

NLRP3 INHIBITORS AND GLP-1 AGONISTS COMBINATION
THERAPIES**RELATED APPLICATION**

[0001] This application claims priority to, and the benefit of, U.S. Provisional Application No. 63/621,412 filed January 16, 2024, the content of which is hereby incorporated by reference in its entirety.

BACKGROUND

[0002] Autoimmune and autoinflammatory diseases are associated with the overproduction of proinflammatory factors. One of them is interleukin-1 (IL-1), produced by activated macrophages, monocytes, fibroblasts, and other components of the innate immune system like dendritic cells. IL-1 is involved in a variety of cellular activities, including cell proliferation, differentiation and apoptosis (Masters, S. L., et. al., Annu. Rev. Immunol. 2009. 27:621–68).

[0003] In humans, 22 NLR proteins are divided into four NLR subfamilies according to their N-terminal domains. NLRA contains a CARD-AT domain, NLRB (NAIP) contains a BIR domain, NLRC (including NOD1 and NOD2) contains a CARD domain, and NLRP contains a pyrin domain. Multiple NLR family members are associated with inflammasome formation.

[0004] Although inflammasome activation appears to have evolved as an important component of host immunity to pathogens, the NLRP3 inflammasome is unique in its ability activate in response to endogenous sterile danger signals. Many such sterile signals have been elucidated, and their formation is associated with specific disease states. For example, uric acid crystals found in gout patients are effective triggers of NLRP3 activation. Similarly, cholesterol crystals found in atherosclerotic patients can also promote NLRP3 activation. Recognition of the role of sterile danger signals as NLRP3 activators led to IL-1 and IL-18 being implicated in a diverse range of pathophysiological indications including metabolic, physiologic, inflammatory, hematologic and immunologic disorders.

[0005] Glucagon-like peptide-1 receptor (GLP-1) agonists provide effective treatment of weight disorders. Combining the beneficial effects of an NLRP3 inflammasome inhibitor with the effects of a GLP-1 receptor agonist may result in additive or synergistic effects that provide a more effective treatment of diseases or disorders related to weight (*e.g.*, obesity, metabolic syndromes, diabetes mellitus, diabetic retinopathy, hyperglycemia, dyslipidemia, Non-Alcoholic SteatoHepatitis (NASH) and/or atherosclerosis) and Parkinson's disease.

[0006] The disclosure arises from a need to provide further treatments of weight disorders. In particular, use of compounds with improved physicochemical, pharmacological and

pharmaceutical properties to existing compounds or combinations are desirable. Combination therapies can yield unexpected synergistic and advantageous effects as compared to administration of one agent alone. Developing new combination therapies for the treatment of various weight disorders remains a critical unmet clinical need.

SUMMARY

[0007] In some aspects, the present disclosure provides an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, for use in combination for treating or preventing a GLP-1 linked disease and/or a weight disorder in a subject.

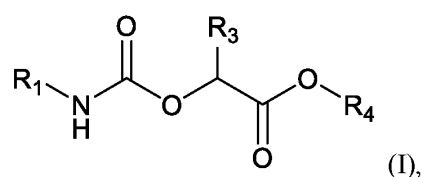
[0008] In some aspects, the present disclosure provides an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, for use in combination for treating or preventing a GLP-1 linked disease or a weight disorder in a subject;

wherein the GLP-1 linked disease or the weight disorder is selected from cardiovascular disease or disorder (*e.g.*, angina pectoris, coronary heart disease, ischemic heart disease, myocardial infarction, reperfusion injury, heart disease, heart failure, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), right ventricular diastolic dysfunction, coronary microvascular dysfunction, aortic valve disease, cardiovascular risk reduction, major adverse cardiac events (MACE)), metabolism disorder (*e.g.*, type I diabetes, type II diabetes, glucose intolerance, hyperglucagonemia, hyperglycemia, metabolic syndrome, insulin resistance), bone disease (*e.g.*, osteoporosis, bone metabolism, osteoarthritis), renal disease (*e.g.*, chronic kidney disease, chronic renal insufficiency, diabetic nephropathy, fibrosis), hepatic disease (*e.g.*, alcoholic fatty liver disease (AFLD), alcohol related steatohepatitis (ASH), nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), nonalcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), fibrosis), gastrointestinal disease or disorder (*e.g.*, motility disorders, inflammatory bowel disease), central nervous system (CNS) disease or disorder (*e.g.*, neurodegenerative diseases such as cognition, Parkinson's disease, or Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, depression, anxiety, schizophrenia, stroke, traumatic brain injury), skin disease (*e.g.*, psoriasis), muscle disease (*e.g.*, sarcopenia), lung disease (*e.g.*, cystic fibrosis, interstitial lung disease, idiopathic pulmonary fibrosis), and others (*e.g.*, polycystic ovary syndrome (PCOS), fibrosis, addiction

(e.g., drug addiction or alcohol addiction), smoking cessation, binge eating disorder, post bariatric surgery treatment, multiple sclerosis, obstructive sleep apnea (OSA), rheumatoid arthritis, neuropathic pain).

[0009] In some aspects, the present disclosure provides an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, for use in combination for treating or preventing a weight disorder in a subject.

[0010] In some aspects, the NLRP3 inflammasome inhibitor is a compound of Formula I, Formula II, or Formula III:



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

R₁ is C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, C₅-C₁₀ aryl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein the C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl is optionally substituted by one or more R₆;

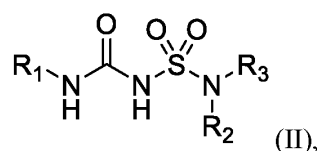
R₃ is H or C₁-C₄ alkyl optionally substituted with one or more R₇;

R₄ is H, C₁-C₆ alkyl, -(CH₂)₀₋₃-(C₃-C₆ cycloalkyl), or -(CH₂)₀₋₃-C₅-C₆ aryl;

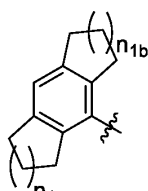
R₆ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, halo, oxo, -OH, -CN, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃;

R₇ is -OR₈, C₅-C₁₀ aryl, or 5- to 10- membered heteroaryl, wherein the C₅-C₁₀ aryl or 5- to 10-membered heteroaryl is optionally substituted by one or more R_{7S}, wherein each R_{7S} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, 5- to 10-membered heteroaryl, halo, -OH, -CN, -(CH₂)₀₋₃-NH₂, -(CH₂)₀₋₃-NH(C₁-C₆ alkyl), -(CH₂)₀₋₃-N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃; and

R₈ is C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl, wherein the C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl is optionally substituted by one or more R_{7S}; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:



R_1 is --- , wherein n_{1a} and n_{1b} each independently are 0 or 1;

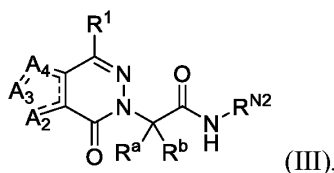
R_2 is $-(CH_2)_{n_2}-R_{2S}$, wherein n_2 is 1 or 2;

R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more R_{2SS} ;

each R_{2SS} independently is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, halo, -CN, -OH, -O(C_1 - C_6 alkyl), -NH₂, -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)₂, or oxo;

R_3 is 5- or 6-membered heteroaryl optionally substituted with one or more R_{3S} ; and

each R_{3S} independently is halo, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

each --- is independently a single bond or double bond as valency permits;

A_2 is CR^2 , N, NR^{2a} , O, or S, as valency allows;

A_3 is CR^2 , N, NR^{2a} , O, or S, as valency allows;

A_4 is CR^2 , N, NR^{2a} , O, or S, as valency allows,

wherein at least one of A_2 , A_3 , or A_4 is N, NR^{2a} , O, or S, provided that when A_2 is S, A_4 is CR^2 , NR^{2a} , O, or S;

R^1 is H, -N(C_1 - C_6 alkyl)₂, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_3 - C_{12} cycloalkyl, wherein the -N(C_1 - C_6 alkyl)₂, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_3 - C_{12} cycloalkyl is optionally substituted with one or more R^{1S} ;

each R^{1S} independently is halogen, cyano, -OH, or C_1 - C_6 alkyl;

each R^2 independently is H, halogen, cyano, -OH, -NH₂, -NO₂, -C(=O)NH₂, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, -O(C_1 - C_6 alkyl), -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)₂, C_3 - C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6 - C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, -O(C_1 - C_6 alkyl), -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)₂, C_3 - C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6 - C_{10} aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{2S} ;

or two R² together with the atoms to which they are attached form a C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl, wherein the C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{2S};

each R^{2S} independently is halogen, -OH, -O(C₁-C₆ alkyl), -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, or C₃-C₁₂ cycloalkyl;

each R^{2a} independently is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, -(CH₂)₀₋₃-(C₃-C₁₂ cycloalkyl), or -(CH₂)₀₋₃-(3- to 12-membered heterocycloalkyl);

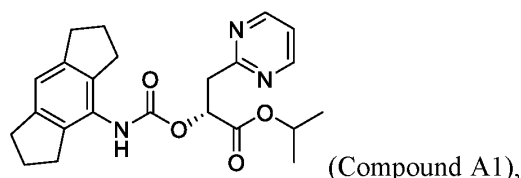
each R^a independently is H or C₁-C₆ alkyl; or two R^a, together with the atom they attach to, form C₃-C₁₂ cycloalkyl;

R^{N2} is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2a};

each R^{N2a} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2ab}; and

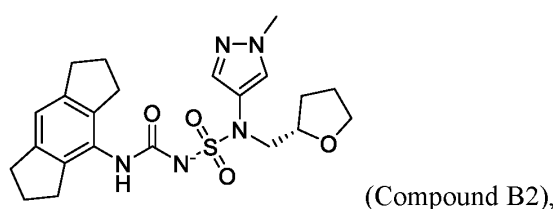
each R^{N2ab} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), or -S(=O)₂N(C₁-C₆ alkyl)₂.

[0011] In some aspects, the NLRP3 inflammasome inhibitor is Compound A1:



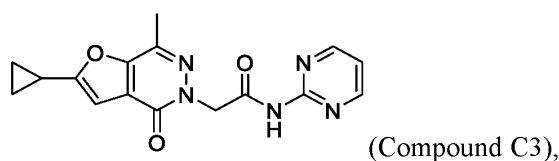
or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0012] In some aspects, the NLRP3 inflammasome inhibitor is Compound B2:



or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0013] In some aspects, the NLRP3 inflammasome inhibitor is Compound C3:



or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0014] In some aspects, the GLP-1 receptor agonist is semaglutide.

[0015] In some aspects, the present disclosure provides a method of treating or preventing a weight disorder, comprising administering to a subject:

(a) an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and

(b) a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0016] In some aspects, the present disclosure provides a method of treating or preventing a GLP-1 linked disease and/or a weight disorder, comprising administering to a subject:

(a) an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and

(b) a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0017] In some aspects, the present disclosure provides a method of treating or preventing a GLP-1 linked disease or a weight disorder, comprising administering to a subject:

(a) an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and

(b) a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof;

[0018] wherein the GLP-1 linked disease and/or the weight disorder is selected from cardiovascular disease or disorder (*e.g.*, angina pectoris, coronary heart disease, ischemic heart disease, myocardial infarction, reperfusion injury, heart disease, heart failure, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), right ventricular diastolic dysfunction, coronary microvascular dysfunction, aortic valve disease, cardiovascular risk reduction, major adverse cardiac events (MACE)), metabolism disorder (*e.g.*, type I diabetes, type II diabetes, glucose intolerance, hyperglucagonemia, hyperglycemia, metabolic syndrome, insulin resistance), bone disease (*e.g.*, osteoporosis, bone metabolism, osteoarthritis), renal disease (*e.g.*, chronic kidney disease, chronic renal insufficiency, diabetic nephropathy, fibrosis), hepatic disease (*e.g.*, alcoholic fatty liver disease (AFLD), alcohol related steatohepatitis (ASH), nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), nonalcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), fibrosis), gastrointestinal disease or disorder (*e.g.*, motility disorders, inflammatory bowel disease), central nervous system (CNS) disease or disorder (*e.g.*, neurodegenerative diseases such as cognition, Parkinson's disease, or Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, depression, anxiety, schizophrenia, stroke, traumatic brain injury), skin disease (*e.g.*, psoriasis), muscle disease (*e.g.*, sarcopenia), lung disease (*e.g.*, cystic fibrosis, interstitial lung disease, idiopathic pulmonary fibrosis), and others (*e.g.*, polycystic ovary syndrome (PCOS), fibrosis, addiction (*e.g.*, drug addiction or alcohol addiction), smoking cessation, binge eating disorder, post bariatric surgery treatment, multiple sclerosis, obstructive sleep apnea (OSA), rheumatoid arthritis, neuropathic pain). In some aspects, the present disclosure provides an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for a combinatorial therapy for the treatment or prevention of a GLP-1 linked disease and/or a weight disorder in a subject.

[0019] In some aspects, the present disclosure provides an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor

agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for a combinatorial therapy for the treatment or prevention of a GLP-1 linked disease and/or a weight disorder in a subject;

[0020] wherein the GLP-1 linked disease and/or the weight disorder is selected from cardiovascular disease or disorder (*e.g.*, angina pectoris, coronary heart disease, ischemic heart disease, myocardial infarction, reperfusion injury, heart disease, heart failure, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), right ventricular diastolic dysfunction, coronary microvascular dysfunction, aortic valve disease, cardiovascular risk reduction, major adverse cardiac events (MACE)), metabolism disorder (*e.g.*, type I diabetes, type II diabetes, glucose intolerance, hyperglucagonemia, hyperglycemia, metabolic syndrome, insulin resistance), bone disease (*e.g.*, osteoporosis, bone metabolism, osteoarthritis), renal disease (*e.g.*, chronic kidney disease, chronic renal insufficiency, diabetic nephropathy, fibrosis), hepatic disease (*e.g.*, alcoholic fatty liver disease (AFLD), alcohol related steatohepatitis (ASH), nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), nonalcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), fibrosis), gastrointestinal disease or disorder (*e.g.*, motility disorders, inflammatory bowel disease), central nervous system (CNS) disease or disorder (*e.g.*, neurodegenerative diseases such as cognition, Parkinson's disease, or Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, depression, anxiety, schizophrenia, stroke, traumatic brain injury), skin disease (*e.g.*, psoriasis), muscle disease (*e.g.*, sarcopenia), lung disease (*e.g.*, cystic fibrosis, interstitial lung disease, idiopathic pulmonary fibrosis), and others (*e.g.*, polycystic ovary syndrome (PCOS), fibrosis, addiction (*e.g.*, drug addiction or alcohol addiction), smoking cessation, binge eating disorder, post bariatric surgery treatment, multiple sclerosis, obstructive sleep apnea (OSA), rheumatoid arthritis, neuropathic pain). In some aspects, the present disclosure provides an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for a combinatorial therapy for the treatment or prevention of a weight disorder in a subject.

[0021] In some aspects, the present disclosure provides use of an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for the treatment or prevention of a GLP-1 linked disease and/or a weight disorder in a subject.

[0022] In some aspects, the present disclosure provides use of an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for the treatment or prevention of a weight disorder in a subject.

[0023] In some aspects, the present disclosure provides use of an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for the treatment or prevention of a GLP-1 linked disease and/or a weight disorder;

wherein the GLP-1 linked disease and/or the weight disorder is selected from cardiovascular disease or disorder (*e.g.*, angina pectoris, coronary heart disease, ischemic heart disease, myocardial infarction, reperfusion injury, heart disease, heart failure, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), right ventricular diastolic dysfunction, coronary microvascular dysfunction, aortic valve disease, cardiovascular risk reduction, major adverse cardiac events (MACE)), metabolism disorder (*e.g.*, type I diabetes, type II diabetes, glucose intolerance, hyperglucagonemia, hyperglycemia, metabolic syndrome, insulin resistance), bone disease (*e.g.*, osteoporosis, bone metabolism, osteoarthritis), renal disease (*e.g.*, chronic kidney disease, chronic renal insufficiency, diabetic nephropathy, fibrosis), hepatic disease (*e.g.*, alcoholic fatty liver disease (AFLD), alcohol related steatohepatitis (ASH), nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), nonalcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), fibrosis), gastrointestinal disease or disorder (*e.g.*, motility disorders, inflammatory bowel disease), central nervous system (CNS) disease or disorder (*e.g.*, neurodegenerative diseases such as cognition, Parkinson's disease, or Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, depression, anxiety, schizophrenia, stroke, traumatic brain injury), skin disease (*e.g.*, psoriasis), muscle disease (*e.g.*, sarcopenia), lung disease (*e.g.*, cystic fibrosis, interstitial lung disease, idiopathic pulmonary fibrosis), and others (*e.g.*, polycystic ovary syndrome (PCOS), fibrosis, addiction (*e.g.*, drug addiction or alcohol addiction), smoking cessation, binge eating disorder, post bariatric surgery treatment, multiple sclerosis, obstructive sleep apnea (OSA), rheumatoid arthritis, neuropathic pain).

[0024] In some aspects, the present disclosure provides a kit comprising an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug

thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0025] In some aspects, the present disclosure provides a pharmaceutical package comprising an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0026] In some aspects, the GLP-1 linked disease and/or the weight disorder is selected from cardiovascular disease or disorder (*e.g.*, angina pectoris, coronary heart disease, ischemic heart disease, myocardial infarction, reperfusion injury, heart disease, heart failure, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), right ventricular diastolic dysfunction, coronary microvascular dysfunction, aortic valve disease, cardiovascular risk reduction, major adverse cardiac events (MACE)), metabolism disorder (*e.g.*, type I diabetes, type II diabetes, glucose intolerance, hyperglucagonemia, hyperglycemia, metabolic syndrome, insulin resistance), bone disease (*e.g.*, osteoporosis, bone metabolism, osteoarthritis), renal disease (*e.g.*, chronic kidney disease, chronic renal insufficiency, diabetic nephropathy, fibrosis), hepatic disease (*e.g.*, alcoholic fatty liver disease (AFLD), alcohol related steatohepatitis (ASH), nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), nonalcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), fibrosis), gastrointestinal disease or disorder (*e.g.*, motility disorders, inflammatory bowel disease), central nervous system (CNS) disease or disorder (*e.g.*, neurodegenerative diseases such as cognition, Parkinson's disease, or Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, depression, anxiety, schizophrenia, stroke, traumatic brain injury), skin disease (*e.g.*, psoriasis), muscle disease (*e.g.*, sarcopenia), lung disease (*e.g.*, cystic fibrosis, interstitial lung disease, idiopathic pulmonary fibrosis), and others (*e.g.*, polycystic ovary syndrome (PCOS), fibrosis, addiction (*e.g.*, drug addiction or alcohol addiction), smoking cessation, binge eating disorder, post bariatric surgery treatment, multiple sclerosis, obstructive sleep apnea (OSA), rheumatoid arthritis, neuropathic pain).

[0027] In some aspects, the weight disorder is selected from a metabolic disorder, obesity, excessive body weight, and enhanced appetite.

[0028] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those

described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to be prior art to the claimed invention. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting. In the case of conflict between the chemical structures and names of the compounds disclosed herein, the chemical structures will control.

[0029] Other features and advantages of the disclosure will be apparent from the following detailed description and claims.

BRIEF DESCRIPTION OF THE FIGURES

[0030] FIG. 1 depicts effects of Compound A1, semaglutide or combined treatment with Compound A1 and semaglutide in Diet-Induced Obesity (DIO) hCES1 mice. FIG. 1A depicts % change in baseline body weights of DIO hCES1 mice treated therapeutically with Vehicle (orally (p.o.), three times a day (t.i.d.)), Compound A1 (100 mg/kg p.o., t.i.d.), semaglutide (0.005 mg/kg subcutaneous (s.c.), daily (q.d.)) or combined treatment of Compound A1 and semaglutide for 28 days. FIG. 1B depicts Average daily calorie intake of control chow fed hCES1 and DIO hCES1 mice, from FIG. 1A over the 28 days. Data are expressed as mean $\pm$ SEM and analysed by two-way ANOVA with Tukey's multiple comparisons test using GraphPad Prism v10.0.2. Significance is calculated relative to semaglutide only group * $p < 0.001$; ** $p < 0.05$ (A).

[0031] FIG. 2 depicts effects of Compound C3, semaglutide or combined treatment with Compound C3 and semaglutide in DIO hCES1 mice. FIG. 2A depicts % change in baseline body weights of DIO hCES1 mice treated therapeutically with Vehicle (p.o., t.i.d.), Compound C3 (100 mg/kg p.o., t.i.d.), semaglutide (0.005 mg/kg s.c., q.d.) or combined treatment of Compound C3 and semaglutide for 28 days. FIG. 2B depicts Average daily calorie intake of control chow fed hCES1 and DIO hCES1 mice, from FIG. 2A over the 28 days. Data are expressed as mean $\pm$ SEM.

[0032] FIG. 3 depicts effects of Compound A1 on weight re-gain following semaglutide cessation in DIO hCES1 mice. FIG. 3A depicts % change in baseline body weights of DIO hCES1 mice initially treated therapeutically in the main study (0-28 days) with semaglutide (0.005 mg/kg s.c., q.d) or semaglutide (0.005 mg/kg s.c., q.d.) and Compound A1 (100 mg/kg p.o., t.i.d.), followed by an extension study (28-56 days) consisting of treatment with Vehicle

(p.o., t.i.d.) or Compound A1 (100 mg/kg p.o., t.i.d.) only. FIG. 3B depicts Average daily calorie intake of DIO hCES1 mice, from FIG. 3A during the extension study (days 28-56). Data are expressed as mean $\pm$ SEM.

[0033] FIG. 4 depicts effects of Compound A1, semaglutide or a combination of Compound A1 and semaglutide on body weight change in DIO mice switched to a Polyunsaturated Fatty Acid (PUFA) diet. DIO mice fed high-fat diet (HFD) were dosed therapeutically with Compound A1 (100 mg/kg, p.o., t.i.d.), semaglutide (0.005 mg/kg, s.c., q.d.), or in combination from day 0-28. On day 29, diet was switched to PUFA diet and the respective treatment continued (over days 29-56). An additional group of mice served as calorie restricted controls whose body weights were maintained as close to Compound A1-dosed mice as possible by controlling the degree of calorie restriction throughout the experiment. Overnight fasting into day 55 was performed to facilitate the analysis of further exploratory endpoints. Data are expressed as mean and analysed by two-way ANOVA with Tukey's multiple comparisons test using GraphPad Prism v10.4.1. Significance is calculated using GraphPad Prism v10.4.1, ****p<0.0001, ***p<0.001, **p<0.01, *p<0.05.

[0034] FIG. 5 depicts effects of Compound A1, semaglutide or a combination of Compound A1 and semaglutide on absolute body weight in DIO mice switched to a PUFA diet. DIO mice were dosed as in FIG. 4. Data are expressed as mean and analysed by two-way ANOVA with Tukey's multiple comparisons test using GraphPad Prism v10.4.1. Significance is calculated using GraphPad Prism v10.4.1, ****p<0.0001, ***p<0.001, **p<0.01.

[0035] FIG. 6 depicts effects of Compound A1, semaglutide or a combination of Compound A1 and semaglutide on A) average daily food intake or B) average daily calorie (kcal) intake during HFD exposure (days 0-28). Data are expressed as mean $\pm$ SEM and analysed by one-way ANOVA with Tukey's multiple comparisons test using GraphPad Prism v10.4.1. Significance is calculated using GraphPad Prism v10.4.1, ****p<0.0001.

[0036] FIG. 7 depicts effects of Compound A1, semaglutide or a combination of Compound A1 and semaglutide on A) fat mass (%), B) lean mass (%) or C) bone mineral content (%) as assessed by body composition DEXA scans at day 28. Data are expressed as mean $\pm$ SEM and analysed by one-way ANOVA with Tukey's multiple comparisons test using GraphPad Prism v10.4.1. Significance is calculated using GraphPad Prism v10.4.1, ***p<0.001, ****p<0.0001.

[0037] FIG. 8 depicts effects of Compound A1, semaglutide or a combination of Compound A1 and semaglutide on A) average daily food intake or B) average daily calorie (kcal) intake during PUFA diet exposure (days 29-56). Data are expressed as mean $\pm$ SEM and analysed by

one-way ANOVA with Tukey's multiple comparisons test using GraphPad Prism v10.4.1. Significance is calculated using GraphPad Prism v10.4.1, * $p < 0.05$, **** $p < 0.0001$.

[0038] FIG. 9 depicts effects of Compound A1, semaglutide or a combination of Compound A1 and semaglutide on hypothalamic Glial Fibrillary Acidic Protein (GFAP) expression. GFAP immunoreactivity was assessed within the arcuate nucleus (ARC) and dorsomedial hypothalamus (DMH) and ventral medial hypothalamus (VMH) of DIO mice following continuous dosing with Compound A1 (100 mg/kg, p.o., t.i.d.), semaglutide (0.005 mg/kg, s.c., q.d.), the combination of Compound A1 and semaglutide, or calorie restriction over 56 days in DIO mice. A) Average total GFAP staining (%), B) average strong GFAP staining (%), or C) total GFAP positive cell numbers per mm², across the ARC, DMH and VMH was calculated. Data are expressed as mean $\pm$ SEM and analysed by one-way ANOVA with Tukey's multiple comparisons test using GraphPad Prism v10.2.2. Significance is calculated using GraphPad Prism v10.2.2, * $p < 0.05$, ** $p < 0.01$.

[0039] FIG. 10 depicts effects of Compound A1, semaglutide or a combination of Compound A1 and semaglutide on organ body weights at study end (day 56). A) liver, B) heart, C) brain, D) left kidney, E) right kidney, F) colon weights (mg). Data are expressed as mean $\pm$ SEM and analysed by one-way ANOVA with Tukey's multiple comparisons test using GraphPad Prism v10.2.2. Significance is calculated using GraphPad Prism v10.2.2, **** $p < 0.0001$, *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

DETAILED DESCRIPTION

Definitions

[0040] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

[0041] Without wishing to be limited by this statement, it is understood that, while various options for variables are described herein, the disclosure intends to encompass operable embodiments having combinations of the options. The disclosure may be interpreted as excluding the non-operable embodiments caused by certain combinations of the options.

[0042] It is to be understood that a compound of the present disclosure may be depicted in a neutral form, a cationic form (*e.g.*, carrying one or more positive charges), or an anionic form (*e.g.*, carrying one or more negative charges), all of which are intended to be included in the scope of the present disclosure. For example, when a compound of the present disclosure is depicted in an anionic form, such depiction also refers to the various neutral forms, cationic forms, and anionic forms of the compound. For another example, when a compound the present

disclosure is depicted in an anionic form, such depiction also refers to various salts (*e.g.*, sodium salt) of the anionic form of the compound. In some embodiments, the amine of a compound of the present disclosure is protonated.

[0043] A “therapeutically effective amount” means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[0044] As used herein, “alkyl,” “C₁, C₂, C₃, C₄, C₅ or C₆ alkyl” or “C₁-C₆ alkyl” is intended to include C₁, C₂, C₃, C₄, C₅ or C₆ straight chain (linear) saturated aliphatic hydrocarbon groups and C₃, C₄, C₅ or C₆ branched saturated aliphatic hydrocarbon groups. For example, C₁-C₆ alkyl is intended to include C₁, C₂, C₃, C₄, C₅ and C₆ alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl (*i.e.*, CH₃), ethyl (*i.e.*, CH₂CH₃), n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl or n-hexyl. In some embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (*e.g.*, C₁-C₆ for straight chain, C₃-C₆ for branched chain), and in another embodiment, a straight chain or branched alkyl has four or fewer carbon atoms.

