

SUBSTITUTED CYCLOPENTANES, TETRAHYDROFURANES AND PYRROLIDINES AS OREXIN RECEPTOR ANTAGONISTS

The present invention relates to amide derivatives, processes for their preparation,
5 pharmaceutical compositions containing them and their use in therapy, particularly in the
treatment or prevention of conditions having an association with the orexin sub-type 1
receptor.

The orexin peptides (orexin A and orexin B, OxA and OxB), also known as hypocretins,
10 were discovered in 1998 by two groups (Sakurai *et al.*, *Cell*, **1998**, 92, 573 and De Lecea *et al.*, *Proc. Nat. Acad. Sci.*, **1998**, 95, 322). These neuropeptides are both derived from the
common precursor pre-pro-orexin and are produced in the lateral hypothalamus. OxA is a
33 amino acid residue which has similar potency at both the Ox1R (orexin 1 receptors) and
Ox2R (orexin 2 receptors) whereas OxB is made up of 28 amino acids and binds
15 selectively to the Ox2R.

Orexin receptors are believed to be implicated in both feeding behaviour (Sakurai *et al.*,
Cell, **1998**, 92, 573) and also in regulating sleep architecture (Chemelli *et al.*, *Cell*, **1999**,
98, 437). More recently, it has been shown that orexin receptors are implicated in arousal,
20 reward, learning and memory (Harris *et al.*, *Trends Neurosci.*, **2006**, 29, 571).

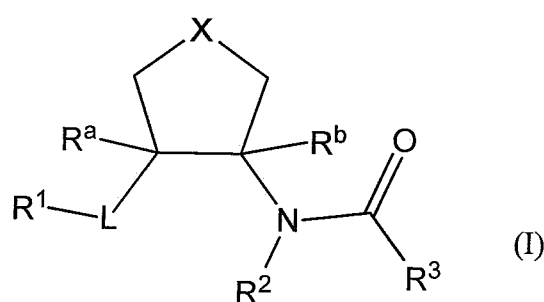
WO 2003/099276 describes a broad class of compounds, including certain amides, which
are useful as factor Xa inhibitors for treating thromboembolic disorders.

25 We have now discovered a class of compounds that are orexin receptor antagonists.
Furthermore, certain compounds of the invention show selectivity for the orexin 1 receptor
over the orexin 2 receptor.

SUMMARY

30 In one aspect, the present invention refers to a compound of formula

1a



wherein

R^1 represents an 8- to 10-membered fused bicyclic heteroaromatic group optionally substituted by at least one substituent independently selected from halogen, cyano, hydroxyl, C₃-C₆ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ alkoxy, C₁-C₃ alkoxycarbonyl, C₁-C₃ alkoxycarbonylamino, C₁-C₃ haloalkoxy, -NR⁴R⁵, C₃-C₆ cycloalkylamino, C₁-C₃ alkylcarbonyloxy, C₁-C₃ alkylcarbonylamino, sulphonamido, C₁-C₃ alkylsulphonyl, C₁-C₃ alkylsulphonylamino and -C(O)NR⁶R⁷;

L represents a bond, CH₂, O, NH or N(CH₃);

R^a represents a hydrogen atom or a C₁-C₃ alkyl or C₁-C₃ haloalkyl group;

R^b represents a hydrogen atom or a C₁-C₃ alkyl or C₁-C₃ haloalkyl group;

X represents CF₂, or CHR⁸;

R^2 represents a hydrogen atom or a C₁-C₆ alkyl or C₃-C₆ cycloalkyl group;

R^3 represents a 5- or 6-membered monocyclic heteroaromatic group optionally substituted by at least one substituent independently selected from halogen, hydroxyl, cyano, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ hydroxyalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₂-C₄ alkenyl, C₁-C₃ alkylcarbonyloxy, C₁-C₃ alkoxycarbonyl, -NR¹⁰R¹¹, -C(O)NR¹²R¹³, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyloxy,

C₃-C₆ cycloalkylmethyl or a 5- or 6-membered heteroaryl group, the heteroaryl group being optionally substituted by at least one substituent independently selected from C₁-C₆ alkyl, C₁-C₆ alkoxy and C₁-C₆ haloalkoxy;

R^4 and R^5 each independently represent a hydrogen atom or a C₁-C₃ alkyl or C₃-C₆ cycloalkyl group, or R^4 and R^5 may together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by at least one substituent independently selected from halogen, hydroxyl and C₁-C₃ alkoxy;

