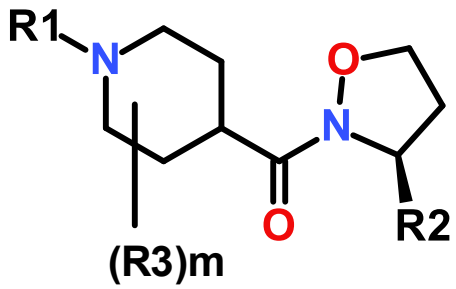
Claims

1. A compound of formula I:



(I)

wherein

R1 represents a 5-6 membered heteroaryl in which 1 to 3 ring atoms are independently selected from -N- or -S- and wherein R1 is substituted by 1 or 2 substituents independently selected from

halogen,

-(C1-C4)alkyl,

-O(C1-C4)alkyl,

-S(C1-C4)alkyl,

-S(O)(C1-C4)alkyl,

-$S(O)_2$(C1-C4)alkyl,

-O(C1-C4)alkyl-R4,

-(CO)OH,

-CN,

-(CO)O(C1-C4)alkyl,

-NRaRb,

-(CO)NRaRb, and

-(CO)NRcRd;

wherein Ra and Rb are H; and

wherein Rc is H; and

wherein Rd is –$(CH_2)_x$-(C3-C7)cycloalkyl or –$(CH_2)_x$-(C3-C7)heterocyclyl, wherein cycloalkyl or heterocyclyl is unsubstituted or substituted with 1 substituents selected from (C1-C4)alkyl or (CO)O(C1-C4)alkyl;

x is an integer 0, 1 or 2;

R2
is a 5-10 membered heteroaryl or 5 to 6 membered heterocycle, wherein 1 to 3 ring atoms are independently selected from -N-, -O- or -S-, and wherein heteroaryl or heterocycle is unsubstituted or substituted by 1 or 2 substituents selected from halogen, CN, -(C1-C4)alkyl, -(C1-C4)alkyl-OH, -(CO)NReRf and -NReRf, wherein Re and Rf are independently selected from H, (C1-C4)alkyl or -CO(C1-C4)alkyl; or wherein Re and Rf form together with the nitrogen atom to which they are attached a 4 to 6 membered ring, which is unsubstituted or substituted with oxo;

R3 is Halogen or (C1-C2)alkyl;

m is an integer 0, 1 or 3;

R4 is CN, -(CO)OH, -(CO)NRgRh or -(CO)O(C1-C4)alkyl;
wherein Rg and Rh are H;

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

2. A compound of the formula I according to claim 1, with a TPSA (topological polar surface area) value of 90 $Å^2$ or more;
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

3. A compound of the formula I according to claim 1, with a TPSA (topological polar surface area) value of 105 $Å^2$ or more;
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

4. A compound of the formula I according to claims 1, 2 or 3, wherein
R1 represents a 5-6 membered heteroaryl in which 1 to 2 ring atoms are -N- atoms and wherein R1 is substituted by 1 or 2 substituents independently selected from
halogen,
-(C1-C4)alkyl,
-O(C1-C4)alkyl,
-S(C1-C4)alkyl,
-S(O)(C1-C4)alkyl,
-$S(O)_2$(C1-C4)alkyl,
-O(C1-C4)alkyl-R4,
-(CO)OH,
-CN,
-(CO)O(C1-C4)alkyl,
-NRaRb,
-(CO)NRaRb, and
-(CO)NRcRd;
wherein Ra, Rb are H; and
wherein Rc is H; and
wherein Rd is –$(CH_2)_x$-(C3-C7)cycloalkyl or –$(CH_2)_x$-(C3-C7)heterocyclyl, wherein cycloalkyl or heterocyclyl is unsubstituted or substituted with 1 substituents selected from (C1-C4)alkyl or COO(C1-C4)alkyl;
x is an integer 0, 1 or 2;

