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(54) Title: INHIBITION OF SHIP1 AS A THERAPEUTIC STRATEGY FOR THE TREATMENT OF ALZHEIMER'S DISEASE

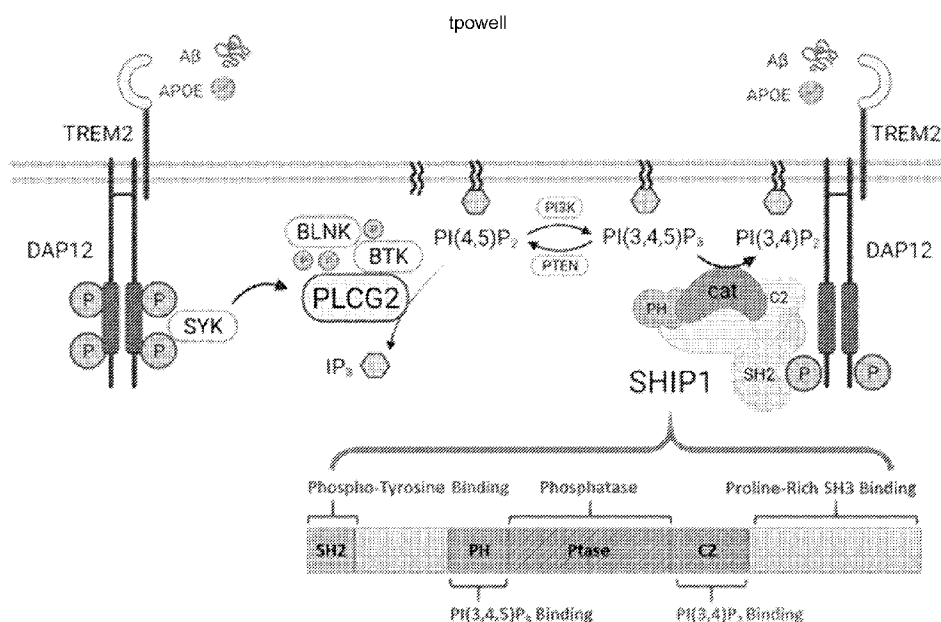


Fig. 1

(57) Abstract: The general field of the present disclosure are novel approaches to the treatment of Alzheimer's and other neurodegenerative disorders using novel therapeutics comprising SHIP1 phosphatase inhibitors. Specifically, the invention provides compounds and pharmaceutical compositions for use in methods of treating and preventing or ameliorating such disorders.



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INHIBITION OF SHIP1 AS A THERAPEUTIC STRATEGY FOR THE TREATMENT OF ALZHEIMER'S DISEASE

[0001] CROSS REFERENCE TO RELATED APPLICATIONS

[0002] The present application claims the benefit under 35 U.S.C. § 119 of United States Provisional Application 63/419,766 filed October 27, 2022 and United States Provisional Application 63/421,318 filed November 1, 2022, the contents of each of which are incorporated herein by reference in their entireties.

[0003] REFERENCE TO GOVERNMENT GRANTS

[0004] This invention was made with government support under AG065181 awarded by National Institutes of Health. The Government has certain rights in the invention.

[0005] SEQUENCE LISTING

[0006] This application incorporates by reference the material in the Extensible Markup Language (XML) file titled IUIC-102_sequence_listing_18OCT2023.XML, which was created on October 18, 2023 and is 2,499 bytes in size.

[0007] FIELD

[0008] The general field of the present disclosure are novel approaches to the treatment of Alzheimer's and other neurodegenerative disorders using novel therapeutics comprising SHIP1 phosphatase inhibitors.

[0009] BACKGROUND

[0010] Alzheimer's disease (AD) is a fatal, neurodegenerative disorder, characterized by histopathological accumulation of extracellular β -amyloid (A β) plaques and intra-neuronal neurofibrillary tangles (NFTs), which have been hypothesized to result in neurotoxicity and progressive cognitive decline. See Kumar et al., "A review on Alzheimer's disease pathophysiology and its management: an update, (2015) *Pharmacol Rep* 67: pp. 195–203; Hardy et al., "Alzheimer's disease: the amyloid cascade hypothesis: an update and reappraisal," (2006) *J Alzheimers Dis* 9: pp. 151–153; Shen et al., "Complement activation by neurofibrillary tangles in Alzheimer's disease," (2001) *Neurosci Lett* 305: pp. 165–168; Scheltens et al., "Alzheimer's disease, (2021) *Lancet* 397: pp. 1577–1590. The amyloid cascade hypothesis postulates that various forms of A β oligomers and plaques are instrumental in a neuropathological process that triggers subsequent NFT pathology, neuroinflammation, and neuronal loss; however, the mechanisms by which A β influences neurotoxic signaling including NFT formation remain an area of intense

study. Recently, the amyloid cascade hypothesis has come under increased scrutiny due to inadequate efficacy of **drugs targeting A β peptide processing** and various forms of A β . See Panza et al., “A critical appraisal of amyloid-beta-targeting therapies for Alzheimer disease,” (2019) *Nat Rev Neurol* 15: pp. 73–88.

[0011] More recent evidence including genome-wide association studies (GWAS), whole genome sequencing, differential gene expression, and gene-expression network analyses **comparing normal to affected Alzheimer’s brain tissue have identified risk and protective variants** in genes such as *TREM2*, *CD33*, *APOE*, *ABCA7*, *PLCG2*, and *INPP5D*, which are essential to microglia function. See Malik et al., “Genetics ignite focus on microglial inflammation in Alzheimer’s disease,” (2015) *Mol Neurodegener* 10: p. 52. Microglia are the non-neuronal, macrophage-like cells that serve as resident immune cells in the brain. See Vaughan et al., “Neuroglial cells in the cerebral cortex of rats from young adulthood to old age: an electron microscope study,” (1974) *J Neurocytol* 3: pp. 405–429.

[0012] During development microglia originate from stem cells in the yolk sac and differentiate into CD45⁺, CX3CR1⁺ immune cells that migrate to the central nervous system (CNS). See Kierdorf et al., “Microglia emerge from erythromyeloid precursors via Pu.1- and Irf8-dependent pathways,” (2013) *Nat Neurosci* 16: pp. 273–280. Once resident, these cells renew slowly in humans at a rate of approximately 28 percent per year, thus providing a mechanism to renew microglia. See Reu et al., “The Lifespan and Turnover of Microglia in the Human Brain,” (2017) *Cell Rep* 20: pp. 779–784. Disease associated microglia (DAM) have been characterized **at sites of A β plaques and neurodegeneration in animal models**. See Keren-Shaul et al., “A Unique Microglia Type Associated with Restricting Development of Alzheimer’s Disease,” (2017) *Cell* 169: pp. 1276–1290. Although their relevance to human microglia in AD remains a current area of intense study, they have gene signatures associated with lipid metabolism and phagocytosis hypothesized to reflect the neuroprotective role of microglia in the clearance of extracellular toxins. See Olah et al., “Single cell RNA sequencing of human microglia uncovers a subset associated with Alzheimer’s disease,” (2020) *Nat Commun* 11: pp. 6129. A two-state model of DAM induction has been proposed, in which homeostatic microglia that are associated with and support the health of neurons become activated with increased expression of *DAP12*, *APOE*, and Triggering receptor expressed on myeloid cells-2 (*TREM2*). *TREM2* ligands such as apolipoproteins (including, e.g., *APOE*) **and A β induce microglial differentiation into stage-2 DAMs with increased expression of *LPL*, *CST7*, and *AXL***. Deczkowska et al., “Disease-Associated Microglia: A Universal Immune Sensor of Neurodegeneration,” (2018) *Cell* 173: pp. 1073–1081; Keren-Shaul et al. 2017.

[0013] TREM2 is a receptor expressed on the surface of microglia. Genetic evidence suggests that lower *TREM2* expression and inactivating variants increase risk of AD. *See* Jonsson et al., “Variant of TREM2 associated with the risk of Alzheimer's disease,” (2013) *N Engl J Med* 368: pp. 107–116. **TREM2 binds A β and APOE, which activates microgliosis and the clearance of extracellular debris.** *See* Yeh et al., “TREM2 Binds to Apolipoproteins, Including APOE and CLU/APOJ, and Thereby Facilitates Uptake of Amyloid-Beta by Microglia,” (2016) *Neuron* 91: pp. 328–340. The *TREM2*^{R47H} variant reduces the affinity of TREM2 ligands and cellular activation downstream, which requires DAP12, an adapter protein on the intracellular side of the plasma membrane that associates with numerous signal transduction mediators. *See* Sudom et al., “Molecular basis for the loss-of-function effects of the Alzheimer's disease-associated R47H variant of the immune receptor TREM2,” (2018) *J Biol Chem* 293: pp. 12634–12646. For example, recruitment of SYK to phosphorylated tyrosine residues at the C-terminus of DAP12 mediates signaling through phosphorylation of PLC γ 2 and subsequent formation of intracellular IP₃ and Ca²⁺ release. *See* Konishi et al., “Microglial TREM2/DAP12 Signaling: A Double-Edged Sword in Neural Diseases,” (2018) *Front Cell Neurosci* 12: p. 206. Importantly, an activating variant of PLCG2, *PLCG2*^{P522R} is protective in AD. *See* Magno et al., “Alzheimer's disease phospholipase C-gamma-2 (PLCG2) protective variant is a functional hypermorph,” (2019) *Alzheimer's Res Ther* 11: p. 16. This human genetic evidence suggests that dampened microglia activity increases risk of neurodegeneration while activated microglia are protective, clearing A β oligomers and plaques, and mitigating an inflammatory microenvironment that is toxic to neurons. *See* Deczkowska et al., 2018.

[0014] The recent regulatory approval of the anti-amyloid antibody aducanumab provides evidence for the role of activated microglia in the treatment of AD. *See* Dunn et al., “Approval of Aducanumab for Alzheimer Disease-The FDA's Perspective,” (2021) *JAMA Intern Med* 181: pp. 1276–1278. **Cell surface Fc γ receptors (Fc γ Rs) on microglia recognize the Fc portion of IgG antibodies triggering downstream effector functions.** *See* Bournazos et al., “The role of IgG Fc receptors in antibody-dependent enhancement,” (2020) *Nat Rev Immunol* 20: pp. 633–643. **The clearance of A β deposits by aducanumab has been demonstrated to occur by targeting A β via the variable region of the antibody coupled to Fc γ R-mediated enhancement of microglia recruitment and phagocytosis.** *See* Sevigny et al., “The antibody aducanumab reduces Abeta plaques in Alzheimer's disease,” (2016) *Nature* 537: pp. 50–56.

[0015] The *INPP5D* gene encodes the Src homology 2 (SH2) domain-containing phosphatase-1 (SHIP1), which is a phosphatidylinositol phosphatase that plays a key role regulating pathways

downstream from TREM2. *See Peng et al.*, “TREM2- and DAP12-dependent activation of PI3K requires DAP10 and is inhibited by SHIP1,” (2010) *Sci Signal* 3: p. 38; Pauls et al., “Regulation of immune cell signaling by SHIP1: A phosphatase, scaffold protein, and potential therapeutic target,” (2017) *Eur J Immunol* 47: pp. 932–945. SHIP1 is a complex, multi-domain protein with a phosphatase (Ptase) domain flanked by a pleckstrin-homology (PH) domain that binds phosphatidylinositol (3,4,5)-trisphosphate [PI(3,4,5)P₃] and a C2 domain that binds phosphatidylinositol (3,4)-bisphosphate [PI(3,4)P₂]. *See Damen et al.*, “The 145-kDa protein induced to associate with Shc by multiple cytokines is an inositol tetraphosphate and phosphatidylinositol 3,4,5-triphosphate 5-phosphatase,” (1996) *Proc Natl Acad Sci USA* 93: pp. 1689–1693; Blunt et al., “Pharmacological targeting of phosphoinositide lipid kinases and phosphatases in the immune system: success, disappointment, and new opportunities,” (2012) *Front Immunol* 3: p. 226. The PH and C2 domains locate and orient the catalytic site towards its PI(3,4,5)P₃ substrate at the intracellular side of the membrane. The C2 domain is essential for cellular function and interactions between the Ptase and C2 domains modulate enzymatic activity. *See Le Coq et al.*, “Structural basis for interdomain communication in SHIP2 providing high phosphatase activity,” (2017) *eLife* 6: p. 26640. SHIP1 converts PI(3,4,5)P₃ to PI(3,4)P₂. SHIP1 also contains an N-terminal SH2 domain that binds immunoreceptor tyrosine-based activation motifs (ITAMs) and a C-terminal proline rich domain that binds many other proteins including PLCγ2 and the Tec and Syk family kinases. PI(3,4,5)P₃ binds and activates other PH-containing proteins such as PLCγ2, PDK1, and AKT. *See Scheffzek et al.*, “Pleckstrin homology (PH) like domains—versatile modules in protein-protein interaction platforms,” (2012) *FEBS Lett* 586: pp. 2662–2673. Because SHIP1 binds ITAMs, competes with kinases, and converts PI(3,4,5)P₃ to PI(3,4)P₂, it limits downstream signaling in multiple ways, and is therefore understood as a brake on microglia activation. *See Pauls et al.* 2017.

[0016] Taken together, this understanding of AD risk and protective variants in genes critical to the activity of microglia, the role of microglia in the clearance of Aβ, and SHIP1 as a limiting node downstream from TREM2 and FCγRIIB, suggests that inhibition of SHIP1 would activate microglia, and would therefore be an effective therapeutic strategy in disease. This therapeutic intervention could be synergistically combined with anti-amyloid and/or TREM2 agonist antibodies. Therefore, inhibitors of SHIP1 would increase the protective functions of microglia and could therefore be used to prevent or treat disease, reduce the rate of disease progression and cognitive decline in patients, and reverse neurodegeneration.

[0017] The present disclosure provides novel compounds that are SHIP1 inhibitors that address the need for a potent and effective treatment for Alzheimer's disease and Alzheimer's disease-related dementias. The present disclosure also provides a pharmaceutical composition for the prevention of Alzheimer's disease and Alzheimer's disease-related dementias.

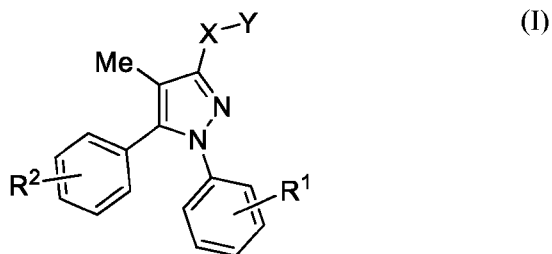
[0018] **SUMMARY**

[0019] Recent evidence including genome-wide association studies (GWAS), whole genome sequencing, differential gene expression, and gene-expression network analyses comparing normal to affected Alzheimer's brain tissue have identified risk and protective variants in genes such as TREM2, PLCG2 and INPP5D that are essential to microglia function. INPP5D encodes SHIP1, a multi-domain protein with a phosphatase that converts $\text{PI}(3,4,5)\text{P}_3$ to $\text{PI}(3,4)\text{P}_2$, a SH2 domain that interacts with receptor ITAMs and competes with SYK, and a proline rich region that binds many other proteins. SHIP1 therefore limits microglia activation in multiple ways. Inhibition of SHIP1 early in disease would increase microglial protective functions and reduce the rate of disease progression and cognitive decline in Alzheimer's patients.

