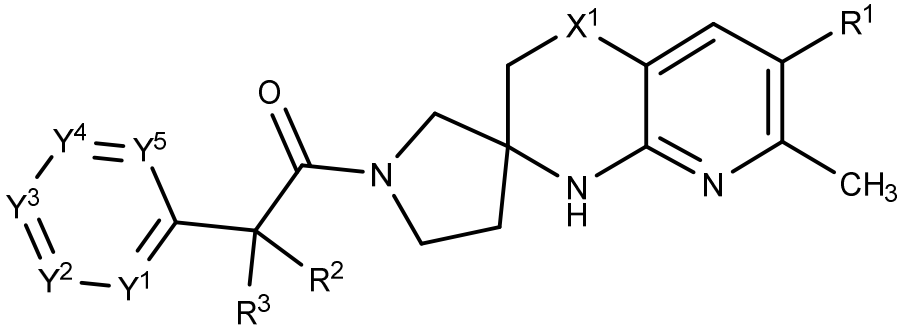
CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, 4- to 7-membered heterocycloalkyl, phenyl, or R^{1a}, wherein each of the C_{3-6} cycloalkyl and 4- to 7-membered heterocycloalkyl optionally substituted with 1, 2, 3, or 4 independently selected C_{1-4} alkyl, and wherein the phenyl is optionally substituted with 1, 2, 3, or 4 independently selected R^B, wherein each R^B is halogen, -OH, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-4} cycloalkyl, or R^{B1}; or two adjacent R^B together with the two ring-forming atoms of the phenyl to which they are attached form a fused 5- or 6-membered heteroaryl, each of which each is optionally substituted with 1, 2, or 3 substituents each independently selected from halogen, -OH, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy;

R^{1a} is 5- or 6-membered heteroaryl optionally substituted with 1, 2, 3, or 4 independently selected R^A, wherein each R^A is halogen, -OH, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-4} cycloalkyl, -N(C_{1-4} alkyl)$_2$, R^{A1}, or (C_{3-4} cycloalkyl)-C_{1-4} alkyl-, wherein each of the C_{1-4} alkyl, C_{3-4} cycloalkyl, and (C_{3-4} cycloalkyl)-C_{1-4} alkyl- is optionally substituted with 1, 2, 3, 4, or 5 substituents each independently selected from halogen, -OH, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy; or two adjacent R^A together with the two ring-forming atoms of the 5- or 6-membered heteroaryl to which they are attached form a fused benzene ring or a fused 5- or 6-membered heteroaryl or a fused 5- or 6-membered heterocycloalkyl or a fused 5- or 6-membered cycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents each independently selected from halogen, -OH, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy;

R^{A1} is 5- or 6-membered heteroaryl or 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents each independently selected from halogen, -OH, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy;

R^{B1} is 5- or 6-membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents each independently selected from halogen, -OH, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy;

X^1 is $C(R^X)_2$, wherein each R^X is independently H or C_{1-4} alkyl;

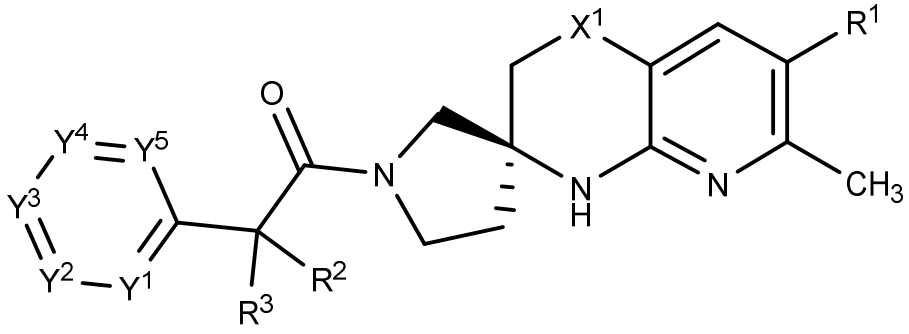
each of R^2 and R^3 is independently H, halogen, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, (C_{1-4} alkoxy)-C_{1-4} alkyl-, C_{3-4} cycloalkyl, or (C_{3-4} cycloalkyl)-C_{1-4} alkyl, wherein each of C_{3-4} cycloalkyl and (C_{3-4} cycloalkyl)-C_{1-4} alkyl- is optionally substituted with 1, 2, 3, 4, or 5 substituents each independently selected from halogen, -OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy;

