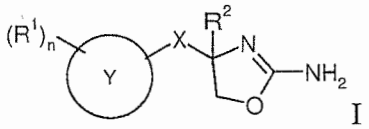
Claims

1. A combination comprising an atypical antipsychotic drug and a TAAR1 agonist.

2. A combination according to claim 1 comprising olanzapine and a TAAR1 agonist of formula



I

wherein

R^1 is hydrogen, deuterium, tritium, lower alkyl, hydroxy, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen, halogen, phenyl optionally substituted by halogen, or is phenyloxy, benzyl, benzyloxy, -COO-lower alkyl, -O-$(CH_2)_o$-O-lower alkyl, NH-cycloalkyl, cycloalkyl or tetrahydropyran-4-yloxy, wherein the substituents for n> 1 may be the same or different;

X is a bond, -CHR-, –CHRCHR'-, -OCH_2-, -NRCHR', –OCHRCHR', -CH_2OCHR-, -$CH_2CH_2CH_2$-, -SCH_2-, -$S(O)_2CH_2$-, -CH_2SCH_2-, -$CH_2N(R)CH_2$-, -cycloalkyl-CH_2- or SiRR'-CH_2-;

R/R' may be independently from each other hydrogen, lower alkyl or lower alkyl substituted by halogen;

R^2 is hydrogen, phenyl or lower alkyl;

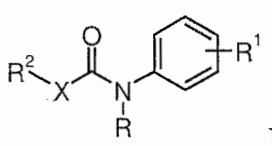
Y is phenyl, naphthyl, thiophenyl, pyridinyl, cycloalkyl, 1,2,3,4-tetrahydro-naphthalen-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl or benzo[1,3]dioxol-5-yl;

n is 0, 1, 2 or 3;

o is 2 or 3;

or a pharmaceutically suitable acid addition salt.thereof,

or a TAAR1 agonist of formula



II

wherein

R is hydrogen or lower alkyl;

R^1 is $-(CH_2)_n-(O)_o$-heterocycloalkyl, optionally substituted by lower alkyl, hydroxy, halogen, or by $-(CH_2)_p$-aryl;

n is 0, 1 or 2;

o is 0 or 1;

p is 0, 1 or 2;

R^2 is cycloalkyl, heterocycloalkyl, or is aryl or heteroaryl, wherein the aromatic rings are optionally substituted by one or two substituents, selected from lower alkyl, halogen, heteroaryl, CF_3, OCF_3, OCH_2CF_3, lower alkoxy, CH_2-lower alkoxy, lower alkinyl or cyano;

X is a bond, -NR'-, $-CH_2NH-$, -CHR''-, $-(CH_2)_q-O-$ or $-(CH_2)_2-$;

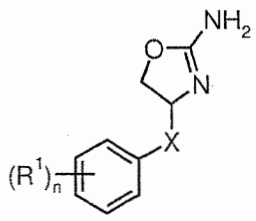
R' is hydrogen or lower alkyl,

R'' is hydrogen, lower alkyl, lower alkoxy,

q is 0, 1 or 2;

or a pharmaceutically suitable acid addition salt thereof.

3. A combination according to claim 2, comprising olanzapine and a TAAR1 agonist of formula



I-1

wherein

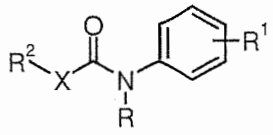
R^1 is hydrogen, lower alkyl, hydroxy, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or halogen, wherein the substituents for n=2 may be the same or different;

X is a bond, -NRCHR', –CHRCHR' or –OCHRCHR';

R/R' may be independently from each other hydrogen, lower alkyl;

n is 1 or 2;

or a TAAR1 agonist of formula



II-1

wherein

R is hydrogen;

R^1 is pyrrolidinyl;

R^2 is aryl or heteroaryl, wherein the aromatic rings are optionally substituted by halogen;

X is a bond or -NR'-;

R' is hydrogen or lower alkyl,

or a pharmaceutically suitable acid addition salt thereof.

4. A combination according to claims 1 - 3, comprising olanzapine and a TAAR1 agonist, which TAAR1 agonists are

S1 = (S)-4-((S)-2-phenyl-butyl)-4,5-dihydro-oxazol-2-ylamine

S2 = (S)-4-(3-fluoro-2-methyl-phenyl)-4,5-dihydro-oxazol-2-ylamine

S3 = (S)-4-(4-chloro-2-trifluoromethyl-phenyl)-4,5-dihydro-oxazol-2-ylamine

S4 = (S)-4-[(ethyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

S5 = 3-[(S)-1-((S)-2-amino-4,5-dihydro-oxazol-4-ylmethyl)-propoxy]-phenol

S6 = 5-chloro-pyridine-2-carboxylic acid (4-pyrrolidin-3-yl-phenyl)-amide

S7 = 4-chloro-N-(4-pyrrolidin-3-yl-phenyl)-benzamide

S8 = 1-(5-chloro-pyridin-2-yl)-3-(4-pyrrolidin-3-yl-phenyl)urea

S9 = (S)-4-[(S)-1-(4-fluoro-phenyl)-ethoxymethyl]-4,5-dihydro-oxazol-2-ylamine

S10 = 5-chloro-pyrimidine-2-carboxylic acid {4-[2-((S)-2-amino-4,5-dihydro-oxazol-4-yl)-ethyl]-phenyl}-amide

S11 = N-{4-[2-((S)-2-amino-4,5-dihydro-oxazol-4-yl)-ethyl]-phenyl}-4-chloro-benzamide

S12 = (R)-2-chloro-6-methyl-*N*-(4-(morpholin-2-yl)phenyl)isonicotinamide

S13 = (S)-N-(4-(morpholin-2-yl)phenyl)-6-(2,2,2-trifluoroethoxy)nicotinamide

S14 = (S)-*N*-(4-(morpholin-2-yl)phenyl)-2-(trifluoromethyl)isonicotinamide

S15 = (S)-1-(4-fluorobenzyl)-3-(4-(morpholin-2-yl)phenyl)urea

S16 = (S)-1-(3-cyanophenyl)-3-(4-(morpholin-2-yl)phenyl)urea and

S17 = (S)-6-chloro-*N*-(4-(morpholin-2-yl)phenyl)nicotinamide.

5. The compound S2 = (S)-4-(3-fluoro-2-methyl-phenyl)-4,5-dihydro-oxazol-2-ylamine, encompassed by formulas I and I-1 according to claims 2 and 3.

6. A combination according to claims 1 –4 comprising olanzapine and a TAAR1 agonist for the treatment of schizophrenia and manic episodes associated with bipolar disorders with reduced incidence of metabolic syndrome.

7. A combination according to claim 6 comprising olanzapine and a TAAR1 agonist for the treatment of schizophrenia and manic episodes associated with bipolar disorders with antidiabetic efficacy.

8. A combination according to claims 7 comprising olanzapine and a TAAR1 agonist for the treatment of schizophrenia and manic episodes associated with bipolar disorders with antidiabetic efficacy, which results in lowering blood glucose excursion.

9. A combination according to claims 8 comprising olanzapine and a TAAR1 agonist for the treatment of schizophrenia and manic episodes associated with bipolar disorders with antidiabetic efficacy which results in lowering fat mass and body weight

10. The use of a combination according to claims 1 - 4 for the manufacturing of a medicament for the treatment of schizophrenia and manic episodes associated with bipolar disorders with reduced incidence of metabolic syndrome.

11. The use of a combination according to claim 10 for the manufacturing of a medicament for the treatment of schizophrenia and manic episodes associated with bipolar disorders with antidiabetic efficacy.

12. The use of a combination according to claim 1 1 for the manufacturing of a medicament for the treatment of schizophrenia and manic episodes associated with bipolar disorders with antidiabetic efficacy which results in lowering blood glucose excursion.

13. The use of a combination according to claim 12 comprising olanzapine and a TAAR1 agonist for the manufacturing of a medicament for the treatment of schizophrenia and manic episodes associated with bipolar disorders with antidiabetic efficacy which results in lowering fat mass and body weight.

14. The use of a combination according to claim 10, wherein the reduced incidence of metabolic syndrome results from antidiabetic efficacy with lowering blood glucose excursion fat mass and body weight.

15. A pharmaceutical composition comprising a combination of an atypical antipsychotic drug and a TAAR1 agonist as described in claims 2, 3 and 4 together with pharmaceutically acceptable excipients for the treatment of schizophrenia and manic episodes associated with bipolar disorders with reduced incidence of metabolic syndrome.

16. A pharmaceutical composition comprising a combination of an atypical antipsychotic drug and a TAAR1 agonist as described in claims 2, 3 and 4 together with pharmaceutically acceptable excipients for the treatment of schizophrenia and manic episodes associated with bipolar disorders with reduced incidence of metabolic syndrome, wherein the reduced incidence

of metabolic syndrome results from antidiabetic efficacy with lowering blood glucose excursion, fat mass and body weight.

17. The compound S14 =(S)-N-(4-(morpholin-2-yl)phenyl)-2-(trifluoromethyl)isonicotinamide, encompassed by formula II according to claim 2.

Claims

1. A combination comprising olanzapine and a TAAR1 agonist, selected from

S1 = (S)-4-((S)-2-phenyl-butyl)-4,5-dihydro-oxazol-2-ylamine

S2 = (S)-4-(3-fluoro-2-methyl-phenyl)-4,5-dihydro-oxazol-2-ylamine

S3 = (S)-4-(4-chloro-2-trifluoromethyl-phenyl)-4,5-dihydro-oxazol-2-ylamine

S4 = (S)-4-[(ethyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

S5 = 3-[(S)-1-((S)-2-amino-4,5-dihydro-oxazol-4-ylmethyl)-propoxy]-phenol

S6 = 5-chloro-pyridine-2-carboxylic acid (4-pyrrolidin-3-yl-phenyl)-amide

S7 = 4-chloro-N-(4-pyrrolidin-3-yl-phenyl)-benzamide

S8 = 1-(5-chloro-pyridin-2-yl)-3-(4-pyrrolidin-3-yl-phenyl)urea

S9 = (S)-4-[(S)-1-(4-fluoro-phenyl)-ethoxymethyl]-4,5-dihydro-oxazol-2-ylamine

S10 = 5-chloro-pyrimidine-2-carboxylic acid {4-[2-((S)-2-amino-4,5-dihydro-oxazol-4-yl)-ethyl]-phenyl}-amide

S11 = N-{4-[2-((S)-2-amino-4,5-dihydro-oxazol-4-yl)-ethyl]-phenyl}-4-chloro-benzamide

S12 = (R)-2-chloro-6-methyl-*N*-(4-(morpholin-2-yl)phenyl)isonicotinamide

S13 = (S)-N-(4-(morpholin-2-yl)phenyl)-6-(2,2,2-trifluoroethoxy)nicotinamide

S14 = (S)-*N*-(4-(morpholin-2-yl)phenyl)-2-(trifluoromethyl)isonicotinamide

S15 = (S)-1-(4-fluorobenzyl)-3-(4-(morpholin-2-yl)phenyl)urea

S16 = (S)-1-(3-cyanophenyl)-3-(4-(morpholin-2-yl)phenyl)urea and

S17 = (S)-6-chloro-*N*-(4-(morpholin-2-yl)phenyl)nicotinamide.

2. A combination according to claim 1 for use in the treatment of schizophrenia and manic episodes associated with bipolar disorders with reduced incidence of metabolic syndrome.

3. A combination according to claim 2 for use in the treatment of schizophrenia and manic episodes associated with bipolar disorders with anti-diabetic efficacy.

4. A combination according to claims 3 for use in the treatment of schizophrenia and manic episodes associated with bipolar disorders with anti-diabetic efficacy, which results in lowering blood glucose excursion.

5. A combination according to claim 4 for use in the treatment of schizophrenia and manic episodes associated with bipolar disorders with anti-diabetic efficacy which results in lowering fat mass and body weight

6. The use of a combination according to claim 1 in the manufacture of a medicament for the treatment of schizophrenia and manic episodes associated with bipolar disorders with reduced incidence of metabolic syndrome.

7. The use of a combination according to claim 6 in the manufacture of a medicament for the treatment of schizophrenia and manic episodes associated with bipolar disorders with anti-diabetic efficacy.

8. The use of a combination according to claims 7 in the manufacture of a medicament for the treatment of schizophrenia and manic episodes associated with bipolar disorders with anti-diabetic efficacy which results in lowering blood glucose excursion.

9. The use of a combination according to claim 8 in the manufacture of a medicament for the treatment of schizophrenia and manic episodes associated with bipolar disorders with anti-diabetic efficacy which results in lowering fat mass and body weight.

10. A pharmaceutical composition comprising a combination as described in claim 1, together with pharmaceutically acceptable excipients for the treatment of schizophrenia and manic episodes associated with bipolar disorders with reduced incidence of metabolic syndrome.

11. A pharmaceutical composition as described in claim 1in accordance with claim 10 together with pharmaceutically acceptable excipients for the treatment of schizophrenia and manic episodes associated with bipolar disorders with reduced incidence of metabolic syndrome, wherein the reduced incidence of metabolic syndrome results from anti-diabetic efficacy with lowering blood glucose excursion, fat mass and body weight.