
Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

Title: ACYLATED SPIROPIPERIDINE DERIVATIVES AS MELANOCORTIN-4 RECEPTOR MODULATORS

Abstract: Certain novel N-acylated spiropiperidine derivatives are ligands of the human melanocortin receptor(s) and, in particular, are selective ligands of the human melanocortin-4 receptor (MC-4R). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the modulation of MC-4R, such as obesity, diabetes, nicotine addiction, alcoholism, sexual dysfunction, including erectile dysfunction and female sexual dysfunction.
1. A compound of structural formula I:

or a pharmaceutically acceptable salt thereof; wherein

A is a heteroaryl ring containing at least one heteroatom selected from nitrogen, oxygen, and sulfur, wherein the carbon, nitrogen or sulfur in A is unsubstituted or substituted with one to two groups selected from R4;

X and Y taken together form \(-C(R_6)\&C(R_6)\), or one of X and Y is \(C(R_6)_2\) and the other is selected from the group consisting of:

1. \(C(R_6)_2\),
2. \(N(R_6)\),
3. \(C(O)\),
4. \(C=N(R_6)\),
5. \(C=C(R_6)_2\),
6. oxygen,
7. sulfur,
8. \(S(O)\), and
9. \(S(O)_2\),

or one of X and Y is NR9 and the other is selected from the group consisting of:

1. \(C(R_6)_2\),
2. \(C(O)\),
3. \(C=N(R_6)\),
4. \(C=C(R_6)_2\),
5. \(S(O)\), and
(6) \( \text{S(O)}_2 \),
or one of \( X \) and \( Y \) is \( \text{C(O)} \) and the other is selected from the group consisting of:

(1) \( \text{C(R\text{\( 6 \)}}_2 \),
(2) \( \text{N(R6)} \),
(3) \( \text{C=N(R6)} \),
(4) oxygen, and
(5) sulfur;

\( Z \) is independently selected from the group consisting of:

(1) \( \text{CH} \), and
(2) \( \text{N} \),

provided that when \( Z \) is \( \text{N} \), \( R^1 \) is not \(-\text{NR7R8} \);

\( R^1 \) is selected from the group consisting of:

(1) hydrogen,
(2) \( -(\text{CH}_2)_n-\text{NR7R8} \),
(3) amidino,
(4) Ci-4 alkyliminoyl,
(5) Ci-alkyl,
(6) \( -(\text{CH}_2)_n-\text{C3-7 cycloalkyl} \),
(7) \( -(\text{CH}_2)_n-\text{C2-7heterocycloalkyl} \),
(8) \( -(\text{CH}_2)_n-\text{phenyl} \),
(9) \( -(\text{CH}_2)_n-\text{naphthyl} \),
(10) \( -(\text{CH}_2)_n-\text{heteroaryl} \),
(11) \( -\text{C(O)Ci}_6\text{alkyl} \),
(12) \( -\text{C(O)C3-8cycloalkyl} \),
(13) \( -\text{C(O)C2-7heterocycloalkyl} \),
(14) \( -\text{C(O)heteroaryl} \),
(15) \( -\text{C(O)phenyl}, \) and
(16) \( -\text{C(O)naphthyl} \),

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from \( R^3 \), and wherein alkyl, cycloalkyl and heterocycloalkyl are unsubstituted or substituted with one to three groups independently selected from \( R^3 \) and oxo;

\( R^2 \) is selected from the group consisting of:
wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three substituents independently selected from R10:

(1) phenyl,
(2) naphthyl, and
(3) heteroaryl,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three substituents independently selected from R10:

(1) phenyl,
(2) naphthyl, and
(3) heteroaryl,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three substituents independently selected from R10:

(1) phenyl,
(2) naphthyl, and
(3) heteroaryl,
wherein alkyl, cycloalkyl, heterocycloalkyl, and (CH2) are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C1.4 alkyl, trifluoromethyl, and C1.4 alkoxy, or wherein two substituents when on the same methylene (CH2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

5 each R.4 is independently selected from the group consisting of:

(1) hydrogen,
(2) C1-8 alkyl,
(3) -(CH2)nC3-7 cycloalkyl,
(4) halogen,
(5) OR5,
(6) -(CH2)nN(R5)2,
(7) -(CH2)nON,
(8) CF3,
(9) CH2CF3,
(10) OCF3, and
(11) OCH2CF3,

wherein alkyl, cycloalkyl, and (CH2) are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C1.4 alkyl, trifluoromethyl, and C1.4 alkoxy, or wherein two substituents when on the same methylene (CH2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