R2
is a 5-10 membered heteroaryl or 5 to 6 membered heterocycle, wherein 1 to 3 ring atoms are independently selected from -N-, -O- or -S-, and wherein heteroaryl or heterocycle is unsubstituted or substituted by 1 or 2 substituents selected from halogen, CN, -(C1-C4)alkyl, -(C1-C4)alkyl-OH, (CO)NReRf and -NReRf, wherein Re and Rf are independently selected from H, (C1-C4)alkyl or -CO(C1-C4)alkyl; or wherein Re and Rf form together with the nitrogen atom to which they are attached a

4 to 6 membered ring, which is unsubstituted or substituted with oxo;

R3 is F, Cl, methyl or ethyl;
m is an integer 0 or 1.

R4 is CN, -(CO)OH, -(CO)NH_2, or -(CO)O(C1-C4)alkyl;
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

5. A compound of the formula I as claimed in any of claims 1 to 4, wherein

R1 is pyridyl, pyrazinyl or pyrimidinyl and wherein R1 is substituted by 1 to 2 substituents independently selected from
halogen,
-(C1-C4)alkyl,
-O(C1-C4)alkyl,
-S(C1-C4)alkyl,
-S(O)(C1-C4)alkyl,
-$S(O)_2$(C1-C4)alkyl,
-O(C1-C4)alkyl-R4,
-(CO)OH,
-CN,
-(CO)O(C1-C4)alkyl,
-NRaRb,
-(CO)NRaRb, and
-(CO)NRcRd;
wherein Ra, Rb are H; and
wherein Rc is H; and
wherein Rd is –$(CH_2)_x$-(C3-C7)cycloalkyl or –$(CH_2)_x$-(C3-C7)heterocyclyl,
wherein cycloalkyl or heterocyclyl is unsubstituted or substituted with 1 to 3 substituents selected from (C1-C4)alkyl or (CO)O(C1-C4)alkyl;

x is an integer 0, 1 or 2;

R2
is a 5-10 membered heteroaryl wherein 1 to 3 ring atoms are independently selected from -N-, or -S-, or a 5 to 6 membered heterocycle, wherein 1 or 2 ring atoms are independently selected from -N-, -O- or -S-,
and wherein heteroaryl or heterocycle is unsubstituted or substituted by 1 or 2 substituents selected from
halogen, CN, -(C1-C4)alkyl, -(C1-C4)alkyl-OH, (CO)NReRf and -NReRf, wherein Re and Rf are independently selected from H, (C1-C4)alkyl or -CO(C1-C4)alkyl; or wherein Re and Rf form together with the nitrogen atom to which they are attached a 4 to 6 membered ring, which is unsubstituted or substituted with oxo at the position adjacent to the nitrogen atom;

R3 is F or methyl;
m is an integer 0 or 1;

R4 is CN, -(CO)OH, -(CO)NH_2 or -(CO)O(C1-C4)alkyl;
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

6. A compound of the formula I as claimed in any one of claims 1 to 5, wherein

R1 is pyridyl, pyrazinyl or pyrimidinyl and wherein R1 is substituted by 1 to 2 substituents independently selected from
F, Cl,
methyl,
-O-methyl,
-S methyl,
-S(O) methyl,
-$S(O)_2$ methyl,

-O-CH_2-R4,
-(CO)OH,
-CN,
-(CO)O-CH_3, -(CO)O-CH_2-CH_3,
-NH_2,
-(CO)NH_2,and
-(CO)NRcRd;
wherein Rc is H; and
wherein Rd is –(CH_2)-(C3-C7)cycloalkyl or –(CH_2)-(C3-C7)heterocyclyl,
wherein cycloalkyl or heterocyclyl is unsubstituted or substituted with methyl, ethyl or (CO)O(C1-C4)alkyl;

