100%) (M-H).

Example 2

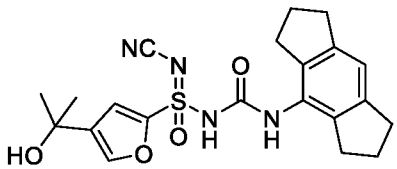
N'-cyano-4-fluoro-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide



^{1}H NMR (400 MHz, DMSO): δ = 8.13 (dd, J=2.4Hz, J=7.6Hz, 1H), 8.00 (bs, 1H), 7.68-7.64 (m, 1H), 7.24-7.19 (m, 2H), 6.79 (s, 1H), 2.76-2.60 (m, 8H), 1.95-1.85 (m, 4H), 1.50 (s, 3H), 1.48 (s, 3H); MS (ESI): *m/z* (%) = 456.88 (100%) $(M+H)^+$.

Example – 3

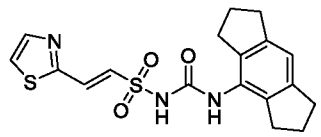
N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)furan-2-sulfonimidamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.10 (bs, 1H), 7.55 (s, 1H), 6.82 (s, 1H), 6.79 (s, 1H), 5.03 (s, 1H), 2.77 (t, J = 7.2 Hz, 4H), 2.68 (t, J = 7.2 Hz, 4H), 1.94 (qui, J = 7.2 Hz, 4H), 1.38 (s, 6H); MS (ESI): *m/z* (%) = 429.20 (100%) $(M+H)^+$, 427.30 (100%) (M-H).

Example 4

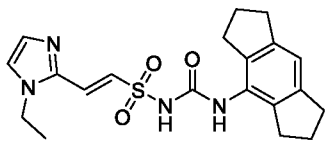
(E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(thiazol-2-yl)ethenesulfonamide



^{1}H NMR (400 MHz, DMSO-d_6, *D2O-X*): δ = 10.7 (br, s, 1H), 8.23 (s, 1H), 8.05 (d, *J* = 2.8 Hz, 1H), 8.02 (d, *J* = 2.8 Hz, 1H), 7.74 (d, *J* = 15.2 Hz, 1H), 7.58 (d, *J* = 15.2 Hz, 1H), 6.96 (s, 1H), 2.79 (t, *J* = 7.2 Hz, 4H), 2.66 (t, *J* = 6.8 Hz, 4H), 1.98 – 1.91 (m, 4H); MS (ESI): *m/z* (%) = 389.92 (100%) $(M+H)^+$, 411.90 (20%) $(M+Na^+)$.

Example 5

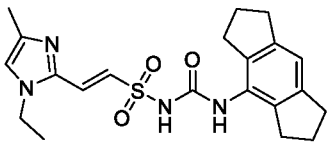
(E)-2-(1-ethyl-1H-imidazol-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethenesulfonamide



^{1}H NMR (400 MHz, DMSO): δ = 10.55 (bs, 1H), 8.20 (s, 1H), 7.46-7.42 (m, 2H), 7.29 (d, *J*=14.8Hz, 1H), 7.13 (s, 1H), 6.95 (s, 1H), 4.16 (q, *J*=7.2Hz, 2H), 2.82-2.78 (m, 4H), 2.67-2.64 (m, 4H), 1.98-1.91 (m, 4H), 4.16 (t, *J*=7.2Hz, 3H); MS (ESI): *m/z* (%) = 401.15 (100%) $(M+H)^+$; 423.15 (50%) $(M+Na)^+$.

Example 6

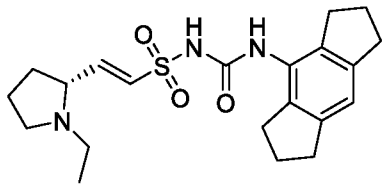
(E)-2-(1-ethyl-4-methyl-1H-imidazol-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethenesulfonamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.55 (s, 1H), 8.16 (s, 1H), 7.36 (d, J = 14.8 Hz, 1H), 7.21 (d, J = 14.8 Hz, 1H), 7.17 (s, 1H), 6.95 (s, 1H), 4.08 (q, J = 7.2 Hz, 2H), 2.80 (t, J = 7.2 Hz, 4H), 2.66 (t, J = 7.2 Hz, 4H), 2.12 (s, 3H), 1.98 – 1.91 (m, 4H), 1.27 (d, J = 7.2 Hz, 3H); MS (ESI): *m/z* (%) = 415.18 (100%) $(M+H)^+$.

Example-7

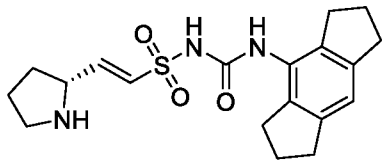
(R,E)-2-(1-ethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-ethanesulfonamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.03 (s, 1H), 6.92 (s, 1H), 6.87 (d, J=14.8Hz, 1H), 6.60-6.54 (m, 1H), 3.27-3.16 (m, 3H), 2.80 (t, J=7.2Hz, 4H), 2.67 (t, J=7.2Hz, 4H), 2.35-2.33 (m, 2H), 2.09-1.94 (m, 6H), 1.81-1.73 (m, 2H), 1.03 (t, J=7.2Hz, 3H); **MS (ESI): *m/z* (%)** = 404.20 (100%) $(M+H)^+$.

Example-8

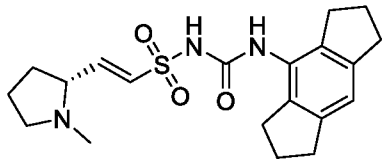
(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(pyrrolidin-2-yl)ethene-1-sulfonamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.71 (brs, 1H), 7.49 (s, 1H), 6.95 (d, J = 15.2 Hz, 1H), 6.80 (s, 1H), 6.36 (dd, J = 7.2 Hz, J = 15.2 Hz, 1H), 4.08 – 4.02 (m, 1H), 3.18 – 3.03 (m, 2H), 2.77 (t, J = 7.2 Hz, 4H), 2.70 (t, J = 7.2 Hz, 4H), 2.14 – 2.07 (m, 4H), 2.03 – 1.80 (m, 6H), 1.70 – 1.60 (m, 1H); **MS (ESI): *m/z* (%)** = 376.10 (100%) $(M+H)^+$, 374.05 (100%) (M-1).

Example-9

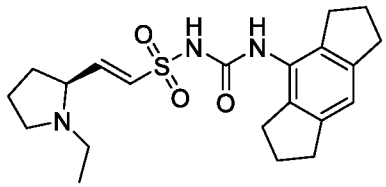
(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(1-methylpyrrolidin-2-yl)ethene-1-sulfonamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.53 (brs, 1H), 7.97 (s, 1H), 6.92 (s, 1H), 6.84 (d, *J* = 15.2 Hz, 1H), 6.53 (dd, *J* = 7.6 Hz, *J* = 15.2 Hz, 1H), 3.13 – 3.04 (m, 1H), 3.05 – 2.92 (m, 1H), 2.80 (t, *J* = 7.2 Hz, 4H), 2.67 (t, *J* = 7.2 Hz, 4H), 2.33 – 2.28 (m, 1H), 2.26 (s, 3H), 2.05 – 1.91 (m, 5H), 1.79 – 1.72 (m, 2H), 1.59 – 1.54 (m, 1H); **MS (ESI): *m/z* (%)** = 390.17 (100%) $(M+H)^+$, 388.07 (30%) (M-1).

