The current invention demonstrates for the first time that the use of an NK3R antagonist prevents adiposity-induced weight gain. It is also evidenced that the use of an NK3R antagonist enables weight loss by reduction of fat mass, without substantial muscle loss.

SUMMARY

This present disclosure thus relates to a NK-3 receptor antagonist for use in the therapeutic treatment of excess body weight and/or excess body fat. Especially, the present disclosure relates to a NK-3 receptor antagonist for use in the therapeutic treatment of excess body fat or in the prevention of body fat gain in patients; provided that the NK-3 receptor antagonist is not 3-Methyl-2-phenyl-N-[(1S)-1-phenylpropyl]-4-quinolinecarboxamide.

In one aspect of the present disclosure, there is provided a use of an NK-3 receptor antagonist in the manufacture of a medicament for the therapeutic treatment of excess body fat or in the prevention of body fat gain in patients; provided that the NK-3 receptor antagonist is not 3-Methyl-2-phenyl-N-[(1S)-1-phenylpropyl]-4-quinolinecarboxamide.

In another aspect of the present disclosure, there is provided a use of an NK-3 receptor antagonist in the manufacture of a medicament for the treatment of a leptin-related disease.

In yet another aspect of the present disclosure, there is provided a cosmetic treatment method for improving the bodily appearance by stimulating the loss of body fat in a subject, comprising the administration to said subject of a NK-3 receptor antagonist, and optionally the renewal of said administration until the expected cosmetic effect is obtained, provided that the NK-3 receptor antagonist is not 3-Methyl-2-phenyl-N-[(1S)-1-phenylpropyl]-4-quinolinecarboxamide.

According to one embodiment, the NK-3 receptor antagonist is selected from the group consisting of:

(a) 3-Methyl-2-phenyl-N-[(1S)-1-phenylpropyl]-4-quinolinecarboxamide

(b) (R)-N-(1-(3-(1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl)propyl)-4-phenyl piperidin-4-yl)-N-methylacetamide

(c) (R)-[[2-Phenyl-4-quinolinyl)carbonyl]amino]-methyl ester benzeneacetic acid

(d) N1-[1-3-[(3R)-1-Benzoyl-3-(3-(3,4-dichlorophenyl)-3-piperidinyl]propyl]-4-phenyl-piperidinyl]-N,N-dimethylurea hydrochloride

(e) 3-methanesulfonamido-2-phenyl-N-[(1S)-1-phenylpropyl]quinoline-4-carbox amide

(f) 3-Hydroxy-2-phenyl-N-[(1S)-1-phenylpropyl]-4-quinolinecarboxamide

(g) methyl 2-(3-((4-(tert-butyl)piperazin-1-yl)methyl)-8-fluoro-2-phenylquinoline-4-carbonyl)-1-phenylhydrazinecarboxylate

(h) compounds of general formula A:

R^3 is H, F, Cl, methyl, trifluoromethyl, nitrile or R^3 is thiophen-2-yl under the condition that R^5 is not methyl;

R^4 is methyl, ethyl, *n*-propyl, hydroxyethyl, methoxyethyl, trifluoromethyl, difluoromethyl or fluoromethyl;

R^5 is methyl, ethyl, methoxymethyl, trifluoromethyl, difluoromethyl, fluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl or 2,2,2-trifluoroethyl, preferably R^5 is methyl, ethyl, methoxymethyl, trifluoromethyl, difluoromethyl or fluoromethyl;

X^1 is N and X^2 is S or O; or X^1 is S and X^2 is N;

=== represents a single or a double bound depending on X^1 and X^2;

*- - -stands for the (*R*)-enantiomer or for the racemate of compound of formula III.

According to one embodiment, the NK-3 receptor antagonist for use according to the present disclosure is under the form of a pharmaceutical composition comprising the NK-3 receptor antagonist and at least one pharmaceutically acceptable vehicle.

According to one embodiment, the NK-3 receptor antagonist is for the treatment of patients suffering from pathological excess of body fat and/or of excess body weight. According to one embodiment, the NK-3 receptor antagonist is for the treatment of patients suffering from pathological excess of body fat or for the prevention of body fat gain in patients prone to suffer from pathological excess body fat.

According to one embodiment, patients suffering from pathological excess of body fat and/or of excess body weight are selected from individuals suffering from hormonal imbalance; individuals suffering from genetic susceptibility to excess body weight; and individuals where an adipose-specific decrease in weight is deemed to be of therapeutic benefit. According to one embodiment, patients suffering from pathological excess of body fat or patients prone to suffer from pathological excess body fat are selected from individuals suffering from hormonal imbalance; individuals suffering from genetic susceptibility to excess body weight; and individuals where an adipose-specific decrease in weight is deemed to be of therapeutic benefit.