R2
is a 5-10 membered heteroaryl, wherein 1 or 2 ring atoms are -N-, and additionally up to 1 ring atom is -S-; or
a 5 to 6 membered heterocycle, wherein 1 or 2 ring atoms are -O-,
and wherein heteroaryl or heterocycle is unsubstituted or substituted by 1 or 2 substituents selected from
halogen, CN, -(C1-C4)alkyl, -(C1-C4)alkyl-OH, (CO)NReRf and -NReRf, wherein Re and Rf are independently selected from H, (C1-C4)alkyl or -CO(C1-C4)alkyl; or
wherein Re and Rf form together with the nitrogen atom to which they are attached a 4 to 6 membered ring, which is unsubstituted or substituted with oxo at the position adjacent to the nitrogen atom;

R3 is F or methyl;
m is an integer 0 or 1;

R4 is CN, -(CO)OH, -(CO)NH_2 or -(CO)O(C1-C4)alkyl;
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

7. A compound of the formula I as claimed in any one of claims 1 to 5, wherein

R1 is pyridyl, pyrazinyl or pyrimidinyl and wherein R1 is substituted by -(CO)NRaRb, wherein Ra and Rb are H, or -(CO)NRcRd;
wherein Rc is H; and
wherein Rd is –(CH_2)-(C3-C7)cycloalkyl or –(CH_2)-(C3-C7)heterocyclyl,
wherein cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl,
and wherein heterocyclyl is selected from azirine, azetidine, pyrrolidine and piperidine, and
wherein cycloalkyl or heterocyclyl, is optionally substituted with methyl, ethyl or (CO)O(C1-C4)alkyl;
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

8. A compound of the formula I as claimed in any one of claims 1 to 6, wherein
R1 is pyrimidinyl and wherein R1 is either substituted by -(CO)NH_2, or unsubstituted by –(CO)NH_2 and optionally additionally by F;

R2
is selected from pyridyl and pyrazinyl, and is unsubstituted or substituted by-methyl or -CN,

m is an integer 0;
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

9. A compound of the formula I as claimed in any one of claims 1 to 6, wherein
R1 is pyridyl, pyrazinyl or pyrimidinyl and wherein R1 is substituted by -(CO)NRaRb, wherein Ra and Rb are H, or

-(CO)NRcRd

wherein Rc is H; and

wherein Rd is –(CH_2)-cyclopropyl, –(CH_2)-azetidine or –(CH_2)-piperidine, wherein the cyclic group, is unsubstituted or substituted with methyl, ethyl or (CO)O(C1-C4)alkyl;

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

10. A compound of the formula I as claimed in any one of claims 1 to 9, wherein R2

is selected from pyrazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, imidazo[1,2a]pyridinyl or tetrahydropyranyl, and is unsubstituted or substituted by 1 or 2 substituents selected from

F, Cl, Br, CN, -methyl, -(CH_2)-OH , NH_2, NH(C1-C4)alkyl, NH(CO)-(C1-C4)alkyl, (CO)NH_2, -(CO)NH(C1-C4)alkyl, -(CO)NH(CO)-(C1-C4)alkyl, 1-oxo-azirinyl, 1-oxo-azetidinyl, 1-oxo-pyrrolidinyl and 1-oxo-piperidinyl;

R3 is F or methyl;

m is an integer 0 or 1;

R4 is CN, -(CO)OH, -(CO)NH_2, -(CO)O-CH_3 or -(CO)O-CH_2-CH_3;

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

11. A compound of the formula I as claimed in any of claim 1, 2 or 3 wherein the compound of formula I is selected from

6-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide

2-[4-[(3S)-3-Pyrimidin-5-ylisoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide

2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-

4-carboxamide

6-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carbonitrile

2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxylic acid

Methyl 2-[4-[(3S)-3-(5-cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxylate

2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carbonitrile

2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyridine-4-carbonitrile

5-[(3S)-2-[1-[4-(Cyanomethoxy)-5-fluoro-2-pyridyl]-4-methyl-piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile

2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-4-methyl-1-piperidyl]pyrimidine-4-carboxamide