Example-10

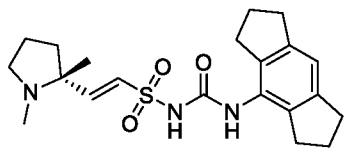
(S,E)-2-(1-ethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-ethanesulfonamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.03 (s, 1H), 6.92 (s, 1H), 6.87 (d, *J*=14.8Hz, 1H), 6.60-6.54 (m, 1H), 3.27-3.16 (m, 3H), 2.80 (t, *J*=7.2Hz, 4H), 2.67 (t, *J*=7.2Hz, 4H), 2.35-2.33 (m, 2H), 2.09-1.94 (m, 6H), 1.81-1.73 (m, 2H), 1.03 (t, *J*=7.2Hz, 3H); **MS (ESI): *m/z* (%)** = 404.20 (100%) $(M+H)^+$.

Example-11

(R,E)-2-(1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide

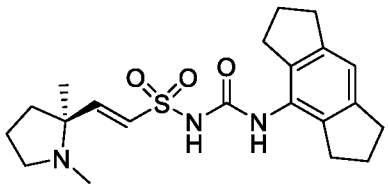


^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.04 (s, 1H), 6.93 (s, 1H), 6.74 (d, *J* = 15.6 Hz, 1H), 6.65 (d, *J* = 15.2 Hz, 1H), 2.93 – 2.86 (m, 1H), 2.80 (t, *J* = 7.2 Hz, 4H), 2.67 (t, *J* = 7.2 Hz, 4H), 2.19

(s, 3H), 1.99 – 1.91 (m, 5H), 1.80 – 1.69 (m, 4H), 1.13 (s, 3H), MS (ESI): *m/z* (%) = 404.16 (100%) $(M+H)^+$.

Example-12

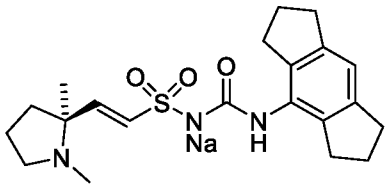
(S,E)-2-(1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide



1H NMR (400 MHz, DMSO-d6): δ =8.04 (s, 1H), 6.93 (s, 1H), 6.73 (d, *J* = 15.2 Hz, 1H), 6.65 (d, *J*= 15.2 Hz, 1H), 2.80 (t, *J* = 7.2 Hz, 4H) , 2.68 (t, *J* = 7.2 Hz, 4H) , 2.20 (s, 3H), 1.96 (m, 4H), 1.72 (m, 4H), 1.13 (s, 3H); MS (ESI): m/z (%) = 404.25 (100%) (M+1).

Example-13

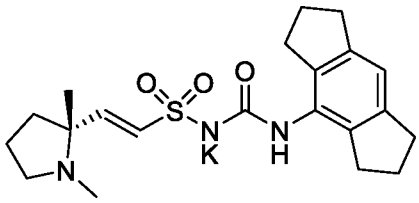
sodium(S,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide



1H NMR (400 MHz, DMSO-d6): δ =7.33 (s, 1H), 6.77 (s, 1H), 6.56 (d, *J* = 15.2 Hz, 1H), 6.16 (d, *J*= 16 Hz, 1H), 2.76 (t, *J* = 7.2 Hz, 4H) , 2.69 (t, *J* = 7.2 Hz, 4H) , 2.62 (m, 1H), 2.08 (s, 3H), 1.90 (m, 4H), 1.72 (m, 4H), 1.60 (m, 3H), 1.01 (s, 3H); MS (ESI): m/z (%) = 404.20 (100%) (M+1).

Example-14

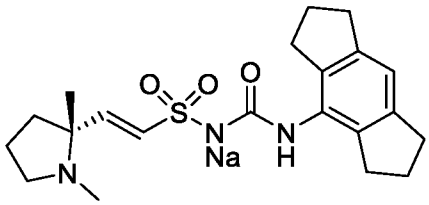
potassium (R,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.33 (s, 1H), 6.77 (s, 1H), 6.58 (d, J = 15.6 Hz, 1H), 6.18 (d, J = 15.6 Hz, 1H), 2.77 – 2.72 (m, 5H), 2.69 (t, J = 7.2 Hz, 4H), 2.64 – 2.58 (m, 1H), 2.08 (s, 3H), 1.90 (quin, J = 7.6 Hz, 4H), 1.75 – 1.70 (m, 3H), 1.62 – 1.60 (m, 1H), 1.01 (s, 3H); MS (ESI): *m/z* (%) = 404.21 (100%) $(M-K)^+$.

Example-15

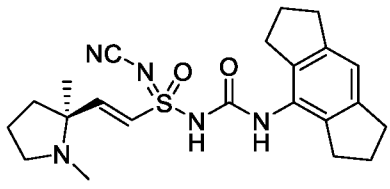
Sodium(R,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.36 (s, 1H), 6.77 (s, 1H), 6.57 (d, J = 15.6 Hz, 1H), 6.19 (d, J = 15.6 Hz, 1H), 2.76 (t, J = 7.2 Hz, 5H), 2.69 (t, J = 7.2 Hz, 4H), 2.64 – 2.59 (m, 1H), 2.08 (s, 3H), 1.91 (quin, J = 7.6 Hz, 4H), 1.74 – 1.68 (m, 3H), 1.62 – 1.60 (m, 1H), 1.01 (s, 3H); MS (ESI): *m/z* (%) = 404.17 (100%) $(M-Na)^+$.

Example-16

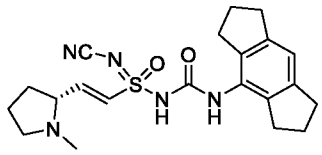
(E)-N'-cyano-2-((S)-1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonimidamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.94 (s, 1H), 8.06 (s, 1H), 6.97 (d, J = 16.0 Hz, 1H), 6.83 (s, 1H), 6.56 – 6.48 (m, 1H), 3.58 (br s, 1H), 3.24 – 3.12 (m, 1H), 2.77 (t, J = 7.2 Hz, 4H), 2.69 (t, J = 7.2 Hz, 7H), 2.10 – 1.99 (m, 3H), 1.95 – 1.88 (m, 5H), 1.53 – 1.36 (m, 3H); ESI-Q-TOF-MS: *m/z* $[M-HCl+H]^+$ calcd for $[C22H30N5O2S]^+$: 428.2120; found: 428.2052

Example-17

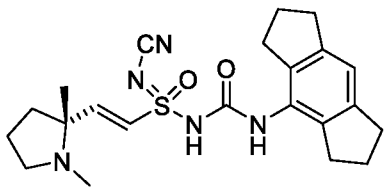
(E)-N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-((R)-1-methylpyrrolidin-2-yl)ethene-1-sulfonimidamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.82 (s, 1H), 8.06 (s, 1H), 7.11 – 7.02 (m, 1H), 6.83 (s, 1H), 6.43 – 6.35 (m, 1H), 4.99 (br s, 1H), 3.62 – 3.61 (m, 1H), 3.09 – 3.07 (m, 1H), 2.77 (t, J = 7.2 Hz, 7H), 2.70 (t, J = 7.2 Hz, 4H), 2.33 – 2.27 (m, 1H), 2. 1 – 1.88 (m, 7H); MS (TOF): *m/z* (%) = 414.1897 (100%) $(M+H)^+$, 412.1765 (100%) $(M-1)^-$.