10 each R5 is independently selected from the group consisting of:

(1) hydrogen,
(2) C1-8 alkyl,
(3) -(CH2)nC3-7 cycloalkyl,
(4) -(CH2)nC2-7 heterocycloalkyl,
(5) -(CH2)n-phenyl,
(6) -(CH2)n-naphthyl,
(7) -(CH2)n-heteroaryl, and
(8) -(CH2)nC3-7 bicycloalkyl,

wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, naphthyl, cycloalkyl, bicycloalkyl and (CH2) are unsubstituted or substituted with one to three groups independently selected from halogen, C1.4 alkyl, hydroxy, and C1.4 alkoxy, or wherein two R5 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and -NC1.4 alkyl;
each R₆ is independently selected from the group consisting of:

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<table>
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<td>(1)</td>
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<tr>
<td>(2)</td>
<td>C₆₋₆ alkyl,</td>
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<tr>
<td>(3)</td>
<td>-(CH₂)ₙ C3-7 cycloalkyl,</td>
</tr>
<tr>
<td>(4)</td>
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<td>(5)</td>
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<td>(7)</td>
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<tr>
<td>(8)</td>
<td>-(CH₂)ₙ C(O)R₅,</td>
</tr>
<tr>
<td>(9)</td>
<td>-(CH₂)ₙ C(O)OR₅,</td>
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<tr>
<td>(10)</td>
<td>-(CH₂)ₙ C(O)N(R₅)₂,</td>
</tr>
<tr>
<td>(11)</td>
<td>-(CH₂)ₙ C(O)N(R₅)₂C(O)R₅,</td>
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<tr>
<td>(12)</td>
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<td>(13)</td>
<td>-(CH₂)n OC(O)R₅,</td>
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<tr>
<td>(14)</td>
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<td>(15)</td>
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<td>(18)</td>
<td>-(CH₂)ₙ N(C(O)R₅)₂,</td>
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<tr>
<td>(19)</td>
<td>-(CH₂)ₙ N(R₅)C(O)OR₅,</td>
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<tr>
<td>(20)</td>
<td>-(CH₂)ₙ N(C(O)OR₅)₂,</td>
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<tr>
<td>(21)</td>
<td>-(CH₂)ₙ N(R₅)C(O)(CH₂)ₙ N(R₅)₂,</td>
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<tr>
<td>(22)</td>
<td>-(CH₂)ₙ N(R₅)-S(O)-C₈₉ alkyl,</td>
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<tr>
<td>(23)</td>
<td>-(CH₂)ₙ N(R₅)-S(O)₂-C₈₉ alkyl,</td>
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<td>(24)</td>
<td>-(CH₂)ₙ S-R₅,</td>
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<td>(25)</td>
<td>-(CH₂)ₙ S(O)-R₅, and</td>
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<tr>
<td>(26)</td>
<td>-(CH₂)ₙ S(O)₂-R₅,</td>
</tr>
</tbody>
</table>

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³, and wherein alkyl, cycloalkyl and heterocycloalkyl are unsubstituted or substituted with one to three groups independently selected from R₃ and oxo, and wherein any methylene carbon (CH₂) in R₆ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl, or wherein two R₆ groups together with the atoms to which they are attached form a 3- to 7-membered monocyclic ring optionally containing an additional heteroatom selected from O, S, and N, wherein the monocyclic ring is unsubstituted or substituted on carbon or nitrogen with one to three groups independently selected from R₃ and oxo;
each K and R is independently selected from the group consisting of:

1. hydrogen,
2. C<sub>1-6</sub> alkyl,
3. C<sub>3-7</sub> cycloalkyl,
4. C<sub>2-7</sub> heterocycloalkyl,
5. phenyl,
6. naphthyl, and
7. heteroaryl,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R3, and wherein alkyl, cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three groups independently selected from R3 and oxo;

each R9 is independently selected from the group consisting of:

1. hydrogen,
2. C<sub>1-6</sub> alkyl,
3. -(CH<sub>2</sub>)<sub>n</sub> C<sub>3-7</sub> cycloalkyl,
4. -(CH<sub>2</sub>)<sub>n</sub> C<sub>2-7</sub> heterocycloalkyl,
5. -(CH<sub>2</sub>)<sub>n</sub> heteroaryl,
6. -(CH<sub>2</sub>)<sub>n</sub> C(O)OR5,
7. -(CH<sub>2</sub>)<sub>n</sub> C(O)(CH<sub>2</sub>)<sub>n</sub>-N(R5)2,
8. -(CH<sub>2</sub>)<sub>n</sub>C(O)(CH<sub>2</sub>)<sub>n</sub>-NR7R8,
9. -OR5,
10. -OC(O)R5,
11. -O-(CH<sub>2</sub>)<sub>n</sub>-N(R5)2, and
12. -N(R5)<sub>2</sub>,