Methyl 2-[4-[(3S)-3-(5-cyano-3-pyridyl)isoxazolidine-2-carbonyl]-4-methyl-1-piperidyl]pyrimidine-4-carboxylate

2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-4-methyl-1-piperidyl]pyrimidine-4-carboxylic acid

2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyridine-4-carboxamide

Ethyl 2-[2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-4-methyl-1-piperidyl]-5-fluoro-pyrimidin-4-yl]oxyacetate

5-[(3S)-2-[1-[4-(Cyanomethoxy)-5-fluoro-pyrimidin-2-yl]piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile

2-[2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidin-4-yl]oxyacetic acid

2-[2-[4-[(3S)-3-(5-Carbamoyl-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidin-4-yl]oxyacetic acid

2-[2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidin-4-yl]oxyacetamide

5-[(3S)-2-[1-(4-Amino-5-fluoro-pyrimidin-2-yl)piperidine-4-carbonyl]isoxazolidin-3-

yl]pyridine-3-carbonitrile
2-[4-[(3S)-3-(5-Acetamido-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
2-[4-[(3S)-3-(6-Methylpyrazin-2-yl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
2-[4-[(3S)-3-(6-Methylpyrazin-2-yl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carbonitrile
2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-methyl-pyrimidine-4-carboxamide
2-[4-[(3S)-3-[5-(2-Oxoazetidin-1-yl)-3-pyridyl]isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
2-[4-[(3S)-3-[5-(2-Oxoazetidin-1-yl)-3-pyridyl]isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carbonitrile
Ethyl 6-[4-[(3S)-3-(5-cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidine-4-carboxylate
6-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidine-4-carboxylic acid
2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-4-fluoro-1-piperidyl]-5-fluoro-pyrimidine-4-carboxamide
2-[4-[(3S)-3-[5-(2-Oxopyrrolidin-1-yl)-3-pyridyl]isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
2-[4-Methyl-4-[(3S)-3-pyrimidin-5-ylisoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
2-[5-Fluoro-2-[4-methyl-4-[(3S)-3-pyrimidin-5-ylisoxazolidine-2-carbonyl]-1-piperidyl]pyrimidin-4-yl]oxyacetonitrile
2-[5-Fluoro-2-[4-[(3S)-3-pyrimidin-5-ylisoxazolidine-2-carbonyl]-1-piperidyl]pyrimidin-4-yl]oxyacetonitrile
[1-(5-Fluoro-4-methoxy-pyrimidin-2-yl)-4-piperidyl]-[(3S)-3-pyrimidin-5-ylisoxazolidin-2-yl]methanone
2-[4-[(3S)-3-Pyrimidin-5-ylisoxazolidine-2-carbonyl]-1-piperidyl]pyridine-4-carbonitrile
5-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrazine-2-

carbonitrile
6-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrazine-2-carbonitrile
2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidine-4-carboxamide
2-[4-[(3S)-3-(5-Fluoro-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
6-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrazine-2-carboxamide
5-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrazine-2-carboxamide
6-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidine-4-carboxamide
2-[4-[(3S)-3-Pyrazin-2-ylisoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
5-Fluoro-2-[4-[(3S)-3-pyrazin-2-ylisoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-N-(1-methylazetidin-3-yl)pyrimidine-4-carboxamide
2-[4-[(3S)-3-(5-Cyano-3-pyridyl) isoxazolidine-2-carbonyl]-1-piperidyl]-N-[2-(1-methylcyclo-propyl)ethyl]pyrimidine-4-carboxamide
Tert-butyl 3-[[2-[4-[(3S)-3-(5-cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl] pyrimidine-4-carbonyl]amino] azetidine-1-carboxylate
2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-N-[(1-ethyl-4-piperidyl)methyl]pyrimidine-4-carboxamide
5-Fluoro-2-[4-[(3S)-3-(5-fluoro-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
2-[4-[(3S)-3-(5-Cyano-6-methyl-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
5-Fluoro-2-[4-[(3S)-3-(6-methylpyrazin-2-yl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
2-[4-[(3S)-3-(5-Chloro-2-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-