Example-18

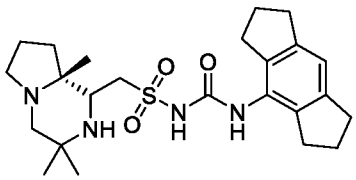
(E)-N'-cyano-2-((R)-1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonimidamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.98 (s, 1H), 8.03 (s, 1H), 6.94 – 6.90 (m, 1H), 6.83 (s, 1H), 6.54 – 6.51 (m, 1H), 2.77 (t, J = 7.2 Hz, 5H), 2.70 (t, J = 7.2 Hz, 5H), 2.62 (br s, 3H), 1.99 – 1.90 (br s, 2H), 1.97 – 1.93 (m, 6H), 1.48 – 1.46 (m, 3H); MS (TOF): *m/z* (%) = 428.2097 (100%) $(M+H)^+$, 426.1941 (60%) $(M-1)^-$.

Example-19

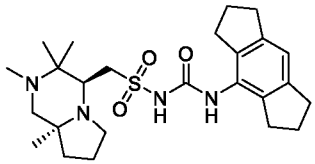
N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-1-((1S,8aR)-3,3,8a-trimethyloctahydropyrrolo[1,2-a]pyrazin-1-yl)methanesulfonamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.92 (s, 1H), 6.87 (s, 1H), 3.42 - 3.26 (m, 5H), 3.07 - 3.01 (m, 1H), 2.89 - 2.80 (m, 1H), 2.89 - 2.80 (m, 1H), 2.77 (t, J=7.2Hz, 4H), 2.73 - 2.67 (m, 4H), 2.58 - 2.44 (m, 1H), 2.38 - 2.33 (m, 1H), 1.98 - 1.92 (m, 4H), 1.69 - 1.61 (m, 2H), 1.31 (s, 3H), 1.18 (s, 3H), 0.78 (s, 3H); MS (TOF): *m/z* (%) = 461.2537 (100%) $(M+H)^+$.

Example-20

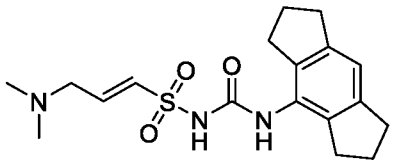
N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-1-((4S,8aS)-2,3,3,8a-tetramethyloctahydropyrrolo[1,2-a]pyrazin-4-yl)methanesulfonamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.03 (s, 1H), 6.93 (s, 1H), 3.52 – 3.48 (m, 2H), 3.18 – 3.09 (m, 1H), 3.09 – 3.01 (m, 1H), 3.00 – 2.88 (m, 1H), 2.81 (t, *J* = 7.2 *Hz*, 4H), 2.70 (t, *J* = 7.2 *Hz*, 4H), 2.36 – 2.33 (m, 2H), 2.19 (s, 3H), 2.01 – 1.93 (m, 4H), 1.76– 1.69 (m, 1H), 1.67 – 1.54 (m, 3H), 1.01 – 1.04 (m, 6H), 0.86 (s, 3H); **MS (TOF): *m/z* (%)** = 475.2709 (100%) $(M+H)^+$,473.2593 (20%) (M-1).

Example-21

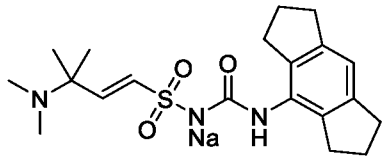
(E)-3-(dimethylamino)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)prop-1-ene-1-sulfonamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.22 (brs, 1H), 7.94 (s, 1H), 6.91 (s, 1H), 6.86 (d, *J* = 15.2 *Hz*, 1H), 6.62 – 6.55 (m, 1H), 3.27 (t, *J* = 6.0 *Hz*, 2H), 2.79 (t, *J* = 7.2 *Hz*, 4H), 2.67 (t, *J* = 7.2 *Hz*, 4H), 2.30 (s, 6H), 1.99 – 1.91 (m, 4H); **MS (ESI): *m/z* (%)** = 364.1513 (100%) $(M+H)^+$.

Example-22

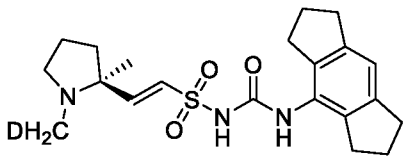
sodium (E)-((3-(dimethylamino)-3-methylbut-1-en-1-yl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.36 (s, 1H), 6.77 (s, 1H), 6.51 (d, *J* = 15.6 *Hz*, 1H), 6.23 (d, *J* = 15.6 *Hz*, 1H), 2.76 (t, *J* = 7.2 *Hz*, 4H), 2.69 (t, *J* = 7.2 *Hz*, 4H), 2.11 (s, 1H), 1.94 – 1.87 (m, 4H), 1.06 (s, 6H); **MS (TOF): *m/z* (%)** = 392.1987 (100%) $(M+H)^+$,390.1841 (20%) (M-1).

Example-23

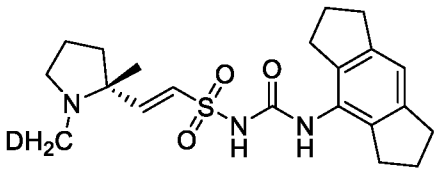
(S,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-methyl-1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.93 (s, 1H), 6.91 (s, 1H), 6.71 (d, *J* = 15.2 Hz, 1H), 6.60 (d, *J* = 15.6 Hz, 1H), 2.85 – 2.83 (m, 1H), 2.80 (t, *J* = 7.2 Hz, 4H), 2.73 – 2.71 (m, 1H), 2.67 (t, *J* = 7.2 Hz, 4H), 2.15 (s, 2H), 1.95 (quin, *J* = 7.2 Hz, 4H), 1.81 – 1.69 (m, 4H), 1.10 (s, 3H). ESI-Q-TOF-MS: *m/z* 405.2268 (100%) $[M+H]^+$, 403.1901 (100%) $[M-H]^-$.

Example-24

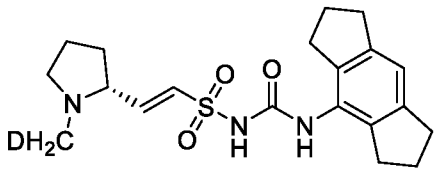
(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-methyl-1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.94 (s, 1H), 6.91 (s, 1H), 6.72 (d, *J* = 15.2 Hz, 1H), 6.61 (d, *J* = 15.2 Hz, 1H), 2.88 – 2.83 (m, 1H), 2.80 (t, *J* = 7.2 Hz, 4H), 2.75 – 2.71 (m, 1H), 2.67 (t, *J* = 7.2 Hz, 4H), 2.15 (s, 2H), 1.95 (quin, *J* = 7.2 Hz, 4H), 1.82 – 1.69 (m, 4H), 1.11 (s, 3H), ESI-Q-TOF-MS: *m/z* 405.2104 (100%) $[M+H]^+$, 403.1915 (100%) $[M-H]^-$.

Example-25

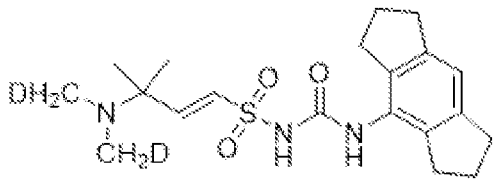
(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.5 (br s, 1H), 7.99 (s, 1H), 6.92 (s, 1H), 6.86 (d, J = 15.2 Hz, 1H), 6.56 (dd, J_1 = 7.6 Hz, J_2 = 15.2 Hz, 1H), 3.12 – 3.06 (m, 2H), 2.80 (t, J = 7.2 Hz, 4H), 2.67 (t, J = 7.2 Hz, 4H), 2.38 – 2.32 (m, 1H), 2.25 (s, 2H), 2.08 – 2.01 (m, 1H), 1.95 (quin, J = 7.2 Hz, 4H), 1.80 – 1.73 (m, 2H), 1.63 – 1.54 (m, 1H), ESI-Q-TOF-MS: *m/z* 391.1956 (100%) $[M+H]^+$, 389.1756 (100%) $[M-H]^-$

Example-26

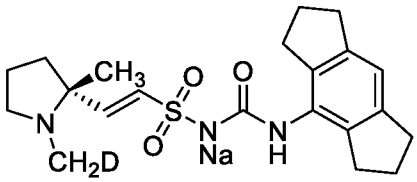
(E)-3-(bis(methyl-d)amino)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-3-methylbut-1-ene-1-sulfonamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.87 (s, 1H), 6.89 (s, 1H), 6.73 (d, J = 15.2 Hz, 1H), 6.61 (d, J = 15.2 Hz, 1H), 2.79 (t, J = 7.6 Hz, 4H), 2.67 (t, J = 7.2 Hz, 4H), 2.30 (s, 4H), 1.97 – 1.93 (m, 4H), 1.21 (s, 6H), ESI-Q-TOF-MS: *m/z* 394.2150 (100%) $[M+H]^+$, 392.1980 (100%) $[M-H]^-$.

Example-27

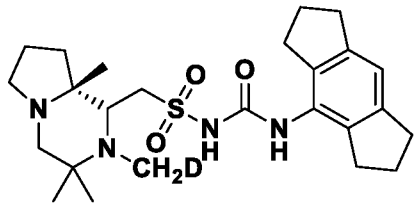
Sodium (R,E)-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)((2-(2-methyl-1-(methyl-d)pyrrolidin-2-yl)vinyl)sulfonyl)amide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.35 (s, 1H), 6.77 (s, 1H), 6.55 (d, *J* = 15.6 Hz, 1H), 6.18 (d, *J* = 15.6 Hz, 1H), 2.78 – 2.68 (m, 9H), 2.64 – 2.59 (m, 1H), 2.06 (s, 2H), 1.94 – 1.87 (m, 4H), 1.74 – 1.70 (m, 3H), 1.60 – 1.57 (m, 1H), 1.01 (s, 3H); **MS (ESI): *m/z* (%)** = 405.2101 (100%) $(M+H)^+$,403.1921 (100%) (M-1).

Example-28

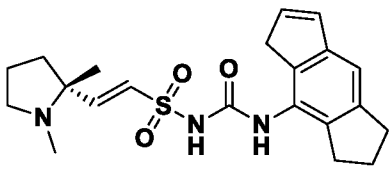
N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-1-((1S,8aR)-3,3,8a-trimethyl-2-(methyl-d)octahydropyrrolo[1,2-a]pyrazin-1-yl)methanesulfonamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.01 (bs, 1H), 6.94 (s, 1H), 3.54 (s, 2H), 2.98 - 2.50 (m, 10H), 2.45 - 2.09 (m, 5H), 1.99 - 1.91 (m, 4H), 1.81 - 1.65 (m, 4H), 1.10 (s, 6H), 0.8 (s, 3H); **MS (TOF): *m/z* (%)** = 476.2797 (100%) $(M+H)^+$; 474.2623 (100%) $(M-1)^-$.

Example-29

(R,E)-2-(1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5-tetrahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide

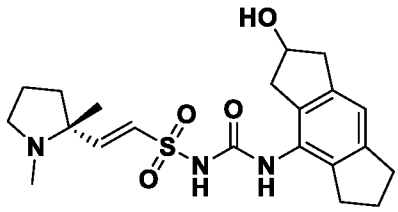


^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.27 (bs, 1H), 7.18 (s, 1H), 6.79 - 6.73 (m, 2H), 6.66 - 6.62 (m, 1H), 6.46 - 6.45 (m, 1H), 3.34 - 3.22 (m, 2H), 2.90 - 2.86 (m, 3H), 2.78 - 2.72 (m, 3H),

2.22 (s, 3H), 2.03 - 1.96 (m, 2H), 1.88 - 1.73 (m, 4H), 1.15 (s, 3H); **MS (TOF): *m/z* (%)** = 402.25 (100%) $(M+H)^+$.

Example-30

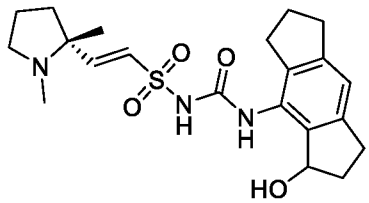
(E)-2-((R)-1,2-dimethylpyrrolidin-2-yl)-N-((2-hydroxy-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.5 (bs, 1H), 8.10 (s, 1H), 6.91 (s, 1H), 6.77 - 6.65 (m, 2H), 4.79 (d, *J*=3.6Hz, 1H), 4.43 (d, *J*=2.8Hz, 1H), 3.03 - 2.97 (m, 3H), 2.81 - 2.78 (m, 7H), 2.33 (s, 3H), 1.99 - 1.76 (m, 6H), 1.16 (s, 3H); **MS (TOF): *m/z* (%)** = 420.19 (100%) $(M+H)^+$.

Example-31

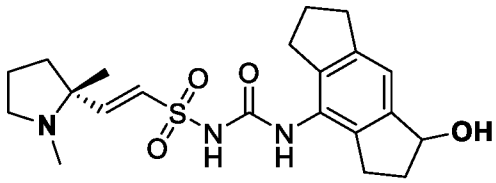
(E)-2-((R)-1,2-dimethylpyrrolidin-2-yl)-N-((3-hydroxy-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.05 (s, 1H), 6.90 (s, 1H), 6.75 (t, *J* = 15.2 *Hz*, 1H), 6.60 (t, *J* = 15.6 *Hz*, 1H), 5.01 (t, *J* = 3.2 *Hz*, 1H), 3.18 – 2.89 (m, 2H), 2.87 – 2.67 (m, 3H), 2.68 – 2.60 (m, 2H), 2.32 – 2.19 (m, 4H), 2.07 – 1.93 (m, 2H), 1.90 – 1.79 (m, 6H), 1.17 (s, 3H);**MS (TOF): *m/z* (%)** = 420.1937 (50%) $(M+H)^+$,418.1843 (5%) (M-1).

