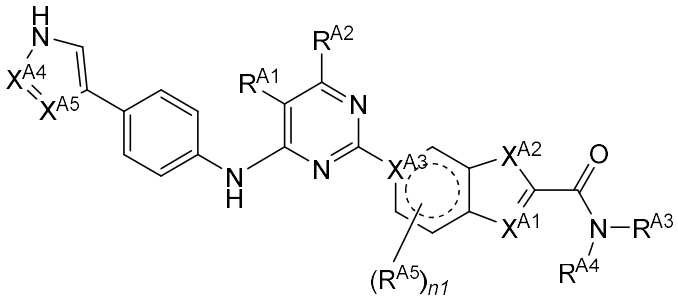
CLAIMS

1. Use of an inhibitor of Rho associated coiled-coil containing protein kinase 2 (ROCK2) in the manufacture of a medicament for reducing or preventing muscle loss in a patient that is undergoing therapy for obesity, weight loss, and/or type 2 diabetes, wherein the therapy for obesity, weight loss, and/or type 2 diabetes comprises one or more of dietary calorie restriction, bariatric surgery, or administration of a pharmaceutical agent selected from an glucagon-like peptide (GLP-1) agonist, a sodium-glucose transporter 2 (SGLT2) inhibitor, a lipase inhibitor; melanocortin-4 receptor agonist, naltrexone-bupropion, phentermine; phentermine-topiramate, metformin, diethylpropion (amfepramone), and combinations thereof .

2. The use of claim 1, wherein the therapy for obesity, weight loss, and/or type 2 diabetes comprises administration of a GLP-1 agonist.

3. The use of claim 1 or claim 2, wherein the ROCK2 inhibitor has a structure of Formula (A-I):



(A-I),

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)$_{x1}$-C(=O)R^{A11}, -O-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, -C(=O)- R^{A11}, -C(=O)OR^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$, -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, and -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-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)$_{x1}$-C(=O)R^{A11}, -O-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$, -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, and -NR^{A11}-(C_1-C_6 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, ox1o, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -$NR^{A11}R^{A12}$, -O-(C_1-C_6 alkyl)-$NR^{A11}R^{A12}$, C_1-C_3 perfluoro alkyl, -NR^{A11}-(C_1-C_6 alkyl)$NR^{A11}R^{A12}$, and -NR^{A11}-(C_1-C_6 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, $C_{6\text{-}12}$ aralkyl, -(C_1-C_6 alkyl)-OR^{A11}, -(C_1-C_6 alkyl)-$NR^{A11}R^{A12}$, -(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, and -(C_1-C_6 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, 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}, ox1o, -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)$_{x1}$-C(=O)R^{A11}, -O-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, -C(=O)-R^{A11}, -

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

the dotted lines represent optional double bonds;

each R^{A5} is independently selected from the group consisting of H, $C_1\text{-}C_6$ alkyl, $C_2\text{-}C_6$ alkenyl, $C_2\text{-}C_6$ alkynyl, $C_3\text{-}C_7$ cycloalkyl, halo, -CN, $C_1\text{-}C_3$ perfluoro alkyl, ox1o, $-OR^{A11}$, $-O\text{-}(C_1\text{-}C_6\text{ alkyl})\text{-}OR^{A11}$, $-(C_1\text{-}C_6\text{ alkyl})\text{-}OR^{A11}$, $-NR^{A11}R^{A12}$, $-O\text{-}(C_1\text{-}C_6\text{ alkyl})\text{-}NR^{A11}R^{A12}$, $-(C_1\text{-}C_6\text{ alkyl})\text{-}NR^{A11}R^{A12}$, $-NR^{A11}\text{-}(C_1\text{-}C_6\text{ alkyl})\text{-}NR^{A11}R^{A12}$, $-NR^{A11}\text{-}(C_1\text{-}C_6\text{ alkyl})\text{-}OR^{A11}$, $-(C_1\text{-}C_6\text{ alkyl})_{x1}\text{-}C(=O)R^{A11}$, $-O\text{-}(C_1\text{-}C_6\text{ alkyl})_{x1}\text{-}C(=O)R^{A11}$, $-(C_1\text{-}C_6\text{ alkyl})_{x1}\text{-}C(=O)OR^{A11}$, $-C(=O)\text{-}R^{A11}$, $-C(=O)OR^{A11}$, $-(C_1\text{-}C_6\text{ alkyl})_{x1}\text{-}C(=O)NR^{A11}R^{A12}$, $-NR^{A11}\text{-}(C_1\text{-}C_6\text{ alkyl})_{x1}\text{-}C(=O)R^{A11}$, and $-NR^{A11}\text{-}(C_1\text{-}C_6\text{ alkyl})_{x1}\text{-}C(=O)OR^{A11}$;