4-carboxamide
2-[4-[(3S)-3-(5-Chloro-2-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidine-4-carboxamide
2-[4-[(3S)-3-(5-Cyano-6-methyl-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidine-4-carboxamide
N-(Azetidin-3-yl)-2-[4-[(3S)-3-(5-cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
2-[4-[(3S)-3-(5-Methylpyrazin-2-yl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
Ethyl 3-[[2-[4-[(3S)-3-(5-cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carbonyl]amino]azetidine-1-carboxylate
5-Fluoro-2-[4-[(3S)-3-(5-methylpyrazin-2-yl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
6-[4-[(3S)-3-(5-Methylpyrazin-2-yl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carbonitrile
2-[(3R,4R)-4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-3-fluoro-1-piperidyl]pyrimidine-4-carboxamide
2-[(3S,4S)-4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-3-fluoro-1-piperidyl]pyrimidine-4-carboxamide
2-[(3R,4S)-4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-3-fluoro-1-piperidyl]pyrimidine-4-carboxamide
2-[(3S,4R)-4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-3-fluoro-1-piperidyl]pyrimidine-4-carboxamide
5-Methyl-2-[4-[(3S)-3-(6-methylpyrazin-2-yl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
2-[4-[(3S)-3-(5-Fluoro-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-methyl-pyrimidine-4-carboxamide
5-Methyl-2-[4-[(3S)-3-pyrazin-2-ylisoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
5-[(3S)-2-[1-(5-Fluoro-4-methylsulfanyl-pyrimidin-2-yl)piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile
5-[(3S)-2-[1-(5-Fluoro-4-methylsulfinyl-pyrimidin-2-yl)piperidine-4-

carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile
5-[(3S)-2-[1-(5-Fluoro-4-methylsulfonyl-pyrimidin-2-yl)piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile
2-[4-[(3S)-3-(5-Cyano-2-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidine-4-carboxamide
6-[4-[(3S)-3-(5-Cyano-2-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
2-[4-[(3S)-3-(5-Cyano-2-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
(S)-6-(4-(3-(5-Methylfuran-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carboxamide
(S)-2-(4-(3-(5-Methylfuran-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carboxamide
2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidine-4-carbonitrile
2-[4-[(3S)-3-(5-Cyano-2-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidine-4-carbonitrile
5-[(3S)-2-[1-(3-Methyl-1,2,4-thiadiazol-5-yl)piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile
5-[(3S)-2-[1-(5-Fluoro-4-methoxy-pyrimidin-2-yl)piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile
2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-3,3,4-trifluoro-1-piperidyl]pyrimidine-4-carboxamide
[1-(5-Fluoro-4-methoxy-pyrimidin-2-yl)-4-piperidyl]-[(3S)-3-(6-methylpyrazin-2-yl)isoxazolidin-2-yl]methanone
2-[4-[(3S)-3-(6-Cyanopyrazin-2-yl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
6-[(3S)-2-[1-(5-Fluoro-4-methoxy-pyrimidin-2-yl)piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile
5-Fluoro-2-[4-[(3S)-3-pyrazin-2-ylisoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carbonitrile
2-Chloro-5-[4-[(3S)-3-(5-cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-

piperidyl]pyrimidine-4-carboxylic acid
2-[3,3,4-Trifluoro-4-[(3S)-3-pyrazin-2-ylisoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-3,3,4-trifluoro-1-piperidyl]pyrimidine-4-carbonitrile
2-[3,3,4-Trifluoro-4-[(3S)-3-pyrazin-2-ylisoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carbonitrile
(S)-5-Fluoro-2-(4-fluoro-4-(3-(5-fluoropyridin-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carboxamide
(S)-2-(4-(3-(6-Methylpyridin-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carbonitrile
(S)-6-(4-(3-(6-Methylpyridin-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carbonitrile
(S)-2-(4-(3-(6-Methylpyridin-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carboxamide
5-[(3S)-2-[1-(2-Chloro-5-fluoro-pyrimidin-4-yl)piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile
(S)-2-(4-(3-(5-Methylpyridin-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carbonitrile
(S)-2-(4-(3-(5-Methylpyridin-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carboxamide
(S)-6-(4-(3-(5-Methylpyridin-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carbonitrile
(S)-6-(4-(3-(5-Methylpyridin-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carboxamide
(S)-6-(4-(3-(6-Methylpyridin-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carboxamide
(S)-2-(4-(3-(5-Fluoro-6-methylpyridin-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carbonitrile
2-[4-[(3S)-3-(5-Fluoro-6-methyl-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
(S)-6-(4-(3-(5-Fluoro-6-methylpyridin-3-yl)isoxazolidine-2-carbonyl)piperidin-1-

yl)pyrimidine-4-carbonitrile
6-[4-[(3S)-3-(5-Fluoro-6-methyl-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
(S)-2-(4-(3-(5-Fluoro-4-methylpyridin-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carbonitrile
(S)-2-(4-(3-(5-Fluoro-4-methylpyridin-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carboxamide
(S)-6-(4-(3-(5-Fluoro-4-methylpyridin-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carboxamide
(S)-6-(4-(3-(5-Fluoro-4-methylpyridin-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carbonitrile
5-[(3S)-2-[1-(2-Methoxypyrimidin-4-yl)piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile
4-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-2-carbonitrile
5-[(3S)-2-[1-(2-Methylsulfanylpyrimidin-4-yl)piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile
5-[(3S)-2-[1-(2-Chloropyrimidin-4-yl)piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile
5-[(3S)-2-[1-(2-Aminopyrimidin-4-yl)piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile
Ethyl 4-[4-[(3S)-3-(5-cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-2-carboxylate
(S)-2-(4-(3-(4-Methylfuran-2-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carbonitrile
(S)-2-(4-(3-(4-Methylfuran-2-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carboxamide
(S)-6-(4-(3-(4-Methylfuran-2-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carbonitrile
(S)-6-(4-(3-(4-Methylfuran-2-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carboxamide
2-[(3R,4R or 3S,4S)-4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-3-

fluoro-1-piperidyl]-5-fluoro-pyrimidine-4-carboxamide
2-[(3S,4S or 3R,4R)-4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-3-fluoro-1-piperidyl]-5-fluoro-pyrimidine-4-carboxamide
4-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-2-carboxamide
5-[(3S)-2-[1-(2-Bromopyrimidin-4-yl)piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile
5-[(3S)-2-[1-(4-Chloropyrimidin-2-yl)piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile
5-[(3S)-2-[1-(6-Chloropyrimidin-4-yl)piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile
5-[(3S)-2-[1-(4-Bromopyrimidin-2-yl)piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile
(S)-2-(4-(3-(5-Methylfuran-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carbonitrile
(S)-6-(4-(3-(5-Methylfuran-3-yl)isoxazolidine-2-carbonyl)piperidin-1-yl)pyrimidine-4-carbonitrile
2-Chloro-5-[4-[(3S)-3-pyrazin-2-ylisoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxylic acid
5-[(3S)-2-[1-(6-Bromopyrimidin-4-yl)piperidine-4-carbonyl]isoxazolidin-3-yl]pyridine-3-carbonitrile
2-[4-[(3S)-3-(5-Cyano-3-thienyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidine-4-carboxamide
2-[4-[(3S)-3-(5-Cyano-3-furyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidine-4-carboxamide
2-[4-[(3S)-3-(5-Cyano-3-thienyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
(S)-5-(2-(1-(6-Fluoropyrimidin-4-yl)piperidine-4-carbonyl)isoxazolidin-3-yl)nicotinonitrile
5-Fluoro-2-[4-[(3S)-3-(2-methylthiazol-4-yl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
2-[4-[(3S)-3-(5-Cyano-3-furyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-

carboxamide
[1-(4-Chloro-1,3,5-triazin-2-yl)-4-piperidyl]-[(3S)-3-pyrazin-2-ylisoxazolidin-2-yl]methanone
5-Fluoro-2-[4-[(3S)-3-(2-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
6-[4-[(3S)-3-(5-Methyl-2-thienyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
2-[4-[(3S)-3-(6-Cyanopyridazin-4-yl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidine-4-carboxamide
2-[4-[(3S)-3-(6-Cyanopyridazin-4-yl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
[1-(4-Chloro-6-methyl-1,3,5-triazin-2-yl)-4-piperidyl]-[(3S)-3-pyrazin-2-ylisoxazolidin-2-yl]methanone
[1-(4-Chloro-6-methoxy-1,3,5-triazin-2-yl)-4-piperidyl]-[(3S)-3-pyrazin-2-ylisoxazolidin-2-yl]methanone
5-Methyl-2-[4-[(3S)-3-(5-methyl-2-thienyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
5-Fluoro-2-[4-[(3S)-3-(5-methyl-2-thienyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
[1-(4-Amino-6-chloro-1,3,5-triazin-2-yl)-4-piperidyl]-[(3S)-3-pyrazin-2-ylisoxazolidin-2-yl]methanone
2-[(3R,4R or 3S,4S)-3-Fluoro-4-[(3S)-3-(6-methyl-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-methyl-pyrimidine-4-carboxamide
2-[(3S,4S or 3R,4R)-3-Fluoro-4-[(3S)-3-(6-methyl-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-methyl-pyrimidine-4-carboxamide
5-Fluoro-6-[4-[(3S)-3-(6-methyl-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide; trifluoroacetic acid
2-[4-[(3S)-3-(2-Cyanothiazol-4-yl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide and
2-[4-[(3S)-3-(2-Cyanothiazol-4-yl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidine-4-carboxamide
or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

12. A compound of the formula I as claimed in claim 1, wherein the compound of formula I is selected from
2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide,
2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidine-4-carboxamide,
2-[4-[(3S)-3-(6-Methylpyrazin-2-yl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide and
5-Fluoro-2-[4-[(3S)-3-pyrazin-2-ylisoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide;
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

13. A compound of the formula I as claimed in claim 1, wherein the compound of formula I is selected from
2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide,
2-[4-[(3S)-3-(5-Cyano-3-pyridyl)isoxazolidine-2-carbonyl]-1-piperidyl]-5-fluoro-pyrimidine-4-carboxamide,
2-[4-[(3S)-3-(6-Methylpyrazin-2-yl)isoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide and
5-Fluoro-2-[4-[(3S)-3-pyrazin-2-ylisoxazolidine-2-carbonyl]-1-piperidyl]pyrimidine-4-carboxamide
with a TPSA (topological polar surface area) value of >120 Å2 or more;
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

14. The compound of any one of claims 1 to 13 for use in human medicine.

15. The compound for use according to claim 14 which is present as an active agent in a pharmaceutical composition together with at least one pharmaceutically acceptable carrier.

16. The compound for use according to claim 14 which is present as an active agent in a pharmaceutical composition together with at least one pharmaceutically acceptable carrier and/or one or more additional active pharmaceutical agent selected from a thrombolytic agent, a tissue plasminogen activator, an anticoagulant, a platelet aggregation inhibitor, an antimicrobial agent (an antibiotic, a broad-spectrum antibiotic, a lactam, an antimycobacterial agent, a bactericidal antibiotic, anti-MRSA therapy), a long acting beta agonist, a combination of an inhaled corticosteroid and a long acting beta agonist, a short acting beta agonist, a leukotriene modifier, an anti-IgE, a methylxanthine bronchodilator, a mast cell inhibitor, a protein tyrosine kinase inhibitor, a CRTH2/D prostanoid receptor antagonist, an epinephrine inhalation aerosol, a phosphodiesterase inhibitor, a combination of a phosphodiesterase-3 inhibitor and a phosphodiesterase-4 inhibitor, a long-acting inhaled anticholinergic, a muscarinic antagonist, a long-acting muscarinic antagonist, a low dose steroid, an inhaled corticosteroid, an oral corticosteroid, a topical corticosteroid, anti-thymocyte globulin, thalidomide, chlorambucil, a calcium channel blocker, a topical emollient, an ACE inhibitor, a serotonin reuptake inhibitor, an endothelin-I receptor inhibitor, an anti-fibrotic agent, a proton-pump inhibitor, a cystic fibrosis transmembrane conductance regulator potentiator, a mucolytic agent, pancreatic enzymes, a bronchodilator, an opthalmalic intravitreal injection, an anti-vascular endothelial growth factor inhibitor, a ciliary neurotrophic growth factor agent, a trivalent (IIV3) inactivated influenza vaccine, a quadrivalent (IIV4) inactivated influenza vaccine, a trivalent recombinant influenza vaccine, a quadrivalent live attenuated influenza vaccine, an antiviral agent, inactivated influenza vaccine, a ciliary neurotrophic growth factor, a gene transfer agent, a topical immunomodulator, calcineurin inhibitor, an interferon gamma, an antihistamine, a monoclonal antibody, a polyclonal anti-Tcell antibody, an anti-thymocyte gamma

globulin-equine antibody, an antithymocyte globulin- rabbit antibody, an anti-CD40 antagonist, a JAK inhibitor, and an anti-TCR murine mAb.

17. The compound for use according to any one of claims 14 to 16 for the treatment of a RIP kinase 1 mediated disease or disorder.

18. The compound for use according to any one of the claims 14 to 16 for the treatment of necrotizing enterocolitis, tuberous sclerosis, Tangier's Disease, Wohlman's Syndrome, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, psoriasis, retinal detachment, retinitis pigmentosa, macular degeneration, pancreatitis (e.g., acute pancreatitis), atopic dermatitis, rheumatoid arthritis (RA), spondyloarthritis, gout, SoJIA, systemic lupus erythematosus, Sjogren’s syndrome, systemic scleroderma, antiphospholipid syndrome, vasculitis, osteoarthritis, non-alcohol steatohepatitis, alcohol steatohepatitis, autoimmune hepatitis autoimmune hepatobiliary diseases, primary sclerosing cholangitis, nephritis, Celiac disease, autoimmune ITP, transplant rejection, ischemia reperfusion injury of solid organs, sepsis, systemic inflammatory response syndrome, cerebrovascular accident, myocardial infarction, allergic diseases, asthma, atopic dermatitis, type I diabetes, Wegener’s granulomatosis, pulmonary sarcoidosis, Behçet's disease, interleukin-1 converting enzyme associated fever syndrome, chronic obstructive pulmonary disease, tumor necrosis factor receptor-associated periodic syndrome, periodontitis, bacterial infection, staphylococcus infection, mycobacterium infection, retinitis pigmentosa, influenza, transplant rejection, burns, or hypoxia.

19. The compound for use according to any one of the claims 14 to 16 for the treatment of rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease (IBD), Crohn’s disease or ulcerative colitis.

20. The compound for use according to any one of the claims 14 to 16 for the treatment of cutaneous lupus erythematosus (CLE), Lichen planus (LP), toxic epidermal necrolysis (TEN) or Stevens–Johnson syndrome (SJS).

21. The compound for use according to any one of the claims 14 to 16 for the treatment of acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS).

22. The compound for use according to any one of the claims 14 to 16 for the treatment of Influenza (e.g. swine flu, H7N9), severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), Respiratory-Syncytial-Virus (RSV) or bronchiolitis.

23. A pharmaceutical composition comprising at least one compound according to any one of claims 1 to 13 or a physiological acceptable salt or solvate of any of them, for use as a pharmaceutical.