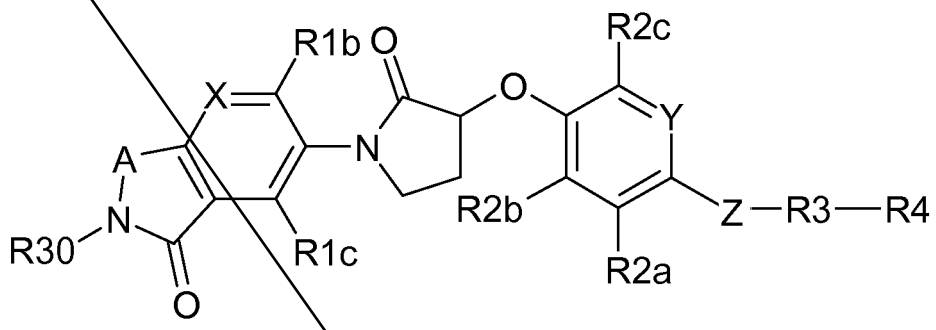
Isoindolinone Compounds as GPR119 Modulators for the Treatment of Diabetes, Obesity, Dyslipidemia and Related Disorders

The present invention relates to isoindolinone compounds of the formula I



(I)

in which A, X, R1b, R1c, R2a, R2b, R2c, R3, R4, R30, Y and Z are defined as indicated below. The isoindolinone compounds I are GPR119 modulators and useful for the prevention and/or treatment of diabetes, obesity, dyslipidemia and related disorders. The invention furthermore relates to the use of isoindolinone compounds of the formula I as active ingredients in pharmaceuticals, and pharmaceutical compositions comprising them.

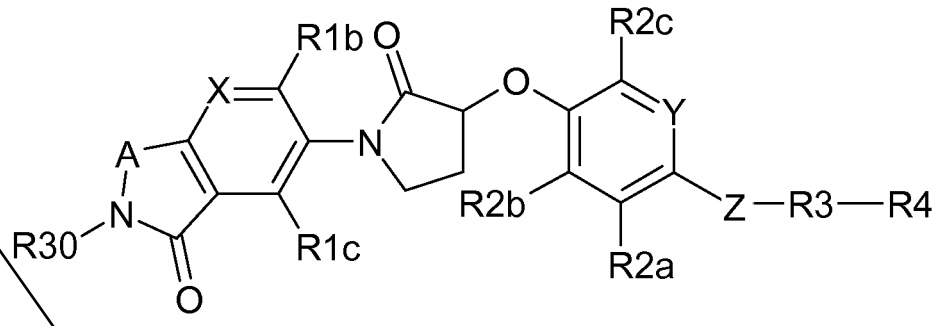
GPR119 is a G-protein coupled receptor which is expressed predominantly in the beta cells of the pancreas and in the K- and L-cells of the intestine. In vitro studies have shown, that agonists of GPR119, via activation of the cAMP pathway in gut and pancreas derived cell lines, mediate the secretion of GLP-1 and insulin respectively. This supports the hypothesis, that modulators of GPR119, agonists in particular, may have utility to treat diabetes and related disorders by augmenting the secretion of insulin and intestinal hormones like GIP, GLP-1 and PYY. As the secretion of insulin was found to be strictly glucose-dependent, induction of hypoglycemic episodes may largely be avoided. Furthermore beneficial effects like reduced food intake may be expected from the release of intestinal peptides. Stimulation of the beta cell by activation of GPR119 may also improve beta cell function and beta cell mass. Studies of GPR119 agonists in rodents showed the predicted glucose lowering effects. For some such animal studies decreased food intake and weight loss was reported. Recently clinical trials with

GPR119 agonists added evidence for a positive impact on lipid parameters i.e. elevation of HDL together with lowering of LDL and triglycerides in humans. WO2013/070463A2 discloses that GPR119 agonists may be used to treat abnormalities in blood lipids. In summary, modulators of GPR119, agonists in particular, may have therapeutic utility in the prevention and/or treatment of metabolic disorders in mammals and especially in humans. Examples of such disorders and diseases include type 2 diabetes mellitus, type 1 diabetes mellitus, impaired glucose tolerance, insulin resistance, loss of beta cell function, hyperglycemia, hypercholesterolemia, dyslipidemia, hypertriglyceridemia, syndrome X, metabolic syndrome, obesity, fatty liver, steatosis, steatohepatitis, cirrhosis, micro- and marcovascular disorders, high blood pressure, chronic low grade inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, coronary heart disease, endothelial dysfunction and bone-related diseases such as osteoporosis, rheumatoid arthritis or osteoarthritis.

Several modulators of GPR119 are known. For example WO2011146335 and WO2012037393 describe piperidinyl-substituted lactams as GPR119 modulators. WO2010048149 describes heterocyclic modulators of GPR119 for the treatment of disease and their preparation. WO2004110994 describes the preparation of piperazinyl-aryloxy and piperazinyl-heteroaryloxy-N-aryl lactams as 5-HT1B ligands.

It was an aim of the invention to provide novel compounds as active ingredients in pharmaceuticals.
It was another aim of the invention to provide novel compounds which will lower blood glucose in mammals and which are suitable for prevention and/or treatment of diabetes, obesity, dyslipidemia and related disorders.
A further aim was to provide novel GPR119 modulators, especially agonists, which can be used therapeutically for the prevention and/or treatment of diabetes, obesity, dyslipidemia and related disorders.

Accordingly a subject of the invention is a compound of the formula I



(I)

in which

X is N or C-R1a;

A is CR31R33, NR31, CR31R33-NR31 or CR31=N;

R30 is H or $(CR11R12)_n$-R32;

R31 is H or $(CR11R12)_n$-R32;

R33 is H or $(C_1$-$C_6)$-alkyl;

R11, R12 are independently of each other H or $(C_1$-$C_6)$-alkyl;

n is 0, 1, 2 or 3;

R32 is $(C_1$-$C_6)$-alkyl, COOR13, CONR14R15, $S(O)_mR16$, OH, CN, $(C_3$-$C_8)$-cycloalkyl, $(C_5$-$C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;

wherein the groups $(C_3$-$C_8)$-cycloalkyl, $(C_5$-$C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkanoyl, hydroxy, hydroxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyloxy, $(C_1$-$C_3)$-alkyloxy-$(C_1$-$C_4)$-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or (C_1-C_6)-alkyl;

R14, R15 are independently of each other H, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted with 1 to 3 groups selected from the list OR17, COOR19 and a 4-, 5- or 6-membered heterocycle;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17;

R16 is (C_1-C_6)-alkyl;

R17 is H or (C_1-C_6)-alkyl;

R18 is H or (C_1-C_6)-alkyl;

R1a, R1b, R1c are independently of each other H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

R2a, R2b, R2c are independently of each other H, F, Cl, Br, (C_1-C_6)-alkyl, (C_1-C_3)-alkyl substituted with COOR19 or CN;

R19 is H or (C_1-C_6)-alkyl;

Y is N or CH;

Z is a bond, O, CR5R5', NR6, C=O, S, SO or SO_2;

R5, R5', R6 are independently of each other H or (C_1-C_4)-alkyl;

R3 is a bond or $(CR7R7')_p$;

p is 0, 1, 2, 3 or 4;

R7, R7' are independently of each other H or (C_1-C_6)-alkyl;

R4 is F, Cl, SF_5, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, OR8, (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, or 5- or 6-membered heteroaryl ring;

wherein the groups (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

R8 is H, (C_1-C_6)-alkyl, hydroxy-(C_1-C_4)-alkyl or (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

In another group of embodiments
the 3-position of the central pyrrolidinone ring has (*R*)-configuration.

In another group of embodiments
X is C-R1a.

In another group of embodiments
X is CH.

In another group of embodiments
A is CR31R33 or NR31.

In another group of embodiments
A is CH_2.

In another group of embodiments
R32 is COOR13, CONR14R15, SO_2R16 or OH.

In another group of embodiments
R32 is COOR13 or CONR14R15.

In another group of embodiments
R14, R15 are independently of each other H, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted with OR17, or (C_3-C_6)-cycloalkyl;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17.

In another group of embodiments
R14, R15 are independently of each other H, (C_1-C_6)-alkyl or (C_1-C_6)-alkyl substituted with OR17.

In another group of embodiments
R16 is CH_3.

In another group of embodiments
R1a, R1c are independently of each other H, F or CH_3.

In another group of embodiments
R1b is H.

In another group of embodiments
R1a is H or F.

In another group of embodiments
R1b and R1c are H.

In another group of embodiments
R2a is H, F or CH_3.

In another group of embodiments
R2b and R2c are H.

In another group of embodiments
R2a, R2b and R2c are H.

In another group of embodiments
Y is N.

In another group of embodiments
Z is O.

In another group of embodiments
R7, R7' are H.

In another group of embodiments
p is 0, 1 or 2.

In another group of embodiments
R4 is (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted with 1 to 3 groups F, (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl or phenyl;
wherein the groups (C_3-C_8)-cycloalkyl and phenyl may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and F.

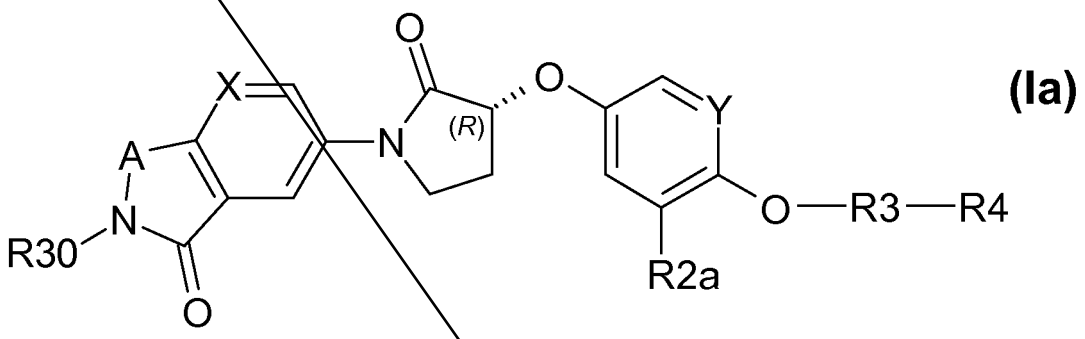
In another group of embodiments
R4 is (C_3-C_6)-cycloalkyl.

In another group of embodiments
R3 is CH_2 or CH_2-CH_2.

In another group of embodiments

R3 is CH_2.

In another group of embodiments the compound of the formula I is a compound of the formula Ia



in which

X is N or C-R1a;

A is CR31R33, NR31, CR31R33-NR31 or CR31=N;

R30 is H or $(CR11R12)_n$-R32;

R31 is H or $(CR11R12)_n$-R32;

R33 is H or $(C_1$-$C_6)$-alkyl;

R11, R12 are independently of each other H or $(C_1$-$C_6)$-alkyl;

n is 0, 1, 2 or 3;

R32 is $(C_1$-$C_6)$-alkyl, COOR13, CONR14R15, $S(O)_mR16$, OH, CN, $(C_3$-$C_8)$-cycloalkyl, 4-, 5- or 6-membered heterocycle or 5- or 6-membered heteroaryl ring;
wherein the groups $(C_3$-$C_8)$-cycloalkyl, 4-, 5- or 6-membered heterocycle, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3

groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyloxy, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or (C_1-C_6)-alkyl;

R14, R15 are independently of each other H, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted with 1 to 3 groups selected from the list OR17, COOR19 and a 4-, 5- or 6-membered heterocycle;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17;

R16 is (C_1-C_6)-alkyl;

R17 is H or (C_1-C_6)-alkyl;

R18 is H or (C_1-C_6)-alkyl;

R1a is H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

R2a is H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

Y is N or CH;

R3 is a bond or $(CR7R7')_p$;

p is 0, 1, 2, 3 or 4;

R7, R7' are independently of each other H or (C_1-C_6)-alkyl;

R4 is (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, OR8, (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring; wherein the groups (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

R8 is H, (C_1-C_6)-alkyl, hydroxy-(C_1-C_4)-alkyl or (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

In another group of embodiments the compound of the formula I is a compound of the formula Ia, in which

X is N or C-R1a;

A is CR31R33, NR31, CR31R33-NR31 or CR31=N;

R30 is H or $(CR11R12)_n$-R32;

R31 is H or $(CR11R12)_n$-R32;

R33 is H or (C_1-C_6)-alkyl;

R11, R12 are independently of each other H or (C_1-C_6)-alkyl;

n is 0, 1, 2 or 3;

R32 is (C_1-C_6)-alkyl, COOR13, CONR14R15, $S(O)_m$R16, OH, CN, (C_3-C_8)-cycloalkyl, 4-, 5- or 6-membered heterocycle or 5- or 6-membered heteroaryl ring;
wherein the groups (C_3-C_8)-cycloalkyl, 4-, 5- or 6-membered heterocycle, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyloxy, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or (C_1-C_6)-alkyl;

R14, R15 are independently of each other H, (C_1-C_6)-alkyl or (C_1-C_6)-alkyl substituted with OR17, or (C_3-C_6)-cycloalkyl;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17;

R16 is (C_1-C_6)-alkyl;

R17 is H or (C_1-C_6)-alkyl;

R18 is H or (C_1-C_6)-alkyl;

R1a is H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

R2a is H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

Y is N or CH;

R3 is a bond or $(CR7R7')_p$;

p is 0, 1, 2, 3 or 4;

R7, R7' are independently of each other H or (C_1-C_6)-alkyl;

R4 is (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, OR8, (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;
wherein the groups (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

R8 is H, (C_1-C_6)-alkyl, hydroxy-(C_1-C_4)-alkyl or (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

In another group of embodiments the compound of the formula I is a compound of the formula Ia, in which

X is C-R1a;

A is CR31R33 or NR31;

R30 is H or $(CR11R12)_n$-R32;

R31 is H or $(CR11R12)_n$-R32;

R33 is H or (C_1-C_6)-alkyl;

R11, R12 are independently of each other H or (C_1-C_6)-alkyl;

n is 0, 1, 2 or 3;

R32 is (C_1-C_6)-alkyl, COOR13, CONR14R15, $S(O)_m$R16, OH, CN, (C_3-C_8)-cycloalkyl, 4-, 5- or 6-membered heterocycle or 5- or 6-membered heteroaryl ring;
wherein the groups (C_3-C_8)-cycloalkyl, 4-, 5- or 6-membered heterocycle, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyloxy, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or (C_1-C_6)-alkyl;

R14, R15 are independently of each other H, (C_1-C_6)-alkyl or (C_1-C_6)-alkyl substituted with OR17, or (C_3-C_6)-cycloalkyl;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17;

R16 is (C_1-C_6)-alkyl;

R17 is H or (C_1-C_6)-alkyl;

R18 is H or (C_1-C_6)-alkyl;

R1a is H or F;

R2a is H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

Y is N or CH;

R3 is a bond or $(CR7R7')_p$;

p is 0, 1, 2, 3 or 4;

R7, R7' are independently of each other H or $(C_1$-$C_6)$-alkyl;

R4 is $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, OR8, $(C_3$-$C_8)$-cycloalkyl, $(C_5$-$C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;
wherein the groups $(C_3$-$C_8)$-cycloalkyl, $(C_5$-$C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkanoyl, hydroxy, hydroxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_3)$-alkyloxy-$(C_1$-$C_4)$-alkyl, oxo, F and Cl;

R8 is H, $(C_1$-$C_6)$-alkyl, hydroxy-$(C_1$-$C_4)$-alkyl or $(C_1$-$C_3)$-alkyloxy-$(C_1$-$C_4)$-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

In another group of embodiments the compound of the formula I is a compound of the formula Ia, in which

X is C-R1a;

A is CH_2, $CH(C_1$-$C_6)$-alkyl or $C((C_1$-$C_6)$-alkyl$)_2$;

R30 is H or $(CR11R12)_n$-R32;

R11, R12 are independently of each other H or $(C_1$-$C_6)$-alkyl;

n is 0, 1, 2 or 3;

R32 is $(C_1$-$C_6)$-alkyl, COOR13, CONR14R15, $S(O)_mR16$, OH, CN, $(C_3$-$C_8)$-cycloalkyl, 4-, 5- or 6-membered heterocycle or 5- or 6-membered heteroaryl ring;
wherein the groups $(C_3$-$C_8)$-cycloalkyl, 4-, 5- or 6-membered heterocycle, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkanoyl, hydroxy, hydroxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyloxy, $(C_1$-$C_3)$-alkyloxy-$(C_1$-$C_4)$-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or $(C_1$-$C_6)$-alkyl;

R14, R15 are independently of each other H, $(C_1$-$C_6)$-alkyl or $(C_1$-$C_6)$-alkyl substituted with OR17, or $(C_3$-$C_6)$-cycloalkyl;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list $(C_1$-$C_4)$-alkyl and OR17;

R16 is $(C_1$-$C_6)$-alkyl;

R17 is H or $(C_1$-$C_6)$-alkyl;

R18 is H or $(C_1$-$C_6)$-alkyl;

R1a is H or F;

R2a is H, F, Cl, Br, $(C_1$-$C_6)$-alkyl or CN;

Y is N or CH;

R3 is CH_2 or CH_2-CH_2;

R4 is (C_3-C_8)-cycloalkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

In another group of embodiments the compound of the formula I is a compound of the formula Ia, in which

X is CH;

A is CH_2;

R30 CH_2-CONR14R15;

R14 is H or (C_1-C_6)-alkyl

R15 is (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted with OR17, or (C_3-C_6)-cycloalkyl;

R17 is H or (C_1-C_6)-alkyl;

R2a is H or F;

Y is N;

R3 is CH_2 or CH_2-CH_2;

R4 is (C_3-C_8)-cycloalkyl;

or a physiologically acceptable salt thereof.

In another embodiment compounds of the formula I are encompassed selected from the list Examples 1-01 to 1-49, 2-01 to 2-48, 3-01 to 3-04, 4-01 to 4-35, 5-01 to 5-06 and 6-01 to 6-04.

In another embodiment compounds of the formula I are encompassed selected from the following list:

Tert-butyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]propanoic acid,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-methyl-3-oxo-isoindolin-1-yl]acetic acid,

methyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]propanoate,

methyl 2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-methyl-3-oxo-isoindolin-1-yl]acetate,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(2-oxotetrahydrofuran-3-yl)isoindolin-1-one,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-methyl-3-oxo-isoindolin-1-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-propyl-isoindolin-1-one,

2-[6-[(3R)-3-[(6-isopropylsulfanyl-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(2-methyltetrazol-5-yl)isoindolin-1-one,

2-[3-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1,1-dimethyl-3-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-isoindolin-2-yl]acetic acid,
methyl 2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-isoindolin-2-yl]acetate,
2-[3-[(3R)-3-[4-(2-cyclopropylacetyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(methylsulfonylmethyl)isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[(2-methyltetrazol-5-yl)methyl]isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(methylsulfinylmethyl)isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(methylsulfanylmethyl)isoindolin-1-one,
2-[6-[(3R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
methyl 2-[6-[(3R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-methyl-isoindolin-1-one,
5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1,2-dihydroindazol-3-one,
2-[6-[(3S)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[5-[(3S)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-indazol-2-yl]-N,N-dimethyl-acetamide,
2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-indazol-2-yl]-N,N-dimethyl-acetamide,
2-[3-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,
ethyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,
2-tert-butyl-6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-isoindolin-1-one,

methyl 2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate,
methyl 2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,
2-tert-butyl-6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-isoindolin-1-one,
methyl 2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate,
6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(2-hydroxyethyl)isoindolin-1-one,
2-[6-[(3R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
methyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N,1-trimethyl-4-oxo-2,3-dihydroquinazoline-2-carboxamide (Stereomer I),
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N,1-trimethyl-4-oxo-2,3-dihydroquinazoline-2-carboxamide (Stereomer II),
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N,3-trimethyl-4-oxo-quinazoline-2-carboxamide,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N-dimethyl-4-oxo-3H-quinazoline-2-carboxamide,
N-(2-hydroxyethyl)-N-methyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-1-one,
2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-1-one,
2-[6-[(3R)-3-[[6-(2,4-difluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

N,N-dimethyl-2-[5-oxo-3-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]-7H-pyrrolo[3,4-b]pyridin-6-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(trifluoromethoxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(3-cyclopropylpropyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-[[(1S,5R)-3-bicyclo[3.1.0]hexanyl]oxy]-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(2-cyclopropylethyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-fluoro-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-methyl-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethylamino)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-(4-fluorophenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[(6-chloro-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-propanoylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-pentanoylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-(4-butanoylphenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(4-fluorobenzoyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(4-fluorophenoxy)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[(6-fluoro-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-[[(1S,5R)-3-bicyclo[3.1.0]hexanyl]oxy]-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethylsulfanyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[(6-cyclopropylsulfanyl-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(2-cyclopropylacetyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(trifluoromethylsulfanyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2-pyridyloxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-(4-morpholinophenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(1,2,4-triazol-1-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[4-(4-acetylpiperazin-1-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(pentafluoro-λ{6}-sulfanyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2-oxopyrrolidin-1-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-(1,3,4-oxadiazol-2-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2,2,2-trifluoroethoxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-(4-methylthiazol-2-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-[(4-oxothiazol-2-yl)amino]phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[4-(3-isopropyl-1,2,4-oxadiazol-5-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(pyrrolidine-1-carbonyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(1,2,4-triazol-4-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-(4-oxazol-5-ylphenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-pyrazin-2-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[4-(1-ethyltetrazol-5-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(thiadiazol-4-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[3-chloro-4-(trifluoromethoxy)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-thiazol-2-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-[(3-methyl-1,2,4-oxadiazol-5-yl)methoxy]phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(tetrazol-1-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
ethyl 3-[2-chloro-5-[(3R)-1-[2-[2-(dimethylamino)-2-oxo-ethyl]-3-oxo-isoindolin-5-yl]-2-oxo-pyrrolidin-3-yl]oxy-phenyl]propanoate,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-pyrrolidin-1-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[5-bromo-6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(cyclopropanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetic acid,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetic acid,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetic acid,
2-[[2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetyl]amino]acetic acid,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(2-oxo-2-pyrrolidin-1-yl-ethyl)isoindolin-1-one,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N-cyclopropyl-2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,
6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,
6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,
2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-diethyl-acetamide,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetamide,
6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(2-oxo-2-pyrrolidin-1-yl-ethyl)isoindolin-1-one,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,
6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,
2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(2-oxo-2-pyrrolidin-1-yl-ethyl)isoindolin-1-one,
2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,
2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(1H-tetrazol-5-ylmethyl)acetamide,
methyl 2-[[2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetyl]amino]acetate,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-[2-hydroxy-1-(hydroxymethyl)ethyl]acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-bis(2-hydroxyethyl)acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-[(2S)-2,3-dihydroxypropyl]acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-[(2R)-2,3-dihydroxypropyl]acetamide,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetonitrile,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetic acid,
6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[(3-methyloxetan-3-yl)methyl]isoindolin-1-one,
6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-methyl-isoindolin-1-one,
6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-isopropyl-isoindolin-1-one,
6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(3-hydroxypropyl)isoindolin-1-one,
2-[4-fluoro-1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(2,2-dimethylpropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[(6-allyloxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide and
2-[6-[(3R)-3-[[6-(cyclobutylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide.

In another embodiment compounds of the formula I are encompassed selected from the following list:
Tert-butyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]propanoic acid,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-methyl-3-oxo-isoindolin-1-yl]acetic acid,
methyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]propanoate,
methyl 2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-methyl-3-oxo-isoindolin-1-yl]acetate,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(2-oxotetrahydrofuran-3-yl)isoindolin-1-one,
2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-methyl-3-oxo-isoindolin-1-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-propyl-isoindolin-1-one,
2-[6-[(3R)-3-[(6-isopropylsulfanyl-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(2-methyltetrazol-5-yl)isoindolin-1-one,
2-[3-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,
2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1,1-dimethyl-3-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-isoindolin-2-yl]acetic acid,
methyl 2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-isoindolin-2-yl]acetate,
2-[3-[(3R)-3-[4-(2-cyclopropylacetyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(methylsulfonylmethyl)isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[(2-methyltetrazol-5-yl)methyl]isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(methylsulfinylmethyl)isoindolin-1-one,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(methylsulfanylmethyl)isoindolin-1-one,
2-[6-[(3R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
methyl 2-[6-[(3R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-methyl-isoindolin-1-one,
5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1,2-dihydroindazol-3-one,
2-[6-[(3S)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[5-[(3S)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-indazol-2-yl]-N,N-dimethyl-acetamide,
2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-indazol-2-yl]-N,N-dimethyl-acetamide,
2-[3-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,
ethyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,
2-tert-butyl-6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-isoindolin-1-one,
methyl 2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate,
methyl 2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,
2-tert-butyl-6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-isoindolin-1-one,
methyl 2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate,
6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(2-hydroxyethyl)isoindolin-1-one,
2-[6-[(3R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
methyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N,1-trimethyl-4-oxo-2,3-dihydroquinazoline-2-carboxamide (Stereomer I),
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N,1-trimethyl-4-oxo-2,3-dihydroquinazoline-2-carboxamide (Stereomer II),
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N,3-trimethyl-4-oxo-quinazoline-2-carboxamide,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N-dimethyl-4-oxo-3H-quinazoline-2-carboxamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(trifluoromethoxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(3-cyclopropylpropyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-[[(1S,5R)-3-bicyclo[3.1.0]hexanyl]oxy]-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(2-cyclopropylethyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-fluoro-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-methyl-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethylamino)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-(4-fluorophenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[(6-chloro-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-propanoylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-pentanoylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-(4-butanoylphenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(4-fluorobenzoyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(4-fluorophenoxy)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[(6-fluoro-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-[[(1S,5R)-3-bicyclo[3.1.0]hexanyl]oxy]-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethylsulfanyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[(6-cyclopropylsulfanyl-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(2-cyclopropylacetyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(trifluoromethylsulfanyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2-pyridyloxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-(4-morpholinophenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(1,2,4-triazol-1-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[4-(4-acetylpiperazin-1-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(pentafluoro-λ{6}-sulfanyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2-oxopyrrolidin-1-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-(1,3,4-oxadiazol-2-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2,2,2-trifluoroethoxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-(4-methylthiazol-2-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-[(4-oxothiazol-2-yl)amino]phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[4-(3-isopropyl-1,2,4-oxadiazol-5-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(pyrrolidine-1-carbonyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(1,2,4-triazol-4-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-(4-oxazol-5-ylphenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-pyrazin-2-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[4-(1-ethyltetrazol-5-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(thiadiazol-4-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[3-chloro-4-(trifluoromethoxy)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-thiazol-2-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-[(3-methyl-1,2,4-oxadiazol-5-yl)methoxy]phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(tetrazol-1-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
ethyl 3-[2-chloro-5-[(3R)-1-[2-[2-(dimethylamino)-2-oxo-ethyl]-3-oxo-isoindolin-5-yl]-2-oxo-pyrrolidin-3-yl]oxy-phenyl]propanoate,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-pyrrolidin-1-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetic acid,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetic acid,
2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetic acid,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(2-oxo-2-pyrrolidin-1-yl-ethyl)isoindolin-1-one,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N-cyclopropyl-2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,
6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,
6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,

2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-diethyl-acetamide,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetamide,
6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(2-oxo-2-pyrrolidin-1-yl-ethyl)isoindolin-1-one,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,
6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,
2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(2-oxo-2-pyrrolidin-1-yl-ethyl)isoindolin-1-one,
2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetonitrile,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetic acid,
6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[(3-methyloxetan-3-yl)methyl]isoindolin-1-one,
6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-methyl-isoindolin-1-one,
6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-isopropyl-isoindolin-1-one,
6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(3-hydroxypropyl)isoindolin-1-one,
2-[4-fluoro-1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(2,2-dimethylpropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[(6-allyloxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide and
2-[6-[(3R)-3-[[6-(cyclobutylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide.

In another embodiment compounds of the formula I are encompassed selected from the following list:
N,N-Dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2,2,2-trifluoroethoxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[4-fluoro-1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]-N,N-dimethyl-acetamide and
N,N-dimethyl-2-[5-oxo-3-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]-7H-pyrrolo[3,4-b]pyridin-6-yl]acetamide.

In another embodiment compounds of the formula I are encompassed selected from the following list:
N,N-Dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2,2,2-trifluoroethoxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[4-fluoro-1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]-N,N-dimethyl-acetamide and

In another embodiment the compound of the formula I is N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide.

In another embodiment the compound of the formula I is N,N-dimethyl-2-[5-oxo-3-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]-7H-pyrrolo[3,4-b]pyridin-6-yl]acetamide.

In another embodiment compounds of the formula I are encompassed selected from the following list:
2-[6-[(3R)-3-[[6-(2-Cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-fluoro-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide and
2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide.

In another embodiment the compound of the formula I is 2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide.

In another embodiment the compound of the formula I is 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide.

In another embodiment the compound of the formula I is 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-fluoro-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide.

In another embodiment compounds of the formula I are encompassed selected from the following list:
2-[3-[(3R)-3-[[6-(4-Fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,
6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one and
2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide.

In another embodiment the compound of the formula I is 2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide.

In another embodiment the compound of the formula I is 2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide.

Structural elements such as groups, substituents, hetero ring members, numbers or other features, for example alkyl groups, groups like R5, R5', R7, R7' etc., which can occur several times in the compounds of the formula I, can all independently of one another have at each occurrence any of the indicated meanings and can in each case be identical to or different from one another. For example, the alkyl groups in a dialkylamino group can be identical or different.

Herein, the terms "including" and "comprising" are used in their open, non-limiting sense. As used herein, the terms "(C_1-C_6)" and so forth refer to moieties having 1 to 6 carbon atoms and so forth, respectively. Within composed terms like "hydroxy-(C_0-C_4)-alkyl" the option "(C_0)-alkyl refers to a bond (i.e. in this case a directly bound hydroxy group), or in case of an unsubstituted "(C_0)-alkyl" it refers to a hydrogen.

The term "alkyl", as used herein, refers to saturated, monovalent hydrocarbon radicals. The term "alkenyl", as used herein, refers to monovalent hydrocarbon radicals, which contain at least one carbon-carbon double bond, wherein each double bond can have E- or Z-configuration. The term "alkynyl", as used herein, refers to monovalent hydrocarbon radicals, which contain at least one carbon-carbon triple bond. The alkyl, alkenyl and alkynyl groups can be linear, i.e. straight-chain, or branched. This also applies when they are part of other groups, for example alkyloxy groups (= alkoxy groups, O-alkyl groups), alkyloxycarbonyl groups or alkyl-substituted amino groups, or when they are substituted. Depending on the respective definition, the number of carbon atoms in an alkyl group can be 1, 2, 3, 4, 5 or 6, or 1, 2, 3, or 4. Examples of alkyl are methyl, ethyl, propyl including n-propyl and isopropyl, butyl including n-butyl, sec-butyl, isobutyl and tert-butyl, pentyl including n-pentyl, 1-methylbutyl, isopentyl, neopentyl and tert-pentyl, hexyl including n-hexyl, 3,3-dimethylbutyl and isohexyl.

Double bonds and triple bonds in alkenyl groups and alkynyl groups respectively can be present in any positions. Examples of alkenyl and alkynyl are ethenyl, prop-1-enyl, prop-2-enyl (= allyl), but-2-enyl, 2-methylprop-2-enyl, 3-methylbut-2-enyl, hex-3-enyl, hex-4-enyl, prop-2-ynyl (= propargyl), but-2-ynyl, but-3-ynyl, hex-4-ynyl or hex-5-ynyl.

Substituted alkyl groups, alkenyl groups and alkynyl groups can be substituted in any positions, provided that the respective compound is sufficiently stable and is suitable for the desired purpose such as use as a drug substance. The prerequisite that a specific group and a compound of the formula I are sufficiently stable and suitable for the desired purpose such as use as a drug substance, applies in general with respect to the definitions of all groups in the compounds of the formula I.

Independently of one another and independently of any other substituents, alkyl groups, divalent alkyl groups, alkenyl groups, alkynyl groups, cycloalkyl groups and heterocycloalkyl groups are optionally substituted by one or more fluorine substituents which can be located in any positions, i.e., the said groups can be unsubstituted by fluorine substituents or substituted by fluorine substituents, for example by 1, 2 or 3, by 1 or 2, or by 1 fluorine substituents. Examples of fluorine-substituted said groups are trifluoromethyl, difluoromethyl and fluoromethyl.

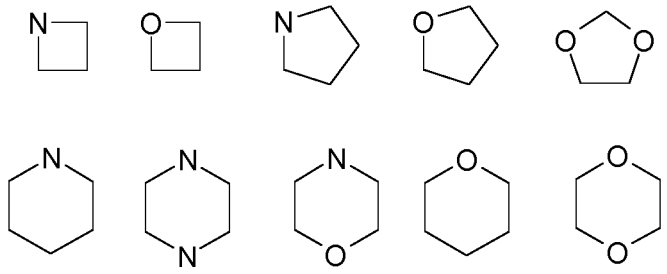
The term “alkanediyl” or “alkylene”, as used herein, refers to saturated, divalent hydrocarbon radicals. The term “alkenediyl”, as used herein, refers to divalent hydrocarbon radicals, which contain at least one carbon-carbon double bond, wherein each double bond can have E- or Z-configuration. The term “alkynediyl”, as used herein, refers to divalent hydrocarbon radicals, which contain at least one carbon-carbon triple bond. As far as applicable, the preceding explanations regarding alkyl, alkenyl and alkynyl groups apply correspondingly to alkanediyl, alkenediyl and alkynediyl groups, which thus can likewise be linear and branched. Examples of divalent alkyl groups are -CH_2- (= methylene), -CH_2-CH_2-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -$CH(CH_3)$-CH_2-, -CH_2-$CH(CH_3)$-, -$C(CH_3)_2$-CH_2- and -CH_2-$C(CH_3)_2$-.

The term “cycloalkyl”, as used herein, unless otherwise indicated, refers to a mono-valent radical of a saturated hydrocarbon ring system, which is monocyclic. In a monocyclic cycloalkyl group the number of ring carbon atoms can be for example 3, 4, 5, 6, 7 or 8. In one embodiment of the invention, the number of ring carbon atoms in a

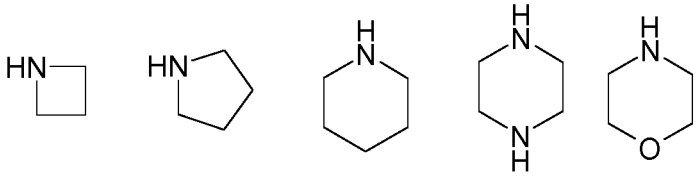
cycloalkyl group, independently of the number of ring carbon atoms in any other cycloalkyl group is 3, 4, 5 or 6, in another embodiment 3 or 4, in another embodiment 3, in another embodiment 5 or 6, in another embodiment 5, in another embodiment 6. Examples of cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "heterocycle", as used herein, unless otherwise indicated, refers to a cycloalkyl as defined above, in which 1, 2, 3 or 4 carbon atoms are replaced by nitrogen or oxygen atoms, provided that the heterocycloalkyl system is stable and suitable as a subgroup for the desired purpose of the compound of the formula I such as use as a drug substance. Depending on the definition of the respective heterocyclic group, in one embodiment of the invention the number of ring heteroatoms which can be present in a heterocyclic group, independently of the number of ring heteroatoms in any other heterocyclic group, is 1 or 2, in another embodiment 2, in another embodiment 1, wherein the ring heteroatoms can be identical or different. The heterocycloalkyl group can be attached by any ring carbon atom or saturated ring nitrogen atom, with the exception of spiro- or bridgehead atoms.

Exemplary monocyclic heterocycloalkyl groups are derived from, but not limited to, the ring systems azetidine, oxetane, pyrrolidine, tetrahydrofuran, 1,3-dioxolane, piperidine, piperazine, morpholine, tetrahydropyran or 1,4-dioxane:



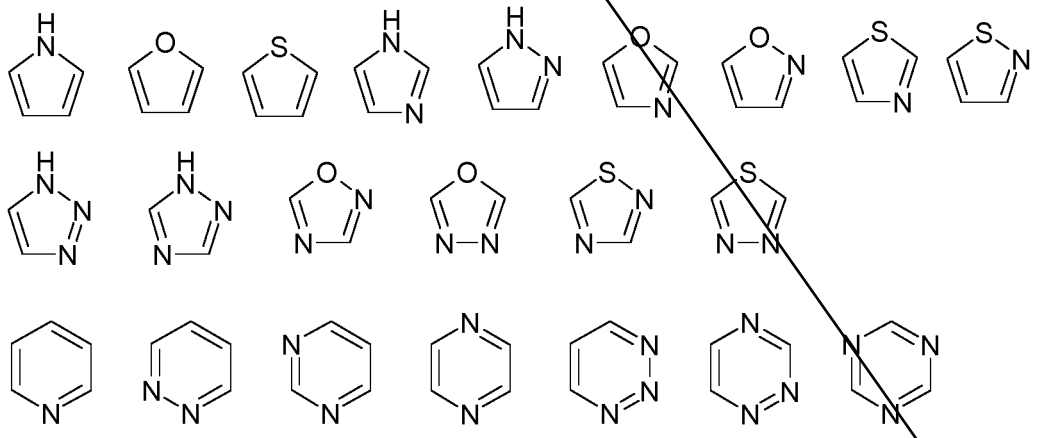
In one embodiment monocyclic heterocycloalkyl groups are derived from azetidine, pyrrolidine, piperidine, piperazine or morpholine:



The term "aryl", as used herein, refers to a radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl.

The term “heteroaryl” as used herein, refers to a radical derived from a fully unsaturated monocyclic ring system, in which 1, 2 or 3 carbon atoms are replaced by heteroatoms. The ring heteroatoms are generally chosen from N, O and S, wherein N includes ring nitrogen atoms which carry a hydrogen atom or a substituent as well as ring nitrogen atoms which do not carry a hydrogen atom or a substituent. Ring heteroatoms can be located in any position, provided that the heterocyclic system is stable and suitable as a subgroup for the desired purpose of the compound of the formula I such as use as a drug substance. Heteroaryl radicals are derived from 5-membered or 6-membered monocyclic rings.

Exemplary heteroaryl systems are derived from, but not limited to, the following ring systems: pyrrole, furan, thiophene, imidazole, pyrazole, oxazole (= [1,3]oxazole), isoxazole (= [1,2]oxazole), thiazole (= [1,3]thiazole), isothiazole (= [1,2]thiazole), [1,2,3]triazole, [1,2,4]triazole, [1,2,4]oxadiazole, [1,3,4]oxadiazole, [1,2,4]thiadiazole, [1,3,4]thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, [1,2,3]triazine, [1,2,4]triazine or [1,3,5]triazine:



Groups like phenyl and residues of aromatic heterocycles which are optionally substituted by one or more substituents, can be unsubstituted or substituted, for example by 1, 2 or 3, or by 1 or 2, or by 1, identical or different substituents which can be located in any positions. Aromatic nitrogen heterocycles which in the parent ring system carry a hydrogen atom on a ring nitrogen atom in a 5-membered ring, such as a pyrrole or imidazole ring, for example, can be substituted on ring carbon atoms and/or on such ring nitrogen atoms. In one embodiment of the invention, substituents on such ring nitrogen atoms are chosen from (C_1-C_4)-alkyl groups, i.e. such ring nitrogen atoms

in aromatic heterocycles carry a hydrogen atom or a (C_1-C_4)-alkyl substituent. When it is stated with respect to ring nitrogen atoms in aromatic heterocycles and any other heterocycles that they can carry a hydrogen atom or a substituent, such ring nitrogen atoms either carry a hydrogen atom or a substituent or they do not carry a hydrogen atom or substituent. Ring nitrogen atoms which carry a hydrogen atom or a substituent, occur in a nitrogen-containing aromatic 5-membered ring as is present in pyrrole or imidazole for example, and in a non-aromatic ring including a saturated ring. Ring nitrogen atoms which do not carry a hydrogen atom or a substituent unless they are present in positively charged form, including any further ring nitrogen atoms in addition to ring nitrogen atoms which carry a hydrogen atom or a substituent, occur in an aromatic ring as is present in thiazole, imidazole or pyridine, for example, and in a non-aromatic ring in which they are part of a double bond, and they occur as ring nitrogen atoms via which a ring is bonded. Suitable ring nitrogen atoms in aromatic heterocycles in the compounds of the formula I, such as the ring nitrogen atom in a pyridine ring, can in general also be present as N-oxide or as quaternary salt, for example as N-(C_1-C_4)-alkyl salt such as N-methyl salt, wherein in one embodiment of the invention the counter anion in such quaternary salt is a physiologically acceptable anion which is derived from an acid that forms a physiologically acceptable salt.

In monosubstituted phenyl groups, the substituent can be located in the 2-position, the 3-position or the 4-position. In disubstituted phenyl groups, the substituents can be located in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl groups, the substituents can be located in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position or 3,4,5-position.

Ring heteroatoms can be located in any positions, provided that the heterocyclic system is known in the art and is stable and suitable as a subgroup for the desired purpose of the compound of the formula I such as use as a drug substance. In one embodiment of the invention, two ring oxygen atoms cannot be present in adjacent ring positions of any heterocycle, in another embodiment two ring heteroatoms chosen from oxygen and sulfur cannot be present in adjacent ring positions of any heterocycle. Substituents on heterocyclic groups can be located in any positions. For example, in a pyridin-2-yl group substituents can be located in the 3-position and/or 4-position and/or 5-position and/or 6-position, in a pyridin-3-yl group substituent can be located in the 2-position and/or 4-

position and/or 5-position and/or 6-position, in a pyridin-4-yl group substituents can be located in the 2-position and/or 3-position and/or 5-position and/or 6-position.

When an oxo group is bonded to a carbon atom, it replaces two hydrogen atoms on a carbon atom of the parent system. Thus, if a CH_2 group in a chain or a ring is substituted by oxo, i.e. by a doubly bonded oxygen atom, it becomes a CO group. Evidently, an oxo group cannot occur as a substituent on a carbon atom in an aromatic ring such as in a phenyl group, for example.

The present invention includes all stereoisomeric forms of the compounds of the formula I and their salts and solvates. With respect to each chiral center, independently of any other chiral center, the compounds of the formula I can be present in S configuration or substantially S configuration, or in R configuration or substantially R configuration, or as a mixture of the S isomer and the R isomer in any ratio. The invention includes all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all ratios. Thus, compounds according to the invention which can exist as enantiomers can be present in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, and in the form of mixtures of the two enantiomers in all ratios including racemates. In the case of a E/Z isomerism, or cis/trans isomerism, for example on double bonds or rings such as cycloalkyl rings, the invention includes both the E form and Z form, or the cis form and the trans form, as well as mixtures of these forms in all ratios. In one embodiment of the invention, a compound which can occur in two or more stereoisomeric forms is a pure, or substantially pure, individual stereoisomer. The preparation of individual stereoisomers can be carried out, for example, by separation of a mixture of isomers by customary methods, for example by chromatography or crystallization, by the use of stereochemically uniform starting materials in the synthesis, or by stereoselective synthesis. Optionally, a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at the stage of the compound of the formula I or at the stage of a starting material or an intermediate during the synthesis. The present invention also includes all tautomeric forms of the compounds of the formula I and their salts and solvates.

In case the compounds of the formula I contain one or more acidic and/or basic groups, i.e. salt-forming groups, the invention also includes their corresponding physiologically or toxicologically acceptable salts, i.e. non-toxic salts, in particular their pharmaceutically acceptable salts.

The present invention furthermore includes all solvates of compounds of the formula I, for example hydrates or adducts with alcohols such as (C_1-C_4)-alkanols, active metabolites of the compounds of the formula I, and also prodrugs and derivatives of the compounds of the formula I which in vitro may not necessarily exhibit pharmacological activity but which in vivo are converted into pharmacologically active compounds, for example esters or amides of carboxylic acid groups.

The compounds of the present invention can be widely combined with other pharmacologically active compounds, such as all drugs mentioned in the Rote Liste 2014, e.g. all antidiabetics mentioned in the Rote Liste 2014, chapter 12, all weight-reducing agents or appetite suppressants mentioned in the Rote Liste 2014, chapter 06, all lipid-lowering agents mentioned in the Rote Liste 2014, chapter 58, all antihypertensives mentioned in the Rote Liste 2014 chapter 17, all nephroprotectives mentioned in the Rote Liste, or all diuretics mentioned in the Rote Liste 2014, chapter 36.

The active ingredient combinations can be applied either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present in one pharmaceutical preparation. When administered separately, administration may occur simultaneously or sequentially, in any order. The amount of the compound of the invention and the other pharmaceutically active ingredient(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. The administration of the combination may be concomitantly in: (1) a unitary pharmaceutical composition including all pharmaceutically active ingredients; or (2) separate pharmaceutical compositions each including at least one of the pharmaceutically active ingredients. Alternatively, the combination may be administered separately in a sequential manner wherein one treatment agent is administered first and the other second or vice versa. Such sequential administration may be close in time or remote in time.

Most of the active ingredients mentioned hereinafter are disclosed in the USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2014.

Therapeutic agents which are suitable for combinations include, for example, antidiabetic agents such as:
Insulin and insulin derivatives, for example: insulin glargine (e.g. Lantus®), higher than 100U/mL concentrated insulin glargine, e.g. 270 - 330U/mL of insulin glargine or 300U/mL of insulin glargine (as disclosed in EP 2387989), insulin glulisine (e.g. Apidra®), insulin detemir (e.g. Levemir®), insulin lispro (e.g. Humalog®, Liprolog®), insulin degludec (e.g. DegludecPlus®, IdegLira (NN9068)), insulin aspart and aspart formulations (e.g. NovoLog®), basal insulin and analogues (e.g. LY2605541, LY2963016, NN1436), PEGylated insulin lispro (e.g. LY-275585), long-acting insulins (e.g. NN1436, Insumera (PE0139), AB-101, AB-102, Sensulin LLC), intermediate-acting insulins (e.g. Humulin®N, Novolin®N), fast-acting and short-acting insulins (e.g. Humulin®R, Novolin®R, Linjeta® (VIAject®), PH20 insulin, NN1218, HinsBet®), premixed insulins, SuliXen®, NN1045, insulin plus Symlin®, PE-0139, ACP-002 hydrogel insulin, and oral, inhalable, transdermal and buccal or sublingual insulins (e.g. Exubera®, Nasulin®, Afrezza®, insulin tregopil, TPM-02 insulin, Capsulin®, Oral-lyn®, Cobalamin® oral insulin, ORMD-0801, Oshadi oral insulin, NN1953, NN1954, NN1956, VIAtab®). Also suitable are those insulin derivatives which are bonded to albumin or another protein by a bifunctional linker.

Glucagon-like-peptide 1 (GLP-1), GLP-1 analogues, and GLP-1 receptor agonists, for example: lixisenatide (e.g. Lyxumia®), exenatide (e.g. exendin-4, rExendin-4, Byetta®, Bydureon®, exenatide NexP), liraglutide (e.g. Victoza®), semaglutide, taspoglutide, albiglutide, dulaglutide, ACP-003, CJC-1134-PC, GSK-2374697, PB-1023, TTP-054, langlenatide (HM-11260C), CM-3, GLP-1 Eligen, AB-201, ORMD-0901, NN9924, NN9926, NN9927, Nodexen, Viador-GLP-1, CVX-096, ZYOG-1, ZYD-1, ZP-3022, CAM-2036, DA-3091, DA-15864, ARI-2651, ARI-2255, exenatide-XTEN (VRS-859), exenatide-XTEN + Glucagon-XTEN (VRS-859 + AMX-808) and polymer-bound GLP-1 and GLP-1 analogues.

Dual GLP-1/GIP agonists (e.g. RG-7697 (MAR-701), MAR-709, BHM081, BHM089, BHM098).
Dual GLP-1/glucagon receptor agonists (e.g. BHM-034, OAP-189 (PF-05212389, TKS-1225), TT-401/402, ZP2929, LAPS-HMOXM25, MOD-6030).
Dual GLP-1/gastrin agonists (e.g. ZP-3022).

Other suitable combination partners are:

Further gastrointestinal peptides such as peptide YY 3-36 (PYY3-36) or analogues thereof and pancreatic polypeptide (PP) or analogues thereof.

Glucagon receptor agonists or antagonists, glucose-dependent insulinotropic polypeptide (GIP) receptor agonists or antagonists, ghrelin antagonists or inverse agonists, xenin and analogues thereof.

Dipeptidyl peptidase-IV (DPP-4) inhibitors, for example: alogliptin (e.g. Nesina®, Kazano®), linagliptin (e.g. Ondero®, Trajenta®, Tradjenta®, Trayenta®), saxagliptin (e.g. Onglyza®, Komboglyze XR®), sitagliptin (e.g. Januvia®, Xelevia®, Tesavel®, Janumet®, Velmetia®, Juvisync®, Janumet XR®), anagliptin, teneligliptin (e.g. Tenelia®), trelagliptin, vildagliptin (e.g. Galvus®, Galvumet®), gemigliptin, omarigliptin, evogliptin, dutogliptin, DA-1229, MK-3102, KM-223, KRP-104, PBL-1427, Rinoxacin hydrochloride, and Ari-2243.

Sodium-dependent glucose transporter 2 (SGLT-2) inhibitors, for example: canagliflozin, dapagliflozin, remogliflozin, remogliflozin etabonate, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, ertugliflozin, EGT-0001442, LIK-066, SBM-TFC-039, and KGA-3235 (DSP-3235).
Dual inhibitors of SGLT-2 and SGLT-1 (e.g. LX-4211, LIK066).
SGLT-1 inhibitors (e.g. LX-2761, KGA-3235) or SGLT-1 inhibitors in combination with anti-obesity drugs such as ileal bile acid transfer (IBAT) inhibitors (e.g. GSK-1614235 + GSK-2330672).

Biguanides (e.g. metformin, buformin, phenformin).

Thiazolidinediones (e.g. pioglitazone, rosiglitazone), glitazone analogues (e.g. lobeglitazone).

Peroxisome proliferator-activated receptors (PPAR-)(alpha, gamma or alpha/gamma) agonists or modulators (e.g. saroglitazar (e.g. Lipaglyn®), GFT-505), or PPAR gamma partial agonists (e.g. Int-131).

Sulfonylureas (e.g. tolbutamide, glibenclamide, glimepiride, Amaryl®, glipizide) and meglitinides (e.g. nateglinide, repaglinide, mitiglinide).

Alpha-glucosidase inhibitors (e.g. acarbose, miglitol, voglibose).

Amylin and amylin analogues (e.g. pramlintide, Symlin®).

G-protein coupled receptor 119 (GPR119) agonists (e.g. GSK-1292263, PSN-821, MBX-2982, APD-597, ARRY-981, ZYG-19, DS-8500, HM-47000, YH-Chem1).

GPR40 agonists (e.g. TUG-424, P-1736, P-11187, JTT-851, GW9508, CNX-011-67, AM-1638, AM-5262).

GPR120 agonists and GPR142 agonists.

Systemic or low-absorbable TGR5 (GPBAR1 = G-protein-coupled bile acid receptor 1) agonists (e.g. INT-777, XL-475, SB756050).

Other suitable combination partners are:

Diabetes immunotherapeutics, for example: oral C-C chemokine receptor type 2 (CCR-2) antagonists (e.g. CCX-140, JNJ-41443532), interleukin 1 beta (IL-1ß) antagonists (e.g. AC-201), or oral monoclonal antibodies (MoA) (e.g. methalozamide, VVR808, PAZ-320, P-1736, PF-05175157, PF-04937319).

Anti-inflammatory agents for the treatment of the metabolic syndrome and diabetes, for example: nuclear factor kappa B inhibitors (e.g. Triolex®).

Adenosine monophosphate-activated protein kinase (AMPK) stimulants, for example: Imeglimin (PXL-008), Debio-0930 (MT-63-78), R-118.

Inhibitors of 11-beta-hydroxysteroid dehydrogenase 1 (11-beta-HSD-1) (e.g. LY2523199, BMS770767, RG-4929, BMS816336, AZD-8329, HSD-016, BI-135585).

Activators of glucokinase (e.g. PF-04991532, TTP-399 (GK1-399), GKM-001 (ADV-1002401), ARRY-403 (AMG-151), TAK-329, TMG-123, ZYGK1).

Inhibitors of diacylglycerol O-acyltransferase (DGAT) (e.g. pradigastat (LCQ-908)), inhibitors of protein tyrosine phosphatase 1 (e.g. trodusquemine), inhibitors of glucose-6-phosphatase, inhibitors of fructose-1,6-bisphosphatase, inhibitors of glycogen phosphorylase, inhibitors of phosphoenol pyruvate carboxykinase, inhibitors of glycogen synthase kinase, inhibitors of pyruvate dehydrogenase kinase.

Modulators of glucose transporter-4, somatostatin receptor 3 agonists (e.g. MK-4256).

One or more lipid lowering agents are also suitable as combination partners, for example: 3-hydroxy-3-methylglutaryl-coenzym-A-reductase (HMG-CoA-reductase) inhibitors such as simvastatin (e.g. Zocor®, Inegy®, Simcor®), atorvastatin (e.g. Sortis®, Caduet®), rosuvastatin (e.g. Crestor®), pravastatin (e.g. Lipostat®, Selipran®), fluvastatin (e.g. Lescol®), pitavastatin (e.g. Livazo®, Livalo®), lovastatin (e.g. Mevacor®, Advicor®), mevastatin (e.g. Compactin®), rivastatin, cerivastatin (Lipobay®), fibrates such as bezafibrate (e.g. Cedur® retard), ciprofibrate (e.g. Hyperlipen®), fenofibrate (e.g. Antara®, Lipofen®, Lipanthyl®), gemfibrozil (e.g. Lopid®, Gevilon®), etofibrate, simfibrate, ronifibrate, clinofibrate, clofibride, nicotinic acid and derivatives thereof (e.g. niacin, including slow release formulations of niacin), nicotinic acid receptor 1 agonists (e.g. GSK-256073), PPAR-delta agonists, acetyl-CoA−acetyltransferase (ACAT) inhibitors (e.g. avasimibe), cholesterol absorption inhibitors (e.g. ezetimibe, Ezetrol®, Zetia®, Liptruzet®, Vytorin®, S-556971), bile acid-binding substances (e.g. cholestyramine, colesevelam), ileal bile acid transport (IBAT) inhibitors (e.g. GSK-2330672, LUM-002), microsomal triglyceride transfer protein (MTP) inhibitors (e.g. lomitapide (AEGR-733), SLx-4090, granotapide), modulators of proprotein convertase subtilisin/kexin type 9

(PCSK9) (e.g. alirocumab (REGN727/SAR236553), AMG-145, LGT-209, PF-04950615, MPSK3169A, LY3015014, ALD-306, ALN-PCS, BMS-962476, SPC5001, ISIS-394814, 1B20, LGT-210, 1D05, BMS-PCSK9Rx-2, SX-PCK9, RG7652), LDL receptor up-regulators, for example liver selective thyroid hormone receptor beta agonists (e.g. eprotirome (KB-2115), MB07811, sobetirome (QRX-431), VIA-3196, ZYT1), HDL-raising compounds such as: cholesteryl ester transfer protein (CETP) inhibitors (e.g. anacetrapib (MK0859), dalcetrapib, evacetrapib, JTT-302, DRL-17822, TA-8995, R-1658, LY-2484595, DS-1442), or dual CETP/PCSK9 inhibitors (e.g. K-312), ATP-binding cassette (ABC1) regulators, lipid metabolism modulators (e.g. BMS-823778, TAP-301, DRL-21994, DRL-21995), phospholipase A2 (PLA2) inhibitors (e.g. darapladib, Tyrisa®, varespladib, rilapladib), ApoA-I enhancers (e.g. RVX-208, CER-001, MDCO-216, CSL-112), cholesterol synthesis inhibitors (e.g. ETC-1002), lipid metabolism modulators (e.g. BMS-823778, TAP-301, DRL-21994, DRL-21995) and omega-3 fatty acids and derivatives thereof (e.g. icosapent ethyl (AMR101), Epanova®, AKR-063, NKPL-66, PRC-4016, CAT-2003).

Other suitable combination partners are one or more active substances for the treatment of obesity, such as for example:
Bromocriptine (e.g. Cycloset®, Parlodel®), phentermine and phentermine formulations or combinations (e.g. Adipex-P, Ionamin, Qsymia®), benzphetamine (e.g. Didrex®), diethylpropion (e.g. Tenuate®), phendimetrazin (e.g. Adipost®, Bontril®), bupropion and combinations (e.g. Zyban®, Wellbutrin XL®, Contrave®, Empatic®), sibutramine (e.g. Reductil®, Meridia®), topiramat (e.g. Topamax®), zonisamid (e.g. Zonegran®), tesofensine, opioid antagonists such as naltrexone (e.g. Naltrexin®, naltrexone + bupropion), cannabinoid receptor 1 (CB1) antagonists (e.g. TM-38837), melanin-concentrating hormone (MCH-1) antagonists (e.g. BMS-830216, ALB-127158(a)), MC4 receptor agonists and partial agonists (e.g. AZD-2820, RM-493), neuropeptide Y5 (NPY5) or NPY2 antagonists (e.g. velneperit, S-234462), NPY4 agonists (e.g. PP-1420), beta-3-adrenergic receptor agonists, leptin or leptin mimetics, agonists of the 5-hydroxytryptamine 2c (5HT2c) receptor (e.g. lorcaserin, Belviq®), pramlintide/metreleptin, lipase inhibitors such as cetilistat (e.g. Cametor®), orlistat (e.g. Xenical®, Calobalin®), angiogenesis inhibitors (e.g. ALS-L1023), betahistidin and histamine H3 antagonists (e.g. HPP-404), AgRP (agouti related protein) inhibitors (e.g. TTP-435), serotonin re-uptake inhibitors such as fluoxetine (e.g. Fluctine®), duloxetine

(e.g. Cymbalta®), dual or triple monoamine uptake inhibitors (dopamine, norepinephrine and serotonin re-uptake) such as sertraline (e.g. Zoloft®), tesofensine, methionine aminopeptidase 2 (MetAP2) inhibitors (e.g. beloranib), and antisense oligonucleotides against production of fibroblast growth factor receptor 4 (FGFR4) (e.g. ISIS-FGFR4Rx) or prohibitin targeting peptide-1 (e.g. Adipotide®).

Moreover, combinations with drugs for influencing high blood pressure, chronic heart failure or atherosclerosis, for example: nitric oxide donors, AT1 antagonists or angiotensin II (AT2) receptor antagonists such as telmisartan (e.g. Kinzal®, Micardis®), candesartan (e.g. Atacand®, Blopress®), valsartan (e.g. Diovan®, Co-Diovan®), losartan (e.g. Cosaar®), eprosartan (e.g. Teveten®), irbesartan (e.g. Aprovel®, CoAprovel®), olmesartan (e.g. Votum®, Olmetec®), tasosartan, azilsartan (e.g. Edarbi®), dual angiotensin receptor blockers (dual ARBs), angiotensin converting enzyme (ACE) inhibitors, ACE-2 activators, renin inhibitors, prorenin inhibitors, endothelin converting enzyme (ECE) inhibitors, endothelin receptor (ET1/ETA) blockers, endothelin antagonists, diuretics, aldosterone antagonists, aldosterone synthase inhibitors, alpha-blockers, antagonists of the alpha-2 adrenergic receptor, beta-blockers, mixed alpha-/beta-blockers, calcium antagonists, calcium channel blockers (CCBs), nasal formulations of the calcium channel blocker diltiazem (e.g. CP-404), dual mineralocorticoid/CCBs, centrally acting antihypertensives, inhibitors of neutral endopeptidase, aminopeptidase-A inhibitors, vasopeptide inhibitors, dual vasopeptide inhibitors such as neprilysin-ACE inhibitors or neprilysin-ECE inhibitors, dual-acting AT receptor-neprilysin inhibitors, dual AT1/ETA antagonists, advanced glycation end-product (AGE) breakers, recombinant renalase, blood pressure vaccines such as anti-RAAS (renin-angiotensin-aldosteron-system) vaccines, AT1- or AT2-vaccines, drugs based on hypertension pharmacogenomics such as modulators of genetic polymorphisms with antihypertensive response, thrombocyte aggregation inhibitors, and others or combinations thereof are suitable.

In another aspect, this invention relates to the use of a compound according to the invention or a physiologically acceptable salt thereof combined with at least one of the active substances described above as a combination partner, for preparing a medicament which is suitable for the treatment or prevention of diseases or conditions which can be affected by binding to the GPR119 and modulating its activity. This is

preferably a disease in the context of the metabolic syndrome, particularly one of the diseases or conditions listed above, most particularly diabetes or obesity or complications thereof.

The use of the compounds according to the invention, or a physiologically acceptable salt thereof, in combination with one or more active substances may take place simultaneously, separately or sequentially.

The use of the compound according to the invention, or a physiologically acceptable salt thereof, in combination with another active substance may take place simultaneously or at staggered times, but particularly within a short space of time. If they are administered simultaneously, the two active substances are given to the patient together; if they are used at staggered times, the two active substances are given to the patient within a period of less than or equal to 12 hours, but particularly less than or equal to 6 hours.

Consequently, in another aspect, this invention relates to a medicament which comprises compounds according to the invention or a physiologically acceptable salt of such a compound and at least one of the active substances described above as combination partners, optionally together with one or more inert carriers and/or diluents.

The compounds according to the invention, or physiologically acceptable salt or solvate thereof, and the additional active substance to be combined therewith may both be present together in one formulation, for example a tablet or capsule, or separately in two identical or different formulations, for example as so-called kit-of-parts.

Compounds according to the invention can be administered to animals, in particular to mammals including humans, as pharmaceuticals by themselves, in mixtures with one another, or in the form of pharmaceutical compositions. The administration can be carried out orally, for example in the form of tablets, film-coated tablets, sugar-coated tablets, granules, hard and soft gelatin capsules, solutions including aqueous, alcoholic and oily solutions, juices, drops, syrups, emulsions or suspensions, rectally, for example in the form of suppositories, or parenterally, for example in the form of solutions for subcutaneous, intramuscular or intravenous injection or infusion, in particular aqueous solutions.

Suitable pharmaceutical compositions for oral administration may be in the form of separate units, for example capsules, cachets, lozenges or tablets, each of which contains a defined amount of the compound of formula I; as powders or granules; as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact. The compositions are generally produced by uniform and homogeneous mixing of the active ingredient with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or molding a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets can be produced by tableting the compound in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one (or more) surfactant(s)/dispersant(s) in a suitable machine. Molded tablets can be produced by molding the compound, which is in powder form and has been moistened with an inert liquid diluent, in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration comprise lozenges which contain a compound of formula I with a flavoring, typically sucrose, and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

Coated formulations and coated slow-release formulations, especially acid- and gastric juice-resistant formulations, also belong within the framework of the invention. Suitable coatings resistant to gastric juice comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Pharmaceutical compositions suitable for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing a compound of formula I with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

Pharmaceutical compositions suitable for parenteral administration comprise preferably sterile aqueous preparations of a compound of formula I, which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions of the invention generally contain 0.1 to 5% by weight of the active compound.

Other suitable administration forms are, for example, percutaneous or topical administration, for example in the form of ointments, creams, tinctures, sprays, powders or transdermal therapeutic systems, or inhalative administration, for example in the form of nasal sprays or aerosol mixtures, or forms such as microcapsules, implants or rods.

Pharmaceutical compositions suitable for topical use on the skin are preferably in the form of ointment, cream, lotion, paste, spray, aerosol or oil. The carriers used may be petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active ingredient is generally present in a concentration of 0.1 to 15% by weight of the composition, for example 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal uses may be in the form of single patches which are suitable for long-term close contact with the patient's epidermis. Such patches suitably contain the active ingredient in an aqueous solution which is buffered where appropriate, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active ingredient concentration is about 1% to 35%, preferably about 3% to 15%. A particular option is for the active ingredient to be released by electrotransport or iontophoresis as described, for example, in Pharmaceutical Research, 2(6): 318 (1986).

Compounds according to the invention can additionally be used in systems for local drug delivery, for example in coated stents for preventing or reducing in-stent restenosis or by applying them locally by means of a catheter. The appropriate administration form depends, among others, on the disease to be treated and on its severity.

The dosing of compounds according to the invention to achieve the desirable therapeutic effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.3 mg to 100 mg (typically from 3 mg to 50 mg) per day and per kilogram of body weight, for example 3-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.3 mg to 1.0 mg/kg, which can suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, 0.1 ng to 100 mg, typically 1 ng to 100 mg, per milliliter. Single doses may contain, for example, 1 mg to 10 g of the active ingredient. Thus, ampoules for injections may contain, for example, from 1 mg to 100 mg, and orally administrable single-dose formulations, for example tablets or capsules, may contain, for example, from 1.0 to 1000 mg, typically from 10 to 600 mg. For prevention and/or treatment of the abovementioned conditions, the compounds of the formula I themselves may be used as the compound, but they are preferably present with a compatible carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain 0.05% to 95% by weight of the active ingredient. Other pharmaceutically active substances may likewise be present, including other compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Another subject of the present invention are processes for the preparation of the compounds of the formula I and their salts and solvates, by which the compounds are obtainable and which are outlined in the following.

Abbreviations

Abbreviations within this document have their common meanings unless defined otherwise herein. An exemplary list of abbreviations used, can be found below.

Abbreviation	Meaning
Ac	acetyl
amu	atomic mass unit

Abbreviation	Meaning
atm	atmosphere (pressure unit, 101325 Pa)
Boc_2O	di-tert-butyl-dicarbonate
BSA	bovine serum albumin
cAMP	cyclic adenosine monophosphate
cat.	catalyst / catalyzed
CDI	carbonyl diimidazole
dba	dibenzylideneacetone
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIPEA	diisopropyl-ethyl-amine
DMAP	4-dimethylaminopyridine
DMEM	Dulbecco's modified eagle medium
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppf	diphenylphosphinoferrocene
EA	ethyl acetate
EC_{50}	concentration causing 50% of the maximal response
EDCI	ethyl dimethylaminopropyl carbodiimide
ESI	electrospray ionization
FA	formic acid
FCS	fetal calf serum
GPR119	G-protein coupled receptor 119
h	hour(s)
Hal	halogen (atom)
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyl-uronium hexafluorophosphate
HBSS	Hank's buffered salt solution
HEK 293	human embryonic kidney 293
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoric acid triamide
HOBt	1-hydroxy-benzotriazole
HPLC	high pressure liquid chromatography
HTRF	homogenous time-resolved fluorescence
IBMX	1-methyl-3-(2-methylpropyl)-7H-purine-2,6-dione
LCMS	liquid chromatography coupled mass spectroscopy
LG	leaving group
MeCN	methyl cyanide (acetonitrile)
min	minute(s)
MS	mass spectroscopy
MTBE	methyl tert.-butyl ether
NMP	*N*-methyl pyrrolidin-2-one
NMR	nuclear magnetic resonance (spectrum)
PBS	phosphate buffered saline

Abbreviation	Meaning
PE	petroleum ether
PMBCl	para-methoxybenzyl chloride
R_t	retention time
RT	room temperature
SGC	silica gel chromatography
SiO_2	silica gel (for chromatography)
TBAF	tetra-n-butylammonium fluoride
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TM	transition metal
TMS	tetramethylsilane
$TMSCHN_2$	trimethylsilyldiazomethane
Ts	para-tolylsulfonyl
UV	ultraviolet (spectrum)

Synthetic Methods

Variables in the formulae of the schemes represent moieties as defined above unless other meanings are given.

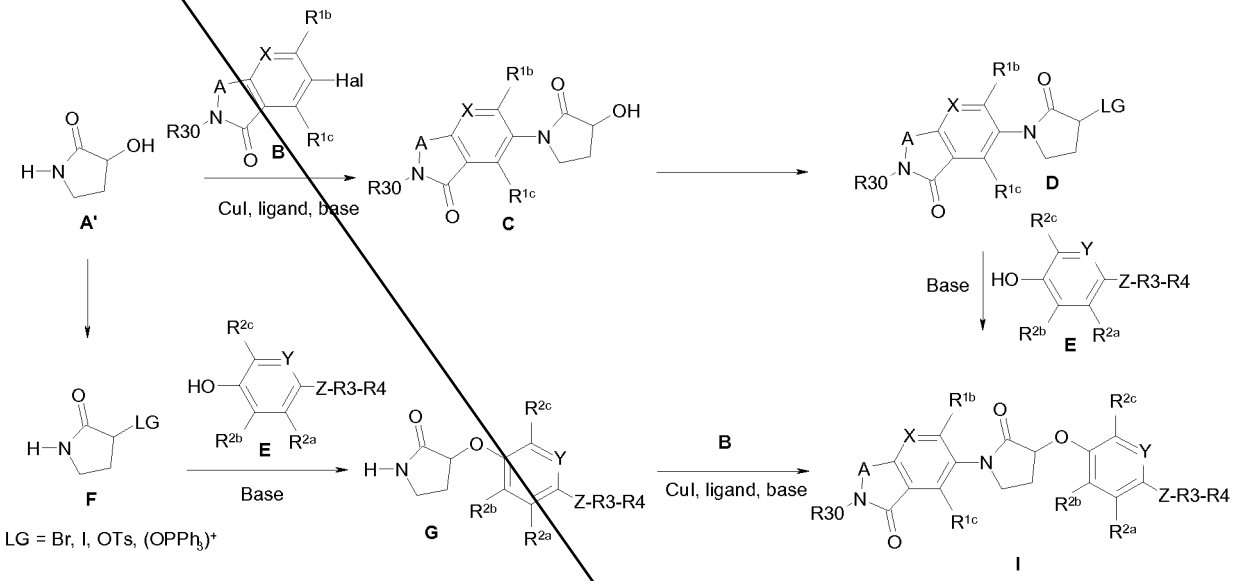
Detailed descriptions of the Typical Procedures to which reference is made in this section can be found in the Examples section.

Compounds of the invention having the formula I may be prepared by combining known synthetic procedures. In a first method 3-hydroxy-pyrrolidin-2-one (A') (commercially available as racemic mixture and in both enantiomeric forms) is coupled with bicyclic aryl halides B (typically Hal is Br or I) to provide intermediates C. An example for suitable coupling conditions (CuI, *N*,*N*'-dimethyl-ethane-1,2-diamine, cesium carbonate) can be found in the Typical Procedure 1. Conversion of the hydroxy group in C to a suitable leaving group (LG is for example Br, I, OTs or $OPPh_3^+$) can be accomplished with various well known reagents (e.g. PPh_3/I_2, PPh_3/CBr_4, PPh_3/DIAD or $TsCl/NEt_3$) providing the intermediates D, which may be isolated or may be reacted without isolation with hydroxy-aryl building blocks of type E using an appropriate base (e.g. Na_2CO_3, K_2CO_3, Cs_2CO_3 or NaH). For example the conditions in the Typical Procedure 3 may be applied to couple intermediates C and E to provide compounds I.

A second method of synthesizing compounds I starts with a pyrrolidin-2-one substituted with a leaving group (LG) in 3-position (structures F), which may be prepared by reacting A' with the reagents mentioned above. Other procedures for making structures F are known (e.g. base-promoted cyclization of 2,4-dibromo-butyramide). Intermediates

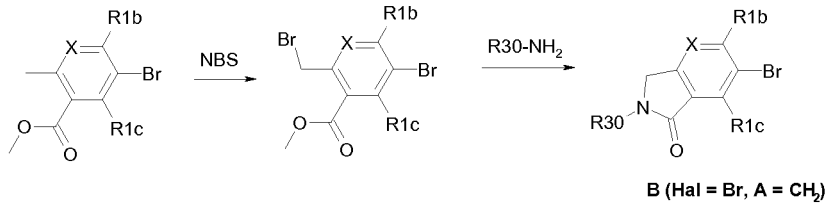
F may be isolated or generated in situ to react with hydroxy-aryls E (typically in the presence of a base as described above) to provide intermediates G. As a final step, for example copper-catalyzed coupling with aryl halides B provides the desired compounds I (Scheme 1).

Scheme 1.



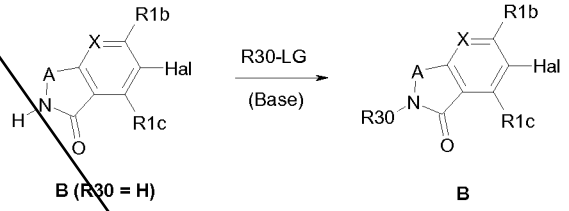
Isoindolinones B (Hal = Br, A = CH_2) may be prepared by reaction of 5-bromo-2-bromomethyl-benzoic acid methyl esters (X = C-R1a) or 5-bromo-2-bromomethyl-nicotinic acid methyl esters (X = N) with amines R30-NH_2 (Scheme 2a).

Scheme 2a.



Alkylation of N-unsubstituted isoindolinones B (R30 = H), for example with R30-LG under the exemplary conditions given in Typical Procedure 2, gives access to further intermediates B as illustrated in Scheme 2b.

Scheme 2b.



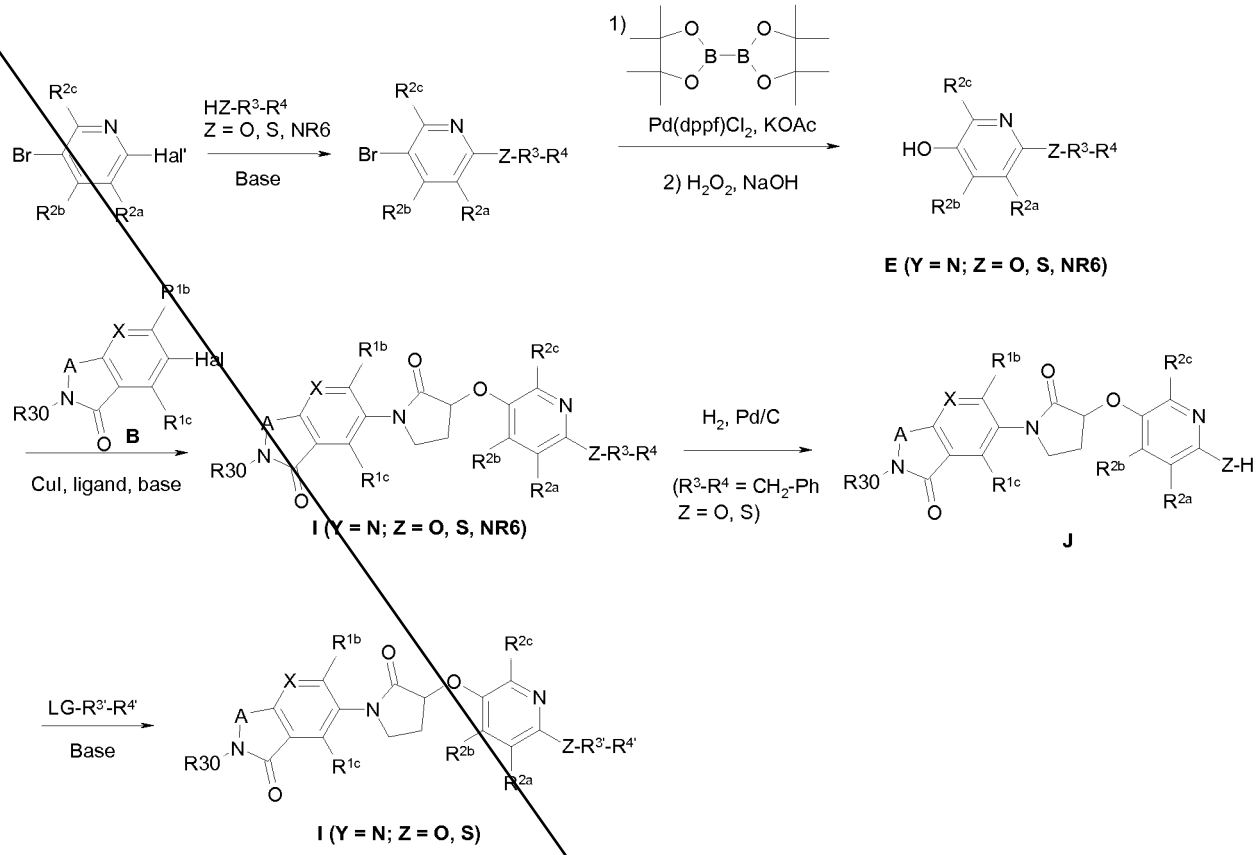
B (R30 = H) B

Certain compounds I (Y = N; Z = O, S, NR6) may be prepared by coupling aryl halides B with hydroxy-pyridines E (Y = N; Z = O, S, NR6). Said hydroxy-pyridines E may be prepared by displacement of a halide (F, Cl, Br or I) in the 2-position of 5-bromo-2-halo-pyridines, which are substituted with R^{2a}, R^{2b} and R^{2c}, using nucleophiles of the type HZ-R^3-R^4 (Z = O, S, NR6) followed by conversion of the 5-bromo-substituent to a hydroxy group (e.g. by oxidation of a boronate group introduced by palladium catalyzed coupling with bis-pinacolato-diboron). See Typical Procedure 6 for exemplary conditions for the nucleophilic displacement reaction, Typical Procedures 5 for examples of boronate-oxidation conditions, Typical Procedure 4 for an example of conditions to install a boronate group and Scheme 3 for illustration of the overall method.

A benzyl group (R^3-R^4 = CH_2-Ph) in compounds I (Y = N, Z = O, S) may be cleaved for example by hydrogenolysis to provide intermediates J, which may be alkylated by LG-$R^{3'}$-$R^{4'}$, $R^{3'}$ and $R^{4'}$ being defined like R^3 and R^4 respectively, to yield compounds I (Y = N; Z = O, S).

For example, the structure J may be a 2-hydroxy-pyridine (Z = O), which may be alkylated under Mitsunobu-conditions (PPh_3/DIAD; see for example Typical Procedure 3) starting with alcohols HO-$R^{3'}$-$R^{4'}$. Triphenylphosphine may be introduced into the reaction as polymer. DIAD may be replaced by other azodicarboxylates (e.g. DEAD). Alternatively, structures J may be reacted with alkyl halides as exemplified in Typical Procedure 10.

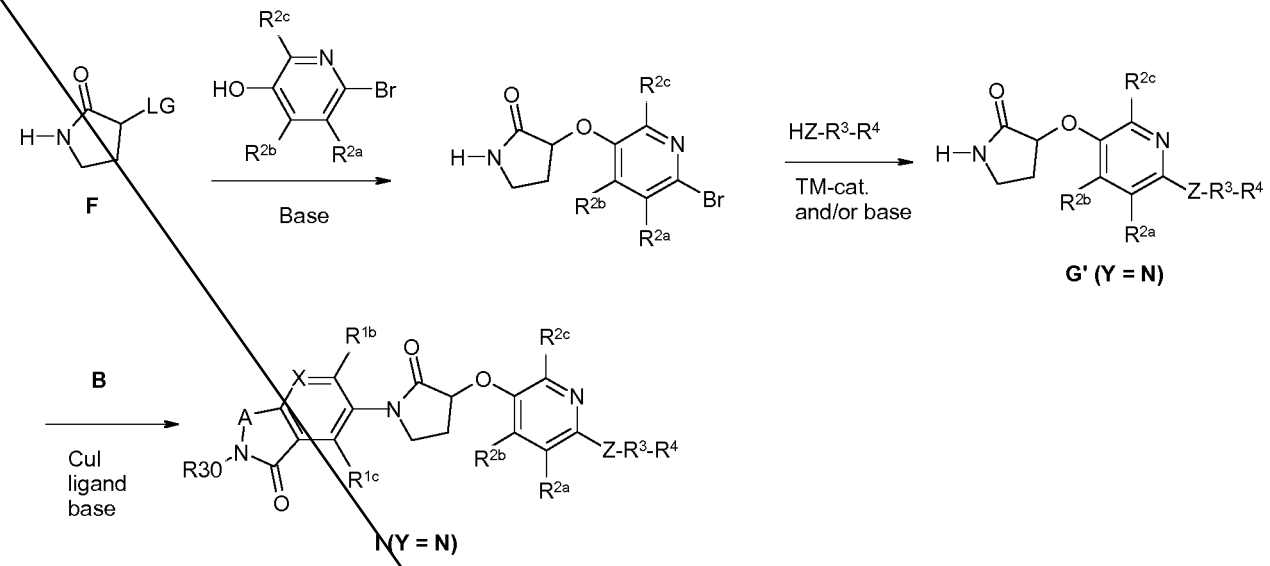
Scheme 3.



Certain other compounds of the invention may be prepared by reaction of hydroxy-pyrrolidinones C with 6-bromo-pyridin-3-ols under Mitsunobu-conditions and subsequent transition metal catalyzed replacement of the Br-atom by Z-R^3-R^4.

Variation of the order of the steps in the synthetic sequence provides further methods to prepare compounds I. For example intermediates F may be reacted with 6-bromo-pyridin-3-ols and subsequently the bromo-substituent may be exchanged for Z-R^3-R^4 to provide intermediates G (Y = N). In a last step, coupling with aryl halides B again provides compounds I (Y = N) as illustrated in Scheme 4.

Scheme 4.



Other derivatives of formula I (e.g. with R30 = CH_2COOH) can be obtained by cleaving the ester functionality in structures I (R30 = $CH_2COO(C_1\text{-}C_6)$-alkyl) for example using the conditions described in Typical Procedures 7a, 7b and 7c. Still other compounds I (R30 = $CH_2CONR14R15$) are provided by the reaction of said acids with amines of the structure HNR14R15 using for example EDCI as coupling reagent (see Typical Procedure 9 for exemplary conditions).

Analytical Methods

Examples were characterized by standard analytical methods. This includes at least two methods (e.g. selected from HPLC, MS, ^{1}H-NMR). In particular, MS and HPLC data were obtained by combined analytical HPLC/MS (LCMS). For example the following LCMS methods were used.

Method A

Column: Waters UPLC BEH C18 2.1*50 mm, 1.7 µm; mobile phase: (H_2O + 0.05% FA) : (MeCN + 0.035% FA) 98:2 (0 min) to 5:95 (2 min) to 5:95 (2.6 min) to 95:5 (2.7 min) to 95:5 (3 min); flow rate: 0.9 mL/min; column temperature: 55°C; ionization method: ES^+; UV wavelength: 220 nm.

Method B

Column: Waters XBridge C18 4.6*50 mm, 2.5 µm; mobile phase: (H_2O + 0.1% FA) : (MeCN + 0.1% FA) 97:3 (0 min) to 40:60 (3.5 min) to 2:98 (4 min) to 2:98 (5 min) to 97:3 (5.2 min) to 97:3 (6.5 min); flow rate: 0.9 mL/min; column temperature: 55°C; ionization method: ES^+; UV wavelength: 220 nm.

Method C

Column: Waters UPLC BEH C18 2.1*50 mm, 1.7 µm; mobile phase: (H_2O + 0.05% FA) : (MeCN + 0.035% FA) 95:5 (0 min) to 5:95 (2 min) to 5:95 (2.6 min) to 95:5 (2.7 min) to 95:5 (3 min); flow rate: 0.9 mL/min; column temperature: 55°C; ionization method: ES^+; UV wavelength: 220 nm.

Method D

Column: Waters UPLC BEH C18 2.1*50 mm, 1.7 µm; mobile phase: (H_2O + 0.1% FA) : MeCN + 0.08% FA) 95:5 (0 min) to 5:95 (1.1 min) to 5:95 (1.7 min) to 95:5 (1.8 min) to 95:5 (2 min); flow rate: 0.9 mL/min; column temperature: 55°C; ionization method: ES^+; UV wavelength: 220 nm.

Method E

Column: Waters UPLC BEH C18 2.1*50 mm; 1.7 µm; mobile phase: (H_2O + 0.05% FA) : (MeCN + 0.035% FA) 95:5 (0 min) to 5:95 (1.1 min) to 5:95 (1.7 min) to 95:5 (1.8 min) to 95:5 (2 min); flow rate: 0.9 mL/min; column temperature: 55°C; ionization method: ES^+; UV wavelength: 220 nm.

In general, HPLC data is represented by the retention time (R_t; in min); MS data is given as the observed mass number (m/z) of the ion $[M+H]^+$ (if present) and ^{1}H-NMR data is reported by lists of chemical shifts δ (in ppm vs. TMS) of the observed signals (the number of hydrogen atoms was determined using the area under the respective signal; signal multiplicity is characterized as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplets, q = quartet, m = multiplet, br = broad; coupling constants *J* are given in Hertz (Hz)). Deuterated solvents were used for NMR spectroscopy.

Examples

The following examples are particular embodiments of the invention. They partially illustrate the scope of the invention without limiting it.

Abbreviations and chemical symbols have their usual and customary meanings unless otherwise indicated.

The examples were prepared, isolated and analyzed by the procedures and methods given. Alternatively they may be prepared by the general synthetic methods detailed above. Further variations of the synthetic procedures may be proposed by a person skilled in the art.

When example compounds containing a basic group were purified by preparative HPLC on reversed phase column material and, as customary, the eluent was a gradient mixture of water and acetonitrile containing trifluoroacetic acid (TFA), they were obtained in part in the form of their addition salt with TFA, depending on the details of the workup such as evaporation or lyophilization conditions. In the names of the example compounds and their structural formulae any such TFA present is not specified.

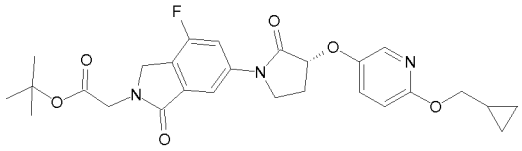
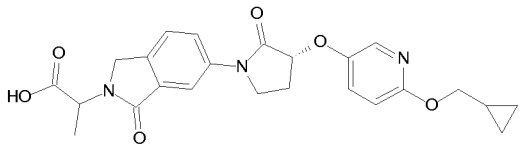
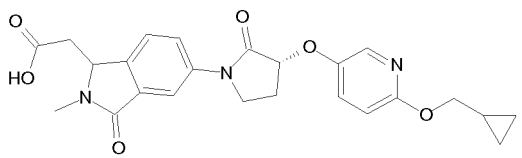
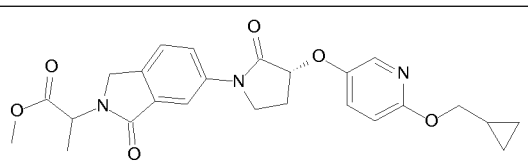
Preparation of Examples 1

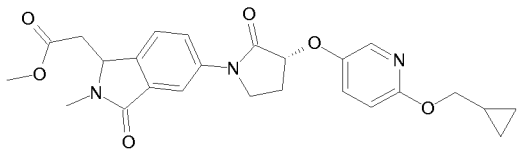
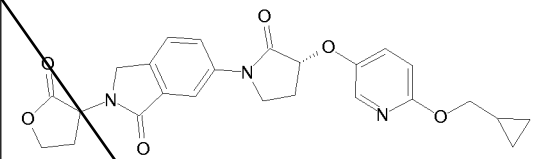
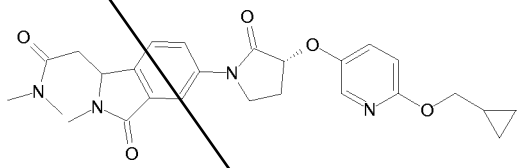
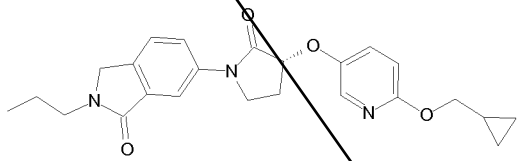
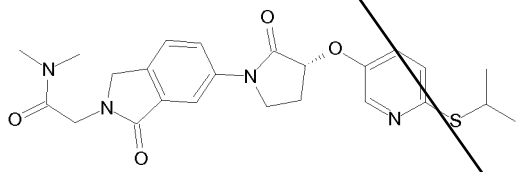
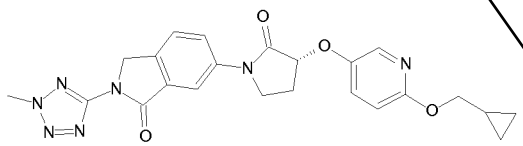
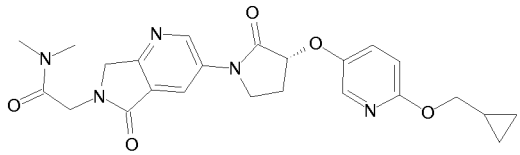
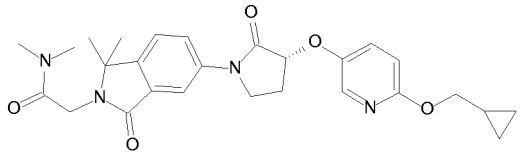
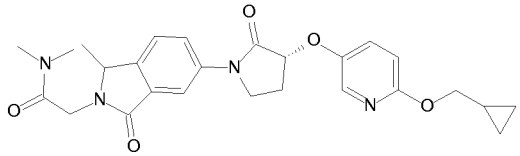
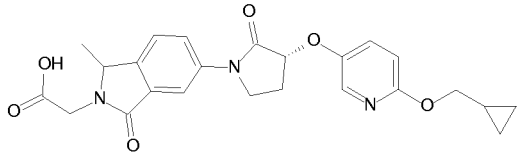
Example 1-01 (Typical Procedure 1)

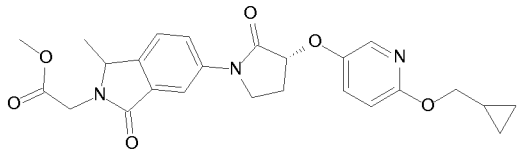
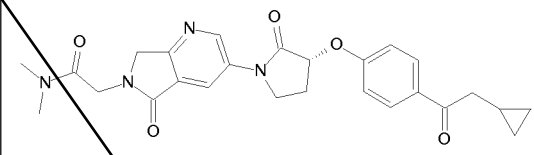
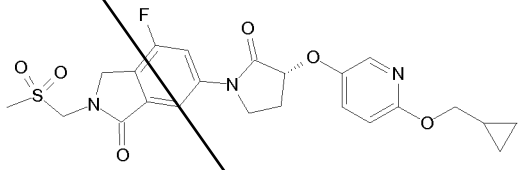
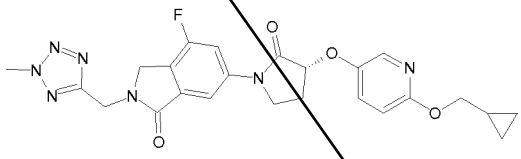
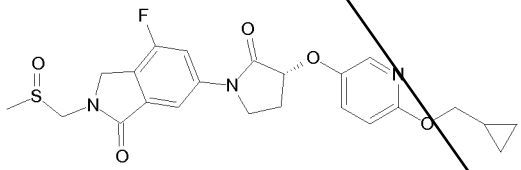
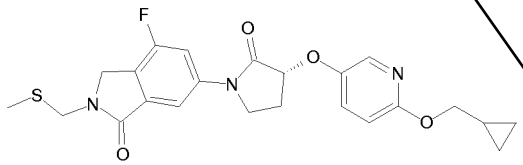
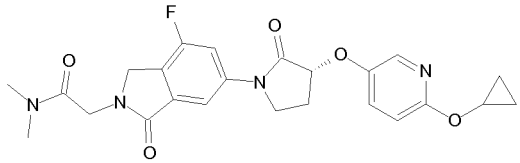
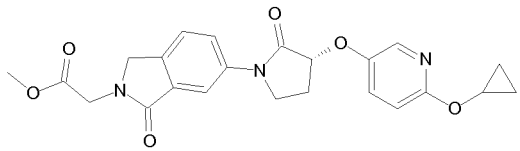
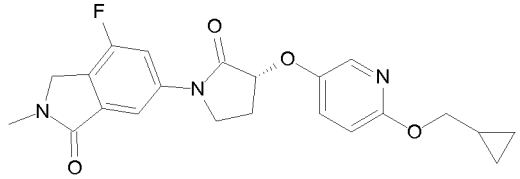
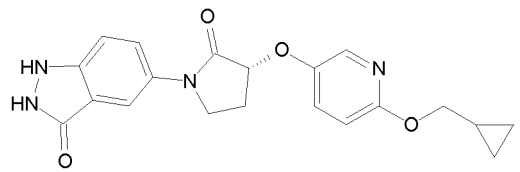
To a mixture of tert-butyl 2-(6-bromo-4-fluoro-1-oxoisoindolin-2-yl)acetate (50 mg), (R)-3-((6-(cyclopropylmethoxy)pyridin-3-yl)oxy)pyrrolidin-2-one (43 mg) and 1,4-dioxane (3 mL) was added *N*,*N*'-dimethyl-ethane-1,2-diamine (128 mg) and cesium carbonate (71 mg). The mixture was purged for 5 minutes with a flow of argon and CuI (17 mg) was added. The mixture was heated at 100°C for 1 hour. After cooling to RT, insoluble material was removed by filtration and the filtrate concentrated. The residue was purified by preparative HPLC to provide example 1-01.

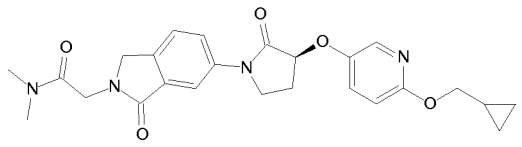
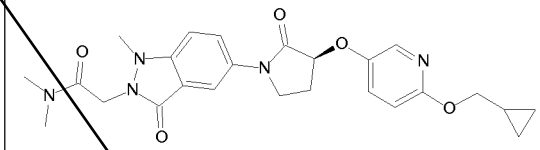
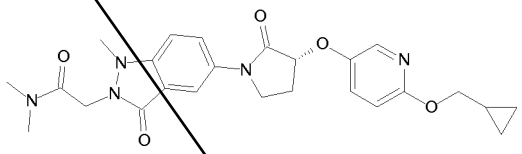
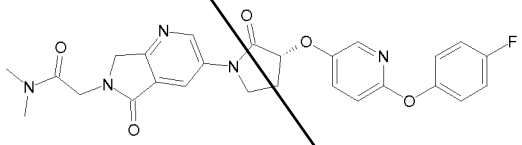
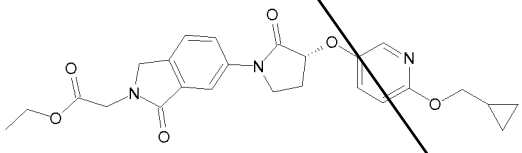
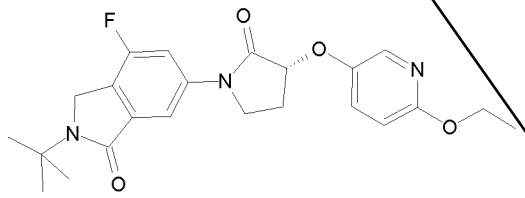
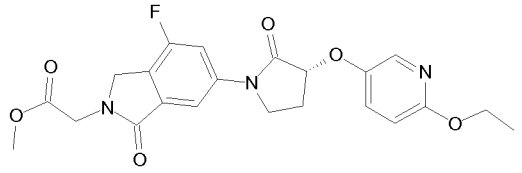
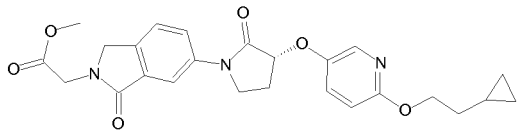
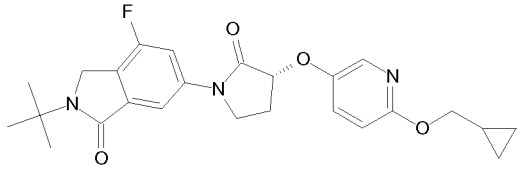
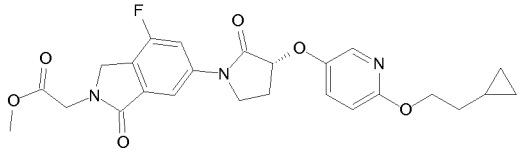
Following essentially the Typical Procedure 1, the Examples 1 in Table 1 were prepared using the respective aryl bromides and 3-substituted pyrrolidinones.

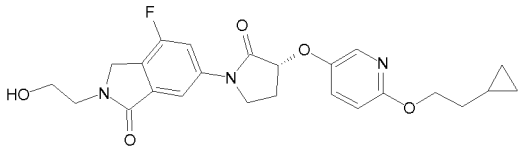
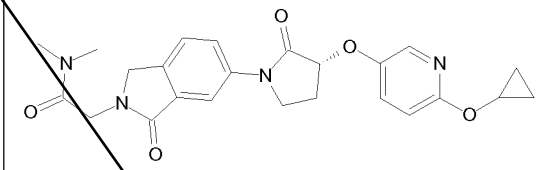
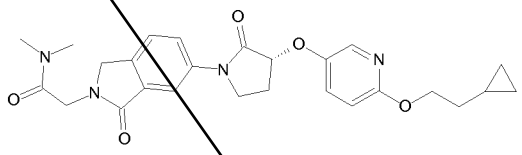
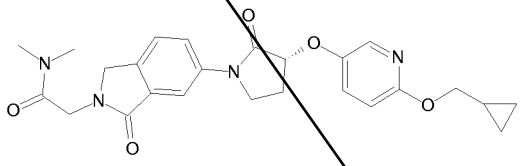
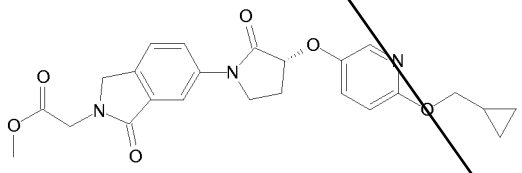
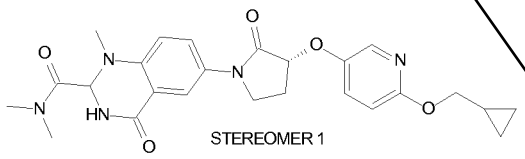
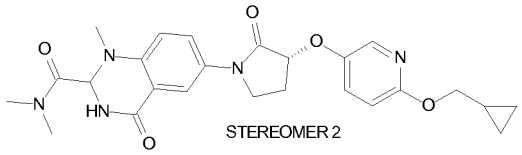
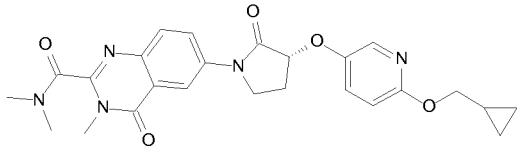
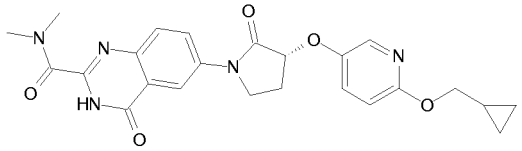
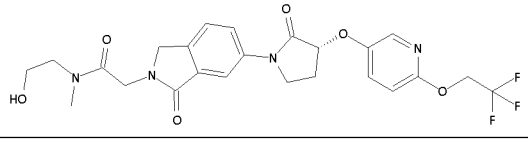
Table1.

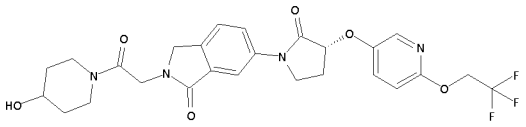
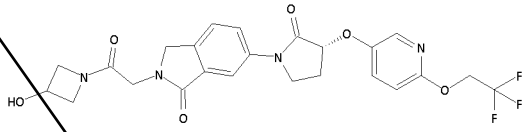
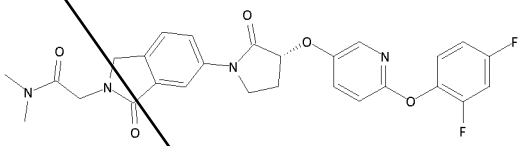
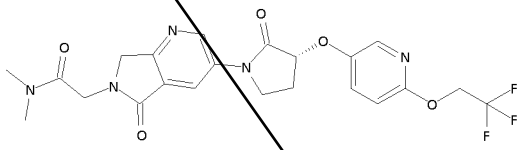
Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
1-01		A	1.89	512.3
1-02		A	1.60	452.2
1-03		A	1.53	452.1
1-04		A	1.70	466.2

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
1-05		A	1.65	466.2
1-06		A	1.63	464.3
1-07		A	1.60	479.4
1-08		A	1.75	422.1
1-09		A	1.62	469.3
1-10		A	1.68	462.4
1-11		A	1.52	466.3
1-12		A	1.68	493.4
1-13		B	3.95	479.4
1-14		B	3.95	452.3

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
1-15		A	1.74	466.3
1-16		C	1.71	477.2
1-17		A	1.68	490.3
1-18		A	1.67	494.4
1-19		A	1.56	474.3
1-20		A	1.81	458.2
1-21		A	1.53	469.2
1-22		A	1.50	438.2
1-23		A	1.67	412.1
1-24		A	1.45	381.1

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
1-25		A	1.59	465.4
1-26		A	1.58	480.3
1-27		A	1.58	480.3
1-28		C	1.74	506.1
1-29		A	1.70	466.1
1-30		A	1.83	428.3
1-31		A	1.65	444.2
1-32		A	1.77	466.2
1-33		A	1.91	454.2
1-35		A	1.84	484.1

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
1-36		A	1.72	456.3
1-37		A	1.40	451.2
1-38		A	1.66	479.2
1-39		A	1.58	465.3
1-40		A	1.65	452.3
1-41	 STEREOMER 1	A	1.60	480.3
1-42	 STEREOMER 2	A	1.60	480.3
1-43		C	1.83	478.1
1-44		A	1.72	464.2
1-45		C	1.58	523.1

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
1-46		C	1.60	549.1
1-47		C	1.57	521.1
1-48		C	1.64	523.2
1-49		C	1.51	494.2

The reaction of (*R*)-3-[6-(2-cyclopropyl-methoxy)-pyridin-3-yloxy]-pyrrolidin-2-one with 2-(5-bromo-1-methyl-3-oxo-1H-indazol-2(3H)-yl)-N,N-dimethylacetamide according to Typical Procedure 1 provided a crude mixture, which was separated by HPLC (column: Chiralcel OD-H/126, 4.6*250 mm; mobile phase: EtOH/MeOH 1:1 with 0.1% TFA; flow rate: 1.0 mL/min; column temperature: 30°C; UV wavelength: 224 nm) to provide examples 1-41 (R_t = 5.00 min), 1-26 (R_t = 6.89 min), 1-27 (R_t = 7.78 min) and 1-42 (R_t = 12.46 min).

Occasionally carboxylic acids (e.g. Examples 1-03 and 1-14, respectively) were obtained as additional products from the reaction mixture due to (partial) ester hydrolysis (for example in the reaction of methyl 2-(6-bromo-1-oxoisoindolin-2-yl)propanoate and methyl 2-(5-bromo-1-methyl-3-oxoisoindolin-2-yl)acetate, respectively, with (*R*)-3-[6-(2-cyclopropyl-methoxy)-pyridin-3-yloxy]-pyrrolidin-2-one according to Typical Procedure 1). The carboxylic acids obtained, can be converted to methyl esters (e.g. Examples 1-05 and 1-15, respectively) by dissolving the respective acid in DCM (5 mL/mmol) and methanol (0.5 mL/mmol) and addition of $TMSCHN_2$ (1.5 equiv.). After the gas evolution has ceased, the reaction mixture is evaporated to provide the desired methyl ester.

Preparation of 3-Substituted Pyrrolidin-2-ones

(*R*)-3-[6-(4-Fluoro-phenoxy)-pyridin-3-yloxy]-pyrrolidin-2-one (Typical Procedure 3)

A mixture of THF (200 mL) and DCM (100 mL) under argon was added triphenylphosphine (polymer, 1.8 mmol/g, 20 g). Diisopropyl azodicarboxylate (8.87 g) was added. After 5 minutes (*S*)-3-hydroxy-pyrrolidin-2-one (3.1 g) and 6-(4-fluoro-phenoxy)-pyridin-3-ol (6.0 g) were added. After 30 minutes the mixture was filtered and the filtrate concentrated. The residue was purified by chromatography (SiO_2; DCM/MeOH 15:1) to provide the title compound. MS ESI$^+$: m/z = 289 $[M+H]^+$.

6-(4-Fluoro-phenoxy)-pyridin-3-ol

A mixture of 6-bromo-pyridin-3-ol (8.0 g), 4-fluorophenol (15.5 g) and cesium carbonate (30 g) was heated to 170°C for 6 hours. After the mixture reached room temperature, it was distributed between water and MTBE. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography (SiO_2; EA/heptane 1:1.5) to provide the subtitle compound. MS ESI$^+$: m/z = 206 $[M+H]^+$.

(*R*)-3-[6-(2-Cyclopropyl-ethoxy)-pyridin-3-yloxy]-pyrrolidin-2-one

A mixture of (*S*)-3-hydroxy-pyrrolidin-2-one (0.79 g), 6-(2-cyclopropyl-ethoxy)-pyridin-3-ol (1.4 g), triphenylphosphine (2.25 g), DCM (30 mL) and THF (20 mL) was added DIAD (1.74 g). After 2 days the mixture was filtered and the filtrate was evaporated. The residue was purified by SGC (eluent: EA/MeOH 9:1) to provide the title compound. MS ESI$^+$: m/z = 263 $[M+H]^+$.

6-(2-Cyclopropyl-ethoxy)-pyridin-3-ol (Typical Procedure 4)

A mixture of 5-bromo-2-(2-cyclopropyl-ethoxy)-pyridine (2.2 g), bis(pinacolato)diboron (2.54 g) and 1,4-dioxane (15 mL) was purged with argon. Potassium acetate (2.68 g) and Pd(dppf)Cl_2 (0.35 g) were added. The mixture was irradiated in a microwave instrument for 1 hour at 80°C. After the mixture reached room temperature, it was distributed between water and EA. The organic phase was dried (Na_2SO_4) and concentrated to obtain the crude boronate.

Typical Procedure 5

The crude boronate from above was dissolved in THF (50 mL) and NaOH (40% in water, 10 mL) and H_2O_2 (30% in water, 3 mL) were added. After 3 hours the mixture was neutralized and extracted with EA. The organic phase was dried (Na_2SO_4) and concentrated to provide the subtitle compound. MS ESI$^+$: m/z = 180 $[M+H]^+$.

5-Bromo-2-(2-cyclopropyl-ethoxy)-pyridine (Typical Procedure 6)

A mixture of 2-cyclopropyl-ethanol (4.1 g) and DMF (15 mL) under argon was treated with NaH (60% in mineral oil, 0.45 g). After 4 hours 5-bromo-2-fluoro-pyridine (3.0 g)

was added at 0°C. After 4 hours at room temperature, the mixture was distributed between water and EA. The organic phase was washed twice (water), dried (Na_2SO_4) and concentrated. The residue was purified by chromatography (SiO_2; EA/heptane 1:4) to provide the subtitle compound. MS ESI$^+$: m/z = 242 $[M+H]^+$.

(R)-3-((6-Ethoxypyridin-3-yl)oxy)pyrrolidin-2-one

The procedures described above for (*R*)-3-[6-(2-cyclopropyl-ethoxy)-pyridin-3-yloxy]-pyrrolidin-2-one were followed substituting ethanol for 2-cyclopropyl-ethanol to provide the title compound. MS ESI$^+$: m/z = 223 $[M+H]^+$.

(*R*)-3-[6-(2-Cyclopropyl-methoxy)-pyridin-3-yloxy]-pyrrolidin-2-one

A mixture of (*S*)-3-hydroxy-pyrrolidin-2-one (3.00 g), 6-(2-cyclopropyl-methoxy)-pyridin-3-ol (4.90 g), triphenylphosphine (polymer, 8.56 g), DCM (30 mL) and THF (50 mL) was added DIAD (6.60 g) keeping the reaction temperature below 30°C. After 12 hours the mixture was filtered and the filtrate was evaporated. The residue was purified by SGC (eluent: EA/MeOH 9:1) to provide the title compound. MS ESI$^+$: m/z = 249 $[M+H]^+$.

6-Cyclopropylmethoxy-pyridin-3-ol

A mixture of 5-bromo-2-cyclopropylmethoxy-pyridine (8.00 g), bis(pinacolato)diboron (8.91 g) and 1,4-dioxane (53 mL) was purged with argon. Potassium acetate (3.44 g) and Pd(dppf)Cl_2 (2.57 g) were added and the mixture heated to 100°C for 1 hour by microwave irradiation. The mixture was filtered and the filtrate diluted with EA, washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by SGC (eluent: EA/heptane 1:6) to provide the crude boronate. MS ESI$^+$: m/z = 276 $[M+H]^+$. The boronate was dissolved in THF (60 mL). Aqueous NaOH (5 M) was added at 0°C. Hydrogen peroxide (30% in water, 30 mL) was added slowly. The mixture was allowed to warm to RT and stirred for 4 hours. The mixture was extracted with MTBE. The aqueous phase was adjusted to pH 3-4 by addition of diluted HCl and extracted with EA. The organic phase was dried (Na_2SO_4) and concentrated to provide the subtitle compound. MS ESI$^+$: m/z = 166 $[M+H]^+$.

5-Bromo-2-cyclopropylmethoxy-pyridine

To a mixture of 2-cyclopropyl-methanol (6.15 g) and DMF (12 mL) was added NaH (60% in mineral oil, 1.5 g) at 0°C. After stirring for 4 hours at RT the mixture was diluted with DMF (5 mL) and 5-bromo-2-fluoro-pyridine (6.00 g) was slowly added keeping the reaction temperature below 30°C. After 30 minutes at RT the mixture was heated to

130°C for 1 hour by microwave irradiation. After cooling to RT, the mixture was diluted with EA and washed with water (3 times). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by SGC to provide the subtitle compound. MS ESI$^+$: m/z = 228 $[M+H]^+$.

(*R*)-3-[6-(2-Cyclopropoxy)-pyridin-3-yloxy]-pyrrolidin-2-one

Typical Procedure 3 was followed. Reaction of 6-cyclopropoxy-pyridin-3-ol and (*S*)-3-hydroxy-pyrrolidin-2-one provided the title compound. MS ESI$^+$: m/z = 235 $[M+H]^+$.

6-Cyclopropoxy-pyridin-3-ol

A mixture of 5-bromo-2-cyclopropoxypyridine (Milestone Pharmtech, 500 mg) in THF (10 mL) was cooled (-78°C) and n-BuLi (2.5 M in toluene, 1.49 mL) was added dropwise within 10 minutes. After 20 minutes trimethyl borate (429 µL) was added. After 2 hours peracetic acid (32% in AcOH, 786 µL) was added dropwise. After 10 minutes the reaction temperature was changed to 0°C. After 1 hour the mixture was poured into aqueous $NaHSO_3$-solution (5%, 5 mL). The mixture was extracted with EA. The organic phase was dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography (silica gel, heptane to EA/heptane 2:3) to provide the subtitle compound. MS ESI$^+$: m/z = 152 $[M+H]^+$.

(*R*)-3-(6-Methylsulfanyl-pyridin-3-yloxy)-pyrrolidin-2-one (Typical Procedure 8)

A mixture of (*R*)-3-(6-bromo-pyridin-3-yloxy)-pyrrolidin-2-one (0.8 g), sodium methanethiolate (327 mg) and DMF (15 mL) was heated to 100°C for 15 minutes.

After the mixture reached room temperature, it was distributed between water and EA. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by preparative HPLC to provide the title compound. MS ESI$^+$: m/z = 225 $[M+H]^+$.

(*R*)-3-(6-Bromo-pyridin-3-yloxy)-pyrrolidin-2-one

Typical Procedure 3 was followed. Reaction of (*S*)-3-hydroxy-pyrrolidin-2-one with 6-bromo-pyridin-3-ol provided the subtitle compound. MS ESI$^+$: m/z = 257 $[M+H]^+$.

(*R*)-3-(6-Isopropylsulfanyl-pyridin-3-yloxy)-pyrrolidin-2-one

Typical Procedure 8 was followed. Reaction of (*R*)-3-(6-bromo-pyridin-3-yloxy)-pyrrolidin-2-one with sodium 2-propanethiolate provided the title compound. MS ESI$^+$: m/z = 253 $[M+H]^+$.

(R)-3-(4-(2-Cyclopropylacetyl)phenoxy)pyrrolidin-2-one

A solution of 2-cyclopropyl-1-(4-hydroxyphenyl)ethanone (1.1 g), (S)-3-hydroxypyrrolidin-2-one (947 mg), PPh_3 (2.78 g) and DIAD (2.15 g) in THF (5 mL) was stirred at 4°C for 15 hours. The reaction mixture was diluted with EA (200 mL), and washed with water (100 mL x 2) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with DCM/MeOH = 50:1 to provide the title compound. MS ESI^+: m/z = 260 $[M+H]^+$.

2-Cyclopropyl-1-(4-hydroxyphenyl)ethanone

To a solution of 1-(4-(tert-butyldimethylsilyloxy)phenyl)-2-cyclopropylethanone (3.8 g) in THF (50 mL) was added a solution of TBAF (6.65 g) in THF (10 mL). The reaction mixture was stirred for 4 hours at RT. The solvent was removed under reduced pressure and the residue was dissolved in EA (100 mL), washed with HCl (0.5 N, 20 mL), brine (20 mL) and dried over Na_2SO_4. The residue was purified by column chromatography on silica gel eluting with DCM/MeOH = 200:1 to provide the subtitle compound. MS ESI^+: m/z = 177 $[M+H]^+$.

1-(4-(Tert-butyldimethylsilyloxy)phenyl)-2-cyclopropylethanone

To a solution of (4-bromophenoxy)(tert-butyl)dimethylsilane (3.15 g) in THF (20 mL) was added a solution of t-BuLi (6.8 mL) dropwise at -78°C. The reaction mixture was stirred for 20 minutes at -78°C and then a solution of 2-cyclopropyl-N-methoxy-N-methylacetamide (1.3 g) in dry THF (5 mL) was added slowly. The reaction mixture was allowed to warm to RT and stirred for 4 hours. The reaction mixture was poured into water (100 mL) and the volatiles were removed under reduced pressure. The aqueous phase was extracted with EA (50 mL x 3). The organic phase was washed with brine and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to provide the subtitle compound. MS ESI^+: m/z = 291 $[M+H]^+$.

(4-Bromophenoxy)(tert-butyl)dimethylsilane

To a solution of 4-bromophenol (5.0 g) in DMF (25 mL) was added tert-butylchlorodimethylsilane (5.0 g) and imidazole (5.0 g) in portions at RT. The mixture was stirred for 3 hours and then poured into water (200 mL). The mixture was extracted with Et_2O (80 mL x 3). The organic phase was washed with water (30 mL x 4), HCl (1 N, 30 mL), saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL).The organic phase was dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to provide the subtitle compound.

2-Cyclopropyl-N-methoxy-N-methylacetamide

To a stirred solution of 2-cyclopropylacetic acid (1.0 g) in DCM (30 mL) was added CDI (1.86 g) at room temperature. The mixture was stirred for 2 hours at RT and then O,N-dimethylhydroxylamine hydrochloride (1.07 g) was added. The reaction mixture was stirred for 20 hours at RT. The reaction mixture was poured into water (100 mL) and then extracted with DCM (30 mL x 3). The organic phase was washed with water (50 mL), HCl (1 N, 30 mL), saturated aqueous $NaHCO_3$ (30 mL) and dried over Na_2SO_4. After filtration the solvent was removed under reduced pressure to provide the subtitle compound.

(R)-3-[6-(2,2,2-Trifluoro-ethoxy)-pyridin-3-yloxy]-pyrrolidin-2-one

Following Typical Procedure 3, reaction of 6-(2,2,2-trifluoroethoxy)pyridin-3-ol with (S)-3-hydroxy-pyrrolidin-2-one provided the title compound. MS ESI^+: m/z = 277 $[M+H]^+$.

(R)-3-[6-(2,4-Difluoro-phenoxy)-pyridin-3-yloxy]-pyrrolidin-2-one

Following Typical Procedure 3, reaction of 6-(2,4-difluoro-phenoxy)-pyridin-3-ol with (S)-3-hydroxy-pyrrolidin-2-one provided the title compound. MS ESI^+: m/z = 307 $[M+H]^+$.

6-(2,4-Difluoro-phenoxy)-pyridin-3-ol

Following Typical Procedures 4 and 5a, conversion of 5-bromo-2-(2,4-difluoro-phenoxy)-pyridine to the boronate and oxidation provided the subtitle compound. MS ESI^+: m/z = 224 $[M+H]^+$.

5-Bromo-2-(2,4-difluoro-phenoxy)-pyridine

A mixture of 2,5-dibromo-pyridine (24.0 g), 2,4-difluoro-phenol (26.4 g) and K_2CO_3 (42.0 g) in DMF (300 mL) was stirred at 150°C overnight. After cooling to room temperature, the mixture was diluted with water (600 mL), extracted with ethyl acetate (400 mL x 3), washed with water (800 mL) and dried over anhydrous Na_2SO_4. The crude product was purified by silica gel chromatography (petrol ether) to provide the subtitle compound. MS ESI^+: m/z = 286 $[M+H]^+$.

<u>Preparation of Aryl Bromides</u>

Tert-butyl 2-(6-bromo-4-fluoro-1-oxoisoindolin-2-yl)acetate (Typical Procedure 2)

To a mixture of 6-bromo-4-fluoroisoindolin-1-one (500 mg), tert-butyl 2-bromoacetate (424 mg) and DMF (10 mL) at 0°C was added NaH (104 mg, 60% in mineral oil). The mixture was allowed to warm to RT and stirred for 2 hours. The mixture was partitioned

between water and EA. The organic layer was dried (Na_2SO_4) and concentrated. The residue obtained was purified by SGC (heptane/EA 5:1) to provide the title compound. MS ESI$^+$: m/z = 344 $[M+H]^+$.

6-Bromo-4-fluoroisoindolin-1-one

A mixture of 6-bromo-2-(tert-butyl)-4-fluoroisoindolin-1-one (2.9 g) and TFA (12 mL) was heated to 130°C by microwave irradiation for 2 hours. The mixture was cooled to RT and neutralized with aqueous sodium carbonate followed by extraction with EA. The organic layer was dried (Na_2SO_4) and concentrated to provide the subtitle compound. MS ESI$^+$: m/z = 230 $[M+H]^+$.

Using essentially the Typical Procedure 2 the following compounds were obtained:
6-Bromo-2-propylisoindolin-1-one from 6-bromo-isoindolin-1-one and propyl iodide;
Methyl 2-(6-bromo-1-oxoisoindolin-2-yl)acetate from 6-bromo-isoindolin-1-one and methyl 2-bromoacetate;
Ethyl 2-(6-bromo-1-oxoisoindolin-2-yl)acetate from 6-bromo-isoindolin-1-one and ethyl 2-bromoacetate;
2-(6-Bromo-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide from 6-bromo-isoindolin-1-one and 2-bromo-N,N-dimethyl-acetamide;
6-Bromo-4-fluoro-2-methyl-2,3-dihydro-isoindol-1-one from 6-bromo-4-fluoroisoindolin-1-one and methyl iodide;
6-Bromo-4-fluoro-2-(2-methyl-2H-tetrazol-5-ylmethyl)-2,3-dihydro-isoindol-1-one from 6-bromo-4-fluoroisoindolin-1-one and 5-chloromethyl-2-methyl-2H-tetrazole;
6-Bromo-4-fluoro-2-methylsulfanylmethyl-2,3-dihydro-isoindol-1-one from 6-bromo-4-fluoroisoindolin-1-one and (iodomethyl)(methyl)sulfane;
(6-Bromo-4-fluoro-1-oxo-1,3-dihydro-isoindol-2-yl)-acetic acid methyl ester from 6-bromo-4-fluoroisoindolin-1-one and methyl 2-bromoacetate;
2-(6-Bromo-4-fluoro-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide from 6-bromo-4-fluoroisoindolin-1-one and 2-bromo-N,N-dimethyl-acetamide;
2-(3-Bromo-5-oxo-5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)-N,N-dimethylacetamide from 3-bromo-6,7-dihydro-pyrrolo[3,4-b]pyridin-5-one and 2-bromo-N,N-dimethyl-acetamide;
2-(5-Bromo-1, 1-dimethyl-3-oxoisoindolin-2-yl)-N, N-dimethylacetamide from 6-bromo-3,3-dimethyl-2,3-dihydro-isoindol-1-one and 2-bromo-N,N-dimethyl-acetamide;
2-(5-Bromo-1-methyl-3-oxoisoindolin-2-yl)-N,N-dimethylacetamide from 6-bromo-3-methyl-2,3-dihydro-isoindol-1-one and 2-bromo-N,N-dimethyl-acetamide;

Methyl 2-(5-bromo-1-methyl-3-oxoisoindolin-2-yl)acetate from 6-bromo-3-methyl-2,3-dihydro-isoindol-1-one and methyl 2-bromoacetate.

6-Bromo-4-fluoro-2-methanesulfonylmethyl-2,3-dihydro-isoindol-1-one

A mixture of 6-bromo-4-fluoro-2-methylsulfanylmethyl-2,3-dihydro-isoindol-1-one (31 mg) and methanol (0.5 mL) was added water (0.5 mL) and Oxone (67 mg) and stirred for 4 hours. The reaction mixture was distributed between water and EA. The organic layer was dried (Na_2SO_4) and concentrated to provide the title compound. MS ESI$^+$: m/z = 322 $[M+H]^+$.

6-Bromo-4-fluoro-2-methanesulfinylmethyl-2,3-dihydro-isoindol-1-one

A mixture of 6-bromo-4-fluoro-2-methylsulfanylmethyl-2,3-dihydro-isoindol-1-one (105 mg) and DCM (5 mL) was added MCPBA (63 mg) at -20°C and stirred for 30 minutes. The reaction mixture was diluted with EA (15 mL) and heptane (5 mL), extracted with aqueous sodium bicarbonate (2 x) and washed with brine. The organic layer was dried (Na_2SO_4) and concentrated to provide the title compound. MS ESI$^+$: m/z = 306 $[M+H]^+$.

6-Bromo-2-(tert-butyl)-4-fluoroisoindolin-1-one

A mixture of compound A (14 g), dodecanoic peroxyanhydride (13.7 g) and 1,2-dichloroethane (100 mL) was heated to reflux for 3 hours. The volatiles were removed and the residue purified by SGC (heptane/EA 87:13) to provide the title compound. MS ESI$^+$: m/z = 286 $[M+H]^+$.

Compound A

To a mixture of N-(4-bromo-2-fluorobenzyl)-2-methylpropan-2-amine (50.5 g) and DCM (400 mL) was added bis(trichloromethyl) carbonate (57.6 g). DIPEA (168 mL) was added dropwise at 0°C. After 1 hour the mixture was evaporated and the residue slurried with heptane. Solids were removed by filtration and the filtrate was concentrated. The residue was dissolved in MeCN (500 mL) and added potassium O-ethyl carbonodithioate (31.1 g). After 3 hours insoluble material was removed by filtration and the filtrate concentrated. The residue obtained was purified by SGC (heptane/EA 9:1) to provide the subtitle compound. MS ESI$^+$: m/z = 408 $[M+H]^+$.

N-(4-Bromo-2-fluorobenzyl)-2-methylpropan-2-amine

A mixture of 4-bromo-2-fluorobenzaldehyde (46.2 g), methanol (400 mL) and molecular sieves (4Å) was allowed to stand for 3 hours and then cooled to 0°C. 2-Methylpropan-2-

amine (47.8 mL) was added. After 5 hours sodium borohydride (9.32 g) was added in portions. After 2 hours the volatiles were removed and the residue partitioned between water and EA. The organic layer was dried (Na_2SO_4) and concentrated to provide the subtitle compound. MS ESI$^+$: m/z = 260 $[M+H]^+$.

6-Bromo-3-methylisoindolin-1-one

To a solution of tert-butyl 5-bromo-1-methyl-3-oxoisoindoline-2-carboxylate (2.0 g) in DCM (100 mL) was added TFA (3.2 g) at 0°C. The reaction mixture was stirred at RT for 2 hours. The resulting mixture was partitioned between water and ethyl acetate, and the phases were separated. The organic phase was washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the resulting residue was purified by column chromatography (silica gel, PE/EA = 8:1) to provide the title compound. MS ESI$^+$: m/z = 226 $[M+H]^+$.

Tert-butyl 5-bromo-1-methyl-3-oxoisoindoline-2-carboxylate

To a solution of tert-butyl 6-bromo-1-oxoisoindoline-2-carboxylate (25.0 g) in THF (240 mL) was added NaHMDS (44.1 mL, 2 M in THF) at -78°C. The reaction solution was stirred at -78°C for 1 hour. MeI (11.4 g) was added dropwise. The reaction solution was stirred at -78°C for 2 hours, allowed to warm to RT and stirred for 1 hour. After the reaction was complete, 80 mL of water was added and the solution was extracted with EA (250 mL x 3). The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by column chromatography (silica gel, EA/PE = 1:40) to provide the subtitle compound. MS ESI$^+$: m/z = 270 $[M+H\text{-}tBu]^+$. Also obtained was 5-bromo-1,1-dimethyl-3-oxo-1,3-dihydro-isoindole-2-carboxylic acid tert-butyl ester. MS ESI$^+$: m/z = 284 $[M+H\text{-}tBu]^+$.

Tert-butyl 6-bromo-1-oxoisoindoline-2-carboxylate

To a mixture of 6-bromo-2,3-dihydro-isoindol-1-one (10.0 g), DMAP (11.5 g) and THF (100 mL), $(Boc)_2O$ (15.4 g) was added and the mixture was stirred at room temperature for 12 hours. The resulting yellow mixture was partitioned between water and ethyl acetate, and the phases were separated. The organic phase was washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the resulting residue was purified by column chromatography (silica gel, PE/EA = 15:1) to provide the subtitle compound. MS ESI$^+$: m/z = 256 $[M+H\text{-}tBu]^+$.

6-Bromo-3, 3-dimethylisoindolin-1-one

To a solution of 5-bromo-1,1-dimethyl-3-oxo-1,3-dihydro-isoindole-2-carboxylic acid tert-butyl ester (1.2 g) in DCM (50 mL) was added TFA (1.7 g) at 0°C. The reaction mixture was stirred at RT for 2 hours. The resulting mixture was partitioned between water and ethyl acetate, and the phases were separated. The organic phase was washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the resulting residue was purified by column chromatography (silica gel, PE/EA = 7:1) to provide the title compound. MS ESI$^+$: m/z = 240 [M+H-tBu]$^+$.

Methyl 2-(6-bromo-1-oxoisoindolin-2-yl)propanoate

To a mixture of methyl 2-aminopropanoate hydrochloride (1.5 g) and MeOH (50 mL) was added TEA (2.2 g) and methyl 5-bromo-2-(bromomethyl)benzoate (3.0 g) at RT. The mixture was heated to reflux with stirring for 5 hours. After cooling to RT, the reaction mixture was evaporated in vacuo. The residue was purified by column chromatography on silica gel eluting with EA/PE = 1: 5 to provide the title compound. MS ESI$^+$: m/z = 298 [M+H]$^+$.

Methyl 2-(5-bromo-2-methylisoindolin-1-yl)acetate

To a solution of 6-bromo-2-methylisoindolin-1-one (10.1 g) in THF (250 mL) was added LDA (33.5 mL, 2 M in THF) at -20°C. The mixture was stirred at 0°C for 30 minutes and then methyl 2-bromoacetate (10.3 g) was added at 0°C. The mixture was allowed to warm to RT and stirred for 20 hours. The mixture was poured into water (300 mL) and then extracted with EA (200 mL x 3). The combined organic phases were washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the obtained residue was purified by column chromatography on silica gel eluting with EA/PE = 1:3 to provide the title compound. MS ESI$^+$: m/z = 298 [M+H]$^+$.

6-Bromo-2-methylisoindolin-1-one

Methyl 5-bromo-2-(bromomethyl)benzoate (23 g) was added to methylamine (300 mL, 30% alcoholic solution). The mixture was heated to reflux with stirring for 5 hours. The reaction mixture was cooled to RT and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel eluting with EA/PE = 1:1 to provide the subtitle compound. MS ESI$^+$: m/z = 226 [M+H]$^+$.

6-Bromo-2-(2-oxotetrahydrofuran-3-yl)isoindolin-1-one

To a mixture of 3-amino-dihydrofuran-2(3H)-one hydrobromide (5.85 g) and MeOH (100 mL) was added TEA (6.5 g) and methyl 5-bromo-2-(bromomethyl)benzoate (9.0 g). The mixture was heated under reflux for 5 hours. The mixture was cooled to RT and the solvent was removed by evaporation under reduced pressure. The residue was dissolved in EA (100 mL) and washed with brine (10 mL). The organic phase was dried over Na_2SO_4. After filtration and evaporation of the solvent, the obtained residue was purified by column chromatography on silica gel eluting with DCM/MeOH = 99:1 to provide the title compound. MS ESI$^+$: m/z = 296 $[M+H]^+$.

2-(5-Bromo-2-methyl-3-oxoisoindolin-1-yl)-N,N-dimethylacetamide

To a suspension of 2-(5-bromo-2-methyl-3-oxoisoindolin-1-yl)acetic acid (1.2 g) in DCM (50 mL) was added DIPEA (1.64 g), EDCI (1.22 g) and HOBt (856 mg). The mixture was stirred for 30 minutes at RT and then dimethylamine (4.2 mL, 2 M in THF) was added. The mixture was stirred for 20 hours at 25-30°C. The reaction mixture was poured into water (20 mL). The organic phase was separated. After concentration, the residue was purified by column chromatography on silica gel eluting with DCM/MeOH = 99:1 to provide the title compound. MS ESI$^+$: m/z = 311 $[M+H]^+$.

2-(5-Bromo-2-methyl-3-oxoisoindolin-1-yl)acetic acid

To a solution of methyl 2-(5-bromo-2-methyl-3-oxoisoindolin-1-yl)acetate (1.3 g) in THF (20 mL) was added NaOH (349 mg in 5 mL water) at RT. The mixture was stirred for 4 hours. The volatiles were removed in vacuo and the aqueous phase was neutralized by adding HCl (1 N) to pH = 2. The precipitate was collected by filtration and dried to provide the subtitle compound. MS ESI$^+$: m/z = 284 $[M+H]^+$.

6-Bromo-2-(2-methyl-2H-tetrazol-5-yl)isoindolin-1-one

A mixture of methyl 5-bromo-2-methylbenzoate (3.8 g), 2-methyl-2H-tetrazol-5-amine (5.0 g) and MeOH (20 mL) was heated at reflux overnight. The solution was concentrated and the crude material was purified by chromatography (hexane/EA = 1:1) to provide the title compound. MS ESI$^+$: m/z = 294 $[M+H]^+$.

5-Bromo-1H-indazol-3(2H)-one

A mixture of methyl 5-bromo-2-fluorobenzoate (2.0 g), hydrazine monohydrate (4.25 mL) and ethanol (10 mL) was heated to 110°C by microwave irradiation for 45 minutes.

After cooling to RT, the mixture was evaporated and the residue purified by preparative HPLC to provide the title compound. MS ESI$^+$: m/z = 213 $[M+H]^+$.

2-(5-Bromo-1-methyl-3-oxo-1H-indazol-2(3H)-yl)-N,N-dimethylacetamide

To a mixture of 5-bromo-1-methyl-1H-indazol-3(2H)-one (1.28 g) and DME (10 mL) was added NaOMe (300 mg). After 1 hour, 2-bromo-N,N-dimethyl-acetamide (985 mg) was added. After 2 days the volatiles were removed and the residue purified by preparative HPLC to provide the title compound. MS ESI$^+$: m/z = 312 $[M+H]^+$.

5-Bromo-1-methyl-1H-indazol-3(2H)-one

A mixture of methyl 5-bromo-2-fluorobenzoate (2.0 g), methyl hydrazine (1.84 mL) and ethanol (8 mL) was stirred at RT for 2 hours. The residue obtained after evaporation of the reaction mixture was partitioned between water and EA. The organic phase was washed with water (2 x), dried over Na_2SO_4, and concentrated to provide the subtitle compound. MS ESI$^+$: m/z = 227 $[M+H]^+$.

6-Bromo-4-fluoro-2-(2-hydroxyethyl)isoindolin-1-one

To a mixture of methyl 2-(6-bromo-4-fluoro-1-oxoisoindolin-2-yl)acetate (0.4 g) and methanol (5 mL) was added $NaBH_4$ (150 mg) at 0°C. The mixture was allowed to warm to RT and stirred for 3 hours. Evaporation of the volatiles gave a crude product that was used without further purification.

6-Bromo-N,N,3-trimethyl-4-oxo-3,4-dihydroquinazoline-2-carboxamide

To a DMF (5 mL) solution of 6-bromo-N,N-dimethyl-4-oxo-3,4-dihydroquinazoline-2-carboxamide (220 mg) and K_2CO_3 (135 mg) was added MeI (140 mg). The mixture was stirred for 1 hour at RT and partitioned between water (100 mL) and EA (50 mL x 3). The organic layers were combined, washed with water and brine, dried over $MgSO_4$, filtered and evaporated. The crude was purified by chromatography on silica gel (PE/EA = 1:2) to provide the title compound. MS ESI$^+$: m/z = 310 $[M+H]^+$.

6-Bromo-N,N-dimethyl-4-oxo-3,4-dihydroquinazoline-2-carboxamide

To a DMF (15 mL) solution of 6-bromo-4-oxo-3,4-dihydroquinazoline-2-carboxylic acid (1.2 g), HATU (2.04 g) and DIPEA (1.16 g) was added dimethylamine hydrochloride (436 mg). The mixture was stirred for 2 hours at RT and partitioned between water (100 mL) and EA (50 mL x 3). The organic layers were combined, washed with water and

brine, dried over $MgSO_4$, filtered and evaporated. The crude was purified by chromatography on silica gel (PE/EA = 1:2) to provide the title compound. MS ESI^+: m/z = 296 $[M+H]^+$.

6-Bromo-4-oxo-3,4-dihydroquinazoline-2-carboxylic acid

To a solution of ethyl 6-bromo-4-oxo-3,4-dihydroquinazoline-2-carboxylate (3.0 g) in THF (30 mL) and H_2O (8 mL) was added $LiOH*H_2O$ (1.7 g). After the mixture was stirred for 30 minutes at RT, the reaction was concentrated and added water (30 mL), the pH was adjusted to 2 with 1 M HCl. The resulting precipitate was filtered and washed with water to provide the subtitle compound. MS ESI^+: m/z = 269 $[M+H]^+$.

Ethyl 6-bromo-4-oxo-3,4-dihydroquinazoline-2-carboxylate

A mixture of 2-amino-5-bromobenzoic acid (5.0 g) and ethyl cyanoformate (2.3 g) was added 4 M HCl in dioxane (30 mL). The mixture was stirred for 3 hours at 85°C. The mixture was concentrated and washed with water (20 mL) and EA (20 mL) to provide the subtitle compound. MS ESI^+: m/z = 297 $[M+H]^+$.

2-(6-Bromo-1-oxo-1,3-dihydro-isoindol-2-yl)-N-(2-hydroxy-ethyl)-N-methyl-acetamide

To a mixture of DIPEA (1.18 g), 2-(methylamino)ethanol (2.75 g) and DCM (50 mL) at 0°C, was added dropwise 2-(6-bromo-1-oxoisoindolin-2-yl)acetyl chloride (2.64 g) in DCM (20 mL). The mixture was stirred 30 minutes at 0°C. The cooling bath was removed. After 2 hours the mixture was concentrated and the residue distributed between ethyl acetate and HCl (1 N). After separation, the organic phase was washed with HCl (1 N) and brine, dried over Na_2SO_4 and concentrated to provide the title compound. MS ESI^+: m/z = 327 $[M+H]^+$.

In a similar manner, 6-bromo-2-[2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-2,3-dihydro-isoindol-1-one and 6-bromo-2-[2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-2,3-dihydro-isoindol-1-one were obtained from 2-(6-bromo-1-oxoisoindolin-2-yl)acetyl chloride and 3-hydroxy-azetidine and 4-hydroxy-piperidine, respectively.

2-(6-Bromo-1-oxoisoindolin-2-yl)acetyl chloride

To a mixture of 2-(6-bromo-1-oxoisoindolin-2-yl)acetic acid (2.4 g) and DCM (20 mL) at 0°C was added oxalyl chloride (2.26 g). After 1 hour the mixture was concentrated. The crude product was co-evaporated with toluene twice and used without further purification.

2-(6-Bromo-1-oxoisoindolin-2-yl)acetic acid

A mixture of 2-(6-bromo-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide (50 g), sodium hydroxide (10 M, 150 mL) and methanol (500 mL) was heated to reflux for 8 hours and then kept at room temperature for 48 hours. The mixture was diluted with water (1 L) and made acidic by addition of HCl (conc.). The precipitate was collected by filtration, washed with water and dried under vacuum to provide the subtitle compound. MS ESI$^+$: m/z = 270 $[M+H]^+$.

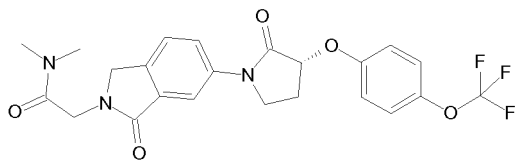
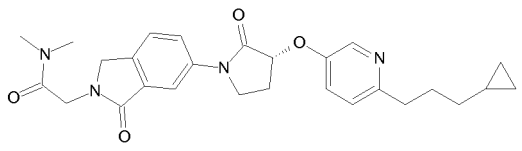
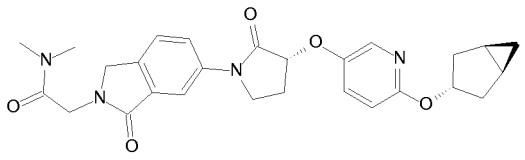
Preparation of Examples 2

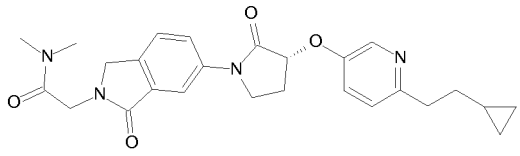
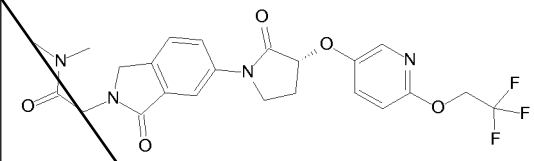
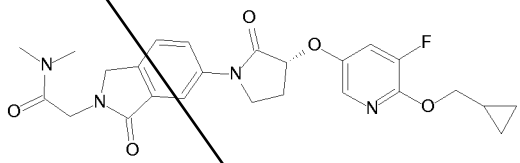
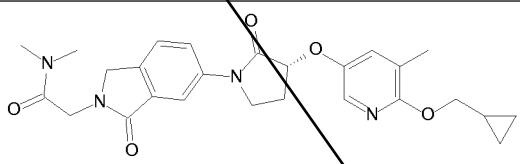
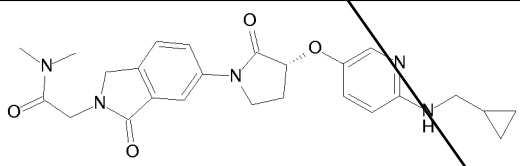
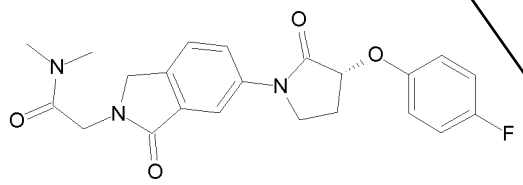
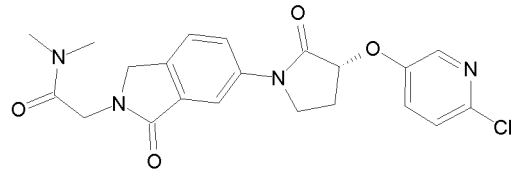
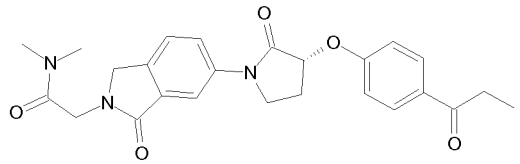
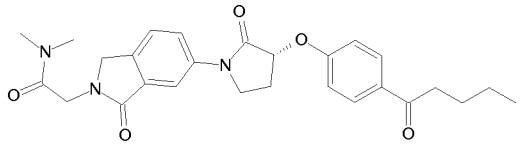
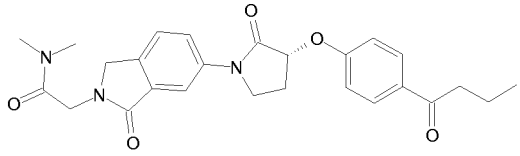
Example 2-01

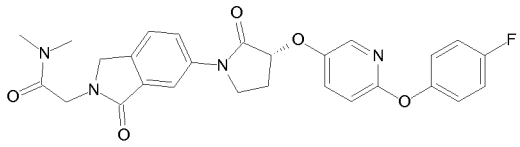
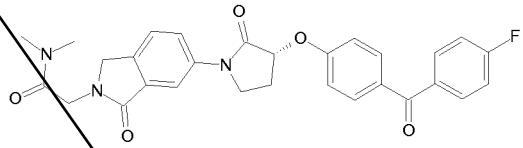
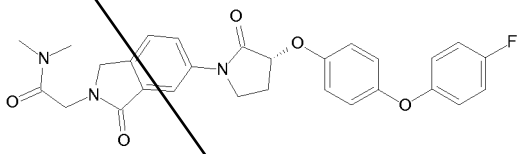
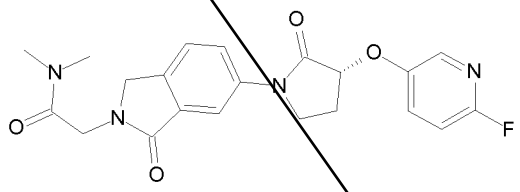
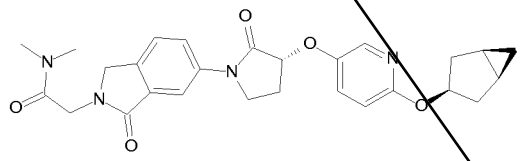
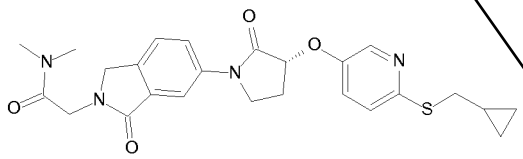
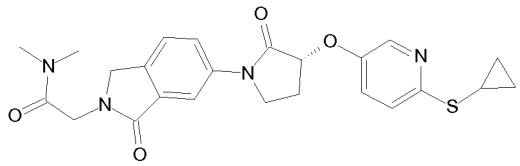
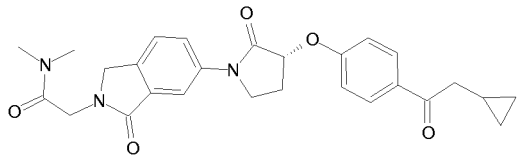
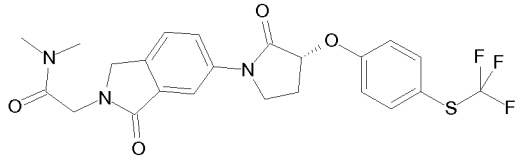
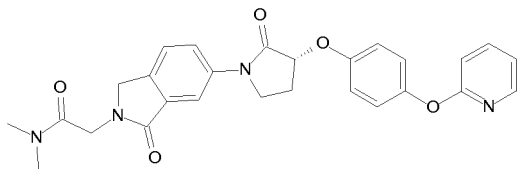
A mixture of triphenyl-phosphine (polymer, 2.3 mmol/g, 165 mg), DEAD (68 mg) and DCM (6 mL) was stirred at 0°C for 15 minutes. (S)-2-(6-(3-hydroxy-2-oxopyrrolidin-1-yl)-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide (100 mg) and 4-trifluoromethoxy-phenol (57 mg) were added. The mixture was allowed to warm to RT and stirred for 12 hours. Insoluble material was filtered off and the filtrate was concentrated to provide a residue, which was purified by preparative HPLC to provide Example 2-01.

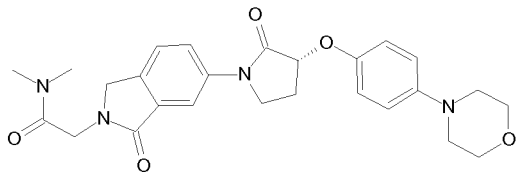
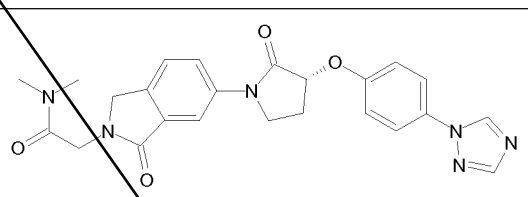
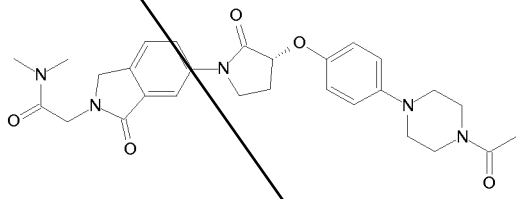
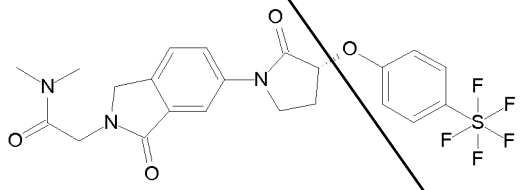
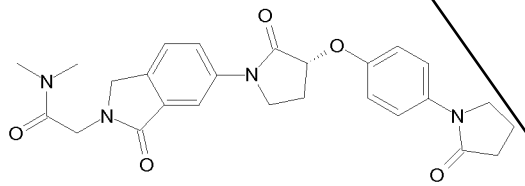
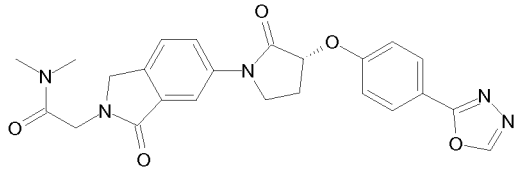
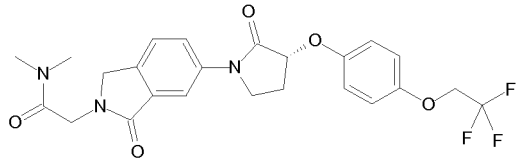
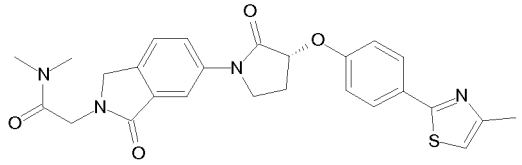
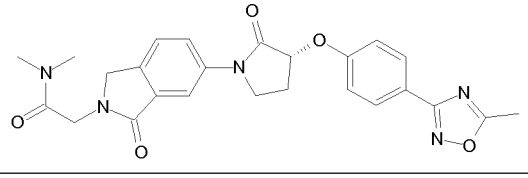
Following essentially this procedure the Examples 2 in Table 2 were obtained by reacting (S)-2-(6-(3-hydroxy-2-oxopyrrolidin-1-yl)-1-oxoisoindolin-2-yl)-N,N-dimethyl-acetamide with the respective phenol or hydroxy-pyridine. DEAD may be substituted by DIAD. DCM may be substituted by THF, or a mixture of both solvents.

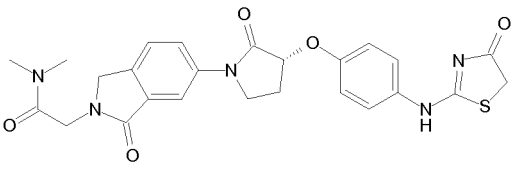
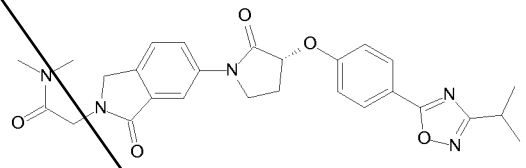
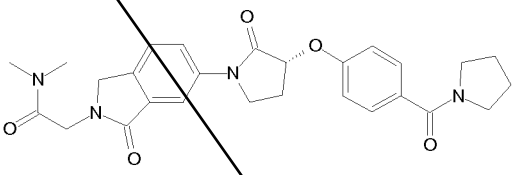
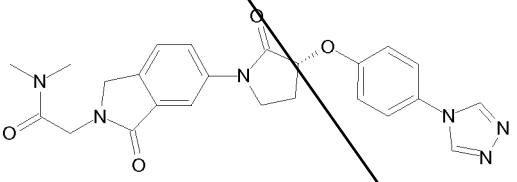
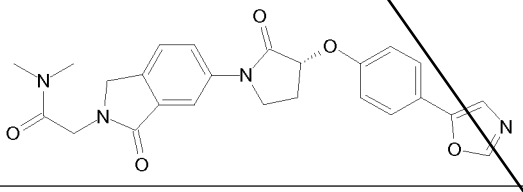
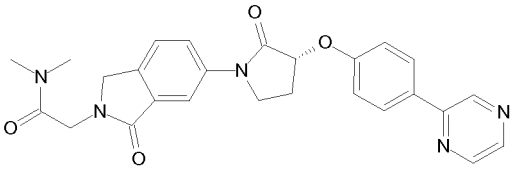
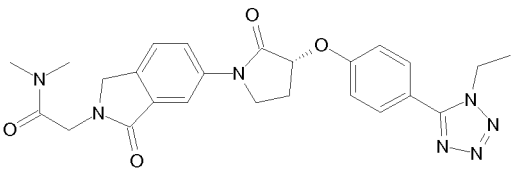
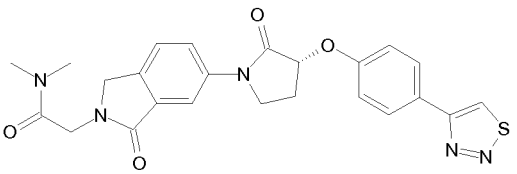
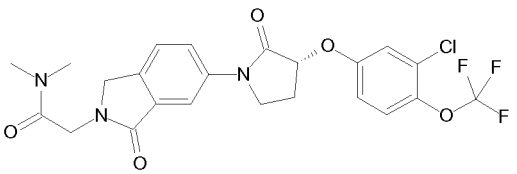
Table 2.

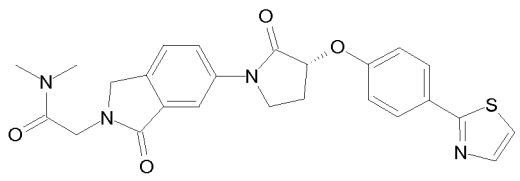
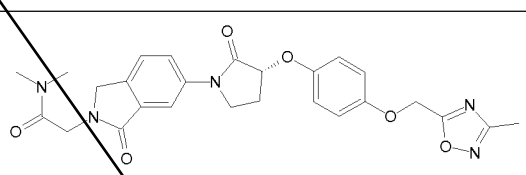
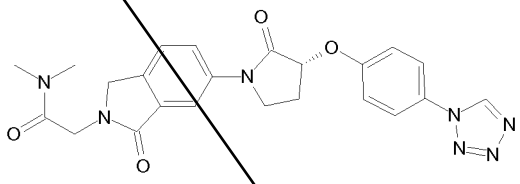
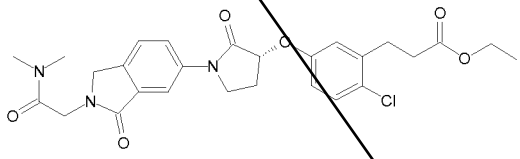
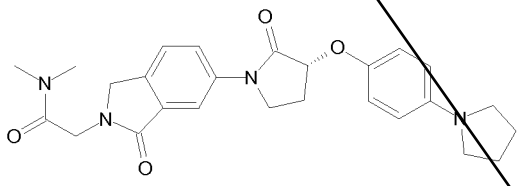
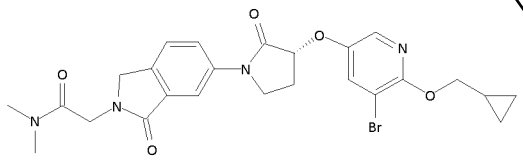
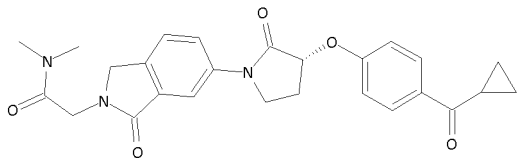
Example	Structure	LCMS Method	R_t [min]	ESI$^+$ m/z [amu]
2-01		A	1.68	478.1
2-02		A	1.40	477.4
2-03		A	1.74	491.4

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
2-04		A	1.32	463.3
2-05		A	1.65	493.3
2-06		A	1.70	483.2
2-07		A	1.72	479.4
2-08		A	1.17	464.3
2-09		A	1.61	412.2
2-10		A	1.51	429.1
2-11		A	1.49	450.1
2-12		A	1.68	478.2
2-13		A	1.58	464.1

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
2-14		A	1.61	505.1
2-15		A	1.66	516.1
2-16		A	1.75	504.1
2-17		A	1.27	413.1
2-18		A	1.71	491.3
2-19		A	1.64	481.3
2-20		A	1.51	467.3
2-21		A	1.61	476.3
2-22		A	1.79	494.3
2-23		A	1.58	487.3

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
2-24		A	1.35	479.3
2-25		A	1.35	461.3
2-26		A	1.32	520.3
2-27		A	1.76	520.3
2-28		A	1.39	477.3
2-29		A	1.37	462.3
2-30		A	1.68	492.3
2-31		A	1.63	491.3
2-32		A	1.53	476.2

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
2-33		A	1.35	508.3
2-34		A	1.73	504.3
2-35		A	1.43	491.3
2-36		A	1.24	461.3
2-37		A	1.47	461.3
2-38		A	1.46	472.3
2-39		A	1.44	490.3
2-40		A	1.53	478.2
2-41		A	1.81	512.2

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
2-42		A	1.57	477.2
2-43		A	1.52	506.3
2-44		A	1.38	462.3
2-45		A	1.77	528.3
2-46		A	1.35	463.4
2-47		C	1.76	543.0
2-48		C	1.50	462.2

Preparation of (S)-2-(6-(3-Hydroxy-2-oxopyrrolidin-1-yl)-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide

Typical Procedure 1 was followed to react 2-(6-bromo-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide with (S)-3-hydroxy-pyrrolidin-2-one to provide the title compound. MS ESI^+: m/z = 318 $[M+H]^+$.

Preparation of Phenols/Hydroxy-pyridines

6-Butylsulfanyl-pyridin-3-ol

Typical Procedure 4 was followed to convert 5-bromo-2-butylsulfanyl-pyridine into the corresponding boronate.

Typical Procedure 5a: The crude boronate (1.03 g) was mixed with THF/water (1:3, 10 mL) and sodium perborate tetrahydrate (1.0 g) was added. After 1 hour the mixture was adjusted to pH 5-6 by addition of HCl (0.1 M) and extracted three times with EA. The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. The residue was separated by preparative HPLC to provide the title compound. MS ESI^+: m/z = 184 $[M+H]^+$.

5-Bromo-2-butylsulfanyl-pyridine

A mixture of 5-bromo-2-chloro-pyridine (2.0 g), 1-butanethiol (1.3 mL), cesium carbonate (4.5 g) and DMF (5 mL) was heated to 60°C for 3 hours. The mixture was diluted with water and extracted three times with EA. The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated to provide the subtitle compound. MS ESI^+: m/z = 246 $[M+H]^+$.

6-(Cyclopropylmethylthio)pyridin-3-ol

Typical Procedures 4 and 5a were followed to convert 5-bromo-2-(cyclopropylmethylthio)pyridine to the title compound. MS ESI^+: m/z = 182 $[M+H]^+$.

5-Bromo-2-(cyclopropylmethylthio)pyridine

To a solution of 5-bromopyridine-2-thiol (3.9 g) in THF (100 mL) was added NaH (1.24 g) at 0°C and the mixture was stirred at 0°C for 30 minutes. Then (bromomethyl)cyclopropane (2.79 g) was added. The mixture was allowed to warm to RT and stirred for 6 hours. The mixture was poured into ice water (200 mL) and extracted with EA (100 mL x 3). The combined organic phases were washed with brine (50 mL) and then dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by SGC (eluent: PE) to provide the subtitle compound. MS ESI^+: m/z = 244 $[M+H]^+$.

6-(Cyclopropylthio)pyridin-3-ol

Typical Procedures 4 and 5a were followed to convert 5-bromo-2-(cyclopropylthio)pyridine to the title compound. MS ESI^+: m/z = 168 $[M+H]^+$.

5-Bromo-2-(cyclopropylthio)pyridine

To a suspension of NaH (60% in mineral oil, 2.40 g) in THF (100 mL) was added dropwise cyclopropanethiol (160 mL, 0.25 M in Et_2O) at 0°C. After stirring for 30

minutes, 5-bromo-2-fluoropyridine (3.52 g) was added in portions at 0°C and then warmed to RT slowly. The reaction mixture was stirred at RT overnight. The reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude product was obtained and used in next step without further purification. MS ESI$^+$: m/z = 230 $[M+H]^+$.

6-Cyclopropylmethoxy-5-fluoro-pyridin-3-ol

Following Typical Procedures 4 and 5a, conversion of 5-bromo-2-cyclopropylmethoxy-3-fluoro-pyridine to the boronate and oxidation with $NaBO_3$ provided the title compound. MS ESI$^+$: m/z = 184 $[M+H]^+$.

5-Bromo-2-cyclopropylmethoxy-3-fluoro-pyridine

Following Typical Procedure 6, reaction of 5-bromo-2,3-difluoro-pyridine with cyclopropyl-methanol provided the subtitle compound. MS ESI$^+$: m/z = 246 $[M+H]^+$.

6-Cyclopropylmethoxy-5-methyl-pyridin-3-ol

Following Typical Procedures 4 and 5a, conversion of 5-bromo-2-cyclopropylmethoxy-3-methyl-pyridine to the boronate and oxidation with $NaBO_3$ provided the title compound. MS ESI$^+$: m/z = 180 $[M+H]^+$.

5-Bromo-2-cyclopropylmethoxy-3-methyl-pyridine

Following Typical Procedure 6, reaction of 5-bromo-2-fluoro-3-methyl-pyridine with cyclopropyl-methanol provided the subtitle compound. MS ESI$^+$: m/z = 242 $[M+H]^+$.

6-(2,2,2-Trifluoroethoxy)pyridin-3-ol

Following Typical Procedures 4 and 5a, conversion of 5-bromo-2-(2,2,2-trifluoroethoxy) pyridine to the boronate and oxidation with $NaBO_3$ provided the title compound. MS ESI$^+$: m/z = 194 $[M+H]^+$.

5-Bromo-2-(2, 2, 2-trifluoroethoxy) pyridine

Following Typical Procedure 6, reaction of 5-bromo-2-fluoro-pyridine with 2,2,2-trifluoroethanol provided the subtitle compound. MS ESI$^+$: m/z = 256 $[M+H]^+$.

6-(Cyclopropylmethylamino)pyridin-3-ol

Following Typical Procedures 4 and 5a, conversion of 5-bromo-N-(cyclopropylmethyl)pyridin-2-amine to the boronate and oxidation with $NaBO_3$ provided the title compound. MS ESI$^+$: m/z = 165 $[M+H]^+$.

5-Bromo-N-(cyclopropylmethyl)pyridin-2-amine

To a seal tube was added 5-bromo-2-fluoropyridine (1.57 g), cyclopropylmethanamine (632 mg), DIPEA (2.3 g), and DMSO (5 mL). The resultant mixture was heated under microwave irradiation at 120°C for 2 hours. The reaction mixture was diluted with EA (100 mL), and washed with water (30 mL x 3) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to obtain the crude product (1.82 g), which was used without further purification.

6-((1R,3r,5S)-Bicyclo[3.1.0]hexan-3-yloxy)pyridin-3-ol

To a stirred solution of 2-((1R,3r,5S)-bicyclo[3.1.0]hexan-3-yloxy)-5-bromopyridine (2.10 g) in THF (37 mL) at -78°C was added n-butyl lithium (6.2 mL, 2.5 M in hexane) dropwise and the resulting mixture was allowed to stir at -78°C for 45 minutes. Trimethyl borate (9.5 mL) was added via syringe and the resulting mixture was stirred for an additional 2 hours. The mixture was allowed to warm to room temperature. Water (300 mL) and $NaBO_3$ (3.93 g) were added. The mixture was stirred at room temperature overnight. The reaction mixture was poured into water (100 mL) and extracted with EtOAc (100 mL x 3). The organic phase was dried over sodium sulphate and concentrated to give a crude, which was purified by column chromatography on silica gel eluting with hexane/EA = 8:2 to provide the title compound. MS ESI$^+$: m/z = 192 $[M+H]^+$.

2-((1R,3r,5S)-Bicyclo[3.1.0]hexan-3-yloxy)-5-bromopyridine

Sodium hydride (730 mg, 60% in mineral oil) was added to a solution of (1R,3r,5S)-bicyclo[3.1.0]hexan-3-ol (2.69 g) in dry DMF (55 mL). The mixture was stirred for 30 minutes at room temperature. 5-Bromo-2-fluoropyridine (1.50 g) was added and the reaction mixture was stirred at 80°C for 5 hours. After cooling to RT, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (100 mL x 3). The organic phase was dried over sodium sulphate and concentrated. The crude was utilized for the next step without further purification.

6-((1S,3S,5R)-Bicyclo[3.1.0]hex-3-yloxy)-pyridin-3-ol

Following Typical Procedures 4 and 5a, conversion of 2-((1S,3S,5R)-bicyclo[3.1.0]hex-3-yloxy)-5-bromo-pyridine to the boronate and oxidation with $NaBO_3$ provided the title compound. MS ESI$^+$: m/z = 192 $[M+H]^+$.

2-((1S,3S,5R)-Bicyclo[3.1.0]hex-3-yloxy)-5-bromo-pyridine

To a mixture of 5-bromo-pyridin-2-ol (1.42 g), (1R,3r,5S)-bicyclo[3.1.0]hexan-3-ol (1.0 g) and triphenylphosphine (2.67 g) in THF (30 mL) at room temperature was added diisopropyl azodicarboxylate (2.06 g) dropwise under N_2. The reaction mixture was stirred at 55°C for two days under N_2. The reaction mixture was cooled to room temperature, and concentrated under vacuum. The residue was purified by silica gel chromatography (hexane to hexane/ethyl acetate 9:1) to provide the title compound. MS ESI$^+$: m/z = 254 $[M+H]^+$.

6-(2-Cyclopropylethyl)pyridin-3-ol

A mixture of 2-(2-cyclopropylethyl)-5-(4-methoxybenzyloxy)pyridine (2.5 g) in TFA (20 mL) was heated under reflux for 30 minutes. The reaction mixture was concentrated and the crude residue was purified by silica gel chromatography eluting with petroleum ether/EtOAc (1:1) to provide the title compound. MS ESI$^+$: m/z = 164 $[M+H]^+$.

2-(2-Cyclopropylethyl)-5-(4-methoxybenzyloxy)pyridine

To a mixture of 2-(cyclopropylethynyl)-5-(4-methoxybenzyloxy)pyridine (2.7 g) in MeOH (20 mL) was added Raney-Ni (270 mg) under N_2 atmosphere. The mixture was stirred at room temperature after exchanging the nitrogen for a H_2 atmosphere for 20 minutes. Filtration through a pad of celite and evaporation of the solvent provided the subtitle compound. MS ESI$^+$: m/z = 284 $[M+H]^+$.

2-(Cyclopropylethynyl)-5-(4-methoxybenzyloxy)pyridine

To a round-bottomed flask was added 2-bromo-5-(4-methoxybenzyloxy)pyridine (4.0 g), ethynylcyclopropane (904 mg), $Pd(dppf)Cl_2$ (787 mg), CuI (200 mg), Et_3N (2.8 g) and DMF (10 mL). The reaction mixture was stirred at 60°C under N_2 atmosphere overnight. After the reaction was complete, the residue was diluted with ethyl acetate (200 mL), washed with water (50 mL x 2), and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude residue was purified by chromatography (silica gel, PE/EA = 4:1) to provide the subtitle compound. MS ESI$^+$: m/z = 280 $[M+H]^+$.

6-(3-Cyclopropylpropyl)pyridin-3-ol

To a solution of 2-(3-cyclopropylpropyl)-5-(4-methoxybenzyloxy)pyridine (800 mg) in EtOH (10 mL) was added TFA (3 mL). The mixture was stirred at RT for 4 hours. The crude obtained after evaporation was purified by chromatography (silica gel, PE/EA = 1:1) to provide the title compound. MS ESI$^+$: m/z = 178 $[M+H]^+$.

2-(3-Cyclopropylpropyl)-5-(4-methoxybenzyloxy)pyridine

To a round-bottomed flask was added 2-(3-cyclopropyl-prop-1-ynyl)-5-(4-methoxy-benzyloxy)-pyridine (820 mg), Raney-Ni (200 mg), and EtOH (10 mL). The reaction mixture was stirred under an hydrogen atmosphere at RT for 15 minutes. The reaction mixture was filtered and the filtrate evaporated to provide the subtitle compound. MS ESI$^+$: m/z = 298 $[M+H]^+$.

2-(3-Cyclopropyl-prop-1-ynyl)-5-(4-methoxy-benzyloxy)-pyridine

To a solution of 2-ethynyl-5-(4-methoxy-benzyloxy)-pyridine (2.19 g) in THF (20 mL) was added n-BuLi (4.51 mL, 2.5 M in hexane) at -78°C over 30 minutes. The resulting mixture was stirred at 0°C for 10 minutes and then re-cooled to -78°C. HMPA (2.4 g) was added, and the mixture was stirred at -78°C for 30 minutes. (Bromomethyl)cyclopropane (1.24 g) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The combined organic layers were washed with water (50 mL x 3) and brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel eluting with EA/PE = 1:6 to provide the subtitle compound. MS ESI$^+$: m/z = 294 $[M+H]^+$.

2-Ethynyl-5-(4-methoxy-benzyloxy)-pyridine

To a 100 mL round-bottomed flask was added 5-(4-methoxybenzyloxy)-2-((trimethylsilyl)ethynyl)pyridine (2.89 g), K_2CO_3 (1.28 g), and MeOH (30 mL). The reaction mixture was stirred at room temperature for 2 hours. The formed precipitate was filtered off and the solid was washed with MeOH (5 mL x 3) to provide the subtitle compound. MS ESI$^+$: m/z = 240 $[M+H]^+$.

5-(4-Methoxybenzyloxy)-2-((trimethylsilyl)ethynyl)pyridine

To a solution of 2-bromo-5-(4-methoxybenzyloxy)pyridine (3.0 g) in DMF (30 mL) was added ethynyltrimethylsilane (1.2 g), $Pd(dppf)Cl_2$ (373 mg), CuI (98 mg), and Et_3N (2.8 mL). After the addition, the mixture was stirred at 70°C for 4 hours. After cooling to RT, the reaction mixture was diluted with water (30 mL) and extracted with EA (50 mL x 3). The combined organic layers were washed with water (50 mL x 3) and brine (50 mL), dried over Na_2SO_4 and concentrated. The crude was purified by column

chromatography on silica gel eluting with EA/PE = 1:10 to provide the subtitle compound. MS ESI$^+$: m/z = 312 $[M+H]^+$.

5-Bromo-6-(cyclopropylmethoxy)pyridin-3-ol

To a solution of 3-bromo-2-(cyclopropylmethoxy)-5-iodopyridine (12.5 g) in dry THF (300 mL) was added *i*-PrMgCl*LiCl (30 mL) dropwise at 0°C. The mixture was stirred at 0°C for 20 min and then $B(OMe)_3$ (5.5 g) was added at 0°C. The mixture was allowed to warm to r.t. and stirred for 3 h. The mixture was quenched by the addition of brine (50 mL). The organic phase was separated and the aqueous phase was extracted with EA (50 mL x 3). The organic phases were combined and the solvent was removed under reduced pressure. The residue was treated according Typical Procedure 5a to obtain the title compound. MS ESI$^+$: m/z = 244 $[M+H]^+$.

3-Bromo-2-(cyclopropylmethoxy)-5-iodopyridine

To a suspension of NaH (60% in mineral oil, 4.32 g) in THF (300 mL) was added cyclopropylmethanol (5.83 g) at 0°C and the mixture was stirred for 30 min at 0°C. A solution of 3-bromo-2-fluoro-5-iodopyridine (16.3 g) in THF (50 mL) was added to the suspension at 0°C. The suspension was allowed to warm to r.t. and stirred for 18 h. The suspension was poured into ice water and then extracted with EA (200 mL x 3). The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by SGC (eluent: PE) to give the subtitle compound. MS ESI$^+$: m/z = 354 $[M+H]^+$.

Preparation of Examples 3

Example 3-01 (Typical Procedure 7a)

A mixture of (R)-tert-butyl 2-(6-(3-((6-(cyclopropylmethoxy)pyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-4-fluoro-1-oxoisoindolin-2-yl)acetate (23 mg), TFA (1 mL) and DCM (1.5 mL) was stirred for 1 hour. Evaporation of the volatiles provided Example 3-01.

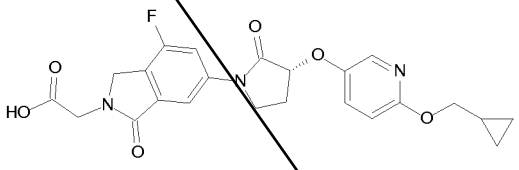
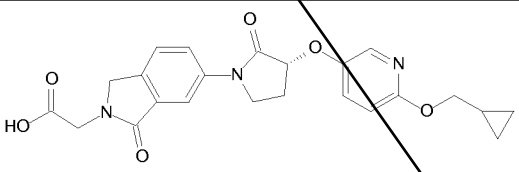
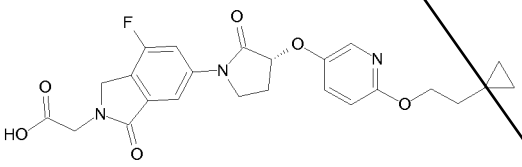
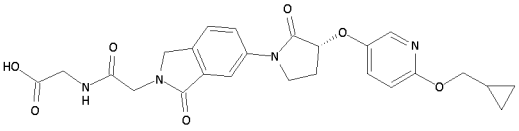
Example 3-02 (Typical Procedure 7b)

A mixture of (R)-ethyl 2-(6-(3-((6-(cyclopropylmethoxy)pyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-1-oxoisoindolin-2-yl)acetate (10 mg) and THF/MeOH/H_2O/DIPEA (2:2:1:1, 0.5 mL) was heated by microwave irradiation to 120°C for 1 hour. Example 3-02 (containing residual amounts of DIPEA) was obtained by evaporation of the volatiles.

Example 3-03 (Typical Procedure 7c)

A mixture of (R)-methyl 2-(6-(3-((6-(2-cyclopropylethoxy)pyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-4-fluoro-1-oxoisoindolin-2-yl)acetate (750 mg), LiOH (1.16 mL, 2 M in water) and THF (20 mL) was stirred for 2 hours. The reaction mixture was acidified with HCl (2 M) and extracted with EA. The organic layer was dried over Na_2SO_4, and concentrated to provide Example 3-03.

Table 3.

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
3-01		A	1.62	456.2
3-02		C	1.56	438.2
3-03		A	1.87	470.2
3-04		C	1.52	495.2

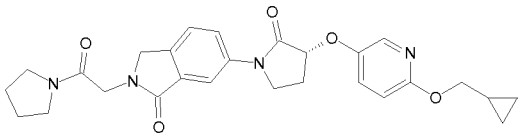
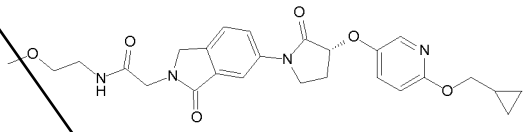
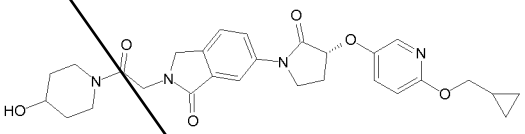
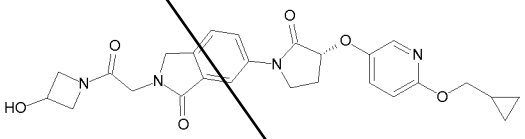
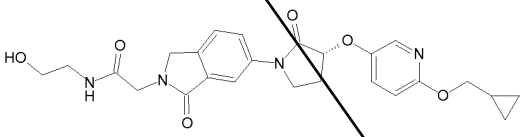
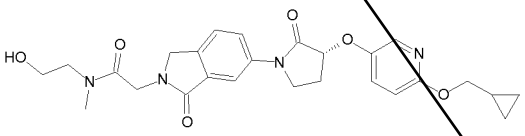
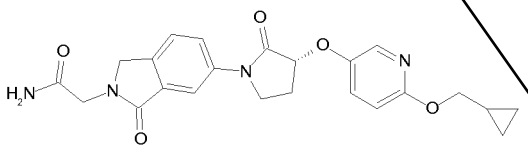
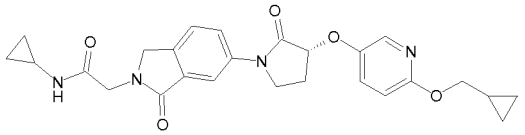
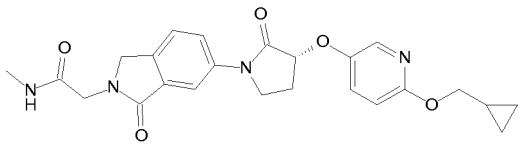
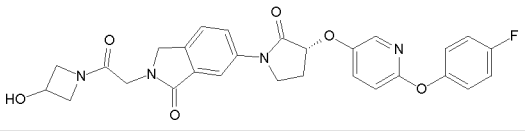
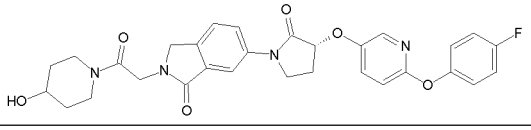
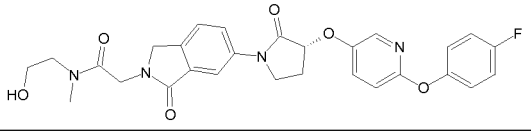
Preparation of Examples 4

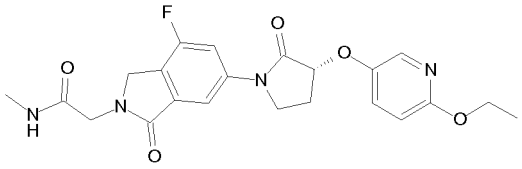
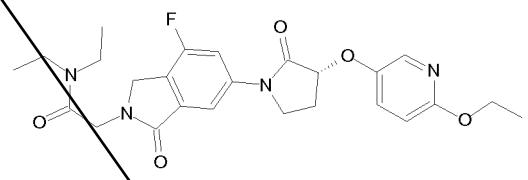
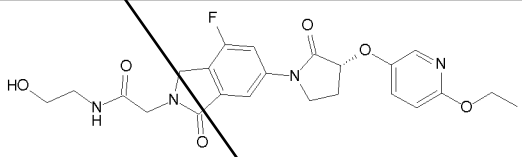
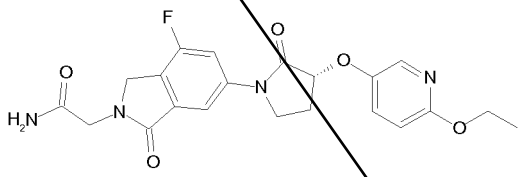
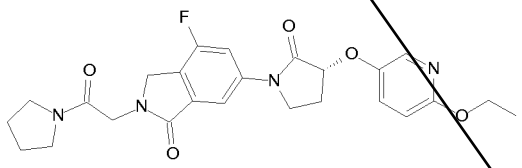
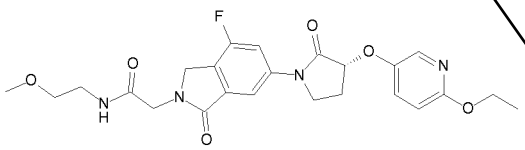
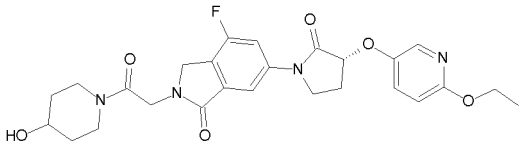
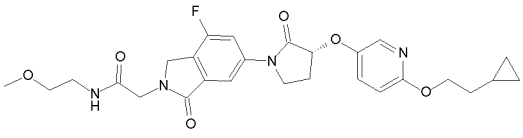
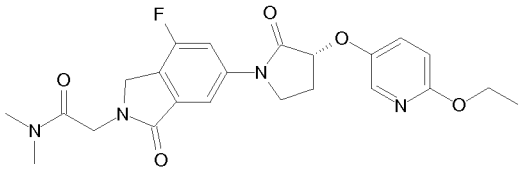
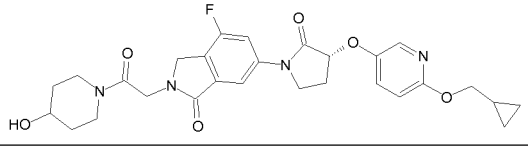
Example 4-01 (Typical Procedure 9)

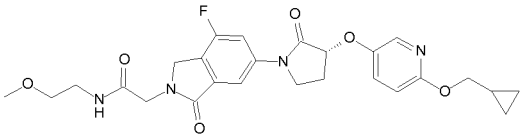
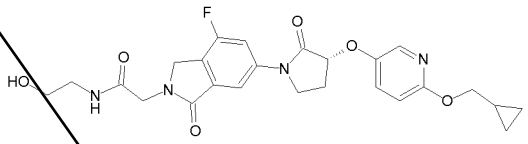
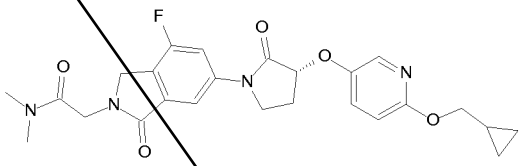
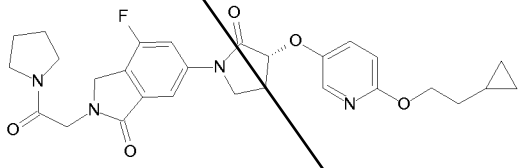
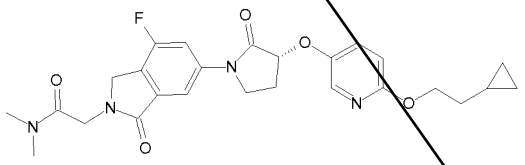
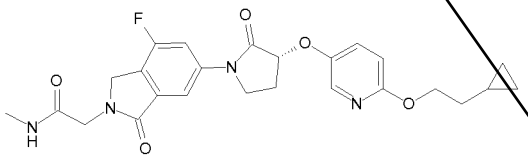
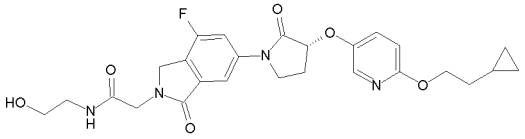
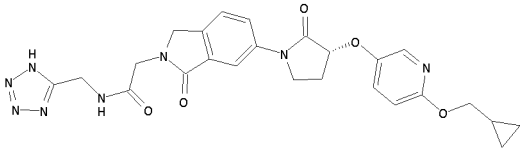
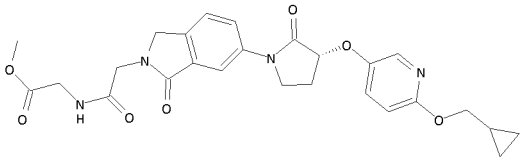
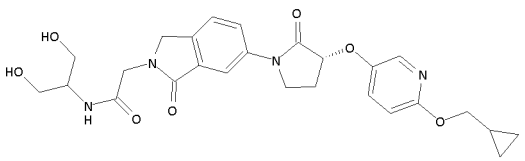
To a mixture of (R)-2-(6-(3-((6-(cyclopropylmethoxy)pyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-1-oxoisoindolin-2-yl)acetic acid (100 mg), DIPEA (40 µL) and DMF (2 mL) was added EDCI (44 mg) and HOBt (31 mg). After 10 minutes pyrrolidine (16 mg) was added. After 2 hours the mixture was separated by preparative HPLC to provide Example 4-01.

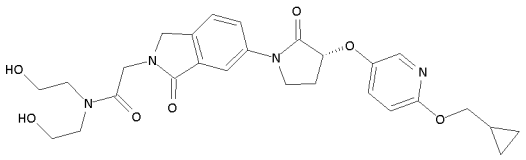
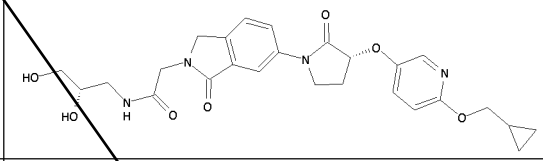
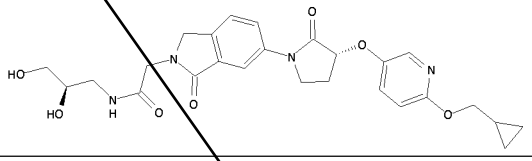
Following essentially this procedure the Examples 4 in Table 4 were obtained by coupling of the appropriate carboxylic acid with the respective amine.

Table 4.

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
4-01		A	1.73	491.2
4-02		A	1.68	495.2
4-03		A	1.64	521.2
4-04		A	1.62	537.3 ESI-: [M-H+FA]-
4-05		A	1.60	481.2
4-06		A	1.63	495.2
4-07		A	1.61	437.1
4-08		A	1.70	477.2
4-09		A	1.65	451.1
4-10		C	1.57	533.1
4-11		C	1.60	561.1
4-12		C	1.58	535.1

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
4-13		A	1.50	443.2
4-14		A	1.68	485.3
4-15		A	1.44	473.2
4-16		B	3.33	429.2
4-17		A	1.61	483.2
4-18		A	1.53	487.3
4-19		A	1.50	513.2
4-20		A	1.74	527.3
4-21		A	1.55	457.2
4-22		A	1.61	539.4

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
4-23		A	1.64	513.4
4-24		A	1.55	499.3
4-25		A	1.64	483.2
4-26		A	1.92	523.3
4-27		A	1.88	497.3
4-28		A	1.85	483.3
4-29		A	1.80	513.3
4-30		C	1.54	519.3
4-31		C	1.60	509.3
4-32		C	1.48	511.3

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
4-33		C	1.50	525.3
4-34		C	1.48	511.3
4-35		C	1.48	511.3

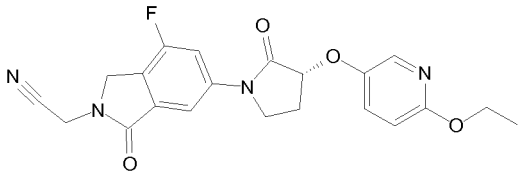
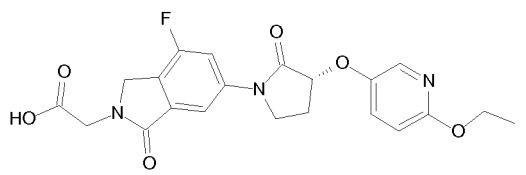
Preparation of Examples 5

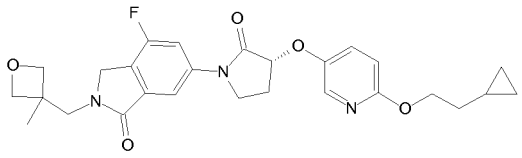
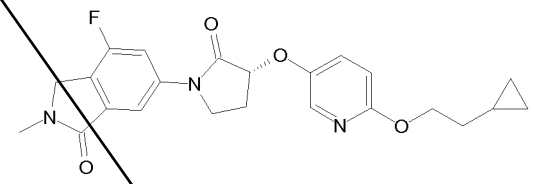
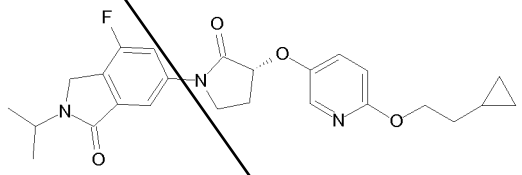
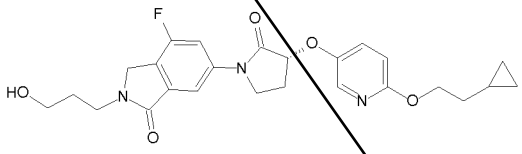
Example 5-01

Following Typical Procedure 2, (R)-6-(3-((6-ethoxypyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-4-fluoroisoindolin-1-one was reacted with 2-bromoacetonitrile to provide Example 5-01. Similarly the other Examples 5 in Table 5 were obtained by alkylation of the appropriate N-unsubstituted isoindolinone and the respective alkyl bromide or iodide.

Example 5-04 was obtained by adding water to the reaction mixture promoting the saponification of the primary reaction product ({6-[(R)-3-(6-ethoxy-pyridin-3-yloxy)-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-1,3-dihydro-isoindol-2-yl}-acetic acid methyl ester).

Table 5.

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
5-01		A	1.63	411.2
5-02		A	1.52	430.2

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
5-03		A	1.62	496.3
5-04		A	1.93	426.2
5-05		A	2.04	454.3
5-06		A	1.75	470.3

(R)- 6-(3-((6-Ethoxypyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-4-fluoroisoindolin-1-one

A mixture of (R)-2-(tert-butyl)-6-(3-((6-ethoxypyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-4-fluoroisoindolin-1-one (1.6 g) and TFA (5 mL) was heated by microwave irradiation to 130°C for 1 hour. After cooling to RT, the reaction mixture was evaporated. Residual TFA was removed by co-evaporation with toluene (3 x 30 mL) to provide the title compound. MS ESI^+: m/z = 372 $[M+H]^+$.

6-{(R)-3-[6-(2-Cyclopropyl-ethoxy)-pyridin-3-yloxy]-2-oxo-pyrrolidin-1-yl}-4-fluoro-2,3-dihydro-isoindol-1-one

Following Typical Procedure 1, (R)-3-((6-(cyclopropylethoxy)pyridin-3-yl)oxy)pyrrolidin-2-one was reacted with 6-bromo-4-fluoroisoindolin-1-one to provide the title compound. MS ESI^+: m/z = 412 $[M+H]^+$.

Preparation of Examples 6

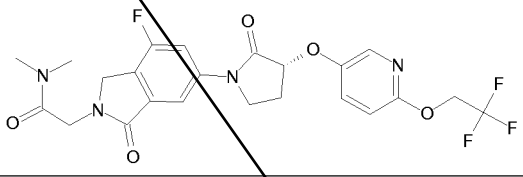
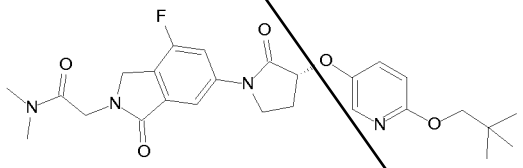
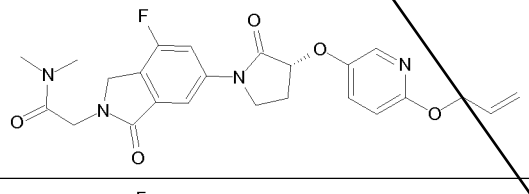
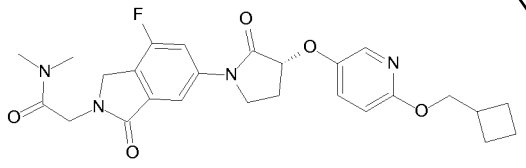
Example 6-01 (Typical Procedure 10)

A mixture of (R)-2-(4-fluoro-6-(3-((6-hydroxypyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide (90 mg), 2-bromo-1,1,1-trifluoroethane (34 mg), potassium carbonate (58 mg) and DMF (3 mL) was heated to 130°C for 1 hour.

The reaction mixture was filtered and separated by preparative HPLC to provide Example 6-01.

Similarly the other Examples 6 in Table 6 were obtained by alkylating (R)-2-(4-fluoro-6-(3-((6-hydroxypyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide with the respective alkyl bromide.

Table 6.

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
6-01		A	1.66	511.2
6-02		A	1.81	499.5
6-03		A	1.59	469.3
6-04		A	1.76	497.3

(R)-2-(4-Fluoro-6-(3-((6-hydroxypyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide

A mixture of (R)-2-(6-(3-((6-(benzyloxy)pyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-4-fluoro-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide (2.2 g), Pd/C (452 mg, 10%) and methanol (50 mL) was stirred under an atmosphere of hydrogen (1 atm) for 8 hours. The catalyst was filtered off and the filtrate concentrated. The crude was purified by SGC (DCM/MeOH 9:1) to provide the title compound. MS ESI^+: m/z = 429 $[M+H]^+$.

(R)-2-(6-(3-((6-(benzyloxy)pyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-4-fluoro-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide

Following Typical Procedure 1, (R)-3-((6-(benzyloxy)pyridin-3-yl)oxy)pyrrolidin-2-one was reacted with 2-(6-bromo-4-fluoro-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide to provide the subtitle compound. MS ESI$^+$: m/z = 519 $[M+H]^+$.

(*R*)-3-(6-Benzyloxy-pyridin-3-yloxy)-pyrrolidin-2-one

Following the sequence described for (*R*)-3-[6-(2-cyclopropyl-ethoxy)-pyridin-3-yloxy]-pyrrolidin-2-one, the subtitle compound was prepared from phenyl-methanol, 5-bromo-2-fluoro-pyridine and (*S*)-3-hydroxy-pyrrolidin-2-one. MS ESI$^+$: m/z = 285 $[M+H]^+$.

Pharmacological Utility

The biological activity of the compounds of the invention may be demonstrated by known in vitro assays. Examples include in vitro cellular assays for recombinant and non-recombinant GPR119 as described in the following.

Functional Cellular Assays Measuring GPR119-mediated cAMP Release

Compounds of the invention, which are agonists of GPR119, were characterized by functional assays measuring the cAMP response of HEK-293 cell lines stably expressing recombinant GPR119 from man, mouse or rat, or by using a hamster cell line HIT-T15 expressing GPR119 endogenously. The cAMP content was determined using a kit based on homogenous time-resolved fluorescence (HTRF) from Cisbio Corp. (cat. no. 62AM4PEC). For preparation, cells were split into T175 culture flasks and grown to near confluency in medium (DMEM / 10% FCS for HEK-293 cells, and F-12K medium / 10% horse serum / 2.5% FCS for HIT-T15 cells, respectively). Medium was then removed and cells washed with PBS lacking calcium and magnesium ions, followed by proteinase treatment with accutase (Sigma-Aldrich, cat. no. A6964). Detached cells were washed and resuspended in assay buffer (1 x HBSS; 20 mM HEPES, 0.1% BSA, 2 mM IBMX) and cellular density determined. They were then diluted to 400000 cells/mL and 25 µL-aliquots dispensed to the wells of 96-well plates. For measurement, 25 µL of test compound in assay buffer was added and incubated for 30 minutes at room temperature. After addition of HTRF reagents diluted in lysis buffer, the plates were incubated for 1 hour, followed by measuring the fluorescence ratio at 665 vs. 620 nm. Potency of the agonists was quantified by determining the concentrations that caused 50% of the maximal response/activation (EC_{50}). See Table 7 for exemplary data obtained using the cell line expressing human GPR119.

Compounds of the invention show EC_{50} values typically in the range of about 0.001 to 100 µM, preferably from about 0.001 to 10 µM, more preferably from about 0.001 to 1 µM and most preferably from about 0.001 to 0.3 µM.

Table 7.

Example	EC_{50} [µM]	Example	EC_{50} [µM]	Example	EC_{50} [µM]	Example	EC_{50} [µM]
1-01	0.089	1-39	0.060	2-27	0.160	4-12	0.297
1-02	2.030	1-40	0.044	2-28	1.470	4-13	0.326
1-03	10.900	1-41	2.030	2-29	3.390	4-14	0.288
1-04	0.540	1-42	0.366	2-30	0.082	4-15	0.547
1-05	0.313	1-43	0.449	2-31	0.343	4-16	0.271
1-06	0.151	1-44	0.276	2-32	0.268	4-17	0.191
1-07	1.900	1-45	0.179	2-33	2.210	4-18	0.381
1-08	1.050	1-46	0.184	2-34	0.084	4-19	0.297
1-09	0.163	1-47	0.218	2-35	8.660	4-20	0.062
1-10	0.267	1-48	0.073	2-36	32.800	4-21	0.222
1-11	0.202	1-49	0.106	2-37	0.862	4-22	0.088
1-12	29.400	2-01	0.106	2-38	0.808	4-23	0.157
1-13	0.237	2-02	0.056	2-39	27.000	4-24	0.266
1-14	4.440	2-03	0.054	2-40	0.337	4-25	0.080
1-15	0.221	2-04	0.156	2-41	0.470	4-26	0.048
1-16	0.360	2-05	0.062	2-42	0.117	4-27	0.046
1-17	0.030	2-06	0.082	2-43	1.500	4-28	0.049
1-18	0.065	2-07	0.115	2-44	14.700	4-29	0.157
1-19	0.071	2-08	2.120	2-45	1.510	4-30	0.749
1-20	0.046	2-09	0.739	2-46	6.370	4-31	0.153
1-21	0.346	2-10	2.070	2-47	0.090	4-32	0.448
1-22	0.242	2-11	0.267	2-48	0.202	4-33	0.598
1-23	0.695	2-12	0.044	3-01	1.050	4-34	0.541
1-24	14.300	2-13	0.075	3-02	0.443	4-35	0.556
1-25	0.441	2-14	0.085	3-03	0.087	5-01	0.067
1-26	14.200	2-15	0.066	3-04	0.807	5-02	6.080
1-27	0.488	2-16	0.047	4-01	0.106	5-03	2.530
1-28	0.976	2-17	9.360	4-02	0.144	5-04	1.240
1-29	0.015	2-18	0.074	4-03	0.206	5-05	5.040
1-30	>100	2-19	0.047	4-04	0.197	5-06	0.609
1-31	0.065	2-20	0.233	4-05	0.249	6-01	0.077
1-32	0.063	2-21	0.072	4-06	0.281	6-02	0.126
1-33	8.510	2-22	0.041	4-07	0.163	6-03	0.064
1-35	0.019	2-23	0.261	4-08	0.168	6-04	0.035
1-36	0.142	2-24	21.000	4-09	0.107	empty	empty
1-37	1.040	2-25	12.000	4-10	0.208	empty	empty
1-38	0.035	2-26	1.060	4-11	0.218	empty	empty

Based on the demonstrated ability of the compounds of the invention to activate GPR119 it is predicted that said compounds are useful for treatment of diseases and/or prevention of conditions which are modulated by GPR119.