[0045] As used herein, the term “optionally substituted alkyl” refers to unsubstituted alkyl or alkyl having designated substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy, aryloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonate, phosphinate, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonate, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0046] As used herein, the term “alkenyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. For example, the term “alkenyl” includes straight chain alkenyl groups (*e.g.*, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl), and branched alkenyl groups. In certain embodiments, a straight chain or branched alkenyl group has six or fewer carbon atoms in its backbone (*e.g.*, C₂-C₆ for straight chain, C₃-C₆ for branched

chain). The term “C₂-C₆” includes alkenyl groups containing two to six carbon atoms. The term “C₃-C₆” includes alkenyl groups containing three to six carbon atoms.

[0047] As used herein, the term “optionally substituted alkenyl” refers to unsubstituted alkenyl or alkenyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0048] As used herein, the term “alkynyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. For example, “alkynyl” includes straight chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl), and branched alkynyl groups. In certain embodiments, a straight chain or branched alkynyl group has six or fewer carbon atoms in its backbone (*e.g.*, C₂-C₆ for straight chain, C₃-C₆ for branched chain). The term “C₂-C₆” includes alkynyl groups containing two to six carbon atoms. The term “C₃-C₆” includes alkynyl groups containing three to six carbon atoms. As used herein, “C₂-C₆ alkenylene linker” or “C₂-C₆ alkynylene linker” is intended to include C₂, C₃, C₄, C₅ or C₆ chain (linear or branched) divalent unsaturated aliphatic hydrocarbon groups. For example, C₂-C₆ alkenylene linker is intended to include C₂, C₃, C₄, C₅ and C₆ alkenylene linker groups.

[0049] As used herein, the term “optionally substituted alkynyl” refers to unsubstituted alkynyl or alkynyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio,

thiocarboxylate, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0050] Other optionally substituted moieties (such as optionally substituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl) include both the unsubstituted moieties and the moieties having one or more of the designated substituents. For example, substituted heterocycloalkyl includes those substituted with one or more alkyl groups, such as 2,2,6,6-tetramethyl-piperidiny and 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridiny.

[0051] As used herein, the term “cycloalkyl” refers to a saturated or partially unsaturated hydrocarbon monocyclic or polycyclic (*e.g.*, fused, bridged, or spiro rings) system having 3 to 30 carbon atoms (*e.g.*, C₃-C₁₂, C₃-C₁₀, or C₃-C₈). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, 1,2,3,4-tetrahydronaphthalenyl, and adamantyl. In the case of polycyclic cycloalkyl, only one of the rings in the cycloalkyl needs to be non-aromatic.

[0052] As used herein, the term “heterocycloalkyl” refers to a saturated or partially unsaturated 3-8 membered monocyclic, 6-12 membered bicyclic (fused, bridged, or spiro rings), or 11-14 membered tricyclic ring system (fused, bridged, or spiro rings) having one or more heteroatoms (such as O, N, S, P, or Se), *e.g.*, 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, or *e.g.*, 1, 2, 3, 4, 5, or 6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulphur, unless specified otherwise. Examples of heterocycloalkyl groups include, but are not limited to, piperidiny, piperaziny, pyrrolidiny, dioxany, tetrahydrofurany, isoindolinyl, indolinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, oxirany, azetidiny, oxetany, thietany, 1,2,3,6-tetrahydropyridiny, tetrahydropyrany, dihydropyrany, pyrany, morpholinyl, tetrahydrothiopyrany, 1,4-diazepany, 1,4-oxazepany, 2-oxa-5-azabicyclo[2.2.1]heptany, 2,5-diazabicyclo[2.2.1]heptany, 2-oxa-6-azaspiro[3.3]heptany, 2,6-diazaspiro[3.3]heptany, 1,4-dioxa-8-azaspiro[4.5]decany, 1,4-dioxaspiro[4.5]decany, 1-oxaspiro[4.5]decany, 1-azaspiro[4.5]decany, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, 3-azabicyclo[3.1.0]hexany, 3-azabicyclo[3.1.0]hexan-3-yl, 1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazolyl, 3,4,5,6,7,8-hexahydropyrido[4,3-d]pyrimidinyl, 4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridinyl, 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidinyl, 2-azaspiro[3.3]heptany, 2-methyl-2-azaspiro[3.3]heptany, 2-azaspiro[3.5]nonany, 2-methyl-2-azaspiro[3.5]nonany, 2-azaspiro[4.5]decany, 2-methyl-2-azaspiro[4.5]decany, 2-oxa-

amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl and heteroaryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (*e.g.*, tetralin, methylenedioxyphenyl such as benzo[d][1,3]dioxole-5-yl).

As used herein, the term “substituted,” means that any one or more hydrogen atoms on the designated atom is replaced with a selection from the indicated groups, provided that the designated atom’s normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is oxo or keto (*i.e.*, =O), then 2 hydrogen atoms on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N or N=N). “Stable compound” and “stable structure” are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0057] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such formula. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0058] When any variable (*e.g.*, R) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R moieties, then the group may optionally be substituted with up to two R moieties and R at each occurrence is selected independently from the definition of R. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0059] As used herein, the term “hydroxy” or “hydroxyl” includes groups with an -OH or -O⁻.

[0060] As used herein, the term “halo” or “halogen” refers to fluoro, chloro, bromo and iodo.

[0061] The term “haloalkyl” or “haloalkoxyl” refers to an alkyl or alkoxy substituted with one or more halogen atoms.

[0062] As used herein, the term “optionally substituted haloalkyl” refers to unsubstituted haloalkyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl,

alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0063] As used herein, the term “alkoxy” or “alkoxyl” includes substituted and unsubstituted alkyl, alkenyl and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups or alkoxy radicals include, but are not limited to, methoxy, ethoxy, isopropoxy, propoxy, butoxy and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy and trichloromethoxy.

[0064] As used herein, the expressions “one or more of A, B, or C,” “one or more A, B, or C,” “one or more of A, B, and C,” “one or more A, B, and C,” “selected from the group consisting of A, B, and C,” “selected from A, B, and C,” and the like are used interchangeably and all refer to a selection from a group consisting of A, B, and/or C, *i.e.*, one or more As, one or more Bs, one or more Cs, or any combination thereof, unless indicated otherwise.

[0065] It is to be understood that the present disclosure provides methods for the synthesis of the compounds of any of the Formulae described herein. The present disclosure also provides detailed methods for the synthesis of various disclosed compounds of the present disclosure according to the following schemes as well as those shown in the Examples.

[0066] It is to be understood that, throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated those compositions also consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

[0067] It is to be understood that the synthetic processes of the disclosure can tolerate a wide variety of functional groups, therefore various substituted starting materials can be used. The processes generally provide the desired final compound at or near the end of the overall process, although it may be desirable in certain instances to further convert the compound to a pharmaceutically acceptable salt thereof.

[0068] It is to be understood that compounds of the present disclosure can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled artisan in light of the teachings herein. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as Smith, M. B., March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th edition, John Wiley & Sons: New York, 2001; Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999; R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), incorporated by reference herein, are useful and recognised reference textbooks of organic synthesis known to those in the art.

[0069] One of ordinary skill in the art will note that, during the reaction sequences and synthetic schemes described herein, the order of certain steps may be changed, such as the introduction and removal of protecting groups. One of ordinary skill in the art will recognise that certain groups may require protection from the reaction conditions via the use of protecting groups. Protecting groups may also be used to differentiate similar functional groups in

molecules. A list of protecting groups and how to introduce and remove these groups can be found in Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999.

[0070] It is to be understood that, unless otherwise stated, any description of a method of treatment includes use of the compounds to provide such treatment or prophylaxis as is described herein, as well as use of the compounds to prepare a medicament to treat or prevent such condition. The treatment includes treatment of human or non-human animals including rodents and other disease models.

[0071] As used herein, the term “subject” includes human and non-human animals, as well as cell lines, cell cultures, tissues, and organs. In some embodiments, the subject is a mammal. The mammal can be *e.g.*, a human or appropriate non-human mammal, such as primate, mouse, rat, dog, cat, cow, horse, goat, camel, sheep or a pig. The subject can also be a bird or fowl. In some embodiments, the subject is a human.

[0072] As used herein, the term “subject in need thereof” refers to a subject having a disease or having an increased risk of developing the disease. A subject in need thereof can be one who has been previously diagnosed or identified as having a disease or disorder disclosed herein. A subject in need thereof can also be one who is suffering from a disease or disorder disclosed herein. Alternatively, a subject in need thereof can be one who has an increased risk of developing such disease or disorder relative to the population at large (*i.e.*, a subject who is predisposed to developing such disorder relative to the population at large). A subject in need thereof can have a refractory or resistant a disease or disorder disclosed herein (*i.e.*, a disease or disorder disclosed herein that does not respond or has not yet responded to treatment). The subject may be resistant at start of treatment or may become resistant during treatment. In some embodiments, the subject in need thereof received and failed all known effective therapies for a disease or disorder disclosed herein. In some embodiments, the subject in need thereof received at least one prior therapy.

[0073] As used herein, the term “treating” or “treat” describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder. The term “treat” can also include treatment of a cell *in vitro* or an animal model.

[0074] It is to be understood that a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, can or may also be used to prevent a relevant disease, condition, or disorder, or used to identify suitable candidates for such purposes.

[0075] As used herein, the term “preventing,” “prevent,” or “protecting against” describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

[0076] It is to be understood that one skilled in the art may refer to general reference texts for detailed descriptions of known techniques discussed herein or equivalent techniques. These texts include Ausubel *et al.*, *Current Protocols in Molecular Biology*, John Wiley and Sons, Inc. (2005); Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (3rd edition), Cold Spring Harbor Press, Cold Spring Harbor, New York (2000); Coligan *et al.*, *Current Protocols in Immunology*, John Wiley & Sons, N.Y.; Enna *et al.*, *Current Protocols in Pharmacology*, John Wiley & Sons, N.Y.; Fingl *et al.*, *The Pharmacological Basis of Therapeutics* (1975), *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA, 18th edition (1990). These texts can, of course, also be referred to in making or using an aspect of the disclosure.

[0077] It is to be understood that the present disclosure also provides pharmaceutical compositions comprising any compound described herein in combination with at least one pharmaceutically acceptable excipient or carrier.

[0078] As used herein, the term “pharmaceutical composition” is a formulation containing the compounds of the present disclosure in a form suitable for administration to a subject. In one embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (*e.g.*, a formulation of the disclosed compound or salt, hydrate, solvate or isomer thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, and inhalants. In one embodiment, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that are required.

[0079] As used herein, the term “pharmaceutically acceptable” refers to those compounds, anions, cations, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0080] As used herein, the term “pharmaceutically acceptable excipient” means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A “pharmaceutically acceptable excipient” as used in the specification and claims includes both one and more than one such excipient.

[0081] It is to be understood that a pharmaceutical composition of the disclosure is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, ingestion), inhalation, transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulphite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0082] As used herein, the term “therapeutically effective amount,” refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject’s body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration.

[0083] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities,

and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[0084] The pharmaceutical compositions containing active compounds of the present disclosure may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilising processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[0085] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol and sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0086] The active compounds can be prepared with pharmaceutically acceptable diluents, adjuvants, excipients, or carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl

acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0087] It is to be understood that the pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0088] It is to be understood that, for the compounds of the present disclosure being capable of further forming salts, all of these forms are also contemplated within the scope of the claimed disclosure.

[0089] As used herein, the term “pharmaceutically acceptable salts” refer to derivatives of the compounds of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulphonic, acetic, ascorbic, benzene sulphonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulphonic, 1,2-ethane sulphonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulphonic, maleic, malic, mandelic, methane sulphonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulphamic, sulphanilic, sulphuric, tannic, tartaric, toluene sulphonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0090] In some embodiments, the pharmaceutically acceptable salt is a sodium salt, a potassium salt, a calcium salt, a magnesium salt, a diethylamine salt, a choline salt, a meglumine salt, a benzathine salt, a tromethamine salt, an ammonia salt, an arginine salt, or a lysine salt.

[0091] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulphonic acid, 2-naphthalenesulphonic acid, 4-toluenesulphonic acid, camphorsulphonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ratio other than 1:1, *e.g.*, 3:1, 2:1, 1:2, or 1:3.

[0092] It is to be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[0093] The compounds, or pharmaceutically acceptable salts thereof, are administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally, and parenterally. In one embodiment, the compound is administered orally. One skilled in the art will recognise the advantages of certain routes of administration.

[0094] Techniques for formulation and administration of the disclosed compounds of the disclosure can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In an embodiment, the compounds described herein, and the pharmaceutically acceptable salts thereof, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[0095] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

[0096] In the synthetic schemes described herein, compounds may be drawn with one particular configuration for simplicity. Such particular configurations are not to be construed as limiting the disclosure to one or another isomer, tautomer, regioisomer or stereoisomer, nor does it exclude mixtures of isomers, tautomers, regioisomers or stereoisomers; however, it will be understood that a given isomer, tautomer, regioisomer or stereoisomer may have a higher level of activity than another isomer, tautomer, regioisomer or stereoisomer.

[0097] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow.

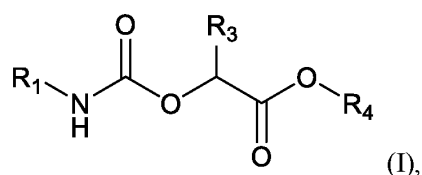
[0098] As used herein, the phrase “compound of the disclosure” refers to those compounds which are disclosed herein, both generically and specifically.

[0099] “Combination therapy” or “combination treatment” refers to the use of two or more drugs or agents in treatment, *e.g.*, the use of a compound of Formula (I), (II), or (III) of the present disclosure together with another agent useful to treat a GLP-1 linked disease or a weight disorders (*e.g.*, a GLP-1 receptor agonist), and symptoms and manifestations of each thereof is a combination therapy. Administration in “combination” refers to the administration of two agents (*e.g.*, a compound of Formula (I), (II), or (III) of the present disclosure, and another agent) in any manner in which the pharmacological effects of both manifest in the subject. Thus, administration in combination does not require that a single pharmaceutical composition, the same dosage form, or even the same route of administration be used for administration of both agents or that the two agents be administered at precisely the same time. Both agents can also be formulated in a single pharmaceutically acceptable composition. In some embodiments, the each agent may be administered in temporal proximity, sequentially, or in alternation.

NLRP3 Inflammasome Inhibitor

[0100] In some embodiments, an NLRP3 inflammasome inhibitor can be used in accordance with the combinations and/or methods described herein.

[0101] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula I:



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

R₁ is C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, C₅-C₁₀ aryl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein the C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, C₅-C₁₀ aryl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl is optionally substituted by one or more R₆;

R₃ is H or C₁-C₄ alkyl optionally substituted with one or more R₇;

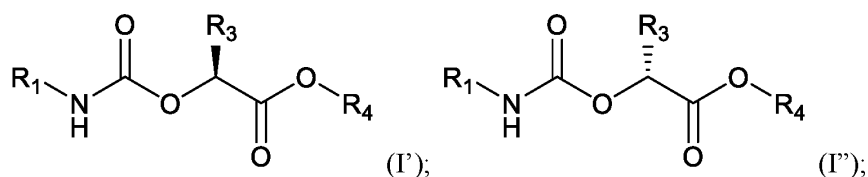
R₄ is H, C₁-C₆ alkyl, -(CH₂)₀₋₃-(C₃-C₆ cycloalkyl), or -(CH₂)₀₋₃-C₅-C₆ aryl;

R₆ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, halo, oxo, -OH, -CN, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃;

R₇ is -OR₈, C₅-C₁₀ aryl, or 5- to 10- membered heteroaryl, wherein the C₅-C₁₀ aryl or 5- to 10-membered heteroaryl is optionally substituted by one or more R_{7S}, wherein each R_{7S} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, 5- to 10-membered heteroaryl, halo, -OH, -CN, -(CH₂)₀₋₃-NH₂, -(CH₂)₀₋₃-NH(C₁-C₆ alkyl), -(CH₂)₀₋₃-N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃; and

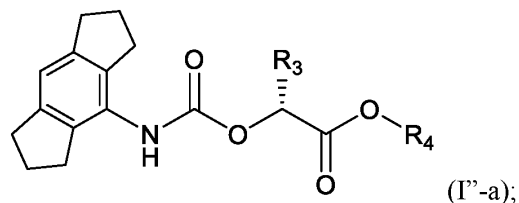
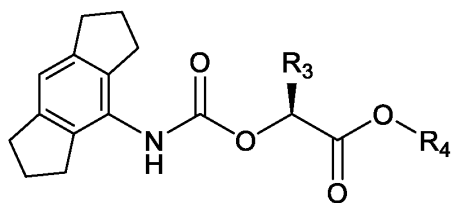
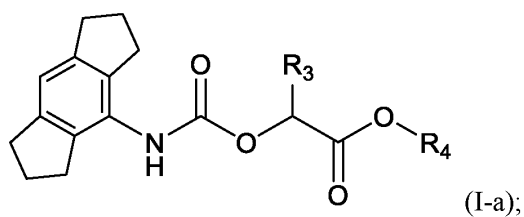
R₈ is C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl, wherein the C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl is optionally substituted by one or more R_{7S}.

[0102] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula (I') or (I''):



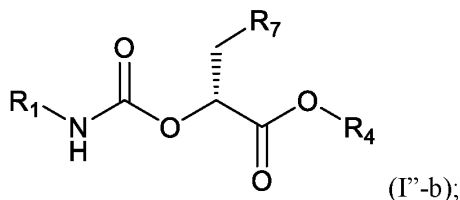
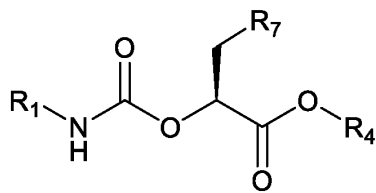
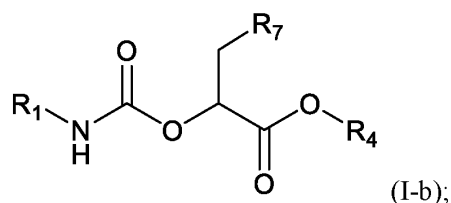
or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein R₁, R₃, and R₄ are as described herein for Formula (I).

[0103] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of any one of Formulae (I-a), (I'-a), and (I''-a):



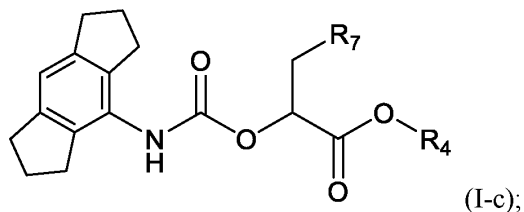
or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein R_3 and R_4 are as described herein for Formula (I).

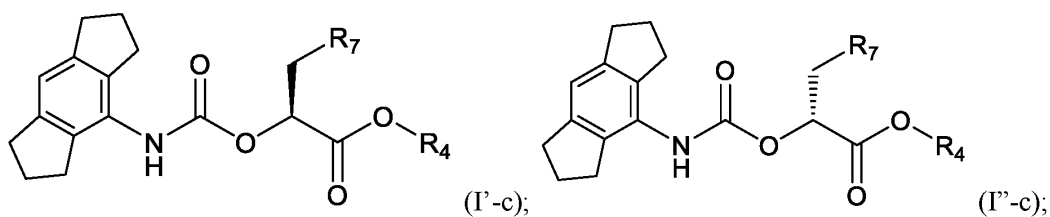
[0104] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of any one of Formulae (I-b), (I'-b), and (I''-b):



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 , R_4 , and R_7 are as described herein for Formula (I).

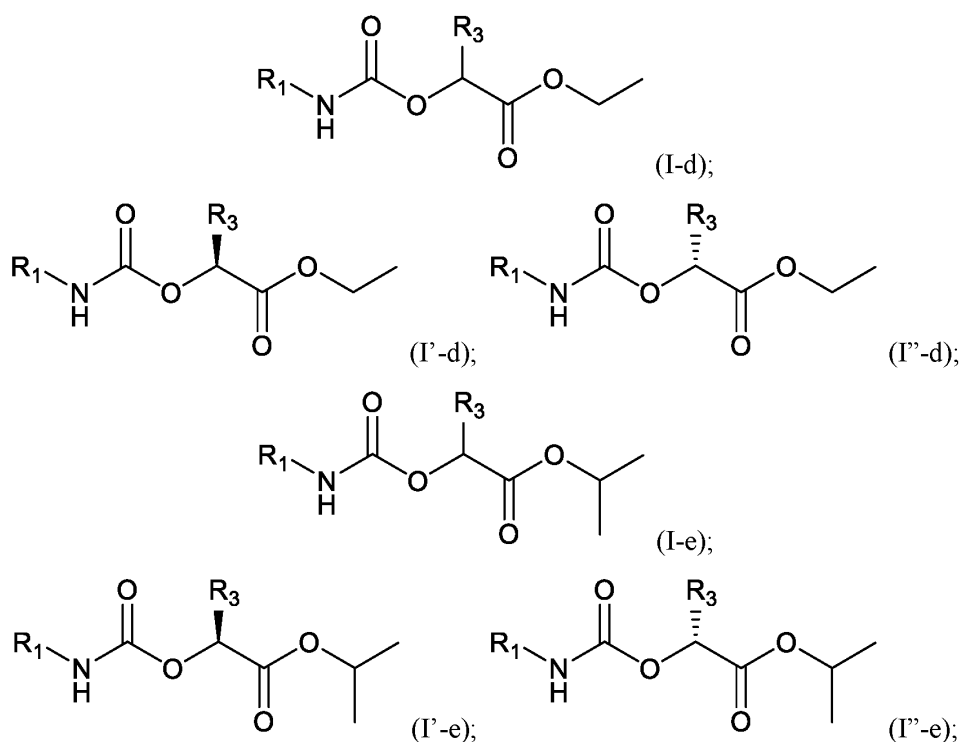
[0105] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of any one of Formulae (I-c), (I'-c), and (I''-c):





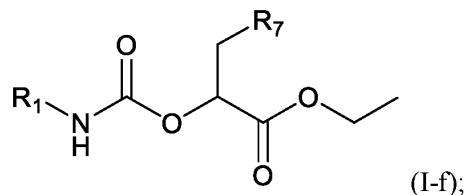
or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein R₄ and R₇ are as described herein for Formula (I).

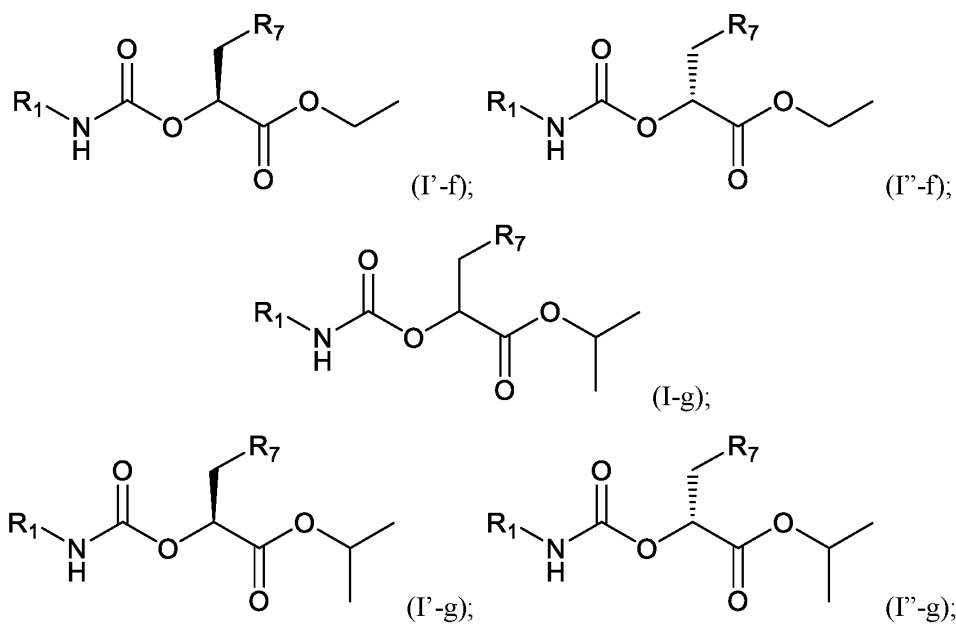
[0106] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of any one of Formulae (I-d), (I'-d), (I''-d), (I-e), (I'-e), and (I''-e):



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein R₁ and R₃ are as described herein for Formula (I).

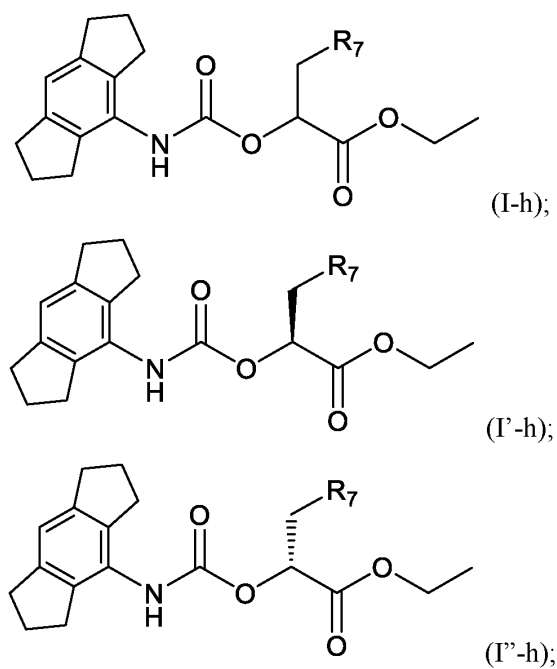
[0107] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of any one of Formulae (I-f), (I'-f), (I''-f), (I-g), (I'-g), and (I''-g):

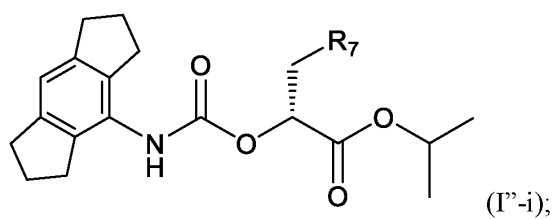
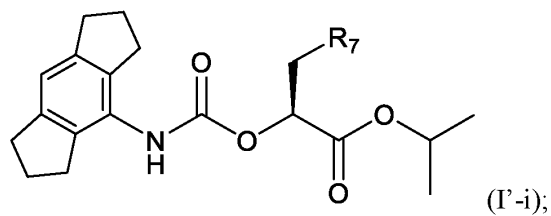
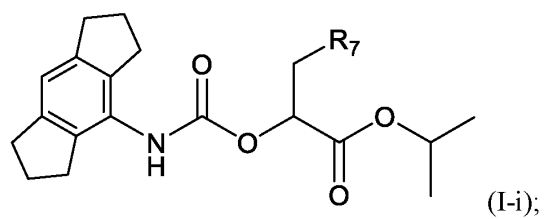




or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 and R_7 are as described herein for Formula (I).