According to one embodiment, individuals suffering from hormonal imbalance are selected from women subjected to estrogen-lowering therapies; and women experiencing natural, age-related decreases in estrogen.

According to one embodiment, individuals suffering from hormonal imbalance are selected from women that undergo changes in ovarian hormone levels.

According to one embodiment, individuals suffering from hormonal imbalance are selected from men subjected to androgen-lowering therapies; and men experiencing natural, age-related decreases in circulating testosterone.

According to one embodiment, individuals where an adipose-specific decrease in weight is deemed to be of therapeutic benefit are selected from overweight individuals; individuals receiving medical treatments that are accompanied with weight gain comprising but not limited to hormonal treatment as well as steroids, pain or antipsychotic medications; individuals having inappropriate eating behaviors.

According to one embodiment, patients are leptin-sensitive patients, preferably leptin sensitive women patients.

The present disclosure also relates to a NK-3 receptor antagonist for use in the treatment of a leptin-related disease.

According to one embodiment, the leptin-related disease is selected from metabolic disorders such as diabetes, cardiovascular diseases or metabolic syndrome; lipid regulation disorders such as lipodystrophy, including congenital and acquired lipodystrophy, dyslipidemia, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis or hyperlipidemia; Congenital Leptin Deficiency; hypothalamic amenorrhea, including exercise-induced hypothalamic amenorrhea, Rabson-Mendenhall syndrome; and osteoporosis.

According to one embodiment, the NK-3 receptor antagonist for use in the treatment of a leptin-related disease is selected from the group consisting of (b), (c), (d), (e), (f), (g), (h) and (i) as defined above.

According to one embodiment, in the treatment of leptin-related diseases, the NK-3 receptor antagonist is of formula I as defined above, and pharmaceutically acceptable salts and solvates thereof. According to one embodiment, in the treatment of leptin-related diseases, the NK-3 receptor antagonist is of formula III, as defined above. According to a specific embodiment, in the treatment of leptin-related diseases, the NK-3 receptor antagonist is **k-5**.

The present disclosure also relates to a cosmetic treatment method for improving the bodily appearance by stimulating the loss of body weight and/or of body fat in a subject, comprising the administration to said subject of a NK-3 receptor antagonist, and optionally the renewal of said administration until the expected cosmetic effect is obtained. Especially, the present disclosure relates to a cosmetic treatment method for improving the bodily appearance by stimulating the loss of body weight and/or of body fat in a subject, comprising the administration to said subject of a NK-3 receptor antagonist, and optionally the renewal of said administration until the expected cosmetic effect is obtained, provided that the NK-3 receptor antagonist is not 3-Methyl-2-phenyl-N-[(1S)-1-phenylpropyl]-4-quinolinecarboxamide.

According to one embodiment, in the cosmetic treatment method of the present disclosure, the subject is an individual being in good health and having a BMI from 18.5 to 25 kg/m^2.

According to one embodiment, in the cosmetic treatment method of the present disclosure, the NK-3 receptor antagonist is selected from the group consisting of:

(a) 3-Methyl-2-phenyl-N-[(1S)-1-phenylpropyl]-4-quinolinecarboxamide

(b) (R)-N-(1-(3-(1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl)propyl)-4-phenyl piperidin-4-yl)-N-methylacetamide

(c) (R)-[[2-Phenyl-4-quinolinyl)carbonyl]amino]-methyl ester benzeneacetic acid

(d) N1-[1-3-[(3R)-1-Benzoyl-3-(3-(3,4-dichlorophenyl)-3-piperidinyl]propyl]-4-phenyl-piperidinyl]-N,N-dimethylurea hydrochloride

(e) 3-methanesulfonamido-2-phenyl-N-[(1S)-1-phenylpropyl]quinoline-4-carbox amide

(f) 3-Hydroxy-2-phenyl-N-[(1S)-1-phenylpropyl]-4-quinolinecarboxamide

(g) methyl 2-(3-((4-(tert-butyl)piperazin-1-yl)methyl)-8-fluoro-2-phenylquinoline-4-carbonyl)-1-phenylhydrazinecarboxylate

(h) compounds of general formula A, as defined above

(i) compounds of general formula I, as defined above;

and stereoisomers, mixture of stereoisomers, prodrugs, pharmaceutically acceptable salts, hydrates, solvates, acid salt hydrates, N-oxides and isomorphic crystalline forms thereof.