or R^2 and R^3 together with the carbon atom to which they are attached form C_{3-6} cycloalkyl optionally substituted with 1, 2, 3, 4, or 5 substituents each independently selected from halogen, -OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy;

each of Y^1, Y^2, Y^3, Y^4, and Y^5 is independently CR^4 or N, provided that no more than 3 of Y^1, Y^2, Y^3, Y^4, and Y^5 are N; and

each R^4 is independently H, halogen, -OH, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, -N(C_{1-2} alkyl)$_2$, C_{3-4} cycloalkyl, or (C_{3-4} cycloalkyl)-C_{1-4} alkyl-, wherein each of the C_{1-4} alkyl, C_{3-4} cycloalkyl, and (C_{3-4} cycloalkyl)-C_{1-4} alkyl- is optionally substituted with 1, 2, 3, 4, or 5 substituents each independently selected from halogen, -OH, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy.

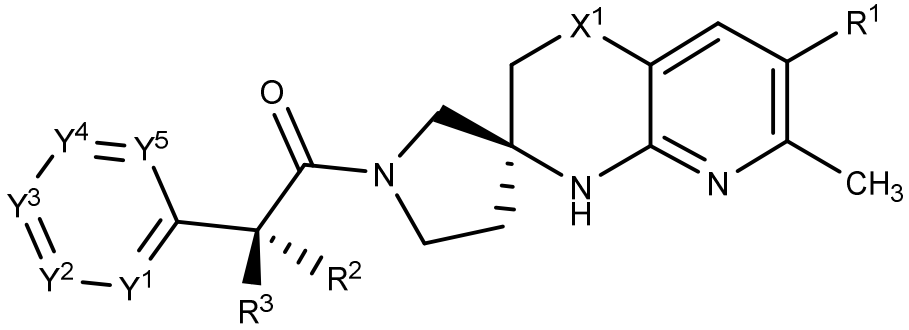
2. The compound or pharmaceutically acceptable salt of claim 1 wherein the compound is a compound of Formula Ia:



Ia

or a pharmaceutically acceptable salt thereof.

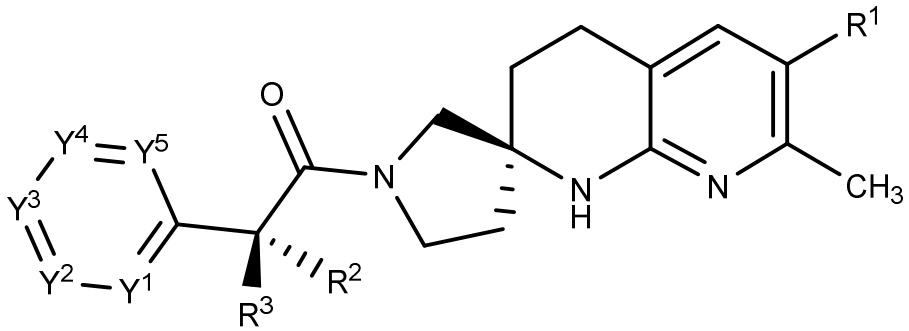
3. The compound or pharmaceutically acceptable salt of claim 1 or 2 wherein the compound is a compound of Formula II:



II

or a pharmaceutically acceptable salt thereof.

4. The compound or pharmaceutically acceptable salt of any one of claims 1 to 3 wherein the compound is a compound of Formula III:



III

or a pharmaceutically acceptable salt thereof.

5. The compound or pharmaceutically acceptable salt of any one of claims 1 to 4 wherein:

R^1 is R^{1a}; and

R^{1a} is 6-membered heteroaryl optionally substituted with 1, 2, 3, or 4 independently selected R^A, wherein each R^A is halogen, -OH, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-4} cycloalkyl, or (C_{3-4} cycloalkyl)-C_{1-4} alkyl-, wherein each of the C_{1-4} alkyl, C_{3-4} cycloalkyl, and (C_{3-4} cycloalkyl)-C_{1-4} alkyl- is optionally substituted with 1, 2, 3, 4, or 5 substituents each independently selected from halogen, -OH, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy; or two adjacent R^A together with the two ring-atoms of the 6-membered heteroaryl to which they are attached form a fused benzene ring or a fused 5- or 6-membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents each independently selected from halogen, -OH, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy.

6. The compound or pharmaceutically acceptable salt of claim 5 wherein R^{1a} is pyrimidinyl optionally substituted with 1, 2, or 3 independently selected R^A, wherein each R^A is halogen, -OH, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, or C_{3-4} cycloalkyl.

7. The compound or pharmaceutically acceptable salt of claim 6 wherein R^{1a} is pyrimidin-2-yl.

8. The compound or pharmaceutically acceptable salt of any one of claims 1 to 3 and 5 to 7 wherein X^1 is CH_2.

9. The compound or pharmaceutically acceptable salt of any one of claims 1 to 8 wherein each of R^2 and R^3 is independently H, F, or C_{1-4} alkyl.

10. The compound or pharmaceutically acceptable salt of any one of claims 1 to 9 wherein R^2 is methyl and R^3 is H.

11. The compound or pharmaceutically acceptable salt of any one of claims 1 to 10 wherein Y^3 is N, and each of Y^1, Y^2, Y^4, and Y^5 is independently CR^4.

12. The compound or pharmaceutically acceptable salt of any one of claims 1 to 11 wherein each R^4 is independently H, halogen, or C_{1-2} alkoxy.

13. A compound of claim 1 selected from:

(2*R*)-2-(5-chloro-2-methoxypyridin-4-yl)-1-[7-methyl-6-(2-methyl-2*H*-tetrazol-5-yl)-3,4-dihydro-1*H*-spiro[1,8-naphthyridine-2,3'-pyrrolidin]-1'-yl]propan-1-one, DIAST-1;

2-(6-methoxy-2-methylpyrimidin-4-yl)-1-[(2*S*)-7-methyl-6-(2-methyl-2*H*-tetrazol-5-yl)-3,4-dihydro-1*H*-spiro[1,8-naphthyridine-2,3'-pyrrolidin]-1'-yl]propan-1-one, DIAST-1;

2-[6-(difluoromethoxy)pyridin-3-yl]-1-[(2*S*)-7-methyl-6-(pyrimidin-2-yl)-3,4-dihydro-1*H*-spiro[1,8-naphthyridine-2,3'-pyrrolidin]-1'-yl]propan-1-one, DIAST-2;

1-[(2*S*)-7-methyl-6-(pyrimidin-2-yl)-3,4-dihydro-1*H*-spiro[1,8-naphthyridine-2,3'-pyrrolidin]-1'-yl]-2-[4-(trifluoromethyl)phenyl]propan-1-one, DIAST-1;

1-(4,7-dimethyl-3,4-dihydro-1*H*-spiro[1,8-naphthyridine-2,3'-pyrrolidin]-1'-yl)-2-(4-fluorophenyl)ethan-1-one, DIAST-1;

(2*R*)-2-(5-fluoro-2-methoxypyridin-4-yl)-1-[(2*S*)-7-methyl-6-(2-methyl-2*H*-tetrazol-5-yl)-3,4-dihydro-1*H*-spiro[1,8-naphthyridine-2,3'-pyrrolidin]-1'-yl]propan-1-one;

(2*R*)-2-(5-fluoro-2-methoxypyridin-4-yl)-1-[(2*S*)-7-methyl-6-(pyrimidin-2-yl)-3,4-dihydro-1*H*-spiro[1,8-naphthyridine-2,3'-pyrrolidin]-1'-yl]propan-1-one;

(2*R*)-2-(5-chloro-2-methoxypyridin-4-yl)-1-[(2*S*)-7-methyl-6-(pyrimidin-2-yl)-3,4-dihydro-1*H*-spiro[1,8-naphthyridine-2,3'-pyrrolidin]-1'-yl]propan-1-one;

(2*R*)-2-(5-fluoro-2-methoxypyridin-4-yl)-1-[7-methyl-6-(1-methyl-1*H*-pyrazol-4-yl)-3,4-dihydro-1*H*-spiro[1,8-naphthyridine-2,3'-pyrrolidin]-1'-yl]propan-1-one, DIAST-1; and

(2*R*)-2-(5-fluoro-2-methoxypyridin-4-yl)-1-{(2*S*)-7-methyl-6-[(4,6-$^{2}H_{2}$)pyrimidin-2-yl]-3,4-dihydro-1*H*-spiro[1,8-naphthyridine-2,3'-pyrrolidin]-1'-yl}propan-1-one,

or pharmaceutically acceptable salt thereof.

14. A compound of claim 1 that is (2*R*)-2-(5-fluoro-2-methoxypyridin-4-yl)-1-[(2*S*)-7-methyl-6-(pyrimidin-2-yl)-3,4-dihydro-1*H*-spiro[1,8-naphthyridine-2,3'-pyrrolidin]-1'-yl]propan-1-one, or pharmaceutically acceptable salt thereof.

15. A compound of claim 1 that is a crystalline form of (2*R*)-2-(5-fluoro-2-methoxypyridin-4-yl)-1-[(2*S*)-7-methyl-6-(pyrimidin-2-yl)-3,4-dihydro-1*H*-spiro[1,8-naphthyridine-2,3'-pyrrolidin]-1'-yl]propan-1-one.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound or pharmaceutically acceptable salt of any one of claims 1 to 15 and a pharmaceutically acceptable carrier.

17. A ~~method for treating an MC4R-related condition, disease, or disorder in a human, where the method comprises administering to the human in need thereof a~~ compound or pharmaceutically acceptable salt of any one of claims 1 to 15 for use in the treatment of an MC4R-related condition, disease, or disorder in a human.

18. A ~~method for treating a condition, disease, or disorder in a human, where the method comprises administering to the human in need thereof a~~ compound or pharmaceutically acceptable salt of any one of claims 1 to 15~~,~~ for use in the treatment of ~~wherein the condition, disease, or disorder is selected from~~ cachexia [including for example, cachexia associated with a chronic illness, such as cachexia associated with cancer, cachexia associated with acquired immunodeficiency syndrome (AIDS), cachexia associated with heart failure for example cachexia associated with congestive heart failure (CHF), cachexia associated with chronic kidney disease (CKD); cachexia associated with treatment of a chronic illness, such as, cachexia associated with treatment of cancer or cachexia associated with treatment of heart failure (e.g. CHF)]; anorexia or anorexia nervosa (e.g., geriatric anorexia, anorexia associated with chemotherapy and/or radiotherapy); nausea; emesis; weight loss (e.g., involuntary weight loss); failure to thrive; sarcopenia; muscle wasting; muscle weakness; frailty; osteoporosis; bone disorders (e.g., bone loss); pain; neuropathic pain; anxiety (e.g.,

posttraumatic stress disorder, or PTSD); depression; hypertension; malnutrition; obesity (e.g. sarcopenia resulting from chronic obesity); sexual dysfunction; and inflammatory disease (e.g. an inflammatory disease associated with anorexia or cachexia or sarcopenia or muscle wasting).

19. Use of a compound or pharmaceutically acceptable salt of any one of claims 1 to 15 in treating a condition, disease, or disorder selected from selected from cachexia [including for example, cachexia associated with a chronic illness, such as cachexia associated with cancer, cachexia associated with acquired immunodeficiency syndrome (AIDS), cachexia associated with heart failure for example cachexia associated with congestive heart failure (CHF), cachexia associated with chronic kidney disease (CKD); cachexia associated with treatment of a chronic illness, such as, cachexia associated with treatment of cancer or cachexia associated with treatment of heart failure (e.g. CHF)]; anorexia or anorexia nervosa (e.g., geriatric anorexia, anorexia associated with chemotherapy and/or radiotherapy); nausea; emesis; weight loss (e.g., involuntary weight loss); failure to thrive; sarcopenia; muscle wasting; muscle weakness; frailty; osteoporosis; bone disorders (e.g., bone loss); pain; neuropathic pain; anxiety (e.g., posttraumatic stress disorder, or PTSD); depression; hypertension; malnutrition; obesity (e.g. sarcopenia resulting from chronic obesity); sexual dysfunction; and inflammatory disease (e.g. an inflammatory disease associated with anorexia or cachexia or sarcopenia or muscle wasting).

20. A method for antagonizing a melanocortin-4 receptor (MC4R) comprising contacting the MC4R with a compound or pharmaceutically acceptable salt of any one of claims 1 to 15.