R^6 and R^7 each independently represent a hydrogen atom or a C₁-C₃ alkyl or C₃-C₆ cycloalkyl group, or R^6 and R^7 may together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by at least one substituent independently selected from halogen and hydroxyl;

R^8 represents a hydrogen or halogen atom or a hydroxyl group;

R^{10} and R^{11} each independently represent a hydrogen atom or a C₁-C₃ alkyl or C₃-C₆ cycloalkyl group, or R^{10} and R^{11} may together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by at least one substituent independently selected from halogen, hydroxyl and C₁-C₃ alkoxy; and

R^{12} and R^{13} each independently represent a hydrogen atom or a C₁-C₃ alkyl or C₃-C₆ cycloalkyl group, or R^{12} and R^{13} may together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by at least one substituent independently selected from halogen and hydroxyl;

or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention refers to a compound of formula (I) as claimed in the present invention selected from the group consisting of:

3-Bromo-*N*-[(1*S*,2*S*)-2-[(6-fluoro-1,3-benzothiazol-2-yl)amino] cyclopentyl]-pyridine-2-carboxamide;

6-Bromo-*N*-[(1*S*,2*S*)-2-[(6-fluoro-1,3-benzothiazol-2-yl)amino] cyclopentyl]-3-methoxypyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-methoxypyridine-2-carboxamide;

3-Chloro-*N*-[(1*S*,2*S*)-2-[(6-fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-pyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-methoxy-*N*-methylpyridine-2-carboxamide;

5 *N*-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(2*H*-1,2,3-triazol-2-yl)pyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzoxazol-2-yl)amino]cyclopentyl]-3-methoxypyridine-2-carboxamide;

10 *N*-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(propan-2-yloxy)pyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-methoxy-6-methylpyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(1*H*-pyrazol-1-yl)pyridine-2-carboxamide;

15 3-Fluoro-*N*-[(1*S*,2*S*)-2-[(6-fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]pyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(piperidin-1-yl)pyridine-2-carboxamide;

20 3-(Azetidin-1-yl)-*N*-[(1*S*,2*S*)-2-[(6-fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]pyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(pyrrolidin-1-yl)pyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

25 3-Methoxy-*N*-[(1*S*,2*S*)-2-[(quinoxalin-2-yl)amino]cyclopentyl]pyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-methoxy-6-(trifluoromethyl)pyridine-2-carboxamide;

30 3-Ethoxy-*N*-[(1*S*,2*S*)-2-[(6-fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]pyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(trifluoromethoxy)pyridine-2-carboxamide;

3-(Difluoromethoxy)-*N*-[(1*S*,2*S*)-2-[(6-fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]pyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Chloro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(2*H*-1,2,3-triazol-2-yl)pyridine-2-carboxamide;

5 *N*-[(1*S*,2*S*)-2-[(6-Chloro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(difluoromethoxy)pyridine-2-carboxamide;

3-(Difluoromethoxy)-*N*-[(1*S*,2*S*)-2-[(6-fluoro-1,3-benzoxazol-2-yl)amino]cyclopentyl]pyridine-2-carboxamide;

10 *N*-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(1*H*-1,2,3-triazol-1-yl)pyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Chloro-1,3-benzoxazol-2-yl)amino]cyclopentyl]-3-(difluoromethoxy)pyridine-2-carboxamide;

3-Ethoxy-6-methyl-*N*-[2-(quinolin-2-ylmethyl)cyclopentyl]pyridine-2-carboxamide;

3-Ethoxy-6-methyl-*N*-[2-(quinolin-2-ylmethyl)cyclopentyl]pyridine-2-carboxamide;

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enantiomers thereof and pharmaceutically acceptable salts of any of the foregoing.

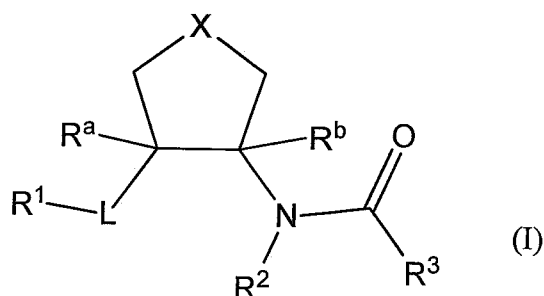
In yet another aspect, the present invention refers to a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as
20 claimed in the present invention, in association with a pharmaceutically acceptable adjuvant, diluent or carrier, and optionally one or more other therapeutic agents.

DETAILED DESCRIPTION

In accordance with the present disclosure, there is therefore provided a compound of
25 formula

CLAIMS

1. A compound of formula



5 wherein

R^1 represents an 8- to 10-membered fused bicyclic heteroaromatic group optionally substituted by at least one substituent independently selected from halogen, cyano, hydroxyl, C₃-C₆ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ alkoxy, C₁-C₃ alkoxycarbonyl, C₁-C₃ alkoxycarbonylamino, C₁-C₃ haloalkoxy, -NR⁴R⁵, C₃-C₆ cycloalkylamino, C₁-C₃ alkylcarbonyloxy, C₁-C₃ alkylcarbonylamino, sulphonamido, C₁-C₃ alkylsulphonyl, C₁-C₃ alkylsulphonylamino and -C(O)NR⁶R⁷;

L represents a bond, CH₂, O, NH or N(CH₃);

R^a represents a hydrogen atom or a C₁-C₃ alkyl or C₁-C₃ haloalkyl group;

R^b represents a hydrogen atom or a C₁-C₃ alkyl or C₁-C₃ haloalkyl group;

15 X represents CF₂, or CHR⁸;

R^2 represents a hydrogen atom or a C₁-C₆ alkyl or C₃-C₆ cycloalkyl group;

R^3 represents a 5- or 6-membered monocyclic heteroaromatic group optionally substituted by at least one substituent independently selected from halogen, hydroxyl, cyano, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ hydroxyalkyl, C₁-C₃ alkoxy,

20 C₁-C₃ haloalkoxy, C₂-C₄ alkenyl, C₁-C₃ alkylcarbonyloxy,

C₁-C₃ alkoxycarbonyl, -NR¹⁰R¹¹, -C(O)NR¹²R¹³, C₃-C₆ cycloalkyl,

C₃-C₆ cycloalkyloxy, C₃-C₆ cycloalkylmethyl or a 5- or 6-membered heteroaryl group, the heteroaryl group being optionally substituted by at least one substituent independently selected from C₁-C₆ alkyl, C₁-C₆ alkoxy and C₁-C₆ haloalkoxy;

R^4 and R^5 each independently represent a hydrogen atom or a C_1 - C_3 alkyl or C_3 - C_6 cycloalkyl group, or R^4 and R^5 may together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by at least one substituent independently selected from halogen, hydroxyl and C_1 - C_3 alkoxy;

5 R^6 and R^7 each independently represent a hydrogen atom or a C_1 - C_3 alkyl or C_3 - C_6 cycloalkyl group, or R^6 and R^7 may together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by at least one substituent independently selected from halogen and hydroxyl;

R^8 represents a hydrogen or halogen atom or a hydroxyl group;

10 R^{10} and R^{11} each independently represent a hydrogen atom or a C_1 - C_3 alkyl or C_3 - C_6 cycloalkyl group, or R^{10} and R^{11} may together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by at least one substituent independently selected from halogen, hydroxyl and C_1 - C_3 alkoxy; and

15 R^{12} and R^{13} each independently represent a hydrogen atom or a C_1 - C_3 alkyl or C_3 - C_6 cycloalkyl group, or R^{12} and R^{13} may together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally substituted by at least one substituent independently selected from halogen and hydroxyl;

20 or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R^1 represents a 9- or 10-membered fused bicyclic heteroaromatic group containing one or two ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the heteroaromatic group being optionally substituted by one or more halogen atoms.

3. A compound according to claim 1, wherein R^1 represents a 9- or 10-membered fused bicyclic heteroaromatic group selected from quinoxaliny, benzothiazoly, benzoxazoly, quinolinyl and quinazolinyl, all optionally substituted as claimed in claim 1.

4. A compound according to claim 1, wherein X represents CH₂.
5. A compound according to claim 1, wherein L represents NH.
6. A compound according to claim 1, wherein R² represents a hydrogen atom or methyl group.
7. A compound according to claim 1, wherein R³ represents a 5- or 6-membered monocyclic heteroaromatic group selected from pyridinyl, pyrimidinyl and pyrazinyl, all optionally substituted as claimed in claim 1.
8. A compound according to claim 1, wherein R³ is optionally substituted by at least one substituent independently selected from fluorine, chlorine, bromine, C₁-C₃ alkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkyl, C₁-C₃ haloalkoxy, -NR¹⁰R¹¹, or a 5- or 6-membered heteroaryl group, the heteroaryl group being optionally substituted by one or two substituents independently selected from C₁-C₂ alkyl, C₁-C₂ alkoxy and C₁-C₂ haloalkoxy.
9. A compound according to claim 1, wherein R³ is optionally substituted by at least one 5- or 6-membered heteroaryl group selected from triazolyl, pyrazolyl, oxadiazolyl, pyrimidinyl and imidazolyl, all optionally substituted by one or two substituents independently selected from C₁-C₂ alkyl.
10. A compound of formula (I) as claimed in claim 1 selected from the group consisting of:
 - 3-Bromo-*N*-[(*1S,2S*)-2-[(6-fluoro-1,3-benzothiazol-2-yl)amino] cyclopentyl]-pyridine-2-carboxamide;
 - 6-Bromo-*N*-[(*1S,2S*)-2-[(6-fluoro-1,3-benzothiazol-2-yl)amino] cyclopentyl]-3-methoxypyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-methoxypyridine-2-carboxamide;

3-Chloro-*N*-[(1*S*,2*S*)-2-[(6-fluoro-1,3-benzothiazol-2-yl)amino] cyclopentyl]-pyridine-2-carboxamide;

5 *N*-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-methoxy-*N*-methylpyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(2*H*-1,2,3-triazol-2-yl)pyridine-2-carboxamide;

10 *N*-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzoxazol-2-yl)amino]cyclopentyl]-3-methoxypyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(propan-2-yloxy)pyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-methoxy-6-methylpyridine-2-carboxamide;

15 *N*-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(1*H*-pyrazol-1-yl)pyridine-2-carboxamide;

3-Fluoro-*N*-[(1*S*,2*S*)-2-[(6-fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]pyridine-2-carboxamide;

20 *N*-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(piperidin-1-yl)pyridine-2-carboxamide;

3-(Azetidin-1-yl)-*N*-[(1*S*,2*S*)-2-[(6-fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]pyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(pyrrolidin-1-yl)pyridine-2-carboxamide;

25 *N*-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

3-Methoxy-*N*-[(1*S*,2*S*)-2-[(quinoxalin-2-yl)amino]cyclopentyl]pyridine-2-carboxamide;

30 *N*-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-methoxy-6-(trifluoromethyl)pyridine-2-carboxamide;

3-Ethoxy-*N*-[(1*S*,2*S*)-2-[(6-fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]pyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(trifluoromethoxy)pyridine-2-carboxamide;

3-(Difluoromethoxy)-*N*-[(1*S*,2*S*)-2-[(6-fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]pyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Chloro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(2*H*-1,2,3-triazol-2-yl)pyridine-2-carboxamide;

5 *N*-[(1*S*,2*S*)-2-[(6-Chloro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(difluoromethoxy)pyridine-2-carboxamide;

3-(Difluoromethoxy)-*N*-[(1*S*,2*S*)-2-[(6-fluoro-1,3-benzoxazol-2-yl)amino]cyclopentyl]pyridine-2-carboxamide;

10 *N*-[(1*S*,2*S*)-2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]cyclopentyl]-3-(1*H*-1,2,3-triazol-1-yl)pyridine-2-carboxamide;

N-[(1*S*,2*S*)-2-[(6-Chloro-1,3-benzoxazol-2-yl)amino]cyclopentyl]-3-(difluoromethoxy)pyridine-2-carboxamide;

3-Ethoxy-6-methyl-*N*-[2-(quinolin-2-ylmethyl)cyclopentyl]pyridine-2-carboxamide;

3-Ethoxy-6-methyl-*N*-[2-(quinolin-2-ylmethyl)cyclopentyl]pyridine-2-carboxamide;

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enantiomers thereof and pharmaceutically acceptable salts of any of the foregoing.

11. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in claim 1, in association with a
20 pharmaceutically acceptable adjuvant, diluent or carrier, and optionally one or more other therapeutic agents.

12. A composition according to claim 11, wherein the one or more other therapeutic agents are selected from carbamazepine, olanzapine, quetiapine, verapamil, lamotrigine,
25 oxcarbazepine, risperidone, aripiprazole, ziprasidone and lithium.