[0108] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of any one of Formulae (I-h), (I'-h), (I''-h), (I-i), (I'-e), and (I''-e):

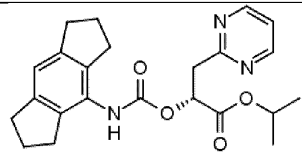
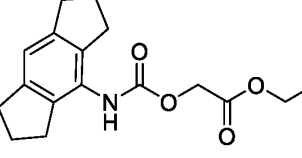
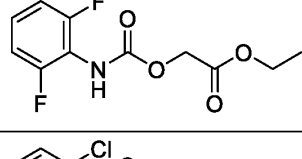
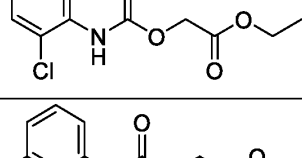
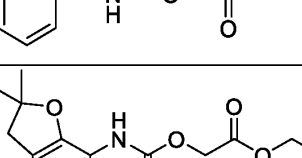
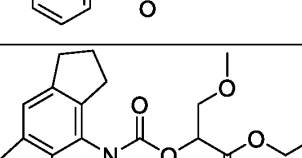
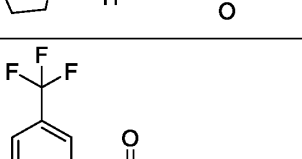
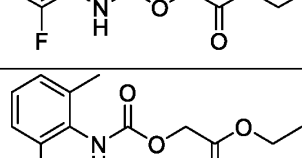
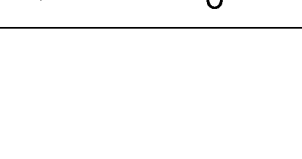


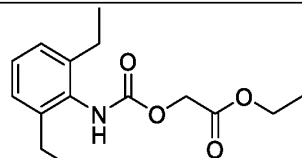
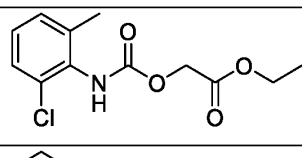
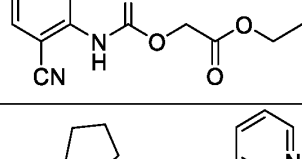
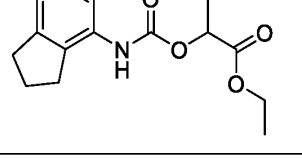
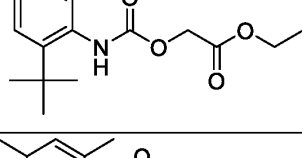
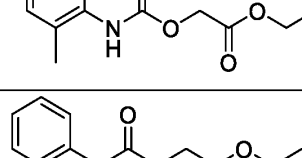
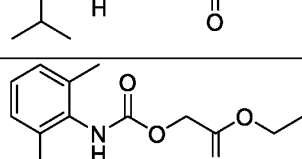
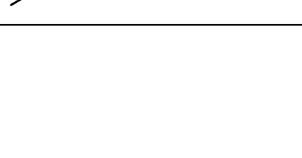


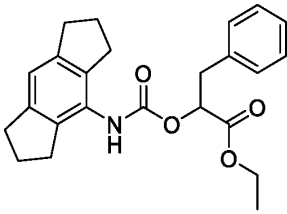
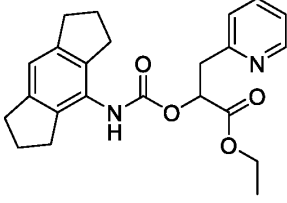
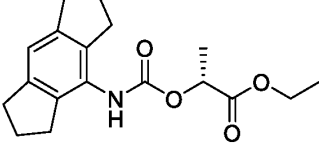
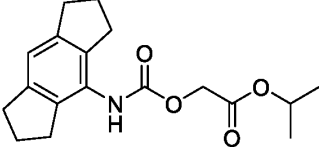
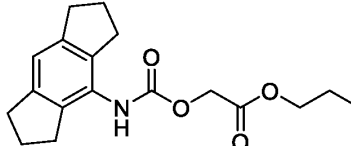
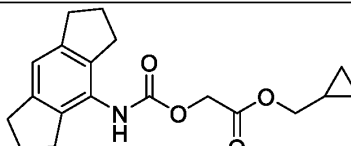
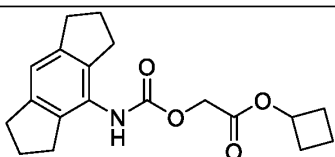
or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein R₇ is as described herein for Formula (I).

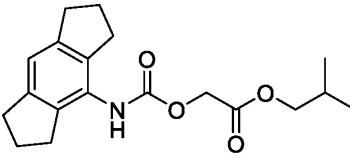
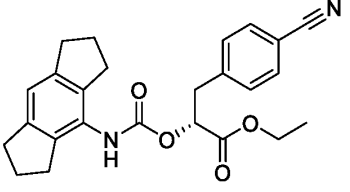
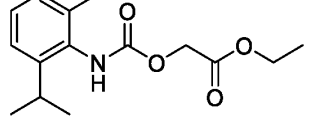
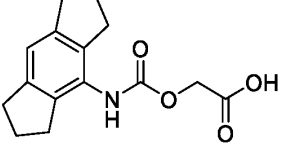
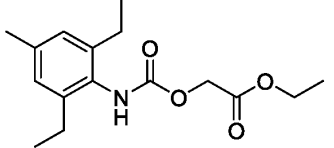
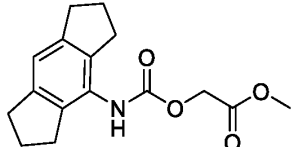
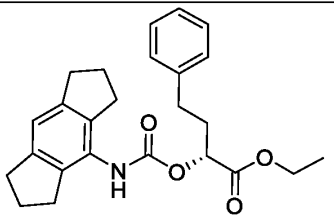
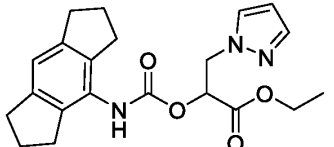
[0109] In some embodiments, the NLRP3 inflammasome inhibitor is selected from Table 1A.

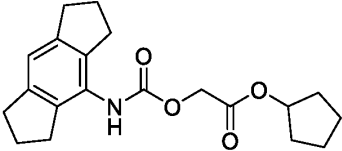
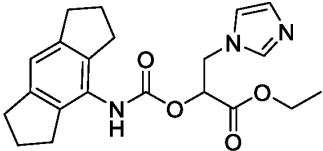
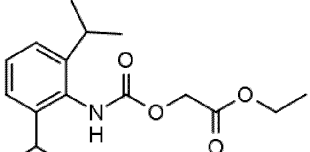
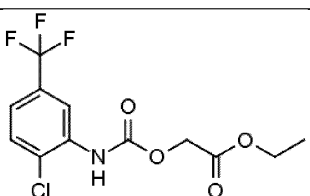
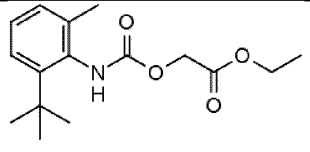
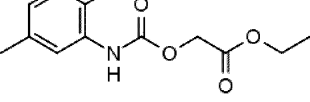
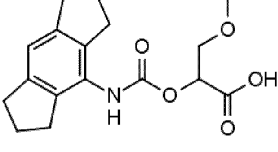
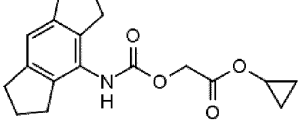
Table 1A

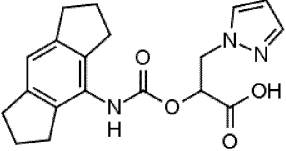
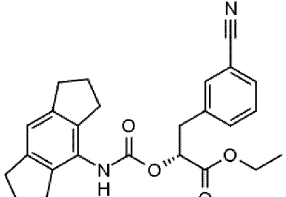
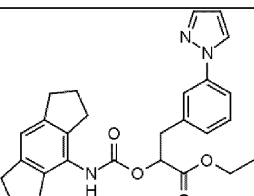
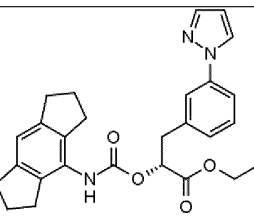
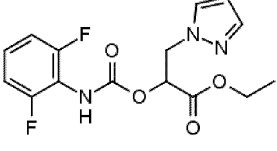
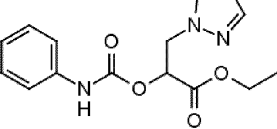
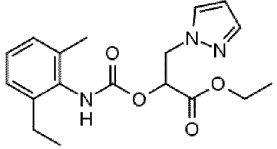
Compound No.	Structure
A1	
A2	
A3	
A4	
A5	
A6	
A7	
A8	
A9	

Compound No.	Structure
A10	
A11	
A12	
A13	
A14	
A15	
A16	
A17	

Compound No.	Structure
A18	
A19	
A20	
A21	
A22	
A23	
A24	

Compound No.	Structure
A25	
A26	
A27	
A28	
A29	
A30	
A31	
A32	

Compound No.	Structure
A33	
A34	
A35	
A36	
A37	
A38	
A39	
A40	

Compound No.	Structure
A41	
A42	
A43	
A44	
A45	
A46	
A47	

Compound No.	Structure
A48	
A49	
A50	
A51	
A52	
A53	
A54	
A55	

Compound No.	Structure
A56	
A57	
A58	
A59	
A60	
A61	
A62	

Compound No.	Structure
A63	
A64	
A65	
A66	
A67	
A68	
A69	
A70	

Compound No.	Structure
A71	
A72	
A73	
A74	
A75	
A76	
A77	

Compound No.	Structure
A78	
A79	
A80	
A81	
A82	
A83	
A84	

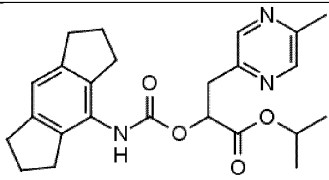
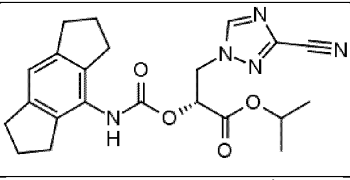
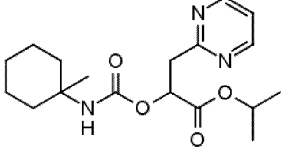
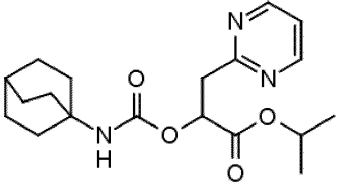
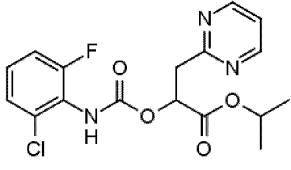
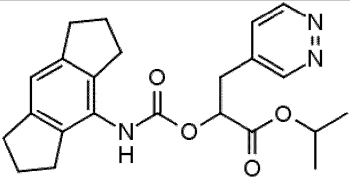
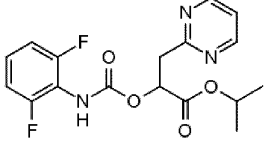
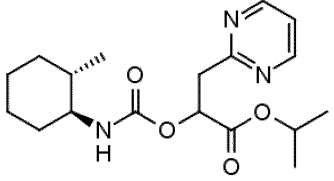
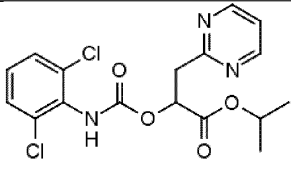
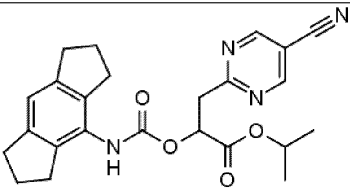
Compound No.	Structure
A85	
A86	
A87	
A88	
A89	
A90	
A91	

Compound No.	Structure
A92	
A93	
A94	
A95	
A96	
A97	
A98	

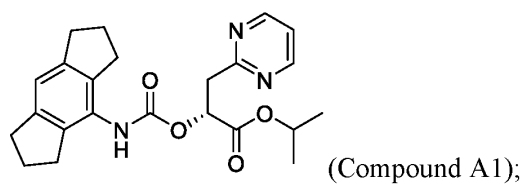
Compound No.	Structure
A99	
A100	
A101	
A102	
A103	
A104	
A105	

Compound No.	Structure
A106	
A107	
A108	
A109	
A110	
A111	
A112	

Compound No.	Structure
A113	
A114	
A115	
A116	
A117	
A118	
A119	
A120	

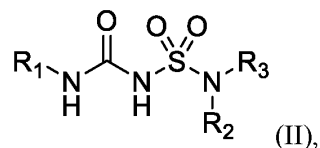
Compound No.	Structure	Compound No.	Structure
A121		A126	
A122		A127	
A123		A128	
A124		A129	
A125		A130	

[0110] In some embodiments, the NLRP3 inflammasome inhibitor is Compound A1:

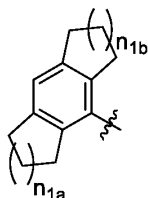


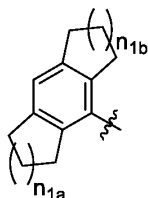
or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0111] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula II:



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:



R_1 is , wherein n_{1a} and n_{1b} each independently are 0 or 1;

R_2 is $-(CH_2)_{n_2}-R_{2S}$, wherein n_2 is 1 or 2;

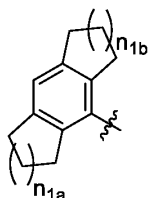
R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more R_{2SS} ;

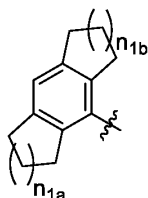
each R_{2SS} independently is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, halo, -CN, -OH, -O(C_1 - C_6 alkyl), -NH₂, -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)₂, or oxo;

R_3 is 5- or 6-membered heteroaryl optionally substituted with one or more R_{3S} ; and

each R_{3S} independently is halo, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl.

[0112] In some aspects, the NLRP3 inflammasome inhibitor is of Formula (II) or pharmaceutically acceptable salt thereof, wherein:



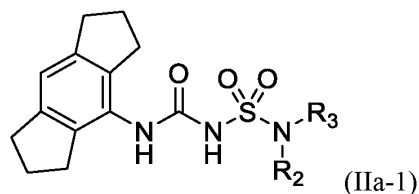
R_1 is , wherein n_{1a} and n_{1b} each independently are 0 or 1;

R_2 is $-(CH_2)_{n_2}-R_{2S}$, wherein n_2 is 1 or 2;

R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more -OH; and

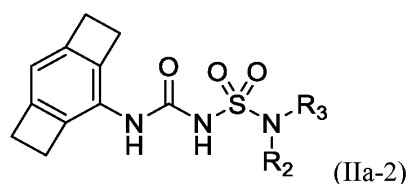
R_3 is 5- or 6-membered heteroaryl optionally substituted with one or more C_1 - C_6 alkyl.

[0113] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula (IIa-1):



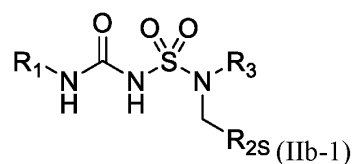
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_2 and R_3 are as described herein for Formula (II).

[0114] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula (IIa-2):



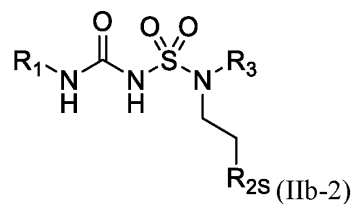
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 , R_2 and R_3 are as described herein for Formula (II).

[0115] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula (IIb-1):



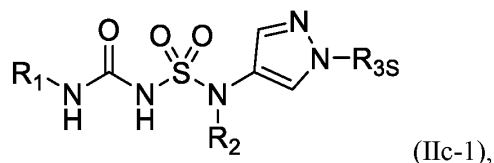
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 , R_{2s} , and R_3 are as described herein for Formula (II).

[0116] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula (IIb-2):



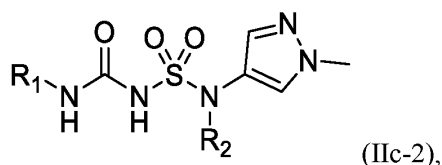
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 , R_{2s} , and R_3 are as described herein for Formula (II).

[0117] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula (IIc-1):



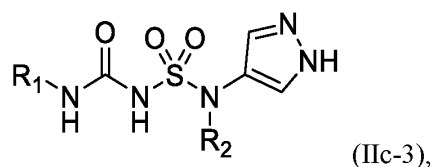
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 , R_2 , and R_{3s} are as described herein for Formula (II).

[0118] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula (IIc-2):



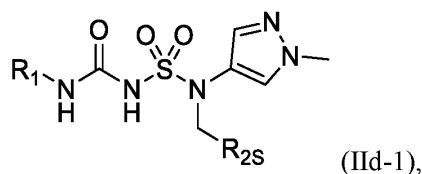
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 and R_2 are as described herein for Formula (II).

[0119] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula (IIc-3):



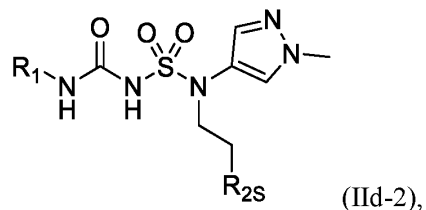
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 and R_2 are as described herein for Formula (II).

[0120] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula (IId-1):



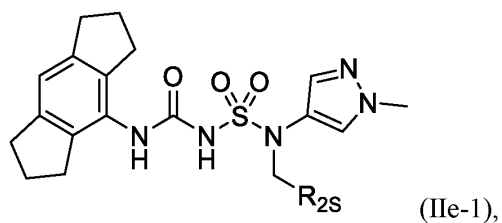
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 and R_{2s} are as described herein for Formula (II).

[0121] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula (IId-2):



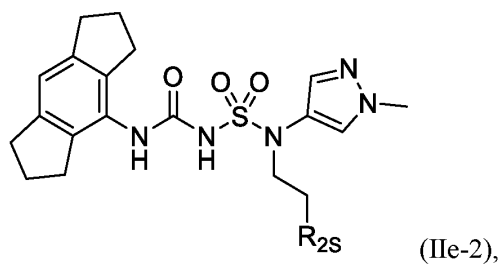
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_1 and R_{2s} are as described herein for Formula (II).

[0122] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula (IIe-1):



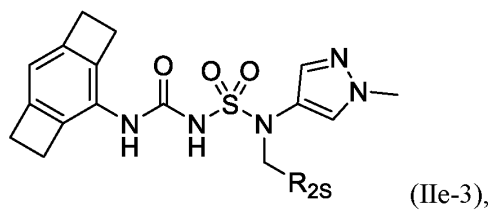
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_{2s} is as described herein for Formula (II).

[0123] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula (IIe-2):



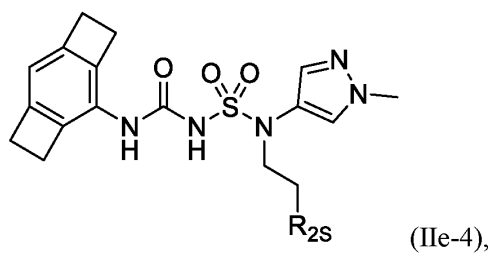
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_{2s} is as described herein for Formula (II).

[0124] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula (IIe-3):



or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_{2S} is as described herein for Formula (II).

[0125] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula (IIe-4):

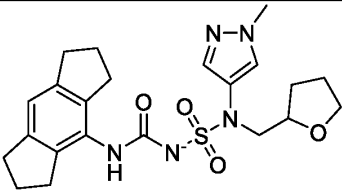
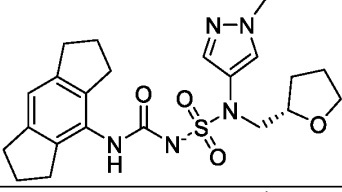
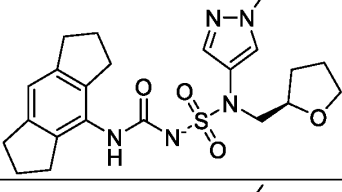
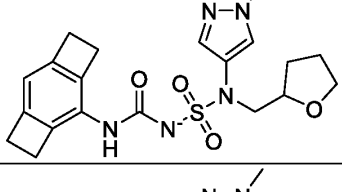
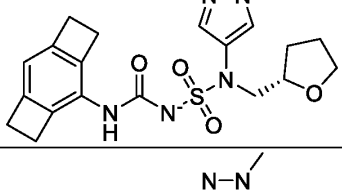
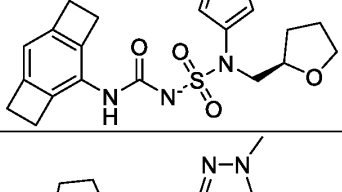
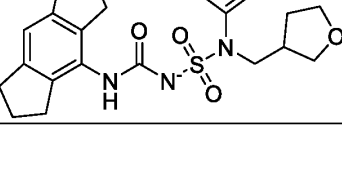


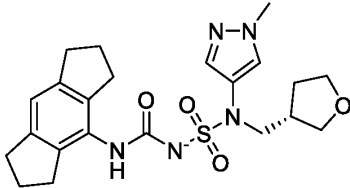
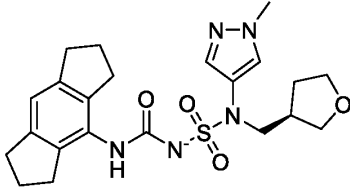
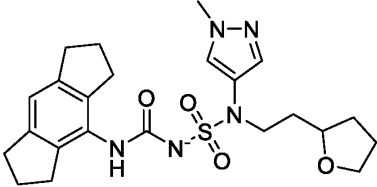
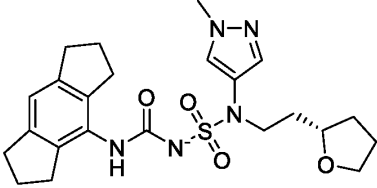
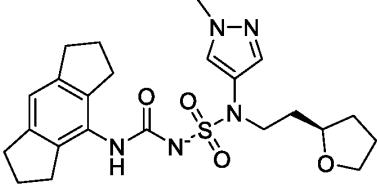
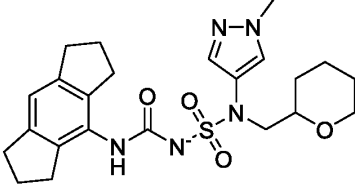
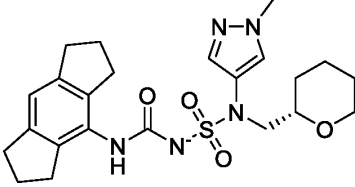
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R_{2S} is as described herein for Formula (II).

[0126] In some embodiments, the NLRP3 inflammasome inhibitor is selected from Table 1B.

Table 1B

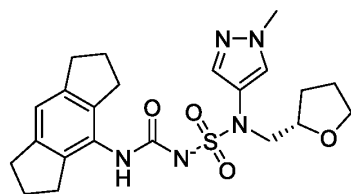
Compound No.	Structure
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B1A	
B1B	

Compound No.	Structure
B2'	
B2	
B2B	
B3	
B3A	
B3B	
B4	

Compound No.	Structure
B4A	
B4B	
B5	
B5A	
B5B	
B6	
B6A	

Compound No.	Structure
B6B	
B7	
B7A	
B7B	
B8	
B8A	
B8B	

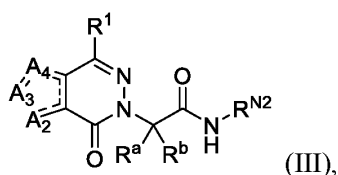
[0127] In some embodiments, the NLRP3 inflammasome inhibitor is Compound B2:



(Compound B2);

or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0128] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula (III):



(III),

or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

each  is independently a single bond or double bond as valency permits;

A₂ is CR², N, NR^{2a}, O, or S, as valency allows;

A₃ is CR², N, NR^{2a}, O, or S, as valency allows;

A₄ is CR², N, NR^{2a}, O, or S, as valency allows,

wherein at least one of A₂, A₃, or A₄ is N, NR^{2a}, O, or S, provided that when A₂ is S, A₄ is CR², NR^{2a}, O, or S;

R¹ is H, -N(C₁-C₆ alkyl)₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₃-C₁₂ cycloalkyl, wherein the -N(C₁-C₆ alkyl)₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₃-C₁₂ cycloalkyl is optionally substituted with one or more R^{1S};

each R^{1S} independently is halogen, cyano, -OH, or C₁-C₆ alkyl;

each R² independently is H, halogen, cyano, -OH, -NH₂, -NO₂, -C(=O)NH₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{2S},

or two R² together with the atoms to which they are attached form a C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl, wherein the C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{2S};

each R^{2S} independently is halogen, -OH, -O(C₁-C₆ alkyl), -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, or C₃-C₁₂ cycloalkyl;

each R^{2a} independently is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, -(CH₂)₀₋₃-(C₃-C₁₂ cycloalkyl), or -(CH₂)₀₋₃-(3- to 12-membered heterocycloalkyl);

each R^a independently is H or C₁-C₆ alkyl; or two R^a, together with the atom they attach to, form C₃-C₁₂ cycloalkyl;

R^{N2} is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2a},

each R^{N2a} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2ab}, and

each R^{N2ab} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), or -S(=O)₂N(C₁-C₆ alkyl)₂.

[0129] In some embodiments, the NLRP3 inflammasome inhibitor is a compound of Formula (III), wherein:

each  is independently a single bond or double bond as valency permits;

A₂ is CR², N, NR^{2a}, O, or S, as valency allows;

A₃ is CR², N, NR^{2a}, O, or S, as valency allows;

A₄ is CR², N, NR^{2a}, O, or S, as valency allows,

wherein at least one of A₂, A₃, or A₄ is N, NR^{2a}, O, or S, wherein when A₂ is S, A₄ is CR², NR^{2a}, O, or S;

R¹ is H, -N(C₁-C₆ alkyl)₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₃-C₁₂ cycloalkyl, wherein the -N(C₁-C₆ alkyl)₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₃-C₁₂ cycloalkyl is optionally substituted with one or more R^{1S};

each R^{1S} independently is halogen, cyano, -OH, or C₁-C₆ alkyl;

each R² independently is H, halogen, cyano, -OH, -NH₂, -NO₂, -C(=O)NH₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{2S},

or two R₂ together with the atoms to which they are attached form a C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl, wherein the C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{2S};

each R^{2S} independently is halogen, -OH, -O(C₁-C₆ alkyl), -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, or C₃-C₁₂ cycloalkyl;

each R^{2a} independently is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, -(CH₂)₀₋₃-C₃-C₁₂ cycloalkyl, or -(CH₂)₀₋₃-(3- to 12-membered heterocycloalkyl);

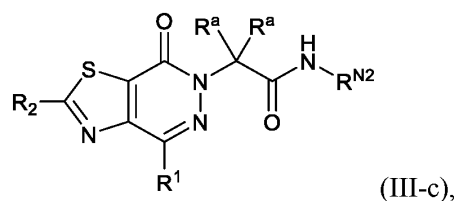
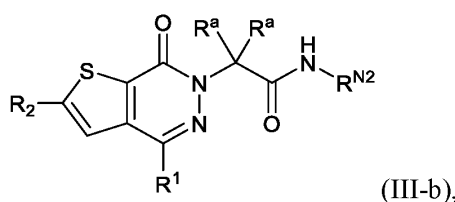
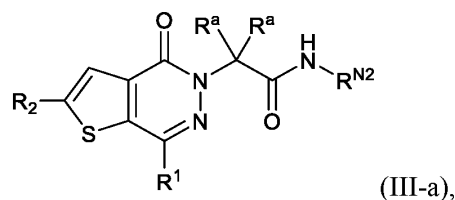
each R^a independently is H or C₁-C₆ alkyl; or two R^a, together with the atom they attach to, form C₃-C₁₂ cycloalkyl;

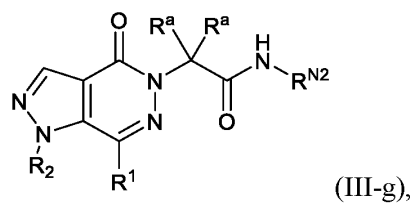
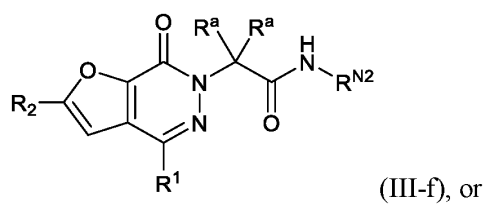
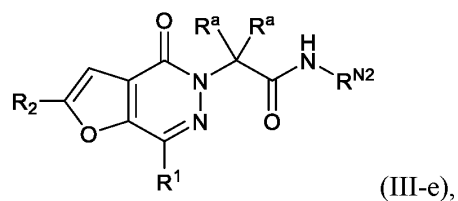
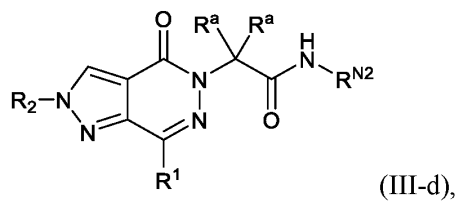
R^{N2} is C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl; wherein the C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{N2a};

each R^{N2a} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2ab} ; and

each R^{N2ab} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), or -S(=O)₂N(C₁-C₆ alkyl)₂.

[0130] In some embodiments, the NLRP3 inflammasome inhibitor is selected from a compound of Formula (III-a), (III-b), (III-c), (III-d), (III-e), (III-f), or (III-g):





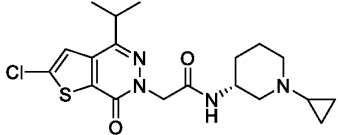
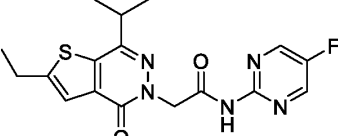
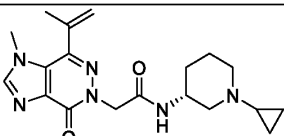
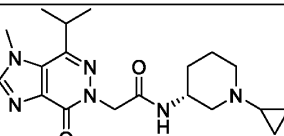
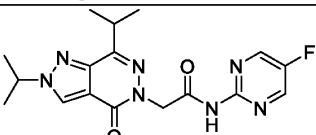
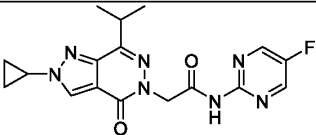
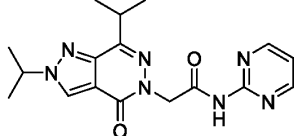
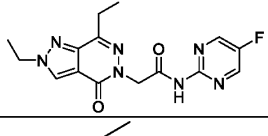
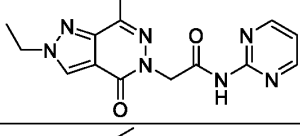
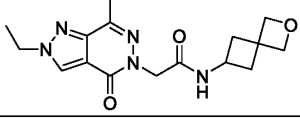
or a prodrug, solvate, or pharmaceutically acceptable salt thereof, wherein R^1 , R_2 , R^a , and R^{N2} are as described herein for Formula (III).

[0131] In some embodiments, the NLRP3 inflammasome inhibitor is selected from Table 1C.

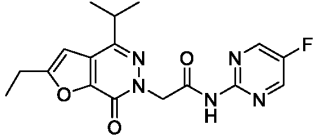
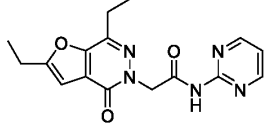
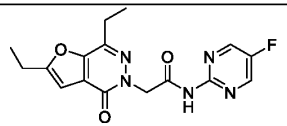
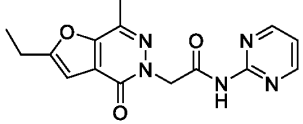
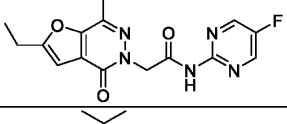
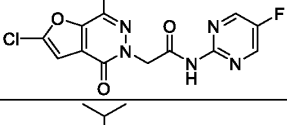
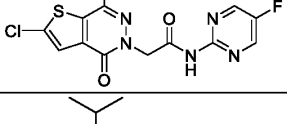
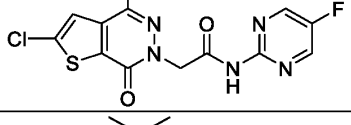
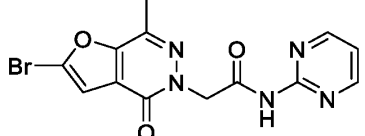
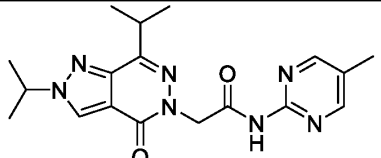
Table 1C

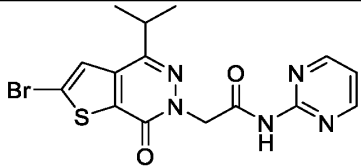
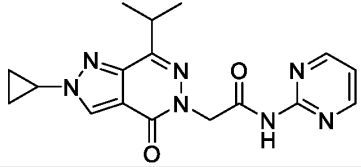
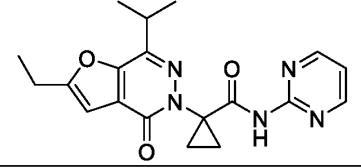
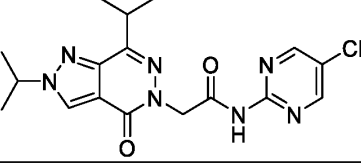
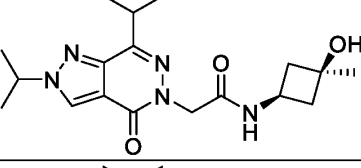
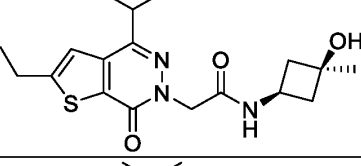
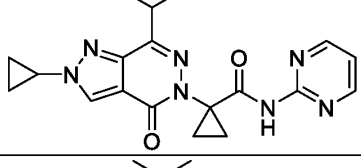
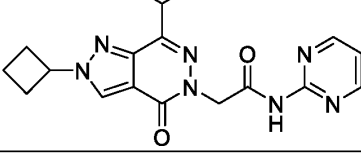
Compound No	Structure
C1	
C2	

Compound No	Structure
C3	
C4	
C5	
C6	
C7	
C8	
C9	
C10	
C11	

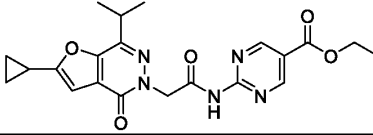
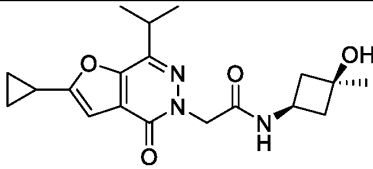
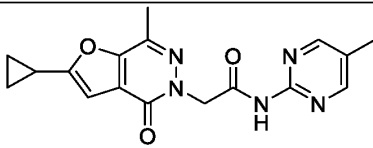
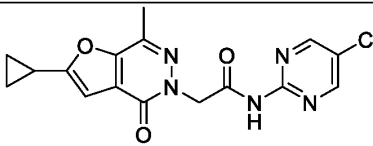
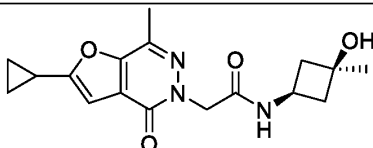
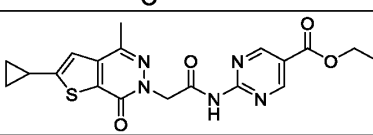
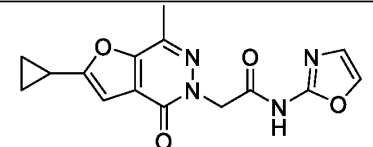
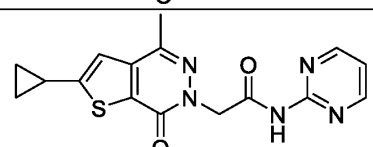
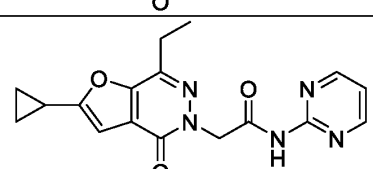
Compound No	Structure
C12	
C13	
C14	
C15	
C16	
C17	
C18	
C19	
C20	
C21	

Compound No	Structure
C22	
C23	
C24	
C25	
C26	
C27	
C28	
C29	
C30	
C31	

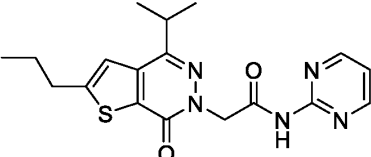
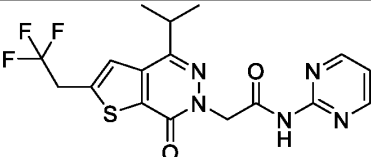
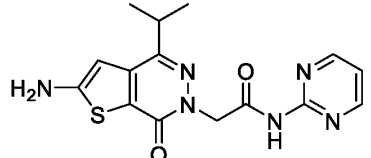
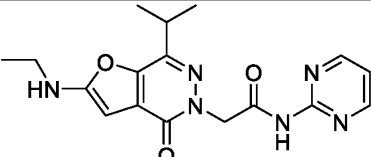
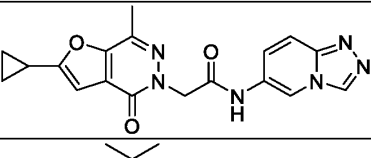
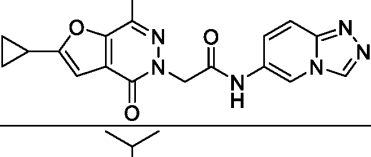
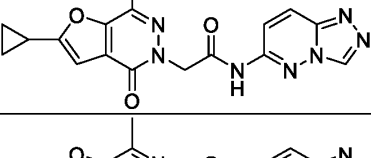
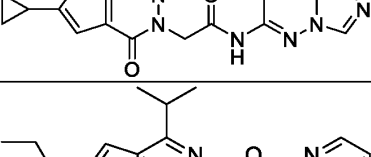
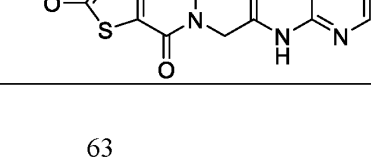
Compound No	Structure
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C33	
C34	
C35	
C36	
C37	
C38	
C39	
C40	
C41	

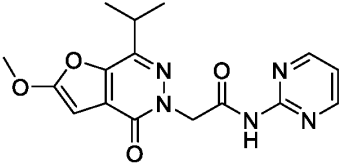
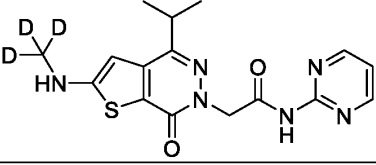
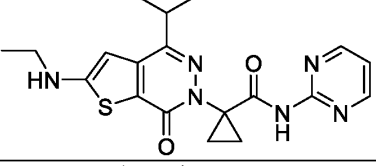
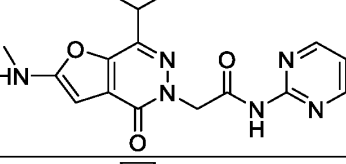
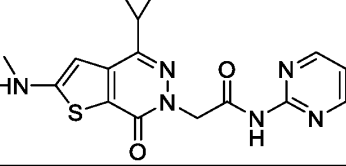
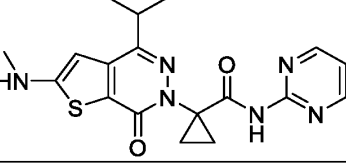
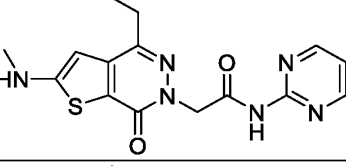
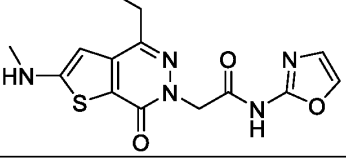
Compound No	Structure
C42	
C43	
C44	
C45	
C46	
C47	
C48	
C49	

Compound No	Structure
C50	
C51	
C52	
C53	
C54	
C55	
C56	
C57	

Compound No	Structure
C58	
C59	
C60	
C61	
C62	
C63	
C64	
C65	
C66	

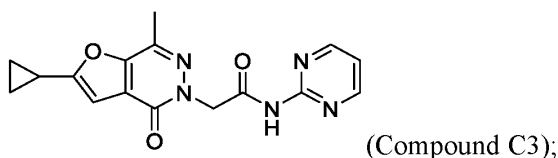
Compound No	Structure
C67	
C68	
C69	
C70	
C71	
C72	
C73	
C74	
C75	

Compound No	Structure
C76	
C77	
C78	
C79	
C80	
C81	
C82	
C83	
C84	

Compound No	Structure
C85	
C86	
C87	
C88	
C89	
C90	
C91	
C92	

Compound No	Structure
C93	
C94	
C95	
C96	
C97	

[0132] In some embodiments, the NLRP3 inflammasome inhibitor is Compound C3:



or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

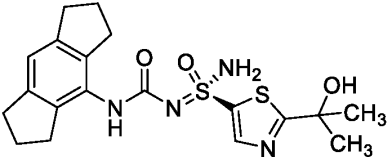
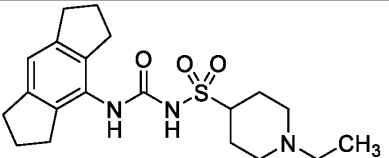
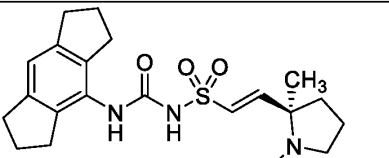
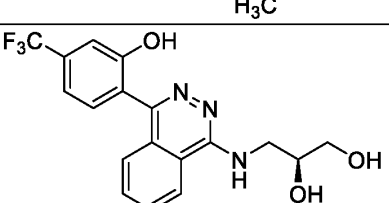
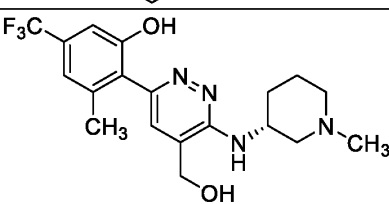
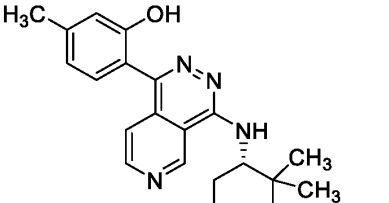
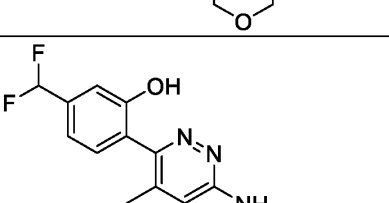
[0133] In some embodiments, the NLRP3 inflammasome inhibitor is selected from the compounds disclosed in: US 2023/250070; WO 2020/254697; WO 2021/255279; WO 2023/118521; EP 4129986; WO 2021/193897; WO 2022/230912; WO 2023/003002; WO 2023/275366; US 2023/0051130; WO 2022/204227; WO 2023/147468; WO 2021/093820; WO 2022/237780; WO 2022/237781; WO 2022/237782; WO 2023/137885; WO 2022/006433; WO 2022/035204; WO 2022/109268; WO 2022/232632; WO 2023/044043; WO 2023/192390; WO 2023/288039; WO

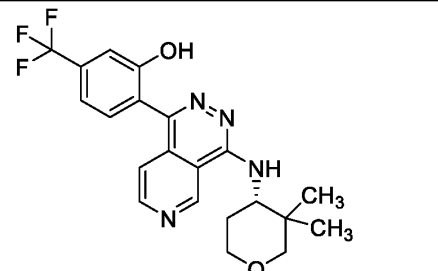
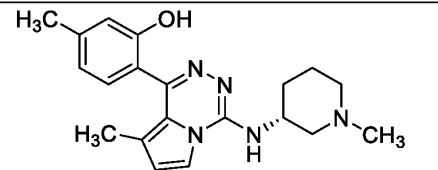
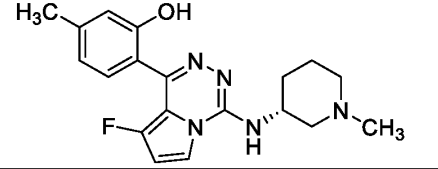
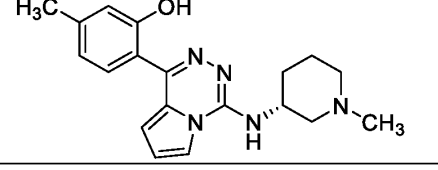
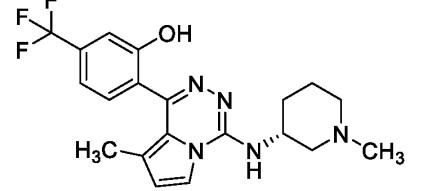
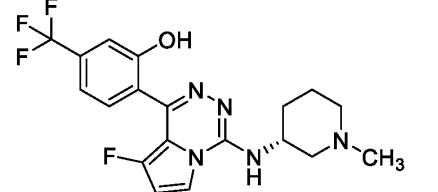
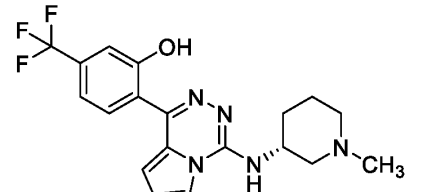
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[0134] In some embodiments, the NLRP3 inflammasome inhibitor is selected from Table 1D.

Table 1D

Compound No	Structure
D1	
D2	
D3	
D4	
D5	
D6	
D7	

D8	
D9	
D10	
D11	
D12	
D13	
D14	

GLP-1 Receptor Agonist

[0135] In some embodiments, the GLP-1 receptor agonist that can be used in accordance with the combinations and/or methods described herein may be an agonists of more than one target.

[0136] In some embodiments, the GLP-1 receptor agonist is a dual agonist (*e.g.*, targeting GLP-1 and GIP).

[0137] In some embodiments, the GLP-1 receptor agonist is a triple agonist (*e.g.*, targeting GLP-1, GIP, and glucagon).

[0138] In some embodiments, the GLP-1 receptor agonist targets, at least, GLP-1.

[0139] In some embodiments, the GLP-1 receptor agonist is selected from Table 2.

[0140] In some embodiments, the GLP-1 receptor agonist is semaglutide, or a pharmaceutically acceptable salt thereof.

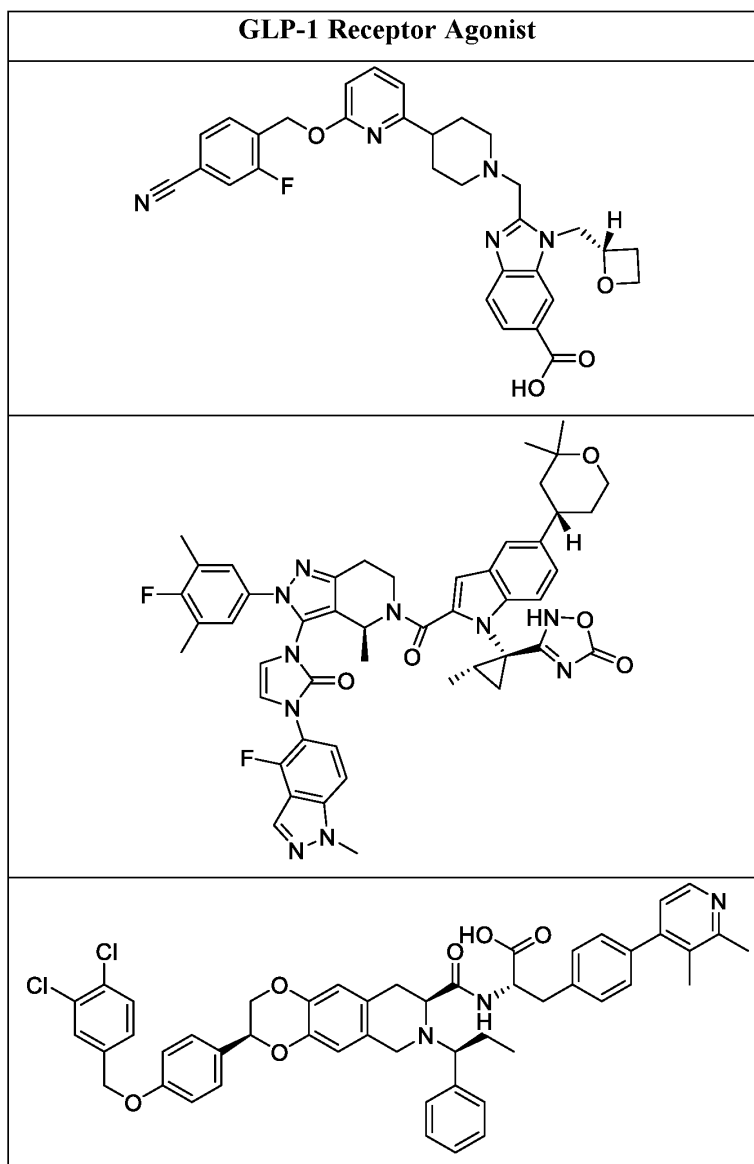
[0141] In some embodiments, the GLP-1 receptor agonist is semaglutide.

Table 2

GLP-1 Receptor Agonist
Albiglutide
Danuglipron
Dulaglutide
Exenatide
Liraglutide
Lixisenatide
Semaglutide
Taspoglutide
Tirzepatide
Cotadutide
Retatrutide
Orforglipron
Lotiglopron

[0142] In some embodiments, the GLP-1 receptor agonist is selected from Table 3.

Table 3



Compositions

[0143] In some aspects, composition or pharmaceutical compositions are disclosed herein.

[0144] In some embodiments, the present disclosure provides a pharmaceutical compositions comprising an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt thereof (e.g.,

an NLRP3 inflammasome inhibitor of Formula (I), (II), or (III)), a GLP-1 receptor agonist, and a pharmaceutically acceptable carrier, diluent, adjuvant, or excipient.

Methods of Use

[0145] In some aspects, the present disclosure provides an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, for use in combination for treating or preventing a GLP-1 linked disease and/or a weight disorder in a subject.

[0146] In some aspects, the present disclosure provides an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, for use in combination for treating or preventing a GLP-1 linked disease and/or a weight disorder in a subject;

wherein the GLP-1 linked disease or the weight disorder is selected from cardiovascular disease or disorder (*e.g.*, angina pectoris, coronary heart disease, ischemic heart disease, myocardial infarction, reperfusion injury, heart disease, heart failure, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), right ventricular diastolic dysfunction, coronary microvascular dysfunction, aortic valve disease, cardiovascular risk reduction, major adverse cardiac events (MACE)), metabolism disorder (*e.g.*, type I diabetes, type II diabetes, glucose intolerance, hyperglucagonemia, hyperglycemia, metabolic syndrome, insulin resistance), bone disease (*e.g.*, osteoporosis, bone metabolism, osteoarthritis), renal disease (*e.g.*, chronic kidney disease, chronic renal insufficiency, diabetic nephropathy, fibrosis), hepatic disease (*e.g.*, alcoholic fatty liver disease (AFLD), alcohol related steatohepatitis (ASH), nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), nonalcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), fibrosis), gastrointestinal disease or disorder (*e.g.*, motility disorders, inflammatory bowel disease), central nervous system (CNS) disease or disorder (*e.g.*, neurodegenerative diseases such as cognition, Parkinson's disease, or Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, depression, anxiety, schizophrenia, stroke, traumatic brain injury), skin disease (*e.g.*, psoriasis), muscle disease (*e.g.*, sarcopenia), lung disease (*e.g.*, cystic fibrosis, interstitial lung disease, idiopathic pulmonary fibrosis), and others (*e.g.*, polycystic ovary syndrome (PCOS),

fibrosis, addiction (*e.g.*, drug addiction or alcohol addiction), smoking cessation, binge eating disorder, post bariatric surgery treatment, multiple sclerosis, obstructive sleep apnea (OSA), rheumatoid arthritis, neuropathic pain).

[0147] In some aspects, the present disclosure provides an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, for use in combination for treating or preventing a weight disorder in a subject.

[0148] In some aspects, the present disclosure provides Compound A1, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, for use in combination for treating or preventing a weight disorder in a subject. In some aspects, the present disclosure provides Compound B2, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, for use in combination for treating or preventing a weight disorder in a subject.

[0149] In some aspects, the present disclosure provides Compound C3, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, for use in combination for treating or preventing a weight disorder in a subject.

[0150] In some aspects, the present disclosure provides an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide, for use in combination for treating or preventing a GLP-1 linked disease and/or a weight disorder in a subject.

[0151] In some aspects, the present disclosure provides an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide, for use in combination for treating or preventing a GLP-1 linked disease and/or a weight disorder in a subject;

wherein the GLP-1 linked disease or the weight disorder is selected from cardiovascular disease or disorder (*e.g.*, angina pectoris, coronary heart disease, ischemic heart disease, myocardial infarction, reperfusion injury, heart disease, heart failure, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), right ventricular diastolic dysfunction, coronary microvascular dysfunction, aortic valve disease, cardiovascular risk reduction, major adverse cardiac events (MACE)), metabolism disorder (*e.g.*, type I diabetes,

type II diabetes, glucose intolerance, hyperglucagonemia, hyperglycemia, metabolic syndrome, insulin resistance), bone disease (*e.g.*, osteoporosis, bone metabolism, osteoarthritis), renal disease (*e.g.*, chronic kidney disease, chronic renal insufficiency, diabetic nephropathy, fibrosis), hepatic disease (*e.g.*, alcoholic fatty liver disease (AFLD), alcohol related steatohepatitis (ASH), nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), nonalcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), fibrosis), gastrointestinal disease or disorder (*e.g.*, motility disorders, inflammatory bowel disease), central nervous system (CNS) disease or disorder (*e.g.*, neurodegenerative diseases such as cognition, Parkinson's disease, or Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, depression, anxiety, schizophrenia, stroke, traumatic brain injury), skin disease (*e.g.*, psoriasis), muscle disease (*e.g.*, sarcopenia), lung disease (*e.g.*, cystic fibrosis, interstitial lung disease, idiopathic pulmonary fibrosis), and others (*e.g.*, polycystic ovary syndrome (PCOS), fibrosis, addiction (*e.g.*, drug addiction or alcohol addiction), smoking cessation, binge eating disorder, post bariatric surgery treatment, multiple sclerosis, obstructive sleep apnea (OSA), rheumatoid arthritis, neuropathic pain).

[0152] In some aspects, the present disclosure provides an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide, for use in combination for treating or preventing a weight disorder in a subject.

[0153] In some aspects, the present disclosure provides Compound A1, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide for use in combination for treating or preventing a weight disorder in a subject.

[0154] In some aspects, the present disclosure provides Compound B2, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide for use in combination for treating or preventing a weight disorder in a subject.

[0155] In some aspects, the present disclosure provides Compound C3, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide for use in combination for treating or preventing a weight disorder in a subject.

[0156] In some aspects, the present disclosure provides a method of treating or preventing a GLP-1 linked disease and/or a weight disorder, comprising administering to a subject:

(a) an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and

(b) a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0157] In some aspects, the present disclosure provides a method of treating or preventing a GLP-1 linked disease and/or a weight disorder, comprising administering to a subject:

(a) an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and

(b) a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof;

wherein the GLP-1 linked disease and/or the weight disorder is selected from cardiovascular disease or disorder (*e.g.*, angina pectoris, coronary heart disease, ischemic heart disease, myocardial infarction, reperfusion injury, heart disease, heart failure, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), right ventricular diastolic dysfunction, coronary microvascular dysfunction, aortic valve disease, cardiovascular risk reduction, major adverse cardiac events (MACE)), metabolism disorder (*e.g.*, type I diabetes, type II diabetes, glucose intolerance, hyperglucagonemia, hyperglycemia, metabolic syndrome, insulin resistance), bone disease (*e.g.*, osteoporosis, bone metabolism, osteoarthritis), renal disease (*e.g.*, chronic kidney disease, chronic renal insufficiency, diabetic nephropathy, fibrosis), hepatic disease (*e.g.*, alcoholic fatty liver disease (AFLD), alcohol related steatohepatitis (ASH), nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), nonalcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), fibrosis), gastrointestinal disease or disorder (*e.g.*, motility disorders, inflammatory bowel disease), central nervous system (CNS) disease or disorder (*e.g.*, neurodegenerative diseases such as cognition, Parkinson's disease, or Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, depression, anxiety, schizophrenia, stroke, traumatic brain injury), skin disease (*e.g.*, psoriasis), muscle disease (*e.g.*, sarcopenia), lung disease (*e.g.*, cystic fibrosis, interstitial lung disease, idiopathic pulmonary fibrosis), and others (*e.g.*, polycystic ovary syndrome (PCOS), fibrosis, addiction (*e.g.*, drug addiction or alcohol addiction), smoking cessation, binge eating disorder, post bariatric surgery treatment, multiple sclerosis, obstructive sleep apnea (OSA), rheumatoid arthritis, neuropathic pain).

[0158] In some aspects, the present disclosure provides a method of treating or preventing a weight disorder, comprising administering to a subject:

(a) an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and

(b) a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0159] In some aspects, the present disclosure provides a method of treating or preventing a weight disorder, comprising administering to a subject:

(a) Compound A1, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and

(b) a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0160] In some aspects, the present disclosure provides a method of treating or preventing a weight disorder, comprising administering to a subject:

(a) Compound B2, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and

(b) a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0161] In some aspects, the present disclosure provides a method of treating or preventing a weight disorder, comprising administering to a subject:

(a) Compound C3, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and

(b) a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0162] In some aspects, the present disclosure provides a method of treating or preventing a weight disorder, comprising administering to a subject:

(a) an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and

(b) semaglutide.

[0163] In some aspects, the present disclosure provides a method of treating or preventing a weight disorder, comprising administering to a subject:

- (a) Compound A1, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and
- (b) semaglutide.

[0164] In some aspects, the present disclosure provides a method of treating or preventing a weight disorder, comprising administering to a subject:

- (a) Compound B2, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and
- (b) semaglutide.

[0165] In some aspects, the present disclosure provides a method of treating or preventing a weight disorder, comprising administering to a subject:

- (a) Compound C3, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and
- (b) semaglutide.

[0166] In some aspects, the present disclosure provides an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for a combinatorial therapy for the treatment or prevention of a GLP-1 linked disease and/or a weight disorder in a subject.

[0167] In some aspects, the present disclosure provides an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for a combinatorial therapy for the treatment or prevention of a GLP-1 linked disease and/or a weight disorder;

wherein the GLP-1 linked disease and/or the weight disorder is selected from cardiovascular disease or disorder (*e.g.*, angina pectoris, coronary heart disease, ischemic heart disease, myocardial infarction, reperfusion injury, heart disease, heart failure, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), right ventricular diastolic dysfunction, coronary microvascular dysfunction, aortic valve disease, cardiovascular risk reduction, major adverse cardiac events (MACE)), metabolism disorder (*e.g.*,

type I diabetes, type II diabetes, glucose intolerance, hyperglucagonemia, hyperglycemia, metabolic syndrome, insulin resistance), bone disease (*e.g.*, osteoporosis, bone metabolism, osteoarthritis), renal disease (*e.g.*, chronic kidney disease, chronic renal insufficiency, diabetic nephropathy, fibrosis), hepatic disease (*e.g.*, alcoholic fatty liver disease (AFLD), alcohol related steatohepatitis (ASH), nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), nonalcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), fibrosis), gastrointestinal disease or disorder (*e.g.*, motility disorders, inflammatory bowel disease), central nervous system (CNS) disease or disorder (*e.g.*, neurodegenerative diseases such as cognition, Parkinson's disease, or Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, depression, anxiety, schizophrenia, stroke, traumatic brain injury), skin disease (*e.g.*, psoriasis), muscle disease (*e.g.*, sarcopenia), lung disease (*e.g.*, cystic fibrosis, interstitial lung disease, idiopathic pulmonary fibrosis), and others (*e.g.*, polycystic ovary syndrome (PCOS), fibrosis, addiction (*e.g.*, drug addiction or alcohol addiction), smoking cessation, binge eating disorder, post bariatric surgery treatment, multiple sclerosis, obstructive sleep apnea (OSA), rheumatoid arthritis, neuropathic pain).

[0168] In some aspects, the present disclosure provides an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for a combinatorial therapy for the treatment or prevention of a weight disorder in a subject.

[0169] In some aspects, the present disclosure provides Compound A1, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for a combinatorial therapy for the treatment or prevention of a weight disorder in a subject.

[0170] In some aspects, the present disclosure provides Compound B2, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a

medicament for a combinatorial therapy for the treatment or prevention of a weight disorder in a subject.

[0171] In some aspects, the present disclosure provides Compound C3, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for a combinatorial therapy for the treatment or prevention of a weight disorder in a subject.

[0172] In some aspects, the present disclosure provides an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide in the manufacture of a medicament for a combinatorial therapy for the treatment or prevention of a weight disorder in a subject.

[0173] In some aspects, the present disclosure provides Compound A1, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide in the manufacture of a medicament for a combinatorial therapy for the treatment or prevention of a weight disorder in a subject.

[0174] In some aspects, the present disclosure provides Compound B2, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide in the manufacture of a medicament for a combinatorial therapy for the treatment or prevention of a weight disorder in a subject.

[0175] In some aspects, the present disclosure provides Compound C3, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide in the manufacture of a medicament for a combinatorial therapy for the treatment or prevention of a weight disorder in a subject.

[0176] In some aspects, the present disclosure provides use of an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for the treatment or prevention of a weight disorder in a subject.

[0177] In some aspects, the present disclosure provides use of Compound A1, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with a GLP-

1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for the treatment or prevention of a weight disorder in a subject.

[0178] In some aspects, the present disclosure provides use of Compound B2, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for the treatment or prevention of a weight disorder in a subject.

[0179] In some aspects, the present disclosure provides use of Compound C3, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for the treatment or prevention of a weight disorder in a subject.

[0180] In some aspects, the present disclosure provides use of an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for the treatment or prevention of a GLP-1 linked disease and/or a weight disorder in a subject.

[0181] In some aspects, the present disclosure provides use of an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for the treatment or prevention of a GLP-1 linked disease and/or a weight disorder;

wherein the GLP-1 linked disease and/or the weight disorder is selected from cardiovascular disease or disorder (*e.g.*, angina pectoris, coronary heart disease, ischemic heart disease, myocardial infarction, reperfusion injury, heart disease, heart failure, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), right ventricular diastolic dysfunction, coronary microvascular dysfunction, aortic valve disease, cardiovascular risk reduction, major adverse cardiac events (MACE)), metabolism disorder (*e.g.*, type I diabetes, type II diabetes, glucose intolerance, hyperglucagonemia, hyperglycemia, metabolic syndrome, insulin resistance), bone disease (*e.g.*, osteoporosis, bone metabolism, osteoarthritis), renal disease (*e.g.*, chronic kidney disease, chronic renal insufficiency, diabetic nephropathy, fibrosis), hepatic disease (*e.g.*, alcoholic fatty liver disease (AFLD), alcohol related steatohepatitis (ASH), nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-

associated fatty liver disease (MAFLD), nonalcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), fibrosis), gastrointestinal disease or disorder (*e.g.*, motility disorders, inflammatory bowel disease), central nervous system (CNS) disease or disorder (*e.g.*, neurodegenerative diseases such as cognition, Parkinson's disease, or Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, depression, anxiety, schizophrenia, stroke, traumatic brain injury), skin disease (*e.g.*, psoriasis), muscle disease (*e.g.*, sarcopenia), lung disease (*e.g.*, cystic fibrosis, interstitial lung disease, idiopathic pulmonary fibrosis), and others (*e.g.*, polycystic ovary syndrome (PCOS), fibrosis, addiction (*e.g.*, drug addiction or alcohol addiction), smoking cessation, binge eating disorder, post bariatric surgery treatment, multiple sclerosis, obstructive sleep apnea (OSA), rheumatoid arthritis, neuropathic pain).

[0182] In some aspects, the present disclosure provides use of an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with semaglutide in the manufacture of a medicament for the treatment or prevention of a weight disorder in a subject.

[0183] In some aspects, the present disclosure provides use of Compound A1, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with semaglutide in the manufacture of a medicament for the treatment or prevention of a weight disorder in a subject.

[0184] In some aspects, the present disclosure provides use of Compound B2, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with semaglutide in the manufacture of a medicament for the treatment or prevention of a weight disorder in a subject.

[0185] In some aspects, the present disclosure provides use of Compound C3, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with semaglutide in the manufacture of a medicament for the treatment or prevention of a weight disorder in a subject.

[0186] In some aspects, the present disclosure provides a kit comprising an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0187] In some aspects, the present disclosure provides a kit comprising Compound A1, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0188] In some aspects, the present disclosure provides a kit comprising Compound B2, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0189] In some aspects, the present disclosure provides a kit comprising Compound C3, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0190] In some aspects, the present disclosure provides a kit comprising an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide.

[0191] In some aspects, the present disclosure provides a kit comprising Compound A1, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide.

[0192] In some aspects, the present disclosure provides a kit comprising Compound B2, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide.

[0193] In some aspects, the present disclosure provides a kit comprising Compound C3, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide.

[0194] In some aspects, the present disclosure provides a pharmaceutical package comprising an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0195] In some aspects, the present disclosure provides a pharmaceutical package comprising Compound A1, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0196] In some aspects, the present disclosure provides a pharmaceutical package comprising Compound B2, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0197] In some aspects, the present disclosure provides a pharmaceutical package comprising Compound C3, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0198] In some aspects, the present disclosure provides a pharmaceutical package comprising an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide.

[0199] In some aspects, the present disclosure provides a pharmaceutical package comprising Compound A1, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide.

[0200] In some aspects, the present disclosure provides a pharmaceutical package comprising Compound B2, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide.

[0201] In some aspects, the present disclosure provides a pharmaceutical package comprising Compound C3, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and semaglutide.

[0202] In some embodiments, the kit or pharmaceutical package further comprises instructions for use.

[0203] In some embodiments, after treatment of the combination of NLRP3 inflammasome inhibitor and GLP-1 receptor agonist for about 7 days, about 14 days, about 28 days, or about 35 days, the NLRP3 inflammasome inhibitor is administered as a monotherapy.

[0204] In some embodiments, after treatment of the combination of NLRP3 inflammasome inhibitor and GLP-1 receptor agonist for about 7 days, the NLRP3 inflammasome inhibitor is administered as a monotherapy.

[0205] In some embodiments, after treatment of the combination of NLRP3 inflammasome inhibitor and GLP-1 receptor agonist for about 14 days, the NLRP3 inflammasome inhibitor is administered as a monotherapy.

[0206] In some embodiments, after treatment of the combination of NLRP3 inflammasome inhibitor and GLP-1 receptor agonist for about 28 days, the NLRP3 inflammasome inhibitor is administered as a monotherapy.

[0207] In some embodiments, after treatment of the combination of NLRP3 inflammasome inhibitor and GLP-1 receptor agonist for about 35 days, the NLRP3 inflammasome inhibitor is administered as a monotherapy.

[0208] In some embodiments, the NLRP3 inflammasome inhibitor is administered as a monotherapy after treatment of the combination of NLRP3 inflammasome inhibitor and GLP-1 receptor agonist for 7 days.

[0209] In some embodiments, the NLRP3 inflammasome inhibitor is administered as a monotherapy after treatment of the combination of NLRP3 inflammasome inhibitor and GLP-1 receptor agonist for 14 days.

[0210] In some embodiments, the NLRP3 inflammasome inhibitor is administered as a monotherapy after treatment of the combination of NLRP3 inflammasome inhibitor and GLP-1 receptor agonist for 28 days.

[0211] In some embodiments, the NLRP3 inflammasome inhibitor is administered as a monotherapy after treatment of the combination of NLRP3 inflammasome inhibitor and GLP-1 receptor agonist for 35 days.

[0212] In some embodiments, the weight disorder is selected from a metabolic disorder, obesity, excessive body weight, and enhanced appetite.

[0213] In some embodiments, the weight disorder is a metabolic disorder.

[0214] In some embodiments, the weight disorder is obesity.

[0215] In some embodiments, the weight disorder is excessive body weight.

[0216] In some embodiments, the weight disorder is enhanced appetite.

[0217] In some embodiments, the GLP-1 linked disease and/or the weight disorder is selected from cardiovascular disease or disorder (*e.g.*, angina pectoris, coronary heart disease, ischemic heart disease, myocardial infarction, reperfusion injury, heart disease, heart failure, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), right ventricular diastolic dysfunction, coronary microvascular dysfunction, aortic valve disease, cardiovascular risk reduction, major adverse cardiac events (MACE)), metabolism disorder (*e.g.*, type I diabetes, type II diabetes, glucose intolerance, hyperglucagonemia, hyperglycemia, metabolic syndrome, insulin resistance), bone disease (*e.g.*, osteoporosis, bone metabolism, osteoarthritis), renal disease (*e.g.*, chronic kidney disease, chronic renal insufficiency, diabetic nephropathy, fibrosis), hepatic disease (*e.g.*, alcoholic fatty liver disease (AFLD), alcohol related steatohepatitis (ASH), nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), nonalcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), fibrosis), gastrointestinal disease or disorder (*e.g.*,

motility disorders, inflammatory bowel disease), central nervous system (CNS) disease or disorder (*e.g.*, neurodegenerative diseases such as cognition, Parkinson's disease, or Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, depression, anxiety, schizophrenia, stroke, traumatic brain injury), skin disease (*e.g.*, psoriasis), muscle disease (*e.g.*, sarcopenia), lung disease (*e.g.*, cystic fibrosis, interstitial lung disease, idiopathic pulmonary fibrosis), and others (*e.g.*, polycystic ovary syndrome (PCOS), fibrosis, addiction (*e.g.*, drug addiction or alcohol addiction), smoking cessation, binge eating disorder, post bariatric surgery treatment, multiple sclerosis, obstructive sleep apnea (OSA), rheumatoid arthritis, neuropathic pain).

[0218] In some embodiments, the GLP-1 linked disease and/or the weight disorder is a cardiovascular disease or disorder.

[0219] In some embodiments, the cardiovascular disease or disorder is selected from angina pectoris, coronary heart disease, ischemic heart disease, myocardial infarction, reperfusion injury, heart disease, heart failure, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), right ventricular diastolic dysfunction, coronary microvascular dysfunction, aortic valve disease, cardiovascular risk reduction, and major adverse cardiac events (MACE).

[0220] In some embodiments, the GLP-1 linked disease and/or the weight disorder is a metabolism disorder.

[0221] In some embodiments, the metabolism disorder is selected from type I diabetes, type II diabetes, glucose intolerance, hyperglucagonemia, hyperglycemia, metabolic syndrome, and insulin resistance.

[0222] In some embodiments, the GLP-1 linked disease and/or the weight disorder is a bone disease.

[0223] In some embodiments, the bone disease is selected from osteoporosis, bone metabolism, and osteoarthritis.

[0224] In some embodiments, the GLP-1 linked disease and/or the weight disorder is a renal disease.

[0225] In some embodiments, the renal disease is selected from chronic kidney disease, chronic renal insufficiency, diabetic nephropathy, and fibrosis.

[0226] In some embodiments, the GLP-1 linked disease and/or the weight disorder is a hepatic disease.

[0227] In some embodiments, the hepatic disease is selected from alcoholic fatty liver disease (AFLD), alcohol related steatohepatitis (ASH), nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), nonalcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), and fibrosis.

[0228] In some embodiments, the GLP-1 linked disease and/or the weight disorder is a gastrointestinal disease or disorder.

[0229] In some embodiments, the gastrointestinal disease or disorder is selected from motility disorders and inflammatory bowel disease.

[0230] In some embodiments, the GLP-1 linked disease and/or the weight disorder is a central nervous system (CNS) disease or disorder.

[0231] In some embodiments, the central nervous system (CNS) disease or disorder is selected from neurodegenerative diseases such as cognition, Parkinson's disease, or Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, depression, anxiety, schizophrenia, stroke, and traumatic brain injury.

[0232] In some embodiments, the GLP-1 linked disease and/or the weight disorder is a skin disease.

[0233] In some embodiments, the skin disease is psoriasis.

[0234] In some embodiments, the GLP-1 linked disease and/or the weight disorder is a muscle disease.

[0235] In some embodiments, the muscle disease is sarcopenia.

[0236] In some embodiments, the GLP-1 linked disease and/or the weight disorder is a lung disease.

[0237] In some embodiments, the lung disease is selected from cystic fibrosis, interstitial lung disease, and idiopathic pulmonary fibrosis.

[0238] In some embodiments, the GLP-1 linked disease and/or the weight disorder is selected from polycystic ovary syndrome (PCOS), fibrosis, addiction (*e.g.*, drug addiction or alcohol addiction), smoking cessation, binge eating disorder, post bariatric surgery treatment, multiple sclerosis, obstructive sleep apnea (OSA), rheumatoid arthritis, and neuropathic pain.

[0239] In some embodiments, the subject is a human.

[0240] In some embodiments, the NLRP3 inflammasome inhibitor and GLP-1 receptor agonist are administered in temporal proximity, sequentially, or in alternation.

[0241] In some embodiments, the NLRP3 inflammasome inhibitor and GLP-1 receptor agonist are administered in temporal proximity.

[0242] In some embodiments, the NLRP3 inflammasome inhibitor and GLP-1 receptor agonist are administered sequentially.

[0243] In some embodiments, the NLRP3 inflammasome inhibitor and GLP-1 receptor agonist are administered in alternation.

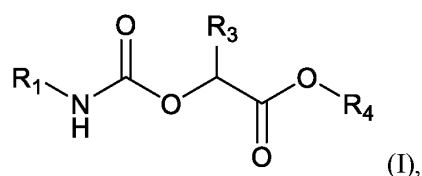
[0244] In some embodiments, the NLRP3 inflammasome inhibitor and GLP-1 receptor agonist are administered as different formulations.

EXEMPLARY EMBODIMENTS

[0245] Embodiment 1. An NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, for use in combination for treating or preventing a GLP-1 linked disease and/or a weight disorder in a subject.

[0246] Embodiment 2. An NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, for use in combination for treating or preventing a weight disorder in a subject.

[0247] Embodiment 3. The NLRP3 inflammasome inhibitor of Embodiment 1 or Embodiment 2, wherein the NLRP3 inflammasome inhibitor is a compound of Formula I, Formula II, or Formula III:



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

R₁ is C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, C₅-C₁₀ aryl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein the C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl is optionally substituted by one or more R₆;

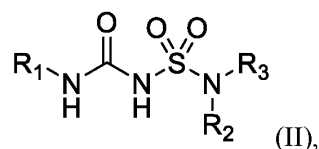
R₃ is H or C₁-C₄ alkyl optionally substituted with one or more R₇;

R₄ is H, C₁-C₆ alkyl, -(CH₂)₀₋₃-(C₃-C₆ cycloalkyl), or -(CH₂)₀₋₃-C₅-C₆ aryl;

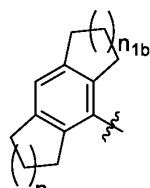
R₆ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, halo, oxo, -OH, -CN, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃;

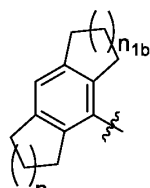
R₇ is -OR₈, C₅-C₁₀ aryl, or 5- to 10- membered heteroaryl, wherein the C₅-C₁₀ aryl or 5- to 10-membered heteroaryl is optionally substituted by one or more R_{7S}, wherein each R_{7S} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, 5- to 10-membered heteroaryl, halo, -OH, -CN, -(CH₂)₀₋₃-NH₂, -(CH₂)₀₋₃-NH(C₁-C₆ alkyl), -(CH₂)₀₋₃-N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃; and

R₈ is C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl, wherein the C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl is optionally substituted by one or more R_{7S}; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:



R₁ is , wherein n_{1a} and n_{1b} each independently are 0 or 1;

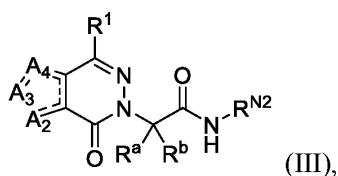
R₂ is -(CH₂)_{n2}-R_{2S}, wherein n₂ is 1 or 2;

R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more R_{2SS};

each R_{2SS} independently is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, halo, -CN, -OH, -O(C₁-C₆ alkyl), -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, or oxo;

R₃ is 5- or 6-membered heteroaryl optionally substituted with one or more R_{3S}; and

each R_{3S} independently is halo, C₁-C₆ alkyl, or C₁-C₆ haloalkyl; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

each  is independently a single bond or double bond as valency permits;

A₂ is CR², N, NR^{2a}, O, or S, as valency allows;

A₃ is CR², N, NR^{2a}, O, or S, as valency allows;

A₄ is CR², N, NR^{2a}, O, or S, as valency allows,

wherein at least one of A₂, A₃, or A₄ is N, NR^{2a}, O, or S, provided that when A₂ is S, A₄ is CR², NR^{2a}, O, or S;

R¹ is H, -N(C₁-C₆ alkyl)₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₃-C₁₂ cycloalkyl, wherein the -N(C₁-C₆ alkyl)₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₃-C₁₂ cycloalkyl is optionally substituted with one or more R^{1S};

each R^{1S} independently is halogen, cyano, -OH, or C₁-C₆ alkyl;

each R² independently is H, halogen, cyano, -OH, -NH₂, -NO₂, -C(=O)NH₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{2S},

or two R² together with the atoms to which they are attached form a C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl, wherein the C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{2S};

each R^{2S} independently is halogen, -OH, -O(C₁-C₆ alkyl), -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, or C₃-C₁₂ cycloalkyl;

each R^{2a} independently is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, -(CH₂)₀₋₃-(C₃-C₁₂ cycloalkyl), or -(CH₂)₀₋₃-(3- to 12-membered heterocycloalkyl);

each R^a independently is H or C₁-C₆ alkyl; or two R^a, together with the atom they attach to, form C₃-C₁₂ cycloalkyl;

R^{N2} is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-

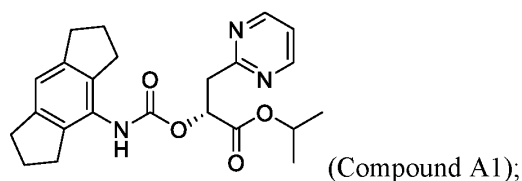
C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2a},

each R^{N2a} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2ab}; and

each R^{N2ab} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), or -S(=O)₂N(C₁-C₆ alkyl)₂.

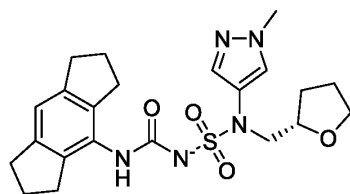
[0248] Embodiment 4. The NLRP3 inflammasome inhibitor of any one of Embodiments 1-3, wherein the NLRP3 inflammasome inhibitor is selected from Table 1A, Table 1B, or Table 1C.

[0249] Embodiment 5. The NLRP3 inflammasome inhibitor of any one of Embodiments 1-4, wherein the NLRP3 inflammasome inhibitor is Compound A1:



or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

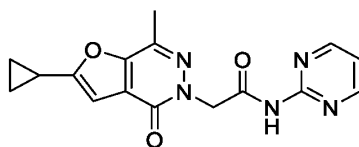
[0250] Embodiment 6. The NLRP3 inflammasome inhibitor of any one of Embodiments 1-4, wherein the NLRP3 inflammasome inhibitor is Compound B2:



(Compound B2);

or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0251] Embodiment 7. The NLRP3 inflammasome inhibitor of any one of Embodiments 1-4, wherein the NLRP3 inflammasome inhibitor is Compound C3:



(Compound C3);

or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0252] Embodiment 8. The GLP-1 receptor agonist of any one of the preceding Embodiments, wherein the GLP-1 receptor agonist is selected from Table 2.

[0253] Embodiment 9. The GLP-1 receptor agonist of any one of the preceding Embodiments, wherein the GLP-1 receptor agonist is semaglutide.

[0254] Embodiment 10. A method of treating or preventing a GLP-1 linked disease and/or a weight disorder, comprising administering to a subject:

(a) an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and

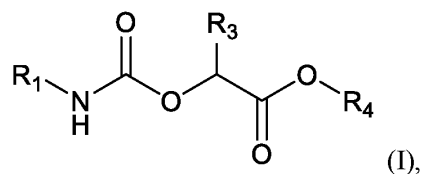
(b) a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0255] Embodiment 11. A method of treating or preventing a weight disorder, comprising administering to a subject:

(a) an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and

(b) a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0256] Embodiment 12. The method of Embodiment 10 or Embodiment 11, wherein the NLRP3 inflammasome inhibitor is a compound of Formula I, Formula II, or Formula III:



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

R₁ is C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, C₅-C₁₀ aryl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein the C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl is optionally substituted by one or more R₆;

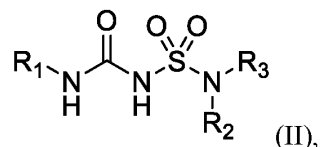
R₃ is H or C₁-C₄ alkyl optionally substituted with one or more R₇;

R₄ is H, C₁-C₆ alkyl, -(CH₂)₀₋₃-(C₃-C₆ cycloalkyl), or -(CH₂)₀₋₃-C₅-C₆ aryl;

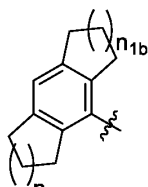
R₆ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, halo, oxo, -OH, -CN, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃;

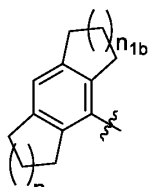
R₇ is -OR₈, C₅-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₅-C₁₀ aryl or 5- to 10-membered heteroaryl is optionally substituted by one or more R_{7S}, wherein each R_{7S} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, 5- to 10-membered heteroaryl, halo, -OH, -CN, -(CH₂)₀₋₃-NH₂, -(CH₂)₀₋₃-NH(C₁-C₆ alkyl), -(CH₂)₀₋₃-N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃; and

R₈ is C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl, wherein the C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl is optionally substituted by one or more R_{7S}; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:



R₁ is , wherein n_{1a} and n_{1b} each independently are 0 or 1;

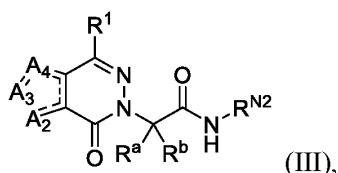
R₂ is -(CH₂)_{n2}-R_{2S}, wherein n₂ is 1 or 2;

R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more R_{2SS};

each R_{2SS} independently is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, halo, -CN, -OH, -O(C_1 - C_6 alkyl), -NH₂, -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)₂, or oxo;

R_3 is 5- or 6-membered heteroaryl optionally substituted with one or more R_{3S} ; and

each R_{3S} independently is halo, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

each is independently a single bond or double bond as valency permits;

A_2 is CR^2 , N, NR^{2a} , O, or S, as valency allows;

A_3 is CR^2 , N, NR^{2a} , O, or S, as valency allows;

A_4 is CR^2 , N, NR^{2a} , O, or S, as valency allows,

wherein at least one of A_2 , A_3 , or A_4 is N, NR^{2a} , O, or S, provided that when A_2 is S, A_4 is CR^2 , NR^{2a} , O, or S;

R^1 is H, -N(C_1 - C_6 alkyl)₂, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_3 - C_{12} cycloalkyl, wherein the -N(C_1 - C_6 alkyl)₂, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_3 - C_{12} cycloalkyl is optionally substituted with one or more R^{1S} ;

each R^{1S} independently is halogen, cyano, -OH, or C_1 - C_6 alkyl;

each R^2 independently is H, halogen, cyano, -OH, -NH₂, -NO₂, -C(=O)NH₂, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, -O(C_1 - C_6 alkyl), -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)₂, C_3 - C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6 - C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, -O(C_1 - C_6 alkyl), -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)₂, C_3 - C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6 - C_{10} aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{2S} ,

or two R^2 together with the atoms to which they are attached form a C_3 - C_{12} cycloalkyl or 3- to 12-membered heterocycloalkyl, wherein the C_3 - C_{12} cycloalkyl or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{2S} ;

each R^{2S} independently is halogen, -OH, -O(C_1 - C_6 alkyl), -NH₂, -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)₂, or C_3 - C_{12} cycloalkyl;

each R^{2a} independently is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, - (CH₂)₀₋₃-(C₃-C₁₂ cycloalkyl), or -(CH₂)₀₋₃-(3- to 12-membered heterocycloalkyl);

each R^a independently is H or C₁-C₆ alkyl; or two R^a , together with the atom they attach to, form C₃-C₁₂ cycloalkyl;

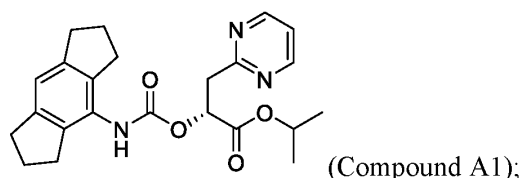
R^{N2} is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2a} ;

each R^{N2a} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2ab} , and

each R^{N2ab} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), or -S(=O)₂N(C₁-C₆ alkyl)₂.

