

ROCK2 INHIBITORS IN THE TREATMENT OF OBESITY**REFERENCE TO AN ELECTRONIC SEQUENCE LISTING**

[0001] This application contains a Sequence Listing which has been submitted electronically in xml format and is hereby incorporated by reference in its entirety. Said xml copy, created on September 26, 2024, is named SeqList-332930-48376.xml and is 31,680 bytes in size.

FIELD

[0002] The present disclosure provides methods for the treatment of obesity and/or type 2 diabetes. The present disclosure provides therapies using a Rho-associated coiled-coil containing protein kinase 2 (ROCK2) inhibitor and optionally a glucagon-like peptide 1 receptor (GLP-1) agonist for treating obesity, treating type 2 diabetes, and/or promoting weight loss in a subject. The present disclosure also provides methods for treating obesity and/or promoting weight loss in a subject, while preserving muscle mass of the subject, by administering to the subject a therapeutically effective amount of a ROCK2 inhibitor. Also, provided are methods for using the combination of a ROCK2 and a GLP-1 agonist and kits using the same.

SUMMARY

[0003] Described herein are methods of treating obesity and/or promoting weight loss in a subject by administering to the subject a therapeutically effective amount of a ROCK2 inhibitor.

[0004] Also described herein are method for reduction of HbA1c; and/or the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; and/or prevention or treatment of obesity or reducing body weight; wherein the method comprises administration of a therapeutically effective amount of a ROCK2 inhibitor, and optionally a therapeutically effective amount of a GLP-1 agonist to a patient in need thereof.

[0005] Also described herein are methods of preserving muscle mass in a subject that is being treated for obesity and/or undergoing weight loss by administering to the subject during the treatment/weight loss a therapeutically affective amount of ROCK2 inhibitor. The subject being treated for obesity and/or weight loss may be undergoing one or more of dietary calorie restriction, bariatric or other surgical intervention, and administration of a

pharmaceutical agent for weight loss, such as: a GLP-1 agonist; a sodium-glucose transporter 2 (SGLT2) inhibitor such as bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, sotagliflozin and tofogliflozin; a lipase inhibitor such as orlistat (Alli, Xenical); melanocortin-4 receptor agonist, such as setmelanotide (Imcivree); naltrexone-bupropion; phentermine; phentermine-topiramate; metformin; diethylpropion (amfepramone); and combinations thereof. Advantageously in the methods of this disclosure, the ROCK2 inhibitor is administered to the subject and reduces the loss of muscle in the subject during the weight loss.

[0006] In other aspects, this disclosure provides a method for treating obesity and/or promoting weight loss in a subject by administering to the subject a therapeutically effective amount of a ROCK2 inhibitor and optionally a therapeutically effective amount of a GLP-1 agonist. In an aspect, this disclosure also provided a method of treating obesity in a subject, the method comprising administering to the subject a combination of a therapeutically effective amount of a ROCK2 inhibitor, and a therapeutically effective amount of a GLP-1 agonist. In another aspect, the disclosure provides methods for promoting weight loss in a subject, comprising administering to the subject a combination of a therapeutically effective amount of a ROCK2 inhibitor, and a therapeutically effective amount of a GLP-1 agonist. Advantageously in the methods of the inventions, the ROCK2 inhibitor is administered to the subject and reduces the loss of muscle in the subject during the weight loss.

[0007] Also described herein are methods for treating type 2 diabetes and/or for the reduction of HbA1c in a subject by administering to the subject a therapeutically effective amount of a ROCK2 inhibitor. Also described herein are methods of preserving muscle mass in a subject that is being treated for type 2 diabetes by administering to the subject a therapeutically effective amount of ROCK2 inhibitor. The subject being treated for type 2 diabetes may be undergoing one or more of a dietary calorie restriction, and administration of a pharmaceutical agent for type 2 diabetes, such as: a GLP-1 agonist; a sodium-glucose transporter 2 (SGLT2) inhibitor such as bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, sotagliflozin and tofogliflozin; a lipase inhibitor such as orlistat (Alli, Xenical); melanocortin-4 receptor agonist, such as setmelanotide (Imcivree); naltrexone-bupropion; phentermine; phentermine-topiramate; metformin; diethylpropion (amfepramone); and combinations thereof.

[0008] In an aspect, the disclosure provides methods for treating type 2 diabetes in a subject in need thereof. The method comprises administering to the subject a combination of

a therapeutically effective amount of a ROCK2 inhibitor, and a therapeutically effective amount of a GLP-1 agonist.

[0009] In some embodiments, the ROCK2 inhibitor is a ribonucleic acid (RNA). In some embodiments, the ROCK2 inhibitor is antisense RNA against ROCK2 transcription. In some embodiments, the ROCK2 inhibitor is small interfering RNA (siRNA) or micro RNA (miRNA). In some embodiments, the combination includes the ROCK2 inhibitor that is a compound according to one or more of the formulae (A-I), (B-I), (C-I), (D-I), (E-I), (F-I), (G-I), (H-I), (J-I), (K-I), (L-I) and their subordinates, and exemplary compounds thereof. In some embodiments, the ROCK2 inhibitor is belumosudil (2-(3-(4-((1H-indazol-5-yl)amino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide), or a pharmaceutically acceptable salt thereof. In other embodiments the ROCK2 inhibitor is Zelasudil or a pharmaceutically acceptable salt thereof. In other embodiments, the ROCK2 inhibitor is selected from Compound A, Compound B, Compound C, and Compound D, or a pharmaceutically acceptable salt thereof. In an embodiment, the ROCK2 inhibitor is (6-(4-((4-(1H-pyrazol-4-yl)phenyl)amino)pyrimidin-2-yl)-1-methyl-1H-indol-2-yl)(3,3-difluoroazetidin-1-yl)methanone (Compound A), or a pharmaceutically acceptable salt thereof.

[0010] In some embodiments, the GLP-1 agonist is a compound having the structure of formula (M-I), (N-I), (O-I), (O-II), (P-I), (Q-I), (R-I), and their subordinates, or exemplary compounds thereof. In some embodiments, the GLP-1 agonist is a peptide having amino acid sequences of SEQ ID. Nos. 4-8, 9, 18, and 19-30, but are not limited thereto. In some embodiments, the GLP-1 agonist may be a peptide including amino acid sequences of SEQ ID. Nos. 1-30, but are not limited thereto. In some embodiments, the GLP-1 agonist is semaglutide, exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide, tirzepatide, lotiglipron, retatrutide, taspoglutide, orforglipron or danuglipron. In certain embodiments, the GLP-1 agonist is semaglutide. In other embodiments, the GLP-1 agonist is tirzepatide.

[0011] Further provided are kits including the combination of (i) a therapeutically effective amount of a ROCK2 inhibitor, and (ii) a therapeutically effective amount of a GLP-1 agonist. In some embodiments, the kits may be used for treating type 2 diabetes in a subject. In some embodiments, the kits may be used for treating obesity in a subject. In some embodiments, the kits may be used for weight loss program.

[0012] Other aspects of the invention are disclosed *infra*.

BRIEF DESCRIPTION OF THE FIGURES

[0013] **FIG. 1** shows absolute body weight change of obese mice after treating with ROCK2 inhibitor (Compound A) and/or semaglutide in comparison to non-treated mice and mice on a lean chow diet.

[0014] **FIG. 2** shows the dose-dependent reduction in body weight for mice treated with Compound A over the duration of the study (2A) and at termination (2B).

[0015] **FIG. 3** shows the reduction in fed blood glucose for mice treated with Compound A.

[0016] **FIG. 4** shows the measurement of fed blood glucose levels for mice treated with Compound A at baseline (week -1, 4A), at week 3 (4B), and week 6 (4C).

[0017] **FIG. 5** shows the reduction in blood levels of HbA1c for mice treated with Compound A.

[0018] **FIG. 6** shows the body weight over the study days in a diet induced obesity (DIO) model for mice treated with a ROCK2 inhibitor (Comp. A), a GLP-1 agonist (tirzepatide, TZP) or a combination of Compound A and TZP.

[0019] **FIG. 7** shows the oral glucose tolerance of mice after oral administration of glucose.

[0020] **FIG. 8** shows the effect of Compound A and/or tirzepatide on fasting blood glucose levels of mice during the DIO study.

[0021] **FIG. 9** shows the effect of Compound A and/or tirzepatide on HbA1c levels of mice during the DIO study.

[0022] **FIG. 10** shows the relative lean mass (%) at baseline, week 4, week 7 and week 12 for the mouse cohorts during the DIO study.

[0023] **FIG. 11** shows the shows the weight of adipose tissue (eWAT, iWAT and scWAT) for the mouse cohorts of the DIO study, demonstrating that treatment of the DIO mice with a ROCK2 inhibitor (Comp. A) lead to a reduction in adipose tissue.

[0024] **FIG. 12** shows that energy expenditure is elevated in the mouse cohorts that were administered Comp. A in the DIO study.

[0025] **FIG. 13** shows the amount of Uncoupling Protein 1 (UCP1) in adipose tissue is elevated in the mouse cohorts that were administered Comp. A in the DIO study.

[0026] **FIG. 14** shows that liver glycogen is reduced in the diet induced obesity (DIO) model for mice treated with Compound A or a combination of Compound A and TZP.

[0027] **FIG. 15** shows that GLUT4 levels in muscle is improved and restored in the diet induced obesity (DIO) model for mice treated with Compound A.

[0028] FIG. 16 shows the fasting plasma insulin at (A) baseline, (B) week 7 and (C) week 12 in the mouse cohorts of the DIO study, demonstrating that treatment of the DIO mice with a ROCK2 inhibitor (Comp. A) lead to a greatly reduced plasma insulin/improved insulin sensitivity.

[0029] FIG 17 shows fasting plasma leptin at (A) baseline, (B) week 7 and (C) week 12 in the mouse cohorts of the DIO study, demonstrating that treatment of the DIO mice with a ROCK2 inhibitor (Comp. A) lead to a greatly reduced plasma leptin.

DETAILED DESCRIPTION

[0030] The present invention will now be further described. In the following passages, different aspects of the invention are provided. Each aspect presented may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

[0031] Provided herein, *inter alia*, are therapies comprising a Rho-associated coiled-coil containing protein kinase 2 (ROCK2) inhibitor, and methods of using the ROCK2 inhibitor in the treatment of conditions or diseases, including but not limited to type 2 diabetes and/or obesity. The methods provided herein may be used for the reduction of HbA1c and/or for reduction of blood glucose levels in a patient.

[0032] The method provided herein may be used for the treatment of hyperglycemia and/or impaired glucose tolerance.

[0033] In other aspects, the method may be used in the prevention or treatment of obesity and/or reducing body weight, particularly in conjunction with the preservation of muscle mass or the reduction in the loss of muscle mass in the patient.

[0034] Also provided herein, are combination therapies comprising a ROCK2 inhibitor and a glucagon-like peptide 1 receptor (GLP-1) agonist, methods of using the combination therapy in the treatment of conditions or diseases, including but not limited to type 2 diabetes and/or obesity, and kits comprising a dosage form of a ROCK2 inhibitor and a dosage form of the GLP-1 agonist.

[0035] The combination therapy may be used in the treatment of type 2 diabetes in a subject. A combination therapy disclosed herein comprises a therapeutically effective amount of a ROCK2 inhibitor and a therapeutically effective amount of a GLP-1 agonist, which may synergistically enhance the treating the type 2 diabetes.

[0036] The combination therapy may also be used in a weight loss program and a kit, and the kit includes a dosage form of a ROCK2 inhibitor and a dosage form of the GLP-1 agonist. The combination therapies may be used in weight loss program or routine in a subject with or without type 2 diabetes or a risk thereof. Advantageously, the administration of the ROCK2 inhibitor may reduce the muscle loss experienced by the patient that is often associated with the use of the GLP-1 agonist.

ROCK2 Inhibitors

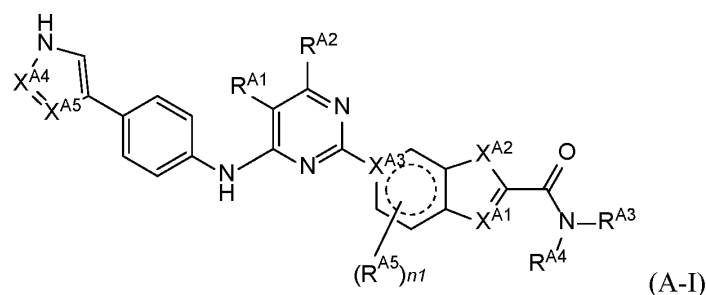
[0037] In the present disclosure, the therapy includes the use of ROCK2 inhibitors, and in particular ROCK2 selective inhibitors.

[0038] Rho-associated coiled-coil containing protein kinase 2 (ROCK) is a serine/threonine kinase from the AGC (PKA, PKG, and PKC) kinase family and comprises two isoforms, ROCK1 and ROCK2. The two isoforms are expressed and regulated differently in specific tissues. For example, ROCK1 is ubiquitously expressed at a relatively high level, while ROCK2 is preferentially expressed in certain tissues including heart, brain and skeletal muscle. ROCK2 inhibitors has been shown efficacious effects in inflammatory disease models.

[0039] The compounds for use in the methods and compositions disclosed herein are ROCK inhibitors, and in particular ROCK2 selective inhibitors. The compounds provide excellent inhibitory activity of ROCK2, and preferably have good selectivity (higher selectivity towards ROCK2 as compared with ROCK1). The compounds may additionally provide one or more of good physicochemical properties (e.g., solubility, physical and/or chemical stability), good pharmacokinetic properties (e.g., improved bioavailability, proper half-life and duration of action), and acceptable safety (low toxicity and/or less side effects, wide therapeutic window).

[0040] ROCK2 inhibitors are disclosed in, for example, WO2019/000682, WO 2019/000683, WO2019/001572, WO2020/094111, WO2020/177587, WO2020/259528, WO2022/042711, WO2022/042712, WO2006/105081, WO2019/145729, WO2007/007737, WO90/05723, WO2011/130740, WO2005/037197, WO2008/110846, WO2005/082890, WO2005/037197; US Pat. Nos. 10,323,023, 10,329,282, 11,390,609, 8,357,693, 9,815,820, 10,183,931, 10,696,660, 11,311,541, 11,497,751, 8,193,193, 4,997,834, 9,221,808, 7,547,779, 8,497,294, 7,592,357, 7,547,779; WO2023/209692 (entitled Inhibitors of ROCK2) and WO2024/110851, the disclosures of each are incorporated herein by reference.

[0041] In one aspect, the ROCK2 inhibitor has the structure of Formula (A-I):



or a pharmaceutically acceptable salt thereof, wherein:

R^{A1} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{x1}-C(=O)OR^{A11};

R^{A2} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{x1}-C(=O)OR^{A11};

alternatively, R^{A1} and R^{A2} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is substituted or unsubstituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, C₁-C₃ perfluoro alkyl, -NR^{A11}-(C₁-C₆ alkyl)NR^{A11}R^{A12}, and -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11};

R^{A3} and R^{A4} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆₋₁₂ aralkyl, -(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)OR^{A11}, and -(C₁-C₆ alkyl)_{x1}-C(=O)NR^{A11}R^{A12};

alternatively R^{A3} and R^{A4} are taken together with the nitrogen to which they are attached to provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, oxo, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11};

the dotted lines represent optional double bonds;

each R^{A5} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, oxo, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11};

$n1$ is 0 to 3;

X^{A1} is CR^{A6} or N;

X^{A2} is CHR^{A6}, NR^{A7}, O or S;

X^{A3} is C, CH or N;

X^{A4} is N or CH;

X^{A5} is N or CH;

each R^{A6} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11};

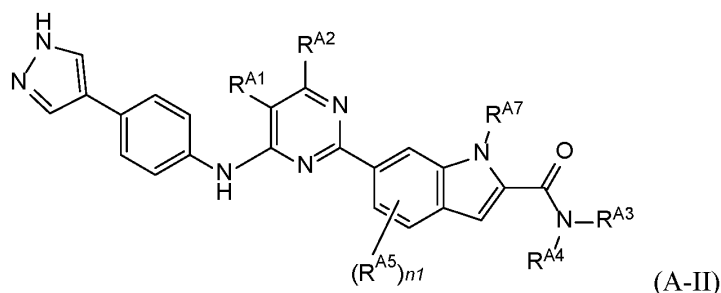
each R^{A7} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11}, and -(C₁-C₆ alkyl)_{xl}-C(=O)NR^{A11}R^{A12};

each x_1 is independently selected from 0 and 1; and

each R^{A11} and R^{A12} are independently selected from the group consisting of H and C₁-C₆ alkyl;

or alternatively, R^{A11} and R^{A12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, -NH₂, C₁-C₃ perfluoro alkyl, -OH, -O-(C₁-C₆ alkyl), and -(C₁-C₆ alkyl)-OH.

[0042] In embodiments, the ROCK2 inhibitor has the structure of Formula (A-II):



or a pharmaceutically acceptable salt thereof, wherein:

R^{A1} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -(C₁-C₆ alkyl)_x-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)OR^{A11}.

R^{A2} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -

$C(=O)OR^{A11}$, $-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)R^{A11}$, and $-NR^{A11}-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)OR^{A11}$;

alternatively, R^{A1} and R^{A2} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C_1-C_6 alkyl, halo, $-CN$, $-OH$, oxo, $-O-(C_1-C_6 \text{ alkyl})$, $-O-(C_1-C_6 \text{ alkyl})-OH$, $-O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-NR^{A11}R^{A12}$, $-O-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, C_1-C_3 perfluoro alkyl, $-NR^{A11}-(C_1-C_6 \text{ alkyl})NR^{A11}R^{A12}$, and $-NR^{A11}-(C_1-C_6 \text{ alkyl})-OR^{A11}$;

R^{A3} and R^{A4} are each independently selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, 3- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 14-membered heteroaryl, C_{6-12} aralkyl, $-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)R^{A11}$, $-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)OR^{A11}$, and $-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)NR^{A11}R^{A12}$;

alternatively R^{A3} and R^{A4} are taken together with the nitrogen to which they are attached to provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring to heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, halo, $-CN$, C_1-C_3 perfluoro alkyl, $-OR^{A11}$, oxo, $-O-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-NR^{A11}R^{A12}$, $-O-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)R^{A11}$, $-O-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)R^{A11}$, $-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)OR^{A11}$, $-C(=O)-R^{A11}$, $-C(=O)OR^{A11}$, $-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)R^{A11}$, and $-NR^{A11}-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)OR^{A11}$;

the dotted lines represent optional double bonds;

each R^{A5} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, halo, $-CN$, C_1-C_3 perfluoro alkyl, oxo, $-OR^{A11}$, $-O-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-NR^{A11}R^{A12}$, $-O-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)R^{A11}$, $-O-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)R^{A11}$, $-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)OR^{A11}$,

$-C(=O)-R^{A11}$, $-C(=O)OR^{A11}$, $-(C_1-C_6 \text{ alkyl})_{x/l}-C(=O)NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})_{x/l}-C(=O)R^{A11}$, and $-NR^{A11}-(C_1-C_6 \text{ alkyl})_{x/l}-C(=O)OR^{A11}$;

n/l is 0 to 3;

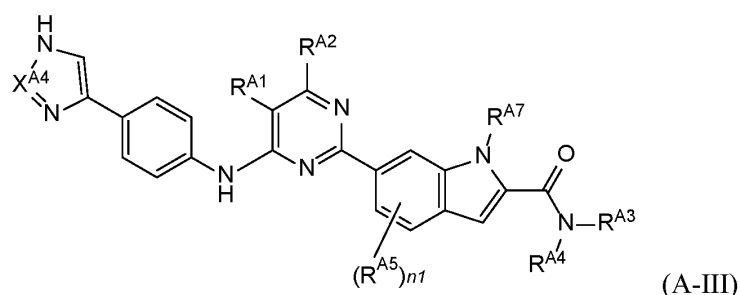
R^{A7} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, $-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-(C_1-C_6 \text{ alkyl})_{x/l}-C(=O)R^{A11}$, $-(C_1-C_6 \text{ alkyl})_{x/l}-C(=O)OR^{A11}$, and $-(C_1-C_6 \text{ alkyl})_{x/l}-C(=O)NR^{A11}R^{A12}$;

each x/l is independently selected from 0 and 1; and

each R^{A11} and R^{A12} are independently selected from the group consisting of H and C_1-C_6 alkyl;

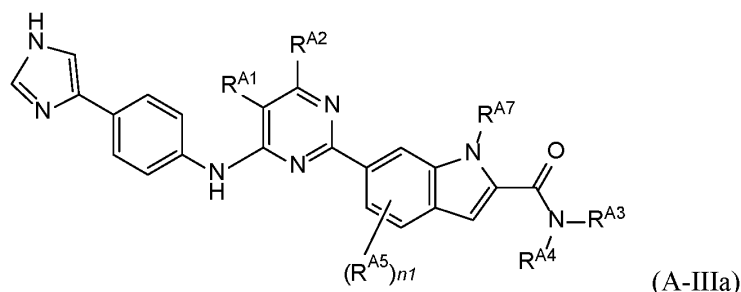
or alternatively, R^{A11} and R^{A12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, $-CN$, $-NH_2$, C_1-C_3 perfluoro alkyl, $-OH$, $-O-(C_1-C_6 \text{ alkyl})$, and $-(C_1-C_6 \text{ alkyl})-OH$.

[0043] In some embodiments, the ROCK2 inhibitor has the structure of Formula (A-III):



or a pharmaceutically acceptable salt thereof. R^{A1} , R^{A2} , R^{A3} , R^{A4} , R^{A5} , R^{A7} , X^4 and $n1$ are as described above.

[0044] In some embodiments, the ROCK2 inhibitor has the structure of Formula (A-IIIa):



or a pharmaceutically acceptable salt thereof, wherein:

R^{A1} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -(C₁-C₆ alkyl)_x-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)OR^{A11};

R^{A2} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -(C₁-C₆ alkyl)_x-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)OR^{A11};

alternatively, R^{A1} and R^{A2} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, C₁-C₃ perfluoro alkyl, -NR^{A11}-(C₁-C₆ alkyl)NR^{A11}R^{A12}, and -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11};

R^{A3} and R^{A4} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆-₁₂ aralkyl, -(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -(C₁-C₆ alkyl)_x-C(=O)OR^{A11}, and -(C₁-C₆ alkyl)_x-C(=O)NR^{A11}R^{A12};

alternatively R^{A3} and R^{A4} are taken together with the nitrogen to which they are attached to provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, oxo, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-

C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{xI}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{xI}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xI}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{xI}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{xI}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{xI}-C(=O)OR^{A11},

the dotted lines represent optional double bonds;

each R^{A5} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆

alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, oxo, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{xI}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{xI}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xI}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{xI}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{xI}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{xI}-C(=O)OR^{A11},

nI is 0 to 3;

R^{A7} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-

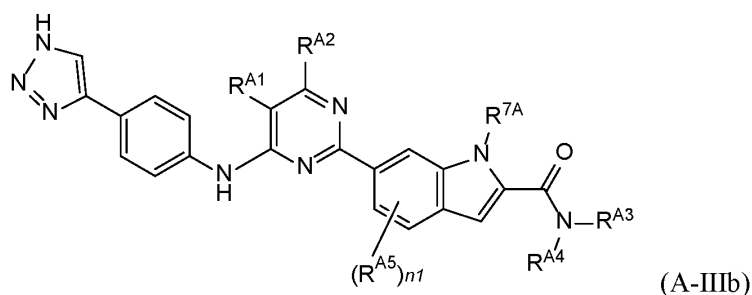
C₆ alkynyl, C₃-C₇ cycloalkyl, -(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)_{xI}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xI}-C(=O)OR^{A11}, and -(C₁-C₆ alkyl)_{xI}-C(=O)NR^{A11}R^{A12},

each *xI* is independently selected from 0 and 1; and

each R^{A11} and R^{A12} are independently selected from the group consisting of H and C₁-C₆ alkyl;

or alternatively, R^{A11} and R^{A12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, -NH₂, C₁-C₃ perfluoro alkyl, -OH, -O-(C₁-C₆ alkyl), and -(C₁-C₆ alkyl)-OH.

[0045] In some embodiments, the ROCK2 inhibitor has the structure of Formula (A-IIIb):



or a pharmaceutically acceptable salt thereof, wherein:

R^{A1} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{x/l}-C(=O)OR^{A11};

R^{A2} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{x/l}-C(=O)OR^{A11};

alternatively, R^{A1} and R^{A2} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, C₁-C₃ perfluoro alkyl, -NR^{A11}-(C₁-C₆ alkyl)NR^{A11}R^{A12}, and -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11};

R^{A3} and R^{A4} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆₋₁₂ aralkyl, -(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)OR^{A11}, and -(C₁-C₆ alkyl)_{x/l}-C(=O)NR^{A11}R^{A12};

alternatively R^{A3} and R^{A4} are taken together with the nitrogen to which they are attached to provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring to heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, oxo, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11};

the dotted lines represent optional double bonds;

each R^{A5} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, oxo, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11};

nl is 0 to 3;

R^{A7} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11}, and -(C₁-C₆ alkyl)_{xl}-C(=O)NR^{A11}R^{A12};

each xl is independently selected from 0 and 1; and

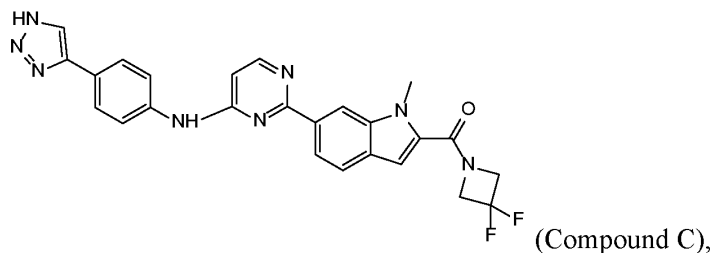
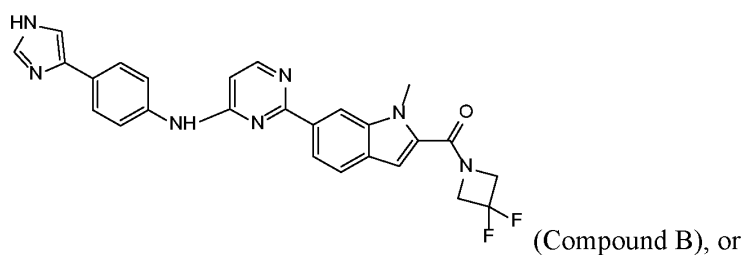
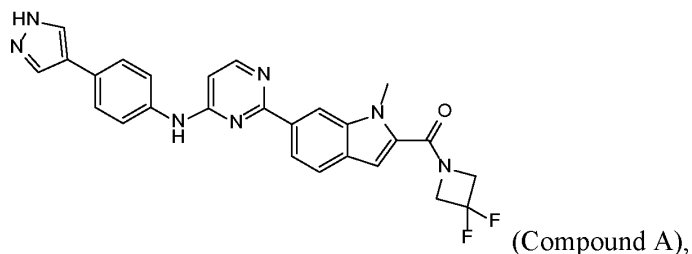
each R^{A11} and R^{A12} are independently selected from the group consisting of H and C₁-C₆ alkyl;

or alternatively, R^{A11} and R^{A12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group

consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, -NH₂, C₁-C₃ perfluoro alkyl, -OH, -O-(C₁-C₆ alkyl), and -(C₁-C₆ alkyl)-OH.

[0046] In some embodiments, R^{A5} is hydrogen, or n1 is 0.

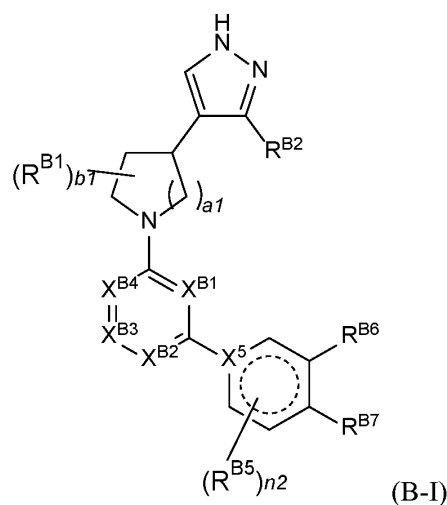
[0047] In some embodiments, the ROCK2 inhibitor has the structure:



or a pharmaceutically acceptable salt thereof.

[0048] The compounds of Formula (A-I) and its subordinates, as well as other disclosed ROCK2 inhibitors, may be synthesized and assayed for ROCK2 inhibition activity *in vitro* as described in, for example, WO2019/000682, WO 2019/000683, WO2019/001572, WO2020/094111, WO2020/177587, WO2020/259528, WO2022/042711, WO2022/042712 and US Pat. No. 10,323,023, 10,329,282 and 11,390,609, and WO2023/209692, the entire contents of which are each incorporated herein by reference.

[0049] In another aspect, the ROCK2 inhibitor has the structure of Formula (B-I):



or a pharmaceutically acceptable salt thereof, wherein:

X^{B1} is N or CH;

X^{B2} is N or CH;

X^{B3} is N or CR^{B3} ;

X^{B4} is N or CR^{B4} ;

X^{B5} is selected from the group consisting of C, CH and N;

$a1$ is selected from 1 or 2;

the dotted lines represent optional double bonds;

each R^{B1} is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_7 cycloalkyl, halo, oxo, -CN, C_1 - C_3 perfluoro alkyl, $-OR^{B11}$, and $-NR^{B11}R^{B12}$;

or alternatively, two R^{B1} attached to the same carbon or to adjacent carbons are taken together to form a 3- to 6-membered ring, which may optionally contain 0 to 2 ring heteroatoms selected from O, S and N, and which may be unsubstituted or optionally substituted by 1 to 3 substituents selected from halo, C_1 - C_3 alkyl, NH_2 , OH, and O - C_1 - C_3 alkyl;

$b1$ is selected from 0, 1, and 2;

R^{B2} is selected from H, halo, C_1 - C_3 alkyl, NH_2 , OH, and O - C_1 - C_3 alkyl;

R^{B3} is selected from the group consisting of H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_7 cycloalkyl, halo, -CN, C_1 - C_3 perfluoro alkyl, $-OR^{B11}$, $-O$ -(C_1 - C_6 alkyl)- OR^{B11} , $-(C_1$ - C_6 alkyl)- OR^{B11} , $-NR^{B11}R^{B12}$, $-O$ -(C_1 - C_6 alkyl)- $NR^{B11}R^{B12}$, $-(C_1$ - C_6 alkyl)- $NR^{B11}R^{B12}$, $-NR^{B11}$ -(C_1 - C_6 alkyl)- $NR^{B11}R^{B12}$, $-NR^{B11}$ -(C_1 - C_6 alkyl)- OR^{B11} , $-(C_1$ - C_6 alkyl) $_2$ - $C(=O)R^{B11}$, $-O$ -(C_1 - C_6 alkyl) $_2$ - $C(=O)R^{B11}$, $-(C_1$ - C_6 alkyl) $_2$ - $C(=O)OR^{B11}$, $-C(=O)-R^{B11}$, -

$C(=O)OR^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)NR^{B11}R^{B12}$, $-NR^{B11}-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)R^{B11}$, and $-NR^{B11}-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)OR^{B11}$;

R^{B4} is selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, halo, $-CN$, C_1-C_3 perfluoro alkyl, $-OR^{B11}$, $-O-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-NR^{B11}R^{B12}$, $-O-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-NR^{B11}-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-NR^{B11}-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)R^{B11}$, $-O-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)R^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)OR^{B11}$, $-C(=O)-R^{B11}$, $-C(=O)OR^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)NR^{B11}R^{B12}$, $-NR^{B11}-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)R^{B11}$, and $-NR^{B11}-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)OR^{B11}$;

alternatively, R^{B3} and R^{B4} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is substituted or unsubstituted with 1 to 3 substituents selected from the group consisting of C_1-C_6 alkyl, halo, $-CN$, $-OH$, oxo, $-O-(C_1-C_6 \text{ alkyl})$, $-O-(C_1-C_6 \text{ alkyl})-OH$, $-O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-NR^{B11}R^{B12}$, $-O-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, C_1-C_3 perfluoro alkyl, $-NR^{B11}-(C_1-C_6 \text{ alkyl})NR^{B11}R^{B12}$, and $-NR^{B11}-(C_1-C_6 \text{ alkyl})-OR^{B11}$;

each R^{B5} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, halo, $-CN$, C_1-C_3 perfluoro alkyl, oxo, $-OR^{B11}$, $-O-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-NR^{B11}R^{B12}$, $-O-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-NR^{B11}-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-NR^{B11}-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)R^{B11}$, $-O-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)R^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)OR^{B11}$, $-C(=O)-R^{B11}$, $-C(=O)OR^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)NR^{B11}R^{B12}$, $-NR^{B11}-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)R^{B11}$, and $-NR^{B11}-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)OR^{B11}$;

$n2$ is 0 to 3;

R^{B6} and R^{B7} are independently selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, halo, $-CN$, C_1-C_3 perfluoro alkyl, $-OR^{B11}$, $-O-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-NR^{B11}R^{B12}$, $-O-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-O-(C_1-C_6 \text{ alkyl})-C(=O)NR^{B11}R^{B12}$, $-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{B11}R^{B12}$, $-NR^{B11}-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-NR^{B11}-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)R^{B11}$, $-O-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)R^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)OR^{B11}$, $-C(=O)-R^{B11}$, $-C(=O)OR^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)NR^{B11}R^{B12}$, $-NR^{B11}-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)R^{B11}$, and $-NR^{B11}-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)OR^{B11}$;

alternatively, R^{B6} and R^{B7} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the

group consisting of N, O, and S, and which is substituted or unsubstituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₅-C₁₀ aryl, C₅-C₁₀ heteroaryl, 3- to 10-membered heterocyclyl, -C₁-C₆ alkyl-(C₃-C₇ cycloalkyl), -C₁-C₆ alkyl-(C₅-C₁₀ aryl), -C₁-C₆ alkyl-(C₅-C₁₀ heteroaryl), -C₁-C₆ alkyl-(3- to 10-membered heterocyclyl), halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, C₁-C₃ perfluoro alkyl, -NR^{B11}-(C₁-C₆ alkyl)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, and -C(=O)-N(R^{B8})(R^{B9}), and wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclyl may optionally be substituted with one to three substituents selected from C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, oxo, halo, -CN, -OH, and NH₂;

R^{B8} and R^{B9} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆₋₁₂ aralkyl, -(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, and -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, wherein each alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl may optionally be substituted with one to three substituents selected from C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, oxo, halo, -CN, -OH, and NH₂;

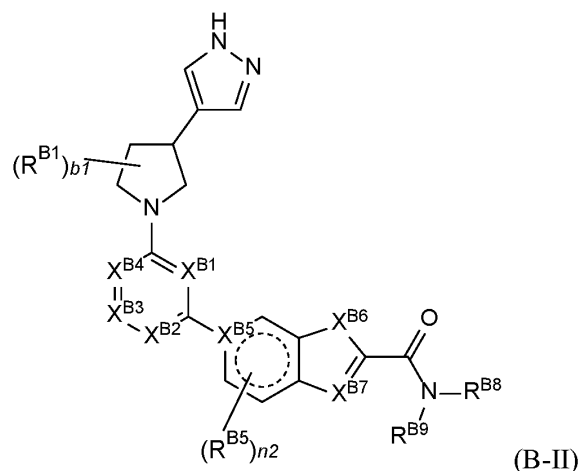
alternatively R^{B8} and R^{B9} are taken together with the nitrogen to which they are attached provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, C₁-C₆ fluoroalkyl, C₁-C₃ perfluoro alkyl, -OR^{B11}, oxo, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

each x2 is independently selected from 0 and 1; and

each R^{B11} and R^{B12} are independently selected from the group consisting of H and C₁-C₆ alkyl;

or alternatively, R^{B11} and R^{B12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_7 cycloalkyl, -CN, - NH_2 , C_1 - C_3 perfluoroalkyl, -OH, -O-(C_1 - C_6 alkyl), and -(C_1 - C_6 alkyl)-OH.