wherein heteroaryl is unsubstituted or substituted with one to three groups independently selected from R3, and wherein alkyl, cycloalkyl and heterocycloalkyl are unsubstituted or substituted with one to three groups independently selected from R3 and oxo, and wherein any methylene (CH<sub>2</sub>) in R9 is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C<sub>1-4</sub> alkyl; or wherein two R9 groups together with the atoms to which they are attached form a 3- to 7-membered monocyclic ring optionally containing an additional heteroatom selected from O, S, and N, wherein the monocyclic ring is unsubstituted or substituted on carbon or nitrogen with one to three groups independently selected from R3 and oxo;

each R10 is independently selected from the group consisting of:

1. hydrogen,
2. C<sub>1-6</sub> alkyl,
(3) -(CH₂)n-phenyl,
(4) -(CH₂)n-naphthyl,
(5) -(CH₂)n-heteroaryl,
(6) -(CH₂)n C2-7 heterocycloalkyl,
(7) -(CH₂)n C3-7 cycloalkyl,
(8) halogen,
(9) OR5,
(10) -(CH₂)nN(R⁵)₂,
(11) -(CH₂)nC≡N,
(12) -(CH₂)n CO₂ R⁵,
(13) NO₂,
(14) -(CH₂)nNR₅S(O)pR⁵
(15) -(CH₂)n S(O)pN(R⁵)₂,
(16) -(CH₂)n S(O)pR₅,
(17) -(CH₂)n NR₅c(O)N(R⁵)₂,
(18) -(CH₂)n C(O)N(R⁵)₂,
(19) -(CH₂)n NR₅C(O)R⁵,
(20) -(CH₂)n NR₅CO₂ R⁵,
(21) -(CH₂)n NR₅C(O)-heteroaryl,
(22) -(CH₂)n C(O) NR₅N(R⁵)₂,
(23) -(CH₂)n C(O)NR₅NR₅C(O)R⁵,
(24) O(CH₂)n C(O)N(R⁵)₂,
(25) CF₃,
(26) CH₂ CF₃,
(27) OCF₃, and
(28) OCH₂ CF₃;

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, Ci_4 alkyl, trifluoromethyl, and C1.4 alkoxy, and wherein alkyl, cycloalkyl, heterocycloalkyl, and (CH₂) are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C1.4 alkyl, trifluoromethyl, and C1.4 alkoxy, or wherein two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group; each R11 is independently selected from the group consisting of:

(1) hydrogen,
(2) -OH,
(3) Ci-galkyl,
(4) -OCi-salkyl,
(5) halogen;
(6) -NR5,
(7) -SR5, and
(8) -CF₃,

wherein two Ci₈alkyl substituents along with the atoms to which they are attached can form a 4- to 8-membered ring;

r is 1 or 2;

s is 1 or 2;
n is 0, 1, 2, or 3; and
p is 0, 1, or 2.

2. The compound of Claim 1 wherein A is a heteroaryl ring selected from the group consisting of: pyridine, thiophene, furan, thiazole, pyrazole, pyrimidine, pyrazine and quinoline, wherein the carbon, nitrogen or sulfur in A is unsubstituted or substituted with one to two groups selected from R₄, or a pharmaceutically acceptable salt thereof.

4. The compound of Claim 1 wherein R₂ is phenyl or pyridine, unsubstituted or substituted with one to three groups independently selected from R₁₀, or a pharmaceutically acceptable salt thereof.

5. The compound of Claim 4 wherein R₂ is phenyl unsubstituted or substituted with one to three groups independently selected from R₁₀, or a pharmaceutically acceptable salt thereof.

6. The compound of Claim 1 wherein Z is CH, or a pharmaceutically acceptable salt thereof.

7. The compound of Claim 1 wherein Z is N, or a pharmaceutically acceptable salt thereof.

8. The compound of Claim 1 wherein r is 1 or 2 and s is 1, or a pharmaceutically acceptable salt thereof.

9. A compound of structural formula Ha or lib of the indicated trans relative stereochemical configuration:
or a pharmaceutically acceptable salt thereof; wherein

U and V are independently selected from the group consisting of N and CR₄, and at least one of U and V is N;

X is selected from the group consisting of:

1. CH₂,
2. CHCl-₆alkyl,
3. NR₉,
4. oxygen, and
5. sulfur;

Y is selected from the group consisting of:

1. -(R₆)₂,
2. -NR₆,
3. C(O),
4. C=CH(R₆),
5. C=N(R₆),
6. oxygen,
7. sulfur,
8. S(O), and
9. S(O)₂,

provided that when Y is -NR₆, sulfur or oxygen, then X is not oxygen, sulfur, or -NR₇R₈;

Z is independently selected from the group consisting of:

1. CH, and
2. N,

provided that when Z is N, R₁ is not -NR₇R₈;

R₁ is selected from the group consisting of:
(1) hydrogen,
(2) -(CH2)n-NR7R8,
(3) amidino,
(4) C1-4 alkyliminoyl,
(5) Ci-i θ alkyl,
(6) -(CH2)n-C3-7 cycloalkyl,
(7) -(CH2)n-C2-7heterocycloalkyl,
(8) -(CH2)n-phenyl,
(9) -(CH2)n-naphthyl,
(10) -(CH2)n-heteroaryl,
(11) -C(O)Ci_6alkyl,
(12) C(O)C3-8cycloalkyl,
(13) C(O)C2-7heterocycloalkyl,
(14) -C(O)heteroaryl,
(15) -C(O)phenyl, and
(16) -C(O)naphthyl,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R3, and wherein alkyl, cycloalkyl and heterocycloalkyl are unsubstituted or substituted with one to three groups independently selected from R3 and oxo;

R2 is selected from the group consisting of:
(1) phenyl,
(2) naphthyl, and
(3) heteroaryl,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R3;

R3 is selected from the group consisting of:
(1) Ci-8 alkyl,
(2) -(CH2)n-phenyl,
(3) -(CH2)n-naphthyl,
(4) -(CH2)n-heteroaryl,
(5) -(CH2)n-C2-7 heterocycloalkyl,
(6) -(CH2)n-C3-7 cycloalkyl,
(7) halogen,
(8) OR5,
(9) -(CH2)nN(R5)2,
(10) -(CH2)nC=N,
(11) -(CH$_2$)$_n$CO$_2$R$_5$,
(12) -(CH$_2$)$_n$OC(O)R$_5$,
(13) NO$_2$,
(14) -(CH$_2$)$_n$NR$_5$S(O)$_p$R$_5$,
(15) -(CH$_2$)$_n$N(S(O)$_p$R$_5$)$_2$,
(16) -(CH$_2$)$_n$S(O)$_p$N(R$_5$)$_2$,
(17) -(CH$_2$)$_n$S(O)$_p$R$_5$,
(18) -(CH$_2$)$_n$NR$_5$C(O)(O)R$_5$,
(19) -(CH$_2$)$_n$C(O)N(R$_5$)$_2$,
(20) -(CH$_2$)$_n$NR$_5$C(O)R$_5$,
(21) -(CH$_2$)$_n$NR$_5$CO$_2$R$_5$,
(22) -(CH$_2$)$_n$NR$_5$C(O)-heteroaryl,
(23) -(CH$_2$)$_n$C(O)NR$_5$N(R$_5$)$_2$,
(24) -(CH$_2$)$_n$C(O)NR$_5$NR$_5$C(O)R$_5$,
(25) O(CH$_2$)$_n$C(O)N(R$_5$)$_2$,
(26) CF$_3$,
(27) CH$_2$CF$_3$,
(28) OCF$_3$, and
(29) OCH$_2$CF$_3$,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C$_1$-4 alkyl, trifluoromethyl, and C$_1$-4 alkoxy, and wherein alkyl, cycloalkyl, heterocycloalkyl, and (CH$_2$) are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C$_1$-4 alkyl, trifluoromethyl, and C$_1$-4 alkoxy, or wherein two substituents when on the same methylene (CH$_2$) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

R$_4$a and R$_4$b are independently selected from the group consisting of:

(1) hydrogen,
(2) Ci-8 alkyl,
(3) -(CH$_2$)$_n$C$_3$-7 cycloalkyl,
(4) halogen,
(5) OR$_5$,
(6) -(CH$_2$)$_n$N(R$_5$)$_2$,
(7) -(CH$_2$)$_n$C≡N,
(8) CF$_3$,
(9) CH$_2$CF$_3$. 

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(10) OCF3, and
(11) OCH2CF3,
wherein alkyl, cycloalkyl, and (CH2) are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C1.4 alkyl, trifluoromethyl, and C1.4 alkoxy, or wherein two substituents when on the same methylene (CH2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;
each R5 is independently selected from the group consisting of:
(1) hydrogen,
(2) C1.8 alkyl,
(3) -(CH2)n C3-7 cycloalkyl,
(4) -(CH2)n C2-7 heterocycloalkyl,
(5) -(CH2)n phenyl,
(6) -(CH2)n naphthyl,
(7) -(CH2)n heteroaryl, and
(8) -(CH2)n C3-7 bicycloalkyl;
wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, naphthyl, cycloalkyl, bicycloalkyl and (CH2) are unsubstituted or substituted with one to three groups independently selected from halogen, C1.4 alkyl, hydroxy, and C1.4 alkoxy, or wherein two R5 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and -NC1.4 alkyl;
each R6 is independently selected from the group consisting of:
(1) hydrogen,
(2) C1.6 alkyl,
(3) -(CH2)n C3-7 cycloalkyl,
(4) -(CH2)n C2-7heterocycloalkyl,
(5) -(CH2)n phenyl,
(6) -(CH2)n naphthyl,
(7) -(CH2)n heteroaryl,
(8) -(CH2)n C(O)R5,
(9) -(CH2)n C(O)OR5,
(10) -(CH2)n C(O)N(R5)2,
(11) -(CH2)n C(O)N(R5)N(R5)C(O)R5,
(12) -(CH2)n OR5,
(13) -(CH2)n OC(O)R5,
(14) -(CH2)n O-(CH2)n N(R5)2,
(15) \(-(CH_2)_n-CN,\)
(16) \(-(CH_2)_nN\((R^5)\)\_2,\)
(17) \(-(CH_2)_nN(R^5)C(O)R^5,\)
(18) \(-(CH_2)_nN(C(O)R^5)\_2,\)
(19) \(-(CH_2)_nN(R^5)C(O)OR^5,\)
(20) \(-(CH_2)_nN(C(O)OR^5)\_2,\)
(21) \(-(CH_2)_nN(R^5)C(O)(CH_2)_nN(R^5)\_2,\)
(22) \(-(CH_2)_nN(R^5)-S(O)-Cl-8\) alkyl,
(23) \(-(CH_2)_nN(R^5)-S(O)\_2-\) Ci-8 alkyl,
(24) \(-(CH_2)n-S-R^5,\)
(25) \(-(CH_2)n-S(O)-R^5,\) and
(26) \(-(CH_2)_n-S(O)\_2-R^5,\)

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R3, and wherein alkyl, cycloalkyl and heterocycloalkyl are unsubstituted or substituted with one to three groups independently selected from R3 and oxo, and wherein any methylene (CH₂) in R6 is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and Cl-4 alkyl, or wherein two R6 groups together with the atoms to which they are attached form a 3- to 7-membered monocyclic ring optionally containing an additional heteroatom selected from O, S, and N, wherein the monocyclic ring is unsubstituted or substituted on carbon or nitrogen with one to three groups independently selected from R3 and oxo;
each R7 and R8 is independently selected from the group consisting of:

(1) hydrogen,
(2) Ci-6alkyl,
(3) C₃₋₇cycloalkyl,
(4) C₅₋₇heterocycloalkyl,
(5) phenyl,
(6) naphthyl, and
(7) heteroaryl,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R3, and wherein alkyl, cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three groups independently selected from R3 and oxo;
each R9 is independently selected from the group consisting of:

(1) hydrogen,
(2) Ci-6 alkyl,
(3) \(-(CH_2)_nC_3₋₇\) cycloalkyl,
(4) -(CH₂)n C₂-7 heterocycloalkyl,
(5) -(CH₂)n heteroaryl,
(6) -(CH₂)n C(O)OR₅,
(7) -(CH₂)n C(O)(CH₂)n-N(R₅)₂,
(8) -(CH₂)n C(O)(CH₂)n-NR₇R₈,
(9) -OR₅,
(10) -OC(O)RS,
(11) -O-(CH₂)ₙ-N(R₅)₂, and
(12) -N(R₅)₂,

wherein heteroaryl is unsubstituted or substituted with one to three groups independently selected from R₃, and wherein alkyl, cycloalkyl and heterocycloalkyl are unsubstituted or substituted with one to three groups independently selected from R₃ and oxo, and wherein any methylene (CH₂) in R₉ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and Ci-4 alkyl; or wherein two R⁹ groups together with the atoms to which they are attached form a 3- to 7-membered monocyclic ring optionally containing an additional heteroatom selected from O, S, and N, wherein the monocyclic ring is unsubstituted or substituted on carbon or nitrogen with one to three groups independently selected from R₃ and oxo;

each R₁₀ is independently selected from the group consisting of:

(1) hydrogen,
(2) Ci-6 alkyl,
(3) -(CH₂)n-phenyl,
(4) -(CH₂)n-naphthyl,
(5) -(CH₂)n-heteroaryl,
(6) -(CH₂)n C₂-7 heterocycloalkyl,
(7) -(CH₂)n C₃-7 cycloalkyl,
(8) halogen,
(9) OR₅,
(10) -(CH₂)n N(R₅)₂,
(11) -(CH₂)n C≡N,
(12) -(CH₂)n CO₂R₅,
(13) NO₂,
(14) -(CH₂)n NR₅S(O)pR₅
(15) -(CH₂)n S(O)pN(R₅)₂,
(16) -(CH₂)n S(O)pR₅,
(17) -(CH₂)n NR₅C(O)N(R₅)₂,
(18) -(CH₂)nC(O)N(R5)₂,
(19) -(CH₂)nNR₅C(O)R₅,
(20) -(CH₂)nNR₅CO₂R₅,
(21) -(CH₂)nNR₅C(O)-heteroaryl,
(22) -(CH₂)nC(O)NR₅N(R₅)₂,
(23) -(CH₂)nC(O)NR₅NR₅c(O)R₅,
(24) O(CH₂)nC(O)N(R₅)₂,
(25) CF₃,
(26) CH₂CF₃,
(27) OCF₃, and
(28) OCH₂CF₃;

wherein phenyl, napthyl, and heteroaryl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, Cl₄ alkyl, trifluoromethyl, and C₁.₄ alkoxy, and wherein alkyl, cycloalkyl, heterocycloalkyl, and (CH₂)ₙ are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, Cl₄ alkyl, trifluoromethyl, and C₁-₄ alkoxy, or wherein two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R₁ is independently selected from the group consisting of:

(1) hydrogen,
(2) -OH,
(3) Ci-galkyl,
(4) -OCi-galkyl,
(5) halogen;
(6) -NR₅,
(7) -SR₅, and
(8) -CF₃,

wherein two Ci-salkyl substituents with the atom to which they are attached can form a 4- to 8-membered bicyclic ring system;

r is 1 or 2;
s is 1 or 2;
n is 0, 1, 2, or 3; and
p is 0, 1, or 2.

10. A compound of structural formula Η₱a or Μb of the indicated trans relative stereochemical configuration:
or a pharmaceutically acceptable salt thereof; wherein
X is oxygen or CH2;
Y is selected from the group consisting of:

\[
\begin{align*}
5 & \quad (1) \quad \text{C}(\text{R}^6)_{2}, \\
& \quad (2) \quad \text{C}=\text{CH}(\text{R6}), \text{ and} \\
& \quad (3) \quad \text{N}(\text{R}^9),
\end{align*}
\]

provided that when X is oxygen, then Y is not -NR,9;
Z is independently selected from the group consisting of:

\[
\begin{align*}
10 & \quad (1) \quad \text{CH}, \text{ and} \\
& \quad (2) \quad \text{N},
\end{align*}
\]

provided that when Z is N, R1 is not -NR7C2-7heterocycloalkyl;
R1 is selected from the group consisting of

\[
\begin{align*}
15 & \quad (1) \quad \text{C}i_{-6}\text{alkyl}, \\
& \quad (2) \quad \text{N}(\text{R}7)\text{C}2-7\text{heterocycloalkyl}, \\
& \quad (3) \quad \text{-(CH}2)_\text{n}\text{C}2-7\text{heterocycloalkyl}, \\
& \quad (4) \quad \text{C}(\text{O})\text{C}i_{-6}\text{alkyl}, \\
& \quad (5) \quad \text{C}(\text{O})\text{heteroaryl},
\end{align*}
\]

wherein heteroaryl is unsubstituted or substituted with one to three groups independently selected from
R3, and wherein alkyl and heterocycloalkyl are unsubstituted or substituted with one to three groups independently selected from R3 and oxo;
R3 is selected from the group consisting of:

\[
\begin{align*}
20 & \quad (1) \quad \text{hydrogen}, \\
& \quad (2) \quad \text{Ci-8 alkyl}, \\
& \quad (3) \quad \text{-(CH}2)_\text{n}-\text{phenyl}, \\
& \quad (4) \quad \text{-(CH}2)_\text{n}-\text{naphthyl}, \\
& \quad (5) \quad \text{-(CH}2)_\text{n}-\text{heteroaryl},
\end{align*}
\]
(6) -(CH2)nC2-7 heterocycloalkyl,
(7) -(CH2)nC3-7 cycloall<yl,
(8) halogen,
(9) OR5,
(10) -(CH2)nN(R5)2,
(11) -(CH2)nC≡N,
(12) -(CH2)nC(O)OR5,
(13) -(CH2)nOC(O)R5,
(14) NO2,
(15) -(CH2)nNR5S(O)pR5,
(16) -(CH2)nN(S(O)pR5)2,
(17) -(CH2)nS(O)pN(R5)2,
(18) -(CH2)nS(O)pR5,
(19) -(CH2)nNR5C(O)N(R5)2,
(20) -(CH2)nC(O)NR5,
(21) -(CH2)nNR5C(O)R5,
(22) -(CH2)nNR5C(O)R5,
(23) -(CH2)nNR5C(O)-heteroaryl,
(24) -(CH2)nC(O)NR5N(R5)2,
(25) -(CH2)nC(O)NR5NR5C(O)R5,
(26) O(CH2)nC(O)N(R5)2,
(27) CF3,
(28) CH2CF3,
(29) OCF3,
(30) OCH2CF3,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C1-4 alkyl, trifluoromethyl, and C1-4 alkoxy, and wherein alkyl, cycloalkyl, heterocycloalkyl, and (CH2) are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C1-4 alkyl, trifluoromethyl, and C1-4 alkoxy, or wherein two substituents when on the same methylene (CH2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

R4a and R4b are independently selected from the group consisting of:

(1) hydrogen,
(2) C1-8 alkyl,
(3) halogen,
(4) $\text{CF}_3$,

wherein alkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C1-4 alkyl, trifluoromethyl, and C1-4 alkoxy;

each $R^5$ is independently selected from the group consisting of:

1. hydrogen,
2. $\text{C}_1\text{--}8$ alkyl,
3. $-(\text{CH}_2)_n\text{C}_3\text{-}7$ cycloalkyl,
4. $-(\text{CH}_2)_n\text{C}_2\text{-}7$ heterocycloalkyl,
5. $-(\text{CH}_2)_n$-phenyl,

wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, naphthyl, cycloalkyl, bicycloalkyl and ($\text{CH}_2$) are unsubstituted or substituted with one to three groups independently selected from halogen, C1-4 alkyl, hydroxy, and C1-4 alkoxy, or wherein two $R^3$ groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and -NC1.4 alkyl;

each $R^6$ is independently selected from the group consisting of:

1. hydrogen,
2. $-(\text{CH}_2)_n$-heteroaryl,
3. $-(\text{CH}_2)_n\text{C}(\text{O})\text{N}(R^5)_2$,
4. $-(\text{CH}_2)_n\text{C}(\text{O})\text{N}(R^5)\text{N}(R^5)\text{C}(\text{O})\text{R}^5$,
5. $-(\text{CH}_2)_n\text{CN}$,
6. $-(\text{CH}_2)_n\text{N}(R^5)_2$,
7. $-(\text{CH}_2)_n\text{N}(R^5)\text{C}(\text{O})\text{R}^5$,

wherein heteroaryl is unsubstituted or substituted with one to three groups independently selected from R3, and wherein any methylene carbon ($\text{CH}_2$) in R6 is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C1 alkyl;

each $R^7$ and $R^8$ is independently selected from the group consisting of:

1. hydrogen,
2. $\text{C}_1\text{--}6$ alkyl,
3. $\text{C}_3\text{-}7$ cycloalkyl,
4. $\text{C}_2\text{-}7$ heterocycloalkyl,
5. phenyl,
6. naphthyl, and
(7) heteroaryl,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³, and wherein alkyl, cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three groups independently selected from R³ and oxo;

5 each R⁹ is independently selected from the group consisting of:

(1) hydrogen,

(2) C₁-6 alkyl,

(3) -(CH₂)ₙ C₃-7 cycloalkyl,

(4) -(CH₂)ₙ C₂-7 heterocycloalkyl,

(5) -(CH₂)ₙ-heteroaryl,

(6) -(CH₂)ₙ C(O)OR₅,

(7) -(CH₂)ₙ C(O)(CH₂)ₙ-N(R₅)₂,

(8) -(CH₂)ₙ C(O)(CH₂)ₙ-NR₇R₈,

(9) -OR₅,

(10) -OC(O)R₅,

(11) -O-(CH₂)ₙ-N(R₅)₂, and

(12) -N(R₅)₂,

wherein heteroaryl is unsubstituted or substituted with one to three groups independently selected from R³, and wherein alkyl, cycloalkyl and heterocycloalkyl are unsubstituted or substituted with one to three groups independently selected from R³ and oxo, and wherein any methylene (CH₂) in R⁹ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁-4 alkyl; or wherein two R⁹ groups together with the atoms to which they are attached form a 3- to 7-membered monocyclic ring optionally containing an additional heteroatom selected from O, S, and N, wherein the monocyclic ring is unsubstituted or substituted on carbon or nitrogen with one to three groups independently selected from R³ and oxo;

25 each R¹₀ is independently selected from the group consisting of:

(1) hydrogen,

(2) C₁-6 alkyl,

(3) (CH₂)ₙ-phenyl,

(4) halogen,

(5) -OR₅,

(6) (CH₂)ₙ CN,

(7) CF₃,

(8) CH₂CF₃,

(9) OCF₃, and

(10) OCH₂CF₃,
wherein phenyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, Cl.4 alkyl, trifluoromethyl, and C1.4 alkoxy, and wherein alkyl and (CH2) are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, 0x0, C1-4 alkyl, trifluoromethyl, and C1.4 alkoxy, or wherein two substituents when on the same methylene (CH2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;
each R[i] is independently selected from the group consisting of:
   (1) hydrogen,
   (2) -OH,
   (3) Ci-[8] alkyl,
   (4) -OCi-[8] alkyl,
   (5) halogen;
   (6) -NR[5],
   (7) -SR[5], and
   (8) -CF3,
wherein two Cl-8alkyl substituents along with the atoms to which they are attached can form a 4- to 8-membered ring;
   r is 1 or 2;
   s is 1 or 2;
   n is 0, 1, 2, or 3; and
   p is 0, 1, or 2.

11. The compound of Claim 10 selected from the group consisting of:
or a pharmaceutically acceptable salt thereof.

12. The compound of Claim 11 which is:

or a pharmaceutically acceptable salt thereof.

13. The compound of Claim 11 which is:

or a pharmaceutically acceptable salt thereof.
14. The compound of Claim 11 which is:

or a pharmaceutically acceptable salt thereof.

15. The compound of Claim 11 which is:

or a pharmaceutically acceptable salt thereof.

16. The compound of Claim 11 which is:
or a pharmaceutically acceptable salt thereof.

17. The compound of Claim 11 which is:

![Chemical Structure 1]

or a pharmaceutically acceptable salt thereof.

18. The compound of Claim 1 selected from the group consisting of:

![Chemical Structure 2]

![Chemical Structure 3]

![Chemical Structure 4]

or a pharmaceutically acceptable salt thereof.
19. A pharmaceutical composition which comprises a compound of Claim 1 and a pharmaceutically acceptable carrier.

20. The compound of Claim 11 wherein the pharmaceutically acceptable salt thereof is the bis trifluoroacetic acid salt.

21. The use of a compound according to Claim 1 for the manufacture of a medicament useful for the treatment or prevention of a disease mediated by the melanocortin-4 receptor in a subject in need thereof.

22. The use according to Claim 21 wherein the disease mediated by the melanocortin-4 receptor is obesity.

23. The use according to Claim 21 wherein the disease mediated by the melanocortin-4 receptor is diabetes mellitus.

24. The use according to Claim 21 wherein the disease mediated by the melanocortin-4 receptor is male erectile dysfunction.

25. The use of a compound according to Claim 1 for the manufacture of a medicament useful for the treatment or prevention of an obesity-related disorder.
Statement Under Article 19m

Claims 1, 9 and 10 of the international application has been amended to delete "m" in substituent R9. Claim 1 has been amended to delete group (10) of substituent R6, which corresponds to -(CH2)nC(OH)R5. Claims 1 and 2 have been amended to replace "any" with "the". Claim 3 has been canceled. Claims 9 and 10 have been rewritten as independent claims. The amendments are fully supported by the Applicant's description.

The present amendment to Claim 1 deleting "m" impacts the description of the international application where the definition of R9 still contains "m": on page 10, line 33 to page 11, line 1; page 17, line 34 to page 18, line 2; and page 23, lines 14-17. The deletion of group (10) of substituent R6 in Claim 1, which corresponds to -(CH2)nC(OH)R5, impacts the description of the international application on page 9, line 22, where chemical structure of substituent (10) does not include the missing hydrogen atom. The term replacement of the word "any" with the word "the" in the definition of "A" in Claims 1 and 2 impacts the description of the international application on page 5, lines 22 to 24; and page 24, lines 22 to 26, where the definition of "A" still recites "any". The other amendments and cancellations have no impact on the description and the drawings of the international application.