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, $C_1\text{-}C_6$ alkyl, $C_2\text{-}C_6$ alkenyl, $C_2\text{-}C_6$ alkynyl, $C_3\text{-}C_7$ cycloalkyl, halo, -CN, $C_1\text{-}C_3$ perfluoro alkyl, $-OR^{A11}$, $-O\text{-}(C_1\text{-}C_6\text{ alkyl})\text{-}OR^{A11}$, $-(C_1\text{-}C_6\text{ alkyl})\text{-}OR^{A11}$, $-NR^{A11}R^{A12}$, $-O\text{-}(C_1\text{-}C_6\text{ alkyl})\text{-}NR^{A11}R^{A12}$, $-(C_1\text{-}C_6\text{ alkyl})\text{-}NR^{A11}R^{A12}$, $-NR^{A11}\text{-}(C_1\text{-}C_6\text{ alkyl})\text{-}NR^{A11}R^{A12}$, $-NR^{A11}\text{-}(C_1\text{-}C_6\text{ alkyl})\text{-}OR^{A11}$, $-(C_1\text{-}C_6\text{ alkyl})_{x1}\text{-}C(=O)R^{A11}$, $-O\text{-}(C_1\text{-}C_6\text{ alkyl})_{x1}\text{-}C(=O)R^{A11}$, $-(C_1\text{-}C_6\text{ alkyl})_{x1}\text{-}C(=O)OR^{A11}$, $-C(=O)\text{-}R^{A11}$, $-C(=O)OR^{A11}$, $-(C_1\text{-}C_6\text{ alkyl})_{x1}\text{-}C(=O)NR^{A11}R^{A12}$, $-NR^{A11}\text{-}(C_1\text{-}C_6\text{ alkyl})_{x1}\text{-}C(=O)R^{A11}$, and $-NR^{A11}\text{-}(C_1\text{-}C_6\text{ alkyl})_{x1}\text{-}C(=O)OR^{A11}$;

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

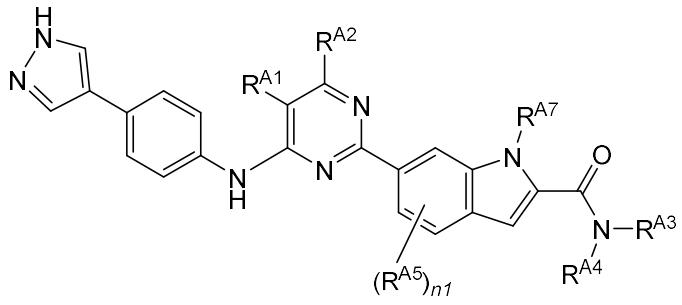
each x1 is independently selected from 0 and 1; and

each R^{A11} and R^{A12} are independently selected from the group consisting of H and $C_1\text{-}C_6$ 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, 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 alkyl), and -(C_1-C_6 alkyl)-OH.

4. The use of claim 3, wherein the ROCK2 inhibitor has a structure of Formula (A-II),



(A-II),

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)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$, -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, and -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-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)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$, -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, and -NR^{A11}-(C_1-C_6 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 alkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -$NR^{A11}R^{A12}$, -O-(C_1-C_6 alkyl)-$NR^{A11}R^{A12}$, C_1-C_3 perfluoro alkyl, -NR^{A11}-(C_1-C_6 alkyl)$NR^{A11}R^{A12}$, and -NR^{A11}-(C_1-C_6 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, $C_{6\text{-}12}$ aralkyl, -(C_1-C_6 alkyl)-OR^{A11}, -(C_1-C_6 alkyl)-$NR^{A11}R^{A12}$, -(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, and -(C_1-C_6 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 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)$_{x1}$-C(=O)R^{A11}, -O-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$, -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, and -NR^{A11}-(C_1-C_6 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 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)$_{x1}$-C(=O)R^{A11}, -O-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$, -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, and -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11};

n1 is 0 to 3;

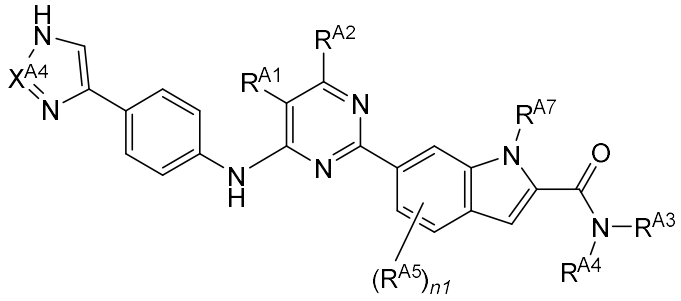
R^{A7} is selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, -(C_1-C_6 alkyl)-OR^{A11}, -(C_1-C_6 alkyl)-$NR^{A11}R^{A12}$, -(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, and -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$;

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 alkyl), and -(C_1-C_6 alkyl)-OH.