According to one embodiment, in the cosmetic treatment method of the present disclosure, the NK-3 receptor antagonist is selected from the group consisting of (b), (c), (d), (e), (f), (g), (h) and (i) as defined above.

According to one embodiment, in the cosmetic treatment method of the present disclosure, the NK-3 receptor antagonist is of formula I as defined above, and pharmaceutically acceptable salts and solvates thereof.

According to one embodiment, in the cosmetic treatment method of the present disclosure, the NK-3 receptor antagonist is of formula III, as defined above.

DEFINITIONS

The definitions and explanations below are for the terms as used throughout the entire application, including both the specification and the claims.

The term "**NK3R antagonist**" or "**NK-3 receptor antagonist**" refers to a compound that can bind to a neurokinin B receptor (NK3R) but has little or no functional activity of its own at the receptor— thus disrupting, blocking or otherwise interfering with the action of the naturally occurring, endogenous ligand (i.e.. NKB). Preferably the NK3R antagonist is a compound which competitively or non-competitively binds to the NK3R at the same site as an agonist (for example, the endogenous ligand), but does not activate an intracellular response initiated by an active form of the receptor. An antagonist thereby inhibits the intracellular response induced by an agonist.

CLAIMS

1. Use of an NK-3 receptor antagonist in the manufacture of a medicament for the therapeutic treatment of excess body fat or in the prevention of body fat gain in patients;

provided that the NK-3 receptor antagonist is not 3-Methyl-2-phenyl-N-[(1S)-1-phenylpropyl]-4-quinolinecarboxamide.

2. The use according to claim **1**, wherein the NK-3 receptor antagonist is selected from the group consisting of:

(b) (R)-N-(1-(3-(1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl)propyl)-4-phenyl piperidin-4-yl)-N-methylacetamide;

(c) (R)-[[2-Phenyl-4-quinolinyl)carbonyl]amino]-methyl ester benzeneacetic acid

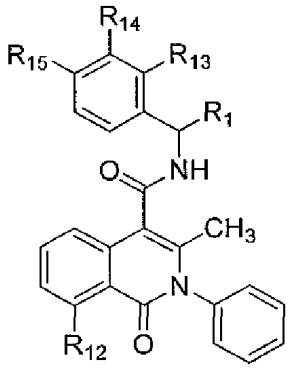
(d) N1-[1-3-[(3R)-1-Benzoyl-3-(3-(3,4-dichlorophenyl)-3-piperidinyl]propyl]-4-phenyl-piperidinyl]-N,N-dimethylurea hydrochloride;

(e) 3-methanesulfonamido-2-phenyl-N-[(1S)-1-phenylpropyl]quinoline-4-carbox amide;

(f) 3-Hydroxy-2-phenyl-N-[(1S)-1-phenylpropyl]-4-quinolinecarboxamide;

(g) methyl 2-(3-((4-(tert-butyl)piperazin-1-yl)methyl)-8-fluoro-2-phenylquinoline-4-carbonyl)-1-phenylhydrazinecarboxylate;

(h) compounds of general formula A:



wherein R_1 represents ethyl, cylopropyl or cyclobutyl;

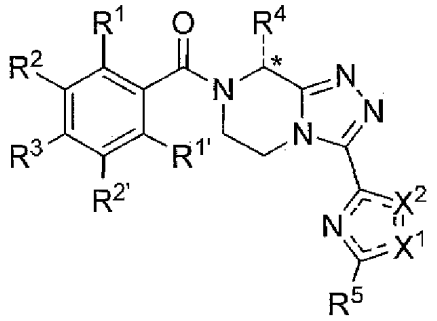
wherein R_{12} represents fluoro or chloro; and

alkylamino, alkylsulfonylamino, alkoxycarbonylamino, aminoalkoxy, or alkoxycarbonylaminoalkoxy;

and stereoisomers, mixture of stereoisomers, prodrugs, pharmaceutically acceptable salts, hydrates, solvates, acid salt hydrates, N-oxides and isomorphic crystalline forms thereof.

3. The use according to claim **1** or claim **2**, wherein the NK-3 receptor antagonist is of formula I as defined in claim **2**, and pharmaceutically acceptable salts and solvates thereof.

