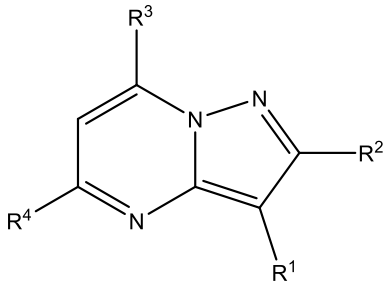
CLAIMS

1. A compound of Formula I:



Formula I

wherein,

R^1 and R^2 are each independently selected from optionally substituted C_{6-10}aryl and optionally substituted C_{5-10}heteroaryl;

R^3 is selected from optionally substituted C_{1-12}alkyl, optionally substituted C_{1-12}alkoxy, optionally substituted alkylamino or dialkylamino, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{3-10}heterocycloalkyl, optionally substituted C_{6-10}aryl, and optionally substituted C_{5-10}heteroaryl, optionally substituted -X^1-C_{3-10}cycloalkyl, optionally substituted -X^1-C_{3-10}heterocycloalkyl, optionally substituted -X^1-C_{6-10}aryl, and optionally substituted -X^1-C_{5-10}heteroaryl;

R^4 is selected from NH_2, optionally substituted C_{1-12}alkoxy, optionally substituted alkylamino or dialkylamino, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{3-10}heterocycloalkyl, optionally substituted -X^2-C_{3-10}cycloalkyl, and optionally substituted -X^2-C_{3-10}heterocycloalkyl;

X^1 is selected from O and NR^5, wherein R^5 is H or an optionally substituted C_{1-6}alkyl; and

X^2 is selected from O and NR^6, wherein R^6 is H or an optionally substituted C_{1-6}alkyl;

or an isomer and/or a tautomer thereof, or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein R^4 is NH_2.

3. The compound of claim 1, wherein R^4 is selected from optionally substituted C_{1-12}alkoxy, optionally substituted alkylamino or dialkylamino, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{3-10}heterocycloalkyl, optionally substituted -X^2-C_{3-10}cycloalkyl, and optionally substituted -X^2-C_{3-10}heterocycloalkyl.

4. The compound of claim 3, wherein R^4 is an optionally substituted C_{1-12}alkoxy, preferably optionally substituted C_{1-6}alkoxy, more preferably optionally substituted C_{1-4}alkoxy.

5. The compound of claim 3, wherein R^4 is an optionally substituted C_{1-12}alkylamino or C_{1-12}dialkylamino, preferably optionally substituted C_{1-6}alkylamino or C_{1-6}dialkylamino, more preferably optionally substituted C_{1-4}alkylamino or C_{1-4}dialkylamino.

6. The compound of claim 4 or 5, wherein said alkyl or alkoxy is substituted with at least one group selected from OH, CO_2H, CO_2NH_2, CO_2NHC_{1-6}alkyl, $CO_2N(C_{1-6}alkyl)_2$, $P(O)(C_{1-6}alkyl)_2$, $NHC(O)C_{1-6}$alkyl, $N(C_{1-6}alkyl)C(O)C_{1-6}$alkyl, preferably OH.

7. The compound of claim 3, wherein R^4 is an optionally substituted C_{3-10}cycloalkyl or optionally substituted C_{3-10}heterocycloalkyl, preferably optionally substituted C_{3-6}cycloalkyl or optionally substituted C_{3-6}heterocycloalkyl, more preferably optionally substituted C_{4-5}cycloalkyl or optionally substituted C_{4-5}heterocycloalkyl.

8. The compound of claim 7, wherein said heterocycloalkyl is linked to the pyrazolopyrimidine core through a nitrogen atom from the heterocycloalkyl.

9. The compound of claim 7 or 8, wherein said heterocycloalkyl is selected from pyrrolidinyl, imidazolidinyl, piperidinyl, and piperazinyl groups.

10. The compound of claim 3, wherein R^4 is an optionally substituted $-X^2-C_{3-10}$cycloalkyl or optionally substituted $-X^2-C_{3-10}$heterocycloalkyl, preferably optionally substituted $-X^2-C_{3-6}$cycloalkyl or optionally substituted $-X^2-C_{3-6}$heterocycloalkyl, more preferably optionally substituted $-X^2-C_{4-5}$cycloalkyl or optionally substituted $-X^2-C_{4-5}$heterocycloalkyl.

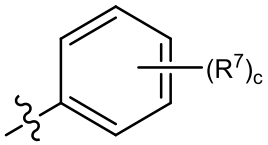
11. The compound of any one of claims 3 to 10, wherein X^2 is NR^6, preferably wherein R^6 is H or C_{1-3}alkyl, preferably methyl.

12. The compound of any one of claims 7 to 11, wherein said cycloalkyl or heteocycloalkyl is substituted with at least one group selected from OH, CO_2H, CO_2NH_2, CO_2NHC_{1-6}alkyl, $CO_2N(C_{1-6}alkyl)_2$, $P(O)(C_{1-6}alkyl)_2$, $NHC(O)C_{1-6}$alkyl, $N(C_{1-6}alkyl)C(O)C_{1-6}$alkyl, each optionally substituted, and wherein said group is optionally linked to the cycloalkyl or heterocycloalkyl through a C_{1-6}alkyl, preferably OH or OH linked through a C_{1-6}alkyl or a C_{1-3}alkyl.

13. The compound of any one of claims 1 to 12, wherein R^3 is an optionally substituted C_{1-6}alkyl group, optionally substituted C_{1-6}alkoxy, or an optionally substituted C_{1-6}alkylamino or diC_{1-6}alkylamino.

14. The compound of any one of claims 1 to 12, wherein R^3 is an optionally substituted C_6aryl, C_{5-6}heteroaryl, C_{4-7}cycloalkyl or C_{4-7}heterocycloalkyl group, or a C_6aryl, C_{5-6}heteroaryl, C_{4-7}cycloalkyl or C_{4-7}heterocycloalkyl linked to the pyrazolopyrimidine core through X^1.

15. The compound of claim 14, wherein the aryl group is of the formula:



wherein,

R^7 is independently in each occurrence selected from halogen, OH, OR^9, CN, NO_2, $C(O)R^9$, $C(O)N(R^8)_2$, $C(R^{10})=NR^{10}$, SO_2R^9, $SO_2N(R^8)_2$, $N(R^{10})C(O)R^9$, $N(R^{10})SO_2R^9$, $N(R^{10})C(O)N(R^8)_2$, $N(R^{10})SO_2N(R^8)_2$, $N(R^8)_2$, $P(O)(R^8)_2$, $P(O)(OR^8)_2$, $B(OR^8)_2$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{6-10}aryl, C_{5-10}heteroaryl, C_{3-10}cycloalkyl, and C_{4-10}heterocycloalkyl;

R^8 is independently in each occurrence selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}heterocycloalkyl, C_6aryl, and C_{5-10}heteroaryl, or two R^8 are taken together with their adjacent atom(s) to form a C_{4-10}heterocycloalkyl group;

R^9 is independently in each occurrence selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{3-7}heterocycloalkyl, C_6aryl, and C_{5-6}heteroaryl;

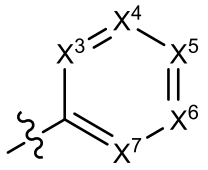
R^{10} is independently in each occurrence selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{3-7}heterocycloalkyl, C_6aryl, and C_{5-6}heteroaryl; and

c is 0, 1, 2, 3, 4 or 5;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is optionally further substituted.

16. The compound of claim 15, wherein R^7 is selected from CN, an optionally substituted C_{1-6}alkyl group (e.g., CH_3, CF_3, etc.), and OR^9, wherein R^9 is an optionally substituted C_{1-6}alkyl group.

17. The compound of claim 14, wherein the aryl or heteroaryl group is of the formula:



wherein,

X^3, X^4, X^5, X^6, and X^7 are each independently selected from N and CR^{11}, wherein at most three of X^3, X^4, X^5, X^6, and X^7 are N, or wherein one of two adjacent X^3, X^4, X^5, X^6, and X^7 is absent and the other is O, S or NR^{10};

R^8, R^9, and R^{10} are as defined in claim 15; and

R^{11} is independently in each occurrence selected from hydrogen, halogen, OH, OR^9, CN, NO_2, $C(O)R^9$, $C(O)N(R^8)_2$, $C(R^{10})=NR^{10}$, SO_2R^9, $SO_2N(R^8)_2$, $N(R^{10})C(O)R^9$, $N(R^{10})SO_2R^9$, $N(R^{10})C(O)N(R^8)_2$, $N(R^{10})SO_2N(R^8)_2$, $N(R^8)_2$, $P(O)(R^8)_2$, $P(O)(OR^8)_2$, $B(OR^8)_2$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{6-10}aryl, C_{5-10}heteroaryl, C_{3-10}cycloalkyl, and C_{4-10}heterocycloalkyl;

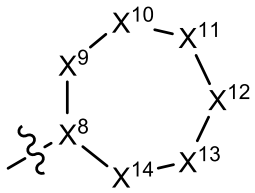
wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is optionally further substituted.

18. The compound of claim 17, wherein one of X^3, X^4, X^5, X^6, and X^7 is N, preferably one of X^4 and X^6.

19. The compound of claim 18, wherein X^4 is N and X^3, X^6, and X^7 are each CH.

20. The compound of any one of claims 17 to 19, wherein X^5 is CR^{11} and R^{11} is selected from CN, an optionally substituted C_{1-6}alkyl group (e.g., CH_3, CF_3, etc.), and OR^9, wherein R^9 is an optionally substituted C_{1-6}alkyl group.

21. The compound of claim 14, wherein the cycloalkyl or heterocycloalkyl group is of the formula:



wherein,

X^8 is selected from N and CR^{11};

X^9, X^{10}, X^{11}, X^{12}, X^{13}, and X^{14} are each independently selected from O, NR^{12}, SO_2, and $C(R^{13})_2$, wherein at most two of X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, and X^{14} are or comprise O, N or S, and/or wherein up to 3 of X^9, X^{10}, X^{11}, X^{12}, X^{13}, and X^{14} are absent to form a 4, 5, or 6-membered ring, and/or two or three of X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, and X^{14} are taken together to form a bridge through one to three additional bridging atoms, e.g. carbon atoms;

R^8, R^9, and R^{10} are as defined in claim 15 and R^{11} is as defined in claim 17;

R^{12} is selected from is independently in each occurrence selected from hydrogen, $C(O)R^9$, $C(O)N(R^8)_2$, SO_2R^9, $SO_2N(R^8)_2$, $P(O)(R^8)_2$, $P(O)(OR^8)_2$, $B(OR^8)_2$, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{6\text{-}10}$aryl, $C_{5\text{-}10}$heteroaryl, $C_{3\text{-}10}$cycloalkyl, and $C_{4\text{-}10}$heterocycloalkyl; and

R^{13} is independently in each occurrence selected from hydrogen, halogen, OH, OR^9, CN, NO_2, $C(O)R^9$, $C(O)N(R^8)_2$, $C(R^{10})=NR^{10}$, SO_2R^9, $SO_2N(R^8)_2$, $N(R^{10})C(O)R^9$, $N(R^{10})SO_2R^9$, $N(R^{10})C(O)N(R^8)_2$, $N(R^{10})SO_2N(R^8)_2$, $N(R^8)_2$, $P(O)(R^8)_2$, $P(O)(OR^8)_2$, $B(OR^8)_2$, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{6\text{-}10}$aryl, $C_{5\text{-}10}$heteroaryl, $C_{3\text{-}10}$cycloalkyl, and $C_{4\text{-}10}$heterocycloalkyl or two R^{13} are taken together with their adjacent atom(s) to form a $C_{4\text{-}10}$cycloalkyl or $C_{4\text{-}10}$heterocycloalkyl group;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is optionally further substituted.

22. The compound of claim 21, wherein X^8 is N.

23. The compound of claim 21 or 22, wherein X^{11} is NR^{12}.

24. The compound of claim 21 or 22, wherein X^{11} is $C(R^{13})_2$.

25. The compound of any one of claims 21 to 24, wherein at least one R^{13} is independently in each occurrence selected from OH, OR^9, $C(O)N(R^8)_2$, $N(R^{10})C(O)R^9$, $N(R^8)_2$, and an optionally substituted $C_{1\text{-}6}$alkyl.

26. The compound of any one of claims 21 to 25, wherein X^{12} is absent.

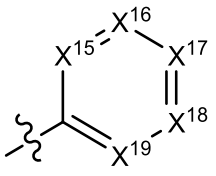
27. The compound of any one of claims 21 to 26, wherein X^9 and X^{14} are absent.

28. The compound of any one of claims 1 to 27, wherein X^1 is absent.

29. The compound of any one of claims 1 to 27, wherein X^1 is present and is NR^5, preferably wherein R^5 is H.

30. The compound of any one of claims 1 to 29, wherein R^2 is an optionally substituted C_6aryl or optionally substituted C_{5-6}heteroaryl.

31. The compound of claim 30, wherein R^2 is of the formula:



wherein,

X^{15}, X^{16}, X^{17}, X^{18}, and X^{19} are each independently selected from N and CR^{11}, wherein at most three of X^{15}, X^{16}, X^{17}, X^{18}, and X^{19} are N, or wherein one of two adjacent X^{15}, X^{16}, X^{17}, X^{18}, and X^{19} is absent and the other is O, S or NR^{10};

wherein R^{10} is as defined in claim 15 and R^{11} is as defined in claim 17; and

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is optionally further substituted.

32. The compound of claim 31, wherein X^{15}, X^{16}, X^{17}, X^{18}, and X^{19} are each CR^{11}.

33. The compound of claim 31 or 32, wherein X^{15} is CR^{11}, wherein R^{11} is selected from halogen and OR^9.

34. The compound of any one of claims 31 to 33, wherein X^{16}, X^{17}, X^{18}, and X^{19} are each CR^{11}, wherein R^{11} is hydrogen.

35. The compound of claim 33 or 34, wherein R^2 is a 2-methoxyphenyl or 2-chlorophenyl group.

36. The compound of claim 31, wherein one of X^{15}, X^{16}, X^{17}, X^{18}, and X^{19} is N.

37. The compound of claim 31, wherein X^{16} is N or CH.

38. The compound of any one of claims 31 to 33 and 37, wherein X^{17} is CR^{11}, and wherein R^{11} is cyano, halogen, halogenated alkyl or OR^9, preferably cyano.

39. The compound of claim 38, wherein R^2 is a 4-cyanophenyl or 6-cyano-3-pyridyl group.

40. The compound of any one of claims 1 to 39, wherein R^1 is an optionally substituted C_6aryl.

41. The compound of claim 40, wherein R^1 is a 4-chlorophenyl group.

42. The compound of claim 1, wherein the compound is selected from Compounds 1 to 78 as defined herein, or an isomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof.

43. The compound of claim 42, wherein the compound is selected from Compounds 1 to 77, as defined herein, or an isomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof.

44. The compound of claim 42, wherein the compound is Compound 78, or a pharmaceutically acceptable salt thereof.

45. The compound of claim 43, wherein the compound is selected from Compounds 1-18, 20-31, 33-61, 63-68, and 70-77, or Compounds 1-18, 20-29, 31, 36-61, 63-68, and 70-77, as defined herein, or an isomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof.

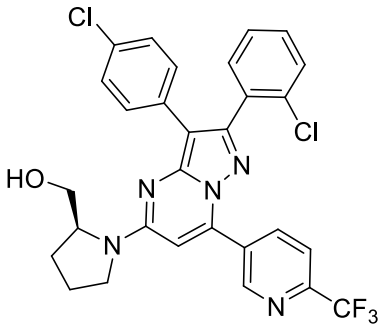
46. The compound of claim 43, wherein the compound is selected from Compounds 1-17, 20-22, 25-27, 37, 38, 42-46, 48-61, 63-68, 70-77, as defined herein, or an isomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof.

47. The compound of claim 43, wherein the compound is selected from Compounds 1-5, 7-11, 13-15, 21, 22, 27, 42, 43, 45, 50-58, 60, 61, 63, 64, 70(R), 70(S), 71(S), 72(R), 72(S), as defined herein, or an isomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof.

48. The compound of claim 43, wherein the compound is selected from Compounds 1, 2, 4, 7-9, 11, 13, 15, 21, 27, 43, 45, 50-53, 56-58, 60, 61, 63, 64, 70(R), 71(S), 72(R), 72(S), as defined herein, or an isomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof.

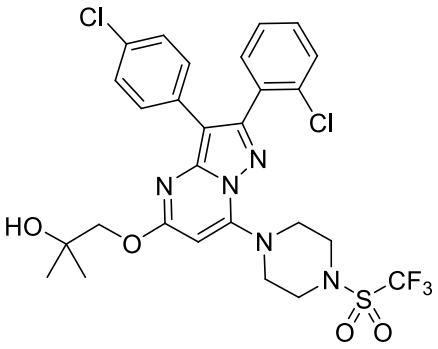
49. The compound of claim 43, wherein the compound is selected from Compound 8, Compound 15, or Compound 45, as defined herein, or an isomer or a tautomer thereof, or a pharmaceutically acceptable salt thereof.