5. The use of claim 3, wherein the ROCK2 inhibitor has a structure of Formula (A-III),



(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)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$, -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, and -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-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)$_{x1}$-C(=O)R^{A11}, -O-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$, -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, and -NR^{A11}-(C_1-C_6 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 alkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -$NR^{A11}R^{A12}$, -O-(C_1-C_6 alkyl)-$NR^{A11}R^{A12}$, C_1-C_3 perfluoro alkyl, -NR^{A11}-(C_1-C_6 alkyl)$NR^{A11}R^{A12}$, and -NR^{A11}-(C_1-C_6 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, $C_{6\text{-}12}$ aralkyl, -(C_1-C_6 alkyl)-OR^{A11}, -(C_1-C_6 alkyl)-$NR^{A11}R^{A12}$, -(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, and -(C_1-C_6 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 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)$_{x1}$-C(=O)R^{A11}, -O-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$, -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, and -NR^{A11}-(C_1-C_6 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 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)$_{x1}$-C(=O)R^{A11}, -O-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$, -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, and -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11};

n1 is 0 to 3;

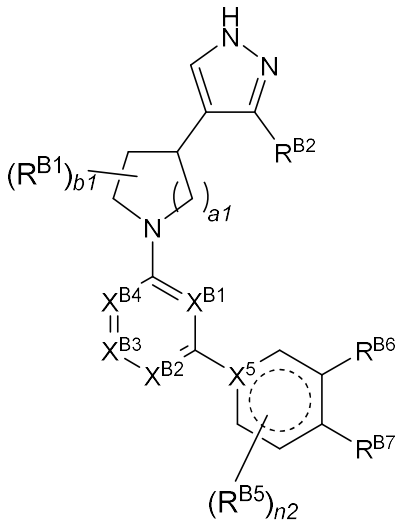
R^{A7} is selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, -(C_1-C_6 alkyl)-OR^{A11}, -(C_1-C_6 alkyl)-$NR^{A11}R^{A12}$, -(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, and -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$;

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 alkyl), and -(C_1-C_6 alkyl)-OH.

6. The use of claim 1 or claim 2, wherein the ROCK2 inhibitor has a structure of Formula (B-I):



(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, 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)$_{x2}$-C(=O)R^{B11}, -O-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)OR^{B11}, -C(=O)- R^{B11}, -C(=O)OR^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, and -NR^{B11}-(C_1-C_6 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 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)$_{x2}$-C(=O)R^{B11}, -O-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)OR^{B11}, -C(=O)- R^{B11}, -C(=O)OR^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, and -NR^{B11}-(C_1-C_6 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 C_1-C_6 alkyl, halo, -CN, -OH, oxo, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -$NR^{B11}R^{B12}$, -O-(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, C_1-C_3 perfluoro alkyl, -NR^{B11}-(C_1-C_6 alkyl)$NR^{B11}R^{B12}$, and -NR^{B11}-(C_1-C_6 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 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)$_{x2}$-C(=O)R^{B11}, -O-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)OR^{B11}, -C(=O)- R^{B11}, -C(=O)OR^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, and -NR^{B11}-(C_1-C_6 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 alkyl)-OR^{B11}, -(C_1-C_6 alkyl)-OR^{B11}, -$NR^{B11}R^{B12}$, -O-(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, -O-(C_1-C_6 alkyl)-C(=O)$NR^{B11}R^{B12}$, -(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, -(C_1-C_6 alkyl)-C(=O)$NR^{B11}R^{B12}$, -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)$_{x2}$-C(=O)R^{B11}, -O-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)OR^{B11}, -C(=O)- R^{B11}, -C(=O)OR^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, and -NR^{B11}-(C_1-C_6 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 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_5-C_{10} aryl, C_5-C_{10} heteroaryl, 3- to 10-membered heterocyclyl, -C_1-C_6 alkyl-(C_3-C_7 cycloalkyl), -C_1-C_6 alkyl-(C_5-C_{10} aryl), -C_1-C_6 alkyl-(C_5-C_{10} heteroaryl), -C_1-C_6 alkyl-(3- to 10-membered heterocyclyl), halo, -CN, -OH, oxo, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -$NR^{B11}R^{B12}$, -O-(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, C_1-C_3 perfluoro alkyl, -NR^{B11}-(C_1-C_6 alkyl)$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 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 C_1-C_3 alkyl, C_1-C_3 perfluoroalkyl, oxo, halo, -CN, -OH, and NH_2;

R^{B8} and R^{B9} 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 alkyl)-OR^{B11}, -(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, -(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)OR^{B11}, and -(C_1-C_6 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 C_1-C_3 alkyl, C_1-C_3 perfluoroalkyl, oxo, halo, -CN, -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, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, -CN, C_1-C_6 fluoroalkyl, C_1-C_3

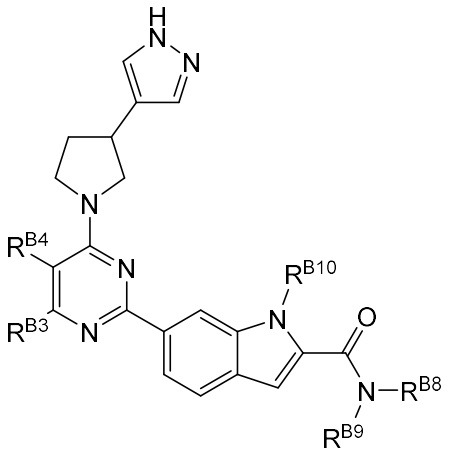
perfluoro alkyl, -OR^{B11}, oxo, -O-(C_1-C_6 alkyl)-OR^{B11}, -(C_1-C_6 alkyl)-OR^{B11}, -$NR^{B11}R^{B12}$, -O-(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, -(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 alkyl)-OR^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11},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

7. The use of claim 6, wherein the ROCK2 inhibitor has a structure of the formula (B-V):



(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 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)$_{x2}$-C(=O)R^{B11}, -O-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)OR^{B11}, -C(=O)- R^{B11}, -C(=O)OR^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, and -NR^{B11}-(C_1-C_6 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 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)$_{x2}$-C(=O)R^{B11}, -O-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)OR^{B11}, -C(=O)- R^{B11}, -C(=O)OR^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, and -NR^{B11}-(C_1-C_6 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 C_1-C_6 alkyl, halo, -CN, -OH, oxo, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -$NR^{B11}R^{B12}$, -O-(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, C_1-C_3 perfluoro alkyl, -NR^{B11}-(C_1-C_6 alkyl)$NR^{B11}R^{B12}$, and -NR^{B11}-(C_1-C_6 alkyl)-OR^{B11};

R^{B8} and R^{B9} 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, $C_{6\text{-}12}$ aralkyl, -(C_1-C_6 alkyl)-OR^{B11}, -(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, -(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)OR^{B11}, and -(C_1-C_6 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 C_1-C_3 alkyl, C_1-C_3 perfluoroalkyl, oxo, halo, -CN, -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, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, -CN, C_1-C_6 fluoroalkyl, C_1-C_3 perfluoro alkyl, -OR^{B11}, oxo, -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)$_{x2}$-C(=O)R^{B11}, -O-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)OR^{B11}, -C(=O)- R^{B11}, -C(=O)OR^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, and -NR^{B11}-(C_1-C_6 alkyl)$_{x2}$-C(=O)OR^{B11};

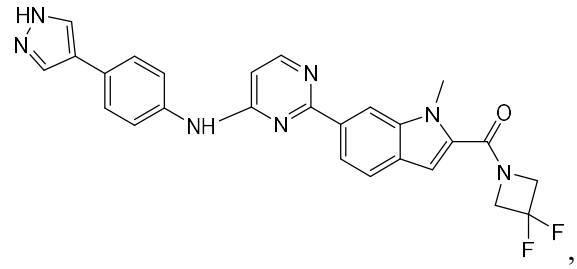
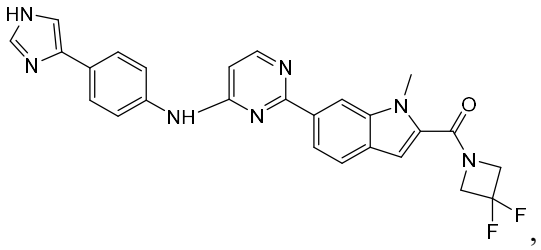
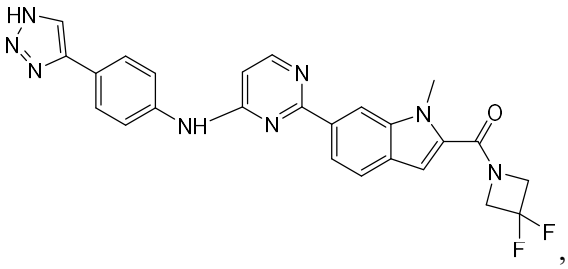
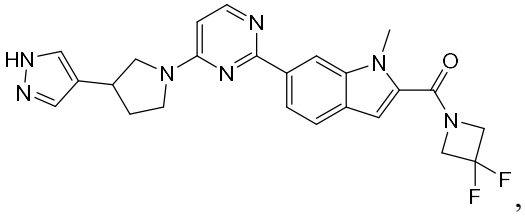
R^{B10} is selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_5-C_{10} aryl, C_5-C_{10} heteroaryl, 3- to 10-membered heterocyclyl, -C_1-C_6 alkyl-(C_3-C_7 cycloalkyl), -C_1-C_6 alkyl-(C_5-C_{10} aryl), -C_1-C_6 alkyl-(C_5-C_{10} heteroaryl), -C_1-C_6 alkyl-(3- to 10-membered heterocyclyl), -(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, -(C_1-C_6 alkyl)$NR^{B11}R^{B12}$, -(C_1-C_6 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 C_1-C_3 alkyl, C_1-C_3 perfluoroalkyl, oxo, halo, -CN, -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 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 alkyl), and -(C_1-C_6 alkyl)-OH.

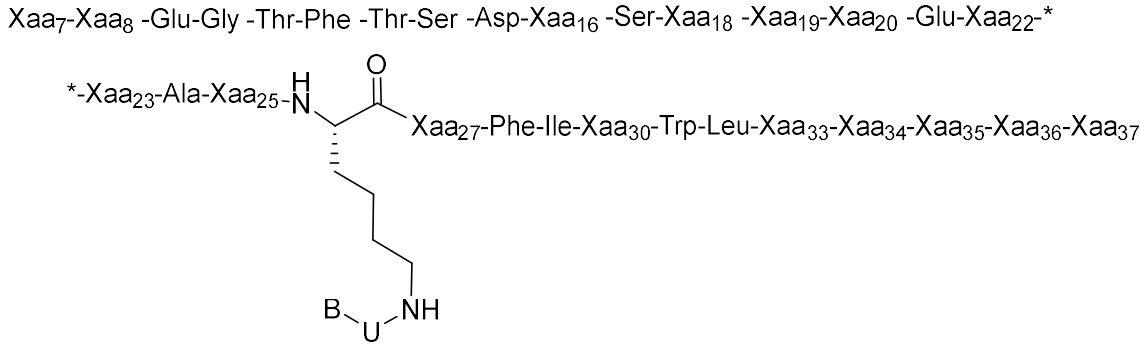
8. The use of claim 1 or claim 2, wherein the ROCK2 inhibitor is


,

,

, or

,

or a pharmaceutically acceptable salt thereof.