4. The use according to anyone of claims **1** to **3**, wherein the NK-3 receptor antagonist is of formula III



and pharmaceutically acceptable solvates thereof, wherein:

$\mathbf{R^1}$ is H, F or methyl;

$\mathbf{R^{1'}}$ is H;

$\mathbf{R^2}$ is H, F, Cl or methoxy;

$\mathbf{R^{2'}}$ is H or F;

$\mathbf{R^3}$ is H, F, Cl, methyl, trifluoromethyl, nitrile or $\mathbf{R^3}$ is thiophen-2-yl under the condition that $\mathbf{R^5}$ is not methyl;

$\mathbf{R^4}$ is methyl, ethyl, *n*-propyl, hydroxyethyl, methoxyethyl, trifluoromethyl, difluoromethyl or fluoromethyl;

$\mathbf{R^5}$ is methyl, ethyl, methoxymethyl, trifluoromethyl, difluoromethyl, fluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl or 2,2,2-trifluoroethyl;

$\mathbf{X^1}$ is N and $\mathbf{X^2}$ is S or O; or $\mathbf{X^1}$ is S and $\mathbf{X^2}$ is N;

$=\!=$ represents a single or a double bound depending on $\mathbf{X^1}$ and $\mathbf{X^2}$;

*---stands for the (*R*)-enantiomer or for the racemate of compound of formula III.

5. The use according to anyone of claims **1** to **4**, under the form of a pharmaceutical composition comprising the NK-3 receptor antagonist and at least one pharmaceutically acceptable vehicle.

6. The use according to anyone of claims **1** to **5**, for the treatment of patients suffering from pathological excess of body fat or for the prevention of body fat gain in patients prone to suffer from pathological excess body fat.

7. The use according to claim **6**, wherein patients suffering from pathological excess of body fat or patients prone to suffer from pathological excess body fat are selected from individuals suffering from hormonal imbalance; individuals suffering from genetic susceptibility to excess body weight; and individuals where an adipose-specific decrease in weight is deemed to be of therapeutic benefit.

8. The use according to claim **7**, wherein the individuals suffering from hormonal imbalance are selected from women subjected to estrogen-lowering therapies; and women experiencing natural, age-related decreases in estrogen.

9. The use according to claim **7**, wherein the individuals suffering from hormonal imbalance are selected from women that undergo changes in ovarian hormone levels.

10. The use according to claim **7**, wherein the individuals suffering from hormonal imbalance are selected from men subjected to androgen-lowering therapies; and men experiencing natural, age-related decreases in circulating testosterone.

11. The use according to claim **7**, wherein the individuals where an adipose-specific decrease in weight is deemed to be of

therapeutic benefit are selected from overweight individuals; individuals receiving medical treatments that are accompanied with weight gain comprising but not limited to hormonal treatment as well as steroids, pain or antipsychotic medications; individuals having inappropriate eating behaviors.

12. The use according to claim **6**, wherein patients are leptin-sensitive patients, preferably leptin sensitive women patients.

13. Use of an NK-3 receptor antagonist in the manufacture of a medicament for the treatment of a leptin-related disease.

14. The use according to claim **13**, wherein the leptin-related disease is selected from metabolic disorders such as diabetes, cardiovascular diseases or metabolic syndrome; lipid regulation disorders such as lipodystrophy, including congenital and acquired lipodystrophy, dyslipidemia, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis or hyperlipidemia; Congenital Leptin Deficiency; hypothalamic amenorrhea, including exercise-induced hypothalamic amenorrhea; Rabson-Mendenhall syndrome; and osteoporosis.

15. The use according to claim **13** or claim **14**, wherein the NK-3 receptor antagonist is selected from the group consisting of:

(b) (R)-N-(1-(3-(1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl)propyl)-4-phenyl piperidin-4-yl)-N-methylacetamide;

(c) (R)-[[2-Phenyl-4-quinolinyl)carbonyl]amino]-methyl ester benzeneacetic acid;

(d) N1-[1-3-[(3R)-1-Benzoyl-3-(3-(3,4-dichlorophenyl)-3-piperidinyl]propyl]-4-phenyl-piperidinyl]-N,N-dimethylurea hydrochloride;

(e) 3-methanesulfonamido-2-phenyl-N-[(1S)-1-phenylpropyl]quinoline-4-carbox amide;

(f) 3-Hydroxy-2-phenyl-N-[(1S)-1-phenylpropyl]-4-quinolinecarboxamide;

(g) methyl 2-(3-((4-(tert-butyl)piperazin-1-yl)methyl)-8-fluoro-2-phenylquinoline-4-carbonyl)-1-phenylhydrazinecarboxylate;

(h) compounds of general formula A: