treatment of obesity as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management.

Insatiable hunger and severe obesity are characteristic features of the Prader-Willi-Syndrome (PWS), a genetically caused orphan disease with a complex pathology. AG levels in plasma of PWS subjects are elevated and AG/UAG ratios are increased suggesting a causal relationship (N. Wierup et al., Regulatory Peptides (2002) 107, 63– 69; R.J. Kuppens et al., Endocrine (2015) 50(3), 633-642). Therefore GOAT inhibitors may be effective in reducing food craving behavior and body weight in PWS patients ameliorating one major burden affecting the patients and their families.

Furthermore the ghrelin system seems to play a major role in glucose homeostasis. Administration of AG to human subjects leads to suppression of glucose-induced insulin secretion and an increase in plasma glucose. Infusion of UAG is able to counteract the hyperglycemic effect of AG (F. Broglio et al., J.Clin.Endocrinol.Metab. (2004) 89, 3062-3065). The expression of GOAT, ghrelin and GHSR1a in human pancreatic islets suggests a paracrine role on insulin secretion (A. DelParigi et al., J. Clin. Endocrinol. Metab. (2002) 87(12), 5461-5464). In addition UAG promotes pancreatic β-cell and human islet cell survival in vitro (R. Granata et al., Endocrinology (2007) 148(2), 512-529) and prevents diabetes in streptozotocin treated rats (R. Granata et al., J. Med. Chem. (2012) 55(6), 2585-2596). Thus treatment with a GOAT inhibitor is expected to improve glucose homeostasis in patients with type 2 diabetes or obese with impaired glucose tolerance.

Object of the present description

The object of the embodiments disclosed herein is to provide new compounds, hereinafter described as compounds of formula **I**, in particular new oxadiazolopyridine derivatives, which are active with regard to the ghrelin O-acyl transferase (GOAT), notably they are ghrelin O-acyl transferase (GOAT) inhibitors.

A further object of the embodiments disclosed herein is to provide new compounds, in particular oxadiazolopyridine derivatives, which have an inhibiting effect on ghrelin O-acyl

transferase (GOAT) *in vitro* and/or *in vivo* and possess suitable pharmacological and pharmacokinetic properties to use them as medicaments.

A further object of the embodiments disclosed herein is to provide effective ghrelin O-acyl transferase (GOAT) inhibitors, in particular for the treatment of metabolic disorders, for obesity, including, but not limited to obesity in patients suffering from Prader-Willi-Syndrome (PWS), insulin resistance and diabetes, in particular type 2 diabetes mellitus.

A further object of the embodiments disclosed herein is to provide methods for treating a disease or condition mediated by the inhibition of ghrelin O-acyl transferase (GOAT) in a patient.

A further object of the embodiments disclosed herein is to provide a pharmaceutical composition comprising at least one compound according to the description.

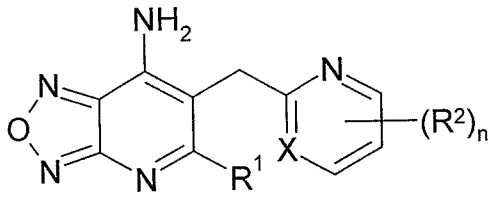
A further object of the embodiments disclosed herein is to provide a combination of at least one compound according to the description with one or more additional therapeutic agents.

Further objects of the embodiments disclosed herein become apparent to the one skilled in the art by the description hereinbefore and in the following and by the examples.

Ghrelin O-acyl transferase (GOAT) inhibitors are known in the art, see for example the compounds disclosed in WO 2013/125732 and WO 2015/073281. The oxadiazolopyridine derivatives of the present description are structurally quite different and may provide several advantages, such as enhanced potency, high metabolic and/or chemical stability, high selectivity and tolerability, enhanced solubility, the ability to cross the blood-brain barrier and the possibility to form stable salts.

Summary

The description relates to a compound of formula



(I),

wherein

X is CH or N;

R^1 is selected from the group R^1-G1 consisting of CH_3, $-CH_2OH$ and Cl;

R^2 is independently of each other selected from the group R^2-G1 consisting of H, F, Cl, Br, I, CN, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, OH, -O-(C_{1-6}-alkyl), -O-(C_{3-7}-cycloalkyl), -O-(C_{1-3}-alkyl)-(C_{3-7}-cycloalkyl), -O-heterocyclyl, -O-(C_{1-3}-alkyl)-heterocyclyl, -O-aryl, -O-heteroaryl, -S-(C_{1-3}-alkyl), -SO-(C_{1-3}-alkyl), $-SO_2$-(C_{1-3}-alkyl), $-NH_2$, -NH-(C_{1-6}-alkyl), -NH-(C_{3-6}-cycloalkyl), -NH-(C_{1-3}-alkyl)-heterocyclyl, -NH-(C_{1-6}-alkyl)-C(=O)-NH_2, -C(=O)-NH_2, -C(=O)-NH-(C_{1-3}-alkyl), -C(=O)-N(C_{1-3}-alkyl)$_2$, -C(=O)OH, -C(=O)-O-(C_{1-4}-alkyl), -C(=O)-(C_{1-4}-alkyl), -C_{1-3}-alkyl-C(=O)-O-(C_{1-4}-alkyl), heterocyclyl, heteroaryl and 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl,

wherein each alkyl or cycloalkyl group is optionally independently substituted with one or more substituents selected from the group consisting of F, CN and OH, and

wherein each heterocyclyl group is selected from a mono- or spirocyclic 4-7-membered cycloalkyl group, in which 1, 2 or 3 CH_2-groups are independently of each other replaced by O, S, NH or C=O, and

wherein each heterocyclyl group is optionally substituted with 1 or 2 substituents independently of each other selected from F, OH and C_{1-3}-alkyl,

wherein each aryl group is selected from a group consisting of phenyl and naphthyl, and

wherein each heteroaryl group is selected from a 5-membered aromatic cycle containing 1 or 2 heteroatoms independently selected from N, O and S or from a 6-membered aromatic cycle containing 1 or 2 N, and

wherein each aryl or heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from a group consisting of F, CN and C_{1-3}-alkyl, which is optionally substituted with one or more F;

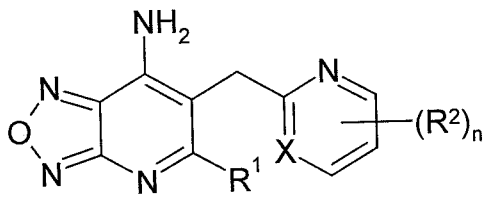
or, if two groups R^2 are attached to adjacent C atoms of the pyridine or pyrimidine group, they may be linked with each other and together form a $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$ or $-O-CH_2-CH_2-CH_2-O-$ bridge, in which 1 or 2 H atoms may be replaced with F or C_{1-3}-alkyl; and

n is 1, 2 or 3;

wherein each of the above-mentioned alkyl groups may be substituted with one or more F;

the isoforms, tautomers, stereoisomers, metabolites, prodrugs, solvates, hydrates, and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases, or the combinations thereof.

In one aspect, this description relates to a compound of formula



(I),

wherein

X is CH or N;

R^1 is selected from the group consisting of CH_3, $-CH_2OH$ and Cl;

R^2 is independently of each other selected from the group consisting of H, F, Cl, Br, I, CN, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, OH, -O-(C_{1-6}-alkyl), -O-(C_{3-7}-cycloalkyl), -O-(C_{1-3}-alkyl)-(C_{3-7}-cycloalkyl), -O-heterocyclyl, -O-(C_{1-3}-alkyl)-heterocyclyl, -O-aryl, -O-heteroaryl, -S-(C_{1-3}-alkyl), -SO-(C_{1-3}-alkyl), $-SO_2$-(C_{1-3}-alkyl), $-NH_2$, -NH-(C_{1-6}-alkyl), -NH-(C_{3-6}-cycloalkyl), -NH-(C_{1-3}-alkyl)-heterocyclyl, -NH-(C_{1-6}-alkyl)-C(=O)-NH_2, -C(=O)-NH_2, -C(=O)-NH-(C_{1-3}-alkyl), -C(=O)-N(C_{1-3}-alkyl)$_2$, -C(=O)OH, -C(=O)-O-(C_{1-4}-alkyl), -C(=O)-(C_{1-4}-alkyl), -C_{1-3}-alkyl-C(=O)-O-(C_{1-4}-alkyl), heterocyclyl, heteroaryl and 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl,

wherein each alkyl or cycloalkyl group is optionally independently substituted with one or more substituents selected from the group consisting of F, CN and OH, and

wherein each heterocyclyl group is selected from a mono- or spirocyclic 4-7-membered cycloalkyl group, in which 1, 2 or 3 CH_2-groups are independently of each other replaced by O, S, NH or C=O, and

wherein each heterocyclyl group is optionally substituted with 1 or 2 substituents independently of each other selected from F, OH and C_{1-3}-alkyl,

wherein each aryl group is selected from a group conistsing of phenyl and naphthyl, and

wherein each heteroaryl group is selected from a 5-membered aromatic cycle containing 1 or 2 heteroatoms independently selected from N, O and S or from a 6-membered aromatic cycle containing 1 or 2 N, and

wherein each aryl or heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from a group conisting of F, CN and C_{1-3}-alkyl, which is optionally substituted with one or more F;

or, if two groups R^2 are attached to adjacent C atoms of the pyridine or pyrimidine group, they may be linked with each other and together form a –O-CH_2-O-, -O-CH_2-CH_2-O- or –O-CH_2-CH_2-CH_2-O- bridge, in which 1 or 2 H atoms may be replaced with F or C_{1-3}-alkyl; and

n is 1, 2 or 3;

wherein each of the above-mentioned alkyl groups may be substituted with one or more F;

or a salt thereof.

The extension -Gn used within the definitions is meant to identify genus n of the respective substituent. For example, R-G1 defines genus 1 of the substituent R.

The expression "optionally substituted with 1 or more F atoms" means that none or one up to successively all H atoms bound to carbon atoms of the respective group or submoiety may be replaced by F atoms, preferably 1 to 5 H atoms or, more preferred, 1 to 3 H atoms may be replaced by F atoms.

In another aspect this description relates to a pharmaceutically acceptable salt of a compound as defined herein.

In a further aspect this description relates to a pharmaceutical composition, comprising one or more compounds of general formula I or one or more pharmaceutically acceptable salts thereof as defined herein, optionally together with one or more inert carriers and/or diluents.

This description also relates to a method for treating diseases or conditions which are mediated by inhibiting ghrelin O-acyl transferase (GOAT) in a patient in need thereof characterized in that a compound of general formula I or a pharmaceutically acceptable salt thereof is administered to the patient.

There is also provided a method for treating a metabolic disease or disorder, such as obesity, including, but not limited to obesity in patients suffering from Prader-Willi-Syndrome, insulin resistance and diabetes, in particular type 2 diabetes mellitus, in a patient in need thereof characterized in that a therapeutically effective amount of a compound of general formula I or a pharmaceutically acceptable salt thereof is administered to the patient.

There is also provided the use of a compound of the general formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for a therapeutic method as described hereinbefore and hereinafter. In another aspect this description relates to use of a compound as defined herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease or condition which is mediated by inhibiting the activity of the ghrelin O-acyl transferase (GOAT). In another aspect this description relates to use of a compound as defined herein or a pharmaceutically acceptable salt thereof for the prepation of a medicament for treating obesity, including obesity in patients suffering from Prader-Willi-Syndrome, type 2 diabetes mellitus or insulin resistance.

There is also provided a compound of the general formula I or a pharmaceutically acceptable salt thereof for use in a therapeutic method as described hereinbefore and hereinafter. In another aspect this description relates to a compound as defined herein or a pharmaceutically acceptable salt thereof for use as a medicament. In another aspect this description relates to a compound as defined herein or a pharmaceutically acceptable salt thereof for use in treating obesity, type 2 diabetes mellitus, insulin resistance and/or obsesity in patients suffering from Prader-Willi-Syndrome.

This description also relates to a method for treating a disease or condition mediated by the inhibition of ghrelin O-acyl transferase (GOAT) in a patient that includes the step of administering to the patient in need of such treatment a therapeutically effective amount of a compound of the general formula I or a pharmaceutically acceptable salt thereof in combination with a therapeutically effective amount of one or more additional therapeutic agents.

This description also relates to the use of a compound of the general formula **I** or a pharmaceutically acceptable salt thereof in combination with one or more additional therapeutic agents for the treatment of diseases or conditions which are mediated by the inhibition of ghrelin O-acyl transferase (GOAT).

In a further aspect this description relates to a pharmaceutical composition which comprises a compound according to general formula **I** or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents, optionally together with one or more inert carriers and/or diluents.

Other aspects and embodiments of the description become apparent to the one skilled in the art from the specification and the experimental part as described hereinbefore and hereinafter.

Detailed Description

Unless otherwise stated, the groups, residues, and substituents, particularly X, R^1, R^2 and n are defined as above and hereinafter. If residues, substituents, or groups occur several times in a compound, they may have the same or different meanings. Some preferred meanings of individual groups and substituents of the compounds according to the invention will be given hereinafter. Any and each of these definitions may be combined with each other.

X:

X is preferably CH or N.

According to one embodiment, X is CH.

According to another embodiment, X is N.

R^1:

R^1-G1:

The group R_1 is preferably selected from the group R^1-G1 as defined hereinbefore.

R^1-G2:

In one embodiment the group R^1 is selected from the group R^1-G2 consisting of CH_3 and Cl.