9. The use of claim 1 or claim 2, wherein the ROCK2 inhibitor is selected from belumosudil (KD025), zelasudil, RX007, and derivatives, isomers, hydrates, or pharmaceutically acceptable salts thereof.

10. The use of any one of claims 2 to 9, wherein the GLP-1 agonist includes a structure of Formula (M-I):



(M-I),

wherein:

Xaa_7 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

Xaa_8 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;

Xaa_{16} is Val or Leu;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{19} is Tyr or Gln;

Xaa_{20} is Leu or Met;

Xaa_{22} is Gly, Glu or Aib (α-aminoisobutyric acid);

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{25} is Ala or Val;

Xaa_{27} is Glu or Leu;

Xaa_{30} is Ala, Glu or Arg;

Xaa_{33} is Val or Lys;

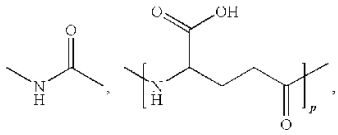
Xaa_{34} is Lys, Glu, Asn or Arg;

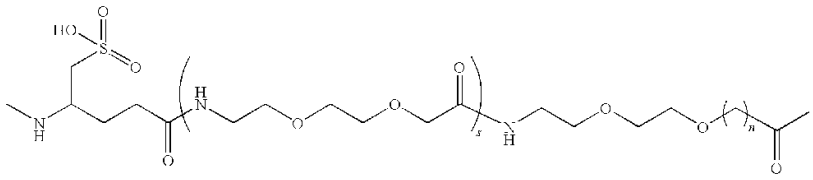
Xaa_{35} is Gly or Aib (α-aminoisobutyric acid);

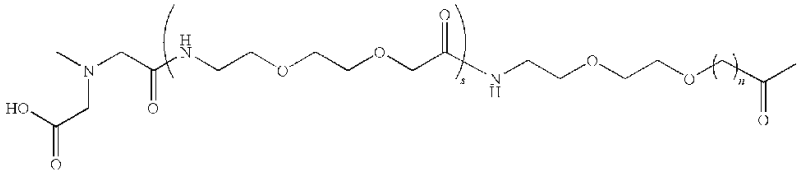
Xaa_{36} is Arg, Gly or Lys, or is absent;

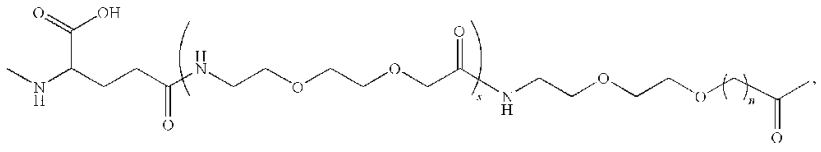
Xaa_{37} is Gly, Ala, Glu, Pro, Lys, or is absent; and

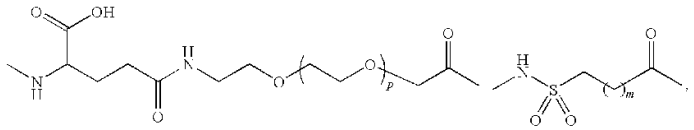
and B and U together is the acylated moiety, where U is selected from