[0020] The present inventors have performed a screen of about 50,000 compounds at the SHIP1 phosphatase, analyzed a publicly available fragment-based screen, and evaluated inhibitors reported in the literature. They utilized the malachite green assay with $\text{PtdIns}(3,4,5)\text{P}_3$ -diC₈ and SHIP1 Ptase-C2 to measure inhibitory potency. A Cellular Thermal Shift Assay was used to confirm target engagement in cells. A high-content imaging assay measuring phagocytosis, cell number, and nuclear intensity was implemented using the BV2 and HMC3 cell lines to characterize cellular pharmacology and cytotoxicity. Mouse microglia were assayed to demonstrate similar activity in primary cells. Inhibitors predicted to have drug-like properties were subjected to assays measuring solubility, cellular permeability, and mouse microsomal stability. A physiological based pharmacokinetic model was compared to measured exposure *in vivo* for select compounds upon oral administration in mice.

[0021] Inhibition of SHIP1 is a novel therapeutic strategy for treatment of Alzheimer's. Identified were structurally distinct molecular scaffolds with varying degrees of enzyme inhibition, cellular activity, and exposure in mice.

[0022] In an aspect, the present disclosure provides one or more compounds of formula (I):



wherein X is selected from the group consisting of CH₂, C=O, or NH; Y is selected from the group consisting of OR³, NH(R³), N(R³)₂, or C=O(R³); R¹ and R² are independently selected for each occurrence from the group consisting of H, halo, C1-7alkyl, OR³, NH(R³), N(R³)₂, or C=O(R³); and R³ is independently selected for each occurrence from the group consisting of H, C1-7alkyl, C3-7cycloalkyl, phenyl, heteroalkyl, cycloheteroalkyl, and heteroaryl; or pharmaceutically acceptable salt thereof.

[0023] In other embodiments, the present disclosure provides a method for treating Alzheimer's disease in a patient, which comprises administering to a patient in need thereof one or more compounds of the present disclosure or a pharmaceutically acceptable salt thereof. Furthermore, the present disclosure encompasses a method for treating Alzheimer's disease-related dementias in a patient, comprising administering to a patient in need thereof one or more compounds of the present disclosure or a pharmaceutically acceptable salt thereof. The present disclosure further provides a method of treating the progression of mild cognitive impairment to Alzheimer's disease or related dementias in a patient, comprising administering to a patient in need of such treatment an effective amount of one or more compounds of the present disclosure. The present disclosure further provides a method of preventing or ameliorating Alzheimer's disease or Alzheimer's disease-related dementias, comprising administering to a patient in need of such treatment an effective amount of one or more compounds of the present disclosure.

[0024] The present disclosure provides a pharmaceutical composition comprising one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers, diluents or excipients. In another embodiment, the composition further comprises one or more additional therapeutic agents. In a further embodiment, the present disclosure provides a pharmaceutical composition for the treatment of Alzheimer's disease, comprising one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers, diluents or excipients. In yet another embodiment, the present disclosure provides a pharmaceutical composition for the treatment of Alzheimer's disease-related dementias, comprising one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, in combination with

one or more carriers, diluents, or pharmaceutically acceptable excipients. In yet another embodiment, the present disclosure provides a pharmaceutical composition for the prevention of Alzheimer's disease and Alzheimer's disease-related dementias, comprising one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, in combination with one or more carriers, diluents, or pharmaceutically acceptable excipients.

[0025] Furthermore, the present disclosure provides one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, for use in therapy, in particular for the treatment of Alzheimer's disease. Furthermore, the present disclosure provides one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, for use in the treatment of Alzheimer's disease. In a further embodiment, the present disclosure provides the use of one or more compounds of the disclosure, of or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of Alzheimer's disease.

[0026] In other embodiments, the present disclosure provides one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, for use in therapy, in particular for the treatment of Alzheimer's disease-related dementias. Furthermore, the present disclosure provides one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, for use in the treatment of Alzheimer's disease-related dementias. In a further embodiment, the present disclosure provides the use of one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of Alzheimer's disease-related dementias.

[0027] Furthermore, the present disclosure provides one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, for use in the prevention of Alzheimer's disease and Alzheimer's disease-related dementias. Furthermore, the present disclosure provides one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, for use in the prevention of Alzheimer's disease and Alzheimer's disease-related dementias. In a further embodiment, the present disclosure provides the use of one or more compounds of the disclosure, of or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in the prevention of Alzheimer's disease and Alzheimer's disease-related dementias.

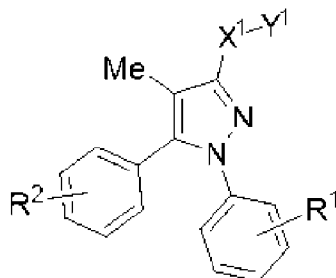
[0028] The present disclosure also encompasses intermediates and processes useful for the synthesis of one or more compounds of the present disclosure.

[0029] Alzheimer's disease-related dementias (ADRD) include Lewy body dementia (LBD), frontotemporal degeneration (FTD), vascular cognitive impairment and dementia (VCID), and multiple etiology dementias. Mild cognitive impairment is defined as the potential prodromal

phase of dementia associated with Alzheimer's disease based on clinical presentation and on progression of patients exhibiting mild cognitive impairment to Alzheimer's disease over time. *See* Morris et al., "Mild cognitive impairment represents early-stage Alzheimer disease," (2001) *Arch Neurol* 58: pp. 397–405; Petersen et al., "Mild cognitive impairment: clinical characterization and outcome," (1999) *Arch Neurol* 56: pp. 303–308.

[0030] In a further aspect, the present disclosure provides a compound of formula (II):

(II)



wherein R^1 is selected from the group consisting of H, halo, OH, OCH_3 , $NH(R^3)$ and $N(R^3)_2$; R^2 is selected from the group consisting of H, halo, OH, OCH_3 , $NH(R^3)$ and $N(R^3)_2$; where R^3 is independently selected from the group consisting of H and CH_3 ; X^1 is selected from the group consisting of -methylene-NH- wherein NH is bound to Y^1 ; -C(O)-NH-, -NHC(O)- and methylene; Y^1 is selected from the group consisting of C5–C6 cycloalkyl, phenyl, C1–C4alkyl; and - $NR^{11}R^{12}$; wherein R^{11} and R^{12} taken together with the nitrogen to which they are bound form a 5–6 membered heterocycle; or a pharmaceutically acceptable salt thereof. In still another aspect, the present disclosure provides a pharmaceutically acceptable composition comprising a compound of formula (II) as described herein, and a pharmaceutically acceptable excipient.

[0031] These and other embodiments and features of the disclosure will become more apparent through reference to the following description, the accompanying figures, and the claims. Furthermore, it is to be understood that the features of the various embodiments described herein are not mutually exclusive and can exist in various combinations and permutations.

[0032] In some embodiments, the disclosure provides for a composition comprising a SHIP1 inhibitor for use in combination with an antibody or antigen-binding fragment for treating Alzheimer's disease and Alzheimer's disease-related dementias.

[0033] BRIEF DESCRIPTION OF THE DRAWINGS

[0034] FIG. 1 is a schematic depicting the SHIP1 complex and associated pathways.

[0035] FIG. 2 is a schematic depicting the malachite green enzyme assay.

[0036] DETAILED DESCRIPTION

[0037] Various quantities, such as amounts, sizes, dimensions, proportions, and the like, are presented in a range format throughout this disclosure. It should be understood that the description of a quantity in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of any embodiment. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as all individual numerical values within that range unless the context clearly dictates otherwise. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual values within that range, for example, 1.1, 2, 2.3, 4.62, 5, and 5.9. This applies regardless of the breadth of the range. The upper and lower limits of these intervening ranges may independently be included in the smaller ranges, and are also encompassed within the disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure, unless the context clearly dictates otherwise.

[0038] The terminology used herein is to describe particular embodiments only and is not intended to be limiting of any embodiment. As used herein, the singular forms “a,” “an,” and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise. It will be further understood that the terms “includes,” “comprises,” “including” and/or “comprising,” when used in this specification, specify the presence of stated features, integers, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, integers, steps, operations, elements, components, and/or groups thereof. As used herein, the term “and/or” includes any and all combinations of one or more of the associated listed items. Additionally, it should be appreciated that items included in a list in the form of “at least one of A, B, and C” can mean (A); (B); (C); (A and B); (B and C); (A and C); or (A, B, and C). Similarly, items listed in the form of “at least one of A, B, or C” can mean (A); (B); (C); (A and B); (B and C); (A and C); or (A, B, and C).

[0039] Unless expressly stated or obvious from context, as used herein, the term “about” in reference to a number or range of numbers is understood to mean the stated number and numbers +/- 10% thereof, or 10% below the lower listed limit and 10% above the higher listed limit for the values listed for a range.

[0040] Recent evidence including genome-wide association studies (GWAS) and differential gene expression comparing normal to affected Alzheimer’s brain tissue have identified risk and

protective variants in genes such as *TREM2*, *PLCG2*, and *INPP5D* that are essential to microglia function. The *INPP5D* gene encodes the Src homology 2 (SH2) domain-containing phosphatase-1 (SHIP1), which is a phosphatidylinositol phosphatase that plays a key role regulating pathways downstream from TREM2. *See* Peng et al. 2010; Pauls et al., 2017. SHIP1 is a complex, multi-domain protein with a phosphatase (Ptase) domain flanked by a pleckstrin-homology (PH) domain that binds phosphatidylinositol (3,4,5)-trisphosphate [PI(3,4,5)P₃] and a C2 domain that binds phosphatidylinositol (3,4)-bisphosphate [PI(3,4)P₂]. *See* FIG. 1; Damen et al. 1996; Blunt et al., 2012. The PH and C2 domains locate and orient the catalytic site towards its PI(3,4,5)P₃ substrate at the intracellular side of the membrane. The C2 domain (SEQ ID NO: 1) is essential for cellular function and interactions between the Ptase and C2 domains modulate enzymatic activity. *See* Le Coq et al., 2017. SHIP1 converts PI(3,4,5)P₃ to PI(3,4)P₂. SHIP1 also contains an N-terminal SH2 domain that binds immunoreceptor tyrosine-based activation motifs (ITAMs) and a C-terminal proline rich domain that binds many other proteins including PLCγ2 and the Tec and Syk family kinases. PI(3,4,5)P₃ binds and activates other PH-containing proteins such as PLCγ2, PDK1, and AKT. *See* Scheffzek et al. 2012. Because SHIP1 binds receptor ITAMs, competes with kinases, and converts PI(3,4,5)P₃ to PI(3,4)P₂, it limits downstream signaling in multiple ways, and is therefore understood as a brake on microglia activation. Therefore, our therapeutic hypothesis is that inhibition of SHIP1 early in disease would increase microglial protective functions and reduce the rate of disease progression and cognitive decline in Alzheimer's patients.

[0041] In any of the embodiments disclosed herein, the term “treating the progression of mild cognitive impairment to Alzheimer's disease” includes restraining, slowing, stopping, or reversing the progression of mild cognitive impairment to Alzheimer's disease in a patient.

[0042] In any of the embodiments disclosed herein, the terms “treating” or “to treat” includes restraining, slowing, stopping, or reversing the progression or severity of an existing symptom or disorder.

[0043] In any of the embodiments disclosed herein, the term “patient” refers to a human.

[0044] One or more compounds of the present disclosure can react to form pharmaceutically acceptable salts. Pharmaceutically acceptable salts and common methodology for preparing them are well known in the art. *See, e.g.*, P. Stahl, et al. Handbook of Pharmaceutical Salts: Properties, Selection and Use (Manual of Pharmaceutical Salts: Properties, Selection and Use), 2nd revised edition (Wiley-VCH, 2011); SM Berge, et al., "Pharmaceutical Salts", Journal of Pharmaceutical Sciences, Vol. 66, No. 1, January 1977.

[0045] Excipients

[0046] Illustrative, non-limiting examples of excipients or carriers include sodium citrate or dicalcium phosphate and/or a) one or more fillers or extenders (a filler or extender may be, but is not limited to, one or more selected from starches, lactose, sucrose, glucose, mannitol, and silicic acid), b) one or more binders (binders may be selected from, but not limited to, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia), c) one or more humectants (a humectant may be, but is not limited to, glycerol), d) one or more disintegrating agents (disintegrating agents may be selected from, but are not limited to, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, silicates, and sodium carbonate), e) one or more solution retarding agents (for example, but not limited to, paraffin), f) one or more absorption accelerators (selected from, but not limited to, quaternary ammonium compounds), g) one or more wetting agents (for example, but not limited to, acetyl alcohol and glycerol monostearate), h) one or more absorbents (selected from, but not limited to, kaolin and bentonite clay), and i) one or more lubricants (selected from, but not limited to, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, and sodium lauryl sulfate). In the case of capsules, tablets and pills, for example, the dosage form may also comprise buffering agents.

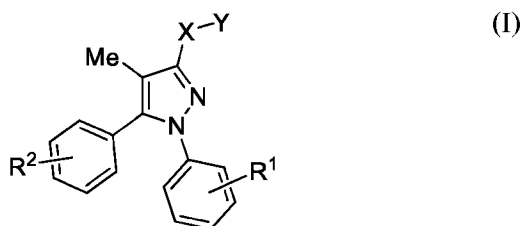
[0047] “Effective or Therapeutic Amount”

[0048] Effective or therapeutic amounts of the compositions of this disclosure include any amount sufficient to inhibit (e.g., slow or stop) the progression of a neurodegenerative disorder. In some embodiments, effective amounts of the compositions include any amount sufficient to inhibit (e.g., slow or stop) the deterioration of the cognitive function of a patient.

[0049] The amount of the active ingredient that may be combined with the optional carrier materials to produce a single dosage form may vary depending upon the host treated and the particular mode of administration. The specific dose level for any particular patient may depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disorder or disease undergoing therapy. A therapeutically effective amount for a given situation can be readily determined by routine experimentation and is within the skill and judgment of the ordinary clinician.

[0050] Embodiments of the compositions and methods of the presents disclosure may be appreciated, without limitation, by reference to the following clauses:

[0051] Clause 1. A method for treating a neurodegenerative disorder or related condition in a patient in need thereof, comprising administering to the patient an effective amount of a compound of formula (I):



wherein

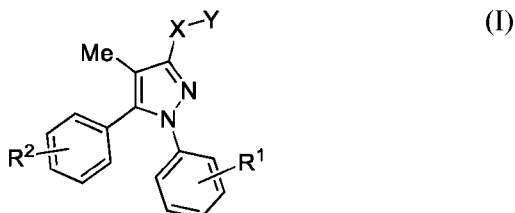
X is selected from the group consisting of CH₂, C=O, or NH;

Y is selected from the group consisting of OR³, NH(R³), N(R³)₂, or C=O(R³);

R¹ and R² are independently selected for each occurrence from the group consisting of H, halo, C1-7alkyl, OR³, NH(R³), N(R³)₂, or C=O(R³); and

R³ is independently selected for each occurrence from the group consisting of H, C1-7alkyl, C3-7cycloalkyl, phenyl, heteroalkyl, cycloheteroalkyl, and heteroaryl;
or a pharmaceutically acceptable salt thereof.

[0052] Clause 2. A method of treating the progression of a neurodegenerative disorder or related condition in a patient in need thereof, comprising administering to the patient an effective amount of a compound of formula (I):



wherein

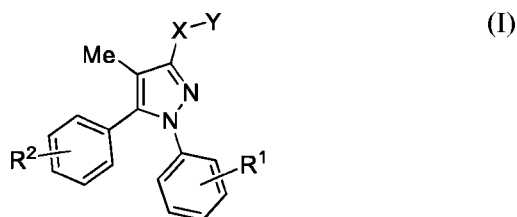
X is selected from the group consisting of CH₂, C=O, or NH;

Y is selected from the group consisting of OR³, NH(R³), N(R³)₂, or C=O(R³);

R¹ and R² are independently selected for each occurrence from the group consisting of H, halo, C1-7alkyl, OR³, NH(R³), N(R³)₂, or C=O(R³); and

R³ is independently selected for each occurrence from the group consisting of H, C1-7alkyl, C3-7cycloalkyl, phenyl, heteroalkyl, cycloheteroalkyl and heteroaryl;
or a pharmaceutically acceptable salt thereof.

[0053] Clause 3. A method of preventing or ameliorating a neurodegenerative disorder or related condition in a patient in need thereof, comprising administering to the patient an effective amount of a compound of formula (I):



wherein

X is selected from the group consisting of CH₂, C=O, or NH;

Y is selected from the group consisting of OR³, NH(R³), N(R³)₂, or C=O(R³);

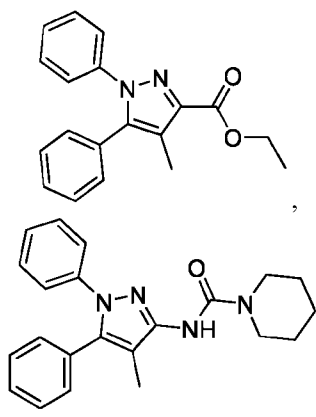
R¹ and R² are independently selected for each occurrence from the group consisting of H, halo, C1-7alkyl, OR³, NH(R³), N(R³)₂, or C=O(R³); and

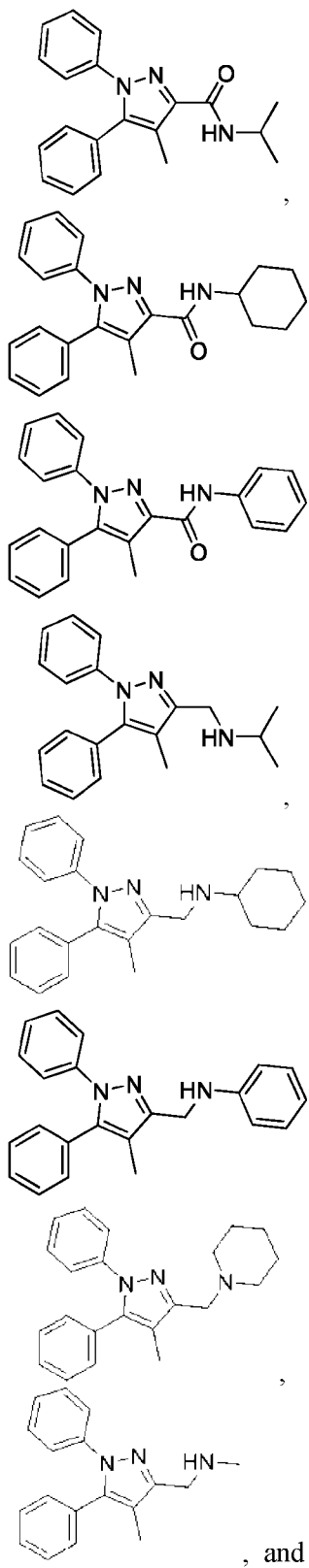
R³ is independently selected for each occurrence from the group consisting of H, C1-7alkyl, C3-7cycloalkyl, phenyl, heteroalkyl, cycloheteroalkyl and heteroaryl; or a pharmaceutically acceptable salt thereof.

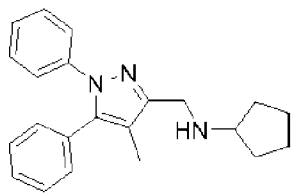
[0054] Clause 4. The method of any of clauses 1–3, wherein the compound or its pharmaceutically acceptable salt thereof, is formulated in a pharmaceutical composition further comprising one or more pharmaceutically acceptable carriers, diluents or excipients.

[0055] Clause 5. The method of any of clauses 1–4, further comprising administering to the patient of one or more additional therapeutic agents.

[0056] Clause 6. The use of a compound selected from the group consisting of:







or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of a neurodegenerative disorder or related condition or to inhibit the progression of said neurological disorder or related condition.

[0057] Clause 7. The use of a compound selected from the group consisting of:

ethyl 4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylate,
N-(4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)piperidine-1-carboxamide,
N-isopropyl-4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxamide,
N-cyclohexyl-4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxamide,
 4-methyl-*N*,1,5-triphenyl-1*H*-pyrazole-3-carboxamide,
N-((4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methyl)propan-2-amine,
N-((4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methyl)cyclohexanamine,
N-((4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methyl)aniline,
 1-((4-Methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methyl)piperidine,
N-Methyl-1-(4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methanamine, and
N-((4-Methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methyl)cyclopentanamine

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of a neurodegenerative disorder or related condition or to inhibit the progression of said neurological disorder or related condition.

[0058] Clause 8. The method of any of clauses 1–5, wherein the neurodegenerative disorder or related condition is selected from the group consisting of Alzheimer's disease, Alzheimer's disease-related dementias or mild cognitive impairment.

[0059] Clause 9. The method of clause 8, wherein the **Alzheimer's disease**-related dementia is selected from the group consisting of Lewy body dementia (LBD), frontotemporal degeneration (FTD), vascular cognitive impairment and dementia (VCID), and multiple etiology dementias.

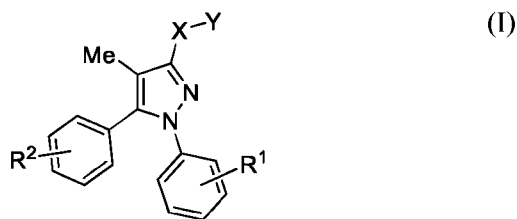
[0060] Clause 10. The compound of any of clauses 6 and 7, wherein the neurodegenerative disorder or related condition is selected from the group consisting of **Alzheimer's disease**, Alzheimer's disease-related dementias or mild cognitive impairment.

[0061] Clause 11. The compound of clause 10, wherein the **Alzheimer's disease**-related dementia is selected from the group consisting of Lewy body dementia (LBD), frontotemporal degeneration (FTD), vascular cognitive impairment and dementia (VCID), and multiple etiology dementias.

[0062] Clause 12. The use of any of clauses 6 and 7, wherein the neurodegenerative disorder or related condition is selected from the group consisting of **Alzheimer's disease**, Alzheimer's disease-related dementias or mild cognitive impairment.

[0063] Clause 13. The use of clause 12, wherein the **Alzheimer's disease**-related dementia is selected from the group consisting of Lewy body dementia (LBD), frontotemporal degeneration (FTD), vascular cognitive impairment and dementia (VCID), and multiple etiology dementias.

[0064] Clause 14. A pharmaceutically acceptable composition comprising a compound of formula (I):



wherein

X is selected from the group consisting of CH₂, C=O, or NH;

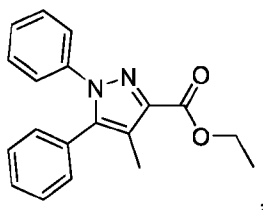
Y is selected from the group consisting of OR³, NH(R³), N(R³)₂, or C=O(R³);

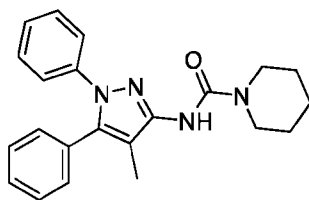
R¹ and R² are independently selected for each occurrence from the group consisting of H, halo, C1-7alkyl, OR³, NH(R³), N(R³)₂, or C=O(R³); and

R³ is independently selected for each occurrence from the group consisting of H, C1-7alkyl, C3-7cycloalkyl, phenyl, heteroalkyl, cycloheteroalkyl, and heteroaryl;

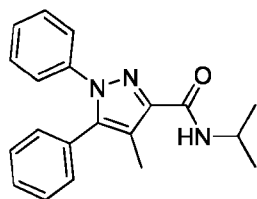
or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.

[0065] Clause 15. The composition of clause 14, comprising a compound selected from the group consisting of:

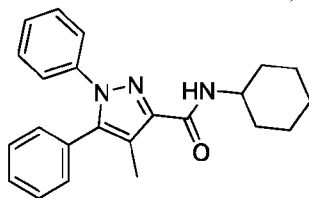




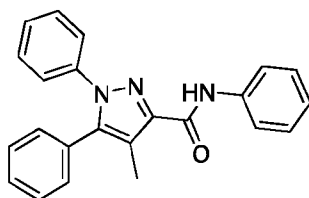
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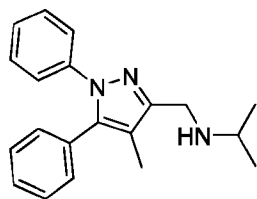
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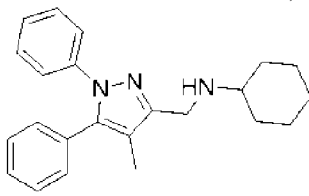
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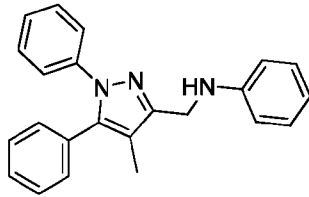
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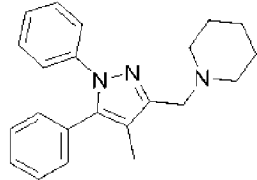
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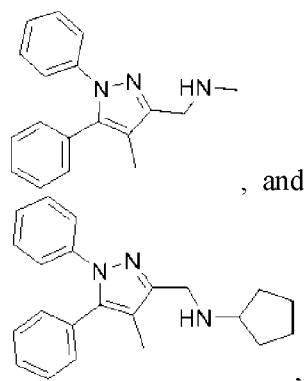
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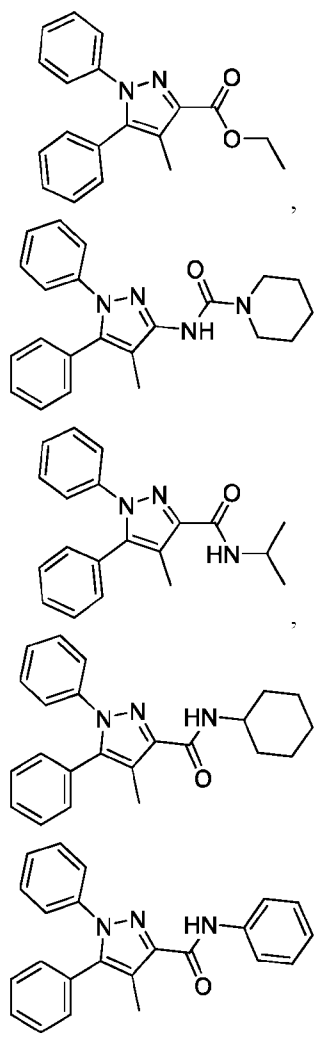


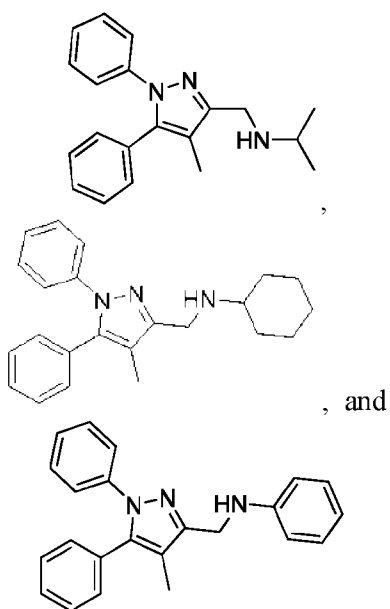
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or a pharmaceutically acceptable salt thereof.

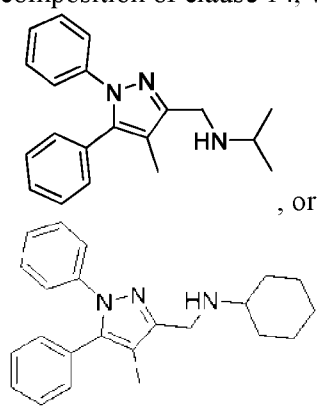
[0066] Clause 16. The composition of clause 14, comprising a compound selected from the group consisting of:





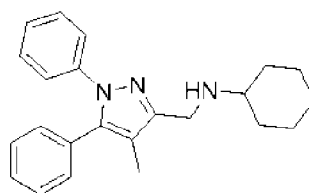
or a pharmaceutically acceptable salt thereof.

[0067] Clause 17. The composition of clause 14, wherein Formula (I) comprises



a mixture thereof, or a pharmaceutically acceptable salt thereof.

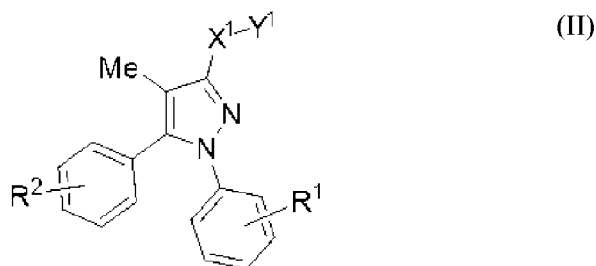
[0068] Clause 18. The composition of clause 14, comprising



or a pharmaceutically acceptable salt thereof.

[0069] Clause 19. The composition of any of clauses 14–18, further comprising one or more additional neurodegenerative disorder therapeutic agents.

[0070] Clause 20. A composition comprising a compound of formula (II):



wherein

R^1 is selected from the group consisting of H, halo, OH, OCH_3 , $NH(R^3)$ and $N(R^3)_2$;

R^2 is selected from the group consisting of H, halo, OH, OCH_3 , $NH(R^3)$ and $N(R^3)_2$;

where R^3 is independently selected from the group consisting of H and CH_3 ;

X^1 is selected from the group consisting of -methylene-NH- wherein NH is bound to Y^1 ; -
C(O)-NH-, -NHC(O)- and methylene;

Y^1 is selected from the group consisting of C5–C6 cycloalkyl, phenyl, C1–C4alkyl;
and $-NR^{11}R^{12}$; wherein R^{11} and R^{12} taken together with the nitrogen to which they are
bound form a 5–6 membered heterocycle;

or a pharmaceutically acceptable salt thereof.

[0071] Clause 21. A pharmaceutically acceptable composition comprising a compound of
clause 20, and a pharmaceutically acceptable excipient.

[0072] Further reference is made to the following experimental examples.

[0073] EXAMPLES

[0074] The following examples are provided for the purpose of illustrating various
embodiments of the disclosure and are not meant to limit the present disclosure in any fashion.
The present examples, along with the methods described herein are presently representative of
preferred embodiments, are provided only as examples, and are not intended as limitations on the
scope of the invention. Changes therein and other uses which are encompassed within the spirit of
the disclosure as defined by the scope of the claims will occur to those skilled in the art.

[0075] General Methods and Procedures

[0076] Chemical Synthesis and Validation. For each of the examples provided herein, reagents
and solvents were purchased from commercial sources and used without further purification. All
reactions involving air- or moisture-sensitive reagents were performed under a nitrogen or argon
atmosphere. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker AVANCE™
NEO 400 MHz or Bruker DRX500-1 500 MHz instruments. For 1H NMR, chemical shifts in ppm

relative to the residual solvent peak, multiplicities, coupling constants in Hertz, and numbers of protons are indicated. Reactions were routinely monitored by analytical thin layer chromatography (TLC) or liquid chromatography-mass spectroscopy (LC-MS). Analytical TLC was performed on silica gel 60 F₂₅₄ silica gel plates, and 254 nm ultraviolet (UV) light and/or I₂ staining were used for visualization. Reaction monitoring LC-MS and high-performance liquid chromatography (HPLC) purity data were obtained on a Waters™ ACQUITY® ultra-performance liquid chromatography (UPLC) system equipped with a Waters™ ACQUITY® BEH C18 column (1.7 µm, 50 mm × 2.1 mm) or other specified column (*see below*), and either TUV and SQD2 detectors or PDA and QDa detectors. Flash normal phase (NP) or reversed-phase (RP) chromatography were performed on a Teledyne ISCO NextGen 300 instrument using preppacked silica gel or C18-functionalized silica gel columns available from Teledyne ISCO, or on a Teledyne ISCO CombiFlash® using preppacked silica gel columns available from Agela or Welch. Preparative reverse-phase (RP) HPLC was performed on a Waters™ AutoPurification HPLC system equipped with PDA and ELSD detectors and a Waters™ XBridge C18 Prep column (10 µm, 250 mm × 19 mm). High-resolution mass spectra were obtained on an Agilent 6550 Q-TOF instrument. All compounds had >95% purity as determined by LC-MS. One of the following specified LC-MS methods was used to determine test compound purity:

[0077] Method 1: gradient table A (below); column, Waters™ ACQUITY® HSS-T3 (1.8 µm, 100 mm × 2.1 mm); mobile phase A, 0.1% TFA in H₂O; mobile phase B, ACN; flow rate, 0.3 mL/min; detection wavelength, 214 nm; column temperature, 35 °C.

[0078] Method 2: gradient table A; column, Waters™ ACQUITY® BEH C-18 (1.7 µm, 100 mm × 2.1 mm); mobile phase A, 5 mM NH₄OAc in H₂O; mobile phase B, ACN; flow rate, 0.3 mL/min; detection wavelength, 214 nm; column temperature, 35 °C.

Gradient Table A		
Time (min)	%A	%B
0.0	90	10
1.0	90	10
2.0	85	15
4.5	45	55
6.0	10	90
8.0	10	90
9.0	90	10
10.0	90	10

[0079] Malachite Green Enzyme Assay. Enzymatic inhibitory potencies (IC₅₀) were determined using PI(3,4,5)P₃-diC₈ as a substrate at 25 °C in 50 mM 4-(2-hydroxyethyl)-1-

piperazineethanesulfonic acid (HEPES) buffer (pH7.4, 150 mM NaCl, 2 mM MgCl₂). Compounds diluted in dimethyl sulfoxide (DMSO) were added to 384-well plates. Enzyme solution was added. After a 20-minute incubation period, the reaction was initiated by addition of PI(3,4,5)P₃-diC₈. Final compound concentrations ranged from 50 nM to 950 μ M. Final reaction concentrations for the PI(3,4,5)P₃-diC₈ substrate and the enzyme were 52 μ M and 10 nM respectively. The reaction was quenched after 10 minutes by adding Malachite BioMol Green (Enzo Lifesciences, PA, USA). Plates were then incubated for 30 minutes at room temperature. Absorbance (620nm) was measured using a SpectraMax® Me5 Microplate Reader (Molecular Devices, LLC, USA). IC₅₀ values were calculated by fitting absorbance versus inhibitor concentration.

[0080] Cellular thermal shift assay (CETSA). A split Nano Luciferase assay (SplitLuc CETSA) was used to demonstrate target engagement of SHIP1 inhibitors in a physiologically relevant cellular context by quantifying changes in the thermal stability of a HiBit-labeled full length SHIP1 protein in intact cells. This assay was run in the following two formats with HMC3/HiBit-INPP5D stably transfected cells.

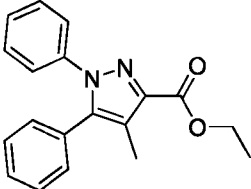
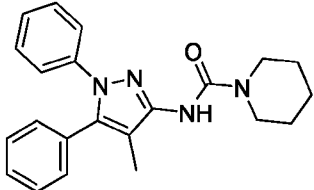
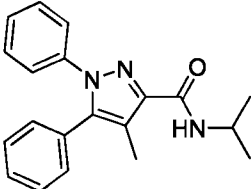
[0081] 1. Thermal shift: Cells were treated with 40 μ M compound for 60 minutes, then heated with a temperature gradient covering 38–52 °C for 3 minutes before luminescence detection. Mean and standard deviation of control T_m were determined to generate a "Mean+3SD" Δ T_m, which was used as threshold to determine a significant Δ T_m of compound from control. When the difference of Δ T_m of compound treated cells from control T_m > 3SD, the compound was considered positive for target engagement, otherwise negative. SD = average standard deviation.

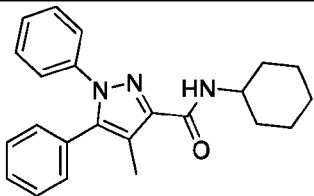
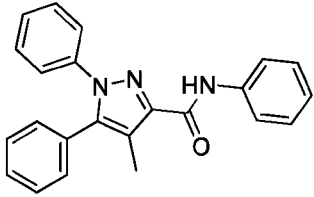
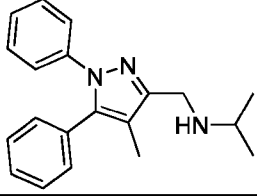
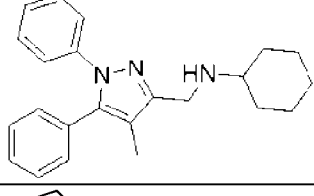
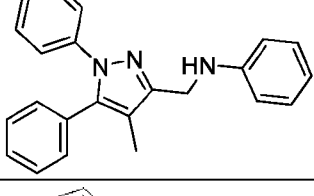
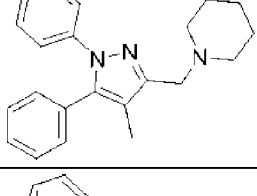
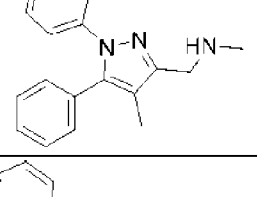
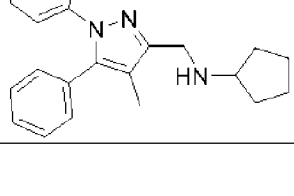
[0082] 2. Compound dose response: Run at target T_m (44.2°C for SHIP1) with compound dosing from 80 μ M or 100 μ M with 1:3 serial dilutions to generate an 8-point curve. Cells were treated for 60 minutes before being heated at target T_m for 3 minutes before luminescence detection. An AC₅₀ was calculated using a four-parameter logistic curve regression model with change at highest concentration noted when difference from control >3SD, otherwise AC₅₀ marked as "NC" for not calculated.

[0083] Table 1:

Compound	Name	MS (ES+)	SHIP1 IC ₅₀ μ M (n)
1	ethyl 4-methyl-1,5-diphenyl-1 <i>H</i> -pyrazole-3-carboxylate	307.20	161 (2)
2	<i>N</i> -(4-methyl-1,5-diphenyl-1 <i>H</i> -pyrazol-3-yl)piperidine-1-carboxamide	361.35	80.7 (2)
3	<i>N</i> -isopropyl-4-methyl-1,5-diphenyl-1 <i>H</i> -pyrazole-3-carboxamide	320.25	220 (2)
4	<i>N</i> -cyclohexyl-4-methyl-1,5-diphenyl-1 <i>H</i> -pyrazole-3-carboxamide	360.25	27.3 (1)
5	4-methyl- <i>N</i> ,1,5-triphenyl-1 <i>H</i> -pyrazole-3-carboxamide	354.25	11.0 (1)
6	<i>N</i> -((4-methyl-1,5-diphenyl-1 <i>H</i> -pyrazol-3-yl)methyl)propan-2-amine	306.30	>909 (2)
7	<i>N</i> -((4-methyl-1,5-diphenyl-1 <i>H</i> -pyrazol-3-yl)methyl)cyclohexanamine	346.35	88.8 (2)
8	<i>N</i> -((4-methyl-1,5-diphenyl-1 <i>H</i> -pyrazol-3-yl)methyl)aniline	340.25	16.6 (2)
9	1-((4-Methyl-1,5-diphenyl-1 <i>H</i> -pyrazol-3-yl)methyl)piperidine	332.25	417 (3)
10	<i>N</i> -Methyl-1-(4-methyl-1,5-diphenyl-1 <i>H</i> -pyrazol-3-yl)methanamine	278.3	>952 (1)
11	<i>N</i> -((4-Methyl-1,5-diphenyl-1 <i>H</i> -pyrazol-3-yl)methyl)cyclopentanamine	332.4	689 (2)

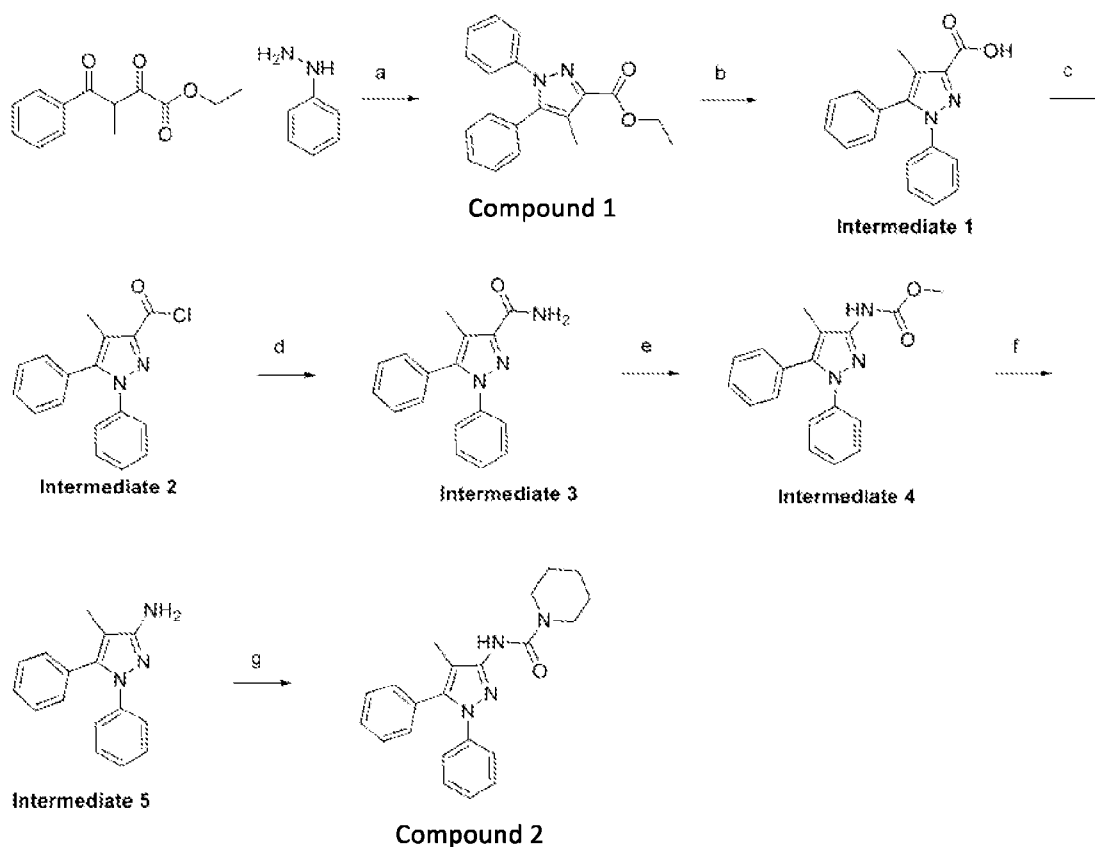
[0084] Table 2:

Compound	Name	MS (ES+)	SHIP1 IC ₅₀ μ M (n)
1		307.20	161 (2)
2		361.35	80.7 (2)
3		320.25	220 (2)

4		360.25	27.3 (1)
5		354.25	11.0 (1)
6		306.30	>909 (2)
7		346.35	88.8 (2)
8		340.25	16.6 (2)
9		332.25	417 (3)
10		278.3	>952 (1)
11		332.4	689 (2)

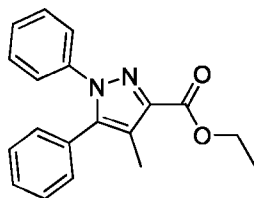
[0085] EXAMPLE 1**[0086]** Overall Synthesis of Compounds 1 and 2

Scheme 1.



[0087] Reagents and conditions: a = EtOH, H₂O, H₂SO₄, 0 °C to 100 °C, 16 hours, 27%; b = LiOH, MeOH, tetrahydrofuran (THF), H₂O, room temperature, 16 hours, 78%; c = thionyl chloride (SOCl₂), *N,N*-dimethylformamide (DMF), reflux, 3 hours, 94%; d = NH₄OH, dichloromethane (DCM), 0 °C to room temperature, 15 minutes, 64%; e = NaOMe, *N*-bromosuccinimide (NBS), MeOH, reflux, 16 hours, 47%; f = MeOH, NaOH, 70 °C, 12 hours, 84%; g = piperidine-1-carboxylic acid, NEt₃, triphosgene, DCM, 0 °C to room temperature, 16 hours, 14%.

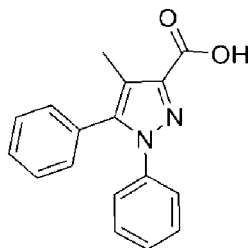
[0088] EXAMPLE 2**[0089]** Compound 1**[0090]** Ethyl 4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylate



[0091] To a stirred solution of ethyl 3-methyl-2,4-dioxo-4-phenylbutanoate (0.5 g, 2.13 mmol) and phenylhydrazine (254 mg, 1.1 eq., 2.35 mmol) in ethanol (10 mL) and water (3 mL) was added sulfuric acid (116 μ L, 2.13 mmol) at 0°C. The reaction mixture was stirred at 100°C for 16 hours. Reaction progress was monitored by TLC and LCMS. The reaction mixture was diluted with chilled water and product was extracted with dichloromethane (DCM). The organic layer was washed with saturated NaHCO_3 , then with water, and then with brine, and dried over sodium sulfate and concentrated. The residue was purified by flash chromatography using 10% EtOAc in hexane as eluent, and the desired fractions were concentrated to provide ethyl 4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylate (175 mg, 571 μ mol, 27%) as a light brown semisolid. MS 307.20.

[0092] EXAMPLE 3

[0093] Intermediate 1

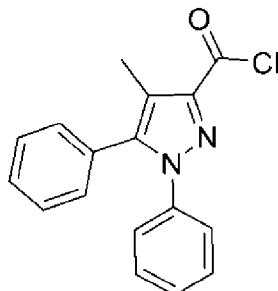


Intermediate 1

[0094] Ethyl 4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylate (140 mg, 457 μ mol) was dissolved in methanol (3 mL), and THF (3 mL) and water (3 mL) were added, followed by lithium hydroxide (21.9 mg, 2 eq., 914 μ mol). The reaction mixture was stirred at room temperature for 16 hours. After completion (TLC & LCMS monitoring), the reaction mixture was diluted with water and washed with diethyl ether. The aqueous layer was then brought to pH 5 using concentrated HCl and product was extracted with EtOAc. The organic solution was dried over sodium sulfate and concentrated to provide 4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid (0.1 g, 356 μ mol, 78%) as a brown solid. MS 278.71.

[0095] EXAMPLE 4

[0096] Intermediate 2

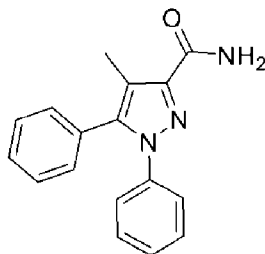


Intermediate 2

[0097] To a stirred solution of 4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid (0.5 g, 1.8 mmol) in SOCl₂ (3 mL) was added DMF (0.1 mL). The reaction mixture was heated to reflux for 3 hours. After completion (TLC monitoring), the reaction mixture was concentrated to provide 4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carbonyl chloride (0.5 g, 1.68 mmol, 94%) as a yellowish low melting solid, which was used without further characterization.

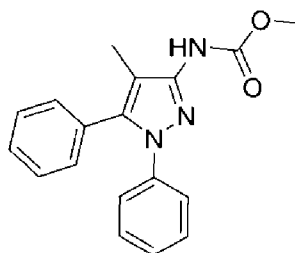
[0098] EXAMPLE 5

[0099] Intermediate 3

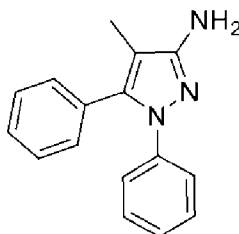


Intermediate 3

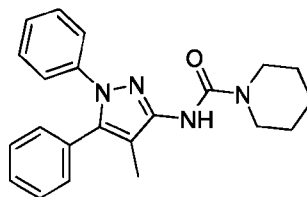
[00100] To a stirred solution of 4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carbonyl chloride (1 g, 3.37 mmol) in dichloromethane (10 mL) was added ammonium hydroxide (5 mL) at 0°C. The reaction mixture was stirred at 0 °C for 15 minutes and then at room temperature for 15 minutes. The mixture was quenched with a saturated solution of ammonium chloride and then partitioned between water and DCM. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by flash chromatography using 10% MeOH in DCM as eluent, and the desired fractions were concentrated to provide 4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxamide (0.8 g, 2.16 mmol, 64%). MS 278.20.

[00101] EXAMPLE 6**[00102] Intermediate 4****Intermediate 4**

[00103] Sodium metal (995 mg, 30 eq., 43.3 mmol) was dissolved in methanol (20 mL). Then 4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxamide (0.4 g, 1.44 mmol) and NBS (385 mg, 1.5 eq., 2.16 mmol) were added to the solution. The reaction mixture was heated to reflux for 16 h, after which time the solvent was concentrated. The crude product was dissolved in EtOAc, and the organic mixture was washed with water and then with brine, and dried over sodium sulfate and concentrated. The residue was purified by flash chromatography using 50% EtOAc in hexane as an eluent, and the desired fractions were concentrated to provide methyl (4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)carbamate (250 mg, 683 μ mol, 47%) as a light yellow semisolid. MS 308.15.

[00104] EXAMPLE 7**[00105] Intermediate 5****Intermediate 5**

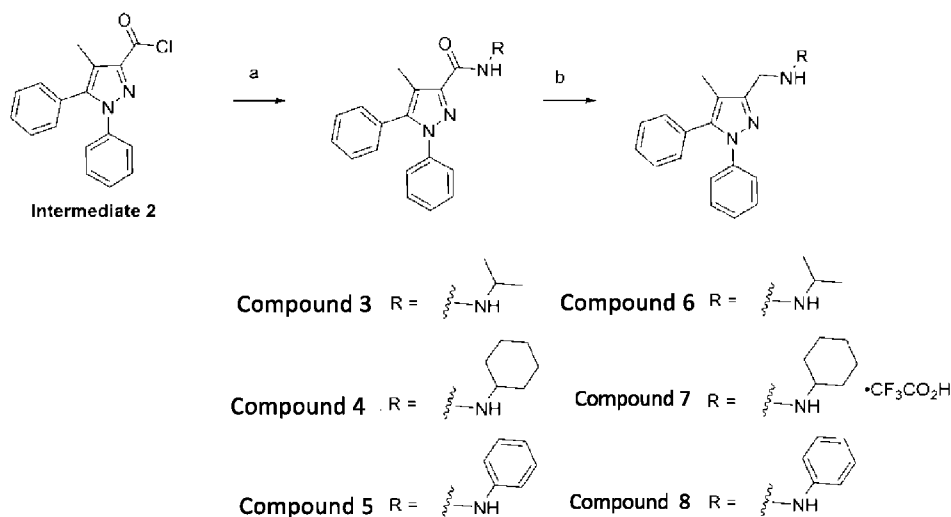
[00106] To a stirred solution of methyl (4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)carbamate (250 mg, 813 μ mol) in methanol (8 mL) was added sodium hydroxide (976 mg, 30 eq., 24.4 mmol). The reaction mixture was heated to 70 °C for 12 hours. After completion of the reaction (TLC & LCMS monitoring), the reaction mixture was concentrated. The residue was dissolved in EtOAc, and the solution was washed with water and then with brine, and dried over anhydrous sodium sulfate and concentrated to provide 4-methyl-1,5-diphenyl-1*H*-pyrazol-3-amine (0.2 g, 682 μ mol, 84%) as a yellowish semisolid. MS 250.10.

[00107] EXAMPLE 8**[00108]** Compound 2**[00109]** *N*-(4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)piperidine-1-carboxamide

[00110] To a stirred solution of 4-methyl-1,5-diphenyl-1*H*-pyrazol-3-amine (0.2 g, 802 μ mol) and piperidine-1-carboxylic acid (207 mg, 2 eq., 1.6 mmol) in dichloromethane (4.55 mL) was added dropwise triethylamine (559 μ L, 5 eq., 4.01 mmol). The reaction mixture was cooled to 0°C and then bis(trichloromethyl) carbonate (476 mg, 2 eq., 1.6 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. After completion (TLC & LCMS monitoring), the reaction mixture was diluted with water, and product was extracted with DCM. The DCM extract was washed with water, and then with brine, and dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash chromatography using 10% MeOH in DCM as an eluent, and the desired fractions were concentrated to afford crude product. The crude product was further purified by preparative HPLC to provide *N*-(4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)piperidine-1-carboxamide (40 mg, 110 μ mol, 14%) as a light yellow solid. MS 361.35.

[00111] EXAMPLE 9**[00112]** Overall Synthesis of Compounds 3–8

Scheme 2

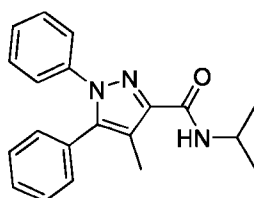


[00113] Reagents and conditions: a = NEt_3 , DCM, propan-2-amine (for Compound 3) or cyclohexanamine (for Compound 4) or aniline (for Compound 5) at 0 °C to room temperature, 16 hours, 77% (for Compound 3) or 27% (for Compound 4) or 51% (for Compound 5); b = LiAlH_4 , THF, -78 °C to 70 °C, 16 hours, 67% (for Compound 6) or 6% (for Compound 7) or 54% (for Compound 8).

[00114] EXAMPLE 10

[00115] Compound 3

[00116] *N*-isopropyl-4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxamide

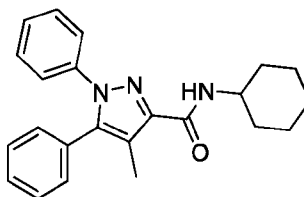


[00117] To a stirred solution of 4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carbonyl chloride (0.3 g, 1.01 mmol) in dichloromethane (5 mL) was added triethylamine (706 μL , 5 eq., 5.05 mmol). The reaction mixture was cooled to 0°C and then propan-2-amine (166 μL , 2 eq., 2.02 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. After completion (TLC & LCMS monitoring), the reaction mixture was diluted with water, and product was extracted with DCM. The DCM extract was washed with water, and then with brine, and dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash chromatography using 10% MeOH in DCM as an eluent, and the desired fractions were concentrated to provide *N*-isopropyl-4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxamide (250 mg, 775 μmol , 77%) as a yellow solid. MS 320.25.

[00118] EXAMPLE 11

[00119] Compound 4

[00120] *N*-cyclohexyl-4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxamide

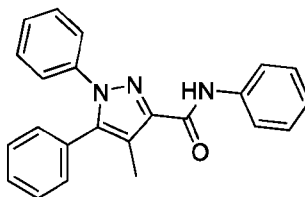


[00121] To a stirred solution of 4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carbonyl chloride (0.1 g, 337 μ mol) in dichloromethane (5 mL) was added triethylamine (235 μ L, 5 eq., 1.68 mmol). The reaction mixture was cooled to 0°C and then cyclohexanamine (58 μ L, 1.5 eq., 505 μ mol) was added. The reaction mixture was stirred at room temperature for 16 hours. After completion (TLC & LCMS monitoring), the reaction mixture was diluted with water, and product was extracted with DCM. The DCM extract was washed with water, and then with brine, and dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash chromatography using 10% MeOH in DCM as an eluent, and the desired fractions were concentrated to provide *N*-cyclohexyl-4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxamide (33 mg, 90 μ mol, 27%) as a yellow solid. MS 360.25.

[00122] EXAMPLE 12

[00123] Compound 5

[00124] 4-methyl-*N*,1,5-triphenyl-1*H*-pyrazole-3-carboxamide

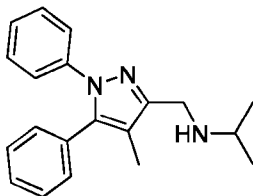


[00125] To a stirred solution of 4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carbonyl chloride (0.4 g, 1.35 mmol) in dichloromethane (5 mL) was added triethylamine (941 μ L, 5 eq., 6.74 mmol). The reaction mixture was cooled to 0 °C and then aniline (185 μ L, 1.5 eq., 2.02 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. After completion (TLC & LCMS monitoring), the reaction mixture was diluted with water and product was extracted with DCM. The DCM extract was washed with water, and then with brine, and dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash chromatography using 10% MeOH in DCM as an eluent, and the desired fractions were concentrated to provide 4-methyl-*N*,1,5-triphenyl-1*H*-pyrazole-3-carboxamide (250 mg, 693 μ mol, 51%) as a yellow solid. MS 354.25.

[00126] EXAMPLE 13

[00127] Compound 6

[00128] *N*-((4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methyl)propan-2-amine

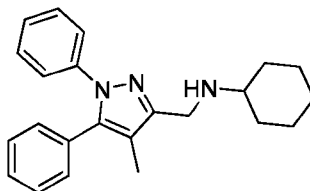


[00129] To a stirred solution of *N*-isopropyl-4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxamide (0.1 g, 313 μ mol) in THF (1 mL) was added dropwise a solution of 2M LiAlH₄ in THF (783 μ L, 5 eq., 1.57 mmol) at -78°C. After the addition was complete, the reaction mixture was heated at 70 °C for 16 hours. After completion (TLC & LCMS monitoring), the reaction mixture was quenched with a saturated solution of ammonium chloride, diluted with water, and extracted with EtOAc. The organic layer was washed with water, then with brine, and dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash chromatography using 50% EtOAc in hexane as an eluent, and the desired fractions were concentrated to provide *N*-((4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methyl)propan-2-amine (65 mg, 211 μ mol, 67%) as a light yellow solid. MS 306.30.

[00130] EXAMPLE 14

[00131] Compound 7

N-((4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methyl)cyclohexanamine

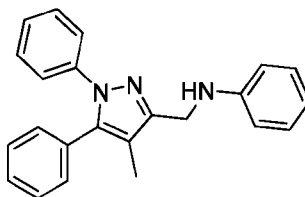


[00132] To a stirred solution of *N*-cyclohexyl-4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxamide (0.1 g, 278 μ mol) in THF (1 mL) was added dropwise a solution of 1M LiAlH₄ in THF (1.39 mL, 5 eq., 1.39 mmol) at -78°C. After the addition was complete, the reaction mixture was heated at 70 °C for 16 hours. After completion (TLC & LCMS monitoring), the reaction mixture was quenched with a saturated solution of ammonium chloride, diluted with water, and extracted with EtOAc. The organic layer was washed with water, then with brine, and dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash chromatography using 50% EtOAc in hexane as an eluent, and the desired fractions were concentrated. The crude product was further purified by preparative HPLC using acetonitrile/water(TFA) as a mobile phase to provide *N*-((4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methyl)cyclohexanamine as the 2,2,2-trifluoroacetate salt (8 mg, 22.5 μ mol, 6%) as an off-white solid. MS 346.35.

[00133] EXAMPLE 15

[00134] Compound 8

[00135] *N*-((4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methyl)aniline

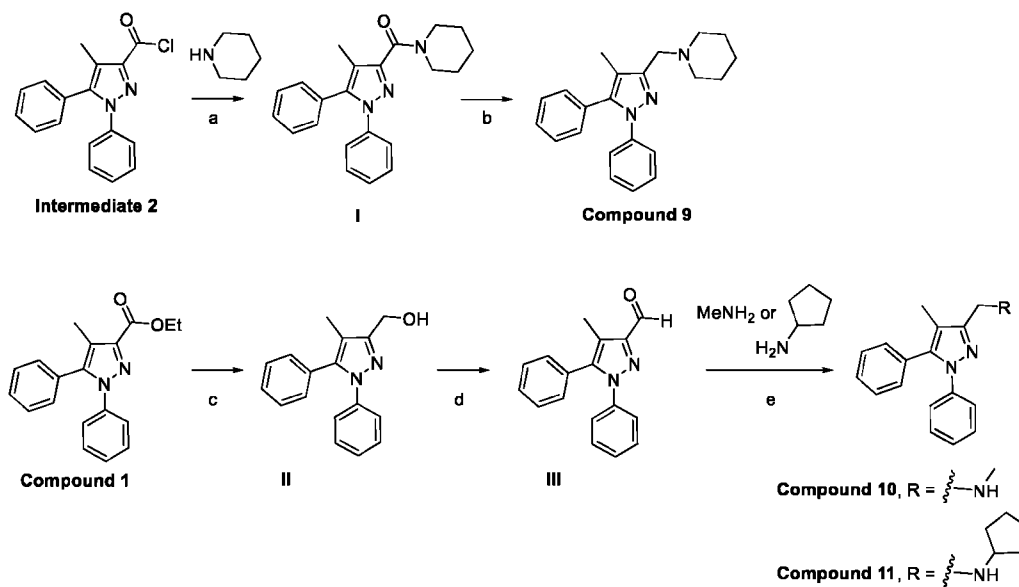


[00136] To a stirred solution of 4-methyl-*N*,1,5-triphenyl-1*H*-pyrazole-3-carboxamide (0.1 g, 283 μ mol) in THF (1 mL) was added dropwise a solution of 2M LiAlH₄ in THF (707 μ L, 5 eq., 1.41 mmol) at -78°C. After the addition was complete, the reaction mixture was heated at 70°C for 16 hours. After completion (TLC & LCMS monitoring), reaction mixture was quenched with a saturated solution of ammonium chloride, diluted with water, and extracted with EtOAc. The organic layer was washed with water, then with brine, and dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash chromatography using 50% EtOAc in hexane as an eluent, and the desired fractions were concentrated to provide *N*-((4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methyl)aniline (51 mg, 143 μ mol, 54%) as a light yellow solid. MS 340.25.

[00137] EXAMPLE 16

[00138] Overall Synthesis of Compounds 9, 10 and 11.

Scheme 3



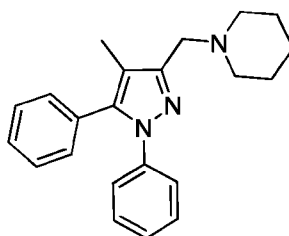
[00139] Reagents and conditions: a = piperidine, NEt_3 , DCM, 0 °C to room temperature, 16 hours, 54%; b = 2M LiAlH_4 in THF, THF, -78 °C to reflux, 16 hours, 57%; c = 2M LiAlH_4 in THF, Et_2O , -78 °C to room temperature, 2 hours, 42%; d = MnO_2 , CHCl_3 , room temperature, 16 hours, 97%; e = 40% w/w methylamine in MeOH (for **Compound 10**) or cyclopentyl amine (for **Compound 11**), MeOH, reflux, 2 hours, then NaBH_4 , 0 °C to room temperature, 16 hours, 20% (for **Compound 10**) or 14% (for **Compound 11**).

[00140] (4-Methyl-1,5-diphenyl-1H-pyrazol-3-yl)(piperidin-1-yl)methanone (**I**). To a stirring solution of 4-Methyl-1,5-diphenyl-1H-pyrazole-3-carbonyl chloride (**Intermediate 2**) (0.40 g, 1.35 mmol, 1 eq) in DCM (5 mL) at 0 °C was added NEt_3 (941 μL , 6.74 mmol, 5 eq) and piperidine (266 μL , 2.7 mmol, 2 eq). The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with H_2O extracted with DCM, washed with H_2O , brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash LC on silica gel eluting with 10% MeOH in DCM to afford **I** (250 mg, 724 μmol , 54%) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.44 – 7.28 (m, 6H), 7.26 – 7.18 (m, 4H), 3.70 – 3.55 (m, 4H), 2.04 (s, 3H), 1.70 – 1.60 (m, 2H), 1.60 – 1.50 (m, 4H); LRMS m/z (ES^+) 346.25 $[\text{M}+\text{H}]^+$.

[00141] EXAMPLE 17

[00142] Compound 9

[00143] 1-((4-Methyl-1,5-diphenyl-1H-pyrazol-3-yl)methyl)piperidine



[00144] 1-((4-Methyl-1,5-diphenyl-1H-pyrazol-3-yl)methyl)piperidine (**Compound 9**).

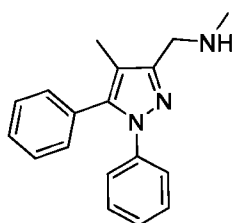
To a stirring solution of (4-Methyl-1,5-diphenyl-1H-pyrazol-3-yl)(piperidin-1-yl)methanone (**I**) (0.10 g, 0.289 mmol, 1 eq) in THF (1 mL) at -78°C was added dropwise a solution of 2M LiAlH_4 in THF (724 μL , 1.45 mmol, 5 eq). After the addition was complete, the reaction mixture was stirred and heated to reflux for 16 hours. The reaction mixture was cooled to room temperature and quenched with saturated aq NH_4Cl solution, diluted with H_2O , and extracted with EtOAc . The organic layer was washed with H_2O , then with brine, and dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash LC on silica gel eluting with 50% EtOAc

in hexane to afford **Compound 9** (55 mg, 166 μ mol, 57%) as a light-yellow solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.42 – 7.21 (m, 6H), 7.21 – 7.11 (m, 4H), 3.47 (s, 2H), 2.45 – 2.35 (m, 4H), 2.03 (s, 3H), 1.55 – 1.45 (m, 4H), 1.45 – 1.35 (m, 2H); LRMS m/z (ES^+) 332.25 $[\text{M}+\text{H}]^+$; HPLC purity 91.31% (Method 1).

[00145] EXAMPLE 18

[00146] Compound 10

[00147] N-Methyl-1-(4-methyl-1,5-diphenyl-1H-pyrazol-3-yl)methanamine

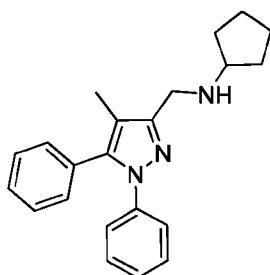


[00148] **(4-Methyl-1,5-diphenyl-1H-pyrazol-3-yl)methanol (II)**. To a stirring solution of ethyl 4-methyl-1,5-diphenyl-1H-pyrazole-3-carboxylate (**Compound 1**) (2.00 g, 6.53 mmol, 1 eq) in Et_2O (20 mL) at -78°C was added dropwise a solution of 2M LiAlH_4 in THF (6.53 mL, 13.1 mmol, 2 eq). After the addition was complete, the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with saturated aq NH_4Cl solution and extracted with EtOAc , washed with H_2O , brine, organic layer dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford **II** (730 mg, 2.76 mmol, 42%) as a pale-yellow solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.44 – 7.21 (m, 6H), 7.21 – 7.11 (m, 4H), 5.06 (t, $J = 5.4$ Hz, 1H), 4.52 (d, $J = 5.2$ Hz, 2H), 2.05 (s, 3H); LRMS m/z (ES^+) 265.20 $[\text{M}+\text{H}]^+$.

[00149] **4-Methyl-1,5-diphenyl-1H-pyrazole-3-carbaldehyde (III)**. To a stirring solution of (4-Methyl-1,5-diphenyl-1H-pyrazol-3-yl)methanol (**II**) (730 mg, 2.76 mmol, 1 eq) in CHCl_3 (10 mL) at room temperature was added MnO_2 (1.20 g, 13.8 mmol, 5 eq). The reaction mixture was stirred at room temperature for 16 hours. The mixture was filtered through celite, and the filtrate was concentrated *in vacuo* to provide **III** (700 mg, 2.67 mmol, 97%) as a brown semisolid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.09 (s, 1H), 7.50 – 7.35 (m, 6H), 7.35 – 7.20 (m, 4H), 2.25 (s, 3H); LRMS m/z (ES^+) 263.02 $[\text{M}+\text{H}]^+$.

[00150] N-Methyl-1-(4-methyl-1,5-diphenyl-1H-pyrazol-3-yl)methanamine

(Compound 10). A stirring solution of 4-Methyl-1,5-diphenyl-1H-pyrazole-3-carbaldehyde (**III**) (0.10 g, 0.381 mmol, 1 eq) and 40% w/w methylamine in MeOH (2 mL, 0.762 mmol, 2 eq) and MeOH (3 mL) was stirred and heated to reflux for 2 hours. Then the reaction mixture was cooled to 0 °C and NaBH₄ (43 mg, 1.14 mmol, 3 eq) was added portion-wise. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo* then diluted with H₂O, extracted with DCM, organic layer dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash LC on silica gel eluting with 70% EtOAc in hexane to afford **Compound 10** (21 mg, 75.7 μmol, 20%) as an off-white semisolid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.45 – 7.23 (m, 6H), 7.23 – 7.11 (m, 4H), 5.98 (brs, 1H), 3.89 (s, 2H), 2.48 (s, 3H), 2.04 (s, 3H); LRMS *m/z* (ES⁺) 278.3 [M+H]⁺; HPLC purity 97.37% (Method 2).

[00151] EXAMPLE 19**[00152] Compound 11****[00153] N-((4-Methyl-1,5-diphenyl-1H-pyrazol-3-yl)methyl)cyclopentanamine****[00154] N-((4-Methyl-1,5-diphenyl-1H-pyrazol-3-yl)methyl)cyclopentanamine**

(Compound 11). A stirring solution of 4-Methyl-1,5-diphenyl-1H-pyrazole-3-carbaldehyde (**III**) (0.20 g, 0.762 mmol, 1 eq) and cyclopentyl amine (130 mg, 1.52 mmol, 2 eq) in MeOH (3 mL) was stirred and heated to reflux for 2 hours. Then the reaction mixture was cooled to 0 °C and NaBH₄ (87 mg, 2.29 mmol, 3 eq) was added portion-wise. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo* then diluted with H₂O, extracted with DCM, organic layer dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash LC on silica gel eluting with 70% EtOAc in hexane to afford **Compound 11** (35 mg, 106 μmol, 14%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.44 – 7.23 (m, 6H), 7.21 – 7.12 (m, 4H), 3.79 (s, 2H), 3.25 – 3.15 (m, 1H), 2.05 (s, 3H), 1.85 –

1.75 (m, 2H), 1.75 – 1.55 (m, 2H), 1.55 – 1.35 (m, 4H), 1.24 (s, 1H); LRMS m/z (ES^+) 332.4 $[M+H]^+$; HPLC purity 95.05% (Method 2).

[00155] EXAMPLE 20

[00156] Malachite Green Enzyme Assay

[00157] Enzymatic inhibitory potencies (IC_{50}) (see table below) were determined using PI(3,4,5)P₃-diC₈ as a substrate at 25 °C in 50 mM HEPES buffer (pH7.4, 150 mM NaCl, 2 mM MgCl₂). *See* FIG. 2. Compounds diluted in DMSO were added to 384-well plates. Enzyme solution was added. After a 20-minute incubation period, the reaction was initiated by addition of PI(3,4,5)P₃-diC₈. Final compound concentrations ranged from 50 nM to 950 μ M. Final reaction concentrations for the PI(3,4,5)P₃-diC₈ substrate and the enzyme were 52 μ M and 10 nM respectively. The reaction was quenched after 10 minutes by adding Malachite BioMol Green (Enzo Lifesciences, PA, USA). Plates were then incubated for 30 minutes at room temperature. Absorbance (620nm) was measured using a SpectraMax® Me5 Microplate Reader (Molecular Devices, LLC, USA). IC_{50} values were calculated by fitting absorbance versus inhibitor concentration and are reported as the geometric mean and standard error of mean with the number of repeats (n) indicated. Compounds and activities are as depicted in Tables 1 and 2 above.

[00158] EXAMPLE 21

[00159] Cellular Thermal Shift Assay (CETSA)

[00160] A split Nano Luciferase assay (SplitLuc CETSA) was used to demonstrate target engagement of SHIP1 inhibitors in a physiologically relevant cellular context by quantifying changes in the thermal stability of a HiBit-labeled full length SHIP1 protein in intact cells. *See* Martinez et al. (2018) *Sci Rep* 8: p. 9472; Oh-Hashi et al. (2017) *Biochem Biophys Res Commun* 500: pp. 40-45. This assay was run in the following two formats with HMC3/HiBit-INPP5D stably transfected cells. Results are depicted in Table 3 below.

[00161] Thermal shift: Cells were treated with 40 μ M compound for 60 minutes, then heated with a temperature gradient covering 38–52°C for 3 minutes before luminescence detection. Mean and standard deviation of control T_m were determined to generate a "Mean+3SD" ΔT_m , which was used as threshold to determine a significant ΔT_m of compound from control. When the difference of ΔT_m of compound treated cells from control $T_m > 3SD$, the compound was considered positive for target engagement, otherwise negative. SD = average standard deviation.

[00162] Compound dose response: Run at target T_m (44.2 °C for SHIP1) with compound dosing from 80 μ M or 100 μ M with 1:3 serial dilutions to generate an 8-point curve. Cells were treated for 60 minutes before being heated at target T_m for 3 minutes before luminescence detection. The concentration that induced a half-maximum response (AC_{50}) was calculated using a four-parameter logistic curve regression model with change at highest concentration noted when difference from control >3SD. Activities are shown in Table 3, below.

[00163] **EXAMPLE 22**

[00164] **pHrodo-Myelin Phagocytosis/Cell Health Assay with Microglial Cells**

[00165] This 384-well plate high content imaging assay was developed to quantify phagocytosis and cell health simultaneously using either BV2 or HMC3 immortalized microglial cell lines or primary microglia isolated from mouse brain. Cells were cultured in Dulbecco modified eagle medium (DMEM) GlutaMAX™ media (ThermoFisher) containing 10% fetal bovine serum (FBS) and Pen-Strep in 37 °C 5% CO₂ incubator.

[00166] Assay Timing

[00167] Day 1: Cells were plated (Corning Falcon 384-well Optilux Black and clear bottom plates for imaging) with BV2 at 400 cells/45 μ L/well, HMC3 at 600 cells/45 μ L/well, or primary at 2000 cell/45 μ L/well.

[00168] Day 2: Cells were treated with 10x serially diluted compounds in a dose range of 60 μ M to 3 nM for 48 hours at 37 °C.

[00169] Day 3: Cells were seeded with pHrodo-myelin (for total 20 hours) 24 hours after starting compound treatment. The pHrodo-myelin stocks were at 1 mg/mL (protein equivalent), and were stored in -20 °C or -80 °C freezer. Stocks were thawed and diluted with culture media into 10x seeding solution (50 μ g/mL) and added 5 μ L/well to a 384-well cell plate.

[00170] Day 4: Cell staining and imaging. Nuclear staining solution was prepared by adding 1 μ L of 10 mg/mL Hoechst-33342 blue-emitting fluorescent dye to every 1 mL culture media that will be added to cell plate at 20 μ L/well. The final concentration of Hoechst-33342 to cells was about 2.5 μ g/mL. Cell plates were incubated for >30 minutes at 37 °C before imaging. Cell plates were scanned with an ArrayScan™ automatic high content imaging system using a 10x objective lens, 4 fields/well collected. Three measurements were obtained: 1) mean total phagocytosis spot intensity per cell, 2) total cell counts per well, and 3) mean average nuclear intensity per cell for cell health. Apoptotic cells showed nuclear intensity increase (early apoptosis) or decrease (later apoptosis).

[00171] Activities are shown in Table 3 below.

Table 3:

Compound #	CETSA SP (%)	CETSA AC ₅₀ (μM)	CETSA Min Inhibition (%)	BV2 Phagocytosis EC ₅₀ (μM)	HMC3 Phagocytosis EC ₅₀ (μM)
1	96.8	NT	NT	>60.0	NC
2	76.5	NC	73.9	NC, >60.0	NC, NC
3	99.2	NT	NT	NT	NT
4	98.6	NT	NT	NC	NC
5	97.7	NT	NT	NC	1.58
6	23.0	109	9.78	7.79	2.31
7	71.5	143	34.5	NC, >6.67	1.17, 0.785
8	106	NT	NT	NT	NT
9	86	NT	NT	NT	NT
10	105	NT	NT	NT	NT
11	87	NT	NT	NT	NT

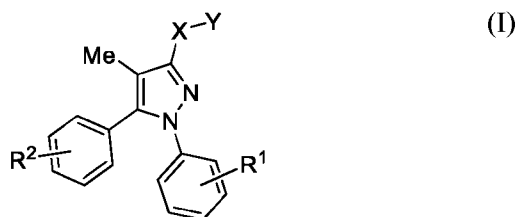
NT = Not Tested. NC = Not calculated due to curve fit error.

[00172] As will be appreciated from the descriptions herein, a wide variety of aspects and embodiments are contemplated by the present disclosure, examples of which include, without limitation, the aspects and embodiments listed below:

[00173] The current disclosure provides methods and compounds directed to inhibiting SHIP1 in order to activate microglia. The methods and compounds disclosed herein allow for the inhibition of SHIP1 early in neurodegenerative diseases leading to increased microglial protective functions and reduce the rate of disease progression and cognitive decline, for example, in Alzheimer's patients.

[00174] More specifically, the present disclosure provides:

[00175] -- one or more compounds of formula (I):



[00176] wherein X is selected from the group consisting of CH₂, C=O, or NH;

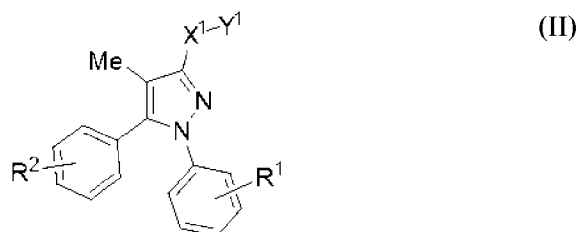
[00177] Y is selected from the group consisting of OR^3 , $NH(R^3)$, $N(R^3)_2$, or $C=O(R^3)$;

[00178] R^1 and R^2 are independently selected for each occurrence from the group consisting of H, halo, C1-7alkyl, OR^3 , $NH(R^3)$, $N(R^3)_2$, or $C=O(R^3)$; and

[00179] R^3 is independently selected for each occurrence from the group consisting of H, C1-7alkyl, C3-7cycloalkyl, phenyl, heteroalkyl cycloheteroalkyl, and heteroaryl;

[00180] or pharmaceutically acceptable salt thereof;

[00181] --one or more compounds of formula (II):



[00182] wherein R^1 is selected from the group consisting of H, halo, OH, OCH_3 , $NH(R^3)$ and $N(R^3)_2$;

[00183] R^2 is selected from the group consisting of H, halo, OH, OCH_3 , $NH(R^3)$ and $N(R^3)_2$; where R^3 is independently selected from the group consisting of H and CH_3 ;

[00184] X^1 is selected from the group consisting of -methylene-NH- wherein NH is bound to Y^1 ; -C(O)-NH-, -NHC(O)- and methylene;

[00185] Y^1 is selected from the group consisting of C5-C6 cycloalkyl, phenyl, C1-C4alkyl;

[00186] and - $NR^{11}R^{12}$; wherein R^{11} and R^{12} taken together with the nitrogen to which they are bound form a 5-6 membered heterocycle;

[00187] or a pharmaceutically acceptable salt thereof;

[00188] -- pharmaceutically acceptable compositions comprising a compound of formula (II), and a pharmaceutically acceptable excipient;

[00189] --methods for treating Alzheimer's disease in a patient in need thereof, which comprises administering to the patient one or more compounds of the present disclosure or a pharmaceutically acceptable salt thereof;

[00190] --methods for treating Alzheimer's disease-related dementias in a patient in need thereof, comprising administering to the patient one or more compounds of the present disclosure or a pharmaceutically acceptable salt thereof;

[00191] --method of treating the progression of mild cognitive impairment to Alzheimer's disease or related dementias in a patient in need thereof, comprising administering to the patient an effective amount of one or more compounds of the present disclosure;

[00192] --methods of preventing or ameliorating Alzheimer's disease or Alzheimer's disease-related dementias, comprising administering to a patient in need of such treatment an effective amount of one or more compounds of the present disclosure;

[00193] --pharmaceutical compositions comprising one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers, diluents or excipients;

[00194] pharmaceutical compositions comprising one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents;

[00195] --pharmaceutical compositions comprising one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, for the treatment of Alzheimer's disease, in combination with one or more pharmaceutically acceptable carriers, diluents or excipients;

[00196] --pharmaceutical compositions for the treatment of Alzheimer's disease-related dementias, comprising one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, in combination with one or more carriers, diluents, or pharmaceutically acceptable excipients;

[00197] --pharmaceutical compositions for the prevention of Alzheimer's disease and Alzheimer's disease-related dementias, comprising one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, in combination with one or more carriers, diluents, or pharmaceutically acceptable excipients;

[00198] --one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, for use in therapy, in particular for the treatment of Alzheimer's disease;

[00199] --one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, for use in the treatment of Alzheimer's disease;

[00200] --use of one or more compounds of the disclosure, of or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of Alzheimer's disease;

[00201] --one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, for use in therapy, in particular for the treatment of Alzheimer's disease-related dementias;

[00202] --one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, for use in the treatment of Alzheimer's disease-related dementias;

[00203] --use of one or more compounds of the disclosure, of or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of Alzheimer's disease-related dementias;

[00204] --one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, for use in the prevention of Alzheimer's disease and Alzheimer's disease-related dementias;

[00205] --one or more compounds of the disclosure, or a pharmaceutically acceptable salt thereof, for use in the prevention of Alzheimer's disease and Alzheimer's disease-related dementias;

[00206] --use of one or more compounds of the disclosure, of or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in the prevention of Alzheimer's disease and Alzheimer's disease-related dementias; and

[00207] --intermediates and processes useful for the synthesis of one or more compounds of the present disclosure.

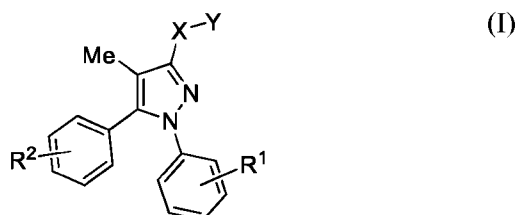
[00208] While embodiments of the present disclosure have been described herein, it is to be understood by those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

[00209] **INCORPORATION BY REFERENCE**

[00210] The contents of all publications cited herein are incorporated by reference in their entireties.

IN THE CLAIMS

1. A method for treating a neurodegenerative disorder or related condition in a patient in need thereof, comprising administering to the patient an effective amount of a compound of formula (I):



wherein

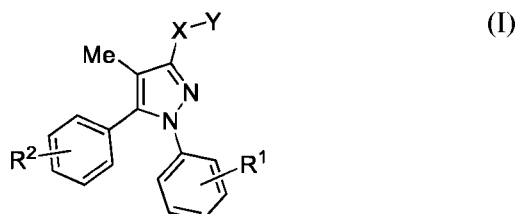
X is selected from the group consisting of CH₂, C=O, or NH;

Y is selected from the group consisting of OR³, NH(R³), N(R³)₂, or C=O(R³);

R¹ and R² are independently selected for each occurrence from the group consisting of H, halo, C1-7alkyl, OR³, NH(R³), N(R³)₂, or C=O(R³); and

R³ is independently selected for each occurrence from the group consisting of H, C1-7alkyl, C3-7cycloalkyl, phenyl, heteroalkyl, cycloheteroalkyl, and heteroaryl;
or a pharmaceutically acceptable salt thereof.

2. A method of treating the progression of a neurodegenerative disorder or related condition in a patient in need thereof, comprising administering to the patient an effective amount of a compound of formula (I):



wherein

X is selected from the group consisting of CH₂, C=O, or NH;

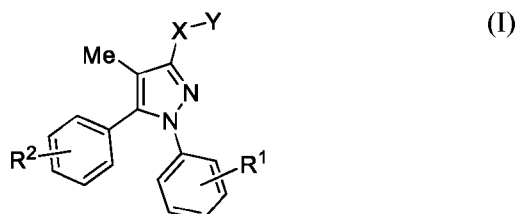
Y is selected from the group consisting of OR³, NH(R³), N(R³)₂, or C=O(R³);

R¹ and R² are independently selected for each occurrence from the group consisting of H, halo, C1-7alkyl, OR³, NH(R³), N(R³)₂, or C=O(R³); and

R³ is independently selected for each occurrence from the group consisting of H, C1-7alkyl, C3-7cycloalkyl, phenyl, heteroalkyl, cycloheteroalkyl and heteroaryl;

or a pharmaceutically acceptable salt thereof.

3. A method of preventing or ameliorating a neurodegenerative disorder or related condition in a patient in need thereof, comprising administering to the patient an effective amount of a compound of formula (I):



wherein

X is selected from the group consisting of CH₂, C=O, or NH;

Y is selected from the group consisting of OR³, NH(R³), N(R³)₂, or C=O(R³);

R¹ and R² are independently selected for each occurrence from the group consisting of H, halo, C1-7alkyl, OR³, NH(R³), N(R³)₂, or C=O(R³); and

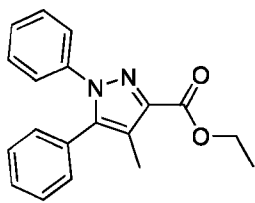
R³ is independently selected for each occurrence from the group consisting of H, C1-7alkyl, C3-7cycloalkyl, phenyl, heteroalkyl, cycloheteroalkyl and heteroaryl;

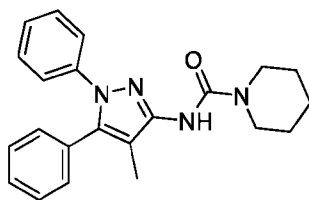
or a pharmaceutically acceptable salt thereof.

4. The method of any of claims 1–3, wherein the compound or its pharmaceutically acceptable salt thereof, is formulated in a pharmaceutical composition further comprising one or more pharmaceutically acceptable carriers, diluents or excipients.

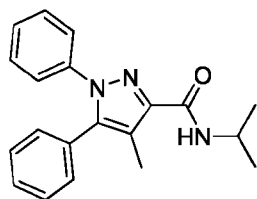
5. The method of any of claims 1–4, further comprising administering to the patient one or more additional therapeutic agents.

6. The use of a compound selected from the group consisting of:

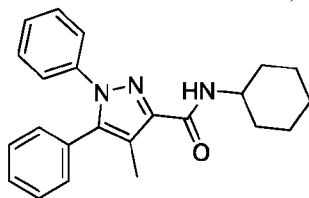




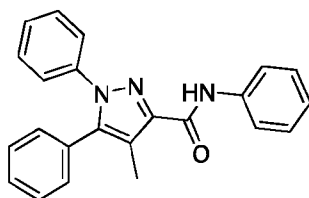
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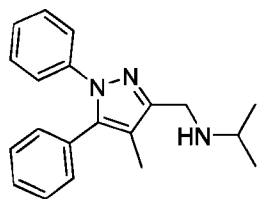
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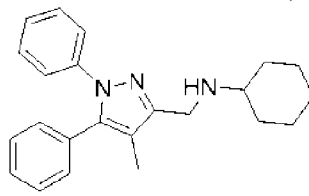
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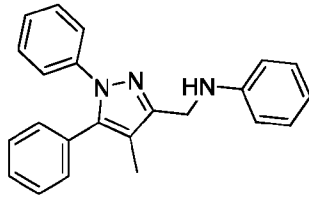
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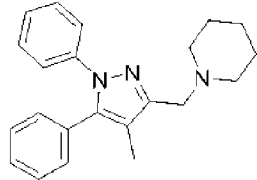
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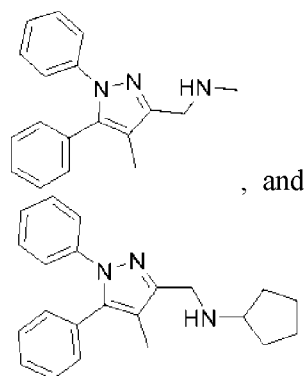
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or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of a neurodegenerative disorder or related condition or to inhibit the progression of said neurological disorder or related condition.

7. The use of a compound selected from the group consisting of:

ethyl 4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylate,

N-(4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)piperidine-1-carboxamide,

N-isopropyl-4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxamide,

N-cyclohexyl-4-methyl-1,5-diphenyl-1*H*-pyrazole-3-carboxamide,

4-methyl-*N*,1,5-triphenyl-1*H*-pyrazole-3-carboxamide,

N-((4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methyl)propan-2-amine,

N-((4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methyl)cyclohexanamine,

N-((4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methyl)aniline,

1-((4-Methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methyl)piperidine,

N-Methyl-1-(4-methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methanamine, and

N-((4-Methyl-1,5-diphenyl-1*H*-pyrazol-3-yl)methyl)cyclopentanamine

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of a neurodegenerative disorder or related condition or to inhibit the progression of said neurological disorder or related condition.

8. The method of any of claims 1–5, wherein the neurodegenerative disorder or related condition is selected from the group consisting of Alzheimer's disease, Alzheimer's disease-related dementias or mild cognitive impairment.

9. The method of claim 8, wherein the **Alzheimer's disease**-related dementia is selected from the group consisting of Lewy body dementia (LBD), frontotemporal degeneration (FTD), vascular cognitive impairment and dementia (VCID), and multiple etiology dementias.

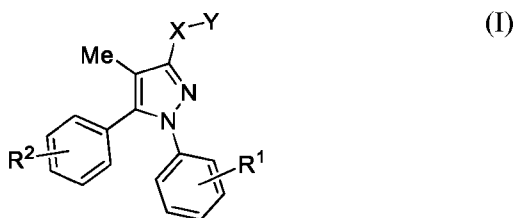
10. The compound of any of claims 6 and 7, wherein the neurodegenerative disorder or related condition is selected from the group consisting of Alzheimer's disease, Alzheimer's disease-related dementias or mild cognitive impairment.

11. The compound of claim 10, wherein the **Alzheimer's disease**-related dementia is selected from the group consisting of Lewy body dementia (LBD), frontotemporal degeneration (FTD), vascular cognitive impairment and dementia (VCID), and multiple etiology dementias.

12. The use of any of claims 6 and 7, wherein the neurodegenerative disorder or related condition is selected from the group consisting of Alzheimer's disease, Alzheimer's disease-related dementias or mild cognitive impairment.

13. The use of claim 12, wherein the **Alzheimer's disease**-related dementia is selected from the group consisting of Lewy body dementia (LBD), frontotemporal degeneration (FTD), vascular cognitive impairment and dementia (VCID), and multiple etiology dementias.

14. A pharmaceutically acceptable composition comprising a compound of formula (I):



wherein

X is selected from the group consisting of CH₂, C=O, or NH;

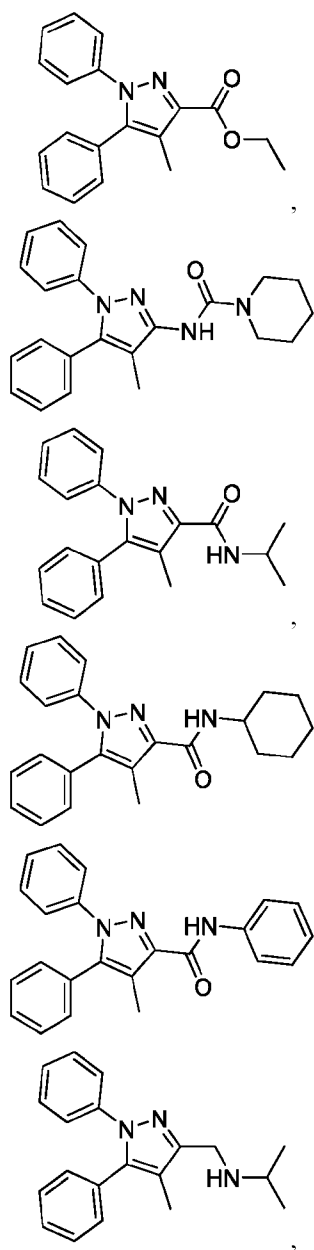
Y is selected from the group consisting of OR³, NH(R³), N(R³)₂, or C=O(R³);

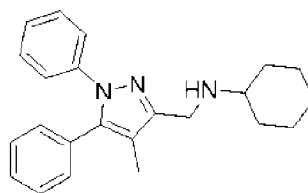
R¹ and R² are independently selected for each occurrence from the group consisting of H, halo, C1-7alkyl, OR³, NH(R³), N(R³)₂, or C=O(R³); and

R³ is independently selected for each occurrence from the group consisting of H, C1-7alkyl, C3-7cycloalkyl, phenyl, heteroalkyl, cycloheteroalkyl, and heteroaryl;

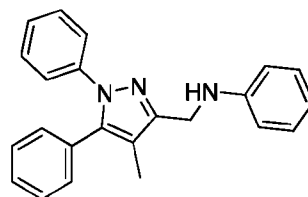
or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.

15. The composition of claim 14, comprising a compound selected from the group consisting of:

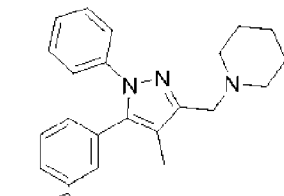




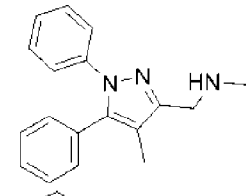
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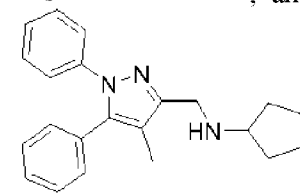


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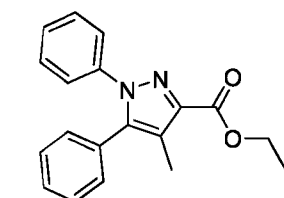
and



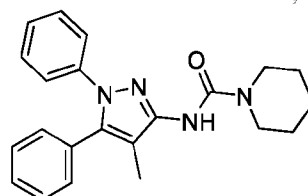
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or a pharmaceutically acceptable salt thereof.

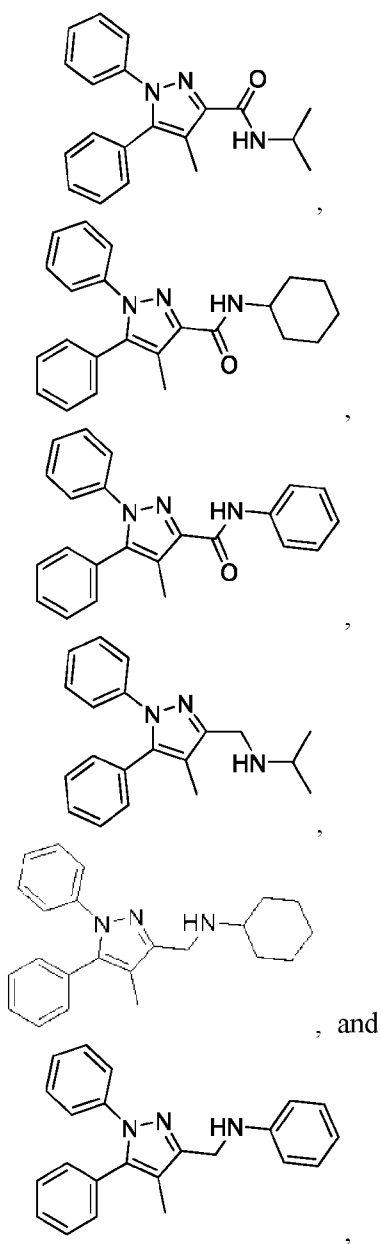
16. The composition of claim 14, comprising a compound selected from the group consisting of:



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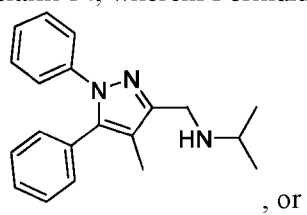


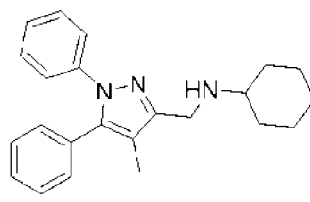
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or a pharmaceutically acceptable salt thereof.

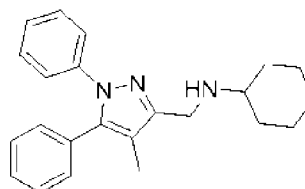
17. The composition of claim 14, wherein Formula (I) comprises





a mixture thereof, or a pharmaceutically acceptable salt thereof.

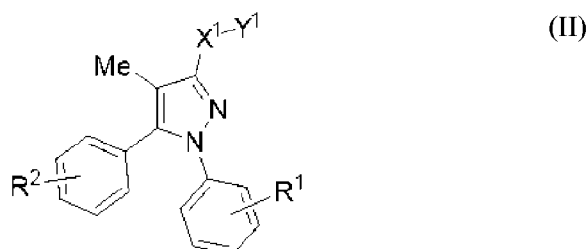
18. The composition of claim 14, comprising



or a pharmaceutically acceptable salt thereof.

19. The composition of any of claims 14–18, further comprising one or more additional neurodegenerative disorder therapeutic agents.

20. A compound of formula (II):



wherein

R^1 is selected from the group consisting of H, halo, OH, OCH_3 , $NH(R^3)$ and $N(R^3)_2$;

R^2 is selected from the group consisting of H, halo, OH, OCH_3 , $NH(R^3)$ and $N(R^3)_2$;

where R^3 is independently selected from the group consisting of H and CH_3 ;

X^1 is selected from the group consisting of -methylene-NH- wherein NH is bound to Y^1 ; - $C(O)-NH$ -; - $NHC(O)$ - and methylene;

Y^1 is selected from the group consisting of C5–C6 cycloalkyl, phenyl, C1–C4alkyl; and $-NR^{11}R^{12}$; wherein R^{11} and R^{12} taken together with the nitrogen to which they are bound form a 5–6 membered heterocycle; or a pharmaceutically acceptable salt thereof.

21. A pharmaceutically acceptable composition comprising a compound of claim 20, and a pharmaceutically acceptable excipient.

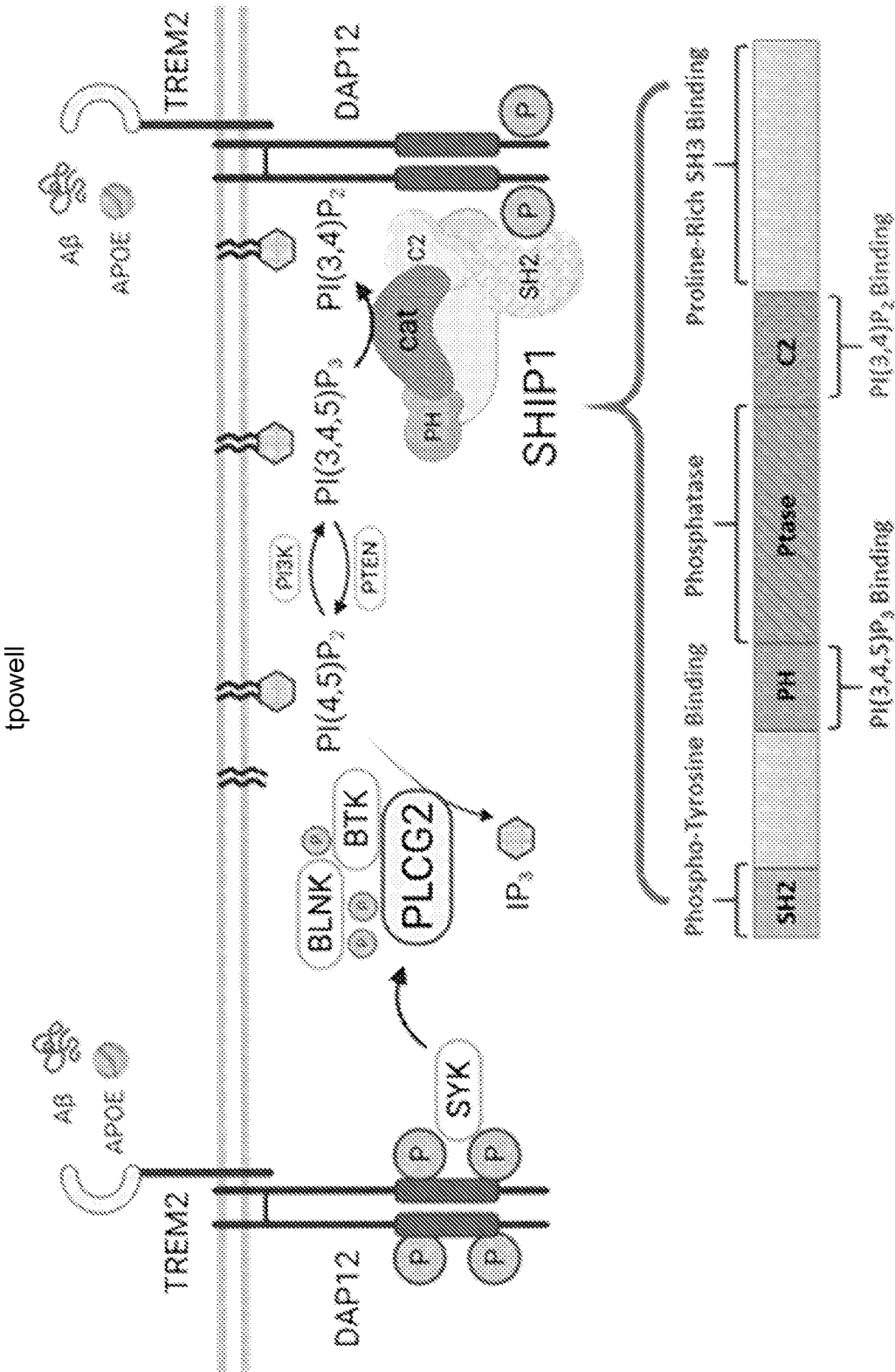


Fig. 1

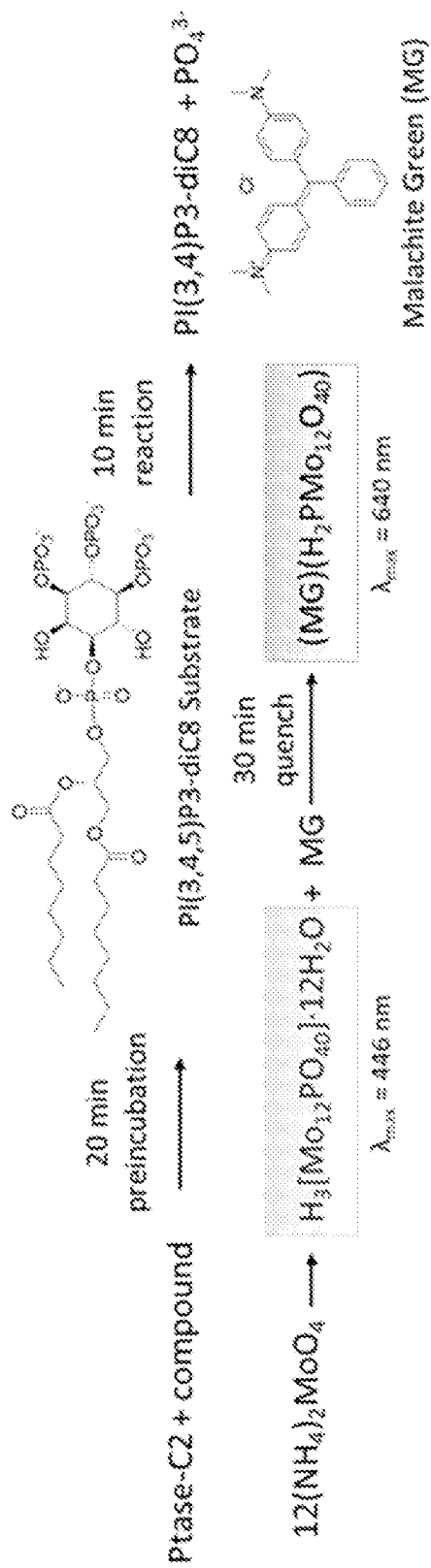


Fig. 2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/078035

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/078035

A. CLASSIFICATION OF SUBJECT MATTER

INV. **A61K31/415** **A61K31/454** **A61K45/06** **A61P25/28** **C07D231/12**
C07D231/40 **C07D231/14**

ADD.

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)

A61K A61P

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

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

EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AU 2004 201 292 A1 (UNIV CONNECTICUT [US]) 6 May 2004 (2004-05-06) page 28, lines 21-33 page 29, lines 15-23 page 29, line 30 - page 30, line 8 pages 37-38; table 3; compounds 3-13, 3-14, 3-16 page 40, last paragraph page 41; table 6 claims 6, 15, 16, 19, 20 -----	1-5, 8, 9, 14, 19-21 6, 7, 10-13, 15-18
A	WO 2008/056377 A2 (CADILA HEALTHCARE LTD [IN]; DHOLAKIA PARIND NARENDRA [IN] ET AL.) 15 May 2008 (2008-05-15) page 1, line 26 - page 2, line 5 page 7, lines 6-10 claims 1, 11-13 -----	1-5, 8, 9, 14, 19-21 6, 7, 10-13, 15-18
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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

2 February 2024

Date of mailing of the international search report

19/02/2024

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INTERNATIONAL SEARCH REPORT

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PCT/US2023/078035

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	CN 1 918 129 A (ASTRAZENECA AB [SE]) 21 February 2007 (2007-02-21) Last compound of scheme; page 27 claims 1, 11, 12 -----	1-5, 8, 9, 14, 19-21 6, 7, 10-13, 15-18
X A	WO 2013/171317 A1 (SANOFI SA [FR]) 21 November 2013 (2013-11-21) page 47, lines 6-17 page 48, line 30 - page 49, line 11 pages 63-65; examples 1, 2 claims 1, 11 -----	1-5, 14, 19 6-13, 15-18, 20, 21
X A	WO 2007/106721 A2 (JENRIN DISCOVERY [US]; MCELROY JOHN F [US]; CHORVAT ROBERT J [US]) 20 September 2007 (2007-09-20) last compound; page 37; figure scheme 7 pages 48-49; table C page 50; table E pages 51-54; table 1a pages 107-109; table 5f claims 1, 15, 16, 19 -----	1-5, 14 8-13, 15-21
X	HERNÁNDEZ-VÁZQUEZ EDUARDO ET AL: "Synthesis, hypoglycemic activity and molecular modeling studies of pyrazole-3-carbohydrazides designed by a ComFA model", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, ELSEVIER, AMSTERDAM, NL, vol. 69, 16 August 2013 (2013-08-16), pages 10-21, XP028762786, ISSN: 0223-5234, DOI: 10.1016/J.EJMECH.2013.07.054 abstract page 12; table 1; compounds 1-3 page 13; table 12 page 19, column 2, paragraph 3 ----- -/--	14-16, 20, 21

INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEN MIAO-MIAO ET AL: "Palladium-catalyzed late-stage mono-arylation of the fully substituted pyrazoles via aromatic C-H bond activation", CHINESE CHEMICAL LETTERS, vol. 30, no. 3, 1 March 2019 (2019-03-01), pages 702-706, XP093126535, AMSTERDAM, NL ISSN: 1001-8417, DOI: 10.1016/j.cclet.2018.09.022 Retrieved from the Internet: URL: https://www.sciencedirect.com/science/article/pii/S1001841718303772?via%3Dihub#u pi0005> abstract compound 1e -----	20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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