Example-32

(E)-2-((R)-1,2-dimethylpyrrolidin-2-yl)-N-((1-hydroxy-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide



^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.4 (br s, 1H), 8.02 (s, 1H), 7.02 (s, 1H), 6.75 (t, J = 15.2 Hz, 1H), 6.65 (t, J = 15.6 Hz, 1H), 5.13 (d, J = 4.4 Hz, 1H), 4.98 (d, J = 3.6 Hz, 1H), 2.88 – 2.79 (m, 3H), 2.77 – 2.60 (m, 4H), 2.56 – 2.54 (m, 1H), 2.30 – 2.24 (m, 1H), 2.20 (s, 3H), 2.00 – 1.91 (m, 2H), 1.84 – 1.67 (m, 5H), 1.13 (s, 3H);**MS (TOF): *m/z* (%)** = 420.1947 (100%) $(M+H)^+$, 418.1800 (20%) (M-1).

Biological Activity:

***In-vitro* assays:**

THP1 monocytes were differentiated with PMA (100ng/ml) and incubated at 37 °C for 20 hrs in presence of 5% CO_2. $2X10^5$ differentiated cells were plated per well of 96 well tissue culture plates. The cells were primed using 500ng/mL Lipopolysaccharide and incubating for 4h under the same condition. The cells were then treated with various concentrations of the compounds for 30 min followed by treatment with 5mM ATP for 1hr. The supernatants were collected and analyzed by IL-1b (Mabtech Cat # 3415-1H-20) or TNF-a (Mabtech; Cat # 3510-1H-20) detection kit. The data were analyzed using GraphPad Prism V7.0. Dose Response Curve (DRC) was constructed to determine the IC_{50} value by fitting percentage cell survival data to the GraphPad Prism using nonlinear regression analysis. The *in vitro* IL-1β inhibitory activity (IC_{50}) for representative compounds are listed in Table 1.

Table 1:

Compound	IL-1β (IC_{50}) (nM)
Example 1	4.8
Example 2	7.8
Example 3	3.3
Example 4	35

Example 5	25
Example 6	20
Example 7	3.9
Example 8	7.1
Example-9	2.0
Example-10	4.3
Example-11	12
Example-12	2.7
Example 16	1.5
Example 17	2.3
Example 18	2.1
Example 19	11
Example 20	7.2
Example 21	3.2
Example 23	1.4
Example 24	4.7
Example-25	3.1

In vitro MPTP induced NLRP3 in microglial cells- assay: The adult mouse brain was utilized to perform this study. Brains were washed with PBS and cut into pieces and then mechanically homogenized. The homogenized suspension was then subjected to digestion with 0.25% trypsin EDTA solution for 10 minutes at 37 degree. The suspension was then filtered through cell strainer, subjected to centrifugation at 365g for 5 minutes at room temperature. The pellet was resuspended in RPMI complete medium and layered over 30% stock isotonic percoll (SIP). This gradient mixture was centrifuged for 10 minutes at 700g at room temperature. Discard the interphase between PBS and 30% percoll containing myelin. Washed the pelleted cells containing microglia and seed 50000 cells/well in poly-L-lysine coated 96 well plate and incubate overnight at $37^{O}C$ in 5% CO_2 incubator. After overnight incubation, test compounds were added and further incubated for 1hr. Following this, LPS (1µg/mL) was added and

incubated for 4h. Later 20µM nigericin was added to respective wells and plate was again incubated for 1h. After 1h, supernatant was collected and IL-1β secretion was measured by Mouse R&D system ELISA kit (MLB00C).

Mouse microglial cells	IC_{50} (nM)
Compound 11	43
MCC950	108

Results:

A substantial induction of NLRP3 was observed through increase in secreted IL-1β when microglial cells were primed with LPS and activated with Nigericin. Both the test compounds, compound 11 of present invention and MCC950 inhibited the inflammasome activation. Compound 11 of present invention showed better activity compared to MCC950 with a half maximal inhibitory concentration of 43nM against 108nM of MCC950.

***In-vivo* efficacy studies:**

Demonstration of *in vivo* efficacy of test compounds in rats mice, oral routes of administration.

Animals: All the animal experiments were carried out in female rats and mice, bred in-house. Animals were housed in groups of 6 animals per cage, for a week, in order to habituate them to vivarium conditions (25 ± 4 °C, 60-65 % relative humidity, 12: 12 h light: dark cycle, with lights on at 7.30 am). All the animal experiments were carried out according to the internationally valid guidelines following approval by the 'Zydus Research Center animal ethical committee'.

In-vivo LPS and ATP induced IL-1β assay:

Female C57 mice (6-8 weeks) received intraperitoneal injection of 50 µg/mouse of lipopolysaccharide (LPS) in PBS. Animals were treated immediately with the test compounds or the vehicle. After 2h of LPS injection, animals were administered with ATP at 12.5 mg/mouse dissolved in PBS via intraperitoneal route. After 30 minutes of ATP injection, serum was collected for IL-1β estimation by ELISA.

Pharmacokinetic analysis in plasma and brain tissue: The objective of the study was to investigate the brain distribution of test compounds following a single oral administration of test compounds to C57 mouse. The study was conducted in male or female C57 mice (n=4 per time point). Animal had free access of food and water throughout the study period. The dose formulation was prepared in 1% v/v Tween® 80, 99% v/v 0.5 % methyl cellulose in purified water. Animals were received test compounds suspension formulation at 30 mg/kg dose via oral gavage at dose volume 10.0 mL /kg. The formulation strength was 3.0 mg/mL. Total 6 blood and brain tissue samples were collected at different time intervals. Following post dose, at specific time point blood sample was collected and then animal was humanly sacrificed for the brain tissue. Blood and brain samples were collected at 0.25, 0.5, 1, 2, 4 and 8 h post dosing (n=4/time point). The blood sampling was performed from retro-orbital plexus under mild isoflurane anesthesia in a tube containing Na-heparin (~20 IU/mL of blood) and placed on ice cold condition. The blood samples were centrifuged at 4000 rpm for 15 min to obtain plasma and stored at -70±20°C until analysis. Immediately after blood sampling, the animal was perfused with 4 mL 1X PBS buffer solution under deep isoflurane anesthesia followed by collection of brain tissue. The collected brain samples were immediately placed on the ice and then stored at -70±20°C until homogenization. Brain tissue samples were homogenized using a Polytron tissue homogenizer in phosphate buffer saline, the brain homogenate density was kept 0.2 g/mL. The plasma and brain tissue homogenate samples were analyzed for total and unbound test compounds concentration using a separately developed fit for research LC-MS/MS assays. The calibration range was linear over 5 to 2000 ng/mL for total and 0.2 to 200 ng/mL for unbound fraction for test compounds.

Example 11: PK parameters in C57 mice

Matrix	Tmax (h)	Unbound C_{max} (ng/mL or g)	Unbound AUC_{last} (ng.h/mL or g)	Unbound AUC_{inf} (ng.h/mL or g)	$T_{1/2}$ (h)
Brain	0.5	12.88	28.80[a]	NC	1.24
Plasma	0.25	191.9	290.53	296.29	1.42

Unit for C_{max} and AUC for brain is (ng/g) and (ng*h/g), respectively; NC, not calculated; n=4;a, AUC_{all}

Matrix	Tmax (h)	Total C_{max} (ng/mL or g)	Total AUC_{last} (ng.h/mL or g)	Total AUC_{inf} (ng.h/mL or g)	$T_{1/2}$ (h)
Brain	0.5	453.84	1127.97	1166.38	1.6
Plasma	0.5	38082.9	54682.47	56012.72	1.71

Unit for C_{max} and AUC for brain is (ng/g) and (ng*h/g), respectively; n=4

Example 21: PK parameters in C57 mice					
Matrix	**Tmax (h)**	**Unbound C_{max} (ng/mL or g)**	**Unbound AUC_{last} (ng.h/mL or g)**	**Unbound AUC_{inf} (ng.h/mL or g)**	**$T_{1/2}$ (h)**
Brain	0.5	79.79	188.47	192.72	1.46
Plasma	0.5	1221.32	1784.31	1805.76	1.31
Unit for C_{max} and AUC for brain is (ng/g) and (ng*h/g), respectively; n=4					

Matrix	**Tmax (h)**	**Total C_{max} (ng/mL or g)**	**Total AUC_{last} (ng.h/mL or g)**	**Total AUC_{inf} (ng.h/mL or g)**	**$T_{1/2}$ (h)**
Brain	0.5	372.79	848.024	877.64	1.63
Plasma	0.5	39001.22	64731.66	65582.51	1.33
Unit for C_{max} and AUC for brain is (ng/g) and (ng*h/g), respectively;n=4					

Phase 2a POC study:

Phase 2a POC study of test compound (compound 11 of the present invention) in patients with Parkinson's disease. Clinically diagnosed patients with Parkinson's disease aged 45 to 75 years and with Modified Hoehn and Yahr Stage of less than 3 are included in the study. Approximately 15 patients with Parkinson's disease are enrolled in the study. Study are conducted with dose range around 25 to 75 mg twice daily for 14 days. Eligible patients are received 27 doses of test compound (compound 11 of the present invention) twice daily from Day 1 to Day 13 in the morning before breakfast and in the evening before dinner. On Day 14, single dose is administered in the morning before breakfast.

Within 28 days of screening period, eligible patients are admitted in the clinical unit on Day (-1). Patients are remain admitted to the clinical unit for 12 hours post first dose on Day 1 and Day 14 for safety assessments, and pharmacokinetic and pharmacodynamics sampling. Patients are again report to the facility on Day 2, Day 4, Day 7, Day 10, Day 14, Day 15 and Day 21(Follow up) for safety assessment and Pharmacokinetic and Pharmacodynamic blood sampling.

Primary objective of the study is to evaluate safety and tolerability of test compound (Compound 11 of the present invention) administered orally in patients with Parkinson's disease. Secondary and exploratory objectives include evaluation of pharmacokinetics and pharmacodynamics of test compound (Compound 11 of the present invention) administered orally twice daily for 14 days. Blood samples are collected at multiple time-point for pharmacokinetics and pharmacodynamics assessment. Cerebrospinal Fluid (CSF) are collected

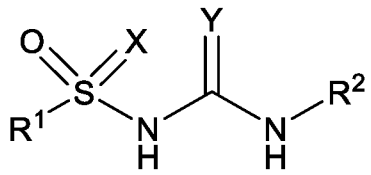
after 2 hours of post last dose to correlate concentration of test compound (Compound 11 of the present invention) in CSF and plasma. Exploratory parameters like α-Synuclein levels, NLRP3, Soluble LAG-3, Toll-interacting protein and hs C-Reactive Protein are measured in the blood at defined time points.

Safety are evaluated by physical examination and neurological examination, vital signs, clinical laboratory tests and ECGs at various time points during the study and documentation of AEs/SAEs.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We claim:

1. A method for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases, which comprises administering a compound of formula (I)



Formula (I)

or its pharmaceutically acceptable salts

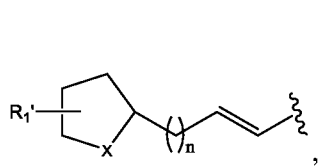
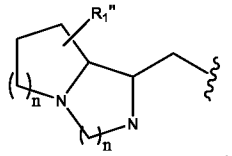
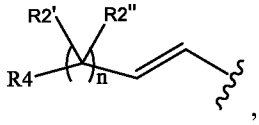
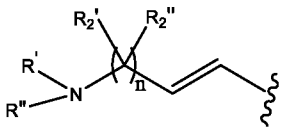
wherein

X is O, NH, or N-R^3 wherein R^3 at each occurrence is independently selected from hydrogen, hydroxyl, halogen, nitro, cyano, haloalkyl, optionally substituted groups selected from $(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_{10})$alkoxy, $(C_3\text{-}C_{10})$cycloalkyl, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, $SO_2(C_1\text{-}C_6)$alkyl, thiol, thioalkyl, thio-alkoxy, $SO(C_1\text{-}C_6)$alkyl, benzyl, aryl, heteroaryl, heterocyclyl;

Y is O, S;

R^1 at each occurrence is independently selected from hydrogen, halogen, haloalkyl, cyano, optionally substituted groups selected from $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_7)$cycloalkyl,$(C_1\text{-}C_6)$alkyl$SO_2(C_1\text{-}C_6)$alkyl,$(C_1\text{-}C_6)$alkyl$N(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl$N(C_3\text{-}C_7)$cycloalkyl, aryl, heteroaryl, heterocyclyl, benzyl, tert-butyloxycarbonyl, $NH(C_1\text{-}C_6)$alkyl, $N((C_1\text{-}C_6)\text{alkyl})_2$, $NH(C_2\text{-}C_6)$alkenyl, $N((C_2\text{-}C_6)\text{alkenyl})_2$, -N-heterocyclyl, $N(C_1\text{-}C_6)$alkyl-heterocyclyl, NR'R'', thiol, mercaptoalkyl, $SO_2(C_1\text{-}C_6)$alkyl, $SO_2(C_3\text{-}C_7)$cycloalkyl, SO_2-aryl, SO_2-heterocyclyl, $(C_1\text{-}C_6)$thioalkyl, $(C_1\text{-}C_6)$thioalkoxy, $(C_1\text{-}C_6)$alkylSO_2NH_2, $-CONH_2$, $-CO(C_1\text{-}C_6)$alkyl, $-CO(C_1\text{-}C_6)$haloalkyl, -CO-aryl, -CO-heteroaryl, -CO-heterocyclyl, 4- to 7-membered heterocyclic ring, 7- to 14-membered bicyclic heterocyclic ring system, bridged or spiro ring system having optionally one or more than one heteroatoms;

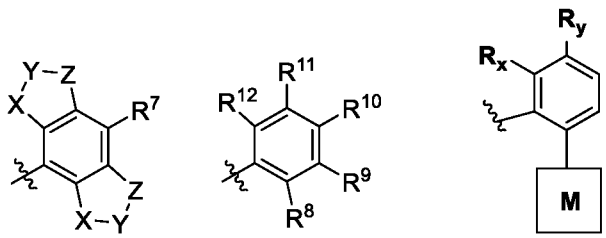
alternatively R^1 is selected from

n, is independently selected from integer 0-3;

each of R', R", R_1', R_1'', R_2' and R_2" at each occurrence is independently selected from hydrogen, halogen, haloalkyl, cyano, optionally substituted groups selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkoxy, (C_3-C_7)cycloalkyl, (C_1-C_6)alkylSO_2(C_1-C_6)alkyl, (C_1-C_6)alkylN(C_1-C_6)alkyl, (C_1-C_6)alkylN(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocyclyl, benzyl, tert-butyloxycarbonyl, thiol, mercaptoalkyl, SO_2(C_1-C_6)alkyl, SO_2(C_3-C_7)cycloalkyl, SO_2-aryl, SO_2-heterocyclyl, (C_1-C_6)thioalkyl, (C_1-C_6)thioalkoxy, (C_1-C_6)alkylSO_2NH_2, -$CONH_2$, -CO(C_1-C_6)alkyl, -CO(C_1-C_6)haloalkyl, -CO-aryl, -CO-heteroaryl, -CO-heterocyclyl, 4- to 7-membered heterocyclic ring, 7- to 14-membered bicyclic heterocyclic ring system, bridged or spiro ring system having optionally one or more than one heteroatoms; in an embodiment R' and R" optionally forms 4- to 7-membered heterocyclic ring system.

R^2 is selected from the following ring system



wherein X, Y, Z at each occurrence independently represents C, N, S, SO_2, and O, which may be optionally substituted;

each of R^7, R^8, R^9, R^{10}, R^{11} and R^{12} at each occurrence are independently selected from hydrogen, halogen, cyano, amide, sulphonamide, acyl, hydroxyl, optionally substituted groups selected from (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy, benzyl, aryl, heteroaryl, heterocyclyl; in one embodiment each of R^8 and R^9, R^9 and R^{10},

R^{10} and R^{11} and R^{11} and R^{12} wherever possible, together may form a 4 to 7 membered saturated or partially saturated ring containing from 0-2 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$; p = 1-2.

R_x and R_y at each occurrence are independently selected from hydrogen, halogen, optionally substituted groups selected from $(C_1\text{-}C_6)$alkyl; alternatively R_x and R_y together may form a 4- to 7-membered heterocyclic ring system;

'M' is selected from aryl, heteroaryl, heterocyclyl; and wherein when any of above defined group is substituted the substitutions on them are selected from those described above or may be selected from hydrogen, hydroxy, cyano, halo, haloalkyl, haloalkyloxy, alkylthio, optionally substituted group selected from $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_{10})$cycloalkyl, $C_1\text{-}C_6$ alkoxy, aryl, heterocyclyl, heteroaryl, $-COR_{11}$, $-CSR_{11}$, $C(O)OR_{11}$, $C(O)\text{-}R_{11}$, $-C(O)\text{-}NR_{11}R_{12}$, $-C(S)\text{-}NR_{11}R_{12}$, $-SO_2R_{11}$ group, wherein each of, R_{11} and R_{12} is independently selected from hydrogen, optionally substituted group selected from $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, heteroaryl, heterocyclyl groups.

2. The method as claimed in claim 1, wherein neuroinflammatory disorders or neurodegenerative disorder diseases are selected from Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

3. The method as claimed in claim 1 and 2, wherein neuroinflammatory disorders or neurodegenerative disorder disease is Parkinson's disease.

4. The method as claimed in claim 1, wherein said compound of Formula (I) is selected from the group:

N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2- N'-cyano-4-fluoro-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide;

N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)furan-2-sulfonimidamide;

(E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(thiazol-2-yl)ethenesulfonamide;

(E)-2-(1-ethyl-1H-imidazol-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethenesulfonamide;

(E)-2-(1-ethyl-4-methyl-1H-imidazol-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethenesulfonamide;

(R,E)-2-(1-ethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-ethanesulfonamide;

(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(pyrrolidin-2-yl)ethene-1-sulfonamide;

(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(1-methylpyrrolidin-2-yl)ethene-1-sulfonamide;

(S,E)-2-(1-ethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-ethanesulfonamide;

(R,E)-2-(1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide;

(S,E)-2-(1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonamide;

sodium(S,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide;

potassium (R,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide;

Sodium(R,E)-((2-(1,2-dimethylpyrrolidin-2-yl)vinyl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide;

(E)-N'-cyano-2-((S)-1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonimidamide;

(E)-N'-cyano-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-((R)-1-methylpyrrolidin-2-yl)ethene-1-sulfonimidamide;

(E)-N'-cyano-2-((R)-1,2-dimethylpyrrolidin-2-yl)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)ethene-1-sulfonimidamide;

N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-1-((1S,8aR)-3,3,8a-trimethyloctahydropyrrolo[1,2-a]pyrazin-1-yl)methanesulfonamide

N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-1-((4S,8aS)-2,3,3,8a-tetramethyloctahydropyrrolo[1,2-a]pyrazin-4-yl)methanesulfonamide;

(E)-3-(dimethylamino)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)prop-1-ene-1-sulfonamide;

sodium (E)-((3-(dimethylamino)-3-methylbut-1-en-1-yl)sulfonyl)((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)amide;

(S,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-methyl-1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide;

(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-methyl-1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide;

(R,E)-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(1-(methyl-d)pyrrolidin-2-yl)ethene-1-sulfonamide;

or pharmaceutically acceptable salts of any of the compounds above.

5. The method as claimed in claim 1, wherein therapeutically effective amount of compound of formula (I) or its pharmaceutically acceptable salt is selected from 1 mg to 500 mg, preferably selected from 1 mg to 250 mg, more preferably selected from 1 mg to 150 mg.

6. The method as claimed in claim 1, wherein compound of formula (I) or its pharmaceutically acceptable salt is administered by oral, topical or parenteral route of administration, preferably administered by an oral route of administration.

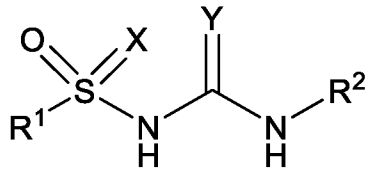
7. The method as claimed in claim 1, wherein compound of formula (I) or its pharmaceutically acceptable salt is administered in combination with other suitable therapeutic agents.

8. The method as claimed in claim 1, wherein compound of formula (I) or its pharmaceutically acceptable salt is administered in the form of pharmaceutical composition.

9. Use of the compound of formula (I) as claimed in claim 1 and 4 for the preparation of a medicament for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases.

10. Use of the compound of formula (I) as claimed in claim 1 and 4, wherein the compound is administrated in a daily dosage range is selected from 1 mg to 500 mg, preferably selected from 1 mg to 250 mg, more preferably selected from 1 mg to 150 mg.

11. A pharmaceutical composition comprising compound of formula (I) or its pharmaceutically acceptable salts for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases wherein compound of formula (I) is



Formula (I)

12. The pharmaceutical composition as claimed in claim 11, wherein neuroinflammatory disorders or neurodegenerative disorder diseases are selected from Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

13. The pharmaceutical composition as claimed in claim 11 and 12, wherein neuroinflammatory disorders or neurodegenerative disorder disease is Parkinson's disease.

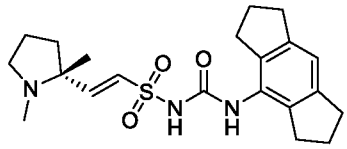
14. The pharmaceutical composition as claimed in claim 11, wherein therapeutically effective amount of compound of formula (I) or its pharmaceutically acceptable salt is selected from 1 mg to 500 mg, preferably selected from 1 mg to 250 mg, more preferably selected from 1 mg to 150 mg.

15. The pharmaceutical composition as claimed in claim 11 comprising compound of formula (I) and other pharmaceutically acceptable excipients for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases.

16. The pharmaceutical composition as claimed in claim 11, wherein compound of formula (I) or its pharmaceutically acceptable salt is administered in combination with other suitable therapeutic agents.

17. Use of the pharmaceutical composition as claimed in claim 11 for the preparation of medicament for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases.

18. A method for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases which comprises administering a compound of formula (11)



Formula 11

or its pharmaceutically acceptable salts.

19. The method as claimed in claim 18, wherein neuroinflammatory disorders or neurodegenerative disorder diseases are selected from Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

20. The method as claimed in claim 18 and 19, wherein neuroinflammatory disorders or neurodegenerative disorder disease is Parkinson's disease.

21. The method as claimed in claim 18, wherein therapeutically effective amount of compound of formula (11) or its pharmaceutically acceptable salt is selected from 1 mg to 500 mg, preferably selected from 1 mg to 250 mg, more preferably selected from 1 mg to 150 mg.

22. The method as claimed in claim 18, wherein compound of formula (11) or its pharmaceutically acceptable salt is administered by oral, topical or parenteral route of administration, preferably administered by an oral route of administration.

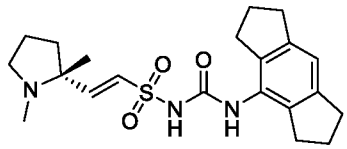
23. The method as claimed in claim 18, wherein compound of formula (11) or its pharmaceutically acceptable salt is administered in combination with other suitable therapeutic agents.

24. The method as claimed in claim 13, wherein compound of formula (11) or its pharmaceutically acceptable salt is administered in the form of pharmaceutical composition.

25. Use of the compound of formula (11) as claimed in any one of the preceding claims for the preparation of a medicament for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases.

26. Use of the compound of formula (11) as claimed in any one of the preceding claims wherein the compound is administrated in a daily dosage range is selected from 1 mg to 500 mg, preferably selected from 1 mg to 250 mg, more preferably selected from 1 mg to 150 mg.

27. A pharmaceutical composition comprising compound of formula (11) or its pharmaceutically acceptable salts for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases, wherein compound of formula (11) is



Formula (11)

28. The pharmaceutical composition as claimed in claim 27, wherein neuroinflammatory disorders or neurodegenerative disorder diseases are selected from Traumatic brain injury (TBI), Amyotrophic lateral sclerosis (ALS), Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease and other related forms of disorders.

29. The pharmaceutical composition as claimed in claim 27 and 28, wherein neuroinflammatory disorders or neurodegenerative disorder disease is Parkinson's disease.

30. The pharmaceutical composition as claimed in claim 27, wherein therapeutically effective amount of compound of formula (11) or its pharmaceutically acceptable salt is selected from 1 mg to 500 mg, preferably selected from 1 mg to 250 mg, more preferably selected from 1 mg to 150 mg.

31. The pharmaceutical composition as claimed in claim 27 comprising compound of formula (11) and other pharmaceutically acceptable excipients for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases.

32. The pharmaceutical composition as claimed in claim 27, wherein compound of formula (11) or its pharmaceutically acceptable salt is administered in combination with other suitable therapeutic agents.

33. Use of the pharmaceutical composition as claimed in claim 27 for the preparation of medicament for the treatment of neuroinflammatory disorders or neurodegenerative disorder diseases.

34. The pharmaceutical composition as claimed in claim 31, wherein other pharmaceutically acceptable excipients are selected from diluents, carriers, binders, disintegrating agents, lubricating agents and surface active agents.

35. The pharmaceutical composition as claimed in any one of the preceding claims, wherein diluents are selected from lactose monohydrate, polymethacrylates selected from Eudragit,

potassium chloride, sulfobutylether b-cyclodextrin, sodium chloride and spray dried lactose and suitable combination thereof.

36. The pharmaceutical composition as claimed in as claimed in any one of the preceding claims, wherein carriers are selected from lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate and kaolin, crystalline cellulose, silicic acid and suitable combination thereof.

37. The pharmaceutical composition as claimed in as claimed in any one of the preceding claims, wherein binders are carbomers selected from carbopol, gellan, gum Arabic, hydrogenated vegetable oil, polymethacrylates selected from Eudragit, xanthan, lactose and Zein and suitable combination thereof.

38. The pharmaceutical composition as claimed in any one of the preceding claims, wherein disintegrating agents are selected from bicarbonate salt, chitin, gellan gum, polacrillin potassium, docusate sodium and suitable combination thereof.

39. The pharmaceutical composition as claimed in any one of the preceding claims, wherein lubricating agents are selected from Glycerin behenate, hydrogenated vegetable oil, sodium stearyl fumarate, myristic acid and suitable combination thereof.

40. The pharmaceutical composition as claimed in any one of the preceding claims wherein surface active agents are nonionic surfactant selected from alkyl polyglucosides, cocamide DEA, cocamide MBA, cocamide TEA, decyl maltoside and octyl glucoside; anionic surfactant selected from arachnidan acid and arachidonic acid; cationic surfactant selected from cetyl trimethylammonium bromide and cetyl pyridinium chloride and suitable combination thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2022/057951

A. CLASSIFICATION OF SUBJECT MATTER
C07D401/06,C07D205/04,C07D405/06,C07D487/04,A61K31/40,A61P25/16,A61P25/28,A61P29/00 Version=2022.01
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, A61K, A61P

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

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
CAS Registry, CAPLUS, PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2020/148619 A1 (CADILA HEALTHCARE LIMITED [IN]) 23 July 2020 (23.07.2020) Example 56, Claims 8-11, Page 3 line 22- page 4 line 2, Page 127 line 7-page 129 line 5;	9-17,25-40
A	WO 2019/008025 A1 (INFLAZOME LIMITED [IE]) 10 January 2019 (10.01.2019) Claims 16-23;	9-17,25-40

☐ 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
"D" document cited by the applicant in the international application
"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
14-12-2022	14-12-2022

Name and mailing address of the ISA/	Authorized officer
Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Veera R Kattula Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2022/057951

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-8,18-24
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matter of claims 1-8, 18-24 is related to a method of treatment of the human or animal body by surgery or therapy or to a diagnostic method, which does not require an international search by this Authority in accordance with PCT Article 17(2)(a)(i) and Rule 39.1(iv).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2022/057951

Citation	Pub.Date	Family	Pub.Date
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		US 20220169605 A1	02-06-2022
		CN 113474333 A	01-10-2021
		KR 20210114967 A	24-09-2021
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