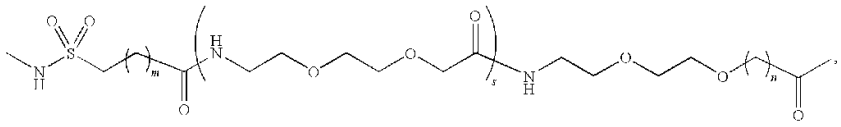


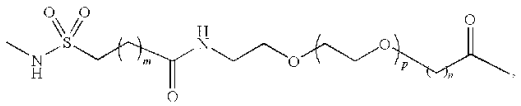


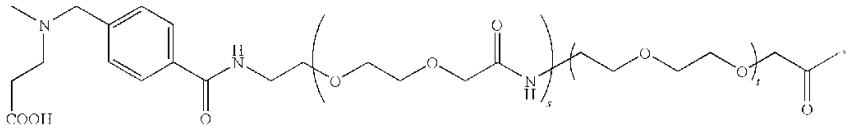


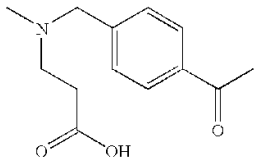


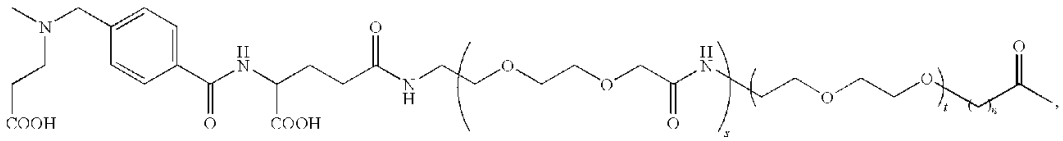












m is 0, 1, 2, 3, 4, 5, or 6,

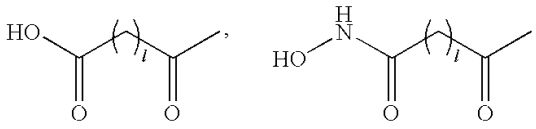
n is 1, 2 or 3

s is 0, 1, 2, or 3,

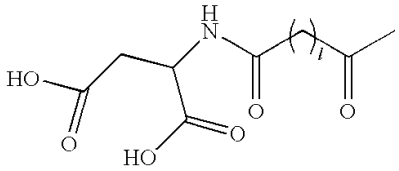
t is 0, 1, 2, 3, or 4

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



,

and


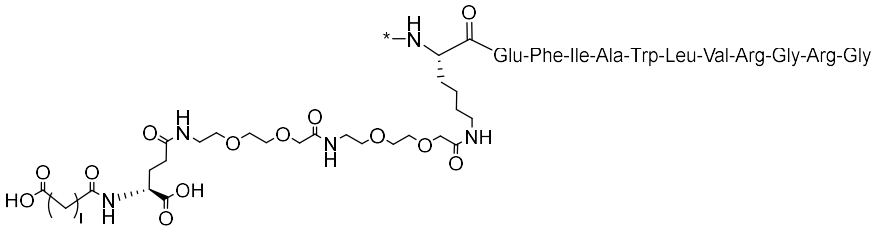
;

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

or a pharmaceutically acceptable salt thereof.

11. The use of claim 10, 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.

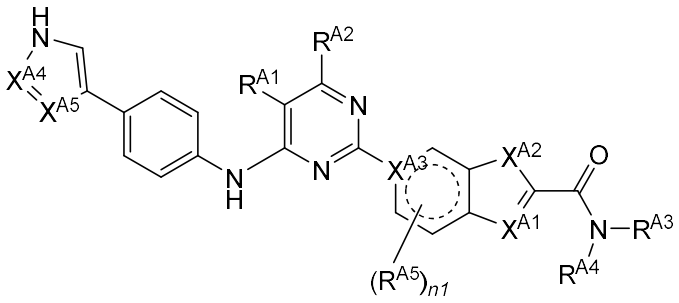
12. The use of claim 2, wherein the GLP-1 agonist is selected from semaglutide, exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide, tirzepatide, lotiglipron, retatrutide, taspoglutide, orforglipron or danuglipron.

13. 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.

14. The combination of claim 13, wherein the ROCK2 inhibitor has a structure of Formula (A-I):



(A-I),

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)$_{x1}$-C(=O)R^{A11}, -O-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, -C(=O)- R^{A11}, -C(=O)OR^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$, -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, and -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-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)$_{x1}$-C(=O)R^{A11}, -O-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$, -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, and -NR^{A11}-(C_1-C_6 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, ox1o, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -$NR^{A11}R^{A12}$, -O-(C_1-C_6 alkyl)-$NR^{A11}R^{A12}$, C_1-C_3 perfluoro alkyl, -NR^{A11}-(C_1-C_6 alkyl)$NR^{A11}R^{A12}$, and -NR^{A11}-(C_1-C_6 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 alkyl)-OR^{A11}, -(C_1-C_6 alkyl)-$NR^{A11}R^{A12}$, -(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, and -(C_1-C_6 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, 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}, ox1o, -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)$_{x1}$-C(=O)R^{A11}, -O-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$, -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, and -NR^{A11}-(C_1-C_6 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, ox1o, -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)$_{x1}$-C(=O)R^{A11}, -O-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, -C(=O)- R^{A11}, -C(=O)OR^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$, -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, and -NR^{A11}-(C_1-C_6 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 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)$_{x1}$-C(=O)R^{A11}, -O-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, -C(=O)- R^{A11}, -C(=O)OR^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$, -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, and -NR^{A11}-(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11};

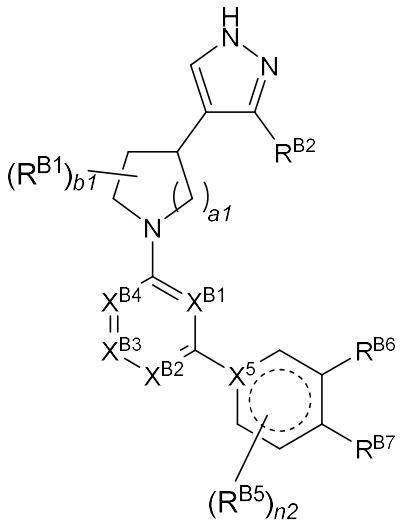
each R^{A7} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, -(C_1-C_6 alkyl)-OR^{A11}, -(C_1-C_6 alkyl)-$NR^{A11}R^{A12}$, -(C_1-C_6 alkyl)$_{x1}$-C(=O)R^{A11}, -(C_1-C_6 alkyl)$_{x1}$-C(=O)OR^{A11}, and -(C_1-C_6 alkyl)$_{x1}$-C(=O)$NR^{A11}R^{A12}$;

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 alkyl), and -(C_1-C_6 alkyl)-OH.

15. The combination of claim 13, wherein the ROCK2 inhibitor has a structure of Formula (B-I),



(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, 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)$_{x2}$-C(=O)R^{B11}, -O-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)OR^{B11}, -C(=O)- R^{B11}, -C(=O)OR^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, and -NR^{B11}-(C_1-C_6 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 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)$_{x2}$-C(=O)R^{B11}, -O-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)OR^{B11}, -C(=O)- R^{B11}, -C(=O)OR^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, and -NR^{B11}-(C_1-C_6 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 C_1-C_6 alkyl, halo, -CN, -OH, oxo, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -$NR^{B11}R^{B12}$, -O-(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, C_1-C_3 perfluoro alkyl, -NR^{B11}-(C_1-C_6 alkyl)$NR^{B11}R^{B12}$, and -NR^{B11}-(C_1-C_6 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 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)$_{x2}$-C(=O)R^{B11}, -O-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)OR^{B11}, -C(=O)- R^{B11}, -C(=O)OR^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, and -NR^{B11}-(C_1-C_6 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 alkyl)-OR^{B11}, -(C_1-C_6 alkyl)-OR^{B11}, -$NR^{B11}R^{B12}$, -O-(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, -O-(C_1-C_6 alkyl)-C(=O)$NR^{B11}R^{B12}$, -(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, -(C_1-C_6 alkyl)-C(=O)$NR^{B11}R^{B12}$, -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)$_{x2}$-C(=O)R^{B11}, -O-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)OR^{B11}, -C(=O)- R^{B11}, -C(=O)OR^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, and -NR^{B11}-(C_1-C_6 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 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_5-C_{10} aryl, C_5-C_{10} heteroaryl, 3- to 10-membered heterocyclyl, -C_1-C_6 alkyl-(C_3-C_7 cycloalkyl), -C_1-C_6 alkyl-(C_5-C_{10} aryl), -C_1-C_6 alkyl-(C_5-C_{10} heteroaryl), -C_1-C_6 alkyl-(3- to 10-membered heterocyclyl), halo, -CN, -OH, oxo, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl)-OH, -O-(C_1-C_6 alkyl)-O-(C_1-C_6 alkyl), -$NR^{B11}R^{B12}$, -O-(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, C_1-C_3 perfluoro alkyl, -NR^{B11}-(C_1-C_6 alkyl)$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 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 C_1-C_3 alkyl, C_1-C_3 perfluoroalkyl, oxo, halo, -CN, -OH, and NH_2;

R^{B8} and R^{B9} 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 alkyl)-OR^{B11}, -(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, -(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)OR^{B11}, and -(C_1-C_6 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 C_1-C_3 alkyl, C_1-C_3 perfluoroalkyl, oxo, halo, -CN, -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, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, -CN, C_1-C_6 fluoroalkyl, C_1-C_3

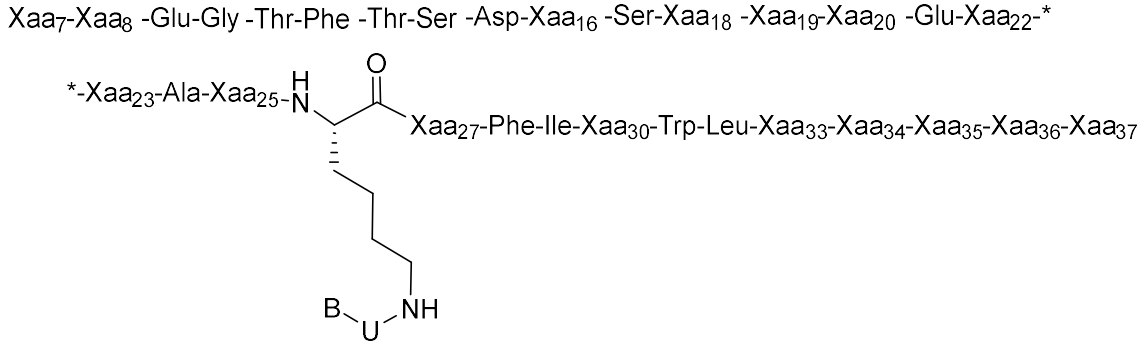
perfluoro alkyl, -OR^{B11}, oxo, -O-(C_1-C_6 alkyl)-OR^{B11}, -(C_1-C_6 alkyl)-OR^{B11}, -$NR^{B11}R^{B12}$, -O-(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, -(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 alkyl)-$NR^{B11}R^{B12}$, -NR^{B11}-(C_1-C_6 alkyl)-OR^{B11}, -(C_1-C_6 alkyl)$_{x2}$-C(=O)R^{B11},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

16. The combination of claim 13, wherein the GLP-1 agonist includes a structure of Formula (M-I),



(M-I),

wherein:

Xaa_7 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

Xaa_8 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;

Xaa_{16} is Val or Leu;

Xaa_{18} is Ser, Lys or Arg;

Xaa_{19} is Tyr or Gln;

Xaa_{20} is Leu or Met;