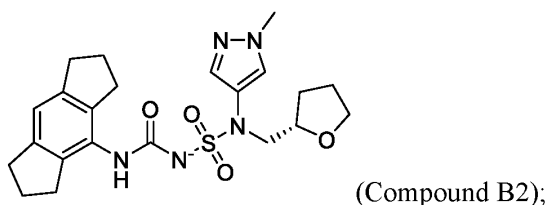
[0257] Embodiment 13. The method of any one of Embodiments 10-12, wherein the NLRP3 inflammasome inhibitor is selected from Table 1A, Table 1B, or Table 1C.

[0258] Embodiment 14. The method of any one of Embodiments 10-13, wherein the NLRP3 inflammasome inhibitor is Compound A1:



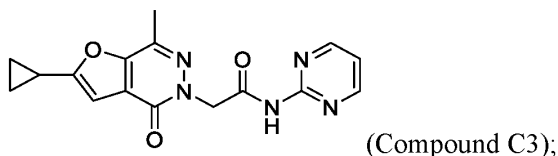
or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0259] Embodiment 15. The method of any one of Embodiments 10-13, wherein the NLRP3 inflammasome inhibitor is Compound B2:



or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0260] Embodiment 16. The method of any one of Embodiments 10-13, wherein the NLRP3 inflammasome inhibitor is Compound C3:



or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

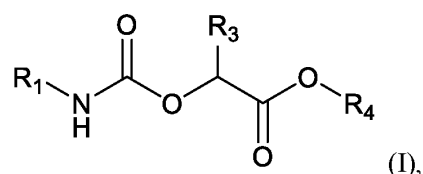
[0261] Embodiment 17. The method of any one of Embodiments 10-16, wherein the GLP-1 receptor agonist is selected from Table 2.

[0262] Embodiment 18. The method of any one of Embodiments 10-17, wherein the GLP-1 receptor agonist is semaglutide.

[0263] Embodiment 19. An NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for a combinatorial therapy for the treatment or prevention of a GLP-1 linked disease and/or a weight disorder in a subject.

[0264] Embodiment 20. An NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for a combinatorial therapy for the treatment or prevention of a weight disorder in a subject.

[0265] Embodiment 21. The NLRP3 inflammasome inhibitor of Embodiment 19 or Embodiment 20, wherein the NLRP3 inflammasome inhibitor is a compound of Formula I, Formula II, or Formula III:



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

R₁ is C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, C₅-C₁₀ aryl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein the C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl is optionally substituted by one or more R₆;

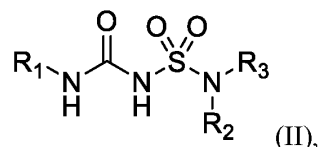
R₃ is H or C₁-C₄ alkyl optionally substituted with one or more R₇;

R₄ is H, C₁-C₆ alkyl, -(CH₂)₀₋₃-(C₃-C₆ cycloalkyl), or -(CH₂)₀₋₃-C₅-C₆ aryl;

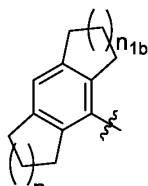
R₆ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, halo, oxo, -OH, -CN, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃;

R₇ is -OR₈, C₅-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₅-C₁₀ aryl or 5- to 10-membered heteroaryl is optionally substituted by one or more R_{7S}, wherein each R_{7S} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, 5- to 10-membered heteroaryl, halo, -OH, -CN, -(CH₂)₀₋₃-NH₂, -(CH₂)₀₋₃-NH(C₁-C₆ alkyl), -(CH₂)₀₋₃-N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃; and

R₈ is C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl, wherein the C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl is optionally substituted by one or more R_{7S}; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:



R_1 is --- , wherein n_{1a} and n_{1b} each independently are 0 or 1;

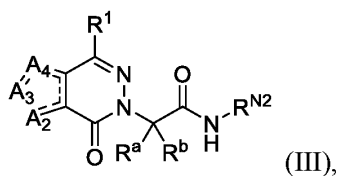
R_2 is $-(CH_2)_{n_2}-R_{2S}$, wherein n_2 is 1 or 2;

R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more R_{2SS} ;

each R_{2SS} independently is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, halo, -CN, -OH, -O(C_1 - C_6 alkyl), -NH₂, -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)₂, or oxo;

R_3 is 5- or 6-membered heteroaryl optionally substituted with one or more R_{3S} ; and

each R_{3S} independently is halo, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl; or



(III),

or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

each --- is independently a single bond or double bond as valency permits;

A_2 is CR^2 , N, NR^{2a} , O, or S, as valency allows;

A_3 is CR^2 , N, NR^{2a} , O, or S, as valency allows;

A_4 is CR^2 , N, NR^{2a} , O, or S, as valency allows,

wherein at least one of A_2 , A_3 , or A_4 is N, NR^{2a} , O, or S, provided that when A_2 is S, A_4 is CR^2 , NR^{2a} , O, or S;

R^1 is H, -N(C_1 - C_6 alkyl)₂, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_3 - C_{12} cycloalkyl, wherein the -N(C_1 - C_6 alkyl)₂, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_3 - C_{12} cycloalkyl is optionally substituted with one or more R^{1S} ;

each R^{1S} independently is halogen, cyano, -OH, or C_1 - C_6 alkyl;

each R^2 independently is H, halogen, cyano, -OH, -NH₂, -NO₂, -C(=O)NH₂, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, -O(C_1 - C_6 alkyl), -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)₂, C_3 - C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6 - C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, -O(C_1 - C_6 alkyl), -NH(C_1 - C_6 alkyl), -N(C_1 -

C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{2S},

or two R² together with the atoms to which they are attached form a C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl, wherein the C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{2S};

each R^{2S} independently is halogen, -OH, -O(C₁-C₆ alkyl), -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, or C₃-C₁₂ cycloalkyl;

each R^{2a} independently is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, -(CH₂)₀₋₃-(C₃-C₁₂ cycloalkyl), or -(CH₂)₀₋₃-(3- to 12-membered heterocycloalkyl);

each R^a independently is H or C₁-C₆ alkyl; or two R^a, together with the atom they attach to, form C₃-C₁₂ cycloalkyl;

R^{N2} is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2a},

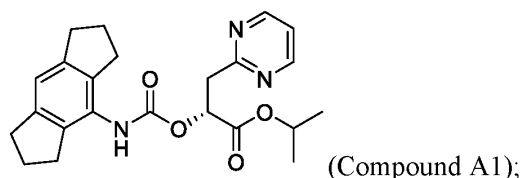
each R^{N2a} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-

membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2ab}, and

each R^{N2ab} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), or -S(=O)₂N(C₁-C₆ alkyl)₂.

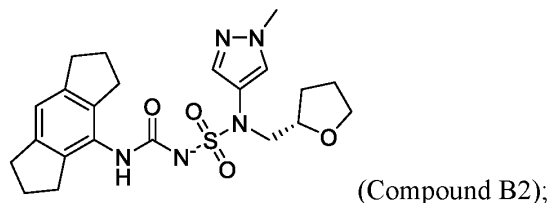
[0266] Embodiment 22. The NLRP3 inflammasome inhibitor of any one of Embodiments 19-21, wherein the NLRP3 inflammasome inhibitor is selected from Table 1A, Table 1B, or Table 1C.

[0267] Embodiment 23. The NLRP3 inflammasome inhibitor of any one of Embodiments 19-22, wherein the NLRP3 inflammasome inhibitor is Compound A1:



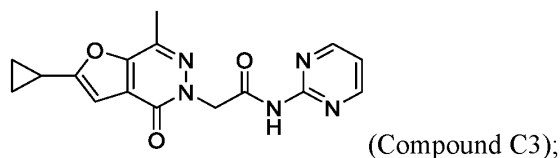
or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0268] Embodiment 24. The NLRP3 inflammasome inhibitor of any one of Embodiments 19-22, wherein the NLRP3 inflammasome inhibitor is Compound B2:



or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0269] Embodiment 25. The NLRP3 inflammasome inhibitor of any one of Embodiments 19-22, wherein the NLRP3 inflammasome inhibitor is Compound C3:



or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

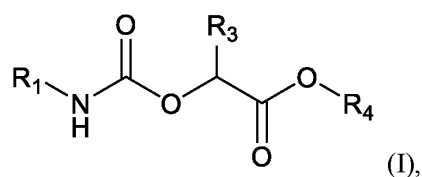
[0270] Embodiment 26. The GLP-1 receptor agonist of any one of Embodiments 19-25, wherein the GLP-1 receptor agonist is selected from Table 2.

[0271] Embodiment 27. The GLP-1 receptor agonist of any one of Embodiments 19-26, wherein the GLP-1 receptor agonist is semaglutide.

[0272] Embodiment 28. Use of an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for the treatment or prevention of a GLP-1 linked disease and/or a weight disorder in a subject.

[0273] Embodiment 29. Use of an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for the treatment or prevention of a weight disorder in a subject.

[0274] Embodiment 30. The use of an NLRP3 inflammasome inhibitor of Embodiment 28 or Embodiment 29, wherein the NLRP3 inflammasome inhibitor is a compound of Formula I, Formula II, or Formula III:



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

R₁ is C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, C₅-C₁₀ aryl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein the C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl is optionally substituted by one or more R₆;

R₃ is H or C₁-C₄ alkyl optionally substituted with one or more R₇;

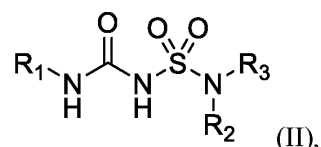
R₄ is H, C₁-C₆ alkyl, -(CH₂)₀₋₃-(C₃-C₆ cycloalkyl), or -(CH₂)₀₋₃-C₅-C₆ aryl;

R₆ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, halo, oxo, -OH, -CN, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃;

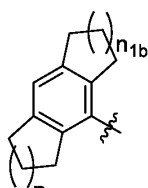
R₇ is -OR₈, C₅-C₁₀ aryl, or 5- to 10- membered heteroaryl, wherein the C₅-C₁₀ aryl or 5- to 10-membered heteroaryl is optionally substituted by one or more R_{7S}, wherein each R_{7S} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, 5- to 10-membered heteroaryl, halo, -OH, -CN, -

$(\text{CH}_2)_{0-3}\text{-NH}_2$, $-(\text{CH}_2)_{0-3}\text{-NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-(\text{CH}_2)_{0-3}\text{-N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, or $-\text{CF}_3$; and

R_8 is $\text{C}_1\text{-C}_6$ alkyl or 5- to 7-membered heterocycloalkyl, wherein the $\text{C}_1\text{-C}_6$ alkyl or 5- to 7-membered heterocycloalkyl is optionally substituted by one or more $\text{R}_{7\text{S}}$; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:



R_1 is $\text{C}_1\text{-C}_6$ alkyl, wherein n_{1a} and n_{1b} each independently are 0 or 1;

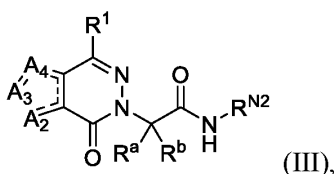
R_2 is $-(\text{CH}_2)_{n_2}\text{-R}_{2\text{S}}$, wherein n_2 is 1 or 2;

$\text{R}_{2\text{S}}$ is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more $\text{R}_{2\text{SS}}$;

each $\text{R}_{2\text{SS}}$ independently is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ haloalkyl, halo, $-\text{CN}$, $-\text{OH}$, $-\text{O}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{NH}_2$, $-\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$, or oxo;

R_3 is 5- or 6-membered heteroaryl optionally substituted with one or more $\text{R}_{3\text{S}}$; and

each $\text{R}_{3\text{S}}$ independently is halo, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_1\text{-C}_6$ haloalkyl; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

each --- is independently a single bond or double bond as valency permits;

A_2 is CR^2 , N, NR^{2a} , O, or S, as valency allows;

A_3 is CR^2 , N, NR^{2a} , O, or S, as valency allows;

A_4 is CR^2 , N, NR^{2a} , O, or S, as valency allows;

wherein at least one of A_2 , A_3 , or A_4 is N, NR^{2a} , O, or S, provided that when A_2 is S, A_4 is CR^2 , NR^{2a} , O, or S;

R^1 is H, $-N(C_1-C_6 \text{ alkyl})_2$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, or $C_3-C_{12} \text{ cycloalkyl}$, wherein the $-N(C_1-C_6 \text{ alkyl})_2$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, or $C_3-C_{12} \text{ cycloalkyl}$ is optionally substituted with one or more R^{1S} ;

each R^{1S} independently is halogen, cyano, $-OH$, or $C_1-C_6 \text{ alkyl}$;

each R^2 independently is H, halogen, cyano, $-OH$, $-NH_2$, $-NO_2$, $-C(=O)NH_2$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $-O(C_1-C_6 \text{ alkyl})$, $-NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, $C_3-C_{12} \text{ cycloalkyl}$, 3- to 12-membered heterocycloalkyl, $C_6-C_{10} \text{ aryl}$, or 5- to 10-membered heteroaryl, wherein the $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $-O(C_1-C_6 \text{ alkyl})$, $-NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, $C_3-C_{12} \text{ cycloalkyl}$, 3- to 12-membered heterocycloalkyl, $C_6-C_{10} \text{ aryl}$, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{2S} ,

or two R^2 together with the atoms to which they are attached form a $C_3-C_{12} \text{ cycloalkyl}$ or 3- to 12-membered heterocycloalkyl, wherein the $C_3-C_{12} \text{ cycloalkyl}$ or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{2S} ;

each R^{2S} independently is halogen, $-OH$, $-O(C_1-C_6 \text{ alkyl})$, $-NH_2$, $-NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, or $C_3-C_{12} \text{ cycloalkyl}$;

each R^{2a} independently is H, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $C_1-C_6 \text{ haloalkyl}$, $-(CH_2)_{0-3}-(C_3-C_{12} \text{ cycloalkyl})$, or $-(CH_2)_{0-3}-(3\text{- to }12\text{-membered heterocycloalkyl})$;

each R^a independently is H or $C_1-C_6 \text{ alkyl}$; or two R^a , together with the atom they attach to, form $C_3-C_{12} \text{ cycloalkyl}$;

R^{N2} is $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $-O(C_1-C_6 \text{ alkyl})$, $-O(C_2-C_6 \text{ alkenyl})$, $-O(C_2-C_6 \text{ alkynyl})$, $-NH(C_1-C_6 \text{ alkyl})$, $-NH(C_2-C_6 \text{ alkenyl})$, $-NH(C_2-C_6 \text{ alkynyl})$, $C_3-C_{12} \text{ cycloalkyl}$, 3- to 12-membered heterocycloalkyl, $C_6-C_{10} \text{ aryl}$, 5- to 10-membered heteroaryl, $-(C_1-C_6 \text{ alkyl})-(C_3-C_{12} \text{ cycloalkyl})$, $-(C_1-C_6 \text{ alkyl})-(3\text{- to }12\text{-membered heterocycloalkyl})$, $-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$, or $-(C_1-C_6 \text{ alkyl})-(5\text{- to }10\text{-membered heteroaryl})$; wherein the $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $-O(C_1-C_6 \text{ alkyl})$, $-O(C_2-C_6 \text{ alkenyl})$, $-O(C_2-C_6 \text{ alkynyl})$, $-NH(C_1-C_6 \text{ alkyl})$, $-NH(C_2-C_6 \text{ alkenyl})$, $-NH(C_2-C_6 \text{ alkynyl})$, $C_3-C_{12} \text{ cycloalkyl}$, 3- to 12-membered heterocycloalkyl, $C_6-C_{10} \text{ aryl}$, 5- to 10-membered heteroaryl, $-(C_1-C_6 \text{ alkyl})-(C_3-C_{12} \text{ cycloalkyl})$, $-(C_1-C_6 \text{ alkyl})-(3\text{- to }12\text{-membered heterocycloalkyl})$, $-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$, or $-(C_1-C_6 \text{ alkyl})-(5\text{- to }10\text{-membered heteroaryl})$ is optionally substituted with one or more R^{N2a} ,

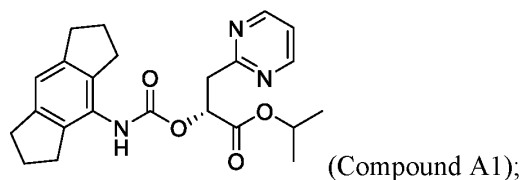
each R^{N2a} independently is oxo, halogen, cyano, $-OH$, $-NH_2$, $-C(=O)H$, $-C(=O)OH$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $-O(C_1-C_6 \text{ alkyl})$, $-NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, $-$

$\text{C}(=\text{O})(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{C}(=\text{O})\text{O}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{NHC}(=\text{O})\text{O}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{S}(=\text{O})_2(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{S}(=\text{O})_2\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$, $\text{C}_3\text{-C}_{12}$ cycloalkyl, 3- to 12-membered heterocycloalkyl, $\text{C}_6\text{-C}_{10}$ aryl, 5- to 10-membered heteroaryl, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-(\text{C}_3\text{-C}_{12} \text{ cycloalkyl})$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-(3\text{- to } 12\text{-membered heterocycloalkyl})$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-(\text{C}_6\text{-C}_{10} \text{ aryl})$, or $-(\text{C}_1\text{-C}_6 \text{ alkyl})-(5\text{- to } 10\text{-membered heteroaryl})$; wherein the $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $-\text{O}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$, $-\text{C}(=\text{O})(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{C}(=\text{O})\text{O}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{NHC}(=\text{O})\text{O}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{S}(=\text{O})_2(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{S}(=\text{O})_2\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$, $\text{C}_3\text{-C}_{12}$ cycloalkyl, 3- to 12-membered heterocycloalkyl, $\text{C}_6\text{-C}_{10}$ aryl, 5- to 10-membered heteroaryl, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-(\text{C}_3\text{-C}_{12} \text{ cycloalkyl})$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-(3\text{- to } 12\text{-membered heterocycloalkyl})$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-(\text{C}_6\text{-C}_{10} \text{ aryl})$, or $-(\text{C}_1\text{-C}_6 \text{ alkyl})-(5\text{- to } 10\text{-membered heteroaryl})$ is optionally substituted with one or more R^{N2ab} ; and

each R^{N2ab} independently is oxo, halogen, cyano, $-\text{OH}$, $-\text{NH}_2$, $-\text{C}(=\text{O})\text{H}$, $-\text{C}(=\text{O})\text{OH}$, $-\text{O}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$, $-\text{C}(=\text{O})(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{C}(=\text{O})\text{O}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{NHC}(=\text{O})\text{O}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{S}(=\text{O})_2(\text{C}_1\text{-C}_6 \text{ alkyl})$, or $-\text{S}(=\text{O})_2\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$.

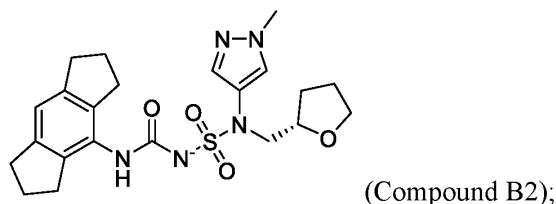
[0275] Embodiment 31. The use of an NLRP3 inflammasome inhibitor of any one of Embodiments 28-30, wherein the NLRP3 inflammasome inhibitor is selected from Table 1A, Table 1B, or Table 1C.

[0276] Embodiment 32. The use of an NLRP3 inflammasome inhibitor of any one of Embodiments 28-31, wherein the NLRP3 inflammasome inhibitor is Compound A1:



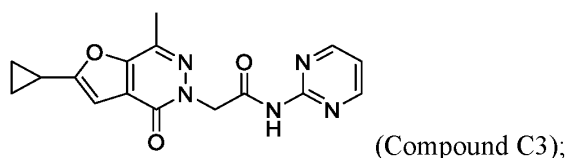
or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0277] Embodiment 33. The use of an NLRP3 inflammasome inhibitor of any one of Embodiments 28-31, wherein the NLRP3 inflammasome inhibitor is Compound B2:



or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0278] Embodiment 34. The use of an NLRP3 inflammasome inhibitor of any one of Embodiments 28-31, wherein the NLRP3 inflammasome inhibitor is Compound C3:



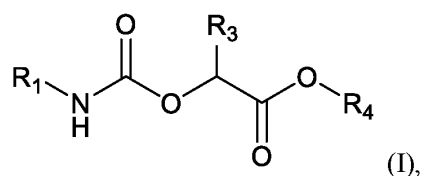
or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0279] Embodiment 35. The use of a GLP-1 receptor agonist of any one of Embodiments 28-34, wherein the GLP-1 receptor agonist is selected from Table 2.

[0280] Embodiment 36. The use of a GLP-1 receptor agonist of any one of Embodiments 28-35, wherein the GLP-1 receptor agonist is semaglutide.

[0281] Embodiment 37. A kit comprising an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0282] Embodiment 38. The kit of Embodiment 37, wherein the NLRP3 inflammasome inhibitor is a compound of Formula I, Formula II, or Formula III:



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

R₁ is C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, C₅-C₁₀ aryl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein the C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl is optionally substituted by one or more R₆;

R₃ is H or C₁-C₄ alkyl optionally substituted with one or more R₇;

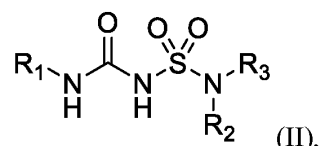
R₄ is H, C₁-C₆ alkyl, -(CH₂)₀₋₃-(C₃-C₆ cycloalkyl), or -(CH₂)₀₋₃-C₅-C₆ aryl;

R₆ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, halo, oxo, -OH, -CN, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃;

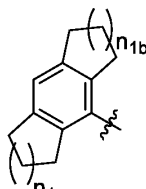
R₇ is -OR₈, C₅-C₁₀ aryl, or 5- to 10- membered heteroaryl, wherein the C₅-C₁₀ aryl or 5-

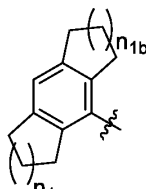
to 10-membered heteroaryl is optionally substituted by one or more R_{7S} , wherein each R_{7S} is independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, 5- to 10-membered heteroaryl, halo, -OH, -CN, - $(CH_2)_{0-3}$ -NH $_2$, - $(CH_2)_{0-3}$ -NH(C_1 - C_6 alkyl), - $(CH_2)_{0-3}$ -N(C_1 - C_6 alkyl) $_2$, -CH $_2$ F, -CHF $_2$, or -CF $_3$; and

R_8 is C_1 - C_6 alkyl or 5- to 7-membered heterocycloalkyl, wherein the C_1 - C_6 alkyl or 5- to 7-membered heterocycloalkyl is optionally substituted by one or more R_{7S} ; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:



R_1 is , wherein n_{1a} and n_{1b} each independently are 0 or 1;

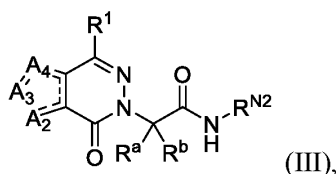
R_2 is $-(CH_2)_{n_2}-R_{2S}$, wherein n_2 is 1 or 2;

R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more R_{2SS} ;

each R_{2SS} independently is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, halo, -CN, -OH, -O(C_1 - C_6 alkyl), -NH $_2$, -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl) $_2$, or oxo;

R_3 is 5- or 6-membered heteroaryl optionally substituted with one or more R_{3S} ; and

each R_{3S} independently is halo, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

each  is independently a single bond or double bond as valency permits;

A_2 is CR^2 , N, NR^{2a} , O, or S, as valency allows;

A_3 is CR^2 , N, NR^{2a} , O, or S, as valency allows;

A_4 is CR^2 , N, NR^{2a} , O, or S, as valency allows;

wherein at least one of A₂, A₃, or A₄ is N, NR^{2a}, O, or S, provided that when A₂ is S, A₄ is CR², NR^{2a}, O, or S;

R¹ is H, -N(C₁-C₆ alkyl)₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₃-C₁₂ cycloalkyl, wherein the -N(C₁-C₆ alkyl)₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₃-C₁₂ cycloalkyl is optionally substituted with one or more R^{1S};

each R^{1S} independently is halogen, cyano, -OH, or C₁-C₆ alkyl;

each R² independently is H, halogen, cyano, -OH, -NH₂, -NO₂, -C(=O)NH₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{2S},

or two R² together with the atoms to which they are attached form a C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl, wherein the C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{2S};

each R^{2S} independently is halogen, -OH, -O(C₁-C₆ alkyl), -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, or C₃-C₁₂ cycloalkyl;

each R^{2a} independently is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, -(CH₂)₀₋₃-(C₃-C₁₂ cycloalkyl), or -(CH₂)₀₋₃-(3- to 12-membered heterocycloalkyl);

each R^a independently is H or C₁-C₆ alkyl; or two R^a, together with the atom they attach to, form C₃-C₁₂ cycloalkyl;

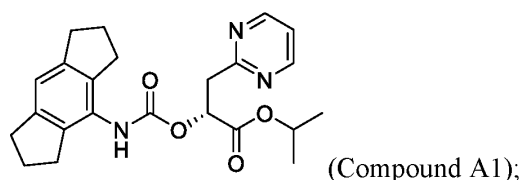
R^{N2} is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2a},

each R^{N2a} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2ab} ; and

each R^{N2ab} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), or -S(=O)₂N(C₁-C₆ alkyl)₂.

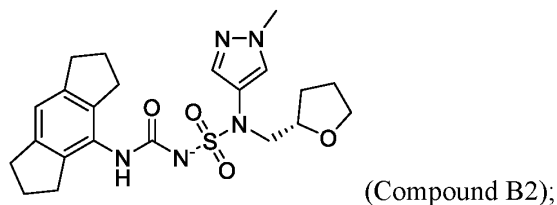
[0283] Embodiment 39. The kit of Embodiment 37 or Embodiment 38, wherein the NLRP3 inflammasome inhibitor is selected from Table 1A, Table 1B, or Table 1C.

[0284] Embodiment 40. The kit of any one of Embodiments 37-39, wherein the NLRP3 inflammasome inhibitor is Compound A1:



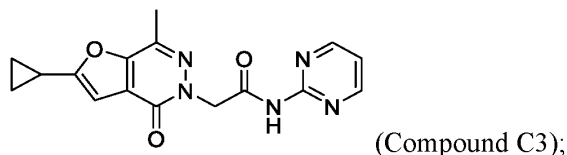
or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0285] Embodiment 41. The kit of any one of Embodiments 37-39, wherein the NLRP3 inflammasome inhibitor is Compound B2:



or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0286] Embodiment 42. The kit of any one of Embodiments 37-39, wherein the NLRP3 inflammasome inhibitor is Compound C3:



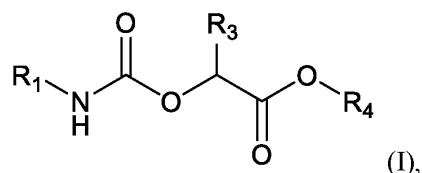
or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0287] Embodiment 43. The kit of any one of Embodiments 37-42, wherein the GLP-1 receptor agonist is selected from Table 2.

[0288] Embodiment 44. The kit of any one of Embodiments 37-43, wherein the GLP-1 receptor agonist is semaglutide.

[0289] Embodiment 45. A pharmaceutical package comprising an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0290] Embodiment 46. The pharmaceutical package of Embodiment 45, wherein the NLRP3 inflammasome inhibitor is a compound of Formula I, Formula II, or Formula III:



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

R₁ is C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, C₅-C₁₀ aryl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein the C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl is optionally substituted by one or more R₆;

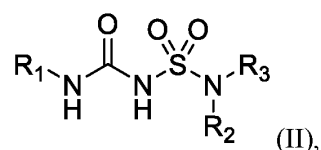
R₃ is H or C₁-C₄ alkyl optionally substituted with one or more R₇;

R₄ is H, C₁-C₆ alkyl, -(CH₂)₀₋₃-(C₃-C₆ cycloalkyl), or -(CH₂)₀₋₃-C₅-C₆ aryl;

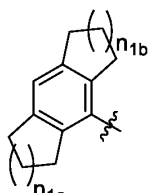
R₆ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, halo, oxo, -OH, -CN, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃;

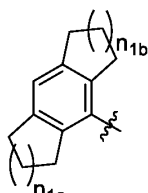
R₇ is -OR₈, C₅-C₁₀ aryl, or 5- to 10- membered heteroaryl, wherein the C₅-C₁₀ aryl or 5- to 10-membered heteroaryl is optionally substituted by one or more R_{7S}, wherein each R_{7S} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, 5- to 10-membered heteroaryl, halo, -OH, -CN, - (CH₂)₀₋₃-NH₂, -(CH₂)₀₋₃-NH(C₁-C₆ alkyl), -(CH₂)₀₋₃-N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃; and

R₈ is C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl, wherein the C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl is optionally substituted by one or more R_{7S}; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:



R₁ is , wherein n_{1a} and n_{1b} each independently are 0 or 1;

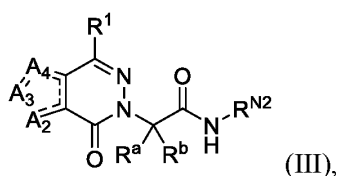
R₂ is -(CH₂)_{n2}-R_{2S}, wherein n₂ is 1 or 2;

R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more R_{2SS};

each R_{2SS} independently is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, halo, -CN, -OH, -O(C₁-C₆ alkyl), -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, or oxo;

R₃ is 5- or 6-membered heteroaryl optionally substituted with one or more R_{3S}; and

each R_{3S} independently is halo, C₁-C₆ alkyl, or C₁-C₆ haloalkyl; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

each  is independently a single bond or double bond as valency permits;

A₂ is CR², N, NR^{2a}, O, or S, as valency allows;

A₃ is CR², N, NR^{2a}, O, or S, as valency allows;

A₄ is CR², N, NR^{2a}, O, or S, as valency allows,

wherein at least one of A₂, A₃, or A₄ is N, NR^{2a}, O, or S, provided that when A₂ is S, A₄ is CR², NR^{2a}, O, or S;

R¹ is H, -N(C₁-C₆ alkyl)₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₃-C₁₂ cycloalkyl, wherein the -N(C₁-C₆ alkyl)₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₃-C₁₂ cycloalkyl is optionally substituted with one or more R^{1S};

each R^{1S} independently is halogen, cyano, -OH, or C₁-C₆ alkyl;

each R² independently is H, halogen, cyano, -OH, -NH₂, -NO₂, -C(=O)NH₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{2S},

or two R² together with the atoms to which they are attached form a C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl, wherein the C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{2S};

each R^{2S} independently is halogen, -OH, -O(C₁-C₆ alkyl), -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, or C₃-C₁₂ cycloalkyl;

each R^{2a} independently is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, -(CH₂)₀₋₃-(C₃-C₁₂ cycloalkyl), or -(CH₂)₀₋₃-(3- to 12-membered heterocycloalkyl);

each R^a independently is H or C₁-C₆ alkyl; or two R^a, together with the atom they attach to, form C₃-C₁₂ cycloalkyl;

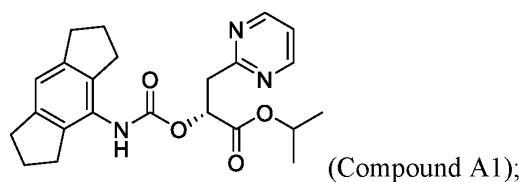
R^{N2} is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2a},

each R^{N2a} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2ab} ; and

each R^{N2ab} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), or -S(=O)₂N(C₁-C₆ alkyl)₂.

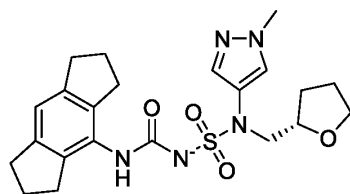
[0291] Embodiment 47. The pharmaceutical package of Embodiment 45 or Embodiment 46, wherein the NLRP3 inflammasome inhibitor is selected from Table 1A, Table 1B, Table 1C, or Table 1D.

[0292] Embodiment 48. The pharmaceutical package of any one of Embodiments 45-47, wherein the NLRP3 inflammasome inhibitor is Compound A1:



or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

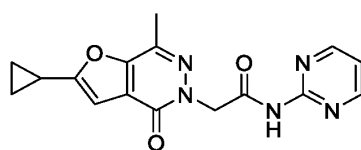
[0293] Embodiment 49. The pharmaceutical package of any one of Embodiments 45-47, wherein the NLRP3 inflammasome inhibitor is Compound B2:



(Compound B2);

or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0294] Embodiment 50. The pharmaceutical package of any one of Embodiments 45-47, wherein the NLRP3 inflammasome inhibitor is Compound C3:



(Compound C3);

or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0295] Embodiment 51. The pharmaceutical package of any one of Embodiments 45-50, wherein the GLP-1 receptor agonist is selected from Table 2 or Table 3.

[0296] Embodiment 52. The pharmaceutical package of any one of Embodiments 45-51, wherein the GLP-1 receptor agonist is semaglutide.

[0297] Embodiment 53. The kit or pharmaceutical package of any one of Embodiments 37-52 further comprising instructions for use.

[0298] Embodiment 54. The combination, use, method, pharmaceutical package, or kit of any one of the preceding Embodiments, wherein after treatment of the combination of NLRP3 inflammasome inhibitor and GLP-1 receptor agonist for about 7 days, about 14 days, about 28 days, or about 35 days, the NLRP3 inflammasome inhibitor is administered as a monotherapy.

[0299] Embodiment 55. The combination, use, method, pharmaceutical package, or kit of any one of the preceding Embodiments, wherein the NLRP3 inflammasome inhibitor is administered as a monotherapy after treatment of the combination of NLRP3 inflammasome inhibitor and GLP-1 receptor agonist for 28 days.

[0300] Embodiment 56. The combination, use, method, pharmaceutical package, or kit of any one of the preceding Embodiments, wherein the weight disorder is selected from a metabolic disorder, obesity, excessive body weight, and enhanced appetite.

[0301] Embodiment 57. The combination, use, method, pharmaceutical package, or kit of any one of the preceding Embodiments, wherein the weight disorder is obesity.

[0302] Embodiment 58. The combination, use, method, pharmaceutical package, or kit of any one of the preceding Embodiments, wherein the subject is a human.

[0303] Embodiment 59. The combination, use, method, pharmaceutical package, or kit of any one of the preceding Embodiments, wherein the NLRP3 inflammasome inhibitor and GLP-1 receptor agonist are administered in temporal proximity, sequentially, or in alternation.

[0304] Embodiment 60. The combination, use, method, pharmaceutical package, or kit of any one of the preceding Embodiments, wherein the NLRP3 inflammasome inhibitor and GLP-1 receptor agonist are administered as different formulations.

EXAMPLES

Example 1. Combination Therapy of NLRP3 Inflammasome Inhibitor and GLP-1 Receptor Agonist in Mice

[0305] Studies with ester pro-drug, Compound A1, and Compound C3 were performed in hCES1 mice, a novel mouse line, engineered to possess more human-like traits with respect to carboxylesterase biology (Smolak P, Nguyen M, Diamond C, Wescott H, Doedens J, Schooley K, Snouwaert J, Bock M, Harrison D, Watt A, Koller B, and Gabel C (2024) Target cell activation of a structurally novel NLRP3 inflammasome inhibitor NT-0796 enhances potency. *J Pharmacol Exp Ther.* 388(3), 798-812) specifically, a lack of murine plasma Ces1c and targeted expression of human CES1 to myeloid cells. This strain originated on, and was maintained on a B6,129 background as a homozygous colony. hCES1 mice were provided by NodThera and maintained at HD Biosciences (China) Co., Ltd. Experimental procedures were performed in accordance with Guide for Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee (IACUC) at HDB. Animals were acclimatized for at least 1 week prior to experiments. All euthanasia was performed using carbon dioxide inhalation and all efforts were made to minimize animal suffering. Animals were group-housed (5 animals per cage) with bedding under controlled temperature (20-25°C), noise, humidity (40-70%), and lighting (12-hour light and 12-hour dark) conditions. All animals had free access to purified water and standard certified rodent chow (Beijing Keao Xieli Feed Co., Ltd., Beijing, China, #2112/2151) *ad libitum*. The

general condition (appearance and activity) of all animals was carefully monitored daily by a veterinarian throughout the study.

DIO model and compound dosing

[0306] hCES1 mice were fed with standard chow diet (SCD) until week 5, then switched to high-fat diet (HFD; Research Diets, New Brunswick, USA, #D12492, Rodent Diet with 60 kcal% Fat, Research diet) for an additional 15 weeks. Prior to compound treatment animals were randomized based on their body weight and total plasma HDL, LDL, TC and TG values. Compound A1 and Compound C3 were prepared in vehicle (0.5% methylcellulose + 0.2% Tween80) at 10 mg/ml with a maximum dosing volume of 10 ml/kg (p.o., t.i.d.). Compound A1 and Compound C3 were each dosed at 100 mg/kg, p.o. t.i.d. at 8 a.m., 3 p.m. and 10 p.m. Semaglutide was prepared in vehicle containing 0.05% Tween80 in PBS at a final concentration of 0.0005 mg/ml with a dosing volume of 10 ml/kg (s.c; q.d).

Calorie intake and body weight

[0307] Food intake was measured by group (per cage) daily throughout study periods. At 8:00 am every day (the beginning of the light cycle), food pellet was weighed and provided to animals *ad libitum*. At 8:00 am on the following day (the beginning of the light cycle), the remaining food pellet was weighed again, and the difference was recorded as the total food consumption by the group of animals over 24 hours. The results were expressed as average food consumption per mouse (g; total food consumption/number of animals in the cage). Body weight of each animal was measured daily after food intake measurement. Overnight fasting into day 25 was performed during DIO studies to facilitate the analysis of further exploratory endpoints. Average calorie intake was calculated for each group (by calculating the average daily food (g) consumption per cage, then multiplying by the kcal content per food type (3.44 kcal/g for normal chow, or 5.24kcal/g for high fat diet).

Results

[0308] The pharmacology of Compound A1, a pro-drug of active metabolite NDT-19795, is enhanced in hCES1 mice, which more closely mimics human expression of carboxylesterase-1 (CES-1) in myeloid cells (Smolak *et al.*, *supra*). We fed mice that transgenically overexpress myeloid hCES1 a high fat diet (HFD) for 15 weeks prior to compound treatment.

[0309] Body weight was recorded every day and expressed as % change from day 0. Compared to the vehicle-treated DIO hCES1 mice group, treatment with Compound A1 (100 mg/kg, p.o. t.i.d.)

or semaglutide (0.005 mg/kg, s.c. q.d) reduced body weight by -17, or -15 %, respectively over 28 days. (FIG. 1A). However, combined treatment with Compound A1 and semaglutide drove enhanced weight loss (-24 % relative to baseline), which was significantly higher than semaglutide alone (FIG. 1A). Average calorie consumption between the vehicle-treated DIO hCES1 mice and a control chow group (non-obese) were similar over the 28-day dosing period. Semaglutide at 0.005 mg/kg, was largely ineffective at lowering average calorie intake (relative to control groups). However, mice dosed with Compound A1, or Compound A1 combined with semaglutide, consumed reduced calories over 28 days relative to the vehicle-treated DIO mice FIG. 1B).

[0310] Compared to vehicle-treated DIO hCES1 mice group, treatment with Compound C3 (100 mg/kg, p.o. t.i.d.) or semaglutide (0.005 mg/kg, s.c. q.d) reduced body weight by -17, or -15 %, respectively over 28 days. (FIG. 2A). However, as with Compound A1, combined treatment with Compound C3 and semaglutide drove enhanced weight loss (-21 % relative to baseline). (FIG. 2A). Mice dosed with Compound C3, or Compound C3 combined with semaglutide, consumed reduced calories over 28 days relative to the vehicle-treated DIO mice (FIG. 2B).

[0311] An extension study was undertaken following the main study with Compound A1, to understand how continual NLRP3 inhibition in DIO hCES1 mice may modulate weight re-gain following the cessation of semaglutide (+/- NLRP3 inhibition) in DIO mice. The extension study period included an additional 28-day period after the main study, running for 56 days in total (FIG. 3A). DIO hCES1 mice dosed initially (in the main study) with semaglutide (0.005 mpk) and on extension study having this treatment removed (being treated with vehicle only from day 28), went on to increase their body weight considerably by day 56 (FIG. 3A). However, this trend for weight re-gain, driven by the semaglutide withdrawal, was prevented by maintaining the hCES1 DIO mice on Compound A1 (FIG. 3A). In addition, hCES1 DIO mice initially dosed with combined semaglutide and Compound A1, before switching to Compound A1 only, maintained a lower body weight throughout the extension study (compared to DIO mice receiving an equivalent dose of Compound A1, but having been dosed with semaglutide only during the main study, FIG. 3A).

[0312] The DIO hCES1 mice dosed initially with semaglutide only, and on extension study having this treatment removed (vehicle only group) had much elevated calorie intake throughout the extension study period (days 28-56; FIG. 3B). The raised calorie intake, on switching from semaglutide to vehicle, was inhibited by maintaining a dose of Compound A1 throughout the extension study (FIG. 3B). Maintenance of Compound A1 dosing in hCES1 DIO mice that had

initially been dosed with semaglutide and Compound A1 (during the main study) also sustained the lowest calorie intake during the course of the extension study (FIG. 3B).

[0313] These data indicate that dosing of a centrally-penetrant NLRP3 inflammasome inhibitor drives weight loss in obese mice, and that the effect of an NLRP3 inflammasome inhibitor is additive to GLP1 receptor agonist, semaglutide. In addition, the data demonstrate that dosing a centrally penetrant NLRP3 inflammasome inhibitor prevents weight re-gain apparent on cessation of semaglutide dosing. Further, if semaglutide treatment is initially combined with an NLRP3 inhibitor, the degree of weight re-gain on semaglutide cessation will be further reduced (compared to animals not having initial NLRP3 inhibition).

Example 2: NLRP3 Inflammasome Inhibitor in Combination with Semaglutide Normalizes Obesity in Mice During Exposure to a Polyunsaturated Fatty Acid Diet

Methods

Animals

[0314] Studies with Compound A1 were performed in hCES1 mice, a mouse line, engineered to possess more human-like traits with respect to carboxylesterase biology (Smolak *et al.*, *supra*) specifically, a lack of murine plasma *Ces1c* and targeted expression of human CES1 to myeloid cells. This strain originated on, and was maintained on a B6,129 background as a homozygous colony. hCES1 mice were provided by NodThera and maintained at HD Biosciences (China) Co., Ltd. Experimental procedures were performed in accordance with Guide for Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee (IACUC) at HDB. Animals were acclimatized for at least 1 week prior to experiments. All euthanasia was performed using carbon dioxide inhalation and all efforts were made to minimize animal suffering. Animals were group-housed (five animals per cage) with bedding under controlled temperature (20-25°C), noise, humidity (40-70%), and lighting (12-hour light and 12-hour dark) conditions. All animals had free access to purified water and standard certified rodent chow (Beijing Keao Xieli Feed Co., Ltd., Beijing, China, #2112/2151) *ad libitum*. The general condition (appearance and activity) of all animals was carefully monitored daily by a veterinarian throughout the study.

Diet-induced obesity model and compound dosing

[0315] All hCES1 mice were fed standard chow diet until week 7, then switched to high-fat diet (HFD; 60 kcal% fat) for an additional 15 weeks to drive diet-induced obesity (DIO). Control animals received standard chow diet throughout the experiments. DIO animals remained on *ad libitum* HFD or *ad libitum* polyunsaturated fatty acid (PUFA) diet (with 40 kcal% fat) where stated. Compound A1 was prepared at 10 mg/mL in a vehicle of 0.5% methylcellulose and 0.2% Tween 80 with a dosing volume of 10 mL/kg for a dose of 100 mg/kg (p.o., t.i.d.). Semaglutide was prepared at a final concentration of 0.0005 mg/mL in a vehicle of 0.05% Tween 80 in PBS with a dosing volume of 10 mL/kg for a dose of 0.005 mg/kg (s.c., q.d.). Combination dosed animals received both Compound A1 (p.o., t.i.d.) and semaglutide (s.c., q.d.). Respective vehicles were dosed to all animals such that each animal received an oral and subcutaneous administration. A calorie restricted group was included that matched the weights of animals dosed with Compound A1 alone. The amount of food supplied to animals under calorie restriction was based on the average food intake of animals dosed with Compound A1 monotherapy.

Food intake and body weight measurement

[0316] Food intake was measured daily for each cage by recording the weight difference of the food pellet provided at 8:00 a.m. and the remaining food the following morning at 8:00 a.m. and noted as the total food consumption by the group in 24 hours. Final results were expressed as average food consumption per mouse by dividing the total food consumption by the number of animals in each cage. Average daily calorie intake was calculated using the average food intake by each group times the calorie content of each diet per gram. Body weight of each animal was measured daily after food intake measurement. First day of each treatment regime was defined as the baseline value for calculating raw weight and percentage weight change for each animal.

Body composition and organ weights

[0317] Body composition (bone mineral content, fat tissue, lean tissue) was measured using an InAlyzer dual-energy X-ray absorptiometry (DEXA) scan at study end. At study end, animals were sacrificed using CO₂ inhalation and all efforts were made to minimize suffering. Organs (liver, heart, brain, kidneys and colon) were collected and weighed.

GFAP immunohistochemistry

[0318] Brain tissues were collected for the assessment of hypothalamic GFAP expression by immunohistochemistry. Following assignment of the arcuate nucleus (ARC), dorsomedial hypothalamic nucleus (DMH) and ventromedial hypothalamic nucleus (VMH) areas, GFAP

immunoreactivity was assessed in Multiplex IHC v3.2.3 module of the HALO® Image Analysis Platform. The average total GFAP staining (%), average strong GFAP staining (%), or the total number of GFAP positive cells (per μm^2) across the ARC, DMH and VMH was calculated.

Statistical analysis

[0319] Statistical analysis was performed in GraphPad Prism 10.4.1 using one- or two-way ANOVA followed by Dunnett's or Tukey's post-hoc statistical analysis. A p-value of ≤ 0.05 was considered to be statistically significant.

Results

[0320] The pharmacology of Compound A1 is enhanced in hCES1 mice, with humanized expression of carboxylesterase-1 (CES-1) in myeloid cells (Smolak *et al.*, *supra*). The combinatorial weight loss efficacy of NLRP3 inflammasome inhibitor, Compound A1 with GLP-1 receptor agonist, semaglutide, was assessed in hCES1 DIO mice during initial exposure (days 0-28) to high fat diet (HFD) and following a switch to translationally-relevant polyunsaturated fatty acid (PUFA) diet (days 29-56).

[0321] Dosing of DIO mice (during HFD exposure), with Compound A1 (100 mg/kg, p.o., t.i.d.) monotherapy or semaglutide (0.005 mg/kg, s.c., q.d.) monotherapy drove significant weight loss, reaching -7.4%, and -12.7%, respectively, by 28 days (FIG. 4). However, the combination of Compound A1 and semaglutide drove -20.0% weight loss, significantly greater than either monotherapy alone at the mid-study point (FIG. 4). On switching to PUFA diet *ad libitum* at day 29, DIO control mice, maintained consistent body weight over days 29-56 (FIG. 4 and FIG. 5). Compound A1-dosed DIO mice, continued to lose additional body weight (-13.8%, by day 56), whereas semaglutide-induced weight loss at day 56 was largely equal to the mid-study point (-12.7 v -11.1%; FIG. 4). The calorie-restricted DIO mice matched the weight loss of the Compound A1 dosed group, reaching -11.8% reduction at day 56 (FIG. 4). Switching DIO mice to a PUFA diet, whilst maintaining combined dosing of Compound A1 and semaglutide, continued to drive further weight loss in these animals, such that by day 43, the obesogenic state had been completely reversed and mice weighed the same as chow fed control mice (FIG. 5). This corresponded to a -30.3% weight loss by day 56 (FIG. 4), in response to Compound A1 and semaglutide combination

treatment, which was significantly greater than reductions achieved by either monotherapy alone (FIG. 4 and FIG. 5).

[0322] Body weight changes during the first 28 days of the study correlated with food intake (FIG. 6A) and calorie intake (FIG. 6B). Compound A1 or semaglutide monotherapy drove significant reductions in calorie intake, and the combination of Compound A1 and semaglutide drove additional calorie intake suppression, greater than either monotherapy alone (FIG. 6B).

[0323] Dual-energy x-ray absorptiometry (DEXA) scans confirmed that combination therapy of Compound A1 and semaglutide was most effective at reducing % body fat relative to DIO control mice at day 28; Compound A1 (-5.1%), semaglutide (-11.9%), Compound A1 and semaglutide combination (-15.7%, FIG. 7A). In addition, combination therapy was most effective at preserving % lean mass relative to DIO control mice at day 28; Compound A1 (+4.7%), semaglutide (+11.4%), Compound A1 and semaglutide combination (+15.2%, FIG. 7B). DEXA scans also revealed that combination therapy provided the greatest preservation of % bone mineral content relative to DIO control mice; Compound A1 (+0.4%), semaglutide (+0.5%), Compound A1 and semaglutide combination (+0.6%, FIG. 7C).

[0324] DIO mice dosed with Compound A1 also consumed less calories on PUFA diet relative to DIO control mice (FIGs. 8A-B). Semaglutide dosing during PUFA diet exposure also lowered calorie intake of DIO mice (FIG. 8B). However, combined dosing of Compound A1 with semaglutide, suppressed calorie intake during the PUFA diet period to a greater extent than monotherapy interventions (FIG. 8B). The calorie restricted group maintained equivalent calorie intake to the Compound A1 monotherapy group (FIG. 8B).

[0325] At study end, the astrogliosis marker, glial fibrillary acidic protein (GFAP) was quantified by immunohistochemistry. Average immunoreactivity across the arcuate nucleus (ARC), dorsomedial (DMH) and ventral hypothalamus (VMH) of mice was assessed. Relative to normal chow fed animals, the average total percent GFAP staining (FIG. 9A), percentage of strongly-stained GFAP (FIG. 9B), and total GFAP positive cell numbers (FIG. 9C) were elevated in DIO control mice. Relative to the DIO control mice, dosing with Compound A1 monotherapy, or Compound A1 in combination with semaglutide, drove significant reductions in average total percent GFAP staining (FIG. 9A), percentage of strongly-stained GFAP (FIG. 9B), and total GFAP positive cell numbers GFAP (FIG. 9C) across these hypothalamic brain regions. Calorie restriction

or semaglutide monotherapy trended to reduce GFAP staining across these regions, but this did not reach significance (FIGs. 9A-C).

[0326] Compared to the DIO control mice, all treatment interventions decreased liver weights (FIG. 10A). Semaglutide monotherapy or semaglutide in combination with Compound A1 provided greatest treatment-driven reductions in liver weight (FIG. 10A). Calorie restriction also significantly reduced liver weights (FIG. 10A). Heart weights were also increased in DIO control mice, relative to chow fed controls (FIG. 10B). Compound A1 or semaglutide monotherapy significantly reduced heart weights relative to DIO controls (FIG. 10B). Combination dosing of semaglutide and Compound A1 provided the largest reductions in heart weights of DIO control mice (FIG. 10B).

[0327] Brain weights remained unchanged across study groups (FIG. 10C). Left and right kidney weights trended to increase in response to DIO challenge (relative to chow fed controls) (FIGs. 10D-E). Compound A1 combined with semaglutide reduced left and right kidney weights, relative to DIO control mice (FIGs. 10D-E). Compound A1 monotherapy also reduced both kidney weights (FIGs. 10D-E). Semaglutide monotherapy trended (left) or significantly reduced (right) kidney weight (FIGs. 10D-E). Calorie restriction was less effective at reducing kidney weights compared to drug interventions (FIGs. 10D-E). Colon weights were reduced in response to DIO challenge but not significantly altered by drug interventions (FIG. 10F).

[0328] These data indicate that dosing of a centrally-penetrant NLRP3 inflammasome inhibitor drives weight loss and that this mechanism combines with that of a GLP-1 receptor agonist, such as semaglutide, to achieve superior efficacy compared to either monotherapy alone. Importantly, the data demonstrate that simultaneous targeting of the NLRP3 inflammasome and the GLP-1 receptor pathway normalizes the obesogenic phenotype in mice, with full correction of body weight within eight weeks of dosing. In addition to the effects on body weight, the combined dosing of an NLRP3 inflammasome inhibitor with semaglutide, a GLP-1 receptor agonist, provides further improvements in obese mice, including greater reductions in neuroinflammation and enhanced preservation of lean mass and bone mineral content.

EQUIVALENTS

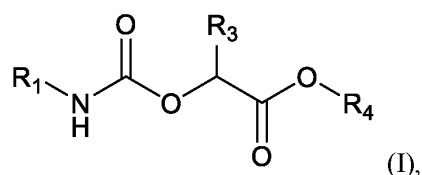
[0329] The details of one or more embodiments of the disclosure are set forth in the accompanying description above. Although any methods and materials similar or equivalent to those described

herein can be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms include plural referents unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated by reference.

[0330] The foregoing description has been presented only for the purposes of illustration and is not intended to limit the disclosure to the precise form disclosed, but by the claims appended hereto.

CLAIMS

1. An NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, for use in combination for treating or preventing a GLP-1 linked disease and/or a weight disorder in a subject.
2. An NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, for use in combination for treating or preventing a weight disorder in a subject.
3. The NLRP3 inflammasome inhibitor of claim 1 or claim 2, wherein the NLRP3 inflammasome inhibitor is a compound of Formula I, Formula II, or Formula III:



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

R₁ is C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, C₅-C₁₀ aryl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein the C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl is optionally substituted by one or more R₆;

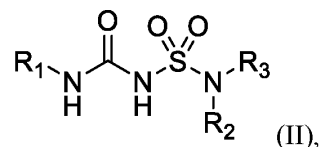
R₃ is H or C₁-C₄ alkyl optionally substituted with one or more R₇;

R₄ is H, C₁-C₆ alkyl, -(CH₂)₀₋₃-(C₃-C₆ cycloalkyl), or -(CH₂)₀₋₃-C₅-C₆ aryl;

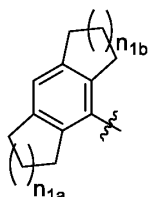
R₆ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, halo, oxo, -OH, -CN, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃;

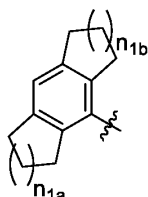
R₇ is -OR₈, C₅-C₁₀ aryl, or 5- to 10- membered heteroaryl, wherein the C₅-C₁₀ aryl or 5- to 10-membered heteroaryl is optionally substituted by one or more R_{7S}, wherein each R_{7S} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, 5- to 10-membered heteroaryl, halo, -OH, -CN, -(CH₂)₀₋₃-NH₂, -(CH₂)₀₋₃-NH(C₁-C₆ alkyl), -(CH₂)₀₋₃-N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃; and

R₈ is C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl, wherein the C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl is optionally substituted by one or more R_{7S}; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:



R₁ is , wherein n_{1a} and n_{1b} each independently are 0 or 1;

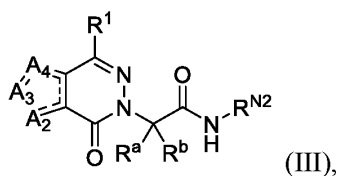
R₂ is -(CH₂)_{n2}-R_{2S}, wherein n₂ is 1 or 2;

R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more R_{2SS};

each R_{2SS} independently is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, halo, -CN, -OH, -O(C₁-C₆ alkyl), -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, or oxo;

R₃ is 5- or 6-membered heteroaryl optionally substituted with one or more R_{3S}; and

each R_{3S} independently is halo, C₁-C₆ alkyl, or C₁-C₆ haloalkyl; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

each  is independently a single bond or double bond as valency permits;

A₂ is CR², N, NR^{2a}, O, or S, as valency allows;

A₃ is CR², N, NR^{2a}, O, or S, as valency allows;

A₄ is CR², N, NR^{2a}, O, or S, as valency allows,

wherein at least one of A₂, A₃, or A₄ is N, NR^{2a}, O, or S, provided that when A₂ is S, A₄ is CR², NR^{2a}, O, or S;

R^1 is H, $-N(C_1-C_6 \text{ alkyl})_2$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, or $C_3-C_{12} \text{ cycloalkyl}$, wherein the $-N(C_1-C_6 \text{ alkyl})_2$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, or $C_3-C_{12} \text{ cycloalkyl}$ is optionally substituted with one or more R^{1S} ;

each R^{1S} independently is halogen, cyano, $-OH$, or $C_1-C_6 \text{ alkyl}$;

each R^2 independently is H, halogen, cyano, $-OH$, $-NH_2$, $-NO_2$, $-C(=O)NH_2$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $-O(C_1-C_6 \text{ alkyl})$, $-NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, $C_3-C_{12} \text{ cycloalkyl}$, 3- to 12-membered heterocycloalkyl, $C_6-C_{10} \text{ aryl}$, or 5- to 10-membered heteroaryl, wherein the $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $-O(C_1-C_6 \text{ alkyl})$, $-NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, $C_3-C_{12} \text{ cycloalkyl}$, 3- to 12-membered heterocycloalkyl, $C_6-C_{10} \text{ aryl}$, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{2S} ,

or two R^2 together with the atoms to which they are attached form a $C_3-C_{12} \text{ cycloalkyl}$ or 3- to 12-membered heterocycloalkyl, wherein the $C_3-C_{12} \text{ cycloalkyl}$ or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{2S} ;

each R^{2S} independently is halogen, $-OH$, $-O(C_1-C_6 \text{ alkyl})$, $-NH_2$, $-NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, or $C_3-C_{12} \text{ cycloalkyl}$;

each R^{2a} independently is H, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $C_1-C_6 \text{ haloalkyl}$, $-(CH_2)_{0-3}-(C_3-C_{12} \text{ cycloalkyl})$, or $-(CH_2)_{0-3}-(3\text{- to }12\text{-membered heterocycloalkyl})$;

each R^a independently is H or $C_1-C_6 \text{ alkyl}$; or two R^a , together with the atom they attach to, form $C_3-C_{12} \text{ cycloalkyl}$;

R^{N2} is $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $-O(C_1-C_6 \text{ alkyl})$, $-O(C_2-C_6 \text{ alkenyl})$, $-O(C_2-C_6 \text{ alkynyl})$, $-NH(C_1-C_6 \text{ alkyl})$, $-NH(C_2-C_6 \text{ alkenyl})$, $-NH(C_2-C_6 \text{ alkynyl})$, $C_3-C_{12} \text{ cycloalkyl}$, 3- to 12-membered heterocycloalkyl, $C_6-C_{10} \text{ aryl}$, 5- to 10-membered heteroaryl, $-(C_1-C_6 \text{ alkyl})-(C_3-C_{12} \text{ cycloalkyl})$, $-(C_1-C_6 \text{ alkyl})-(3\text{- to }12\text{-membered heterocycloalkyl})$, $-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$, or $-(C_1-C_6 \text{ alkyl})-(5\text{- to }10\text{-membered heteroaryl})$; wherein the $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $-O(C_1-C_6 \text{ alkyl})$, $-O(C_2-C_6 \text{ alkenyl})$, $-O(C_2-C_6 \text{ alkynyl})$, $-NH(C_1-C_6 \text{ alkyl})$, $-NH(C_2-C_6 \text{ alkenyl})$, $-NH(C_2-C_6 \text{ alkynyl})$, $C_3-C_{12} \text{ cycloalkyl}$, 3- to 12-membered heterocycloalkyl, $C_6-C_{10} \text{ aryl}$, 5- to 10-membered heteroaryl, $-(C_1-C_6 \text{ alkyl})-(C_3-C_{12} \text{ cycloalkyl})$, $-(C_1-C_6 \text{ alkyl})-(3\text{- to }12\text{-membered heterocycloalkyl})$, $-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$, or $-(C_1-C_6 \text{ alkyl})-(5\text{- to }10\text{-membered heteroaryl})$ is optionally substituted with one or more R^{N2a} ,

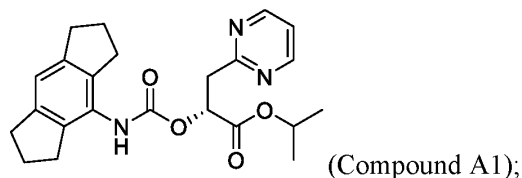
each R^{N2a} independently is oxo, halogen, cyano, $-OH$, $-NH_2$, $-C(=O)H$, $-C(=O)OH$, $C_1-C_6 \text{ alkyl}$, $C_2-C_6 \text{ alkenyl}$, $C_2-C_6 \text{ alkynyl}$, $-O(C_1-C_6 \text{ alkyl})$, $-NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, $-$

$C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)O(C_1-C_6 \text{ alkyl})$, $-NHC(=O)O(C_1-C_6 \text{ alkyl})$, $-S(=O)_2(C_1-C_6 \text{ alkyl})$, $-S(=O)_2N(C_1-C_6 \text{ alkyl})_2$, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-(C_1-C_6 \text{ alkyl})-(C_3-C_{12} \text{ cycloalkyl})$, $-(C_1-C_6 \text{ alkyl})-(3\text{- to }12\text{-membered heterocycloalkyl})$, $-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$, or $-(C_1-C_6 \text{ alkyl})-(5\text{- to }10\text{-membered heteroaryl})$; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-O(C_1-C_6 \text{ alkyl})$, $-NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)O(C_1-C_6 \text{ alkyl})$, $-NHC(=O)O(C_1-C_6 \text{ alkyl})$, $-S(=O)_2(C_1-C_6 \text{ alkyl})$, $-S(=O)_2N(C_1-C_6 \text{ alkyl})_2$, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-(C_1-C_6 \text{ alkyl})-(C_3-C_{12} \text{ cycloalkyl})$, $-(C_1-C_6 \text{ alkyl})-(3\text{- to }12\text{-membered heterocycloalkyl})$, $-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$, or $-(C_1-C_6 \text{ alkyl})-(5\text{- to }10\text{-membered heteroaryl})$ is optionally substituted with one or more R^{N2ab} ; and

each R^{N2ab} independently is oxo, halogen, cyano, $-OH$, $-NH_2$, $-C(=O)H$, $-C(=O)OH$, $-O(C_1-C_6 \text{ alkyl})$, $-NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, $-C(=O)(C_1-C_6 \text{ alkyl})$, $-C(=O)O(C_1-C_6 \text{ alkyl})$, $-NHC(=O)O(C_1-C_6 \text{ alkyl})$, $-S(=O)_2(C_1-C_6 \text{ alkyl})$, or $-S(=O)_2N(C_1-C_6 \text{ alkyl})_2$.

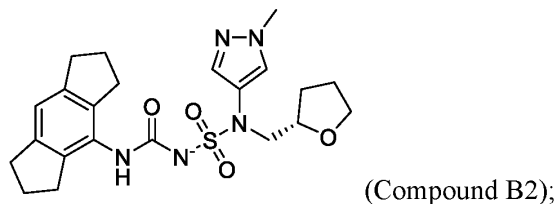
4. The NLRP3 inflammasome inhibitor of any one of claims 1-3, wherein the NLRP3 inflammasome inhibitor is selected from Table 1A, Table 1B, or Table 1C.

5. The NLRP3 inflammasome inhibitor of any one of claims 1-4, wherein the NLRP3 inflammasome inhibitor is Compound A1:



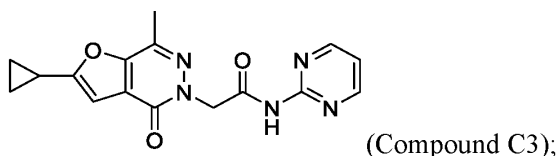
or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

6. The NLRP3 inflammasome inhibitor of any one of claims 1-4, wherein the NLRP3 inflammasome inhibitor is Compound B2:



or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

7. The NLRP3 inflammasome inhibitor of any one of claims 1-4, wherein the NLRP3 inflammasome inhibitor is Compound C3:



or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

8. The GLP-1 receptor agonist of any one of the preceding claims, wherein the GLP-1 receptor agonist is selected from Table 2.

9. The GLP-1 receptor agonist of any one of the preceding claims, wherein the GLP-1 receptor agonist is semaglutide.

10. A method of treating or preventing a GLP-1 linked disease and/or a weight disorder, comprising administering to a subject:

(a) an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and

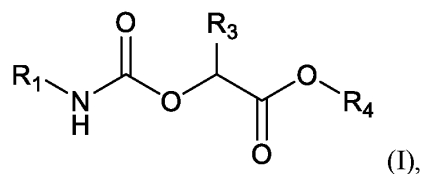
(b) a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

11. A method of treating or preventing a weight disorder, comprising administering to a subject:

(a) an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and

(b) a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

12. The method of claim 10 or claim 11, wherein the NLRP3 inflammasome inhibitor is a compound of Formula I, Formula II, or Formula III:



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

R₁ is C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, C₅-C₁₀ aryl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein the C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl is optionally substituted by one or more R₆;

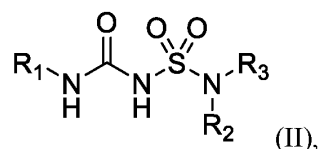
R₃ is H or C₁-C₄ alkyl optionally substituted with one or more R₇;

R₄ is H, C₁-C₆ alkyl, -(CH₂)₀₋₃-(C₃-C₆ cycloalkyl), or -(CH₂)₀₋₃-C₅-C₆ aryl;

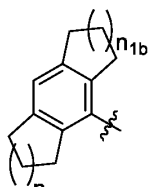
R₆ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, halo, oxo, -OH, -CN, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃;

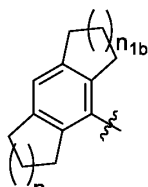
R₇ is -OR₈, C₅-C₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the C₅-C₁₀ aryl or 5- to 10-membered heteroaryl is optionally substituted by one or more R_{7S}, wherein each R_{7S} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, 5- to 10-membered heteroaryl, halo, -OH, -CN, -(CH₂)₀₋₃-NH₂, -(CH₂)₀₋₃-NH(C₁-C₆ alkyl), -(CH₂)₀₋₃-N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃; and

R₈ is C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl, wherein the C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl is optionally substituted by one or more R_{7S}; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:



R₁ is , wherein n_{1a} and n_{1b} each independently are 0 or 1;

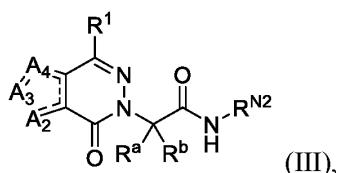
R₂ is -(CH₂)_{n2}-R_{2S}, wherein n₂ is 1 or 2;

R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more R_{2SS};

each R_{2SS} independently is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, halo, -CN, -OH, -O(C_1 - C_6 alkyl), -NH₂, -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)₂, or oxo;

R_3 is 5- or 6-membered heteroaryl optionally substituted with one or more R_{3S} ; and

each R_{3S} independently is halo, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

each is independently a single bond or double bond as valency permits;

A_2 is CR^2 , N, NR^{2a} , O, or S, as valency allows;

A_3 is CR^2 , N, NR^{2a} , O, or S, as valency allows;

A_4 is CR^2 , N, NR^{2a} , O, or S, as valency allows,

wherein at least one of A_2 , A_3 , or A_4 is N, NR^{2a} , O, or S, provided that when A_2 is S, A_4 is CR^2 , NR^{2a} , O, or S;

R^1 is H, -N(C_1 - C_6 alkyl)₂, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_3 - C_{12} cycloalkyl, wherein the -N(C_1 - C_6 alkyl)₂, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_3 - C_{12} cycloalkyl is optionally substituted with one or more R^{1S} ;

each R^{1S} independently is halogen, cyano, -OH, or C_1 - C_6 alkyl;

each R^2 independently is H, halogen, cyano, -OH, -NH₂, -NO₂, -C(=O)NH₂, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, -O(C_1 - C_6 alkyl), -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)₂, C_3 - C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6 - C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, -O(C_1 - C_6 alkyl), -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)₂, C_3 - C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6 - C_{10} aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{2S} ,

or two R^2 together with the atoms to which they are attached form a C_3 - C_{12} cycloalkyl or 3- to 12-membered heterocycloalkyl, wherein the C_3 - C_{12} cycloalkyl or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{2S} ;

each R^{2S} independently is halogen, -OH, -O(C_1 - C_6 alkyl), -NH₂, -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)₂, or C_3 - C_{12} cycloalkyl;

each R^{2a} independently is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, - (CH₂)₀₋₃-(C₃-C₁₂ cycloalkyl), or -(CH₂)₀₋₃-(3- to 12-membered heterocycloalkyl);

each R^a independently is H or C₁-C₆ alkyl; or two R^a , together with the atom they attach to, form C₃-C₁₂ cycloalkyl;

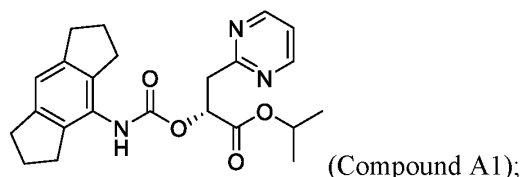
R^{N2} is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2a} ;

each R^{N2a} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2ab} , and

each R^{N2ab} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), or -S(=O)₂N(C₁-C₆ alkyl)₂.

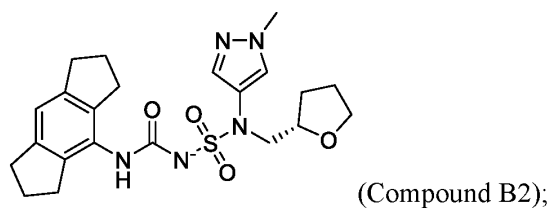
13. The method of any one of claims 10-12, wherein the NLRP3 inflammasome inhibitor is selected from Table 1A, Table 1B, or Table 1C.

14. The method of any one of claims 10-13, wherein the NLRP3 inflammasome inhibitor is Compound A1:



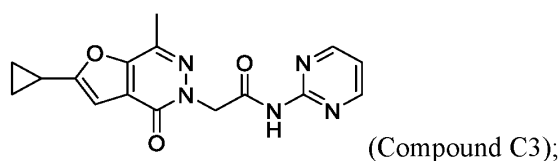
or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

15. The method of any one of claims 10-13, wherein the NLRP3 inflammasome inhibitor is Compound B2:



or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

16. The method of any one of claims 10-13, wherein the NLRP3 inflammasome inhibitor is Compound C3:

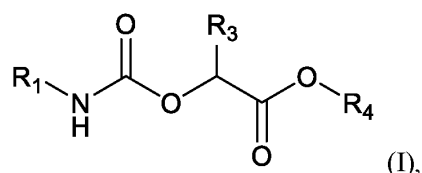


or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

17. The method of any one of claims 10-16, wherein the GLP-1 receptor agonist is selected from Table 2.

18. The method of any one of claims 10-17, wherein the GLP-1 receptor agonist is semaglutide.
19. An NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for a combinatorial therapy for the treatment or prevention of a GLP-1 linked disease and/or a weight disorder in a subject.
20. An NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for a combinatorial therapy for the treatment or prevention of a weight disorder in a subject.
21. Use of an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for the treatment or prevention of a GLP-1 linked disease and/or a weight disorder in a subject.
22. Use of an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in the manufacture of a medicament for the treatment or prevention of a weight disorder in a subject.
23. A kit comprising an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.
24. A pharmaceutical package comprising an NLRP3 inflammasome inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

25. The NLRP3 inflammasome inhibitor of claim 19 or claim 20, the use of an NLRP3 inflammasome inhibitor of claim 21 or claim 22, the kit of claim 23, or the pharmaceutical package of claim 24, wherein the NLRP3 inflammasome inhibitor is a compound of Formula I, Formula II, or Formula III:



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

R₁ is C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, C₅-C₁₀ aryl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl, wherein the C₃-C₇ monocyclic cycloalkyl, polycyclic cycloalkyl, 8- to 12-membered heterocycloalkyl, or 5- to 6-membered heteroaryl is optionally substituted by one or more R₆;

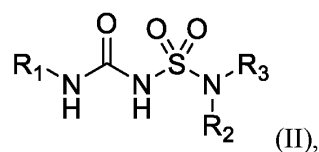
R₃ is H or C₁-C₄ alkyl optionally substituted with one or more R₇;

R₄ is H, C₁-C₆ alkyl, -(CH₂)₀₋₃-(C₃-C₆ cycloalkyl), or -(CH₂)₀₋₃-C₅-C₆ aryl;

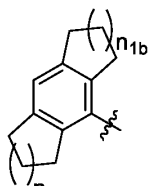
R₆ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, halo, oxo, -OH, -CN, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃;

R₇ is -OR₈, C₅-C₁₀ aryl, or 5- to 10- membered heteroaryl, wherein the C₅-C₁₀ aryl or 5- to 10-membered heteroaryl is optionally substituted by one or more R_{7S}, wherein each R_{7S} is independently C₁-C₆ alkyl, C₁-C₆ alkoxy, 5- to 10-membered heteroaryl, halo, -OH, -CN, -(CH₂)₀₋₃-NH₂, -(CH₂)₀₋₃-NH(C₁-C₆ alkyl), -(CH₂)₀₋₃-N(C₁-C₆ alkyl)₂, -CH₂F, -CHF₂, or -CF₃; and

R₈ is C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl, wherein the C₁-C₆ alkyl or 5- to 7-membered heterocycloalkyl is optionally substituted by one or more R_{7S}; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:



R_1 is --- , wherein n_{1a} and n_{1b} each independently are 0 or 1;

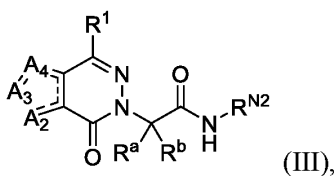
R_2 is $-(CH_2)_{n_2}-R_{2S}$, wherein n_2 is 1 or 2;

R_{2S} is 4- to 8-membered heterocycloalkyl in which at least one heteroatom is O, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with one or more R_{2SS} ;

each R_{2SS} independently is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, halo, -CN, -OH, -O(C_1 - C_6 alkyl), -NH₂, -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)₂, or oxo;

R_3 is 5- or 6-membered heteroaryl optionally substituted with one or more R_{3S} ; and

each R_{3S} independently is halo, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl; or



or a prodrug, hydrate, solvate, or pharmaceutically acceptable salt thereof, wherein:

each --- is independently a single bond or double bond as valency permits;

A_2 is CR^2 , N, NR^{2a} , O, or S, as valency allows;

A_3 is CR^2 , N, NR^{2a} , O, or S, as valency allows;

A_4 is CR^2 , N, NR^{2a} , O, or S, as valency allows,

wherein at least one of A_2 , A_3 , or A_4 is N, NR^{2a} , O, or S, provided that when A_2 is S, A_4 is CR^2 , NR^{2a} , O, or S;

R^1 is H, -N(C_1 - C_6 alkyl)₂, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_3 - C_{12} cycloalkyl, wherein the -N(C_1 - C_6 alkyl)₂, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_3 - C_{12} cycloalkyl is optionally substituted with one or more R^{1S} ;

each R^{1S} independently is halogen, cyano, -OH, or C_1 - C_6 alkyl;

each R^2 independently is H, halogen, cyano, -OH, -NH₂, -NO₂, -C(=O)NH₂, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, -O(C_1 - C_6 alkyl), -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl)₂, C_3 - C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6 - C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, -O(C_1 - C_6 alkyl), -NH(C_1 - C_6 alkyl), -N(C_1 -

C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{2S},

or two R² together with the atoms to which they are attached form a C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl, wherein the C₃-C₁₂ cycloalkyl or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more R^{2S};

each R^{2S} independently is halogen, -OH, -O(C₁-C₆ alkyl), -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, or C₃-C₁₂ cycloalkyl;

each R^{2a} independently is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, -(CH₂)₀₋₃-(C₃-C₁₂ cycloalkyl), or -(CH₂)₀₋₃-(3- to 12-membered heterocycloalkyl);

each R^a independently is H or C₁-C₆ alkyl; or two R^a, together with the atom they attach to, form C₃-C₁₂ cycloalkyl;

R^{N2} is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O-(C₁-C₆ alkyl), -O-(C₂-C₆ alkenyl), -O-(C₂-C₆ alkynyl), -NH-(C₁-C₆ alkyl), -NH-(C₂-C₆ alkenyl), -NH-(C₂-C₆ alkynyl), C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2a},

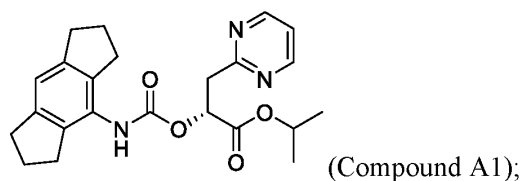
each R^{N2a} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl); wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), -S(=O)₂N(C₁-C₆ alkyl)₂, C₃-C₁₂ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁-C₆ alkyl)-(C₃-C₁₂ cycloalkyl), -(C₁-C₆ alkyl)-(3- to 12-

membered heterocycloalkyl), -(C₁-C₆ alkyl)-(C₆-C₁₀ aryl), or -(C₁-C₆ alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^{N2ab}, and

each R^{N2ab} independently is oxo, halogen, cyano, -OH, -NH₂, -C(=O)H, -C(=O)OH, -O(C₁-C₆ alkyl), -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -C(=O)(C₁-C₆ alkyl), -C(=O)O(C₁-C₆ alkyl), -NHC(=O)O(C₁-C₆ alkyl), -S(=O)₂(C₁-C₆ alkyl), or -S(=O)₂N(C₁-C₆ alkyl)₂.

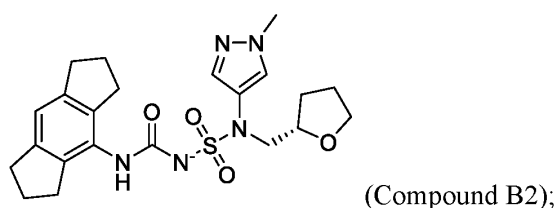
26. The NLRP3 inflammasome inhibitor, the use of an NLRP3 inflammasome inhibitor, the kit, or the pharmaceutical package of any one of claims 19-25, wherein the NLRP3 inflammasome inhibitor is selected from Table 1A, Table 1B, Table 1C, or Table 1D.

27. The NLRP3 inflammasome inhibitor, the use of an NLRP3 inflammasome inhibitor, the kit, or the pharmaceutical package of any one of claims 19-26, wherein the NLRP3 inflammasome inhibitor is Compound A1:



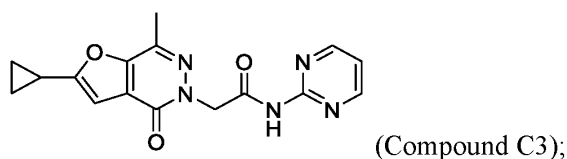
or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

28. The NLRP3 inflammasome inhibitor, the use of an NLRP3 inflammasome inhibitor, the kit, or the pharmaceutical package of any one of claims 19-26, wherein the NLRP3 inflammasome inhibitor is Compound B2:



or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

29. The NLRP3 inflammasome inhibitor, the use of an NLRP3 inflammasome inhibitor, the kit, or the pharmaceutical package of any one of claims 19-26, wherein the NLRP3 inflammasome inhibitor is Compound C3:



or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

30. The NLRP3 inflammasome inhibitor, the use of an NLRP3 inflammasome inhibitor, the kit, or the pharmaceutical package of any one of claims 19-29, wherein the GLP-1 receptor agonist is selected from Table 2 or Table 3.

31. The NLRP3 inflammasome inhibitor, the use of an NLRP3 inflammasome inhibitor, the kit, or the pharmaceutical package of any one of claims 19-30, wherein the GLP-1 receptor agonist is semaglutide.

32. The kit or the pharmaceutical package of any one of claims 23-31 further comprising instructions for use.

33. The combination, use, method, pharmaceutical package, or kit of any one of the preceding claims, wherein after treatment of the combination of NLRP3 inflammasome inhibitor and GLP-1 receptor agonist for about 7 days, about 14 days, about 28 days, or about 35 days, the NLRP3 inflammasome inhibitor is administered as a monotherapy.

34. The combination, use, method, pharmaceutical package, or kit of any one of the preceding claims, wherein the NLRP3 inflammasome inhibitor is administered as a monotherapy after treatment of the combination of NLRP3 inflammasome inhibitor and GLP-1 receptor agonist for 28 days.

35. The combination, use, method, pharmaceutical package, or kit of any one of the preceding claims, wherein the weight disorder is selected from a metabolic disorder, obesity, excessive body weight, and enhanced appetite.

36. The combination, use, method, pharmaceutical package, or kit of any one of the preceding claims, wherein the weight disorder is obesity.
37. The combination, use, method, pharmaceutical package, or kit of any one of the preceding claims, wherein the subject is a human.
38. The combination, use, method, pharmaceutical package, or kit of any one of the preceding claims, wherein the NLRP3 inflammasome inhibitor and GLP-1 receptor agonist are administered in temporal proximity, sequentially, or in alternation.
39. The combination, use, method, pharmaceutical package, or kit of any one of the preceding claims, wherein the NLRP3 inflammasome inhibitor and GLP-1 receptor agonist are administered as different formulations.