[0050] In some embodiments, the ROCK2 inhibitor has the structure of Formula (B-II):



or a pharmaceutically acceptable salt thereof, wherein:

X^{B1} is N or CH;

X^{B2} is N or CH;

X^{B3} is N or CR^{B3} ;

X^{B4} is N or CR^{B4} ;

X^{B5} is selected from the group consisting of C, CH and N;

the dotted lines represent optional double bonds;

each R^{B1} is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_2 - C_6

alkenyl, C_2 - C_6 alkynyl, C_3 - C_7 cycloalkyl, halo, oxo, -CN, C_1 - C_3 perfluoro alkyl, -OR^{B11},

and

-NR^{B11}R^{B12};

or alternatively, two R^{B1} attached to the same carbon or to adjacent carbons are taken together

to form a 3- to 6-membered ring, which may optionally contain 0 to 2 ring heteroatoms

selected from O, S and N, and which may be unsubstituted or optionally substituted by

1 to 3 substituents selected from halo, C_1 - C_3 alkyl, NH_2 , OH, and O- C_1 - C_3 alkyl;

$b1$ is selected from 0, 1, and 2;

R^{B3} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

R^{B4} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x22}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x22}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x22}-C(=O)OR^{B11};

alternatively, R^{B3} and R^{B4} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is substituted or unsubstituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, C₁-C₃ perfluoro alkyl, -NR^{B11}-(C₁-C₆ alkyl)NR^{B11}R^{B12}, and -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11};

each R^{B5} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, oxo, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

$n2$ is 0 to 3;

X^6 is selected from the group consisting of NR^{B10}, O and S;

X^7 is selected from the group consisting of CH and N;

R^{B8} and R^{B9} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆₋₁₂ aralkyl, -(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-

$\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x2}\text{-C(=O)}\text{R}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x2}\text{-C(=O)}\text{OR}^{\text{B11}}$, and $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x2}\text{-C(=O)}\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, wherein each alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl may optionally be substituted with one to three substituents selected from $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_1\text{-C}_3$ perfluoroalkyl, oxo, halo, $-\text{CN}$, $-\text{OH}$, and NH_2 ;

alternatively R^{B8} and R^{B9} are taken together with the nitrogen to which they are attached provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $-\text{CN}$, $\text{C}_1\text{-C}_6$ fluoroalkyl, $\text{C}_1\text{-C}_3$ perfluoro alkyl, $-\text{OR}^{\text{B11}}$, oxo, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x2}\text{-C(=O)}\text{R}^{\text{B11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x2}\text{-C(=O)}\text{R}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x2}\text{-C(=O)}\text{OR}^{\text{B11}}$, $-\text{C(=O)}-\text{R}^{\text{B11}}$, $-\text{C(=O)}\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x2}\text{-C(=O)}\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x2}\text{-C(=O)}\text{R}^{\text{B11}}$, and $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x2}\text{-C(=O)}\text{OR}^{\text{B11}}$;

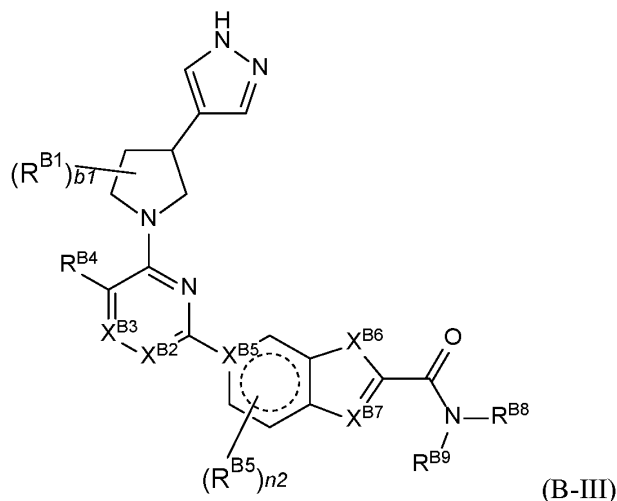
R^{B10} is selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $\text{C}_5\text{-C}_{10}$ aryl, $\text{C}_5\text{-C}_{10}$ heteroaryl, 3- to 10-membered heterocyclyl, $-\text{C}_1\text{-C}_6 \text{ alkyl}-(\text{C}_3\text{-C}_7 \text{ cycloalkyl})$, $-\text{C}_1\text{-C}_6 \text{ alkyl}-(\text{C}_5\text{-C}_{10} \text{ aryl})$, $-\text{C}_1\text{-C}_6 \text{ alkyl}-(\text{C}_5\text{-C}_{10} \text{ heteroaryl})$, $-\text{C}_1\text{-C}_6 \text{ alkyl}-(3\text{- to } 10\text{-membered heterocyclyl})$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, and $-\text{C(=O)}-\text{N}(\text{R}^{\text{B11}})(\text{R}^{\text{B12}})$, and wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclyl may optionally be substituted with one to three substituents selected from $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_1\text{-C}_3$ perfluoroalkyl, oxo, halo, $-\text{CN}$, $-\text{OH}$, and NH_2 ;

each $x2$ is independently selected from 0 and 1; and

each R^{B11} and R^{B12} are independently selected from the group consisting of H and $\text{C}_1\text{-C}_6$ alkyl;

or alternatively, R^{B11} and R^{B12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $-\text{CN}$, $-\text{NH}_2$, $\text{C}_1\text{-C}_3$ perfluoroalkyl, $-\text{OH}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$, and $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OH}$.

[0051] In some embodiments, the ROCK2 inhibitor has the structure of Formula (B-III):



or a pharmaceutically acceptable salt thereof, wherein:

X^{B2} is N or CH;

X^{B^3} is $\mathbf{N}$ or $\mathbf{CR}^{B^3}$.

X^{B5} is selected from the group consisting of C, CH and N;

the dotted lines represent optional double bonds;

each R^{B1} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, oxo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, and -NR^{B11}R^{B12}.

or alternatively, two R^{B1} attached to the same carbon or to adjacent carbons are taken together to form a 3- to 6-membered ring, which may optionally contain 0 to 2 ring heteroatoms selected from O, S and N, and which may be unsubstituted or optionally substituted by 1 to 3 substituents selected from halo, C₁-C₃ alkyl, NH₂, OH, and O-C₁-C₃ alkyl;

b1 is selected from 0, 1, and 2;

R^{B3} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

R^{B4} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

alternatively, R^{B3} and R^{B4} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is substituted or unsubstituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, C₁-C₃ perfluoro alkyl, -NR^{B11}-(C₁-C₆ alkyl)NR^{B11}R^{B12}, and -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11};

each R^{B5} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, oxo, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

$n2$ is 0 to 3;

X^{B6} is selected from the group consisting of NR^{B10}, O and S;

X^{B7} is selected from the group consisting of CH and N;

R^{B8} and R^{B9} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆₋₁₂ aralkyl, -(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)_x-C(=O)R^{B11}, -(C₁-C₆ alkyl)_x-C(=O)OR^{B11}, and -(C₁-C₆ alkyl)_x-C(=O)NR^{B11}R^{B12}, wherein each alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl may optionally be substituted with one to three substituents selected from C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, oxo, halo, -CN, -OH, and NH₂;

alternatively R^{B8} and R^{B9} are taken together with the nitrogen to which they are attached provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring

system having from 0 to 3 additional ring heteroatoms selected from N, O and S;
 wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, C₁-C₆ fluoroalkyl, C₁-C₃ perfluoro alkyl, -OR^{B11}, oxo, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

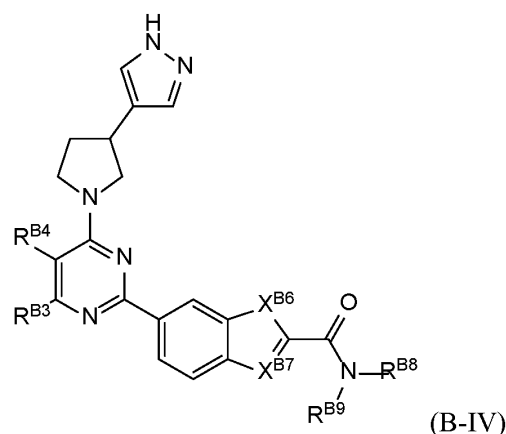
R^{B10} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₅-C₁₀ aryl, C₅-C₁₀ heteroaryl, 3- to 10-membered heterocyclyl, -C₁-C₆ alkyl-(C₃-C₇ cycloalkyl), -C₁-C₆ alkyl-(C₅-C₁₀ aryl), -C₁-C₆ alkyl-(C₅-C₁₀ heteroaryl), -C₁-C₆ alkyl-(3- to 10-membered heterocyclyl), -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-OR^{B11}, and -C(=O)-N(R^{B11})(R^{B12}), and wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclyl may optionally be substituted with one to three substituents selected from C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, oxo, halo, -CN, -OH, and NH₂;

each x₂ is independently selected from 0 and 1; and

each R^{B11} and R^{B12} are independently selected from the group consisting of H and C₁-C₆ alkyl;

or alternatively, R^{B11} and R^{B12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, -NH₂, C₁-C₃ perfluoroalkyl, -OH, -O-(C₁-C₆ alkyl), and -(C₁-C₆ alkyl)-OH.

[0052] In some embodiments, the ROCK2 inhibitor has the structure of Formula (B-IV):



or a pharmaceutically acceptable salt thereof, wherein:

R^{B3} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

R^{B4} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

alternatively, R^{B3} and R^{B4} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is substituted or unsubstituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, C₁-C₃ perfluoro alkyl, -NR^{B11}-(C₁-C₆ alkyl)NR^{B11}R^{B12}, and -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11};

X^{B6} is selected from the group consisting of NR^{B10} , O and S;

X^{B7} is selected from the group consisting of CH and N;

R^{B8} and R^{B9} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆₋₁₂ aralkyl, $-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)R^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)OR^{B11}$, and $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)NR^{B11}R^{B12}$, wherein each alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl may optionally be substituted with one to three substituents selected from C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, oxo, halo, -CN, -OH, and NH₂;

alternatively R^{B8} and R^{B9} are taken together with the nitrogen to which they are attached provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, C₁-C₆ fluoroalkyl, C₁-C₃ perfluoro alkyl, $-OR^{B11}$, oxo, $-O-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-NR^{B11}R^{B12}$, $-O-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-NR^{B11}-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-NR^{B11}-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)R^{B11}$, $-O-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)R^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)OR^{B11}$, $-C(=O)-R^{B11}$, $-C(=O)OR^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)NR^{B11}R^{B12}$, $-NR^{B11}-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)R^{B11}$, and $-NR^{B11}-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)OR^{B11}$;

R^{B10} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₅-C₁₀ aryl, C₅-C₁₀ heteroaryl, 3- to 10-membered heterocyclyl, $-C_1-C_6 \text{ alkyl}-(C_3-C_7 \text{ cycloalkyl})$, $-C_1-C_6 \text{ alkyl}-(C_5-C_{10} \text{ aryl})$, $-C_1-C_6 \text{ alkyl}-(C_5-C_{10} \text{ heteroaryl})$, $-C_1-C_6 \text{ alkyl}-(3- \text{ to } 10\text{-membered heterocyclyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-(C_1-C_6 \text{ alkyl})NR^{B11}R^{B12}$, $-(C_1-C_6 \text{ alkyl})-OR^{B11}$, and $-C(=O)-N(R^{B11})(R^{B12})$, and wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclyl may optionally be substituted with one to three substituents selected from C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, oxo, halo, -CN, -OH, and NH₂;

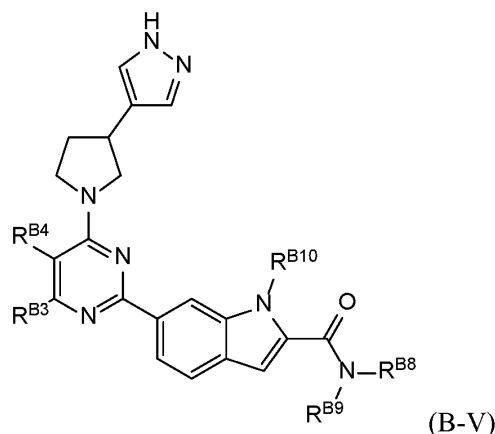
each $x2$ is independently selected from 0 and 1; and

each R^{B11} and R^{B12} are independently selected from the group consisting of H and C₁-C₆ alkyl;

or alternatively, R^{B11} and R^{B12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic

ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, -NH₂, C₁-C₃ perfluoroalkyl, -OH, -O-(C₁-C₆ alkyl), and -(C₁-C₆ alkyl)-OH.

[0053] In some embodiments, the ROCK2 inhibitor has the structure of Formula (B-V):



or a pharmaceutically acceptable salt thereof, wherein:

R^{B3} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

R^{B4} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

alternatively, R^{B3} and R^{B4} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is substituted or unsubstituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{B11}R^{B12}, -O-

(C₁-C₆ alkyl)-NR^{B11}R^{B12}, C₁-C₃ perfluoro alkyl, -NR^{B11}-(C₁-C₆ alkyl)NR^{B11}R^{B12}, and -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11},

R^{B8} and R^{B9} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆₋₁₂ aralkyl, -(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, and -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, wherein each alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl may optionally be substituted with one to three substituents selected from C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, oxo, halo, -CN, -OH, and NH₂;

alternatively R^{B8} and R^{B9} are taken together with the nitrogen to which they are attached provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, C₁-C₆ fluoroalkyl, C₁-C₃ perfluoro alkyl, -OR^{B11}, oxo, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

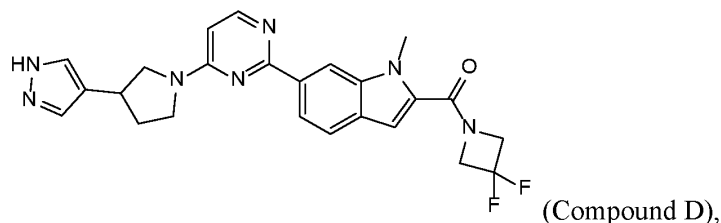
R^{B10} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₅-C₁₀ aryl, C₅-C₁₀ heteroaryl, 3- to 10-membered heterocyclyl, -C₁-C₆ alkyl-(C₃-C₇ cycloalkyl), -C₁-C₆ alkyl-(C₅-C₁₀ aryl), -C₁-C₆ alkyl-(C₅-C₁₀ heteroaryl), -C₁-C₆ alkyl-(3- to 10-membered heterocyclyl), -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-OR^{B11}, and -C(=O)-N(R^{B11})(R^{B12}), and wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclyl may optionally be substituted with one to three substituents selected from C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, oxo, halo, -CN, -OH, and NH₂;

each x2 is independently selected from 0 and 1; and

each R^{B11} and R^{B12} are independently selected from the group consisting of H and C₁-C₆ alkyl;

or alternatively, R^{B11} and R^{B12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, -NH₂, C₁-C₃ perfluoroalkyl, -OH, -O-(C₁-C₆ alkyl), and -(C₁-C₆ alkyl)-OH.

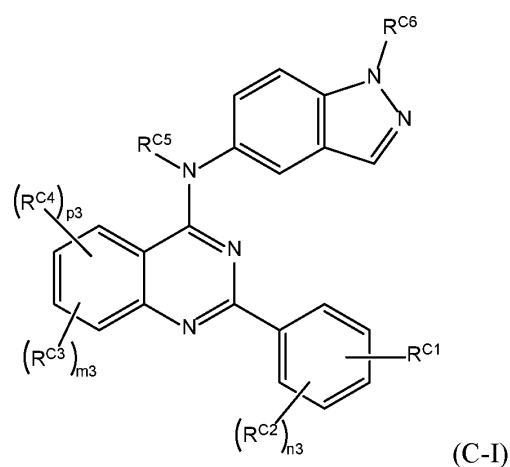
[0054] In some embodiments, the ROCK2 inhibitor has the structure of:



or a pharmaceutically acceptable salt thereof.

[0055] Synthesis and biological assays of Formula (B-I) and its subordinates are described in WO2024/110851 (entitled Inhibitors of ROCK2), the entire disclosure of which is incorporated herein by reference.

[0056] In one aspect, the ROCK2 inhibitor has the structure of Formula (C-I):



or a pharmaceutically acceptable salt thereof, wherein:

R^{C1} is selected from the group consisting of -O-(CH₂)₃-CO₂ R^{C12} , -O-(CH₂)₃-C(=O)NR^{C13} R^{C14} , -O-(CH₂)₃-heteroaryl, -O-(CH₂)₃-cycloalkyl, -O-C(=O)-(CH₂)₃-NR^{C13} R^{C14} , -O-(CH₂)_{2,3}-NR^{C13} R^{C14} , -NH-C(=O)-(CH₂)-NR^{C13} R^{C14} , -NH-C(=O)-X³- R^{C15} , -NH-(CH₂)₃-NR^{C13} R^{C14} ,

R^{C12} is selected from the group consisting of C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR^{C16} R^{C17} , -(C₁-C₆ alkyl)-C(=O)NR^{C16} R^{C17} , -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-

(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted at one or more carbon atoms by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

R^{C13} and R^{C14} are independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR^{C16}R^{C17}, -(C₁-C₆ alkyl)-C(=O)NR^{C16}R^{C17}, aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₇ cycloalkyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R^{C13} and R^{C14} may be taken together to form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₇ cycloalkyl, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

X³ is selected from a covalent bond, O, NH, and C₁-C₆ alkyl;

R^{C15} is selected from the group consisting of heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl,

or R^{C15} is selected from -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR^{C16}R^{C17}, -CO₂R^{C18}, -O-(CH₂)₃-CO₂R^{C18}, and -C(=O)NR^{C16}R^{C17};

R^{C16} and R^{C17} are independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R^{C16} and R^{C17} may be taken together to form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

R^{C18} is selected from the group consisting of H, aryl, aralkyl, heteroaryl, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR^{C16}R^{C17}, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-

(C₁-C₆ alkyl), each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoroalkyl;

x₃ is selected from 0 to 6;

y₃ is selected from 0 to 6;

each R^{C2} is independently selected from the group consisting of lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, and perfluoro lower alkyl;

each R^{C3} is independently selected from the group consisting of lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, and perfluoro lower alkyl;

R^{C4} is selected from H, -(CH₂)_{a3}-NR^{C43}R^{C44}, -Y-R^{C42}, -O-(CH₂)_{a3}-CO₂R^{C42}, -O-(CH₂)_{a3}-C(=O)NR^{C43}R^{C44}, -O-(CH₂)_{a3}-heteroaryl, -O-(CH₂)_{a3}-cycloalkyl, -O-C(=O)-(CH₂)_{a3}-NR^{C43}R^{C44}, -O-(CH₂)_{c3}-NR^{C43}R^{C44}, -NH-C(=O)-(CH₂)_a-NR^{C43}R^{C44}, -NH-C(=O)-Y-R^{C45}, -NH-C(=O)-(CH₂)_{a3}-NR^{C43}R^{C44};

R^{C42} is selected from the group consisting of C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR^{C46}R^{C47}, -(C₁-C₆ alkyl)-C(=O)NR^{C46}R^{C47}, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted at one or more carbon atoms by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

R^{C43} and R^{C44} are independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR^{C46}R^{C47}, -(C₁-C₆ alkyl)-C(=O)NR^{C46}R^{C47}, aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₇ cycloalkyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R^{C43} and R^{C44} may be taken together to form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

Y is selected from a covalent bond, O, NH, and C₁-C₆ alkyl;

R^{C45} is selected from the group consisting of H, aryl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR^{C46}R^{C47}, -CO₂R^{C48}, -O-(CH₂)_{b3}-CO₂R^{C48}, and -C(=O)NR^{C46}R^{C47};

R^{C46} and R^{C47} independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-

C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R^{C46} and R^{C47} may be taken together to form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

R^{C48} is selected from the group consisting of H, aryl, aralkyl, heteroaryl, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR^{C46}R^{C47}, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoroalkyl;

a3 is selected from 0 to 6;

b3 is selected from 0 to 6;

c3 is selected from 2 to 6;

R^{C5} is selected from the group consisting of H, C₁-C₆ alkyl, -(CH₂)_{d3}-C(=O)-NR^{C53}R^{C54}, -C(=O)-(CH₂)_{d3}-NR^{C53}R^{C54}, -C(=O)-X-R^{C55}, and -C(=O)-(CH₂)_{d3}-NR^{C53}R^{C54},

R^{C53} and R^{C54} are independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR^{C56}R^{C57}, -(C₁-C₆ alkyl)-C(=O)NR^{C56}R^{C57}, aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₇ cycloalkyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R^{C53} and R^{C54} may be taken together to form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₇ cycloalkyl, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

R^{C55} is selected from the group consisting of H, aryl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR^{C56}R^{C57}, -CO₂R^{C58}, -O-(CH₂)_{e3}-CO₂R^{C58}, and -C(=O)NR^{C56}R^{C57},

R^{C56} and R^{C57} independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3

heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R^{C56} and R^{C57} may be taken together to form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

R^{C58} is selected from the group consisting of H, aryl, aralkyl, heteroaryl, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR^{C56}R^{C57}, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoroalkyl;

d3 is selected from 0 to 6;

e3 is selected from 0 to 6;

R^{C6} is selected from the group consisting of H, C₁-C₆ alkyl, -(CH₂)₃-C(=O)-NR^{C63}R^{C64}, -C(=O)-(CH₂)₃-NR^{C63}R^{C64}, -C(=O)-X-R^{C65}, and -C(=O)-(CH₂)₃-NR^{C63}R^{C64};

R^{C63} and R^{C64} are independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR^{C66}R^{C67}, -(C₁-C₆ alkyl)-C(=O)NR^{C66}R^{C67}, aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₇ cycloalkyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R^{C63} and R^{C64} may be taken together to form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₇ cycloalkyl, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

R^{C65} is selected from the group consisting of H, aryl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR^{C66}R^{C67}, -CO₂R^{C68}, -O-(CH₂)₃-CO₂R^{C68}, and -C(=O)NR^{C66}R^{C67};

R^{C66} and R^{C67} independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents

independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R^{C66} and R^{C67} may be taken together to form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

R^{C68} is selected from the group consisting of H, aryl, aralkyl, heteroaryl, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR^{C66}R^{C67}, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoroalkyl;

r3 is selected from 0 to 6;

s3 is selected from 0 to 6;

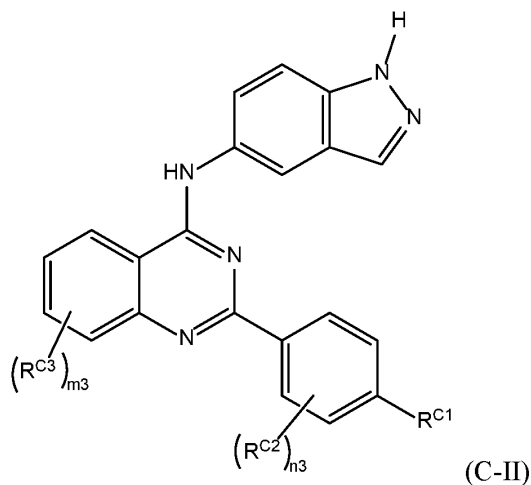
n3 is selected from 0 to 4;

m3 is selected from 0 to 3; and

p3 is selected from 0 and 1.

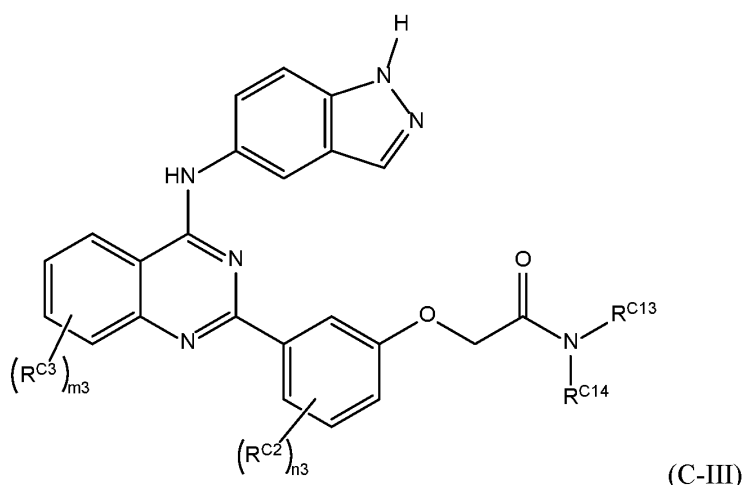
[0057] In some embodiments, in Formula (C-I), each R^{C4} and R^{C5} is independently H or unsubstituted C₁-C₆ alkyl. In some embodiments, R^{C4} and R^{C5} are H.

[0058] In some embodiments, the ROCK2 inhibitor has the structure of Formula (C-II):



or a pharmaceutically acceptable salt thereof. R^{C1}, R^{C2}, R^{C3}, n3 and m3 are as for the compound of the formula I.

[0059] In some embodiments, the ROCK2 inhibitor has the structure of Formula (C-III):



or a pharmaceutically acceptable salt thereof, wherein:

R^{C13} and R^{C14} are independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{C16}R^{C17}$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{C16}R^{C17}$, aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₇ cycloalkyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R^{C13} and R^{C14} may be taken together to form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₇ cycloalkyl, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

R^{C16} and R^{C17} are independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R^{C16} and R^{C17} may be taken together to form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

each R^{C2} is independently selected from the group consisting of lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, and perfluoro lower alkyl;

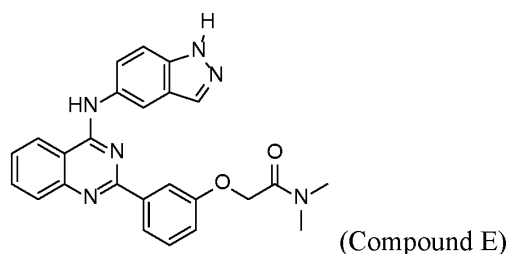
each R^{C3} is independently selected from the group consisting of lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, and perfluoro lower alkyl;

n is selected from 0 to 4; and

m is selected from 0 to 3.

[0060] In some embodiments, in Formula (C-III), each R^{C13} and R^{C14} is independently H or unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^{C13} and R^{C14} is independently unsubstituted C_1 - C_6 alkyl. In some embodiments, each R^{C13} and R^{C14} is independently methyl or ethyl. In some embodiments, R^{C13} and R^{C14} are methyl.

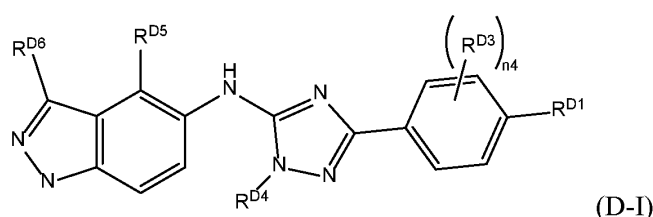
[0061] In some embodiments, the ROCK2 inhibitor has the structure of



or a pharmaceutically acceptable salt thereof. Compound E is also known as belumosudil or KD025.

[0062] The compounds of Formula (C-I) and its subordinates may be synthesized and assayed for ROCK2 inhibition activity *in vitro* as described in, for example, U.S. Pat. Nos. 8,357,693, 9,815,820, 10,183,931, 10,696,660, and 11,311,541, the entire contents of which are incorporated herein by reference.

[0063] In one aspect, the ROCK2 inhibitor has the structure of Formula (D-I):



or pharmaceutically acceptable salts thereof, wherein:

R^{D1} is $L-R^{D2}$, wherein

L is a bond or $-L^{D1}-L^{D2}-$,

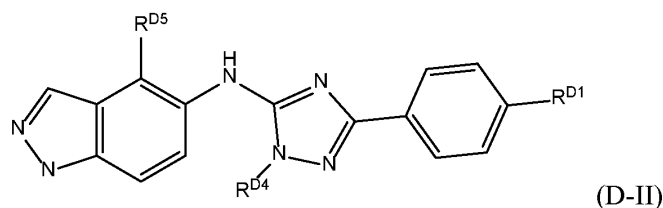
wherein L^{D1} is selected from the group consisting of a bond, $-(CR^A R^B)_{1-3}-$, $-O(CR^A R^B)_{1-3}-$, $-(CR^A R^B)_{0-3}O-$, and $-NR^C(CR^A R^B)_{1-3}-$; and

- L^{D2} is selected from the group consisting of a bond, $-(CR^A R^B)_{1-3}$ -, $-O$ -, $-NR^D$ -, $-C(O)NR^D$ -, $-NR^D C(O)$ -, $-C(O)O$ -, $-OC(O)$ -, $-C(O)$ -, $-S(O)_2 NR^D$ -, $-NR^D S(O)_2$ -, $-S(O)_2$ -, $-S(O)(NR^D)$ -, $-NR^D C(O)NR^E$ -, $-OC(O)NR^D$ -, and $-C(O)NR^D S(O)_2$;- and
- R^{D2} is selected from the group consisting of H, CN, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkyl substituted with $-OR^F$, C_1 - C_6 alkyl substituted with $-NR^F R^G$, C_{1-4} haloalkyl substituted with $-OR^F$, C_{3-8} cycloalkyl substituted with OH, C_{1-4} alkyl substituted with 3 to 8 membered heterocycloalkyl, C_{1-4} alkyl substituted with 6 membered heteroaryl, $-(CR^{H R^I})_{1-3} OR^F$, $-(CR^{H R^I})_{1-3} NR^F R^G$, $-(CR^{N R^O})_{1-3} C(O)OR^F$, $-(CR^{N R^O})_{1-3} C(O)NR^F R^G$, C_{3-10} carbocyclic ring system, and 3 to 10 membered heterocyclic ring system, wherein the carbocyclic ring or heterocyclic ring system is substituted or unsubstituted with: $=O$ -, $-NR^F R^G$, $-C(O)R^F$, halo, $-CN$, C_{1-4} alkyl, C_{1-4} haloalkyl or C_{1-4} alkyl substituted with $-OR^F$;
- R^{D3} is independently selected at each occurrence from the group consisting of halo, C_{1-4} alkyl, C_1 - C_6 haloalkyl, $-CN$, $-OR^J$, $=O$, C_{1-4} alkyl substituted with $-OR^J$, $-NR^J R^K$, C_{1-4} alkyl substituted with $-NR^J R^K$, C_{3-8} cycloalkyl, C_{1-4} alkyl substituted with C_{3-8} cycloalkyl, 3 to 8 membered heterocycloalkyl and C_{1-4} alkyl substituted with 3 to 8 membered heterocycloalkyl; or two R^{D3} are optionally joined to form a phenyl or heteroaryl group may be substituted with halo or C_{1-4} alkyl;
- R^{D4} is selected from the group consisting of H, C_{1-4} alkyl, C_{1-4} alkyl substituted with $-OR^L$, C_{1-4} alkyl substituted with $-NR^L R^L$, C_{3-8} cycloalkyl, substituted or unsubstituted phenyl, 3 to 8 membered heterocycloalkyl, C_{1-4} alkyl substituted with C_{3-8} cycloalkyl, C_{1-4} alkyl substituted with 3 to 8 membered heterocycloalkyl and substituted or unsubstituted 5 or 6 membered heteroaryl, wherein the phenyl or heteroaryl group may be substituted with halo or C_{1-4} alkyl;
- R^{D5} is selected from the group consisting of H, halo, $-OR^J$, C_{1-4} alkyl, C_{1-6} haloalkyl, C_{1-4} alkenyl, $-CN$, and C_{3-8} cycloalkyl;
- R^{D6} is selected from the group consisting of H, halo, C_{1-4} alkyl, C_{1-6} haloalkyl, $-CN$, and C_{3-8} cycloalkyl;
- n_4 is 0, 1, or 2;
- R^A and R^B are selected from the group consisting of H, C_{1-4} alkyl, or C_{1-4} haloalkyl or R^A and R^B together with the atom to which they are attached form a 3 to 6 membered cycloalkyl or a 3 to 6 membered heterocycloalkyl;
- R^C , R^D , R^E , R^F and R^G are each independently selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl;

R^H and R^I are each H except one pair of R^H and R^I on the same carbon atom, together with that carbon atom, form a 3 to 6 membered cycloalkyl or a 3 to 6 membered heterocycloalkyl; and

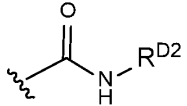
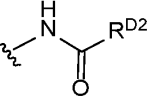
R^J , R^K , R^L , R^M , R^N and R^O are each independently at each occurrence selected from the group consisting of H or C_{1-4} alkyl.

[0064] In some embodiments, the ROCK2 inhibitor has the structure of Formula (D-II):



or pharmaceutically acceptable salts thereof.

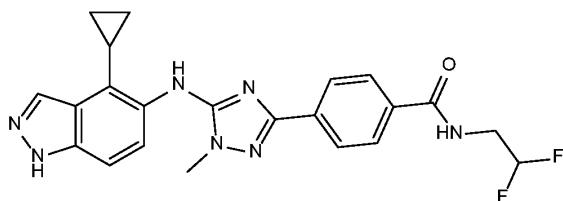
[0065] In some embodiments, in Formula (D-II), R^{D1} is $-L^{D1}-L^{D2}-R^{D2}$. In some embodiments, L^{D1} is a bond and L^{D2} is $-NR^D$ -, $-C(O)NR^D$ -, $-NR^DC(O)$ -, $-C(O)O$ -. In some

embodiments, R^{D1} is  or . In some embodiments, R^{D2} is C_1 - C_6 alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, or t-butyl), or C_1 - C_6 haloalkyl (e.g., mono, di, or per- fluoro C_1 - C_6 alkyl).

[0066] In some embodiments, in Formula (D-II), R^{D4} is hydrogen, or C_{1-4} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, or t-butyl). In some embodiments, R^{D4} is methyl.

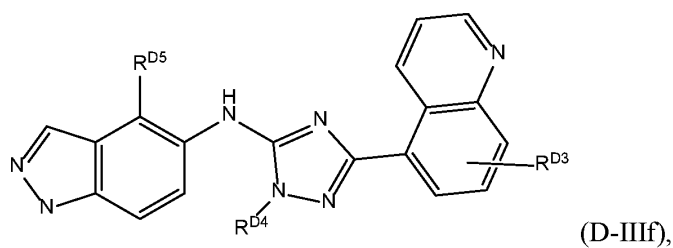
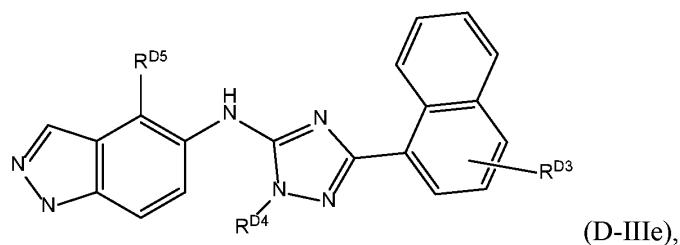
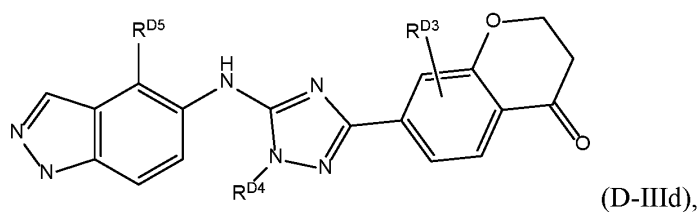
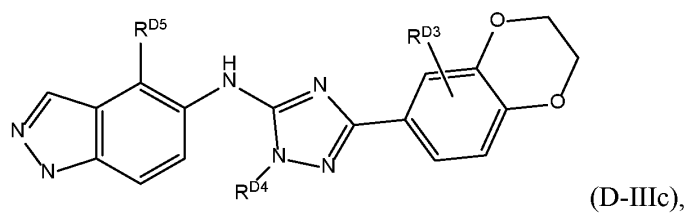
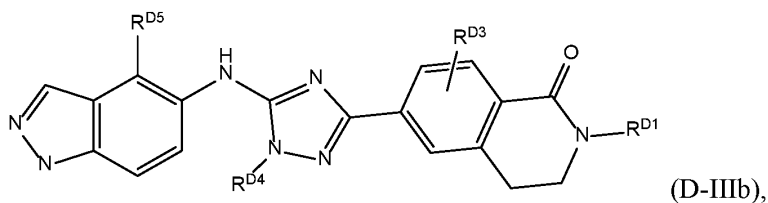
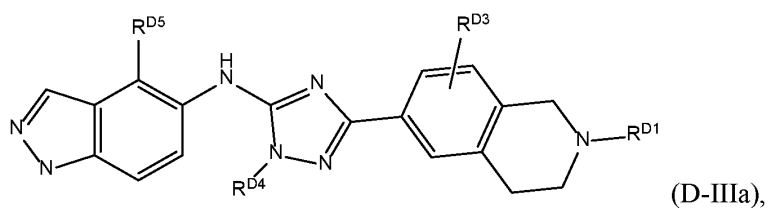
[0067] In some embodiments, in Formula (D-II), R^{D5} is hydrogen, halo, C_{1-4} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, or t-butyl), C_{1-6} haloalkyl (e.g., mono, di, or per-fluoro C_1 - C_6 alkyl), or C_{3-8} cycloalkyl (e.g., cyclopropyl, cyclobutyl, or cyclopentyl, cyclohexyl). In some embodiments, R^{D5} is cyclopropyl.

[0068] In some embodiments, exemplary ROCK2 inhibitor has the structure of



or a pharmaceutically acceptable salt thereof.

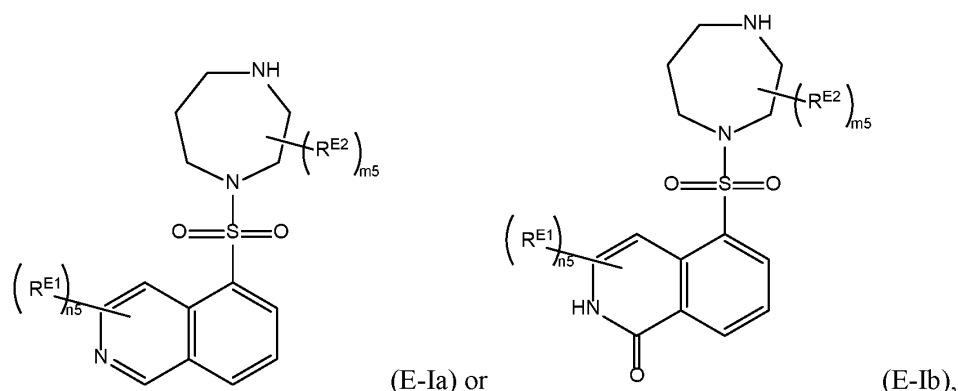
[0069] In some embodiments, the ROCK2 inhibitor has the structure of Formula (D-IIIa) or D-IIIb):



or a pharmaceutically acceptable salt thereof.

[0070] The compounds of Formula (D-I) and its subordinates may be synthesized and assayed for ROCK2 inhibition activity *in vitro* as described in, for example, U.S. Pat. No. 11,497,751, the entire content of which is incorporated herein by reference.

[0071] In one aspect, the ROCK2 inhibitor has the structure of Formula (E-Ia) or (E-Ib):



or pharmaceutically acceptable salts thereof, wherein:

each R^{E1} is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halogen, -CN, -OR^{E11}, or -NR^{E11}R^{E12};

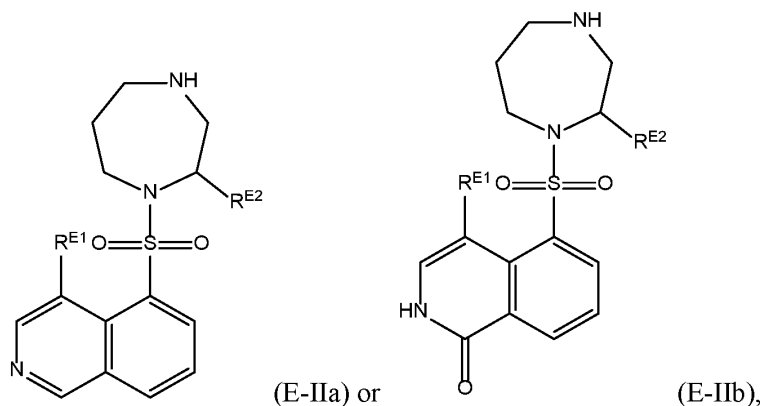
m_5 is an integer of 0 to 3;

each R^{E2} is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halogen, -CN, -OR^{E21}, or -NR^{E21}R^{E22};

m_5 is an integer of 0 to 10; and

each R^{E11} , R^{E12} , R^{E21} , and R^{E22} is independently H and C₁-C₆ alkyl.

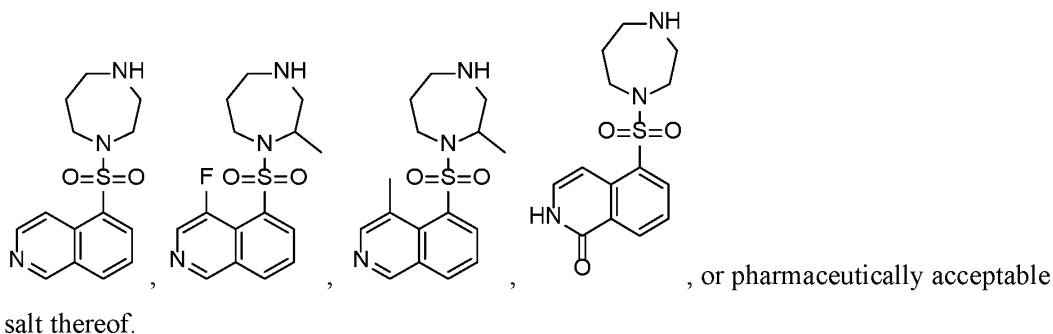
[0072] In some embodiments, the ROCK2 inhibitor has the structure of Formula (E-IIa) or (E-IIb):



or pharmaceutically acceptable salts thereof. R^{E1} and R^{E2} are as described above.

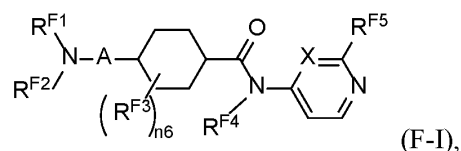
[0073] In some embodiments, R^{E1} is hydrogen or unsubstituted C₁-C₃ alkyl (e.g., methyl, ethyl, or propyl). In some embodiments, R^{E2} is hydrogen, halogen (e.g., F, Cl, or Br) or unsubstituted C₁-C₃ alkyl (e.g., methyl, ethyl, or propyl). In some embodiments, R^{E1} and R^{E2} are hydrogen. In some embodiments, R^{E1} is -F, and R^{E2} is methyl. In some embodiments, R^{E1} is methyl, and R^{E2} is methyl.

[0074] In some embodiments, the ROCK2 inhibitor has the structure of



[0075] The compounds of Formula (E-I) and its subordinates may be synthesized and assayed for ROCK2 inhibition activity *in vitro* as described in, for example, WO2007/007737 and U.S. Pat. No. 8,193,193, the entire contents of which are incorporated herein by reference.

[0076] In one aspect, the ROCK2 inhibitor has the structure of Formula (F-I):



or an isomer thereof; or a pharmaceutically acceptable salt thereof, wherein:

R^{F1} and R^{F2} are the same or different and each is hydrogen, alkyl, or cycloalkyl,

cycloalkylalkyl, phenyl, aralkyl, piperidyl or pyrrolidinyl, any of which may have a substituent on the ring, or $-CR'=NR''$, wherein R' is hydrogen, alkyl, amine, heterocycloalkyl, heteroaryl, or cycloalkyl, R' and R'' are optionally joined to form a heterocycloalkyl or heteroaryl

R^{F1} and R^{F2} form, together with the nitrogen atom, a heterocyclic ring which may have, in the ring, an oxygen atom, sulfur atom or optionally substituted nitrogen atom;

each R^{F3} and R^{F4} is independently hydrogen or alkyl;

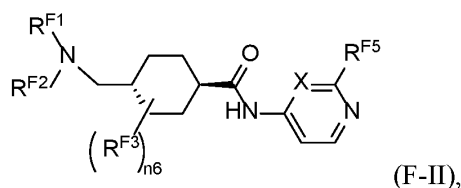
R^{F5} is hydrogen, halogen, alkyl, alkoxy, aralkyl, or haloalkyl;

A is a single bond or alkylene optionally substituted with C_1 - C_3 alkyl;

X is $=CH-$ or $=N-$; and

n_6 is an integer of 0 or 8.

[0077] In some embodiments, the ROCK2 inhibitor has the structure of Formula (F-II):

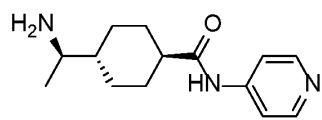


or an isomer or a pharmaceutically acceptable salt thereof. R^{F1} , R^{F2} , R^{F3} , R^{F5} and $n6$ are described above.

[0078] In some embodiments, X is =N-.

[0079] In some embodiments, each R^{F1} , R^{F2} , R^{F3} , and R^{F5} is independently hydrogen or in some embodiments, $n6$ is 0 or 1.

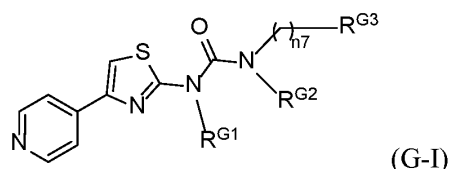
[0080] In some embodiments, the ROCK2 inhibitor has the structure of



, or an isomer or a pharmaceutically acceptable salt thereof.

[0081] These compounds of Formula (F-I) and its subordinates may be synthesized and assayed for ROCK2 inhibition activity *in vitro* as described in, for example, WO90/05723 and U.S. Pat. No. 4,997,834, the entire contents of which are incorporated herein by reference.

[0082] In one aspect, the ROCK2 inhibitor has the structure of (G-I),



(G-I)

or a pharmaceutically acceptable salt thereof, wherein

$n7$ is 1, 2, or 3;

each R^{G1} and R^{G2} is independently hydrogen, alkyl, or acetyl;

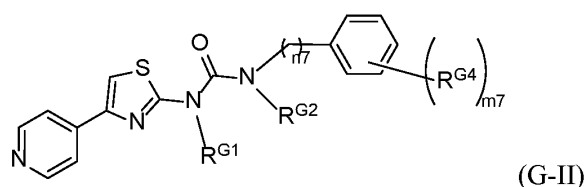
R^{G3} is cycloalkyl or aryl, wherein the cycloalkyl or aryl is optionally substituted with one or more of -OH, -CO₂CH₃, -C(O)NH₂, -C(O)CH₃, -NO₂, -NH₂, -NR⁶R⁷, carbonyl, alkyl, alkoxy, alkylalkoxy, alkoxyalkoxy, cycloalkyl, aryl, -OCX^G, -OCHX^G, -OCH₂X^G, -OSO₂CH₃, -tosyl, or halogen;

R^6 and R^7 are, independently of one another, H, alkyl, -SO₂CH₃, -C(O)CH₃, or -C(O)NH₂;

and

X^G is halogen.

[0083] In some embodiments, the ROCK2 inhibitor has the structure of Formula (G-II):



(G-II)

or a pharmaceutically acceptable salt thereof, wherein:

R^{G4} is -OH, -CO₂CH₃, -C(O)NH₂, -NO₂, -NH₂, -NR^{G5}R^{G6}, alkoxy, alkylalkoxy, alkyl, -OSO₂CH₃, tosyl, or halogen;

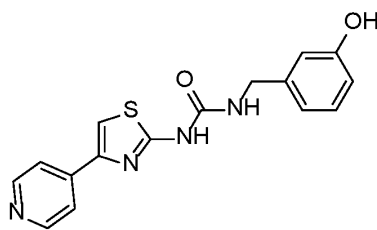
each R^{G5} and R^{G6} is independently hydrogen, or alkyl ;

m7 is an integer of 0 to 6; and

R^{G1} , R^{G2} , and n7 are described above.

[0084] In some embodiments, R^{G4} is attached to the meta position on the phenyl ring. In some embodiments, m7 is 0 or 1. In some embodiments, R^{G4} is -OH.

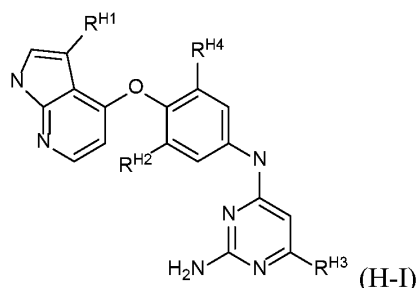
[0085] In some embodiments, the ROCK2 inhibitor has the structure:



or a pharmaceutically acceptable salt thereof.

[0086] The compounds of Formula (G-I) and its subordinates may be synthesized and assayed for ROCK2 inhibition activity *in vitro* as described in, for example, WO2011/130740 and U.S. Pat. No. 9,221,808, the entire contents of which are incorporated herein by reference.

[0087] In one aspect, the ROCK2 inhibitor has the structure of Formula (H-I):



or a pharmaceutically acceptable salt thereof, wherein:

R^{H1} is halogen, cyano, methyl, ethyl, hydroxyethyl, methoxyethyl or cyclopropyl;

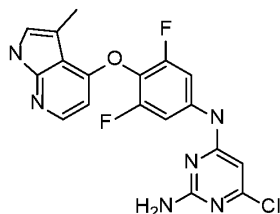
R^{H2} is hydrogen or halogen;

R^{H3} is hydrogen, halogen, trifluoromethyl or pentafluoroethyl; and

R^{H4} is hydrogen or halogen.

[0088] In some embodiments, R^{H1} is hydrogen, or C₁-C₃ alkyl (e.g., methyl, ethyl, or propyl). In some embodiments, R^{H2} is halogen (e.g., F, Cl, or Br). In some embodiments, R^{H3} is halogen (e.g., F, Cl, or Br). In some embodiments, R^{H4} is halogen (e.g., F, Cl, or Br).

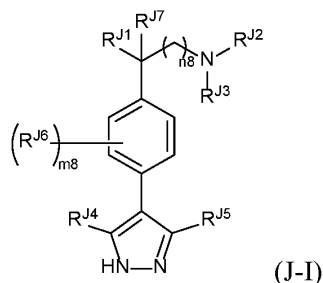
[0089] In some embodiments, the ROCK2 inhibitor has the structure:



or a pharmaceutically acceptable salt thereof.

[0090] These compounds of Formula (H-I) and its subordinates may be synthesized and assayed for ROCK2 inhibition activity *in vitro* as described in, for example, WO2005/037197 and U.S. Pat. No. 7,547,779, entire contents of which are incorporated herein by reference.

[0091] In one aspect, the ROCK2 inhibitor has the structure of Formula (J-I):



or a pharmaceutically acceptable salt thereof, wherein:

R^{J1} is an aryl or heteroaryl group;

each R^{J2} and R^{J3} is independently selected from hydrogen, or C₁-C₄ alkyl;

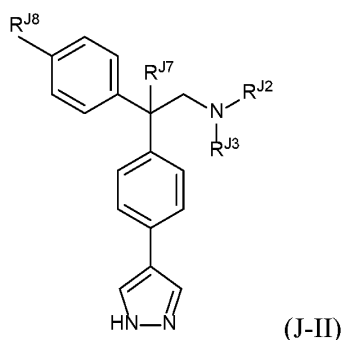
each R^{J4}, R^{J5} and R^{J6} is independently selected from hydrogen, halogen, or C₁-C₄ alkyl;

R^{J7} is hydrogen, halogen, OH, -CO₂CH₃, -C(O)NH₂, -NO₂, or C₁-C₄ alkyl;

n₈ is an integer of 0 to 3; and

m₈ is an integer of 0 to 8.

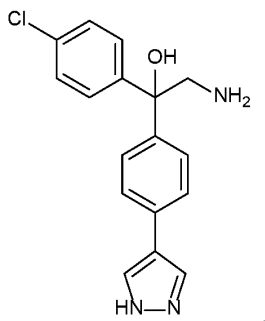
[0092] In some embodiments, the ROCK2 inhibitor has the structure of Formula (J-II),



or a pharmaceutically acceptable salt thereof, wherein:

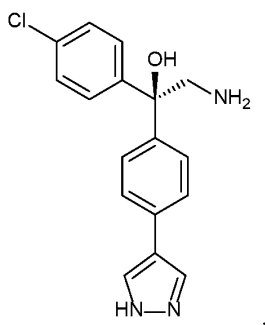
R^{J8} is hydrogen, halogen, OH, $-CO_2CH_3$, $-C(O)NH_2$, $-NO_2$, or C_1 - C_4 alkyl; and R^{J2} , R^{J3} and R^{J7} are described above.

[0093] In some embodiments, the ROCK2 inhibitor has the structure:



or a pharmaceutically acceptable salt thereof.

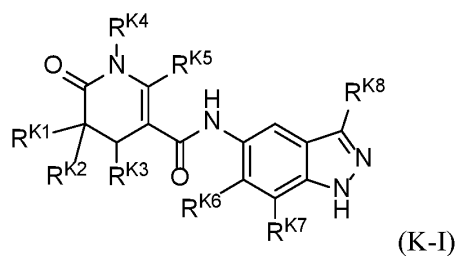
[0094] In some embodiments, the ROCK2 inhibitor has the structure:



or a pharmaceutically acceptable salt thereof.

[0095] These compounds of Formula (J-I) and its subordinates may be synthesized and assayed for ROCK2 inhibition activity *in vitro* as described in, for example, WO2008/110846 and U.S. Pat. No. 8,497,294, entire contents of which are incorporated herein by reference.

[0096] In one aspect, the ROCK2 inhibitor has the structure of Formula (K-I)



or a pharmaceutically acceptable salt thereof, wherein:

each R^{K1} and R^{K2} is independently selected from the group consisting of hydrogen and C_1 - C_6 alkyl;

R^{K3} is phenyl optionally substituted with 1 to 3 substituents selected from the group consisting of F, Cl, trifluoromethyl, and phenyl; naphthyl; and quinolinyl;

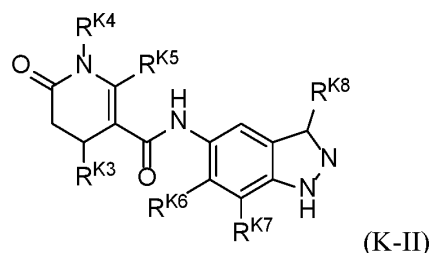
R^{K4} is selected from the group consisting of hydrogen and methyl;

R^{K5} is C_1 - C_3 alkyl;

R^{K6} is hydrogen or hydrogen; and

each R^{K7} and R^{K8} is independently selected from the group consisting of hydrogen, halogen, and C_1 - C_3 alkyl.

[0097] In some embodiments, the ROCK2 inhibitor has the structure of Formula (K-II):



or a pharmaceutically acceptable salt thereof, wherein:

R^{K3} is optionally substituted aryl or heteroaryl;

R^{K4} is hydrogen or optionally substituted C_1 - C_2 alkyl;

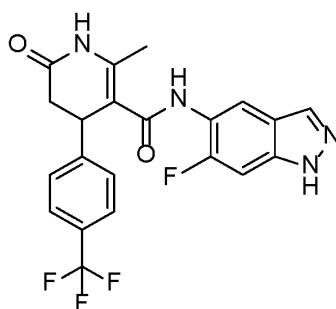
R^{K5} is optionally substituted C_1 - C_2 alkyl;

R^{K6} is hydrogen or halogen; and

each R^{K7} and R^{K8} is hydrogen, halogen, and optionally substituted C_1 - C_3 alkyl.

[0098] In some embodiments, R^{K3} is substituted phenyl. In some embodiments, R^{K4} , R^{K7} and R^{K8} are hydrogen. In some embodiments, R^{K4} is substituted C_1 - C_2 alkyl (e.g., methyl or ethyl). In some embodiments, R^{K6} is halogen (e.g., F, Cl, or Br).

[0099] In some embodiments, the ROCK2 inhibitor has the structure:

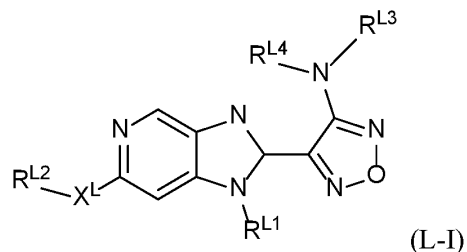


or a pharmaceutically acceptable salt thereof.

[0100] These compounds of Formula (K-I) and its subordinates may be synthesized and assayed for ROCK2 inhibition activity *in vitro* as described in, for example, WO2005/082890

and U.S. Pat. No. 7,592,357, the entire contents of which are incorporated herein by reference.

[00101] In one aspect, the ROCK2 inhibitor has the structure of Formula (L-I):



or a pharmaceutically acceptable salt thereof, wherein:

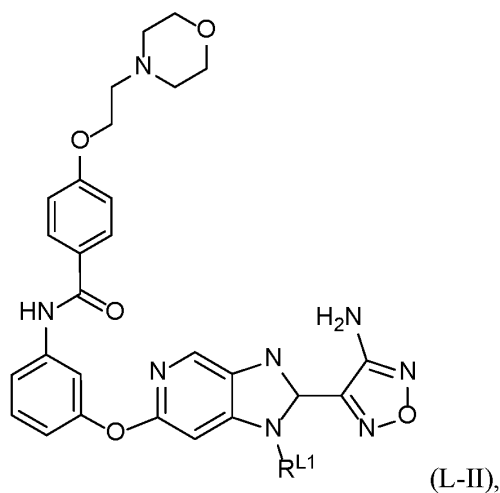
X^L is a bond, C_1 - C_6 alkylene, NH, O, S, SO or $S(O)_2$;

R^{L1} is hydrogen or C_1 - C_6 alkyl;

R^{L2} is C_1 - C_6 alkyl, or phenyl optionally substituted;

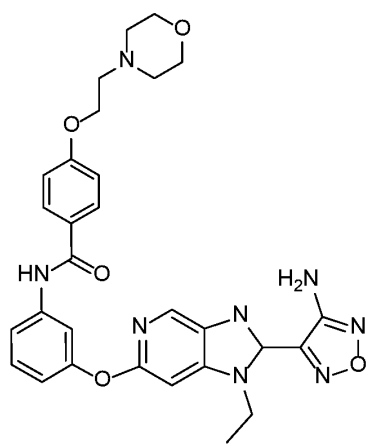
R^{L3} is hydrogen, C_1 - C_6 alkyl, and C_{3-7} cycloalkyl or R^{L3} and R^{L4} together form a ring; and each R^{L4} and R^5 is independently hydrogen, or C_1 - C_6 alkyl.

[00102] In some embodiments, the ROCK2 inhibitor has the structure of Formula (L-II):



or a pharmaceutically acceptable salt thereof. R^{L1} is described above.

[00103] In some embodiments, the ROCK2 inhibitor has the structure:



or a pharmaceutically acceptable salt thereof. In some embodiments, the ROCK2 inhibitor of Formula (L-II) includes a hydrochloride salt.

[00104] These compounds of Formula (L-I) and its subordinates may be synthesized and assayed for ROCK2 inhibition activity *in vitro* as described in, for example, WO2005/037197 and U.S. Pat. No. 7,547,779, the entire contents of which are incorporated herein by reference.

[00105] In some embodiments, the ROCK2 antagonist is a ribonucleic acid (RNA), such as an antisense RNA. Antisense RNA (asRNA), also referred to as antisense transcript or antisense oligonucleotide, is a single stranded RNA that is complementary to a protein coding messenger RNA (mRNA) with which it hybridizes, and thereby blocks the mRNA's translation into protein. Antisense RNA can be classified into short (less than 200 nucleotides) and long (200 or more nucleotides) non-coding RNAs (ncRNAs). The primary function of asRNA is regulating gene expression. asRNA molecules can be designed and produced synthetically and have found widespread use as research tools for gene knockdown. They also have therapeutic applications. In some embodiments, the antisense RNA targeting ROCK2 comprises one or more unnatural nucleic acids. In some embodiments, the antisense RNA is administered via injection or inhalation. In some embodiments, the antisense RNA targeting ROCK2 is selective for the ROCK2 mRNA. In some embodiments, the antisense RNA targeting ROCK2 does not bind the ROCK1 mRNA. The design and use of selective antisense RNA molecules is routine in the art.

[00106] In some embodiments, the ROCK2 antagonist is RNA interference (RNAi), small inhibiting RNA (siRNA), or micro-RNA (miRNA). As used herein, an "RNAi" generally refers to any RNA molecule that induces RNA interference in a cell. Examples of RNAi include without limitation small inhibitory RNAs (siRNAs), micro RNAs (miRNAs), and

small hairpin RNAs (shRNAs). RNA interference (RNAi) has been shown to be a useful tool for gene silencing in determination of gene function and may be used as a therapeutic agent to suppress genes associated with the development of a number of diseases. Gene regulation by RNAi can occur through small RNAs known as micro RNAs (miRNAs). Micro RNAs can be regulators of diverse cellular processes. The siRNA or miRNA may allow the use of the endogenous cellular RNAi machinery to direct the degradation of a target gene product (e.g., gene encoding ROCK2 and genes associated with the production or regulation of ROCK2) with the use of artificial siRNA or miRNAs. In some embodiments, the siRNA or miRNA selectively degrades a ROCK2 mRNA. In some embodiments, the siRNA or miRNA does not degrade a ROCK1 mRNA. The design and use of selective siRNA and miRNA molecules are routine in the art.

[00107] A small inhibitory or interfering RNA (siRNA) may be a double-stranded RNA molecule, such as, for example, RNA having 19-25 (e.g., 19-23) base pairs in length, that induces RNA interference in a cell. A small hairpin RNA (shRNA) may be an RNA molecule, such as, for example, RNA having approximately 19-25 (e.g., 19-23) base pairs of double stranded RNA linked by a short loop (e.g., about 4-11 nucleotides) that induces RNA interference in a cell.

[00108] A microRNA (miRNA) can be an RNA molecule that induces RNA interference in a cell having a short (e.g., 19-25 base pairs) sequence of double-stranded RNA linked by a loop and containing one or more additional sequences of double-stranded RNA comprising one or more bulges (e.g., mis-paired or unpaired base pairs). As used herein, the term “miRNA” encompasses endogenous miRNAs as well as exogenous or heterologous miRNAs. In some embodiments, “miRNA” may refer to a pri-miRNA or a pre-miRNA. During miRNA processing, a pri-miRNA transcript is produced. The pri-miRNA is processed by Drosha-DGCR8 to produce a pre-miRNA by excising one or more sequences to leave a pre-miRNA with a 5'-flanking region, a guide strand, a loop region, a non-guide strand, and a 3'-flanking region; or a 5'-flanking region, a non-guide strand, a loop region, a guide strand, and a 3'-flanking region. The pre-miRNA is then exported to the cytoplasm and processed by Dicer to yield a siRNA with a guide strand and a non-guide (or passenger) strand. The guide strand is then used by the RISC complex to catalyze gene silencing, e.g., by recognizing a target RNA sequence complementary to the guide strand.

[00109] While the exemplary compounds of ROCK2 inhibitors which have been known to the present time are disclosed above, additional compounds shown to have ROCK2 inhibition activities can be used.

[00110] Methods of determining kinase inhibition are disclosed herein. For example, kinase activity of an enzyme and the inhibitory capacity of a test compound can be determined by measuring enzyme specific phosphorylation of a substrate. Commercial assays and kits can be employed. For example, kinase inhibition can be determined using an IMAP® assay (Molecular Devices). This assay method involves the use of a fluorescently tagged peptide substrate. Phosphorylation of the tagged peptide by a kinase of interest promotes binding of the peptide to a trivalent metal-based nanoparticle via the specific, high affinity interaction between the phosphor group and the trivalent metal. Proximity to the nanoparticle results in increased fluorescence polarization. Inhibition of the kinase by a kinase inhibitor prevents phosphorylation of the substrate and thereby limits binding of the fluorescently tagged substrate to the nanoparticle. Such an assay can be compatible with a microwell assay format, allowing simultaneous determination of IC₅₀ of multiple compounds.

[00111] As disclosed above, Rho proteins are members of the small GTP-binding protein family and operate via their downstream mediators, two isoforms: Rho-associated coiled-coil containing protein kinase 1 (ROCK1) and Rho-associated coiled-coil containing protein kinase 2 (ROCK2). These kinases can display various cellular functions, including cell motility, proliferation, adhesion, migration, and apoptosis. Various nonspecific ROCK inhibitors have been developed, such as fasudil (approved for cerebral vasospasm treatment in 1995), and ripasudil (approved for glaucoma treatment in 2014). Lack of isoform selectivity may induce hypotension as a dose-limiting side effect due to ROCK1 inhibition. ROCK2 selective inhibitors, however, may display little or no hypotensive effects. In addition, inhibiting ROCK1 may not produce immunity enhancement due to the distribution of ROCK1 in organs and tissues.

[00112] Thus, the ROCK2 selective inhibitors disclosed herein may be used in the therapies provided herein, while causing little or no adverse health risks. Inhibitors that specifically target ROCK2 over ROCK1 are desirable for the therapies for treatments disclosed herein.

GLP-1 agonists

[00113] A glucagon-like peptide-1 (GLP-1) is a fragment of the mammalian (e.g., human) proglucagon molecule and has been found to be a glucose-dependent insulinotropic agent that stimulates or affects the production of insulin in diabetic patients and to control the further activity of insulin for treatment of diabetes. Another active fragment, glucagon-like

insulinotropic peptide (GLIP), corresponds to GLP-1(7-36), a truncated but active fragment of GLP-1, is a natural form found (secreted) in a body after food intake.

[00114] In the present disclosure, the combination therapy also includes the use of a GLP-1 agonist. The GLP-1 agonist as described herein may be a peptide or a polypeptide that has a substantial similarity of biological or physiological function to that of glucagon-like peptide 1 (GLP-1), e.g., GLP-1 (7-36: SEQ ID NO. 1) or GLP-1 (7-37: SEQ ID NO. 2). In some embodiments, the GLP-1 agonist as described herein is a peptide or a polypeptide that has a substantial similarity of biological or physiological function to exendin (e.g., exendin-4, SEQ ID NO. 3).

SEQ ID NO.	Amino acid sequences
SEQ ID NO. 1	HAEGTFTSDV SSYLEGQAAK EFIAWLVKGR
SEQ ID NO. 2	HAEGTFTSDV SSYLEGNAAK EFIAWLVKGRG
SEQ ID NO. 3	HGEGTFTSDL SKQMEEEAVR LFIEWLKNGGP SSGAPPPS

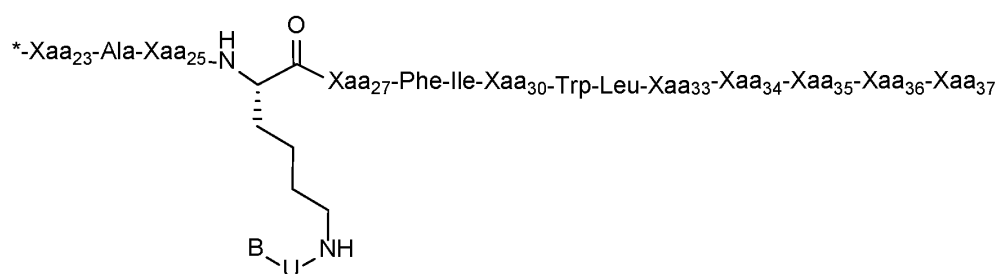
[00115] In some embodiments, the GLP-1 agonist as described herein may contain chemically functional groups or modification which may be introduced on at least one amino acid residue (e.g., side chain). In some embodiments, the GLP-1 agonist as described herein may contain chemically functional groups or modification which may be introduced at least one amino acid residue (e.g., backbone). In some embodiments, the GLP-1 agonist as described herein may contain chemically functional groups or modification which may replace at least one amino acid residue. In some embodiments, the GLP-1 agonist as described herein may contain chemically functional groups or modification which may be introduced at C-terminal amino acid residue of the GLP-1 sequence. In some embodiments, the GLP-1 agonist as described herein may contain chemically functional groups or modification which may be introduced at N-terminal amino acid residue of the GLP-1 sequence. In some embodiments, the GLP-1 agonist as described herein may contain a fused amino acid sequence or a peptide sequence at least at C-terminal or N-terminal of the GLP-1 sequence.

[00116] In some embodiments, the GLP-1 agonist as described herein may have at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% homology with amino acid sequence 1-39 of GLP-1. In some embodiments, the GLP-1 agonist as described herein may have at least about 50%, 60%, 70%, 80%, 90%, 95%, or 99% homology with amino acid sequence 7-36 of GLP-1.

[00117] In some embodiments, the GLP-1 agonist as described herein may have biological or physiological effects similar to, or enhanced from, the GLP-1, e.g., increasing glucose-dependent stimulation of insulin secretion, decreasing gastric emptying, inhibiting food intake, increasing natriuresis and diuresis, extended *in vivo* half-life, and/or modulating β -cell proliferation. For example, the GLP-1 agonists are also disclosed in WO 96/29342, WO 98/08871, WO 99/43708, WO 00/3433, WO 00/69911, WO 02/4622, U.S. Pat. No. 8,129,343, U.S. Pat. No. 5,424,286, U.S. Pat. No. 6,268,343, U.S. Pat. No. 7,452,966, 6,528,486, 9,981,013, the entire contents of which are each incorporated herein by reference.

[00118] In one aspect, the GLP-1 agonist comprises a structure of Formula (M-I):

Xaa₇-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Xaa₁₆-Ser-Xaa₁₈-Xaa₁₉-Xaa₂₀-Glu-Xaa₂₂-*



(M-I),

wherein:

Xaa₇ is L-histidine, imidazopropionyl, α -hydroxy-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β -hydroxy-histidine, homohistidine, N ^{α} -acetyl-histidine, N ^{α} -formyl-histidine, α -fluoromethyl-histidine, α -methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine

Xaa₈ is Ala, Gly, Val, Leu, Ile, Thr, Ser, Lys, Aib (α -aminoisobutyric acid), (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa₁₆ is Val or Leu;

Xaa₁₈ is Ser, Lys or Arg;

Xaa₁₉ is Tyr or Gln;

Xaa₂₀ is Leu or Met;

Xaa₂₂ is Gly, Glu or Aib (α -aminoisobutyric acid);

Xaa₂₃ is Gln, Glu, Lys or Arg;

Xaa₂₅ is Ala or Val;

Xaa₂₇ is Glu or Leu;

Xaa₃₀ is Ala, Glu or Arg;

Xaa₃₃ is Val or Lys;

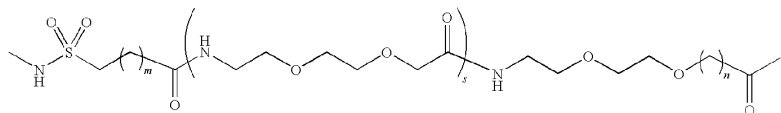
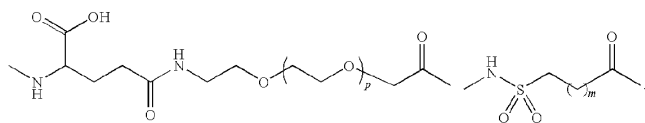
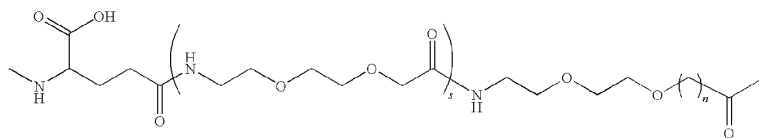
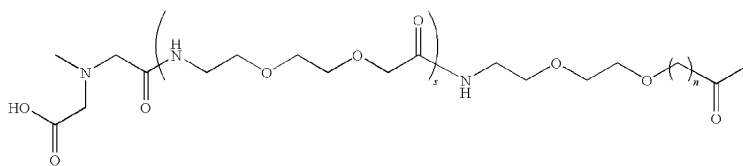
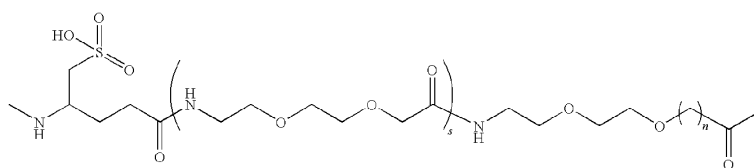
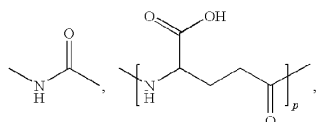
Xaa₃₄ is Lys, Glu, Asn or Arg;

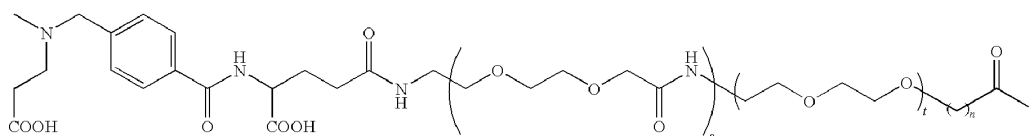
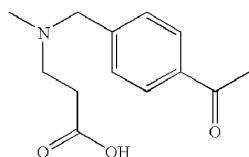
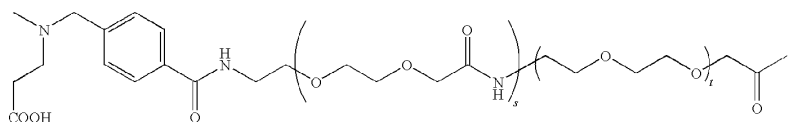
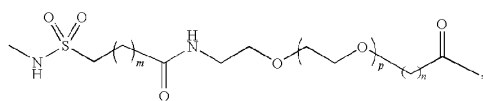
Xaa₃₅ is Gly or Aib (α -aminoisobutyric acid);

Xaa₃₆ is Arg, Gly or Lys, or is absent;

Xaa₃₇ is Gly, Ala, Glu, Pro, Lys, or is absent; and

B and U together is the acylated moiety, where U is selected from





m is 0, 1, 2, 3, 4, 5, or 6,

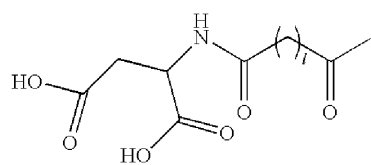
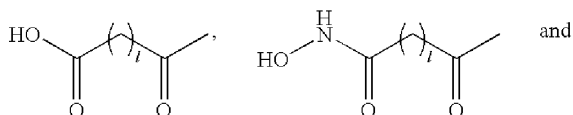
n is 1, 2 or 3

s is 0, 1, 2, or 3,

t is 0, 1, 2, 3, or 4

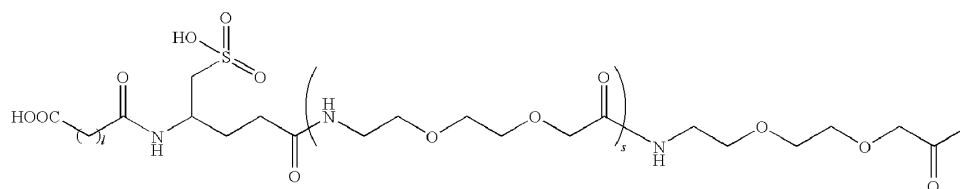
p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

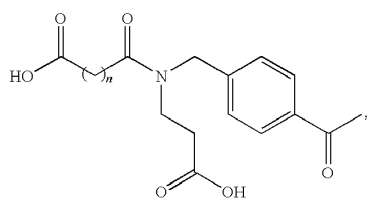
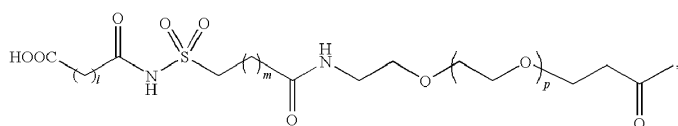
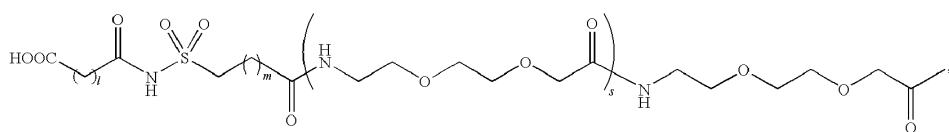
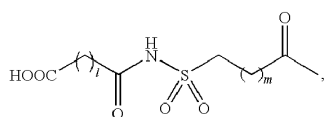
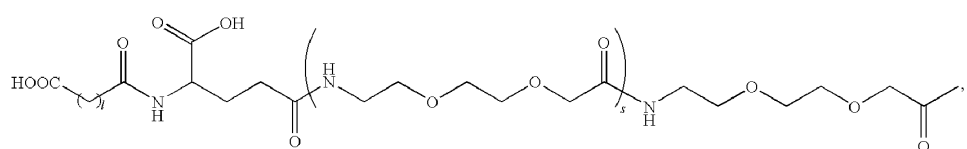
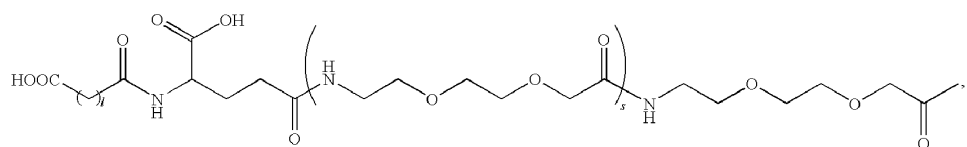
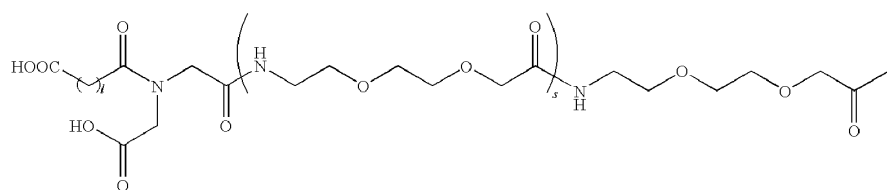
and where B is an acidic group selected from

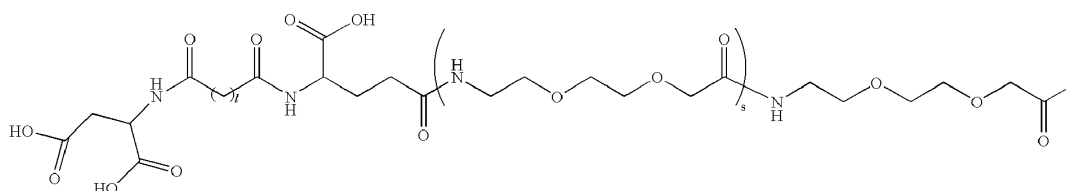
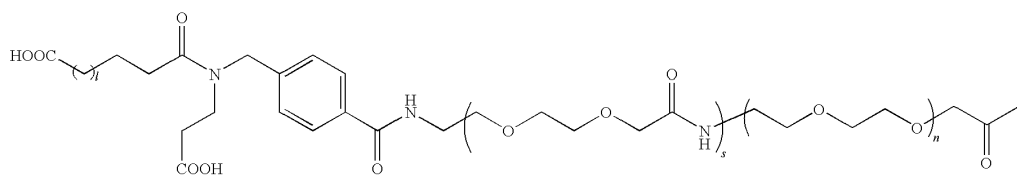


where l is 12, 13, 14, 15, 16, 17, 18, 19 or 20.

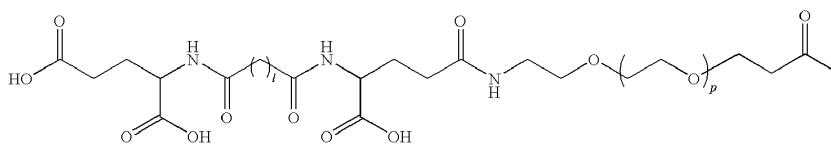
[00119] In some embodiments, in Formula (M-I), B-U- is selected from







and



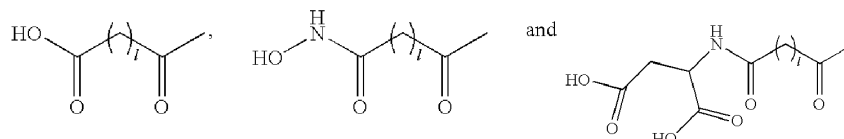
where l is 14, 15, 16, 17, 18, 19 or 20;

p is 1, 2, 3, 4, 7, 8, 9, 10, 11 or 12.

s is 0, 1 or 2

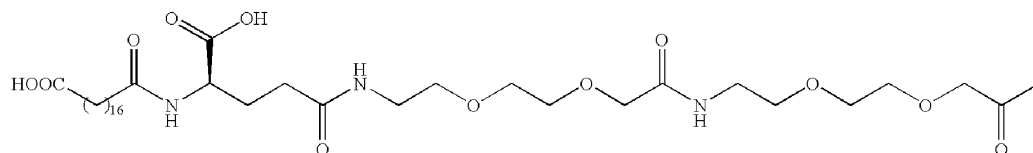
t is 0 or 1.

[00120] In some embodiments, in Formula (M-I) or (M-II), B is

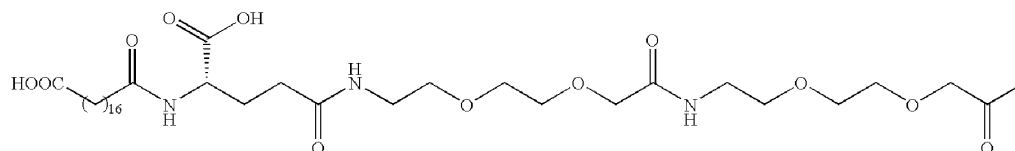


and l is 14, 16, 18 or 20.

[00121] In certain embodiments, in Formula (M-I), B-U is

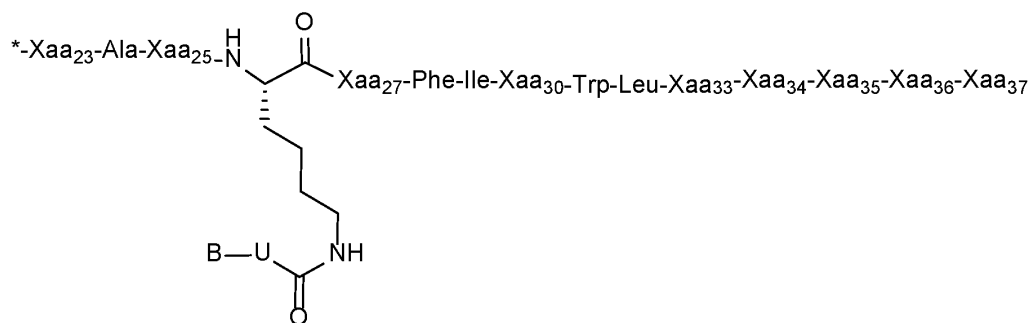


or



[00122] In one aspect, the GLP-1 agonist includes a structure of Formula (M-II):

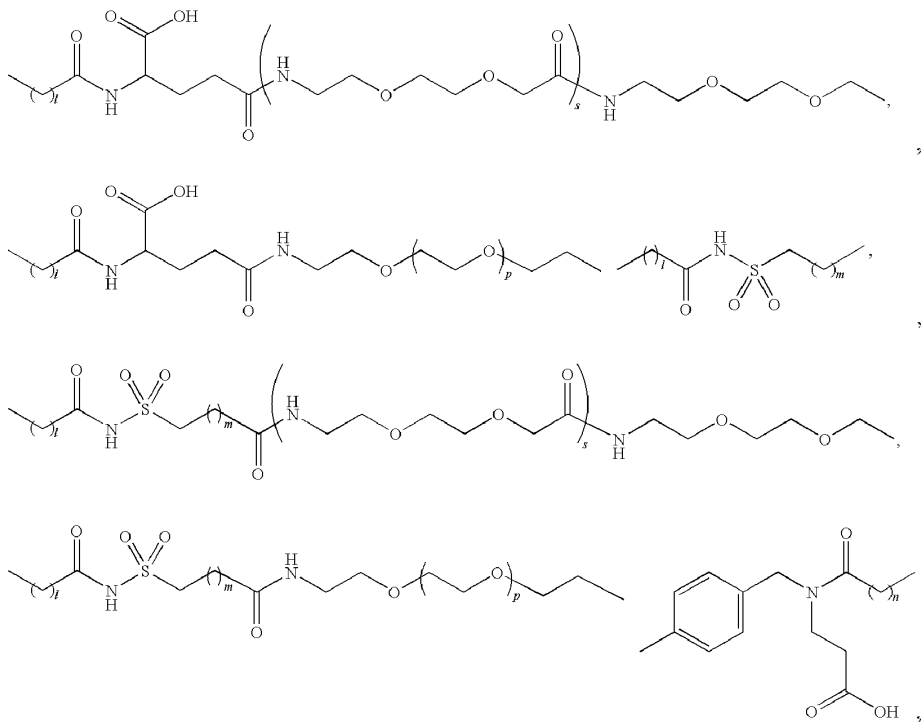
Xaa₇-Xaa₈ -Glu-Gly -Thr-Phe -Thr-Ser -Asp-Xaa₁₆ -Ser-Xaa₁₈ -Xaa₁₉-Xaa₂₀ -Glu-Xaa₂₂-*



(M-II),

wherein:

U is a spacer selected from



where n is 12, 13, 14, 15, 16, 17 or 18,

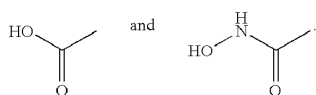
/ is 12, 13, 14, 15, 16, 17 or 18,

m is 0, 1, 2, 3, 4, 5, or 6,

s is 0, 1, 2, or 3,

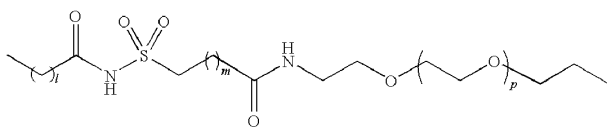
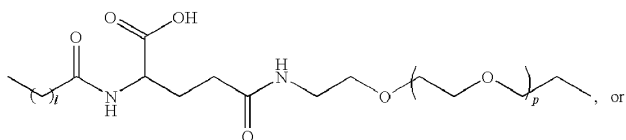
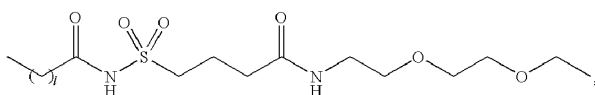
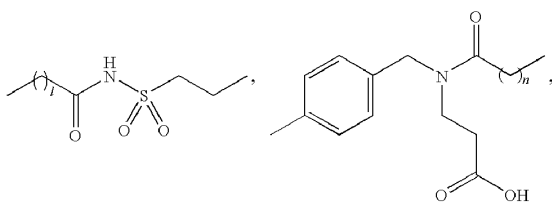
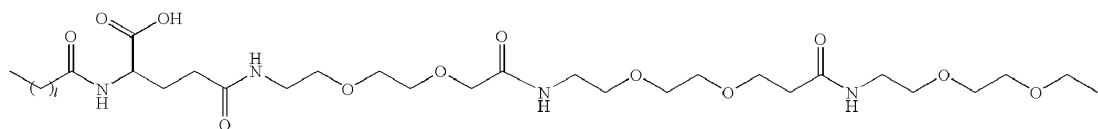
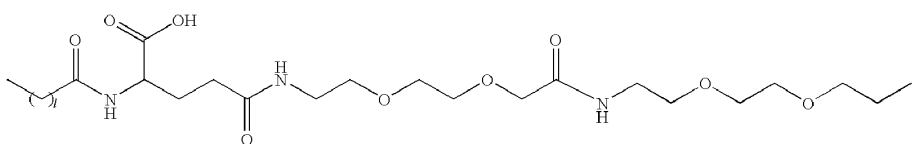
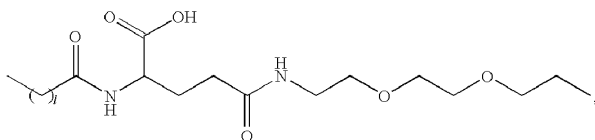
p is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

and where B is an acidic group selected from



Xaa7, Xaa8, Xaa16, Xaa16, Xaa17, Xaa18, Xaa19, Xaa20, Xaa22, Xaa23, Xaa25, Xaa27, Xaa30, Xaa33, Xaa34, Xaa35, Xaa36, and Xaa37.

[00123] In certain embodiments, in Formula (M-II), B-U is selected from:



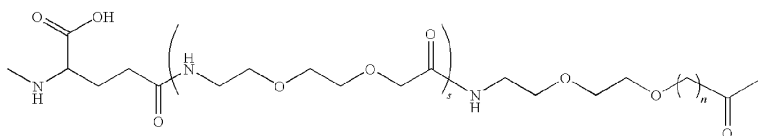
where l is 14, 15 or 16;

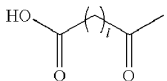
n is 15, 16, 17 or 18;

p is 3, 7, 11 or 24.

- [00124] In certain embodiments, Xaa₇ is His or desamino-histidine.
- [00125] In certain embodiments, Xaa₈ is Ala, Gly, Val, Leu, Ile, Lys or Aib.
- [00126] In certain embodiments, Xaa₁₆ is Val; Xaa₁₈ is Ser.
- [00127] In certain embodiments, Xaa₁₉ is Tyr.
- [00128] In certain embodiments, Xaa₂₀ is Leu.
- [00129] In certain embodiments, Xaa₂₂ is Gly, Glu or Aib.
- [00130] In certain embodiments, Xaa₂₃ is Gln or Glu.
- [00131] In certain embodiments, Xaa₂₅ is Ala.
- [00132] In certain embodiments, Xaa₂₇ is Glu.
- [00133] In certain embodiments, Xaa₃₀ is Ala or Glu.
- [00134] In certain embodiments, Xaa₃₃ is Val.
- [00135] In certain embodiments, Xaa₃₄ is Lys or Arg.
- [00136] In certain embodiments, Xaa₃₅ is Gly or Aib.
- [00137] In certain embodiments, Xaa₃₆ is Arg or Lys.
- [00138] In certain embodiments, Xaa₃₇ is Gly, amide or is absent.
- [00139] In certain embodiments, Xaa₇ is His or desamino-histidine; Xaa₈ is Ala, Gly, Val, Leu, Ile, Lys or Aib; Xaa₁₆ is Val; Xaa₁₈ is Ser; Xaa₁₉ is Tyr; Xaa₂₀ is Leu; Xaa₂₂ is Gly, Glu or Aib; Xaa₂₃ is Gln or Glu; Xaa₂₅ is Ala; Xaa₂₇ is Glu; Xaa₃₀ is Ala or Glu; Xaa₃₃ is Val; Xaa₃₄ is Lys or Arg; Xaa₃₅ is Gly or Aib; Xaa₃₆ is Arg or Lys; and Xaa₃₇ is Gly, amide or is absent.
- [00140] In some embodiments, the GLP-1 agonist includes no more than five, six, seven, eight, nine, ten, or fifteen amino acid residues that have been exchanged, added or deleted. For example, one amino acid near C-terminal or N-terminal amino acid sequence (e.g., Xaa₇ or Xaa₃₇) may be deleted or truncated.

- [00141] In some embodiments, in (M-I), U is

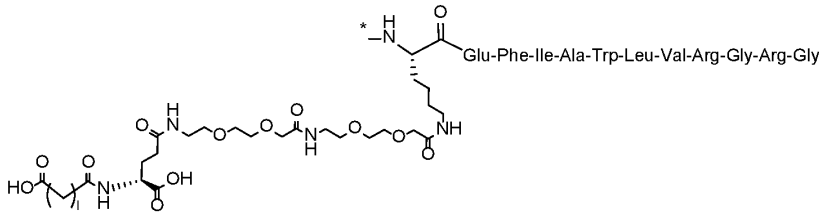




In some embodiments, in (M-I), B is , wherein *l* is 14, 16, or 18.

[00142] In certain embodiments, the GLP-1 agonist has the Formula:

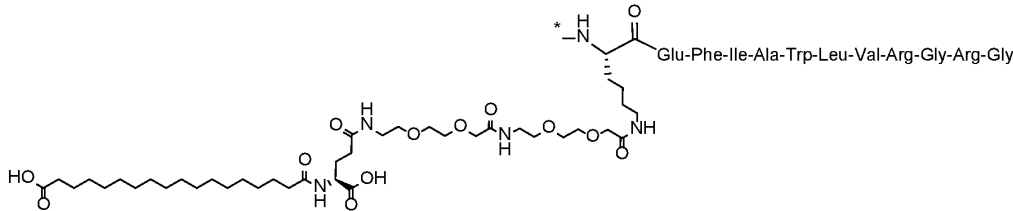
His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-*



l is as described above.

[00143] In certain embodiments, the GLP-1 agonist has the Formula:

His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-*



In certain embodiments, the GLP-1 agonist is semaglutide.

[00144] In some embodiments, the compounds of Formula (M-I) or (M-II) and exemplary compounds can be formulated as subcutaneous injection. In some embodiments, the compounds of Formula (M-I) or (M-II) and exemplary compounds can be formulated as oral dosage.

[00145] These compounds of Formula (M-I) or (M-II) and its subordinates may be synthesized and assayed for *in vitro* as described in, for example, WO2006/097537 or U.S. Pat. Nos. 8,536,122, and 8,129,343 the entire contents of which are incorporated herein by reference.

[00146] In one aspect, the GLP-1 agonist includes a peptide having amino acid sequences of SEQ ID NO: 4-8.

SEQ ID NO.	Amino acid sequences
SEQ ID NO. 4	HSDGTFTSDL SKQMEEEAVR LFIEWLKNGG PSSGAPPPS
SEQ ID NO. 5	HGEGTFTSDL SKQMEEEAVR LFIEWLKNGG PSSGAPPPS
SEQ ID NO. 6	HGEGTFTSDL SKQMEE AVR LFIEWLKNGG P

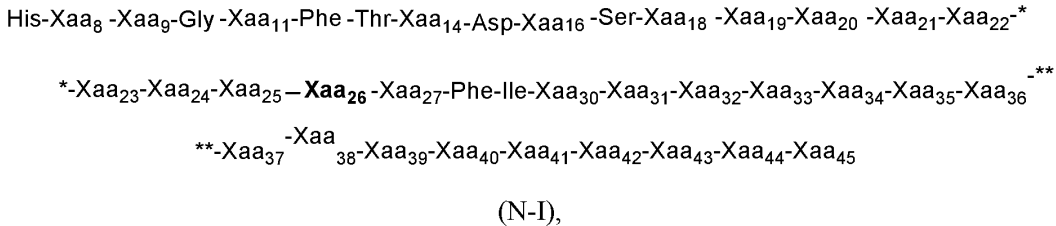
SEQ ID NO. 7	HGEGTFTSDL SKQMEEEAVR LFIEWLKNGG Y
SEQ ID NO. 8	DL SKQMEEEAVR LFIEWLKNGG PSSGAPPPS

[00147] In certain embodiments, an exemplary GLP-1 agonist is exenatide.

[00148] In some embodiments, the peptides of SEQ ID NOs: 4-8 may function as insulin or insulin-like hormones. In some embodiments, the peptides of SEQ ID NOs: 4-8 may stimulate the production of insulin or insulin-like hormones. In some embodiments, the peptides of SEQ ID NOs: 4-8 can be formulated as subcutaneous injection. In some embodiments, the peptides of SEQ ID NOs: 4-8 can be formulated as extended-release subcutaneous injection.

[00149] These peptides of SEQ ID NOs: 4-8 and variants thereof and formulations including thereof may be synthesized or expressed and assayed as described *in vitro or in vivo*, for example, U.S. Pat. Nos. 5,424,286; 6,515,117; and 7,456,254, and the entire contents of which are incorporated herein by reference.

[00150] In one aspect, the GLP-1 agonist includes a structure of Formula (N-I):



- Xaa₇ is His, a modified amino acid or is deleted,
- Xaa₈ is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys, or is deleted,
- Xaa₉ is Glu, Asp, or Lys, or is deleted,
- Xaa₁₀ is Gly or is deleted,
- Xaa₁₁ is Thr, Ala, Gly, Ser, Leu, Ile, Val, Glu, Asp, or Lys or is deleted,
- Xaa₁₂ is Phe or is deleted,
- Xaa₁₃ is Thr or is deleted,
- Xaa₁₄ is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys or is deleted,
- Xaa₁₅ is Asp or is deleted,
- Xaa₁₆ is Val, Ala, Gly, Ser, Thr, Leu, Ile, Glu, Asp, or Lys or is deleted,
- Xaa₁₇ is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys, or is deleted,
- Xaa₁₈ is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
- Xaa₁₉ is Tyr, Phe, Trp, Glu, Asp, or Lys,

Xaa₂₀ is Leu, Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
 Xaa₂₁ is Glu, Asp, or Lys,
 Xaa₂₂ is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
 Xaa₂₃ is Gln, Asn, Arg, Glu, Asp, or Lys,
 Xaa₂₄ is Ala, Gly, Ser, Trp, Leu, Ile, Val, Arg, Glu, Asp, or Lys,
 Xaa₂₅ is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
 Xaa₂₆ is Lys, Arg, Gln, Glu, Asp, or His,
 Xaa₂₇ is Glu, Asp, or Lys,
 Xaa₃₀ is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
 Xaa₃₁ is Trp, Phe, Tyr, Glu, Asp, or Lys,
 Xaa₃₂ is Leu, Gly, Ala, Ser, Thr, Ile, Val, Glu, Asp, or Lys,
 Xaa₃₃ is Val, Gly, Ala, Ser, Thr, Leu, Ile, Glu, Asp, or Lys,
 Xaa₃₄ is Lys, Arg, Glu, Asp, or His,
 Xaa₃₅ is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,
 Xaa₃₆ is Arg, Lys, Glu, Asp, or His,
 Xaa₃₇ is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys, or is deleted,
 Xaa₃₈ is Arg, Lys, Glu, Asp, or His, or is deleted,
 Xaa₃₉ is Arg, Lys, Glu, Asp, or His, or is deleted,
 Xaa₄₀ is Asp, Glu, or Lys, or is deleted,
 Xaa₄₁ is Phe, Trp, Tyr, Glu, Asp, or Lys, or is deleted,
 Xaa₄₂ is Pro, Lys, Glu, or Asp, or is deleted,
 Xaa₄₃ is Glu, Asp, or Lys, or is deleted,
 Xaa₄₄ is Glu, Asp, or Lys, or is deleted, and
 Xaa₄₅ is Val, Glu, Asp, or Lys, or is deleted,
 or an ester, an amide, or a pharmaceutically acceptable salt thereof.

[00151] In some embodiments, when Xaa₃₇, Xaa₃₈, Xaa₃₉, Xaa₄₁, Xaa₄₂, Xaa₄₃ or Xaa₄₄ is deleted, then each amino acid downstream of the amino acid is also deleted. In some embodiments, when the amino acid at position Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆ or Xaa₁₇ is deleted then each amino acid upstream of the amino acid is also deleted.

[00152] In certain aspect, the GLP-1 agonist includes a structure of Formula (N-II):

His-Xaa₈-Xaa₉-Gly-Xaa₁₁-Phe-Thr-Xaa₁₄-Asp-Xaa₁₆-Xaa₁₇-Xaa₁₈-Xaa₁₉-Xaa₂₀-Xaa₂₁-Xaa₂₂-*

*-Xaa₂₃-Xaa₂₄-Xaa₂₅-**Xaa₂₆**-Xaa₂₇-Phe-Ile-Xaa₃₀-Xaa₃₁-Xaa₃₂-Xaa₃₃-Xaa₃₄-Xaa₃₅-Xaa₃₆-Xaa₃₇

(N-II)

[00153] In certain embodiments, in Formula (N-II), Xaa₈ is Ala. In certain embodiments, Xaa₉ is Glu. In certain embodiments, Xaa₁₁ is Thr. In certain embodiments, Xaa₁₄ is Ser. In certain embodiments, Xaa₁₆ is Val. In certain embodiments, Xaa₁₇ is Ser. In certain embodiments, Xaa₁₈ is Ser. In certain embodiments, Xaa₁₉ is Tyr. In certain embodiments, Xaa₂₀ is Leu. In certain embodiments, Xaa₂₁ is Glu. In certain embodiments, Xaa₂₂ is Gly. In certain embodiments, Xaa₂₃ is Gln. In certain embodiments, Xaa₂₄ is Ala. In certain embodiments, Xaa₂₅ is Ala. In certain embodiments, Xaa₂₆ is Lys. In certain embodiments, Xaa₂₇ is Glu. In certain embodiments, Xaa₃₀ is Ala. In certain embodiments, Xaa₃₁ is Trp. In certain embodiments, Xaa₃₂ is Leu. In certain embodiments, Xaa₃₃ is Val. In certain embodiments, Xaa₃₄ is Arg. In certain embodiments, Xaa₃₅ is Gly. In certain embodiments, Xaa₃₆ is Arg. In certain embodiments, Xaa₃₇ is Gly.

[00154] In certain embodiments, in Formula (N-II), Xaa₈ is Ala; Xaa₉ is Glu; Xaa₁₁ is Thr; Xaa₁₄ is Ser; Xaa₁₆ is Val; Xaa₁₇ is Ser; Xaa₁₈ is Ser; Xaa₁₉ is Tyr; Xaa₂₀ is Leu; Xaa₂₁ is Glu; Xaa₂₂ is Gly; Xaa₂₃ is Gln; Xaa₂₄ is Ala; Xaa₂₅ is Ala; Xaa₂₆ is Lys; Xaa₂₇ is Glu; Xaa₃₀ is Ala; Xaa₃₁ is Trp; Xaa₃₂ is Leu; Xaa₃₃ is Val; Xaa₃₄ is Arg; Xaa₃₅ is Gly; Xaa₃₆ is Arg; and Xaa₃₇ is Gly.

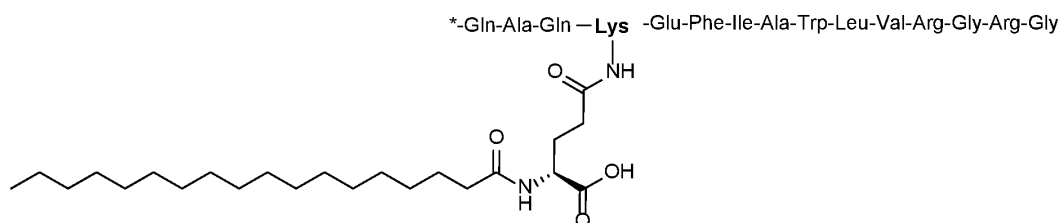
[00155] In some embodiments, in Formula (N-I) or (N-II), the ϵ -amino group of Lys at Xaa₂₆ is substituted with a lipophilic substituent, optionally via a spacer. In some embodiments, the lipophilic substituent is (i) CH₃(CH₂)_nCO— wherein n is 6, 8, 10, 12, 14, 16, 18, 20 or 22, (ii) HOOC(CH₂)_mCO— wherein m is 10, 12, 14, 16, 18, 20 or 22, or (iii) lithochoyl. In some embodiments, the spacer is (i) an unbranched alkane α,ω -dicarboxylic acid group having from 1 to 7 methylene groups, (ii) an amino acid residue except Cys, or (iii) γ -aminobutanoyl. In certain embodiments, the lipophilic substituent is linked to the ϵ -amino group of Lys at Xaa₂₆ via a spacer.

[00156] In certain embodiments, Xaa₂₆ is Lys²⁶(N ^{ϵ} -tetradecanoyl). In certain embodiments, Xaa₂₆ is Lys²⁶(N ^{ϵ} -(ω -carboxynonadecanoyl)). In certain embodiments, Xaa₂₆ is Lys²⁶(N ^{ϵ} -(ω -carboxyheptadecanoyl)). In certain embodiments, Xaa₂₆ is Lys²⁶(N ^{ϵ} -(ω -carboxyundecanoyl)). In certain embodiments, Xaa₂₆ is Lys²⁶(N ^{ϵ} -(ω -carboxypentadecanoyl)). In certain embodiments, Xaa₂₆ is Lys²⁶(N ^{ϵ} -lithochoyl). In certain embodiments, Xaa₂₆ is Lys²⁶(N ^{ϵ} -(γ -glutamyl(N ^{α} -hexadecanoyl))). In certain embodiments, Xaa₂₆ is Lys²⁶(N ^{ϵ} -(γ -glutamyl(N ^{α} -tetradecanoyl))). In certain embodiments, Xaa₂₆ is Lys²⁶(N ^{ϵ} -(γ -glutamyl(N ^{α} -lithochoyl))). In certain embodiments, Xaa₂₆ is Lys²⁶(N ^{ϵ} -(γ -glutamyl(N ^{α} -octadecanoyl))). In certain embodiments, Xaa₂₆ is Lys²⁶(N ^{ϵ} -decanoyl). In

certain embodiments, Xaa₂₆ is Lys²⁶(N^ε-hexadecanoyl). In certain embodiments, Xaa₂₆ is Lys²⁶(N^ε-octanoyl). In certain embodiments, Xaa₂₆ is Lys²⁶(N^ε-dodecanoyl). In certain embodiments, Xaa₂₆ is Lys²⁶(N^ε(N⁶⁸(γaminobutyroyl-(N⁷-hexadecanoyl))). In certain embodiments, Xaa₂₆ is Lys²⁶(N^ε-(γ-D-glutamyl(N^αhexadecanoyl))). In certain embodiments, Xaa₂₆ is Lys²⁶(N^ε-(γglutamyl(N^α-dodecanoyl))). In certain embodiments, Xaa₂₆ is Lys²⁶(N^ε-(βalanlyl(N^α-hexadecanoyl))). In certain embodiments, Xaa₂₆ is Lys²⁶(N^ε-(α-glutamyl(N^α-hexadecanoyl))). In certain embodiments, Xaa₂₆ is Lys²⁶(N^ε-(γ-glutamyl(N^α-decanoyl))). In certain embodiments, Xaa₃₄ is Arg³⁴-GLP-1(7-37). In certain embodiments, Xaa₂₆ is Lys²⁶(N^ε-(γglutamyl(N^α-dodecanoyl))) and Xaa₃₄ is Arg³⁴-GLP-1(7-37).

[00157] In certain embodiments, exemplary GLP-I agonist has a structure of

His-Ala -Glu-Gly -Thr-Phe -Thr-Ser -Asp-Val-Ser-Ser-Tyr-Leu -Glu-Gly-*



In embodiments, the GLP-1 agonist may be liraglutide.

[00158] The GLP-1 agonist having the Formula (N-I) or (N-II), and variants thereof may be synthesized or expressed and assayed as described *in vitro* or *in vivo*, for example, U.S. Pat. No. 6,268,343, the entire contents of which are incorporated herein by reference.

[00159] In one aspect, the GLP-1 agonist include at least one GLP-1 domains which is fused with a recombinant human albumin. In some embodiments, GLP-1 domains has homology of about 80%, 85%, 90%, 95%, or 99% amino acid sequence homology to endogenous human GLP-1 (SEQ ID NO. 1 or 2).

[00160] In certain embodiments, the GLP-1 agonist has the amino acid sequence of SEQ ID NO. 9:

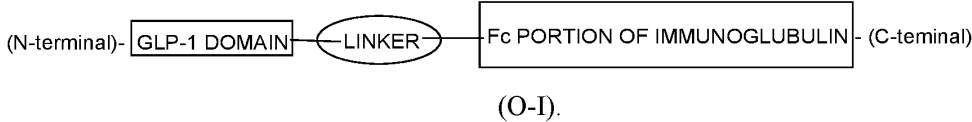
(SEQ ID NO. 9)

```
HGEFTFTSDV SSYLEGQAAK EFWALVKGR HGEFTFTSDV SSYLEGQAAK EFWALVKGR
DAHKSEVAHR FKDLGEENFK ALVLIAFAQY LQQCPFEDHV KLVNEVTEFA KTCVADESSE
NCDKSLHTLF GDKLCTVATL RETYGEMADC CAKQEPERNE CFLQHKDDNP NLPRLVRPEV
DVMCTAFHDN EETFLKKYLY EIARRHPYFY APELLFFAKR YKAAFTTECCQ AADKAACLLP
KLDELRLDEGK ASSAKQRLKC ASLQKFGERA FKAWAVARLS QRFPKAEFAE VSKLVTDLTK
VHTECCHGDL LECADDRADL AKYICENQDS ISSKLKECCE KPLLEKSHCI AEVENDEMPA
DLPSLAADFV ESKDVCKNYA EAKDVFLGMF LYEYARRHPD YSVVLLRLA KTYETTLEKC
CAAADPHECY AKVFDEFKPL VEEPQNLIKQ NCELFEQLGE YKFQNALLVR YTKKVPQVST
```

PTLVEVSRNL GKVGSKCKH PEAKRMPCAE DYLSVVLNQL CVLHEKTPVS DRVTKCCTES
LVNRRPCFSA LEVDETYVPK EFNAETFTFH ADICTLSEKE RQIKKQTALV ELVKHKPKAT
KEQLKAVMDD FAAFVEKCKC ADDKETCFAE EGKKLVAASQ AALGL

[00161] In one aspect, the GLP-1 agonist may include at least one or more GLP-1 domains and a Fc portion of an immunoglobulin fused with the one or more GLP-1 domains. In some embodiment, the linker in (O-I) is a polymer linker (e.g., PEG). In some embodiment, the linker in (O-I) is a peptide linker. For example, N-terminal glycine of the peptide linker is directly fused to the C-terminal glycine residue of the GLP-1 domain and the C-terminal serine of the linker (e.g., peptide or polymer) is directly fused to the N-terminal alanine of the Fc portion.

[00162] In some embodiments, the GLP-1 agonist has a structure of Formula (O-I),



[00163] In some embodiments, GLP-1 domains has homology of about 80%, 85%, 90%, or 95% or greater homology or sequence similarity to endogenous human GLP-1 (SEQ ID NO: 1 or 2).

[00164] In certain embodiments, the GLP-1 agonist may include at least one or more GLP-1 domains selected from SEQ ID NOs. 10-15 a peptide linker of SEQ ID NO. 16; and fused Fc portion of the immunoglobulin has the amino acid sequence of SEQ ID NO. 17.

SEQ ID NO.	Amino acid sequences
SEQ ID NO. 10	His-Xaa8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Gly
SEQ ID NO. 11	His-Xaa8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly-Gly
SEQ ID NO. 12	His-Xaa8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Pro
SEQ ID NO. 13	His-Xaa8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly-Pro

SEQ ID NO. 14	His-Xaa8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly
SEQ ID NO. 15	His-Xaa8-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly
SEQ ID NO. 16	Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser
SEQ ID NO. 17	Ala-Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Cys-Pro-Pro-Cys-Pro-Ala-Pro-Xaa16-Xaa17-Xaa18-Gly-Gly-Pro-Ser-Val-Phe-Leu-Phe-Pro-Pro-Lys-Pro-Lys-Asp-Thr-Leu-Met-Ile-Ser-Arg-Thr-Pro-Glu-Val-Thr-Cys-Val-Val-Val-Asp-Val-Ser-Gln-Glu-Asp-Pro-Glu-Val-Gln-Phe-Asn-Trp-Tyr-Val-Asp-Gly-Val-Glu-Val-His-Asn-Ala-Lys-Thr-Lys-Pro-Arg-Glu-Glu-Gln-Phe-Xaa80-Ser-Thr-Tyr-Arg-Val-Val-Ser-Val-Leu-Thr-Val-Leu-His-Gln-Asp-Trp-Leu-Asn-Gly-Lys-Glu-Tyr-Lys-Cys-Lys-Val-Ser-Asn-Lys-Glu-Leu-Pro-Ser-Ser-Ile-Glu-Lys-Thr-Ile-Ser-Lys-Ala-Lys-Gly-Gln-Pro-Arg-Glu-Pro-Gln-Val-Tyr-Thr-Leu-Pro-Pro-Ser-Gln-Glu-Glu-Met-Thr-Lys-Asn-Gln-Val-Ser-Leu-Thr-Cys-Leu-Val-Lys-Gly-Phe-Tyr-Pro-Ser-Asp-Ile-Ala-Val-Glu-Trp-Glu-Ser-Asn-Gly-Gln-Pro-Glu-Asn-Asn-Tyr-Lys-Thr-Thr-Pro-Pro-Val-Leu-Asp-Ser-Asp-Gly-Ser-Phe-Phe-Leu-Tyr-Ser-Arg-Leu-Thr-Val-Asp-Lys-Ser-Arg-Trp-Gln-Glu-Gly-Asn-Val-Phe-Ser-Cys-Ser-Val-Met-His-Glu-Ala-Leu-His-Asn-His-Tyr-Thr-Gln-Lys-Ser-Leu-Ser-Leu-Ser-Leu-Gly-Xaa230

[00165] In certain embodiments, Xaa8 is Gly. In certain embodiments, Xaa16 is Pro or Glu. In certain embodiments, Xaa17 is Phe, Val, or Ala. In certain embodiments, Xaa18 is Leu, Glu, or Ala. In certain embodiments, Xaa80 is Asn or Ala. In certain embodiments, Xaa230 is Lys or is absent.

[00166] In certain embodiments, the GLP-1 agonist has the amino acid sequence of SEQ ID NO. 18:

(SEQ ID NO: 18)

HGEGTFTSDV SSYLEEQAAK EFLAWLVKGG GGGGSGGGG SGGGSAESK YGPPCPPCPA
PEAAGGPSVF LFPPKPKDTL MISRTPEVTC VVDVSQEDP EVQFNWYVDG VEVHNAKTKP
REEQFNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNGKLPSS IEKTISKAKG QPREPQVYTL
PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTTPVLDSG GSFFLYSRLT
VDKSRWQEGN VFSCSVMEHA LHNHYTQKSL SLSLG

[00167] The GLP-1 agonist having the Formula (O-I) and variants thereof may be synthesized or expressed and assayed as described *in vitro* or *in vivo*, for example, WO2005/000892 and/or U.S. Pat. No. 7,452,966, the entire contents of which are incorporated herein by reference.

[00168] In certain embodiments, the GLP-1 agonist may include 6-lysine conjugated to exendin-4 at the C-terminal or N-terminal of exendin-4 (SEQ ID NO. 19, 20, 22, 24, 25, or 26). The peptide may be further modified such that the C-terminal glycine residue is removed and replaced with an amide group.

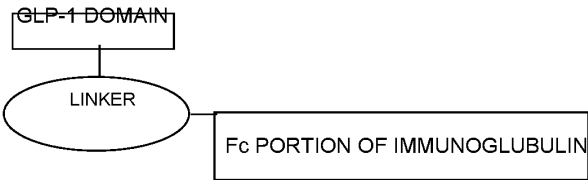
SEQ ID NO.	Amino acid sequences
SEQ ID NO. 19	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser-Lys-Lys-Lys-Lys-Lys-Lys
SEQ ID NO. 20	Lys-Lys-Lys-Lys-Lys-Lys-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser-Lys-Lys-Lys-Lys-Lys-Lys
SEQ ID NO. 21	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Ser
SEQ ID NO. 22	Lys-Lys-Lys-Lys-Lys-Lys-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Ser
SEQ ID NO. 23	Asn-Glu-Glu-Glu-Glu-Glu-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Ser
SEQ ID NO. 24	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Ser-Lys-Lys-Lys-Lys-Lys-Lys
SEQ ID NO. 25	Lys-Lys-Lys-Lys-Lys-Lys-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Ser-Lys-Lys-Lys-Lys-Lys-Lys
SEQ ID NO. 26	Asp-Glu-Glu-Glu-Glu-Glu-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Ser-Lys-Lys-Lys-Lys-Lys-Lys

[00169] In embodiments, the GLP-1 agonist may be lixisenatide.

[00170] The GLP-1 agonist and variants (e.g., conjugates) thereof may be synthesized or expressed and assayed as described *in vitro* or *in vivo*, for example, U.S. Pat. No. 6,528,486, the entire contents of which are incorporated herein by reference.

[00171] In one aspect, the GLP-1 agonist may include at least one or more GLP-1 domains (e.g., exendin-4) and IgG4 (e.g., a Fc portion of an immunoglobulin) fused with the one or more GLP-1 domains. For example, a polymer linker (e.g., PEG) is covalent connected to one of the amino acid of the GLP-1 domain and the IgG4 peptide is fused to the GLP-1 domain.

[00172] In certain embodiments, the GLP-1 agonist has a structure of Formula (O-II),



(O-II).

[00173] In some embodiments, the GLP-1 domain in Formula (O-II) has the sequence homologous to exendin-4 (SEQ ID NO. 3), for example, by about 80%, 85%, 90%, or 95% or greater homology or similarity. In certain embodiments, the GLP-1 domain has a sequence of exendin (e.g., exendin-4, SEQ ID NO. 3).

[00174] In some embodiment, the linker in (O-II) is a polymer linker (e.g., PEG). In some embodiment, the linker in (O-II) is a peptide linker. In some embodiment, the linker in (O-II) is a hybrid of the polymer and peptide.

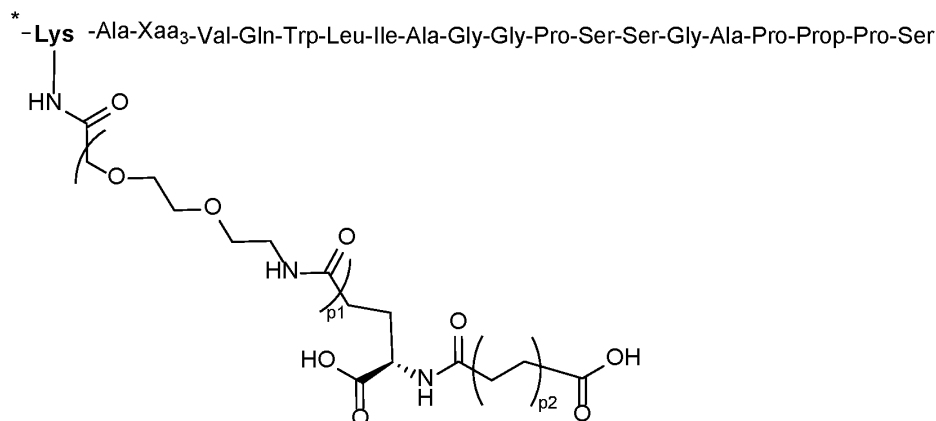
[00175] In certain embodiments, the GLP-1 domain has a sequence of SEQ ID NO. 27. In certain embodiments, the Fc portion of immunoglobulin has a sequence of SEQ ID NO. 28. In certain embodiments, the GLP-1 agonist includes the amino acid sequence of SEQ ID NO. 27 and the amino acid sequence of SEQ ID NO. 28. In certain embodiments, the N terminus of SEQ ID NO. 28 is connected to Lys at 26th amino acid (underlined in SEQ ID No. 27) via a polymer linker.

SEQ ID NO.	Amino acid sequences
SEQ ID NO. 27	GEGTFTSDLS KQMEEEAVRL FIEWL <u>K</u> NGGP SSGAPPPS
SEQ ID NO. 28	PSCPAPFELG GPSVFLFPPK PKDTLMISRT PEVTCVVVDV SQEDPEVQFN WYVDGVEVHN AKTKPREEQF NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK GLPSSIEKTI SKAKGQPREP QVYTLPPSQE EMTKNQVSLT CLVKGFYPSD

	IAVEWESNGQ PENNYKTFPP VLDSDGSFFL YSRLTVDKSR WQEGNVFSCS VMHEALHNHY TQKSLSLSLG K
--	---

[00176] In an aspect, the GLP-1 agonist has a structure of Formula (P-I):

Tyr-Xaa₁-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-Xaa₂-Leu-Asp-Lys-Ile-Ala-Gln-*



(P-I),

wherein:

Xaa₁ is Aib;

Xaa₂ is Aib;

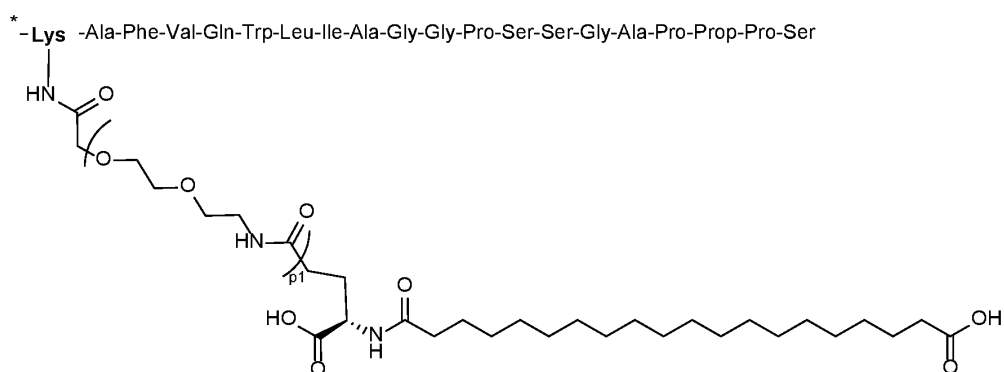
Xaa₃ is Phe or 1-Nal (1-Naphthylalanine);

p₁ is 1 to 2; and

p₂ is 10 to 20.

[00177] In certain embodiments, the GLP-1 agonist has a structure of Formula (P-II):

Tyr-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-Aib-Leu-Asp-Lys-Ile-Ala-Gln-*



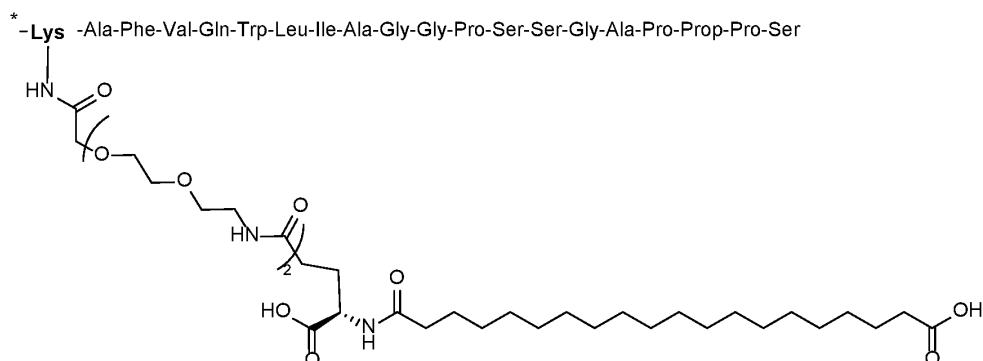
(P-II)

p₁ is as described above.

[00178] In some embodiments, p₁ is 1. In some embodiments, p₁ is 2.

[00179] In certain embodiments, the GLP-1 agonist has a structure of

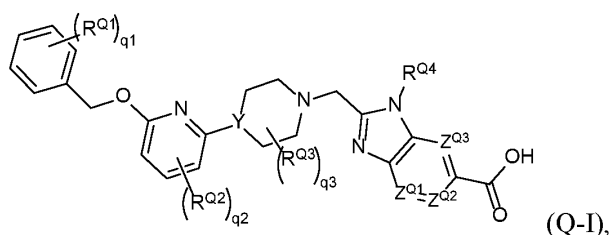
Tyr-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-Aib-Leu-Asp-Lys-Ile-Ala-Gln*



In embodiments, the GLP-1 agonist is tirzepatide.

[00180] The GLP-1 agonist having the Formula (P-I), (P-II), and subordinates thereof may be synthesized or expressed and assayed as described *in vitro* or *in vivo*, for example, Sun B, et al. Proc Natl Acad Sci U S A. 2022 Mar 29;119(13), Bokvist K. B., Coskun T., Cummins R. C., Alsina-Fernandez J., U.S. Patent No. US 9,474,780, the entire contents of which are incorporated herein by reference.

[00181] In one aspect, the GLP-1 agonist has a structure of Formula (Q-I):



or a pharmaceutically acceptable salt thereof,

wherein:

each R^{Q1} is independently F, Cl, $-\text{CN}$, $-\text{CH}_3$, or $-\text{CF}_3$;

$q1$ is 0, 1, 2, or 3;

each R^{Q2} is independently F, Cl, or $-\text{CN}$;

$q2$ is 0, 1 or 2;

each R^{Q3} is independently F, $-\text{OH}$, $-\text{CN}$, $-\text{C}_{1-3}\text{alkyl}$, $-\text{OC}_{1-3}\text{alkyl}$, or $-\text{C}_{3-4}\text{cycloalkyl}$, or

two of R^{Q3} s may together cyclize to form C_{3-4} spirocycloalkyl, wherein the alkyl of $\text{C}_{1-3}\text{alkyl}$ and $-\text{OC}_{1-3}\text{alkyl}$, cycloalkyl, or spirocycloalkyl may be substituted as valency allows with 0 to 3 F atoms and with 0 to 1 $-\text{OH}$;

$q3$ is 0, 1, or 2;

Y is CH or N;

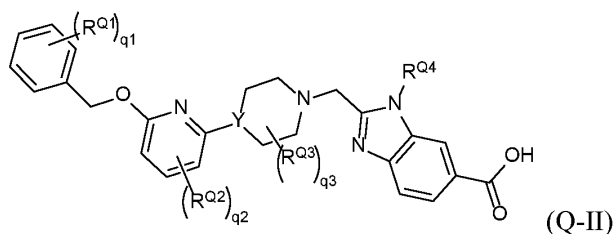
R^{Q4} is $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $\text{C}_{1-3}\text{alkylene}-R^{Q5}$, or $\text{C}_{1-3}\text{alkylene}-R^{Q6}$, wherein R^{Q5} is a substituted (e.g., substituted with halogen, alkyl, amine, or alkoxy) or unsubstituted 4- to 6-membered heterocycloalkyl, and R^{Q6} is a substituted (e.g., substituted with halogen, alkyl, amine, or alkoxy) or unsubstituted 5- to 6-membered heteroaryl;

Z^{Q1} is CH or N;

Z^{Q2} and Z^{Q3} are each independently $-\text{CR}^{QZ}$ or N, provided that when Z^1 or Z^3 is N, then Z^{Q2} is $-\text{CR}^{QZ}$; and

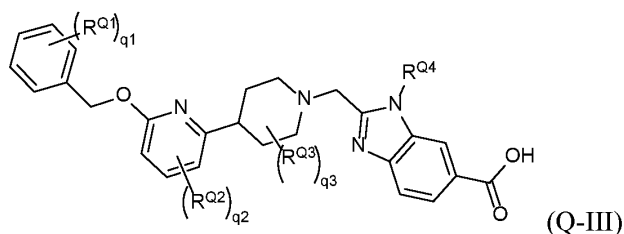
each R^{QZ} is independently H, F, Cl, or $-\text{CH}_3$.

[00182] In some embodiments, Z^{Q1} , Z^{Q2} , and Z^{Q3} are $-\text{CH}=\text{}$. In certain embodiments, the GLP-1 has a structure of (Q-II):



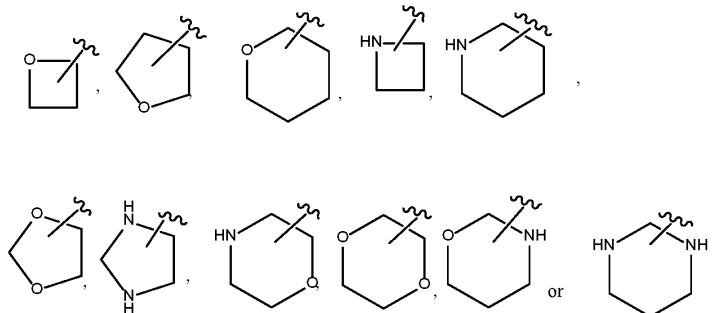
R^{Q1} , R^{Q2} , R^{Q3} , R^{Q4} , $q1$, $q2$, and $q3$ are as described above.

[00183] In some embodiments, Y is $-\text{CH}-$. In certain embodiments, the GLP-1 has a structure of (Q-III):



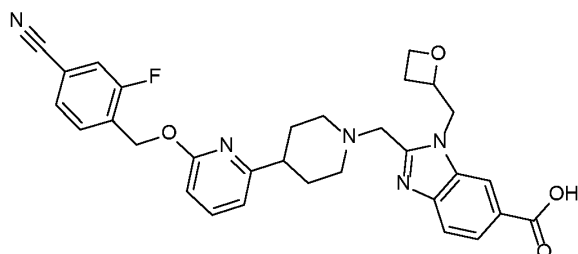
R^{Q1} , R^{Q2} , R^{Q3} , R^{Q4} , $q1$, $q2$, and $q3$ are as described above.

[00184] In some embodiments, R^{Q4} is $-\text{CH}^2-R^{Q5}$, and R^{Q5} is



[00185] In some embodiments, q1 is 1 or 2. In some embodiments, each R^{Q1} is independently halogen, C₁₋₃ alkyl, or -CN. In some embodiments, q2 is 0. In some embodiments, q3 is 0.

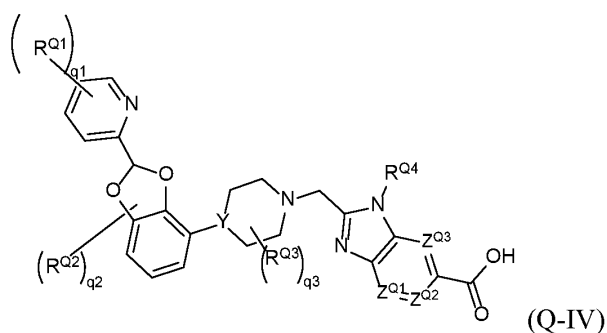
[00186] In certain embodiments, the GLP-1 agonist has a structure:



In embodiments, the GLP-1 agonist may be danuglipron.

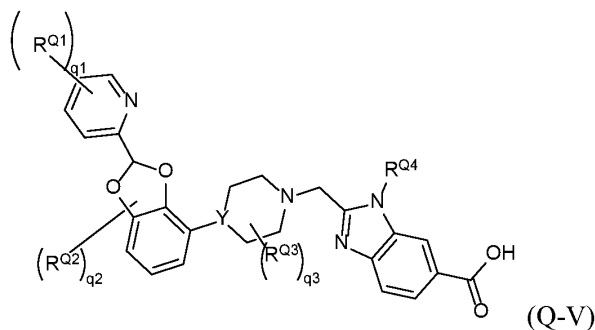
[00187] The GLP-1 agonist having the Formula (Q-I), (Q-II), (Q-III) and subordinates thereof may be synthesized or expressed and assayed as described *in vitro* or *in vivo*, for example, WO2018/109607, and U.S. Patent No. 11,512,070, the entire contents of which are incorporated herein by reference.

[00188] In one aspect, the GLP-1 agonist has a structure of Formula (Q-IV):



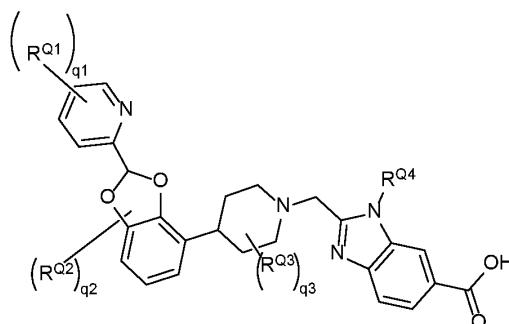
wherein Y, Z^{Q1}, Z^{Q2}, Z^{Q3}, R^{Q1}, R^{Q2}, R^{Q3}, R^{Q4}, q1, q2, and q3 are as described above.

[00189] In some embodiments, Z^{Q1}, Z^{Q2}, and Z^{Q3} are -CH=. In some embodiments, the GLP-1 agonist has a structure of (Q-V):



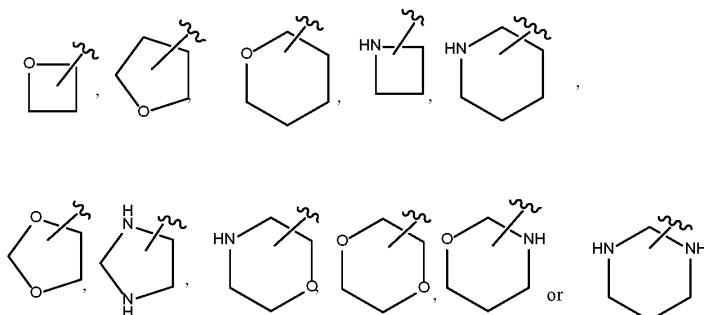
wherein Y, Z^{Q1}, Z^{Q2}, Z^{Q3}, R^{Q1}, R^{Q2}, R^{Q3}, R^{Q4}, q1, q2, and q3 are as described above.

[00190] In some embodiments, Y is -CH-. In certain embodiments, the GLP-1 has a structure of (Q-VI):

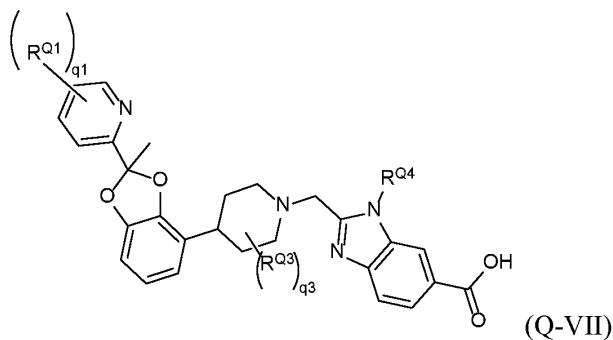


wherein R^{Q1} , R^{Q2} , R^{Q3} , R^{Q4} , $q1$, $q2$, and $q3$ are as described above.

[00191] In some embodiments, R^{Q4} is $-\text{CH}^2-\text{R}^{Q5}$, and R^{Q5} is



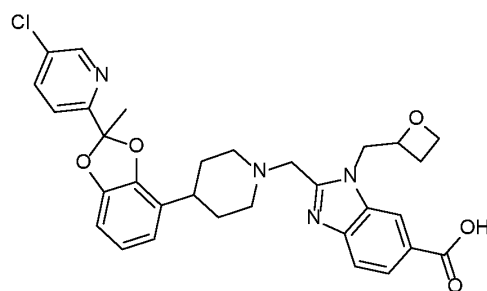
[00192] In some embodiments, $q2$ is 1 and R^{Q2} is $-\text{CH}_3-$. In certain embodiments, the GLP-1 has a structure of (Q-VII):



wherein R^{Q1} , R^{Q3} , R^{Q4} , $q1$, and $q3$ are as described above.

[00193] In some embodiments, $q1$ is 1 or 2. In some embodiments, each R^{Q1} is independently halogen, C_{1-3} alkyl, or $-\text{CN}$. In some embodiments, $q3$ is 0.

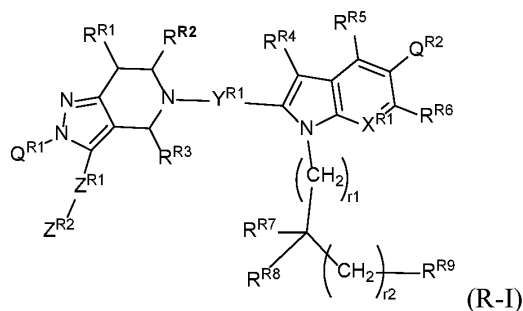
[00194] In certain embodiments, the GLP-1 agonist has a structure:



In embodiments, the GLP-1 agonist may be lotiglipron.

[00195] The GLP-1 agonist having the Formula (Q-IV), (Q-V), (Q-VI), and (Q-VII) and subordinates thereof may be synthesized or expressed and assayed as described *in vitro* or *in vivo*, for example, U.S. Patent Pub. Nos. US2022/0348564 and US2022/0193063, the entire contents of which are incorporated herein by reference.

[00196] In an aspect, the GLP-1 agonist has a structure of Formula (R-I):



wherein, X^{R1} is ---N= or ---CH= ;

Y^{R1} is selected from ---C(=O)--- , ---CH--- , and $\text{---S(=O)}_2\text{---}$;

Q^{R1} is C_{6-10} aryl or 5 to 10 membered heteroaryl, wherein C_{6-10} aryl and 5 to 10 membered heteroaryl are optionally with one to five substituents independently selected from a halogen atom, C_{1-6} alkyl (wherein C_{1-6} alkyl is optionally substituted with one or more halogen atoms), and C_{1-6} alkoxy;

Q^{R2} is 3 to 12 membered heterocyclyl or 5 to 10 membered heteroaryl, wherein 3 to 12 membered heterocyclyl and 5 to 10 membered heteroaryl are optionally substituted with one to three substituents independently selected from a halogen atom, C_{1-6} alkyl (wherein C_{1-6} alkyl is optionally substituted with one or more halogen atoms), C_{1-6} alkoxy, and $\text{---NR}^{Ra}\text{R}^{Rb}$, and two C_{1-6} alkyl groups together with a carbon atom to which they are attached may form C_{3-8} carbocyclic ring; and R^{Ra} and R^{Rb} are independently selected from a hydrogen atom, C_{1-6} alkyl, and $(\text{C}_{1-6} \text{ alkyl})\text{carbonyl}$;

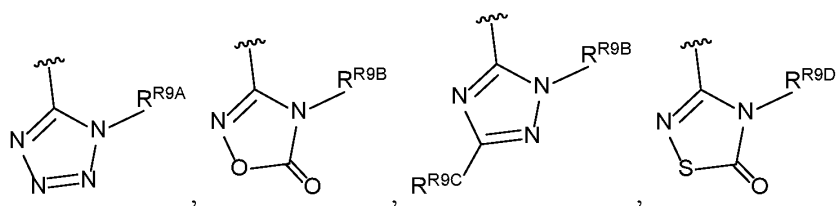
R^{R1} , R^{R2} and R^{R3} are each independently selected from a hydrogen atom and C_{1-6} alkyl (wherein, C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from a halogen atom, C_{1-6} alkoxy, and hydroxy);

R^{R4} , R^{R5} and R^{R6} are independently selected from a hydrogen atom, a halogen atom, and C_{1-6} alkyl;

R^{R7} and R^{R8} are independently a hydrogen atom or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from a halogen atom and C_{3-15} cycloalkyl, or R^{R7} and R^{R8} together with a carbon atom to which they are attached may form C_{3-15} cycloalkane ring, wherein C_{3-15} cycloalkane ring formed by R^{R7} and R^{R8} together is optionally substituted with one to three C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from a halogen atom, hydroxy, $—NR^{7a}R^{7b}$, C_{1-6} alkoxy, and 3 to 12 membered heterocyclyl, and R^{7a} and R^{7b} are independently selected from a hydrogen atom, C_{1-6} alkyl, and $(C_{1-6} \text{ alkyl})\text{carbonyl}$;

$r1$ is an integer of 0 to 3; $r2$ is an integer of 0 to 5;

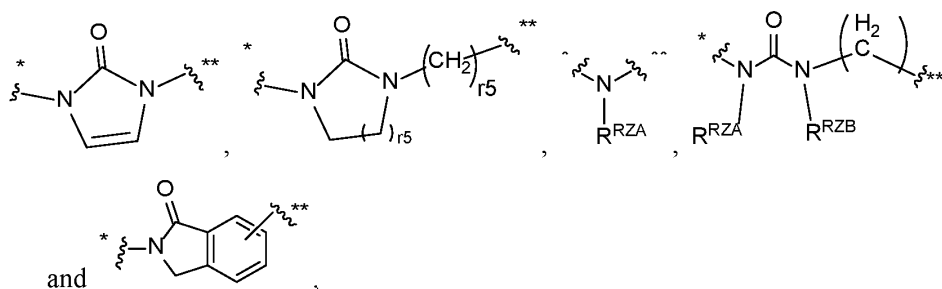
R^{R9} is selected from the group consisting of



$—CO_2R^{R9F}$, and $—C(=O)—NR^{R9G}R^{R9H}$,

R^{R9A} , R^{R9B} , R^{R9C} , R^{R9D} , and R^{R9G} are each independently selected from a hydrogen atom, C_{1-6} alkyl (wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from a halogen atom and C_{1-6} alkoxy), and $(C_{1-6} \text{ alkyl})\text{carbonyl}$; R^{R9E} is a hydrogen atom, or C_{1-6} alkyl that is optionally substituted with one or more halogen atoms; R^{R9G} is a hydrogen atom or C_{1-6} alkyl; R^{R9H} is a hydrogen atom, C_{1-6} alkyl, $(C_{1-6} \text{ alkyl})\text{carbonyl}$, cyano, or $—S(=O)_{r3}—$; R^{R9I} , $R3$ is an integer of 0 to 2; and R^{R9I} is C_{1-6} alkyl;

Z^{R1} is selected from the group consisting of



wherein R^{RZA} is selected from a hydrogen atom, C_{1-6} alkyl, and $(C_{1-6}$ alkyl)carbonyl;

R^{RZB} and R^{RZC} are independently a hydrogen atom or C_{1-6} alkyl; r_4 is an integer of 1 to 3; r_5 and r_6 are independently an integer of 0 to 10 (* represents a binding position with a pyrazolopyridine structure, and ** represents a binding position with Z^{R2});

Z^{R2} is selected from the group consisting of C_{1-6} alkyl, C_{3-15} cycloalkyl, 3 to 12 membered heterocyclyl, C_{6-10} aryl and 5 to 10 membered heteroaryl, wherein C_{3-15} cycloalkyl, 3 to 12 membered heterocyclyl, C_{6-10} aryl, and 5 to 10 membered heteroaryl are optionally substituted with one to five substituents independently selected from:

oxo;

halogen;

-CN;

$—NR^{RZD}R^{RZE}$, wherein R^{RZD} and R^{RZE} are independently selected from a hydrogen atom, C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from hydroxy, a halogen atom and C_{1-6} alkoxy;

$—C(=O)—NR^{RZF}R^{RZG}$, wherein R^{RZF} and R^{RZG} are independently selected from a hydrogen atom, C_{1-6} alkyl and $(C_{1-6}$ alkyl)carbonyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from hydroxy, a halogen atom and C_{1-6} alkoxy,

$—S(=O)_{r7}—R^{RZH}$, wherein r_7 is an integer of 0 to 2; and R^{RZH} is a hydrogen atom or C_{1-6} alkyl, g) C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more substituent independently selected from a halogen atom, hydroxy, $—NR^{RZJ}R^{RZJ}$, C_{1-6} alkoxy, and 3 to 12 membered heterocyclyl, wherein R^{RZJ} and R^{RZJ} are independently a hydrogen atom or C_{1-6} alkyl, and wherein 3 to 12 membered

heterocyclyl is optionally substituted with one or more substituents independently selected from hydroxy, C₁₋₆ alkyl and 3 to 12 membered heterocyclyl;

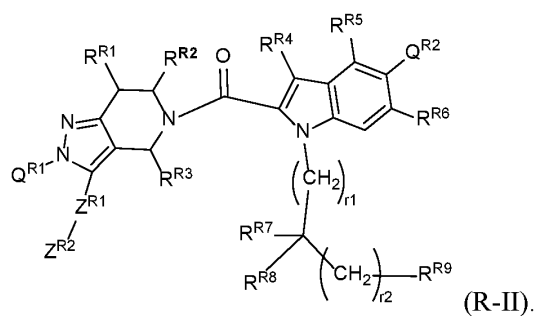
C₁₋₆ alkoxy; wherein C₁₋₆ alkoxy is optionally substituted with one or more substituent independently selected from hydroxy, a halogen atom, and C₁₋₆ alkoxy;

3 to 12 membered heterocyclyl; wherein 3 to 12 membered heterocyclyl is optionally substituted with one or more substituents independently selected from C₁₋₆ alkyl and (C₁₋₆ alkyl)carbonyl;

C₆₋₁₀ aryl; wherein C₆₋₁₀ aryl is optionally substituted with one or more (C₁₋₆ alkyl)carbonyl; 5 to 10 membered heteroaryl, wherein 5 to 10 membered heteroaryl is optionally substituted with one or more substituents independently selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, $\text{---NR}^{\text{RZK}}\text{R}^{\text{RZL}}$, and 3 to 12 membered heterocyclyl, wherein R^{RZK} and R^{RZL} are independently selected from a hydrogen atom, C₁₋₆ alkyl and (C₁₋₆ alkyl)carbonyl, and wherein 3 to 12 membered heterocyclyl is optionally substituted with one or more substituents independently selected from C₁₋₆ alkyl and (C₁₋₆ alkyl)carbonyl;

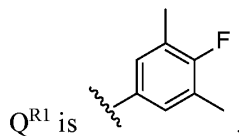
or a salt thereof.

[00197] In some embodiments, Y^{R1} is -C(=O)-. In some embodiments, X^{R1} is -CH=. In certain embodiments, the GLP-1 agonist has a structure:

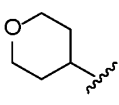


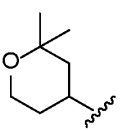
[00198] In some embodiments, Q^{R1} is phenyl or pyridyl, and phenyl or pyridyl is substituted with one to four substituents independently selected from a halogen (e.g., F, Cl, or Br) and C₁₋₆ alkyl. In some embodiments, Q^{R1} is phenyl substituted one or more

independently selected from halogen (e.g., F, Cl, or Br) and methyl. In some embodiments,

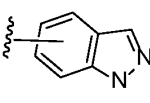


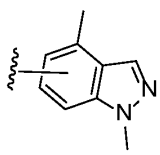
[00199] In some embodiments, Q^{R2} is 6 membered heterocyclyl or 5 to 6 membered heteroaryl, and the 6 membered heterocyclyl and 5 to 6 membered heteroaryl are independently optionally substituted with one or more C_{1-6} alkyl, and two C_{1-6} alkyl groups together with a carbon atom to which they are attached may form C_{3-8} carbocyclic ring. In

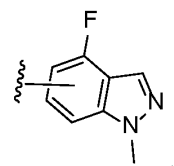
some embodiments, Q^{R2} is  which may be optionally substituted with one or more

C_{1-6} alkyl. In some embodiments, Q^{R2} is 

[00200] In some embodiments, Z^{R2} is selected from C_{1-6} alkyl, C_{3-15} cycloalkyl, 3 to 12 membered heterocyclyl, C_{6-10} aryl, and 5 to 10 membered heteroaryl, wherein C_{3-15} cycloalkyl, 3 to 12 membered heterocyclyl, C_{6-10} aryl, and 5 to 10 membered heteroaryl are optionally substituted with one to four substituents independently selected from oxo, halogen,

and C_{1-6} alkyl. In some embodiments, Z^{R2} is , which is optionally substituted

with oxo, halogen, and C_{1-6} alkyl. In certain embodiments, Z^{R2} is , which is optionally substituted with oxo, halogen, and C_{1-6} alkyl. In some embodiments, Z^{R2} is

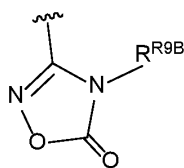


[00201] In some embodiments, each R^{R1} and R^{R3} is independently hydrogen or C_{1-3} alkyl. In some embodiments, R^{R1} is hydrogen. In some embodiments, R^{R1} is C_{1-3} alkyl. In some embodiments, R^{R3} is hydrogen. In some embodiments, R^{R3} is C_{1-3} alkyl. In certain embodiments, R^{R1} is hydrogen and R^{R3} is methyl.

[00202] In some embodiments, each R^{R7} and R^{R8} is independently hydrogen or C_{1-6} alkyl. In some embodiments, R^{R7} and R^{R8} is are both hydrogen. In some embodiments, R^{R7} and R^{R8} is are both C_{1-6} alkyl. In some embodiments, R^{R7} is a hydrogen atom and R^{R8} is C_{1-6} alkyl.

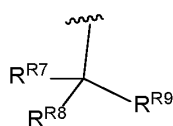
[00203] In some embodiments, R^{R7} and R^{R8} together with a carbon atom to which they are attached form C_{3-8} cycloalkane ring, and the C_{3-8} cycloalkyl formed is optionally substituted with one to two C_{1-6} alkyl, and C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from hydroxy, C_{1-6} alkoxy, and 3 to 12 membered heterocyclyl.

[00204] In some embodiments, $r1$ and $r2$ are both 0. In some embodiments, R^9 is

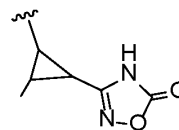


. R^{R9B} is as described above.

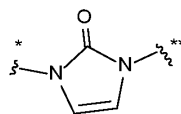
[00205] In certain embodiments,



has a structure of



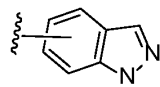
[00206] In some embodiments, Z^{R1} is



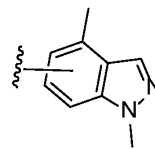
wherein * represents a binding position with a pyrazolopyridine structure, and ** represents a binding position with Z^2 .

[00207] In some embodiments, Z^{R2} is selected from C_{1-6} alkyl, C_{3-15} cycloalkyl, 3 to 12 membered heterocyclyl, C_{6-10} aryl, and 5 to 10 membered heteroaryl, wherein C_{3-15} cycloalkyl, 3 to 12 membered heterocyclyl, C_{6-10} aryl, and 5 to 10 membered heteroaryl are optionally substituted with one to four substituents independently selected from oxo, halogen,

and C_{1-6} alkyl. In some embodiments, Z^{R2} is



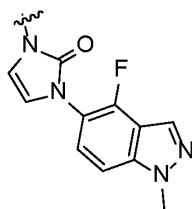
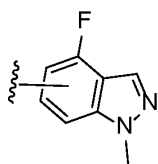
, which is optionally substituted



with oxo, halogen, and C_{1-6} alkyl. In certain embodiments, Z^{R2} is

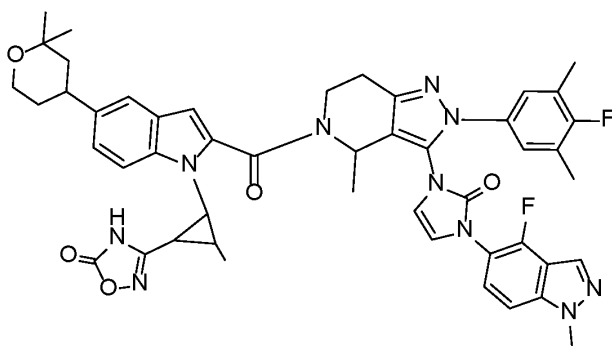
, which is

optionally substituted with oxo, halogen, and C₁₋₆ alkyl. In some embodiments, Z^{R2} is



In some embodiments, -Z^{R1}-Z^{R2}- is

[00208] In certain embodiments, exemplary GLP-1 agonist of Formula (R-I) or (R-II) is



In embodiments, the GLP-1 agonist may be orforglipron.

[00209] The GLP-1 agonist having the Formula (R-I), (R-II), and subordinates thereof may be synthesized or expressed and assayed as described *in vitro*, for example, WO2018/056453, and U.S. Patent No. 10,858,356, the entire contents of which are incorporated herein by reference.

[00210] In one aspect, the GLP-1 agonist may have a sequence of SEQ ID NO. 29-30.

SEQ ID NO.	Amino acid sequences
SEQ ID NO. 29	His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Aib-Arg-NH ₂
SEQ ID NO. 30	Tyr-{Aib}-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-{α-Me-Leu}-Leu-Asp-Lys-{diacid-C20-gamma-Glu-(AEEA)-Lys}-Ala-Gln-{Aib}-Ala-Phe-Ile-Glu-Tyr-Leu-Leu-Glu-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH ₂

In embodiments, the GLP-1 agonist may be retatrutide. In embodiments, the GLP-1 agonist may be taspoglutide.

[00211] Various GLP-1 agonist have been developed, such as semaglutide (e.g., Ozempic (subcutaneous) and Rybelsus (oral) for diabetes, Wegovy (subcutaneous) for obesity, manufactured by Novo Nordisk, approved in 2017), exenatide (e.g., Byetta (subcutaneous) and Bydureon (subcutaneous, ER), manufactured by AstraZeneca, approved in 2005/2012), liraglutide (e.g., Victoza for diabetes, Saxenda for obesity, manufactured by Novo Nordisk, approved in 2010), albiglutide (e.g., Tanzeum, manufactured by GSK, approved in 2014), dulaglutide (e.g., Trulicity, manufactured by Eli Lilly, approved in 2014), lixisenatide (e.g., Adlyxin, manufactured by Sanofi, approved in 2016), and tirzepatide (e.g., Mounjaro, manufactured by Eli Lilly, combined with a GIP analog, approved in 2022). The GLP-1 agonist disclosed herein may be used in the therapy for metabolic diseases, e.g., type 2 diabetes, by playing important physiological roles in glucose homeostasis, e.g., by stimulating insulin production and secretion and promote proliferating of healthy pancreatic β -cells. Further, the GLP-1 agonist disclosed herein may contribute to body weight loss by suppressing appetite, delaying gastric emptying, regulating blood lipid metabolism and reducing fat deposition.

Definition

[00212] The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen (N), oxygen (O), and sulfur (S).

[00213] The term "halogen" or "halo" designates -F, -Cl, -Br or -I. Preferred halo gens are -F, -Cl and -Br.

[00214] The term "hydroxyl" means -OH.

[00215] The term "oxo" as used herein refers to an oxygen atom that has a double bond to another atom (i.e., the substituent =O), particularly to carbon.

[00216] The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups and branched-chain alkyl groups. Accordingly, C₁-C₆ alkyl includes methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, and the like.

[00217] The term "cycloalkyl" refers to saturated, carbocyclic groups having from 3 to 7 carbons in the ring. Cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[00218] The term "alkenyl" refers to a linear or branched hydrocarbyl having a double bond and 2-6 carbon atoms ("C₂-C₆ alkenyl"). The alkenyl includes vinyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-

hexenyl, 5-hexenyl, 2-methyl-2-propenyl, 4-methyl-3-pentenyl, and the like. When the compound of the present disclosure contains an alkenyl group, the compound may exist as the E-form, the Z-form, or any mixture thereof.

[00219] The term “alkynyl” refers to a linear or branched hydrocarbyl having a triple bond and 2-6 carbon atoms (“C₂-C₆ alkynyl”). The alkynyl includes ethynyl, propynyl, and the like.

[00220] The term “aryl” as used herein includes 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as “aryl heterocycles”, “heteroaromatics” or “heteroaryl”. The term “aryl” also includes 7- to 14-membered polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are “fused rings”) wherein at least one of the rings is aromatic (including heteroaryl), e.g., the other cyclic rings can be fused cycloalkyls, cycloalkenyls, aryls, heteroaryl and/or heterocyclic groups. Single-ring heteroaryl groups may have from 1 to 3 ring heteroatoms and fused polycyclic heteroaryl groups may have from 1 to 5 ring heteroatoms, wherein the ring heteroatoms are selected from N, O and S.

[00221] The terms “heterocyclyl”, “heterocyclic” or “heterocycloalkyl” group refer to 3- to 10-membered ring structures, more preferably 5- or 6-membered rings, whose ring structures include one to four heteroatoms. Heterocycles can also be polycycles. Heterocyclic groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like.

[00222] The term “alkylaryl”, “aralkyl”, as used herein, refers to a C₁-C₆ alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

[00223] As used herein, the definition of each expression, e.g. alkyl, m, n, R, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

[00224] It will be understood that "substituted", "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

[00225] Each of the ROCK2 inhibitors and the GLP-1 agonists provided herein may be present and administered as their pharmaceutically acceptable salt. The term "pharmaceutically-acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds disclosed herein and inorganic and organic basic addition salts of the compounds disclosed herein. It is understood that the reference to a ROCK2 inhibitor or to a GLP-1 agonist includes the neutral compound and any pharmaceutically acceptable salt for of the ROCK2 inhibitor or the GLP-1 agonist. The pharmaceutically acceptable salt forms which may be selected on the basis of a chosen route of administration and according to standard pharmaceutical practice.

[00226] As set out above, certain embodiments of the ROCK2 and/or GLP-1 agonists may contain a basic functional group, such as amino, and are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable acids. These salts can be prepared in situ in the administration vehicle or the dosage form manufacturing process, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed during subsequent purification. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", J. Pharm. Sci. 66:1-19).

[00227] The pharmaceutically acceptable salts of the subject compounds include the conventional nontoxic salts or quaternary ammonium salts of the compounds, e.g., from non-toxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids such as hydrochloride, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

[00228] In other cases, the compounds provided in this disclosure may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. These salts can likewise be prepared in situ in the administration vehicle or the dosage form manufacturing process, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary or tertiary amine.

Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge et al., *supra*).

[00229] Certain compounds provided in this disclosure may exist in particular geometric or stereoisomeric forms. The disclosure contemplates all such compounds, including cis- and trans-isomers, R- and S-enantiomers, diastereomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are included in this invention.

[00230] As defined herein, the term “inhibition”, “inhibit”, “inhibiting” and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g., decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g., decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In embodiments, inhibition refers to a reduction of activity of a target protein resulting from a direct interaction (e.g., an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction of activity of a target protein from an indirect interaction (e.g., an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation). The term “inhibitor” may include synthetic or biological molecule (e.g., small molecule, nucleic acid, peptide or antibody) inhibiting or negatively affecting (e.g. decreasing) the activity or function of the protein relative to the

activity or function of the protein in the absence of the inhibitor. Preferred inhibitor is a small molecule. The inhibitor can decrease expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the inhibitor or antagonist. In certain instances, activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or lower than the expression or activity in the absence of the inhibitor.

Obesity/weight loss

[00231] In one aspect, the method is for the prevention or treatment of obesity, or reducing body weight in a subject, the method comprising administering to the subject a therapeutically effective amount of a ROCK2 inhibitor (e.g., a ROCK2 inhibitor disclosed herein).

[00232] Determining whether someone is a candidate for weight loss interventions may begin with an assessment of their body mass index, or BMI. Typically, medications may be prescribed for a subject having a BMI of about 30 or greater, or having a BMI of about 27 or greater if the person has one or more weight-related health conditions. For each individual case, the clinician may consider the patient's current health condition, other medications, and family medical history.

[00233] The methods of treating obesity and/or promoting weight loss in a subject comprise administering to the subject a therapeutically effective amount of a ROCK2 inhibitor, optionally in combination with one or more additional therapies and/or pharmaceutical agents that may promote weight loss in the subject. The subject being treated for obesity and/or weight loss may be undergoing one or more of dietary calorie restriction, and administration of a pharmaceutical agent for weight loss, such as: a GLP-1 agonist; a sodium-glucose transporter 2 (SGLT2) inhibitor such as bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, sotagliflozin and tofogliflozin; a lipase inhibitor such as orlistat (Alli, Xenical); melanocortin-4 receptor agonist, such as setmelanotide (Imcivree); naltrexone-bupropion; phentermine; phentermine-topiramate; metformin; diethylpropion (amfepramone); and combinations thereof. In embodiments, the therapy comprises a therapeutically effective amount of a ROCK2 inhibitor and a therapeutically effective amount of a GLP-1 agonist.

[00234] Weight loss is an important goal in the management of several chronic conditions, including type 2 diabetes. GLP-1 agonists, SGLT2 inhibitors and other therapies may facilitate or induce clinically significant reductions in body weight. However, this weight loss may not be attributed solely to reduction of the fat mass or the subject. When the body

weight of the subject is reduced, not all of the resulting weight loss can be attributed to the reduction in the fat mass of the patient. Rather, a significant portion of the weight loss (for example, about 25% to 33%) may be a result of reductions in lean body mass, and predominantly skeletal muscle loss. This is important because skeletal muscle has several important functions for both physical functioning and quality of life, and also for the subject's metabolic health. Skeletal muscle acts as a primary site of glucose disposal (with lower skeletal muscle mass contributing to poorer glycemic control), and is a strong determinant of resting metabolic rate. Thus, the loss of skeletal muscle that occurs with weight loss may predispose subjects to a greater chance of weight regain. Given the importance of skeletal muscle and lean body mass on metabolic health and physical function, preservation of muscle during weight loss is an important concern. Consequently, the loss of muscle mass in subjects undergoing weight loss induced by GLP-1 agonists, SGLT2 inhibitors, dietary restriction, bariatric surgery or other therapy for the promotion of weight loss warrants attention.

[00235] Advantageously, the inventors have found that when the ROCK2 inhibitor is administered to the subject undergoing weight loss, the amount of lean body mass and/or skeletal muscle lost by the subject during the weight loss is significantly reduced. In aspects, the disclosure provides method of preserving muscle mass in a subject that is being treated for obesity and/or undergoing weight loss by administering to the subject during the treatment/weight loss a therapeutically affective amount of ROCK2 inhibitor. The subject being treated for obesity and/or undergoing weight loss may be undergoing one or more of: dietary calorie restriction, and administration of a pharmaceutical agent for weight loss, such as: a GLP-1 agonist; a sodium-glucose transporter 2 (SGLT2) inhibitor such as bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, sotagliflozin and tofogliflozin; a lipase inhibitor such as orlistat (Alli, Xenical); melanocortin-4 receptor agonist, such as setmelanotide (Imcivree); naltrexone-bupropion; phentermine; phentermine-topiramate; metformin; diethylpropion (amfepramone); and combinations thereof. In embodiments, the therapy comprises a therapeutically effective amount of a ROCK2 inhibitor and a therapeutically effective amount of a GLP-1 agonist.

[00236] In an embodiment, this disclosure provides a method for treating or preventing obesity in a subject comprising administering to the subject (i) a therapeutically effective amount of (6-(4-((4-(1H-pyrazol-4-yl)phenyl)amino)pyrimidin-2-yl)-1-methyl-1H-indol-2-yl)(3,3-difluoroazetidin-1-yl)methanone (Compound A), or a pharmaceutically acceptable

salt thereof, and optionally (ii) a therapeutically effective amount of a glucagon-like peptide (GLP-1) agonist.

[00237] In an embodiment, this disclosure provides a method for promoting weight loss in a subject comprising administering to the subject (i) a therapeutically effective amount of (6-(4-((4-(1H-pyrazol-4-yl)phenyl)amino)pyrimidin-2-yl)-1-methyl-1H-indol-2-yl)(3,3-difluoroazetidin-1-yl)methanone (Compound A), or a pharmaceutically acceptable salt thereof, and optionally (ii) a therapeutically effective amount of a glucagon-like peptide (GLP-1) agonist.

[00238] In an embodiment, this disclosure provides a method for reducing or preventing muscle loss in a patient that is undergoing therapy for obesity, weight loss, and/or type 2 diabetes, the method comprising administering to the subject a therapeutically effective amount of (6-(4-((4-(1H-pyrazol-4-yl)phenyl)amino)pyrimidin-2-yl)-1-methyl-1H-indol-2-yl)(3,3-difluoroazetidin-1-yl)methanone (Compound A), or a pharmaceutically acceptable salt thereof. The therapy for obesity, weight loss, and/or type 2 diabetes may comprise one or more of dietary calorie restriction, bariatric or other surgical intervention, and administration of a pharmaceutical agent for weight loss, such as: a GLP-1 agonist; a sodium-glucose transporter 2 (SGLT2) inhibitor, a lipase inhibitor, a melanocortin-4 receptor agonist, naltrexone-bupropion; phentermine, phentermine-topiramate, metformin, diethylpropion (amfepramone); and combinations thereof.

type 2 diabetes

[00239] In another aspect, the method is used in the reduction of HbA1c; and/or in the prevention or treatment of type 2 diabetes, hyperglycemia, or impaired glucose tolerance, the method comprising administering to the subject in need thereof a therapeutically effective amount of a ROCK2 inhibitor.

[00240] In one aspect, the disclosure provides a method for reducing glycated hemoglobin (HbA1c) in a subject by administering to the subject a therapeutically effective amount of a ROCK2 inhibitor. HbA1c is an important indicator of long-term glycemic control with the ability to reflect the cumulative glycemic history of the preceding two to three months. Levels of HbA1c not only provides a reliable measure of chronic hyperglycemia, but also correlates well with the risk of long-term diabetes complications. Elevated HbA1c is also an independent risk factor for coronary heart disease and stroke in subjects with or without diabetes.

In another aspect, the disclosure provides a method to improve, or even restore, insulin sensitivity in patients suffering from reduced insulin sensitivity (insulin resistance) by administering to the patient a therapeutically effective amount of a ROCK2 inhibitor. In embodiments, the patient may have been diagnosed with type 2 diabetes, or the patient may be one that has been recognized or diagnosed to have a high risk of developing type 2 diabetes, and/or that is recognized or diagnosed to be experiencing the symptoms of the onset, or progression towards, type 2 diabetes (i.e., prediabetes). Insulin resistance impairs glucose transport into cells, resulting in a compensatory increase in beta-cell insulin production and hyperinsulinemia. The metabolic consequences of insulin resistance can result in hyperglycemia, hypertension, dyslipidemia, hyperuricemia, elevated inflammatory markers, endothelial dysfunction, and a prothrombotic state. Insulin resistance is a key factor in the development of type 2 diabetes, cardiovascular disease, fatty liver disease, neurodegenerative disease, and obesity-associated cancers. The treatment of the patient with the ROCK2 inhibitor may reduce or reverse insulin resistance and improve or restore blood glucose levels.

[00241] In another aspect, the disclosure provides a method to attenuate muscle atrophy during various atrophic conditions. Muscle atrophy is caused by an imbalance in contractile protein synthesis and degradation which can be triggered by various conditions including type 2 diabetes. In one embodiment, the method is to reduce or prevent muscle loss associated with type 2 diabetes, the method comprising administration of a therapeutically effective amount of a ROCK2 inhibitor to a patient in need thereof. In patients with poor insulin control, the insufficient action of insulin is thought to result in the suppression of growth and proliferation of muscle cells, which in turn contributes to the decline in skeletal muscle mass in subjects with diabetes. Patients with type 2 diabetes may exhibit muscle atrophy that is initially mild in middle age, and becomes more substantial with older age and diabetic neuropathy. Reduced muscle quality in patients with type 2 diabetes adversely affects muscle function, the capacity to perform activities of daily living, quality of life and ultimately may increase the risk of premature mortality. Systemic inflammation initiated by obesity and prolonged overnutrition not only contributes to insulin resistance, but also promotes muscle atrophy via decreased muscle protein synthesis and increased ubiquitin-proteasome, lysosomal-proteasome and caspase 3-mediated protein degradation. Emerging evidence suggests that the inflammation-sensitive Nuclear Factor κ B (NF- κ B) and Signal Transducer and Activator of Transcription 3 (STAT3) pathways may contribute to muscle atrophy in patients with type 2 diabetes. Furthermore, in muscle from obese patients with

type 2 diabetes, a range of pro-inflammatory pathways are upregulated, including chemokine (c-c motif) ligand (CCL2), STAT3, suppressor of cytokine signaling 3 (SOCS3), and NF- κ B.

[00242] In an embodiment, this disclosure provides a method for treating type 2 diabetes in a subject comprising administering to the subject (i) a therapeutically effective amount of (6-(4-((4-(1H-pyrazol-4-yl)phenyl)amino)pyrimidin-2-yl)-1-methyl-1H-indol-2-yl)(3,3-difluoroazetidin-1-yl)methanone (Compound A), or a pharmaceutically acceptable salt thereof, and optionally (ii) a therapeutically effective amount of a glucagon-like peptide (GLP-1) agonist.

Combination therapy

[00243] The combination therapy comprising a ROCK2 inhibitor and a GLP-1 agonist may be used in the (i) reduction of HbA1c; (ii) prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; and/or (iii) prevention or treatment of obesity, and reducing body weight. The methods comprise administration of a therapeutically effective amount of a GLP-1 agonist and a therapeutically effective amount of a ROCK2 inhibitor to a subject in need thereof.

[00244] The methods disclosed herein comprising administering to the subject a combination therapy providing a therapeutically effective amount of an inhibitor of ROCK2 and a therapeutically effective amount of a GLP-1 agonist. The ROCK2 inhibitor(s) may include one or more compounds having the formulae (A-I), (B-I), (C-I), (D-I), (E-I), (F-I), (G-I), (H-I), (J-I), (K-I), (L-I) and their subordinates, exemplary compounds thereof, or derivatives thereof which may be obtained or known by one of ordinary skill in the art. The GLP-1 agonist(s) may include one or compounds having the structure of formula (M-I), (N-I), (O-I), (O-II), (P-I), (Q-I), (R-I), and their subordinates, or exemplary compounds thereof. Alternatively, the GLP-1 agonist may include amino acid sequences of SEQ ID. Nos. 4-8, 9, 18, and 19-30, but are not limited thereto. In some embodiments, the GLP-1 agonist may include amino acid sequences of SEQ ID. Nos. 1-30, but are not limited thereto. The exemplary compounds or peptides described herein or derivatives thereof may be obtained or known by one of ordinary skill in the art or by reference.

[00245] The ROCK2 inhibitor and the GLP-1 agonist may be co-administered to the subject. The “co-administration” is meant to include simultaneous or sequential administration of the ROCK2 inhibitor and the GLP-1 agonist. The ROCK2 inhibitor and the GLP-1 agonist may be administered to the patient as separate dosage forms, i.e., the combination therapy comprises the administration of a dosage form comprising the ROCK2

inhibitor and a dosage form comprising the GLP-1 agonist. Alternatively, the ROCK2 inhibitor and the GLP-1 agonist may be administered to the patient in a combination formulation, e.g., the dosage form comprises both the ROCK2 inhibitor and the GLP-1 agonist. In some embodiments, the combination formulation is subcutaneous dosage formulation. In some embodiments, the combination formulation is oral dosage formulation. In some embodiments, the ROCK2 inhibitor and the GLP-1 agonist may be administered to the patient in separate formulations, e.g., the ROCK2 in oral formulation and the GLP-1 agonist in subcutaneous formulation, or the ROCK2 in subcutaneous formulation and the GLP-1 agonist in oral formulation. Further, the ROCK2 inhibitor and the GLP-1 agonist may be administered at the same time, or at separate times.

[00246] In some embodiments, the ROCK2 inhibitor and the GLP-1 agonist are co-administered. As used herein, the phrase “co-administration” refers to any form of administration of the therapeutic formulations of the ROCK2 inhibitor and the GLP-1 agonist such that one of the formulations is administered while the other therapeutic formulation is still effective in the body. Accordingly, the ROCK2 inhibitor and the GLP-1 agonist are simultaneously effective in the patient, which may include synergistic effects of the two agents. Thus, the patient who receives such treatment can benefit from a combined, additive effect or synergetic effect of the ROCK2 inhibitor and the GLP-1 agonist. Particularly, the combination treatment may result in improved outcomes, such as reduction of severity, delay or elimination of recurrence, or reduced side effects of a primary agent with pre-treatment with the secondary agent.

[00247] In some embodiments, the efficacy or therapeutic effects of the GLP-1 agonist may be improved by at least about 10 %, 20%, 25%, 30%, 40%, 50%, 60 %, 70%, 80%, 90%, or greater in the combination treatment with the ROCK2 inhibitors when compared to the same treatment with the GLP-1 agonist as a single agent, as determined, for example, in glucose tolerance or by measuring blood glucose. In some embodiments, the production of pancreatic insulin may be increased by at least about 10 %, 20%, 25%, 30%, 40%, 50%, 60 %, 70%, 80%, 90%, or greater in the combination treatment with the ROCK2 inhibitor when compared to the same treatment with the GLP-1 agonist as a single agent, as determined, for example, by measuring blood glucose in the patient. In some embodiments, obesity in the patient may be reduced or lowered by at least about 10 %, 20%, 25%, 30%, 40%, 50%, 60 %, 70%, 80%, 90%, or greater in the combination treatment with the ROCK2 inhibitor when compared to the same treatment with the GLP-1 agonist as a single agent, as determined, for example, by measuring weight loss.

[00248] In some embodiments, the combination therapies using the ROCK2 inhibitor and the GLP-1 agonist and methods of co-administering may also allow reduction in doses and/or frequency of administration of the GLP-1 agonist to achieve the same therapeutic effects and/or improvements in comparison to using a GLP-1 agonist alone or other existing single treatment.

[00249] The administration routes and regimen of the disclosed combination may well vary depending on the condition prior to or after the treatment, extent of progression in insulin production, age and physical condition of the subject, exact combination selected, and other factors. Administration regimen may include multiple doses per period of time, the treatments administered simultaneously or sequentially. When two therapeutic agents are administered sequentially, a first therapeutic agent may be administered 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours before administering a second therapeutic agent.

[00250] In some embodiments, the combination therapy includes administering the ROCK2 inhibitor prior to administering the GLP-1 agonist. For example, the therapeutic agent including the ROCK2 inhibitor may be administered 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, or 96 hours before administering the GLP-1 agonist. The therapeutic agent including the ROCK2 inhibitor may be administered at the same time (simultaneously) as the therapeutic agent including the GLP-1 agonist. In some embodiments, the therapeutic agent including the ROCK2 inhibitor may be additionally administered 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours after administering the therapeutic agent including the GLP-1 agonist.

[00251] The ROCK2 inhibitor described herein may preferably include a compound having a structure of formula (A-I), (B-I), (C-I), (D-I), (E-I), (F-I), (G-I), (H-I), (J-I), (K-I), (L-I), their subordinates, or exemplary compounds thereof. The ROCK2 inhibitor may be selected from Compound A, Compound B, Compound C, Compound D, belumosudil (KD025), Zelasudil, Y-27632, fasudil, GSK429286A, RKI-1447, TC-S 7001, TC-S 7004, hydroxyfasudil, GSK269962A, ripasudil, AT13148, RX007, and derivatives, isomers, hydrates, or pharmaceutically acceptable salts thereof, but the examples of the ROCK2 inhibitors are not limited thereto.

[00252] In an embodiment, the ROCK 2 inhibitor is (6-(4-((4-(1H-pyrazol-4-yl)phenyl)amino)pyrimidin-2-yl)-1-methyl-1H-indol-2-yl)(3,3-difluoroazetidin-1-yl)methanone (Compound A), or a pharmaceutically acceptable salt thereof.

[00253] The GLP-1 agonist described herein may include a compound having a structure of formula (M-I), (N-I), (O-I), (O-II), (P-I), (Q-I), (R-I), and their subordinates, or exemplary compounds thereof. The GLP-1 agonist may include amino acid sequences of SEQ ID. Nos. 4-8, 9, 18, and 19-30, but are not limited thereto. In some embodiments, the GLP-1 agonist may include amino acid sequences of SEQ ID. Nos. 1-30, but are not limited thereto. In some embodiments, the GLP-1 agonist is semaglutide, exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide, tirzepatide, lotiglipron, retatrutide, taspoglutide, orforglipron or danuglipron. In certain embodiments, the GLP-1 agonist is semaglutide. In other embodiments, the GLP-1 agonist is tirzepatide.

[00254] In some embodiments, the ROCK2 inhibitor and the GLP-1 agonist are formulated in a single composition. Alternatively, the ROCK2 inhibitor and the GLP-1 agonist are prepared separately and/or formulated in separate compositions.

[00255] The patient may be one that has been recognized or diagnosed to have a high risk of developing type 2 diabetes, and/or that is recognized or diagnosed to be experiencing the symptoms of the onset, or progression towards, type 2 diabetes (i.e., prediabetes). The patient may have one or more of the following: a relative with type 2 diabetes, blood tests suggesting the patient may develop type 2 diabetes, and/or one or more symptoms associated with the development of type 2 diabetes.

[00256] Blood tests may include assays for the patient's blood sugar level, such as a glycated hemoglobin (A1C) test, a random blood sugar test, or a fasted blood sugar test. An A1C between about 5.7 and 6.4% may indicate pre-diabetes. In random blood sugar tests, a blood sample is taken at a random time, with a random blood sugar level of about 200 mg/dL (11.1 mmol/L) or higher suggesting the onset of diabetes. For a fasting blood sugar test, a fasting blood sugar level from about 100 to 125 mg/dL (5.6 to 6.9 mmol/L) may indicate pre-diabetes, and a fasting blood sugar level of about 126 mg/dL (7 mmol/L) or higher on two separate tests may indicate more advanced disease progression or diabetes.

Pharmaceutical Compositions

[00257] In one aspect, the present disclosure provides pharmaceutically acceptable compositions which comprise a therapeutically effective amount of a ROCK2 inhibitor and a therapeutically effective amount of a GLP-1 agonist, each formulated with one or more pharmaceutically acceptable carriers. As described below, the pharmaceutical compositions of the present disclosure may be formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches

(aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginal or intrarectal administration, for example, as a suppository, pessary, cream or foam; (5) sublingual administration; (6) ocular administration; (7) transdermal administration; or (8) nasal administration.

[00258] The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, 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 with toxicity, irritation, allergic response, or other problems or complications, commensurate with a reasonable benefit/risk ratio.

[00259] The phrase “pharmaceutically-acceptable carrier” as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (e.g., lubricant, talc magnesium, calcium or zinc stearate, or steric acid), solvent, or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier should be compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

[00260] The compounds of this disclosure may be formulated with conventional carriers and excipients, which can be selected in accord with ordinary practice. Tablets can contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally can be isotonic. All formulations can optionally contain excipients such as those set forth in the “Handbook of Pharmaceutical Excipients” (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextran, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

[00261] While it is possible for the ROCK2 inhibitors and/or GLP-1 agonists disclosed herein (herein referred to as the “active ingredients”) to be administered alone, it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the disclosure comprise at least one active ingredient, as provided above, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients, particularly those additional therapeutic ingredients as discussed herein.

[00262] Pharmaceutical compositions may include compositions wherein the active ingredient (e.g. compounds or combinations described herein, including embodiments or examples) is contained in a therapeutically effective amount, i.e., in an amount effective to achieve its intended purpose. The actual amount effective for a particular application may depend, *inter alia*, on the condition being treated. When administered in methods to treat a disease (e.g., type 2 diabetes), such compositions may contain an amount of active ingredient effective to achieve the desired result, e.g., modulating the activity of a target molecule, and/or reducing, eliminating, or slowing the progression of disease symptoms (e.g., increased insulin secretion in pancreas or regrowth of insulin producing cells).

[00263] The formulations include those suitable for the administration routes provided herein. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[00264] Formulations of the present disclosure suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

[00265] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

[00266] When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

[00267] If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

[00268] The oily phase of the emulsions of this disclosure may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

[00269] Emulsifying agents and emulsion stabilizers suitable for use in the formulation of the disclosure include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate. Further emulsifying agents and emulsion stabilizers suitable for use in the formulation of the disclosure include Tween® 80.

[00270] The choice of suitable oils or fats for the formulation is based on achieving the desired properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

[00271] Pharmaceutical formulations according to the present disclosure comprise a combination according to the disclosure together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing an active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing an active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[00272] Formulations for oral use may be also presented as hard gelatin capsules where an active ingredient is mixed with an inert solid diluent, for example starch, mannitol, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

[00273] Aqueous suspensions of the disclosure contain an active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally-occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin. Further non-limiting examples of suspending agents include Cyclodextrin and Captisol (=Sulfobutyl ether beta-cyclodextrin; SEB-beta-CD).

[00274] Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

[00275] Dispersible powders and granules of the disclosure suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[00276] The pharmaceutical compositions of the disclosure may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally-occurring

phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

[00277] The pharmaceutical compositions of the disclosure may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution isotonic sodium chloride solution, and hypertonic sodium chloride solution.

[00278] The amount of an active ingredient that may be combined with the carrier material to produce a single dosage form can vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 µg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

[00279] Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[00280] Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[00281] Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns, such as 0.5, 1, 30, 35 etc., which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds.

[00282] Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

[00283] The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

[00284] The disclosure further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

[00285] Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

[00286] Compounds of the disclosure are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the disclosure (“controlled release formulations”) in which the release of the active ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

[00287] The patient receiving this treatment is any animal in need, including primates, in particular humans, and other mammals such as horse, cattle, swine and sheep; and poultry and pets in general, such as cats and dogs.

[00288] In one aspect, the present disclosure also provides a kit that includes a pharmaceutical composition of formulation including the combination described herein. The kit may include a product instruction for administration of the combination, for example, that a first pharmaceutical composition including the ROCK2 inhibitor and a second pharmaceutical composition including the GLP-1 agonist are administered (co-administered) simultaneously or subsequently. For example, the kit may instruct administration of the ROCK2 inhibitor formulation administered to a subject prior to administration of GLP-1 agonist formulation.

EXAMPLES

Example 1

[00289] ADP-Glo kinase assay (Promega). The ADP-Glo™ Kinase Assay is a luminescent ADP detection assay that allows measurement of kinase activity based on the amount of ADP produced during a kinase reaction. The kinase reaction is performed in the presence of ATP, S6K substrate (KRRRLASLR) and the ROCK kinase in the appropriate Kinase Reaction Buffer (1x). Upon termination of the reaction, the unconsumed ATP is depleted by addition of ADP-Glo™ Reagent. Next, Kinase Detection Reagent is added to convert ADP to ATP and the newly synthesized ATP is measured using a luciferase/luciferin reaction. The luminescence is proportional to the produced ADP and consequently to the kinase activity. The ADP-Glo™ Kinase Assay was performed in a 384 well plate format as follows.

[00290] **Kinase Detection Reagent Preparation:** The Kinase Detection Buffer was thawed at room temperature (RT). If a precipitate was present, the buffer was incubated at 37 °C with constant swirling for 15 minutes to dissolve the precipitate, or the precipitate was removed from the buffer by carefully pipetting the supernatant from the bottle. After equilibrating both the Kinase Detection Buffer and Kinase Detection Substrate to room temperature, the entire volume of Kinase Detection Buffer was transferred into the bottle containing Kinase Detection Substrate to reconstitute the lyophilized substrate, followed by gentle mixing to obtain a homogeneous solution.

[00291] **Kinase Reaction Buffer Preparation:** Kinase reaction buffer was prepared freshly before each experiment. The formulation of this buffer is provided in Table 1 below:

Table 1. Formulation of kinase reaction buffer (1x) for ADP-Glo kinase assay.

Reagent:	Final concentration	Stock concentration
Tris, pH 7.5	40 mM	500 mM in H ₂ O
DTT	0.05 mM	100 mM in H ₂ O
MgCl ₂	20 mM	500 mM in H ₂ O
BSA	0.1 mg/mL	5.0 mg/mL

[00292] ADP-Glo Reagents Preparation. Three mixes were prepared on ice before running the assay:

Mix 1 – containing ROCK1 or ROCK2 in Kinase Reaction Buffer (1x)

Mix 2 – containing S6K peptide in Kinase Reaction Buffer (1x)

Mix 3 – containing ATP in Kinase Reaction Buffer (1x)

[00293] The final conditions for performing the ADP-Glo kinase assay are proved in Table 2 below:

Table 2. Final conditions for ADP-Glo kinase assay for ROCK (concentration in final volume 5 μ L).

Final concentrations:	ROCK1	ROCK2
Kinase	0.1 ng/ μ L	0.1 ng/ μ L
S6K substrate	170 μ M	170 μ M
ATP	10 μ M	40 μ M
Timepoint	120 min	120 min
DMSO	1%	1%

[00294] The ratios of reagent volumes in the assay were 1:1:2 of kinase reaction to ADP-Glo™ Reagent to Kinase Detection Reagent. For 384-well plates, volumes per well were: 5 μ L of kinase reaction, 5 μ L of ADP-Glo™ Reagent and 10 μ L of Kinase Detection Reagent.

[00295] Generating a standard curve for conversion of ATP to ADP. To estimate the amount of ADP produced in the kinase reaction, a standard curve that represents the luminescence corresponding to the conversion of ATP to ADP was prepared based on the ATP concentration used in the kinase reaction. These conversion curves represent the amounts of ATP and ADP available in a reaction at the specified conversion percentage ranging from 100% conversion to 0% conversion. The standard samples used to generate an ATP-to-ADP conversion curve are created by combining the appropriate volumes of ATP and ADP stock solutions.

[00296] Determination of IC₅₀ values of kinase inhibitors

[00297] Each plate contained a positive control (1 μ M Comp. A for ROCK2 and 1 μ M RKI-1447 for ROCK1); a vehicle control (1% DMSO); a blank control (kinase reaction buffer (1x)); a low control (substrate and ATP, without kinase); and an autophosphorylation control (kinase and ATP, without substrate). Test and reference compounds were diluted in 100% DMSO to obtain 10 mM stock solutions. Each compound was tested in 8-serial dilutions in duplicate. The final concentration of DMSO in the reaction was 1% (up to 50 nL).

[00298] 5 μ l/well Kinase Reaction Buffer (1x) was dispensed to blank control wells. 2 μ l/well Kinase Reaction Buffer (1x) was dispensed to control without protein (low control) and without substrate (autophosphorylation) wells. The plate was sealed with adhesive film followed by a short spin (1 min, 1000 rpm).

[00299] 2 μ l/well kinase (2.5x) solution was dispensed into relevant wells of the assay plate. The plate was sealed with adhesive film followed by a short spin (1 min, 1000 rpm).

[00300] 2 μ l/well S6K substrate (2.5x) solution was dispensed into relevant wells of the assay plate. The plate was sealed with adhesive film followed by a short spin (1 min, 1000 rpm).

[00301] 1 μ l/well ATP (5x) solution was dispensed into relevant wells of the assay plate. The final volume of reaction was 15 μ l. The plate was sealed with adhesive film followed by a short spin (1 min, 1000 rpm).

[00302] The plate was incubated at 25 °C for 120 minutes with 450 rpm shaking speed.

[00303] After the incubation was completed the kinase reaction was terminated, residual ATP was depleted from the kinase reaction and ADP was converted to ATP, that is measured in luciferase/luciferin reaction. 5 μ l of ADP-Glo™ Reagent was dispensed to stop the kinase reaction and deplete the unconsumed ATP. The plate was sealed with adhesive film followed by a short spin (1 min, 1000 rpm), and was incubated at 25 °C for 40 minutes with 450 rpm shaking speed.

[00304] 10 μ l of Kinase Detection Reagent was dispensed to convert ADP to ATP and introduce luciferase and luciferin to detect ATP. The plate was sealed with adhesive film followed by a short spin (1 min, 1000 rpm), and was incubated at 25 °C for 60 minutes with 450 rpm shaking speed.

[00305] Following a 5-minute dark adaptation, luminescence was measured using a PHERAstar FSX Multimode Plate Reader (BMG Labtech).

Table 3

Compound	ROCK2 IC ₅₀ (nM)	ROCK1 IC ₅₀ (nM)
Comp. A	5.44	5115.05
Comp. B	473	> 50000
Comp. C	36.67	> 50000
Comp. D	82.6	4004.37

Example 2

[00306] Mice were maintained on a high fat/calorie diet prior to being treated with semaglutide, Compound A, or combinations of semaglutide and Compound A. FIG. 1 shows absolute body weight change of obese mice after treating with ROCK2 inhibitor (Compound A) and/or semaglutide in comparison to non-treated mice and mice on a lean chow diet. The figure shows that the mice treated with a combination of Compound A and semaglutide had improved weight loss.

Example 3

[00307] ReninAAV UNx db/db mouse model of diabetic nephropathy and hypertension: The effects of treatment with the selective ROCK2 inhibitor Compound A on hypertensive female uninephrectomized db/db C57BLKS mice. This mouse model is established in the db/db mouse model on the BKS background BKS.Cg-Dock7m +/- Leprdb/J, which is homozygous for the missense mutation in the Leptin receptor (*Leprdb*) and develops chronic hyperglycemia, pancreatic beta cell atrophy and becomes hypoinsulinemic.

[00308] *Renin-encoding adeno-associated virus (reninAAV)* Hypertension was induced using an adeno-associated virus (AAV) construct AAV8-TBG-m-Ren1d (F61R/P65S) that expresses mouse *Ren1d* gene with F61R/P65S mutations under the control of the liver-specific thyroxin-binding globulin (TBG) promotor. For induction of hypertension, a single bolus of the reninAAV construct was administered by tail vein injection in conscious animals one week prior to uninephrectomy.

[00309] Details about the animal model used for the study are summarized below.

Species	<i>Mus musculus</i>
Strain	Db/db: BKS.Cg-Dock7m +/- LeprdbJ & Heterozygote from the colony and Db/m: BKSDB Heterozygous for Dock7m, Heterozygous for Leprdb
Male / female	Female

Number (n) of animals	10 db/m and 74 db/db
Age at arrival	5-7 weeks
Age at study start	11-13 weeks
Housing	Group housed until UNx, then single housed
Diet	Chow altromin (1324, Brogaarden)
Termination method	Inferior vena cava bleeding under isoflurane anesthesia
Randomization	Body weight, blood glucose and urinary albumin-to-creatinine ratio, week -1
Light-dark cycle	12:12 (lights off at 3 pm)

[00310] Body weight was measured once daily beginning at 3 days prior to the first dose and continued throughout the study. The body weight as measured during the study are reported in Figure 2A and the final body weight in Figure 2B. The data demonstrate that the ROCK 2 inhibitor (Comp. A) promoted weight loss the study mice.

[00311] Uninephrectomy (UNx): Under isoflurane anesthesia, an incision was made above the left kidney enabling it to be exteriorized. The renal hilum was identified and ligated with suture. Hereafter the kidney was removed. The muscle and skin were closed in two layers. Preemptive analgesia and antibiotics were administered and continued for 3 consecutive days after the operation.

[00312] Speckle-tracking echocardiography (Strain): All echocardiographic measurements were obtained by ultrasonography of the heart. Echocardiography was performed under isoflurane anesthesia using a Vevo 3100 system (Visual Sonics, Fujifilm) equipped with a MX400 20-46 MHz linear array transducer. This is a non-invasive procedure and animals regained full consciousness following the procedure. Animals were placed in supine position on a heating pad (40 °C) and chest fur was removed with depilatory cream. Ultrasound gel was preheated in a warm water bath and applied to the chest of the animal. Body temperature was measured with a rectal probe and the electrocardiogram (ECG) was monitored continuously during the examination. Preheated ultrasound gel was applied to the chest of the animal. Two-dimensional (2D) visualization of the left ventricle (LV) in B-mode was recorded from the parasternal long-axis (PLAX) and parasternal short axis (PSAX) view. An optimized recording in PLAX view was used for strain analysis to calculate global longitudinal strain (GLS) and reverse peak longitudinal strain rate (RPLSR) to evaluate systolic and diastolic cardiac function, respectively. 2D guided M-mode images in PSAX were obtained to calculate ejection fraction (EF), fractional shortening (FS), LV wall thickness (LVAW/LVPW), and estimation of LV mass. From the apical 4-chamber view,

pulsed wave doppler and tissue doppler were used to measure diastolic parameters e.g., early (E) and late (A) diastolic transmitral doppler flow velocities, isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT), aorta ejection time (AET) and peak early-diastolic annular velocity (e'). Measurements were calculated using Vevo LAB and VevoStrain software (VisualSonics, Fujifilm).

[00313] Blood glucose: Blood samples (10 μ l) were collected into heparinized glass capillary tubes and immediately suspended in glucose/lactate system solution buffer (EKF-diagnostics, Germany). Blood glucose (BG) was measured using a BIOSEN c-Line glucose meter (EKF-diagnostics, Germany) according to the manufacturer's instructions. The blood glucose (fed) profile, shown in Figures 3 and 4, demonstrates that Compound A reduced blood glucose levels to the levels of the lean control.

[00314] Blood sampling and Plasma preparation

[00315] In vivo blood samples: Tail-vein blood was collected in a Microvette tube of appropriate dimensions with anticoagulant and mixed by inversion 5 times. Blood was placed at 4 °C until it was centrifuged at 3000 g for 10 minutes. The plasma supernatants were transferred to new tubes and immediately frozen on dry ice. The samples were stored at -70 °C.

[00316] Termination blood samples: During anesthesia with isoflurane, the abdominal cavity was opened, and cardiac blood was drawn with a syringe into a Microvette/Vacurette of appropriate dimensions with anticoagulant and mixed by inversion 5 times. Blood was placed at 4 °C until it was centrifuged at 3000 g for 10 minutes. The plasma supernatants were transferred to new tubes and immediately frozen on dry ice. The samples were stored at -70 °C.

[00317] Blood and plasma assays

[00318] Glycated hemoglobin A1c (HbA1c): Blood samples were collected into heparinized glass capillary tubes and immediately suspended in Hemolyzing Reagent (Roche Diagnostics) and stored at -70 °C until analysis. HbA1c was measured using commercial kits (Roche Diagnostics,) on the cobas c 501 autoanalyzer. The HbA1c levels at termination are shown in Figure 5, which demonstrates that Compound A reduced HbA1c levels to the levels of the lean control.

[00319] NT-proANP: Blood samples were collected in EDTA tubes, and plasma was separated and stored at -70°C until analysis. Plasma NT-proANP was measured using a commercial kit (Abcam) according to the manufacturer's instructions.

Example 4

[00320] The effect of treatment with a ROCK 2 inhibitor (Compound A) and combination of Compound A with a GLP-1 agonist (tirzepatide) on metabolic parameters and energy expenditure in a mouse model of diet-induced obesity (DIO) at thermoneutrality is reported here. Details about the animal model used for the study are summarized below.

Species	<i>Mus musculus</i>
Strain	C57BL/6JRj
Male/Female	Male
Vendor	Janvier, France
Number (n) of animals	140
Age at arrival	5 weeks
Age at study start	≥25 weeks
Housing	Single housing from week -2
Diet	60% HFD (D12492, Ssniff) DIO-mice (n=130); Altromin chow (1324, Bro-gaarden) Lean-chow (n=10)
Weight on arrival	~20 g
Termination method	Cardiac puncture under isoflurane anaesthesia
Randomization	Body weight and Fat mass (Echo MRI)
Light-dark cycle	12:12 (lights off at 4 PM)

[00321] Diet-induced Obesity model

[00322] In this mouse model for diet-induced obesity (DIO), the test mice were fed a high fat diet that resulted in rapid weight gain. The DIO mice were male C57BI/6J mice and ready for experiment after 20 weeks on the 60% high fat diet. The high fat diet was maintained throughout the study. The lean control group comprised male C57BI/6J mice fed a Altromin lean chow (1324, Brogaarden).

[00323] Approximately one week before the start of the study, the DIO mice were randomized based on bodyweight and fat mass (Echo MRI) and baseline measurements were obtained (Echo MRI, 4h fasting blood glucose (FBG), 4h plasma insulin (PI), 4h Leptin, HbA1c).

[00324] The test solutions and controls were prepared according to Table 4 below:

Table 4

Name	Frequency of preparation	Dosing solution			Instructions on preparation
		Conc.	Storage temp.	pH	
Vehicle for Comp. A (Veh. A)	weekly	NA	4° C	NA	0.3% polysorbate 80 (room temp)
Vehicle for TZP (Veh. TZP)	weekly	NA	4° C	NA	50mM phosphate buffer + 3.5% mannitol
Comp. A low	weekly	6 mg/ml	4° C	7.4	
Comp A mid	weekly	20 mg/ml	4° C	7.4	

Comp. A high	weekly	40 mg/ml	4° C	7.4	Dilute in 0.3% polysorbate 80 (room temp). Invert gently up and down to mix well before dosing
Tirzepatide (TZP)	weekly	2 nmol/ml	4° C	7.4	Tirzepatide (hydrochloride) from MedChemExpress, 50mM phosphate buffer + 3.5% mannitol

[00325] Beginning on Day 1 of the study, and continuing daily, the Lean and DIO mice were dosed according to Table 5. Compound A was dosed orally (PO) and tirzepatide (TZP) was dosed by subcutaneous injection (SC).

Table 5

Group		n	Model	dosing					dosing days (inclusive)	
#	name			compounds	dose [mg/kg]	route of admin	vol. [mg/kg]	freq.	first	last
1	Lean/Veh. A/Veh. TZP	10	Lean	Veh. A / Veh. TZP	NA / NA	PO / SC	5 / 5	QD	1	84
2	DIO/Veh. A/Veh. TZP	10	DIO	Veh. A / Veh. TZP	NA / NA	PO / SC	5 / 5	QD	1	84
3	DIO/Comp. A low/Veh. TZP	10	DIO	Comp. A / Veh. TZP	30 / NA	PO / SC	5 / 5	QD	1	84
4	DIO/Comp. A mid/Veh. TZP	10	DIO	Comp. A / Veh. TZP	100 / NA	PO / SC	5 / 5	QD	1	84
5	DIO/Comp. A high/Veh. TZP	10	DIO	Comp. A / Veh. TZP	200 / NA	PO / SC	5 / 5	QD	1	84
6	DIO/Veh. A/TZP	10	DIO	Veh. A / TZP	NA / 10 nmol/kg	PO / SC	5 / 5	QD	1	84
7	DIO/Comp. A low/TZP	10	DIO	Comp. A / TZP	30 / 10 nmol/kg	PO / SC	5 / 5	QD	1	84
8	DIO/Comp. A mid/TZP	10	DIO	Comp. A / TZP	100 / 10 nmol/kg	PO / SC	5 / 5	QD	1	84
9	DIO/Veh. A/TZP (w1-4)	10	DIO	Veh. A	NA	PO	5	QD	1	84
				TZP	10 nmol/kg	SC	5	QD	1	28
				Veh. TZP	NA	SC	5	QD	29	84
10	DIO/Comp. A low/TZP (w1-4)	10	DIO	Comp. A	30	PO	5	QD	1	84
				TZP	10 nmol/kg	SC	5	QD	1	28
				Veh. TZP	NA	SC	5	QD	29	84
11	DIO/Comp. A mid/TZP (w1-4)	10	DIO	Comp. A	100	PO	5	QD	1	84
				TZP	10 nmol/kg	SC	5	QD	1	28
				Veh. TZP	NA	SC	5	QD	29	84
12	DIO/Veh. A/TZP (w4-12)	10	DIO	Veh. A	NA	PO	5	QD	1	84
				Veh. TZP	NA	SC	5	QD	1	28
				TZP	10 nmol/kg	SC	5	QD	29	84
13	DIO/Comp. A low/TZP (w4-12)	10	DIO	Comp. A	30	PO	5	QD	1	84
				Veh. TZP	NA	SC	5	QD	1	28
				TZP	10 nmol/kg	SC	5	QD	29	84
14	DIO/Comp. A mid/TZP (w4-12)	10	DIO	Comp. A	100	PO	5	QD	1	84
				Veh. TZP	NA	SC	5	QD	1	28
				TZP	10 nmol/kg	SC	5	QD	29	84

[00326] Each cohort group has a staggered design with 5 teams. The mice received an extra PM dose of Comp. A or Comp. A Vehicle (Veh. A) on the days of energy expenditure measurement. Last dosing was the day before termination.

[00327] Body weight

[00328] Body weight was measured once daily beginning at 3 days prior to the first dose and continued throughout the 12 week study. The body weight as measured during the study are reported in Figure 6. The data demonstrate that the ROCK 2 inhibitor (Comp. A) and the combination of the ROCK 2 inhibitor (Comp. A) and the GLP-1 agonist (TZP) promoted weight loss in obese mice on a high fat diet in the model of diet induced obesity.

[00329] Energy expenditure (EE)

[00330] Before EE measurements were performed, mice were single housed for 48 hours in habituation cages before the same cages are connected to the air-tight lids of the EE system (PhenoMaster, TSE Systems, Germany). A continuous airflow in the cage optimized for indirect calorimetry measurement of O₂ consumption and CO₂ production was used. O₂ consumption and CO₂ production were measured every 20 minutes for a total of 36 hours, including two dark phases and one light phase. Water and food were provided in the cage ad libitum and the dosing regimen was continued during this period. Calibration procedures were performed when needed before each study period.

[00331] O₂ consumption was reported both as measured values and body weight adjusted O₂ and heat production. The objective of body weight adjustment was to obtain a mass-independent measure of differences between treatment groups. Body weight adjusted values were, similar to the approach reported in Muller et al. (Muller et al., Nature Metabolism, VOL 3, Sep 2021, 1134–1136), obtained using a regression approach in which a linear regression is fitted to datapoints from each treatment group individually and used to adjust values. Differences in mean adjusted values between groups were subsequently evaluated using ANOVA and Dunnet's post hoc test. O₂ consumed (VO₂; ml/h) and CO₂ produced (VCO₂; ml/h) are calculated as volumes of inspired and expired O₂ and CO₂. Respiratory Exchange Ratio (RER; VCO₂/VO₂) as a ratio and heat production (heat; (RER*1.232+3.815)*VO₂)/1000 as energy per hour (Kcal/h). Figure 12 shows the energy expenditure (O₂ consumption) is increased in the mouse cohorts administered Compound A.

[00332] EchoMRI Body composition

[00333] The body composition of mice was assessed by an EchoMRI 3-in-1 Body composition analyzer (EchoMRI, US). Non-anaesthetized animals were placed in a plastic

tube inside the MRI scanner for approximately 80 seconds. The body composition was reported as fat mass and fat free mass (lean mass). Figure 10 shows the relative lean mass (%) at baseline, week 4, week 7 and week 12. The data demonstrate that Compound A preserved lean body mass during the study.

[00334] Oral glucose tolerance test (OGTT)

[00335] Animals were housed in a clean cage and fasted for 4 hours prior to oral glucose administration. At timepoint 0, mice received an oral dose of 10 ml/kg of 200 mg/ml standard glucose solution (Fresenius Kabi, DK). Blood samples (10 µl) were collected at various timepoints defined in the study protocol into heparinized glass capillary tubes and immediately suspended in glucose/lactate system solution buffer (EKF-diagnostics, Germany). Blood glucose (BG) was measured using a BIOSEN c-Line glucose meter (EKF-diagnostics, Germany) according to the manufacturer's instructions. After the last blood sample and/or drug dose, the animals are returned to the normal feeding schedule. The results of the oral glucose tolerance test are provided in Figure 7, which shows that the administration of Compound A lowers the blood glucose level following the oral administration of glucose.

[00336] Blood sampling

[00337] Plasma preparation

[00338] In vivo blood samples: Tail-vein blood was collected in a Microvette tube of appropriate dimensions with anticoagulant and mixed by inversion 5 times. Blood was placed at 4°C until it is centrifuged at 3000 g for 10 minutes. The plasma supernatants were transferred to new tubes and immediately frozen on dry ice. The samples were stored at -70°C.

[00339] Termination blood samples: During anesthesia with isoflurane, the abdominal cavity was opened, and cardiac blood was drawn with a syringe into a Microvette/Vacurette of appropriate dimensions with anticoagulant and mixed by inversion 5 times. Blood was placed at 4°C until it was centrifuged at 3000 g for 10 minutes. The plasma supernatants were transferred to new tubes and immediately frozen on dry ice. The samples were stored at -70°C.

[00340] Tissue sampling

[00341] Pancreas: At termination, the splenic lobe of the pancreas was collected, split in two and either frozen at -70°C or immersion fixated in 10% neutral buffered formalin for 24 hours before transferred to 70% EtOH before paraffin embedment.

[00342] Liver: After the animal had been terminated, the liver was collected and weighed. Specific liver samples and biopsies were dissected and processed as specified in table “Termination samples” and further described below.

[00343] The liver was divided into left lateral lobe, medial lobe, right lateral lobe, and caudate lobe. The liver FFPE piece (~200 mg, less than 0.7 x 0.5 cm) was cut from the left lateral lobe and immersion fixated in 10% neutral buffered formalin for 24 hours before transferred to 70% etOH before paraffin embedment. The liver frozen piece (~150 mg) was dissected from the left medial lobe, put in a tube and placed directly into liquid nitrogen. The samples were stored at -70°C.

[00344] Liver samples were assayed for glycogen content by periodic acid-Schiff reagent (PAS) staining. Sections of FFPE tissue were oxidized in 0.5% periodic acid and rinsed in running distilled water. Subsequently, the sections were incubated with Schiff's reagent and washed in water. Counterstaining was performed in Mayer's hematoxylin followed by washing in water. Sections were dehydrated in graded ethanol, cleared in xylene, and cover slipped.

[00345] Quantitative assessment of liver glycogen (PAS): PAS-positive staining was quantified by image analysis using the VIS software (Visiopharm, Denmark). VIS protocols are designed to analyze the virtual slides in two steps: (1) crude detection of tissue at low magnification (1 x objective) with the liver capsule excluded, and (2) detection of PAS-positive staining detecting PAS positive cells at high magnification (10 x objective). The quantitative estimates of PAS-positive staining are calculated as an area fraction (AF) in the following way:

$$AF_{PAS-pos} = (Area_{PAS-pos}) / (Area_{tissue} + Area_{PAS-pos})$$

[00346] The results are shown in Figure 14, which demonstrates that liver glycogen is reduced in DIO model for mice treated with Compound A or a combination of Compound A and TZP.

[00347] Fat

[00348] Subcutaneous white adipose tissue (scWAT) was sampled from the left anterior subcutaneous fat deposit, weighed, and split into two samples, collected in a tube and frozen in liquid nitrogen or immersion fixated in 10% neutral buffered formalin. Inguinal white adipose tissue (iWAT) was sampled from the left posterior subcutaneous fat deposit, weighed, and split into two samples, collected in a tube and frozen in liquid nitrogen or immersion fixated in 10% neutral buffered formalin. Epididymal/gonadal white adipose tissue (eWAT/gWAT) was sampled as the left fat pad encapsulating the testis, with care

taken into not sampling the epididymis, weighed and split into two samples, collected in a tube and frozen in liquid nitrogen or immersion fixated in 10% neutral buffered formalin.

[00349] Muscles

[00350] M. gastrocnemius (GAS) was dissected from the right hind leg, cut longitudinal in two and collected in a tube and frozen in liquid nitrogen and stored at 70°C or immersion fixated in 10% neutral buffered formalin.

[00351] M. Quadriceps (Quad) was dissected from the right hindleg. The ligament at the knee holding the quadriceps in place was cut. Hereafter the top ligament was cut, and the quadriceps can be taken out and used for further processing. The muscle was cut longitudinal in two and collected in a tube and frozen in liquid nitrogen and stored at 70°C or immersion fixated in 10% neutral buffered formalin.

[00352] The Quad muscles were assayed for GLUT4 levels. The results are shown in Figure 15, which demonstrates that GLUT4 levels in muscle is improved and even restored in the diet induced obesity (DIO) model for mice treated with Compound A.

[00353] Immunohistochemistry using single chromogen: Immunohistochemistry (IHC) of GLUT4 was performed using standard procedures. Briefly, after antigen retrieval and blocking of endogenous peroxidase activity, slides were incubated with primary antibody (anti-GLUT4, Abcam, cat. ab33780). The primary antibody was detected using a polymeric HRP-linker antibody conjugate. The primary antibody was visualized with DAB as chromogen. Finally, sections are counterstained in hematoxylin, washed in tap water, dehydrated through graded ethanol, cleared in xylene, and cover slipped.

[00354] Quantitative assessment of immunoreactivity: IHC-positive staining was quantified by image analysis using the VIS software (Visiopharm, Denmark). The VIS protocols are designed to analyze the virtual slides in two steps: (1) crude detection of tissue at low magnification (1 x objective), and (2) detection of IHC-positive staining (immunohistochemical staining detecting GLUT4) and tissue at high magnification (10 x objective).

[00355] M. Tibialis Anterior (TA) was dissected from the right hind leg. Tendons of M. TA were exposed and the fascia covering the muscle was gently removed. The distal tendon was cut and the TA muscle was gently removed at its proximal attachment. The muscle was cut longitudinal in two and collected in a tube and frozen in liquid nitrogen and stored at 70°C or immersion fixated in 10% neutral buffered formalin.

[00356] Microtome sectioning of Formalin fixed paraffin-embedded (FFPE) biopsies

[00357] FFPE biopsies were placed in 10% neutral buffered formalin (10% NBF) for approximately 24h and then transferred to 70% EtOH and stored at 4 °C. The FFPE biopsies were then placed in the Histokinette to infiltrate prior to embedding in blocks. Biopsy tissues were cut at 3µm on a microtome and the sections are mounted on Superfrost Plus slides and stored at 4 °C.

[00358] Blood and plasma assays

[00359] Leptin (Singleplex). Blood samples were collected in heparinized tubes and plasma was separated and stored at -70 °C until analysis. Samples were measured using the commercial MSD platform (Meso Scale Diagnostics). The fasting plasma leptin at (A) baseline, (B) week 7 and (C) week 12 in the mouse cohorts of the DIO study are shown in Figure 17, demonstrating that treatment of the DIO mice with a ROCK2 inhibitor (Comp. A) lead to a greatly reduced plasma leptin.

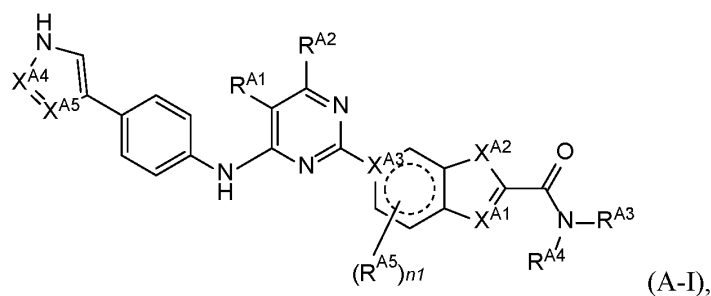
[00360] Insulin. Blood samples were collected in heparinized tubes and plasma was separated and stored at -70 °C until analysis. Insulin was measured using the commercial MSD platform (Meso Scale Diagnostics). The fasting plasma insulin at (A) baseline, (B) week 7 and (C) week 12 in the mouse cohorts of the DIO study are shown in Figure 16, demonstrating that treatment of the DIO mice with a ROCK2 inhibitor (Comp. A) lead to a greatly reduced plasma insulin/improved insulin sensitivity.

[00361] Exposure. Plasma samples were collected in K3 EDTA tubes and stored at -70 °C until analysis. Plasma proteins were removed by addition of organic solvent followed by centrifugation. The supernatant after protein precipitation was analyzed by LC-MS. Mean exposure values were collected for each group along with standard deviation (SD) and coefficient of variation (CV%).

[00362] Glycated hemoglobin A1c (HbA1c): Blood samples were collected into heparinized glass capillary tubes and immediately suspended in Hemolyzing Reagent (Roche Diagnostics) and stored at -70°C until analysis. HbA1c was measured using commercial kits (Roche Diagnostics,) on the cobas c 501 autoanalyzer. The results are shown in Figure 9, which demonstrate that Compound A lowers HbA1c in a dose-dependent manner.

WE CLAIM:

1. A method for treating type 2 diabetes in a subject comprising administering to the subject (i) a therapeutically effective amount of an inhibitor of Rho associated coiled-coil containing protein kinase 2 (ROCK2), and optionally (ii) a therapeutically effective amount of a glucagon-like peptide (GLP-1) agonist.
2. A method for treating or preventing obesity in a subject comprising administering to the subject (i) a therapeutically effective amount of an inhibitor of Rho associated coiled-coil containing protein kinase 2 (ROCK2), and optionally (ii) a therapeutically effective amount of a glucagon-like peptide (GLP-1) agonist.
3. A method for promoting weight loss in a subject comprising administering to the subject (i) a therapeutically effective amount of an inhibitor of Rho associated coiled-coil containing protein kinase 2 (ROCK2), and optionally (ii) a therapeutically effective amount of a glucagon-like peptide (GLP-1) agonist.
4. A method for reducing or preventing muscle loss in a patient that is undergoing therapy for obesity, weight loss, and/or type 2 diabetes, the method comprising administering to the subject a therapeutically effective amount of a ROCK2 inhibitor.
5. The method of any one of claims 1 to 4, wherein the ROCK2 inhibitor has a structure of Formula (A-I):



or pharmaceutically acceptable salt thereof, wherein:

R^{A1} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -

$\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{xI}}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{xI}}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{xI}}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, $-\text{C}(=\text{O})-\text{R}^{\text{A11}}$, $-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{xI}}-\text{C}(=\text{O})\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{xI}}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, and $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{xI}}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$;

R^{A2} is selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, halo, $-\text{CN}$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, $-\text{OR}^{\text{A11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{xI}}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{xI}}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{xI}}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, $-\text{C}(=\text{O})-\text{R}^{\text{A11}}$, $-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{xI}}-\text{C}(=\text{O})\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{xI}}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, and $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{xI}}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$;

alternatively, R^{A1} and R^{A2} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of $\text{C}_1\text{-C}_6$ alkyl, halo, $-\text{CN}$, $-\text{OH}$, oxlo, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OH}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, and $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$;

R^{A3} and R^{A4} are each independently selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, 3- to 10-membered heterocyclyl, $\text{C}_6\text{-C}_{10}$ aryl, 5- to 14-membered heteroaryl, $\text{C}_6\text{-C}_{12}$ aralkyl, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{xI}}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{xI}}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, and $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{xI}}-\text{C}(=\text{O})\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$;

alternatively R^{A3} and R^{A4} are taken together with the nitrogen to which they are attached to provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, halo, $-\text{CN}$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, $-\text{OR}^{\text{A11}}$, oxlo, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{O}$

(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{x1}-C(=O)OR^{A11};

the dotted lines represent optional double bonds;

each R^{A5} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, ox1o, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{x1}-C(=O)OR^{A11};

n1 is 0 to 3;

X^{A1} is CR^{A6} or N;

X^{A2} is CHR^{A6}, NR^{A7}, O or S;

X^{A3} is C, CH or N;

X^{A4} is N or CH;

X^{A5} is N or CH;

each R^{A6} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{x1}-C(=O)OR^{A11};

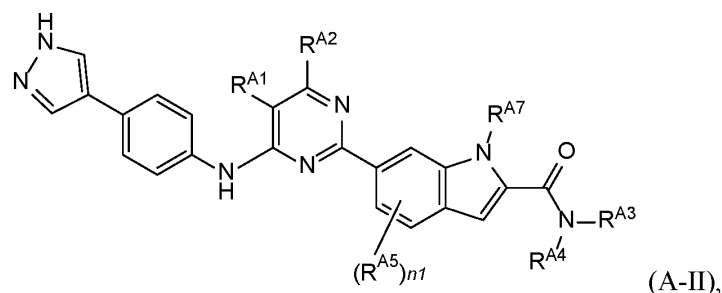
each R^{A7} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)OR^{A11}, and -(C₁-C₆ alkyl)_{x1}-C(=O)NR^{A11}R^{A12};

each x1 is independently selected from 0 and 1; and

each R^{A11} and R^{A12} are independently selected from the group consisting of H and C₁-C₆ alkyl;

or alternatively, R^{A11} and R^{A12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, -NH₂, C₁-C₃ perfluoro alkyl, -OH, -O-(C₁-C₆ alkyl), and -(C₁-C₆ alkyl)-OH.

6. The method of claim 5, wherein the ROCK2 inhibitor has a structure of Formula (A-II),



or pharmaceutically acceptable salt thereof, wherein:

R^{A1} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -(C₁-C₆ alkyl)_x-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)OR^{A11};

R^{A2} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -(C₁-C₆ alkyl)_x-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)OR^{A11};

C_6 alkyl) $_{xI}$ -C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl) $_{xI}$ -C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl) $_{xI}$ -C(=O)OR^{A11};

alternatively, R^{A1} and R^{A2} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, C₁-C₃ perfluoro alkyl, -NR^{A11}-(C₁-C₆ alkyl)NR^{A11}R^{A12}, and -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11};

R^{A3} and R^{A4} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆-₁₂ aralkyl, -(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl) $_{xI}$ -C(=O)R^{A11}, -(C₁-C₆ alkyl) $_{xI}$ -C(=O)OR^{A11}, and -(C₁-C₆ alkyl) $_{xI}$ -C(=O)NR^{A11}R^{A12};

alternatively R^{A3} and R^{A4} are taken together with the nitrogen to which they are attached to provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring to heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, oxo, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl) $_{xI}$ -C(=O)R^{A11}, -O-(C₁-C₆ alkyl) $_{xI}$ -C(=O)R^{A11}, -(C₁-C₆ alkyl) $_{xI}$ -C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl) $_{xI}$ -C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl) $_{xI}$ -C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl) $_{xI}$ -C(=O)OR^{A11};

the dotted lines represent optional double bonds;

each R^{A5} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, oxo, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-

$\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6\text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6\text{ alkyl})_{xI}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-\text{O}-(\text{C}_1\text{-C}_6\text{ alkyl})_{xI}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6\text{ alkyl})_{xI}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, $-\text{C}(=\text{O})-\text{R}^{\text{A11}}$, $-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6\text{ alkyl})_{xI}-\text{C}(=\text{O})\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6\text{ alkyl})_{xI}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, and $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6\text{ alkyl})_{xI}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$;

nI is 0 to 3;

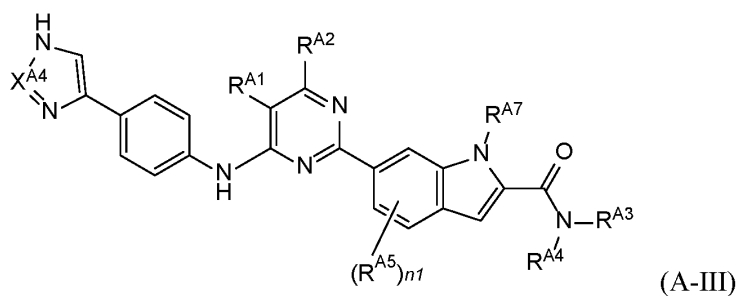
R^{A7} is selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $-(\text{C}_1\text{-C}_6\text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6\text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-(\text{C}_1\text{-C}_6\text{ alkyl})_{xI}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6\text{ alkyl})_{xI}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, and $-(\text{C}_1\text{-C}_6\text{ alkyl})_{xI}-\text{C}(=\text{O})\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$;

each xI is independently selected from 0 and 1; and

each R^{A11} and R^{A12} are independently selected from the group consisting of H and $\text{C}_1\text{-C}_6$ alkyl;

or alternatively, R^{A11} and R^{A12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $-\text{CN}$, $-\text{NH}_2$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, $-\text{OH}$, $-\text{O}-(\text{C}_1\text{-C}_6\text{ alkyl})$, and $-(\text{C}_1\text{-C}_6\text{ alkyl})-\text{OH}$.

7. The method of claim 5, wherein the ROCK2 inhibitor has a structure of Formula (A-III),



or pharmaceutically acceptable salt thereof, wherein:

R^{A1} is selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, halo, $-\text{CN}$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, $-\text{OR}^{\text{A11}}$, $-\text{O}-(\text{C}_1\text{-C}_6\text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6\text{ alkyl})-\text{OR}^{\text{A11}}$, $-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{O}-(\text{C}_1\text{-C}_6\text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-(\text{C}_1\text{-C}_6\text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6\text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, -

$\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_x-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, $-\text{C}(=\text{O})-\text{R}^{\text{A11}}$, $-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/}-\text{C}(=\text{O})\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, and $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$;

R^{A2} is selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, halo, $-\text{CN}$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, $-\text{OR}^{\text{A11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, $-\text{C}(=\text{O})-\text{R}^{\text{A11}}$, $-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/}-\text{C}(=\text{O})\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, and $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$;

alternatively, R^{A1} and R^{A2} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of $\text{C}_1\text{-C}_6$ alkyl, halo, $-\text{CN}$, $-\text{OH}$, oxo, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OH}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, and $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$;

R^{A3} and R^{A4} are each independently selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, 3- to 10-membered heterocyclyl, $\text{C}_6\text{-C}_{10}$ aryl, 5- to 14-membered heteroaryl, $\text{C}_6\text{-C}_{12}$ aralkyl, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, and $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/}-\text{C}(=\text{O})\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$;

alternatively R^{A3} and R^{A4} are taken together with the nitrogen to which they are attached to provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring to heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, halo, $-\text{CN}$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, $-\text{OR}^{\text{A11}}$, oxo, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{O}-$

(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{xI}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{xI}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xI}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{xI}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{xI}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{xI}-C(=O)OR^{A11};

the dotted lines represent optional double bonds;

each R^{A5} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, oxo, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{xI}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{xI}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xI}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{xI}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{xI}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{xI}-C(=O)OR^{A11};

nI is 0 to 3;

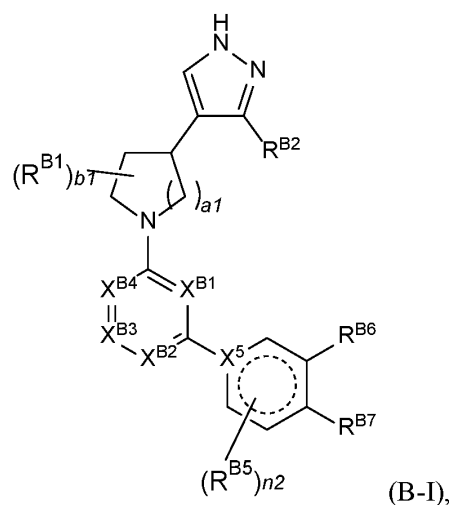
R^{A7} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)_{xI}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xI}-C(=O)OR^{A11}, and -(C₁-C₆ alkyl)_{xI}-C(=O)NR^{A11}R^{A12};

each *xI* is independently selected from 0 and 1; and

each R^{A11} and R^{A12} are independently selected from the group consisting of H and C₁-C₆ alkyl;

or alternatively, R^{A11} and R^{A12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, -NH₂, C₁-C₃ perfluoro alkyl, -OH, -O-(C₁-C₆ alkyl), and -(C₁-C₆ alkyl)-OH.

8. The method of any one of claims 1-4, wherein the ROCK2 inhibitor has a structure of Formula (B-I):



or pharmaceutically acceptable salt thereof, wherein

X^{B1} is N or CH;

X^{B2} is N or CH;

X^{B3} is N or CR^{B3} ;

X^{B4} is N or CR^{B4} ;

X^{B5} is selected from the group consisting of C, CH and N;

$a1$ is selected from 1 or 2;

the dotted lines represent optional double bonds;

each R^{B1} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, oxo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, and -NR^{B11}R^{B12};

or alternatively, two R^{B1} attached to the same carbon or to adjacent carbons are taken together to form a 3- to 6-membered ring, which may optionally contain 0 to 2 ring heteroatoms selected from O, S and N, and which may be unsubstituted or optionally substituted by 1 to 3 substituents selected from halo, C₁-C₃ alkyl, NH₂, OH, and O-C₁-C₃ alkyl;

$b1$ is selected from 0, 1, and 2;

R^{B2} is selected from H, halo, C₁-C₃ alkyl, NH₂, OH, and O-C₁-C₃ alkyl;

R^{B3} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -

$\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{R}^{\text{B11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{R}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{OR}^{\text{B11}}$, $-\text{C}(=\text{O})-\text{R}^{\text{B11}}$, $-\text{C}(=\text{O})\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{R}^{\text{B11}}$, and $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{OR}^{\text{B11}}$;

R^{B4} is selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, halo, $-\text{CN}$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, $-\text{OR}^{\text{B11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{R}^{\text{B11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{R}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{OR}^{\text{B11}}$, $-\text{C}(=\text{O})-\text{R}^{\text{B11}}$, $-\text{C}(=\text{O})\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{R}^{\text{B11}}$, and $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{OR}^{\text{B11}}$;

alternatively, R^{B3} and R^{B4} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of $\text{C}_1\text{-C}_6$ alkyl, halo, $-\text{CN}$, $-\text{OH}$, oxo, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OH}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, and $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$;

each R^{B5} is independently selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, halo, $-\text{CN}$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, oxo, $-\text{OR}^{\text{B11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{R}^{\text{B11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{R}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{OR}^{\text{B11}}$, $-\text{C}(=\text{O})-\text{R}^{\text{B11}}$, $-\text{C}(=\text{O})\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{R}^{\text{B11}}$, and $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{OR}^{\text{B11}}$;

n_2 is 0 to 3;

R^{B6} and R^{B7} are independently selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, halo, $-\text{CN}$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, $-\text{OR}^{\text{B11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{C}(=\text{O})\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{C}(=\text{O})\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$,

-NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

alternatively, R^{B6} and R^{B7} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₅-C₁₀ aryl, C₅-C₁₀ heteroaryl, 3- to 10-membered heterocyclyl, -C₁-C₆ alkyl-(C₃-C₇ cycloalkyl), -C₁-C₆ alkyl-(C₅-C₁₀ aryl), -C₁-C₆ alkyl-(C₅-C₁₀ heteroaryl), -C₁-C₆ alkyl-(3- to 10-membered heterocyclyl), halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, C₁-C₃ perfluoro alkyl, -NR^{B11}-(C₁-C₆ alkyl)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, and -C(=O)-N(R^{B8})(R^{B9}), and wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclyl may optionally be substituted with one to three substituents selected from C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, oxo, halo, -CN, -OH, and NH₂;

R^{B8} and R^{B9} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆-₁₂ aralkyl, -(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, and -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, wherein each alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl may optionally be substituted with one to three substituents selected from C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, oxo, halo, -CN, -OH, and NH₂;

alternatively R^{B8} and R^{B9} are taken together with the nitrogen to which they are attached provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, C₁-C₆ fluoroalkyl, C₁-C₃

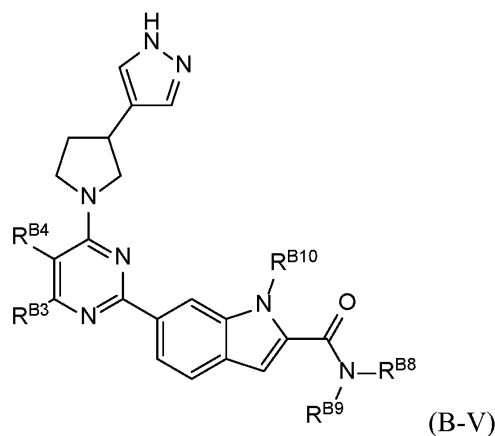
perfluoro alkyl, $-OR^{B11}$, oxo, $-O-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-NR^{B11}R^{B12}$, $-O-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-NR^{B11}-$
 $(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-NR^{B11}-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-$
 $C(=O)R^{B11}$, $-O-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)R^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)OR^{B11}$, $-$
 $C(=O)-R^{B11}$, $-C(=O)OR^{B11}$, $-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)NR^{B11}R^{B12}$, $-NR^{B11}-(C_1-C_6$
 $\text{alkyl})_{x2}-C(=O)R^{B11}$, and $-NR^{B11}-(C_1-C_6 \text{ alkyl})_{x2}-C(=O)OR^{B11}$;

each x_2 is independently selected from 0 and 1; and

each R^{B11} and R^{B12} are independently selected from the group consisting of H and C_1-C_6 alkyl;

or alternatively, R^{B11} and R^{B12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, $-CN$, $-NH_2$, C_1-C_3 perfluoroalkyl, $-OH$, $-O-(C_1-C_6 \text{ alkyl})$, and $-(C_1-C_6 \text{ alkyl})-OH$.

9. The method of claim 8, wherein the ROCK2 inhibitor has a structure of the formula (B-V):



or a pharmaceutically acceptable salt thereof, wherein:

R^{B3} is selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, halo, $-CN$, C_1-C_3 perfluoro alkyl, $-OR^{B11}$, $-O-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-(C_1-C_6 \text{ alkyl})-OR^{B11}$, $-NR^{B11}R^{B12}$, $-O-(C_1-C_6 \text{ alkyl})-$
 $NR^{B11}R^{B12}$, $-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-NR^{B11}-(C_1-C_6 \text{ alkyl})-NR^{B11}R^{B12}$, $-$

$\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{R}^{\text{B11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{R}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{OR}^{\text{B11}}$, $-\text{C}(=\text{O})-\text{R}^{\text{B11}}$, $-\text{C}(=\text{O})\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{R}^{\text{B11}}$, and $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{OR}^{\text{B11}}$;

R^{B4} is selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, halo, $-\text{CN}$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, $-\text{OR}^{\text{B11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{R}^{\text{B11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{R}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{OR}^{\text{B11}}$, $-\text{C}(=\text{O})-\text{R}^{\text{B11}}$, $-\text{C}(=\text{O})\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{R}^{\text{B11}}$, and $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{OR}^{\text{B11}}$;

alternatively, R^{B3} and R^{B4} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of $\text{C}_1\text{-C}_6$ alkyl, halo, $-\text{CN}$, $-\text{OH}$, oxo, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OH}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, and $-\text{NR}^{\text{B11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$;

R^{B8} and R^{B9} are each independently selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, 3- to 10-membered heterocyclyl, $\text{C}_6\text{-C}_{10}$ aryl, 5- to 14-membered heteroaryl, $\text{C}_6\text{-C}_{12}$ aralkyl, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{R}^{\text{B11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{OR}^{\text{B11}}$, and $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{\text{x2}}-\text{C}(=\text{O})\text{NR}^{\text{B11}}\text{R}^{\text{B12}}$, wherein each alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl may optionally be substituted with one to three substituents selected from $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_1\text{-C}_3$ perfluoroalkyl, oxo, halo, $-\text{CN}$, $-\text{OH}$, and NH_2 ;

alternatively R^{B8} and R^{B9} are taken together with the nitrogen to which they are attached provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4

substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, C₁-C₆ fluoroalkyl, C₁-C₃ perfluoro alkyl, -OR^{B11}, oxo, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

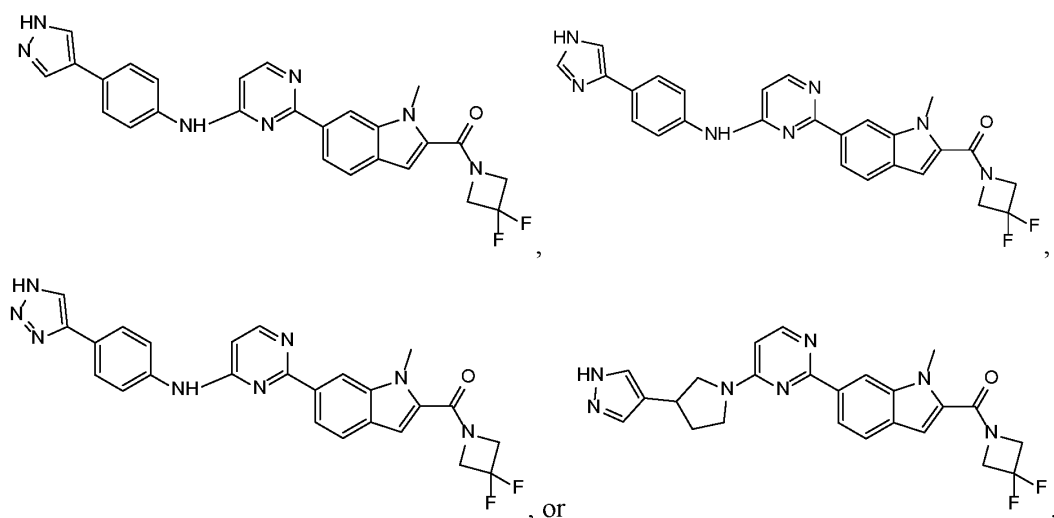
R^{B10} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₅-C₁₀ aryl, C₅-C₁₀ heteroaryl, 3- to 10-membered heterocyclyl, -C₁-C₆ alkyl-(C₃-C₇ cycloalkyl), -C₁-C₆ alkyl-(C₅-C₁₀ aryl), -C₁-C₆ alkyl-(C₅-C₁₀ heteroaryl), -C₁-C₆ alkyl-(3- to 10-membered heterocyclyl), -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-OR^{B11}, and -C(=O)-N(R^{B11})(R^{B12}), and wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclyl may optionally be substituted with one to three substituents selected from C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, oxo, halo, -CN, -OH, and NH₂;

each x₂ is independently selected from 0 and 1; and

each R^{B11} and R^{B12} are independently selected from the group consisting of H and C₁-C₆ alkyl;

or alternatively, R^{B11} and R^{B12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, -NH₂, C₁-C₃ perfluoroalkyl, -OH, -O-(C₁-C₆ alkyl), and -(C₁-C₆ alkyl)-OH.

10. The method of any one of claims 1 to 4, wherein the ROCK2 inhibitor is

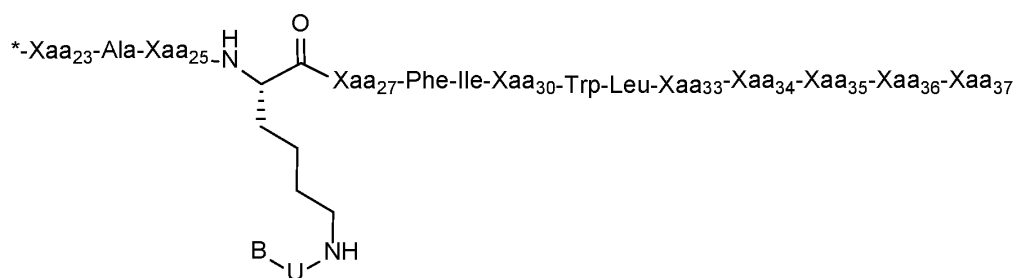


or a pharmaceutically acceptable salt thereof.

11. The method of any one of claims 1 to 4, wherein the ROCK2 inhibitor is selected from belumosudil (KD025), zelasudil, Y-27632, Fasudil, GSK429286A, RKI-1447, Azaindole 1 (TC-S 7001), Hydroxyfasudil, GSK269962A, Ripasudil, AT13148, RX007, and derivatives, isomers, hydrates, or pharmaceutically acceptable salts thereof.

12. The method of any one of claims 1 to 11, wherein the GLP-1 agonist includes a structure of Formula (M-I):

Xaa₇-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Xaa₁₆-Ser-Xaa₁₈-Xaa₁₉-Xaa₂₀-Glu-Xaa₂₂-*



(M-I),

wherein:

Xaa₇ is L-histidine, imidazopropionyl, α -hydroxy-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β -hydroxy-histidine, homohistidine, N^α-acetyl-histidine, N^α-formyl-histidine, α -fluoromethyl-histidine, α -methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine

Xaa₈ is Ala, Gly, Val, Leu, Ile, Thr, Ser, Lys, Aib (α -aminoisobutyric acid), (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa₁₆ is Val or Leu;

Xaa₁₈ is Ser, Lys or Arg;

Xaa₁₉ is Tyr or Gln;

Xaa₂₀ is Leu or Met;

Xaa₂₂ is Gly, Glu or Aib (α -aminoisobutyric acid);

Xaa₂₃ is Gln, Glu, Lys or Arg;

Xaa₂₅ is Ala or Val;

Xaa₂₇ is Glu or Leu;

Xaa₃₀ is Ala, Glu or Arg;

Xaa₃₃ is Val or Lys;

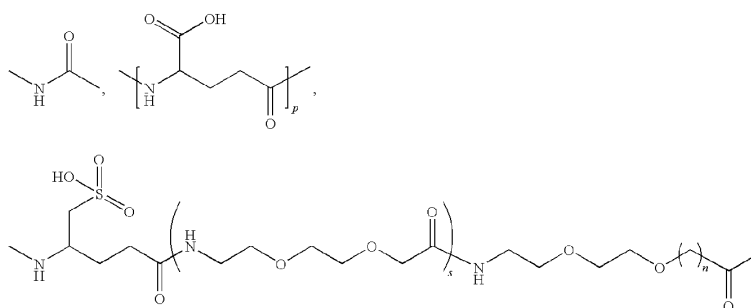
Xaa₃₄ is Lys, Glu, Asn or Arg;

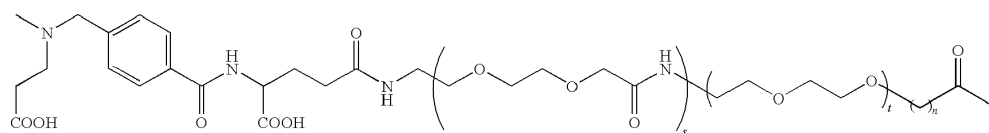
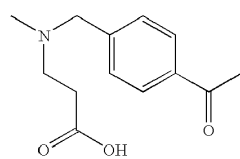
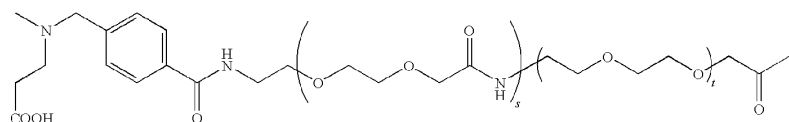
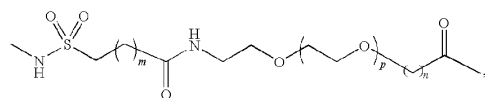
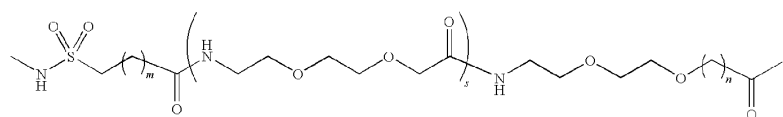
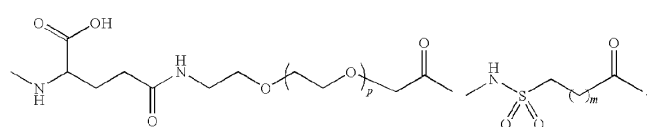
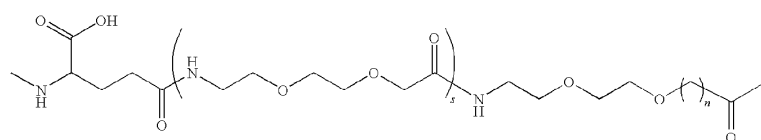
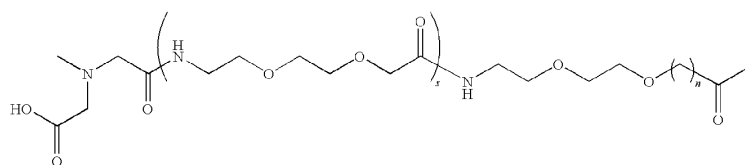
Xaa₃₅ is Gly or Aib (α -aminoisobutyric acid);

Xaa₃₆ is Arg, Gly or Lys, or is absent;

Xaa₃₇ is Gly, Ala, Glu, Pro, Lys, or is absent; and

and B and U together is the acylated moiety, where U is selected from





m is 0, 1, 2, 3, 4, 5, or 6,

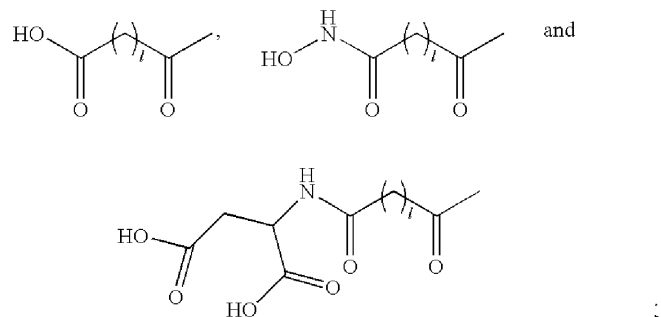
n is 1, 2 or 3

s is 0, 1, 2, or 3,

t is 0, 1, 2, 3, or 4

p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

and where B is an acidic group selected from



where l is 12, 13, 14, 15, 16, 17, 18, 19 or 20,

or a pharmaceutically acceptable salt thereof.

13. The method of claim 12, wherein:

Xaa₇ is His or desamino-histidine;

Xaa₈ is Ala, Gly, Val, Leu, Ile, Lys or Aib;

Xaa₁₆ is Val; Xaa₁₈ is Ser; Xaa₁₉ is Tyr;

Xaa₂₀ is Leu;

Xaa₂₂ is Gly, Glu or Aib;

Xaa₂₃ is Gln or Glu;

Xaa₂₅ is Ala; Xaa₂₇ is Glu;

Xaa₃₀ is Ala or Glu;

Xaa₃₃ is Val;

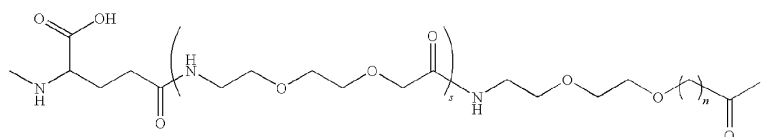
Xaa₃₄ is Lys or Arg;

Xaa₃₅ is Gly or Aib;

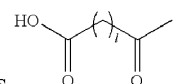
Xaa₃₆ is Arg or Lys; and/or

Xaa₃₇ is Gly, amide or is absent.

14. The method of claim 12 or 13, wherein U is



15. The method of any one of claims 12 to 14, wherein B is

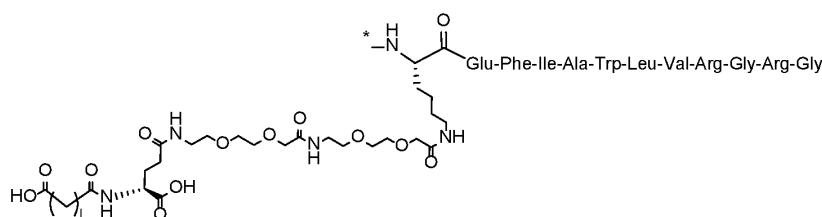


, and / is 14,

16, or

16. The method of any one of claims 12 to 15, wherein the GLP-1 agonist has the structure of Formula (M-III):

His-Alb-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala*

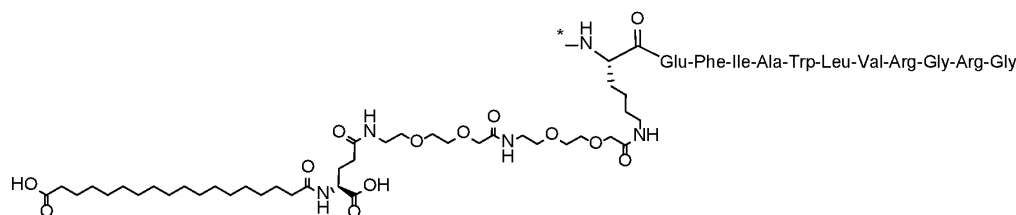


(M-III),

/ is 12, 14, or 16.

17. The method of any one of claims 1 to 4, wherein the GLP-1 agonist is

His-Alb-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala*



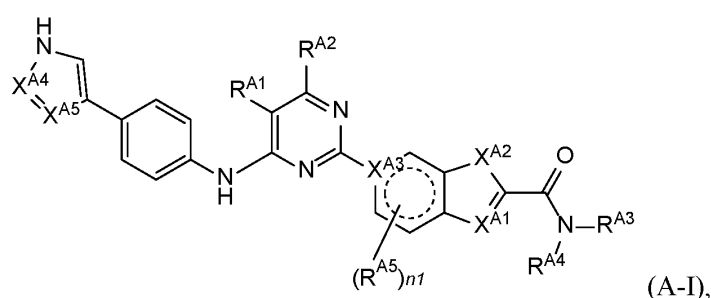
(semaglutide).

18. The method of any one of claims 1 to 4, wherein the GLP-1 agonist is selected from semaglutide, exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide, tirzepatide, lotiglipron, retatrutide, taspoglutide, orforglipron or danuglipron.

19. The method any one of claims 1 to 18, wherein the ROCK2 inhibitor and the GLP-1 agonist are administered simultaneously.

20. The method of any one of claims 1 to 18, wherein the ROCK2 inhibitor and the GLP-1 agonist are administered subsequently.

21. The method of any one of claims 1 to 20, wherein the ROCK2 inhibitor is administered orally and GLP-1 agonist is subcutaneously.
22. A combination comprising:
a therapeutically effective amount of a Rho associated coiled-coil containing protein kinase 2 (ROCK2) inhibitor, and
a therapeutically effective amount of a glucagon-like peptide (GLP-1) agonist.
23. The combination of claim 22, wherein the ROCK2 inhibitor has a structure of Formula (A-I):



or pharmaceutically acceptable salt thereof, wherein:

R^{A1} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{x1}-C(=O)OR^{A11};

R^{A2} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{x1}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{x1}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{x1}-C(=O)OR^{A11};

alternatively, R^{A1} and R^{A2} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, halo, -CN, -OH, oxlo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, C₁-C₃ perfluoro alkyl, -NR^{A11}-(C₁-C₆ alkyl)NR^{A11}R^{A12}, and -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11};

R^{A3} and R^{A4} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆-12 aralkyl, -(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11}, and -(C₁-C₆ alkyl)_{xl}-C(=O)NR^{A11}R^{A12};

alternatively R^{A3} and R^{A4} are taken together with the nitrogen to which they are attached to provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, oxlo, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11};

the dotted lines represent optional double bonds;

each R^{A5} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, oxlo, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -

$C(=O)OR^{A11}$, $-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)R^{A11}$, and $-NR^{A11}-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)OR^{A11}$;

$n1$ is 0 to 3;

X^{A1} is CR^{A6} or N;

X^{A2} is CHR^{A6} , NR^{A7} , O or S;

X^{A3} is C, CH or N;

X^{A4} is N or CH;

X^{A5} is N or CH;

each R^{A6} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, halo, -CN, C_1-C_3 perfluoro alkyl, - OR^{A11} , $-O-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-NR^{A11}R^{A12}$, $-O-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)R^{A11}$, $-O-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)R^{A11}$, $-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)OR^{A11}$, $-C(=O)-R^{A11}$, $-C(=O)OR^{A11}$, $-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)R^{A11}$, and $-NR^{A11}-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)OR^{A11}$;

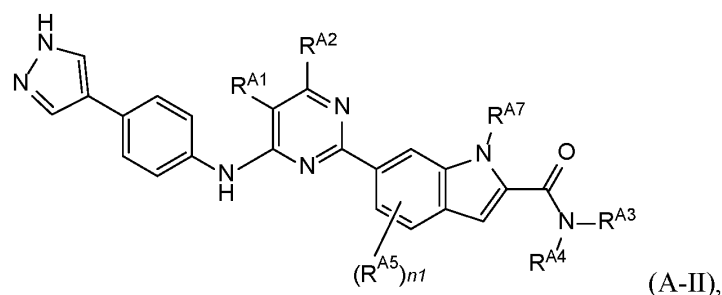
each R^{A7} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, $-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)R^{A11}$, $-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)OR^{A11}$, and $-(C_1-C_6 \text{ alkyl})_{x1}-C(=O)NR^{A11}R^{A12}$;

each $x1$ is independently selected from 0 and 1; and

each R^{A11} and R^{A12} are independently selected from the group consisting of H and C_1-C_6 alkyl;

or alternatively, R^{A11} and R^{A12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, -CN, $-NH_2$, C_1-C_3 perfluoro alkyl, -OH, $-O-(C_1-C_6 \text{ alkyl})$, and $-(C_1-C_6 \text{ alkyl})-OH$.

24. The combination of claim 23, wherein the ROCK2 inhibitor has a structure of Formula (A-II),



or pharmaceutically acceptable salt thereof, wherein:

R^{A1} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -(C₁-C₆ alkyl)_x-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)OR^{A11};

R^{A2} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -(C₁-C₆ alkyl)_x-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)OR^{A11};

alternatively, R^{A1} and R^{A2} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, C₁-C₃ perfluoro alkyl, -NR^{A11}-(C₁-C₆ alkyl)NR^{A11}R^{A12}, and -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11};

R^{A3} and R^{A4} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered

heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆₋₁₂ aralkyl, -(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11}, and -(C₁-C₆ alkyl)_{xl}-C(=O)NR^{A11}R^{A12};

alternatively R^{A3} and R^{A4} are taken together with the nitrogen to which they are attached to provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring to heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, oxo, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11};

the dotted lines represent optional double bonds;

each R^{A5} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, oxo, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11};

nl is 0 to 3;

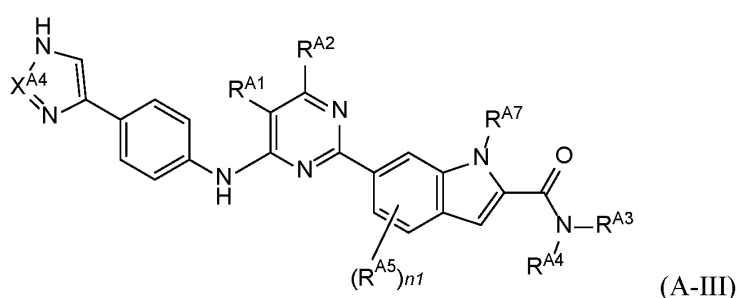
R^{A7} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)_{xl}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{xl}-C(=O)OR^{A11}, and -(C₁-C₆ alkyl)_{xl}-C(=O)NR^{A11}R^{A12};

each *xl* is independently selected from 0 and 1; and

each R^{A11} and R^{A12} are independently selected from the group consisting of H and C₁-C₆ alkyl;

or alternatively, R^{A11} and R^{A12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_7 cycloalkyl, -CN, -NH₂, C_1 - C_3 perfluoro alkyl, -OH, -O-(C_1 - C_6 alkyl), and -(C_1 - C_6 alkyl)-OH.

25. The combination of claim 23, wherein the ROCK2 inhibitor has a structure of Formula (A-III),



or pharmaceutically acceptable salt thereof, wherein:

R^{A1} is selected from the group consisting of H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_7 cycloalkyl, halo, -CN, C_1 - C_3 perfluoro alkyl, -OR^{A11}, -O-(C_1 - C_6 alkyl)-OR^{A11}, -(C_1 - C_6 alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C_1 - C_6 alkyl)-NR^{A11}R^{A12}, -(C_1 - C_6 alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C_1 - C_6 alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C_1 - C_6 alkyl)-OR^{A11}, -(C_1 - C_6 alkyl)_x-C(=O)R^{A11}, -O-(C_1 - C_6 alkyl)_x-C(=O)R^{A11}, -(C_1 - C_6 alkyl)_x-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C_1 - C_6 alkyl)_x-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C_1 - C_6 alkyl)_x-C(=O)R^{A11}, and -NR^{A11}-(C_1 - C_6 alkyl)_x-C(=O)OR^{A11};

R^{A2} is selected from the group consisting of H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_7 cycloalkyl, halo, -CN, C_1 - C_3 perfluoro alkyl, -OR^{A11}, -O-(C_1 - C_6 alkyl)-OR^{A11}, -(C_1 - C_6 alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C_1 - C_6 alkyl)-NR^{A11}R^{A12}, -(C_1 - C_6 alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C_1 - C_6 alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C_1 - C_6 alkyl)-OR^{A11}, -(C_1 - C_6 alkyl)_x-C(=O)R^{A11}, -O-(C_1 - C_6 alkyl)_x-C(=O)R^{A11}, -(C_1 - C_6 alkyl)_x-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C_1 - C_6 alkyl)_x-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C_1 - C_6 alkyl)_x-C(=O)R^{A11}, and -NR^{A11}-(C_1 - C_6 alkyl)_x-C(=O)OR^{A11};

alternatively, R^{A1} and R^{A2} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, C₁-C₃ perfluoro alkyl, -NR^{A11}-(C₁-C₆ alkyl)NR^{A11}R^{A12}, and -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11};

R^{A3} and R^{A4} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆-12 aralkyl, -(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)OR^{A11}, and -(C₁-C₆ alkyl)_{x/l}-C(=O)NR^{A11}R^{A12};

alternatively R^{A3} and R^{A4} are taken together with the nitrogen to which they are attached to provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring to heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, oxo, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{x/l}-C(=O)OR^{A11};

the dotted lines represent optional double bonds;

each R^{A5} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, oxo, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -

$C(=O)OR^{A11}$, $-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)R^{A11}$, and $-NR^{A11}-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)OR^{A11}$;

nI is 0 to 3;

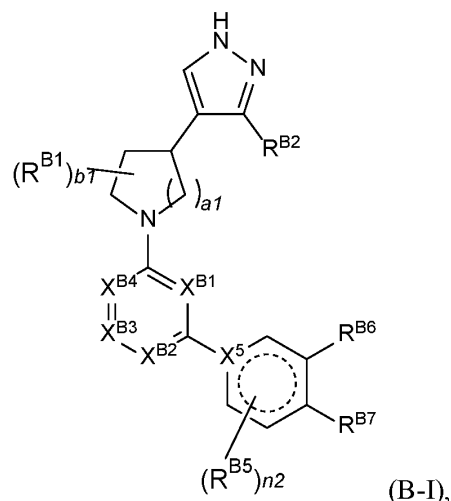
R^{A7} is selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, $-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)R^{A11}$, $-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)OR^{A11}$, and $-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)NR^{A11}R^{A12}$;

each xI is independently selected from 0 and 1; and

each R^{A11} and R^{A12} are independently selected from the group consisting of H and C_1-C_6 alkyl;

or alternatively, R^{A11} and R^{A12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, -CN, -NH₂, C_1-C_3 perfluoro alkyl, -OH, -O-(C_1-C_6 alkyl), and -(C_1-C_6 alkyl)-OH.

26. The combination of claim 22, wherein the ROCK2 inhibitor has a structure of Formula (B-I),



or pharmaceutically acceptable salt thereof, wherein

X^{B1} is N or CH;

X^{B2} is N or CH;

X^{B3} is N or CR^{B3} ;

X^{B4} is N or CR^{B4} ;

X^{B5} is selected from the group consisting of C, CH and N;

al is selected from 1 or 2;

the dotted lines represent optional double bonds;

each R^{B1} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, oxo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, and

-NR^{B11}R^{B12},

or alternatively, two R^{B1} attached to the same carbon or to adjacent carbons are taken together to form a 3- to 6-membered ring, which may optionally contain 0 to 2 ring heteroatoms selected from O, S and N, and which may be unsubstituted or optionally substituted by 1 to 3 substituents selected from halo, C₁-C₃ alkyl, NH₂, OH, and O-C₁-C₃ alkyl;

bl is selected from 0, 1, and 2;

R^{B2} is selected from H, halo, C₁-C₃ alkyl, NH₂, OH, and O-C₁-C₃ alkyl;

R^{B3} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

R^{B4} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

alternatively, R^{B3} and R^{B4} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms

selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, C₁-C₃ perfluoro alkyl, -NR^{B11}-(C₁-C₆ alkyl)NR^{B11}R^{B12}, and -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11};

each R^{B5} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, oxo, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

*n*₂ is 0 to 3;

R^{B6} and R^{B7} are independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-C(=O)NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

alternatively, R^{B6} and R^{B7} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₅-C₁₀ aryl, C₅-C₁₀ heteroaryl, 3- to 10-membered heterocyclyl, -C₁-C₆ alkyl-(C₃-C₇ cycloalkyl), -C₁-C₆ alkyl-(C₅-C₁₀ aryl), -C₁-C₆ alkyl-(C₅-C₁₀ heteroaryl), -C₁-C₆ alkyl-(3- to 10-membered heterocyclyl), halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, C₁-C₃ perfluoro alkyl, -NR^{B11}-(C₁-C₆

alkyl)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, and -C(=O)-N(R^{B8})(R^{B9}), and wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclyl may optionally be substituted with one to three substituents selected from C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, oxo, halo, -CN, -OH, and NH₂;

R^{B8} and R^{B9} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆-12 aralkyl, -(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, and -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, wherein each alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl may optionally be substituted with one to three substituents selected from C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, oxo, halo, -CN, -OH, and NH₂;

alternatively R^{B8} and R^{B9} are taken together with the nitrogen to which they are attached provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, C₁-C₆ fluoroalkyl, C₁-C₃ perfluoro alkyl, -OR^{B11}, oxo, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

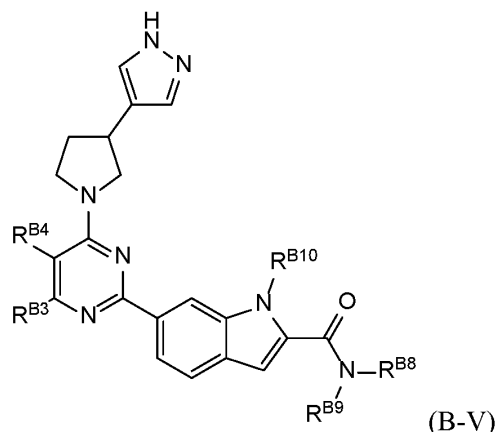
each x2 is independently selected from 0 and 1; and

each R^{B11} and R^{B12} are independently selected from the group consisting of H and C₁-C₆ alkyl;

or alternatively, R^{B11} and R^{B12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆

alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, -NH₂, C₁-C₃ perfluoroalkyl, -OH, -O-(C₁-C₆ alkyl), and -(C₁-C₆ alkyl)-OH.

27. The combination of claim 26, wherein the ROCK2 inhibitor has a structure of the formula (B-V),



or a pharmaceutically acceptable salt thereof, wherein:

R^{B3} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

R^{B4} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{B11}, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

alternatively, R^{B3} and R^{B4} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms

selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, C₁-C₃ perfluoro alkyl, -NR^{B11}-(C₁-C₆ alkyl)NR^{B11}R^{B12}, and -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11};

R^{B8} and R^{B9} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆-₁₂ aralkyl, -(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, and -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, wherein each alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl may optionally be substituted with one to three substituents selected from C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, oxo, halo, -CN, -OH, and NH₂;

alternatively R^{B8} and R^{B9} are taken together with the nitrogen to which they are attached provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, C₁-C₆ fluoroalkyl, C₁-C₃ perfluoro alkyl, -OR^{B11}, oxo, -O-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)-OR^{B11}, -NR^{B11}R^{B12}, -O-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)-OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -O-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11}, -C(=O)-R^{B11}, -C(=O)OR^{B11}, -(C₁-C₆ alkyl)_{x2}-C(=O)NR^{B11}R^{B12}, -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)R^{B11}, and -NR^{B11}-(C₁-C₆ alkyl)_{x2}-C(=O)OR^{B11};

R^{B10} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₅-C₁₀ aryl, C₅-C₁₀ heteroaryl, 3- to 10-membered heterocyclyl, -C₁-C₆ alkyl-(C₃-C₇ cycloalkyl), -C₁-C₆ alkyl-(C₅-C₁₀ aryl), -C₁-C₆ alkyl-(C₅-C₁₀ heteroaryl), -C₁-C₆ alkyl-(3- to 10-membered heterocyclyl), -(C₁-C₆ alkyl)-NR^{B11}R^{B12}, -(C₁-C₆ alkyl)NR^{B11}R^{B12}, -(C₁-C₆ alkyl)-OR^{B11}, and -C(=O)-N(R^{B11})(R^{B12}), and wherein each alkyl, alkenyl, cycloalkyl, aryl,

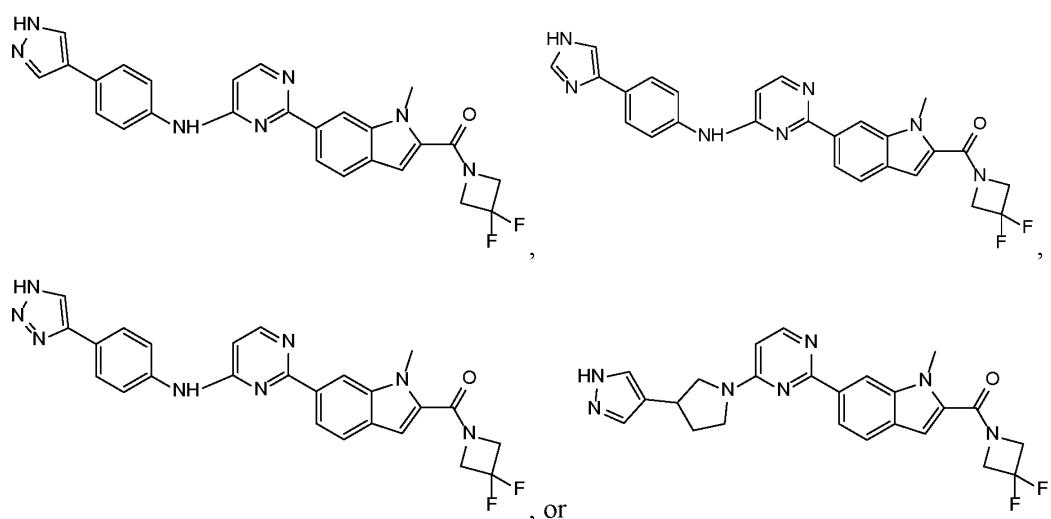
heteroaryl and heterocyclyl may optionally be substituted with one to three substituents selected from C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, oxo, halo, -CN, -OH, and NH₂;

each *x2* is independently selected from 0 and 1; and

each R^{B11} and R^{B12} are independently selected from the group consisting of H and C₁-C₆ alkyl;

or alternatively, R^{B11} and R^{B12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, -NH₂, C₁-C₃ perfluoroalkyl, -OH, -O-(C₁-C₆ alkyl), and -(C₁-C₆ alkyl)-OH.

28. The combination of claim 22, wherein the ROCK2 inhibitor is

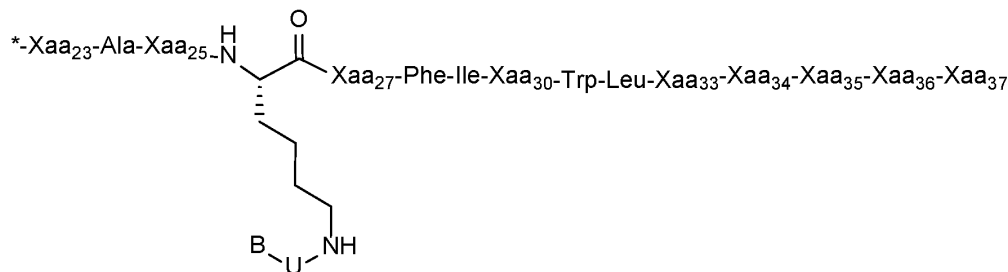


or a pharmaceutically acceptable salt thereof.

29. The combination of claim 22, wherein the ROCK2 inhibitor is selected from belumosudil (KD025), Zelasudil, Y-27632, Fasudil, GSK429286A, RKI-1447, Azaindole 1 (TC-S 7001), Hydroxyfasudil, GSK269962A, Ripasudil, AT13148, RX007, and derivatives, isomers, hydrates, or pharmaceutically acceptable salts thereof.

30. The combination of any one of claims 22 to 29, wherein the GLP-1 agonist includes a structure of Formula (M-I),

Xaa₇-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Xaa₁₆-Ser-Xaa₁₈-Xaa₁₉-Xaa₂₀-Glu-Xaa₂₂-*



(M-I),

wherein:

Xaa₇ is L-histidine, imidazopropionyl, α -hydroxy-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β -hydroxy-histidine, homohistidine, N ^{α} -acetyl-histidine, N ^{α} -formyl-histidine, α -fluoromethyl-histidine, α -methyl-histidine, 3-pyridylalanine, 2-pyridylalanine or 4-pyridylalanine

Xaa₈ is Ala, Gly, Val, Leu, Ile, Thr, Ser, Lys, Aib (α -aminoisobutyric acid), (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa₁₆ is Val or Leu;

Xaa₁₈ is Ser, Lys or Arg;

Xaa₁₉ is Tyr or Gln;

Xaa₂₀ is Leu or Met;

Xaa₂₂ is Gly, Glu or Aib (α -aminoisobutyric acid);

Xaa₂₃ is Gln, Glu, Lys or Arg;

Xaa₂₅ is Ala or Val;

Xaa₂₇ is Glu or Leu;

Xaa₃₀ is Ala, Glu or Arg;

Xaa₃₃ is Val or Lys;

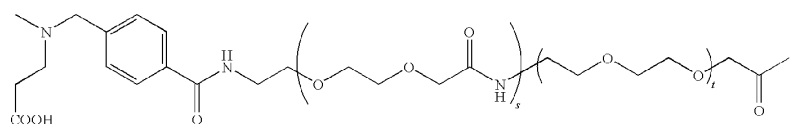
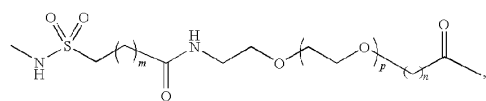
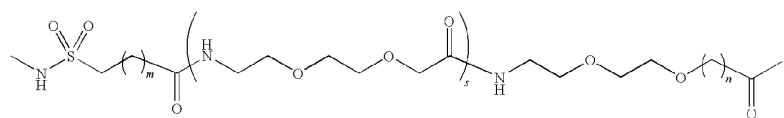
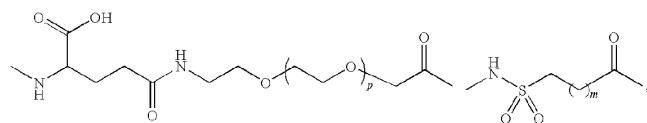
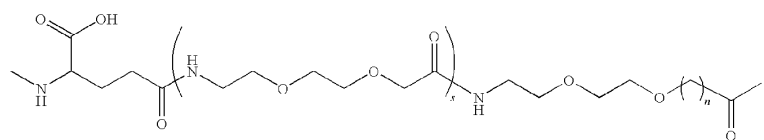
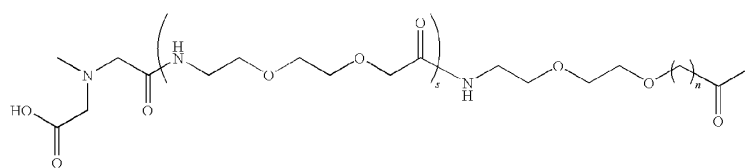
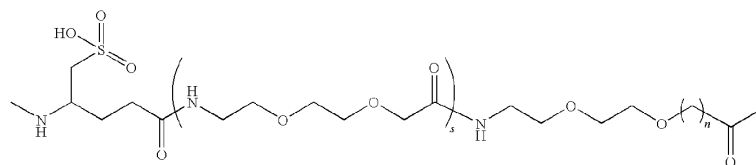
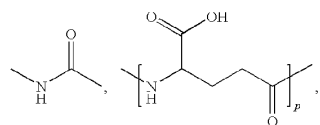
Xaa₃₄ is Lys, Glu, Asn or Arg;

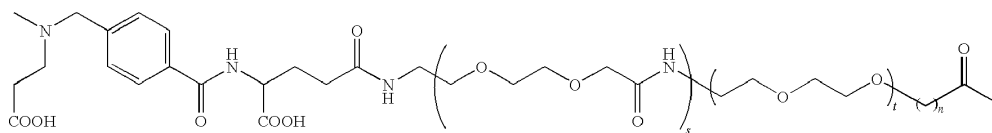
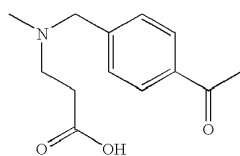
Xaa₃₅ is Gly or Aib (α -aminoisobutyric acid);

Xaa₃₆ is Arg, Gly or Lys, or is absent;

Xaa₃₇ is Gly, Ala, Glu, Pro, Lys, or is absent; and

and B and U together is the acylated moiety, where U is selected from





m is 0, 1, 2, 3, 4, 5, or 6,

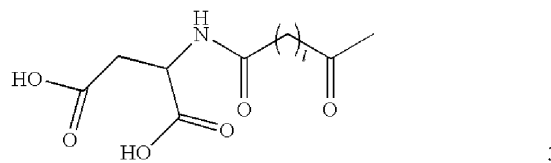
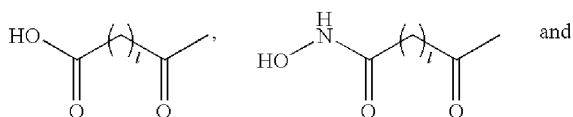
n is 1, 2 or 3

s is 0, 1, 2, or 3,

t is 0, 1, 2, 3, or 4

p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

and where B is an acidic group selected from



where l is 12, 13, 14, 15, 16, 17, 18, 19 or 20,

or a pharmaceutically acceptable salt thereof.

31. The combination of claim 30, wherein:

Xaa₇ is His or desamino-histidine;

Xaa₈ is Ala, Gly, Val, Leu, Ile, Lys or Aib;

Xaa₁₆ is Val; Xaa₁₈ is Ser; Xaa₁₉ is Tyr;

Xaa₂₀ is Leu;

Xaa₂₂ is Gly, Glu or Aib;

Xaa₂₃ is Gln or Glu;

Xaa₂₅ is Ala; Xaa₂₇ is Glu;

Xaa₃₀ is Ala or Glu;

Xaa₃₃ is Val;

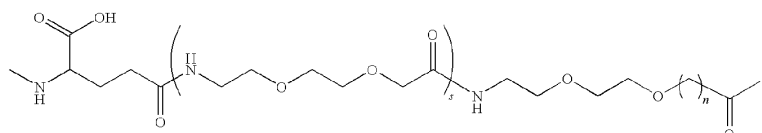
Xaa₃₄ is Lys or Arg;

Xaa₃₅ is Gly or Aib;

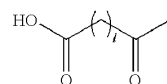
Xaa₃₆ is Arg or Lys; and/or

Xaa₃₇ is Gly, amide or is absent.

32. The method of claim 30 or 31, wherein U is



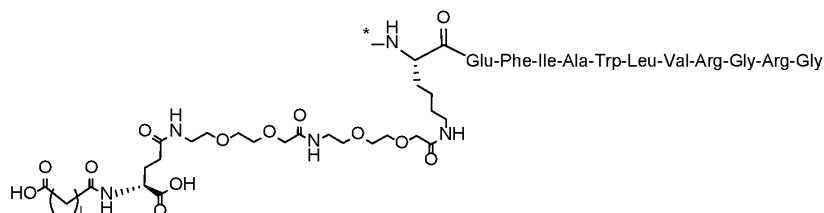
33. The combination of any one of claims 30 to 32, wherein B is



14, 16, or

34. The combination of any one of claims 30 to 33, wherein the GLP-1 agonist has the structure of Formula (M-III):

His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala*

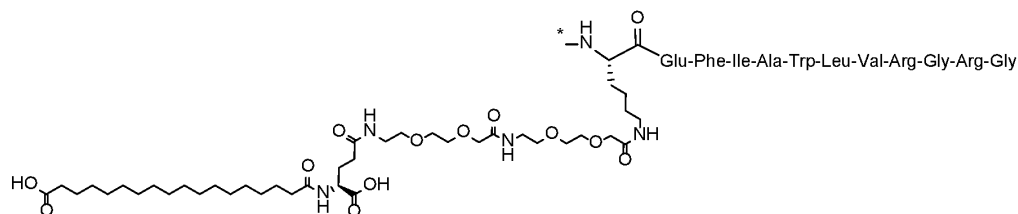


(M-III),

l is 12, 14, or 16.

35. The combination of claims 22, wherein the GLP-1 agonist is

His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala*



(semaglutide).

36. The combination of 22, wherein the GLP-1 agonist is selected from semaglutide, exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide, tirzepatide, lotiglipron, retatrutide, taspoglutide, orforglipron or danuglipron.
37. The combination of any one of claims 22-36, wherein the ROCK2 inhibitor and the GLP-1 agonist are administered simultaneously.
38. The combination of any one of claims 22-36, wherein the ROCK2 inhibitor and the GLP-1 agonist are administered subsequently.
39. The combination of any one of claims 22-38, wherein the ROCK2 inhibitor is administered orally and GLP-1 agonist is subcutaneously.
40. A kit for weight loss comprising a combination of any one of claims 22-39.
41. A kit for treating type 2 diabetes in a subject comprising a combination of any one of claims 22-39.
42. A kit for treating obesity comprising a combination of any one of claims 22-39.