50. A compound which is selected from



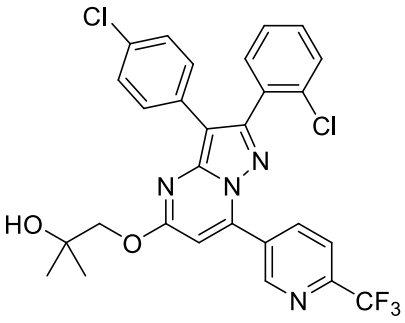
Compound 8;

or



Compound 15;

or



Compound 45.

51. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 50, together with a pharmaceutically acceptable carrier, diluent or excipient.

52. Use of a compound as defined in any one of claims 1 to 50 or a pharmaceutical composition as defined in claim 51 in the manufacture of a medicament for the treatment of a disorder related to appetite or one of its complications, a disorder related to glucose regulation or one of its complications, a fibrosis related disorder or one of its complications, a disorder related to metabolism or one of its complications, a disorder related to skin and hair growth and healing, a disorder related to the GI tract, a disorder related to obesity or one of its complications, or a combination thereof.

53. The use of claim 52, wherein said disorder related to appetite or one of its complications is selected from Prader-Willi Syndrome (PWS), hypothalamic obesity, pro-opiomelanocortin (POMC) deficiency (including POMC obesity, heterozygous POMC deficiency obesity, POMC epigenetic disorders), leptin receptor (LepR) deficiency, Bardet-Biedl (BB) syndrome, and Alström syndrome.

54. The use of claim 52, wherein said disorder related to glucose regulation or one of its complications is selected from diabetes Type I, diabetes Type II, insulin resistance, pre-diabetes, pancreatic diseases (by β-cell protection and/or increased insulin production), and associated nephropathies, neuropathies and retinopathies.

55. The use of claim 52, wherein said fibrosis related disorder or one of its complications is selected from progressive fibrosis associated with interstitial lung disease, idiopathic pulmonary fibrosis (IPF), Hermansky-Pudlak syndrome pulmonary fibrosis (HPS-PF), cirrhosis and other liver fibrosis disorders (such as nonalcoholic steatohepatitis (NASH), primary sclerosing cholangitis, primary biliary cholangitis), skin fibrotic disorders (such as scleroderma), fibrotic renal diseases, and chronic kidney diseases.

56. The use of claim 52, wherein said disorder related to metabolism or one of its complications is selected from metabolic syndrome and hyperlipidemia (e.g. hyper-triglyceridemia, hyper-triglyceridemia in the setting of low HDL-cholesterol, elevation of LDL and/or total cholesterol and/or VLDL and/or elevated Apolipoprotein B, atherosclerotic cardiovascular disease, etc.).

57. The use of claim 52, wherein said disorder related to obesity or one of its complications is selected from sleep apnea, snoring, asthma, pulmonary hypoventilation syndrome, dementia, heart disease, hypertension, gallbladder disease, gastrointestinal disorders, menstrual irregularities, degenerative arthritis, venous statis ulcer, coronary artery disease,

arterial sclerotic disease, pseudotumor cerebri, osteoarthritis, high cholesterol, and increased incidence of malignancies of the liver, ovaries, cervix, uterus, breasts, prostate, or gallbladder.

58. The use of claim 52, wherein said disorder of the skin and hair is selected from alopecia (male pattern baldness and alopecia associated with metabolic syndrome), excessive scar formation (cicatrix and keloid), and scleroderma.

59. The use of claim 52, wherein said disorder related to the GI tract is selected from constipation, irritable bowel syndrome, and inflammatory bowel syndrome, including ulcerative colitis and Crohn's disease.

60. A compound as defined in any one of claims 1 to 50 or a pharmaceutical composition as defined in claim 51 for use in the treatment of a disorder related to appetite or one of its complications, a disorder related to glucose regulation or one of its complications, a fibrosis related disorder or one of its complications, a disorder related to metabolism or one of its complications, a disorder related to skin and hair growth and healing, a disorder related to the GI tract, a disorder related to obesity or one of its complications, or a combination thereof.

61. Use of claim 60, wherein said disorder related to appetite or one of its complications is selected from Prader-Willi Syndrome (PWS), hypothalamic obesity, pro-opiomelanocortin (POMC) deficiency (including POMC obesity, heterozygous POMC deficiency obesity, POMC epigenetic disorders), leptin receptor (LepR) deficiency, Bardet-Biedl (BB) syndrome, and Alström syndrome.

62. Use of claim 60, wherein said disorder related to glucose regulation or one of its complications is selected from diabetes Type I and diabetes Type II.

63. Use of claim 60, wherein said fibrosis related disorder or one of its complications is selected from chronic kidney diseases.