Xaa_{22} is Gly, Glu or Aib (α-aminoisobutyric acid);

Xaa_{23} is Gln, Glu, Lys or Arg;

Xaa_{25} is Ala or Val;

Xaa_{27} is Glu or Leu;

Xaa_{30} is Ala, Glu or Arg;

Xaa_{33} is Val or Lys;

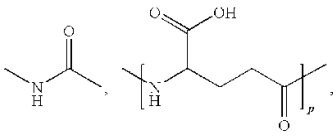
Xaa_{34} is Lys, Glu, Asn or Arg;

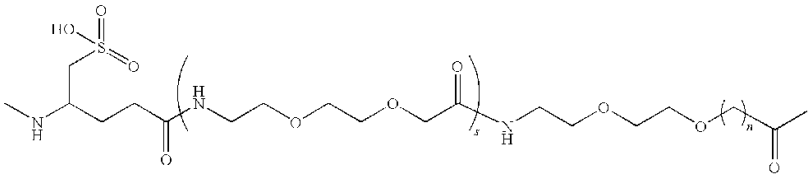
Xaa_{35} is Gly or Aib (α-aminoisobutyric acid);

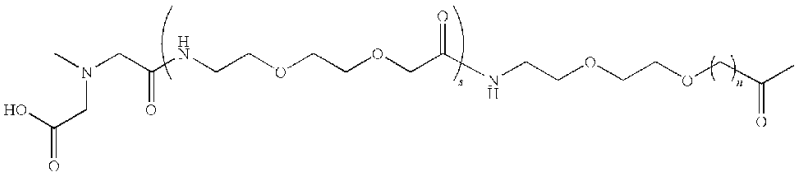
Xaa_{36} is Arg, Gly or Lys, or is absent;

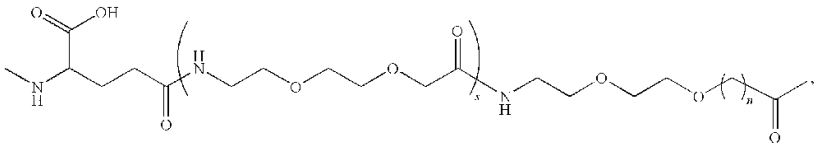
Xaa_{37} is Gly, Ala, Glu, Pro, Lys, or is absent; and

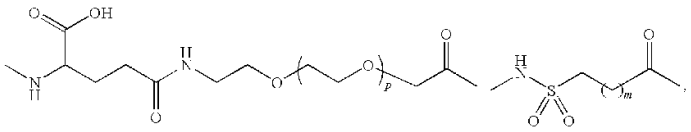
and B and U together is the acylated moiety, where U is selected from

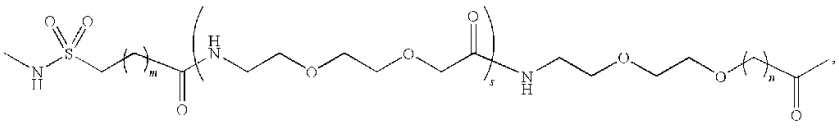


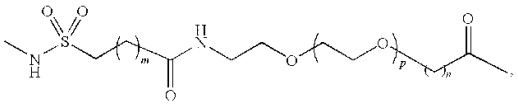


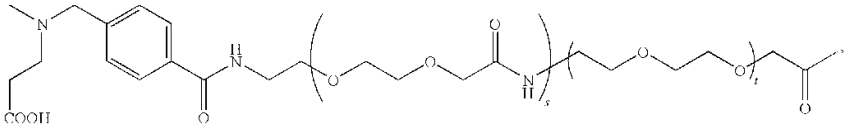


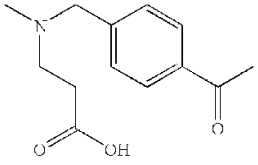


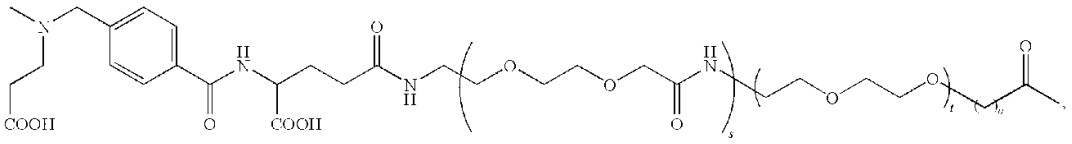












m is 0, 1, 2, 3, 4, 5, or 6,

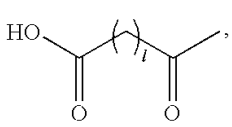
n is 1, 2 or 3

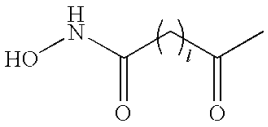
s is 0, 1, 2, or 3,

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

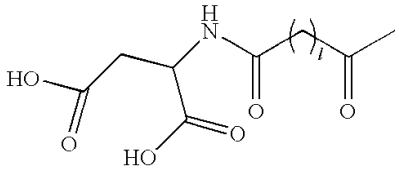
p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23;

and where B is an acidic group selected from



,


and



;

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

or a pharmaceutically acceptable salt thereof.