Especially, the compounds of the invention may be useful to treat GPR119-related diseases and/or prevent GPR119-mediated conditions in humans.

The compounds of the invention are especially suitable for the treatment and/or prevention of:

1a) Disorders of fatty acid metabolism and glucose utilization disorders

1b) Disorders in which insulin resistance is involved

2) Diabetes mellitus, especially type 2 diabetes mellitus, including the prevention of the sequelae associated therewith. Particular aspects in this context are:

- a) Improvement of hyperglycemia
- b) Improvement of insulin resistance
- c) Improvement of glucose tolerance
- d) Protection of pancreatic beta cells
- e) Improvement of beta cell function
- f) Prevention of micro- and macrovascular disorders, such as
    - a. Retinopathy
    - b. Atherosclerosis
    - c. Nephropathy and microalbuminuria
    - d. Neuropathy
- g) Chronic low grade inflammation

3) Various other conditions which may be associated with the metabolic syndrome or the syndrome X, such as

- a) Increased abdominal girth
- b) Obesity
- c) Liver disorders
    - a. Fatty liver
    - b. Steatosis
    - c. Steatohepatitis
    - d. Cirrhosis

d) Dyslipidemia (e.g. hypertriglyceridemia, hypercholesterolemia, hyperlipoproteinemia and/or low HDL)

e) Insulin resistance

f) Hypercoagulability

g) Hyperuricemia

h) Thromboses, hypercoagulable and prothrombotic states (arterial and venous)

i) High blood pressure

j) Endothelial dysfunction

k) Heart failure, for example (but not limited to) following myocardial infarction, hypertensive heart disease or cardiomyopathy

4) Cardiovascular diseases, for example (but not limited to) myocardial infarction and stroke

5) Bone-related diseases and disorders characterized by redcued bone mass, such as:

a) Osteoporosis

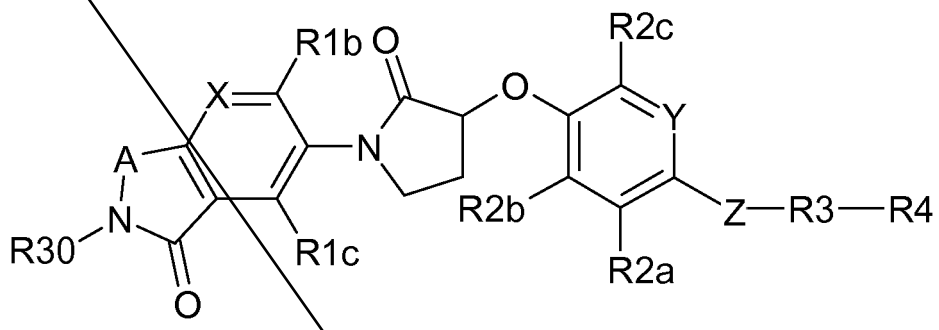
b) Rheumatoid arthritis

c) Osteoarthritis.

DE2014/028WOPCT

Claims:

1. A compound of the formula I



(I)

in which

X is N or C-R1a;

A is CR31R33, NR31, CR31R33-NR31 or CR31=N;

R30 is H or $(CR11R12)_n$-R32;

R31 is H or $(CR11R12)_n$-R32;

R33 is H or $(C_1$-$C_6)$-alkyl;

R11, R12 are independently of each other H or $(C_1$-$C_6)$-alkyl;

n is 0, 1, 2 or 3;

R32 is $(C_1$-$C_6)$-alkyl, COOR13, CONR14R15, $S(O)_mR16$, OH, CN, $(C_3$-$C_8)$-cycloalkyl, $(C_5$-$C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;

wherein the groups (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyloxy, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or (C_1-C_6)-alkyl;

R14, R15 are independently of each other H, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted with 1 to 3 groups selected from the list OR17, COOR19 and a 4-, 5- or 6-membered heterocycle;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17;

R16 is (C_1-C_6)-alkyl;

R17 is H or (C_1-C_6)-alkyl;

R18 is H or (C_1-C_6)-alkyl;

R1a, R1b, R1c are independently of each other H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

R2a, R2b, R2c are independently of each other H, F, Cl, Br, (C_1-C_6)-alkyl, (C_1-C_3)-alkyl substituted with COOR19 or CN;

R19 is H or (C_1-C_6)-alkyl;

Y is N or CH;

Z is a bond, O, CR5R5', NR6, C=O, S, SO or SO_2;

R5, R5', R6 are independently of each other H or $(C_1$-$C_4)$-alkyl;

R3 is a bond or $(CR7R7')_p$;

p is 0, 1, 2, 3 or 4;

R7, R7' are independently of each other H or $(C_1$-$C_6)$-alkyl;

R4 is F, Cl, SF_5, $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, OR8, $(C_3$-$C_8)$-cycloalkyl, $(C_5$-$C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, or 5- or 6-membered heteroaryl ring;

wherein the groups $(C_3$-$C_8)$-cycloalkyl, $(C_5$-$C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkanoyl, hydroxy, hydroxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_3)$-alkyloxy-$(C_1$-$C_4)$-alkyl, oxo, F and Cl;

R8 is H, $(C_1$-$C_6)$-alkyl, hydroxy-$(C_1$-$C_4)$-alkyl or $(C_1$-$C_3)$-alkyloxy-$(C_1$-$C_4)$-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

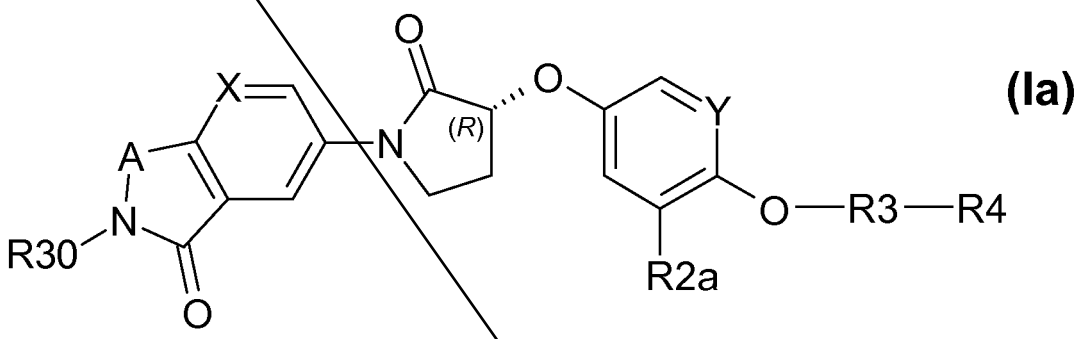
2. A compound of the formula I as claimed in claim 1, wherein

the 3-position of the pyrrolidinone ring has (*R*)-configuration.

3. A compound of the formula I as claimed in claim 1 or 2, wherein

Z is O.

4. A compound of the formula I as claimed in any of claims 1 to 3, which is a compound of the formula Ia



in which

X is N or C-R1a;

A is CR31R33, NR31, CR31R33-NR31 or CR31=N;

R30 is H or $(CR11R12)_n$-R32;

R31 is H or $(CR11R12)_n$-R32;

R33 is H or $(C_1$-$C_6)$-alkyl;

R11, R12 are independently of each other H or $(C_1$-$C_6)$-alkyl;

n is 0, 1, 2 or 3;

R32 is $(C_1$-$C_6)$-alkyl, COOR13, CONR14R15, $S(O)_mR16$, OH, CN, $(C_3$-$C_8)$-cycloalkyl, 4-, 5- or 6-membered heterocycle or 5- or 6-membered heteroaryl ring;

wherein the groups (C_3-C_8)-cycloalkyl, 4-, 5- or 6-membered heterocycle, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyloxy, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or (C_1-C_6)-alkyl;

R14, R15 are independently of each other H, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted with 1 to 3 groups selected from the list OR17, COOR19 and a 4-, 5- or 6-membered heterocycle;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17.

R16 is (C_1-C_6)-alkyl;

R17 is H or (C_1-C_6)-alkyl;

R18 is H or (C_1-C_6)-alkyl;

R1a is H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

R2a is H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

Y is N or CH;

R3 is a bond or $(CR7R7')_p$;

p is 0, 1, 2, 3 or 4;

R7, R7' are independently of each other H or (C_1-C_6)-alkyl;

R4 is (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, OR8, (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;
wherein the groups (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

R8 is H, (C_1-C_6)-alkyl, hydroxy-(C_1-C_4)-alkyl or (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

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

R14, R15 are independently of each other H, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted with OR17, or (C_3-C_6)-cycloalkyl;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17.

6. A compound of the formula I as claimed in claim 5, wherein

X is C-R1a;

A is CR31R33 or NR31;

R30 is H or $(CR11R12)_n$-R32;

R31 is H or $(CR11R12)_n$-R32;

R33 is H or $(C_1$-$C_6)$-alkyl;

R11, R12 are independently of each other H or $(C_1$-$C_6)$-alkyl;

n is 0, 1, 2 or 3;

R32 is $(C_1$-$C_6)$-alkyl, COOR13, CONR14R15, $S(O)_mR16$, OH, CN, $(C_3$-$C_8)$-cycloalkyl, 4-, 5- or 6-membered heterocycle or 5- or 6-membered heteroaryl ring;
wherein the groups $(C_3$-$C_8)$-cycloalkyl, 4-, 5- or 6-membered heterocycle, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkanoyl, hydroxy, hydroxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyloxy, $(C_1$-$C_3)$-alkyloxy-$(C_1$-$C_4)$-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or $(C_1$-$C_6)$-alkyl;

R14, R15 are independently of each other H, $(C_1$-$C_6)$-alkyl or $(C_1$-$C_6)$-alkyl substituted with OR17, or $(C_3$-$C_6)$-cycloalkyl;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list $(C_1$-$C_4)$-alkyl and OR17.

R16 is $(C_1\text{-}C_6)$-alkyl;

R17 is H or $(C_1\text{-}C_6)$-alkyl;

R18 is H or $(C_1\text{-}C_6)$-alkyl;

R1a is H or F;

R2a is H, F, Cl, Br, $(C_1\text{-}C_6)$-alkyl or CN;

Y is N or CH;

R3 is a bond or $(CR7R7')_p$;

p is 0, 1, 2, 3 or 4;

R7, R7' are independently of each other H or $(C_1\text{-}C_6)$-alkyl;

R4 is $(C_1\text{-}C_6)$-alkyl, $(C_2\text{-}C_6)$-alkenyl, OR8, $(C_3\text{-}C_8)$-cycloalkyl, $(C_5\text{-}C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;
wherein the groups $(C_3\text{-}C_8)$-cycloalkyl, $(C_5\text{-}C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkanoyl, hydroxy, hydroxy-$(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_3)$-alkyloxy-$(C_1\text{-}C_4)$-alkyl, oxo, F and Cl;

R8 is H, $(C_1\text{-}C_6)$-alkyl, hydroxy-$(C_1\text{-}C_4)$-alkyl or $(C_1\text{-}C_3)$-alkyloxy-$(C_1\text{-}C_4)$-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

7. A compound of the formula Ia as claimed in claim 5 or 6, wherein

X is C-R1a;

A is CH_2, $CH(C_1\text{-}C_6)$-alkyl or $C((C_1\text{-}C_6)\text{-alkyl})_2$;

R30 is H or $(CR11R12)_n$-R32;

R11, R12 are independently of each other H or $(C_1\text{-}C_6)$-alkyl;

n is 0, 1, 2 or 3;

R32 is $(C_1\text{-}C_6)$-alkyl, COOR13, CONR14R15, $S(O)_mR16$, OH, CN, $(C_3\text{-}C_8)$-cycloalkyl, 4-, 5- or 6-membered heterocycle or 5- or 6-membered heteroaryl ring;
wherein the groups $(C_3\text{-}C_8)$-cycloalkyl, 4-, 5- or 6-membered heterocycle, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkanoyl, hydroxy, hydroxy-$(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_6)$-alkyloxy, $(C_1\text{-}C_3)$-alkyloxy-$(C_1\text{-}C_4)$-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or $(C_1\text{-}C_6)$-alkyl;

R14, R15 are independently of each other H, $(C_1\text{-}C_6)$-alkyl or $(C_1\text{-}C_6)$-alkyl substituted with OR17, or $(C_3\text{-}C_6)$-cycloalkyl;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list $(C_1\text{-}C_4)$-alkyl and OR17;

R16 is (C_1-C_6)-alkyl;

R17 is H or (C_1-C_6)-alkyl;

R18 is H or (C_1-C_6)-alkyl;

R1a is H or F;

R2a is H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

Y is N or CH;

R3 is CH_2 or CH_2-CH_2;

R4 is (C_3-C_8)-cycloalkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

8. A compound of the formula Ia as claimed in claims 5 to 7, wherein

X is CH;

A is CH_2;

R30 CH_2-CONR14R15;

R14 is H or (C_1-C_6)-alkyl;

R15 is (C_1-C_6)-alkyl or (C_1-C_6)-alkyl substituted with OR17, or (C_3-C_6)-cycloalkyl;

R17 is H or (C_1-C_6)-alkyl;

R2a is H or F;

Y is N;

R3 is CH_2 or CH_2-CH_2;

R4 is (C_3-C_8)-cycloalkyl;

or a physiologically acceptable salt thereof.

9. A compound selected from the list

N,N-Dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2,2,2-trifluoroethoxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide and
2-[4-fluoro-1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]-N,N-dimethyl-acetamide;

or a pharmaceutically acceptable salt thereof.

10. A compound as claimed in claim 9, which is

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

or a pharmaceutically acceptable salt thereof.

11. A compound selected from the list

2-[6-[(3R)-3-[[6-(2-Cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-fluoro-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide and
2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide;

or a pharmaceutically acceptable salt thereof.

12. A compound as claimed in claim 11, which is

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

or a pharmaceutically acceptable salt thereof.

13. A compound as claimed in claim 11, which is

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

or a pharmaceutically acceptable salt thereof.

14. A compound as claimed in claim 11, which is

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-fluoro-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

or a pharmaceutically acceptable salt thereof.

15. A compound selected from the list

2-[3-[(3R)-3-[[6-(4-Fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,
6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one and
2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide;

or a pharmaceutically acceptable salt thereof.

16. A compound as claimed in claim 15, which is
2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

or a pharmaceutically acceptable salt thereof.

17. A compound as claimed in claim 15, which is

2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide,

or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising at least one compound as claimed in any of claims 1 to 17 or a physiologically acceptable salt of any of them, for use as a pharmaceutical.

19. A pharmaceutical composition as claimed in claim 18, comprising additionally one or more active ingredients selected from the list:
Insulin and insulin derivatives, GLP-1, GLP-1 analogues and GLP-1 receptor agonists, polymer bound GLP-1 and GLP-1 analogues, dual GLP-1/GIP agonists, dual GLP-1/glucagon receptor agonists, PYY3-36 or analogues thereof, pancreatic polypeptide or analogues thereof, glucagon receptor agonists or antagonists, GIP receptor agonists or antagonists, ghrelin antagonists or inverse agonists, xenin and analogues thereof, DDP-IV inhibitors, SGLT-2 inhibitors, dual SGLT-2/SGLT-1 inhibitors, biguanides, thiazolidinediones, PPAR agonists, PPAR modulators, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, amylin and amylin analogues, GPR119 agonists, GPR40 agonists, GPR120 agonists, GPR142 agonists, TGR5 agonists, AMPK stimulants, AMPK activators, inhibitors of 11-beta-HSD, activators of glucokinase, inhibitors of DGAT, inhibitors of protein tyrosine phosphatase 1, inhibitors of glucose-6-phosphatase, inhibitors of fructose-1,6-bisphosphatase, inhibitors of glycogen phosphorylase, inhibitors of phosphoenol pyruvate carboxykinase, inhibitors of glycogen synthase kinase, inhibitors of pyruvate dehydrogenase kinase, CCR-2 antagonists, modulators of glucose transporter-4, somatostatin receptor 3 agonists, HMG-CoA-reductase inhibitors, fibrates, nicotinic acid and derivatives thereof, nicotinic acid receptor 1 agonists, , ACAT

inhibitors, cholesterol absorption inhibitors, bile acid-binding substances, IBAT inhibitors, MTP inhibitors, modulators of PCSK9, LDL receptor up-regulators (liver selective thyroid hormone receptor beta agonists), HDL-raising compounds, lipid metabolism modulators, PLA2 inhibitors, ApoA-I enhancers, cholesterol synthesis inhibitors, omega-3 fatty acids and derivatives thereof, active substances for the treatment of obesity, CB1 receptor antagonists, MCH-1 antagonists, MC4 receptor agonists and partial agonists, NPY5 or NPY2 antagonists, NPY4 agonists, beta-3 adrenergic receptor agonists, leptin or leptin mimetics, 5HT2c receptor agonists, lipase inhibitors, angiogenesis inhibitors, H3 antagonists, AgRP inhibitors, triple monoamine uptake inhibitors, MetAP2 inhibitors, antisense oligonucleotides against production of fibroblast growth factor receptor 4 or prohibitin targeting peptide-1, drugs for influencing high blood pressure, chronic heart failure or atherosclerosis, angiotensin II receptor antagonists, dual angiotensin receptor blockers (ARB), angiotensin converting enzyme (ACE) inhibitors, angiotensin converting enzyme 2 (ACE-2) activators, , renin inhibitors, prorenin inhibitors, endothelin converting enzyme (ECE) inhibitors, endothelin receptor blockers, endothelin antagonists, diuretics, aldosterone antagonists, aldosterone synthase inhibitors, alpha-blockers, antagonists of the alpha-2 adrenergic receptor, beta-blockers, mixed alpha-/beta-blockers, calcium antagonists/calcium channel blockers (CBBs), dual mineralocorticoid/CCBs, centrally acting antihypertensives, inhibitors of neutral endopeptidase, aminopeptidase-A inhibitors, vasopeptide inhibitors, dual vasopeptide inhibitors, neprilysin-ACE inhibitors, neprilysin-ECE inhibitors, dual-acting Angiotensin (AT) receptor-neprilysin inhibitors, dual AT1/ endothelin-1 (ETA) antagonists, advanced glycation end-product breakers, recombinant renalase, blood pressure vaccines, anti-RAAS vaccines, AT1- or AT2-vaccines, modulators of genetic polymorphisms with antihypertensive response and thrombocyte aggregation inhibitors.

20. A pharmaceutical composition as claimed in claim 18, comprising additionally metformin.

21. A pharmaceutical composition as claimed in claim 18, comprising additionally at least one DPP-IV inhibitor.

22. A pharmaceutical composition as claimed in claim 21, wherein the DPP-IV inhibitor is selected from the list alogliptin, linagliptin, saxagliptin, sitagliptin, anagliptin, teneligliptin, trelagliptin, vildagliptin, gemigliptin, omarigliptin, evogliptin and dutogliptin.

23. A pharmaceutical composition as claimed in claim 18, comprising additionally at least one SGLT-2 inhibitor.

24. A pharmaceutical composition as claimed in claim 23, wherein the SGLT-2 inhibitor is selected from the list canagliflozin, dapagliflozin, remogliflozin, remogliflozin etabonate, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin and ertugliflozin.

25. A pharmaceutical composition as claimed in claim 18, comprising additionally at least one GPR40 agonist.

26. A pharmaceutical composition as claimed in claim 25, wherein the GPR40 agonist is selected from the list TUG-424, P-1736, P-11187, JTT-851, GW9508, CNX-011-67, AM-1638 and AM-5262.

27. A pharmaceutical composition as claimed in claim 18, comprising additionally ezetimibe.

28. A pharmaceutical composition as claimed in claim 18, comprising additionally at least one HMG-CoA reductase inhibitor.

29. A pharmaceutical composition as claimed in claim 28, wherein the HMG-CoA reductase inhibitor is selected from the list simvastatin, atorvastatin, rosuvastatin, pravastatin, fluvastatin, pitavastatin, lovastatin, mevastatin, rivastatin and cerivastatin.

30. A pharmaceutical composition as claimed in claim 18, comprising additionally at least one PPAR agonist or PPAR modulator.

31. A pharmaceutical composition as claimed in claim 30, wherein the PPAR agonist or PPAR modulator is saroglitazar.

32. A pharmaceutical composition as claimed in claim 30, wherein the PPAR agonist or PPAR modulator is selected from the list pioglitazone, rosiglitazone and lobeglitazone.

33. A pharmaceutical composition as claimed in claim 18, comprising additionally acarbose.

34. A compound of the formula I as claimed in any of claims 1 to 17 for use as a pharmaceutical.

35. A compound of the formula I as claimed in any of claims 1 to 17 for the prevention and/or treatment of diabetes, obesity, dyslipidemia and related disorders.

36. A compound of the formula I as claimed in any of claims 1 to 17 for the prevention and/or treatment of diabetes.

37. A compound of the formula I as claimed in any of claims 1 to 17 for the prevention and/or treatment of obesity.

38. A compound of the formula I as claimed in any of claims 1 to 17 for the prevention and/or treatment of dyslipidemia.

39. A compound of the formula I as claimed in any of claims 1 to 17 for prevention and/or treatment of a disease associated with the GPR119.

40. A method for treating diabetes, obesity or dyslipidemia in a patient, the method comprising administering to the patient an effective amount of at least one compound of formula I as claimed in any of claims 1 to 17.

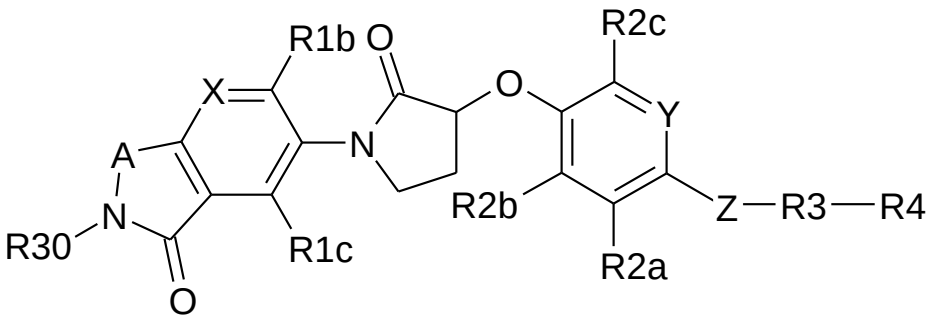
41. A method for treating diabetes, obesity, dyslipidemia or high blood pressure in a patient, the method comprising administering to the patient an effective amount of at least one compound of formula I as claimed in any of claims 1 to 17 and an effective amount of at least one other compound useful for treating diabetes, obesity, dyslipidemia or high blood pressure.

42. The method as claimed in claim 41 wherein the effective amount of at least one compound of formula I as claimed in any of claims 1 to 17 and the additional active ingredient are adminstered to the patient simultaneously.

43. The method as claimed in claim 41 wherein the effective amount of at least one compound of formula I as claimed in any of claims 1 to 17 and the additional active ingredient are adminstered to the patient sequentially.

Isoindolinone Compounds as GPR119 Modulators for the Treatment of Diabetes, Obesity, Dyslipidemia and Related Disorders

The present invention relates to isoindolinone compounds of the formula I



(I)

in which A, X, R1b, R1c, R2a, R2b, R2c, R3, R4, R30, Y and Z are defined as indicated below. The isoindolinone compounds I are GPR119 modulators and useful for the prevention and/or treatment of diabetes, obesity, dyslipidemia and related disorders. The invention furthermore relates to the use of isoindolinone compounds of the formula I as active ingredients in pharmaceuticals, and pharmaceutical compositions comprising them.

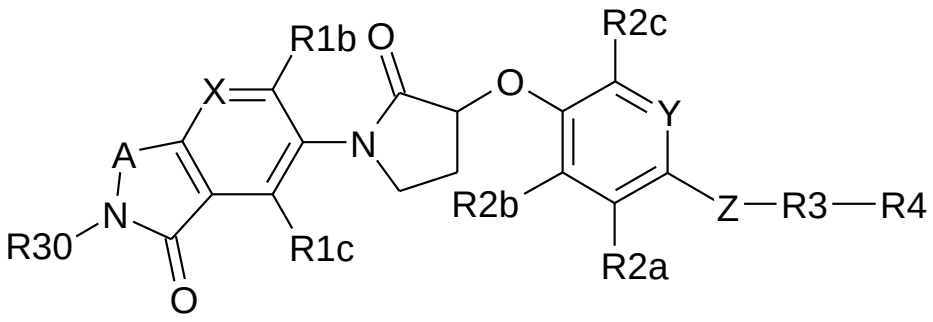
GPR119 is a G-protein coupled receptor which is expressed predominantly in the beta cells of the pancreas and in the K- and L-cells of the intestine. In vitro studies have shown, that agonists of GPR119, via activation of the cAMP pathway in gut and pancreas derived cell lines, mediate the secretion of GLP-1 and insulin respectively. This supports the hypothesis, that modulators of GPR119, agonists in particular, may have utility to treat diabetes and related disorders by augmenting the secretion of insulin and intestinal hormones like GIP, GLP-1 and PYY. As the secretion of insulin was found to be strictly glucose-dependent, induction of hypoglycemic episodes may largely be avoided. Furthermore beneficial effects like reduced food intake may be expected from the release of intestinal peptides. Stimulation of the beta cell by activation of GPR119 may also improve beta cell function and beta cell mass. Studies of GPR119 agonists in rodents showed the predicted glucose lowering effects. For some such animal studies decreased food intake and weight loss was reported. Recently clinical trials with

GPR119 agonists added evidence for a positive impact on lipid parameters i.e. elevation of HDL together with lowering of LDL and triglycerides in humans. WO2013/070463A2 discloses that GPR119 agonists may be used to treat abnormalities in blood lipids. In summary, modulators of GPR119, agonists in particular, may have therapeutic utility in the prevention and/or treatment of metabolic disorders in mammals and especially in humans. Examples of such disorders and diseases include type 2 diabetes mellitus, type 1 diabetes mellitus, impaired glucose tolerance, insulin resistance, loss of beta cell function, hyperglycemia, hypercholesterolemia, dyslipidemia, hypertriglyceridemia, syndrome X, metabolic syndrome, obesity, fatty liver, steatosis, steatohepatitis, cirrhosis, micro- and marcovascular disorders, high blood pressure, chronic low grade inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, coronary heart disease, endothelial dysfunction and bone-related diseases such as osteoporosis, rheumatoid arthritis or osteoarthritis.

Several modulators of GPR119 are known. For example WO2011146335 and WO2012037393 describe piperidinyl-substituted lactams as GPR119 modulators. WO2010048149 describes heterocyclic modulators of GPR119 for the treatment of disease and their preparation. WO2004110994 describes the preparation of piperazinyl-aryloxy and piperazinyl-heteroaryloxy-N-aryl lactams as 5-HT1B ligands.

It was an aim of the invention to provide novel compounds as active ingredients in pharmaceuticals.
It was another aim of the invention to provide novel compounds which will lower blood glucose in mammals and which are suitable for prevention and/or treatment of diabetes, obesity, dyslipidemia and related disorders.
A further aim was to provide novel GPR119 modulators, especially agonists, which can be used therapeutically for the prevention and/or treatment of diabetes, obesity, dyslipidemia and related disorders.

Accordingly a subject of the invention is a compound of the formula I



(I)

in which

X is N or C-R1a;

A is CR31R33, NR31, CR31R33-NR31 or CR31=N;

R30 is H or $(CR11R12)_n$-R32;

R31 is H or $(CR11R12)_n$-R32;

R33 is H or $(C_1$-$C_6)$-alkyl;

R11, R12 are independently of each other H or $(C_1$-$C_6)$-alkyl;

n is 0, 1, 2 or 3;

R32 is $(C_1$-$C_6)$-alkyl, COOR13, CONR14R15, $S(O)_mR16$, OH, CN, $(C_3$-$C_8)$-cycloalkyl, $(C_5$-$C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;

wherein the groups $(C_3$-$C_8)$-cycloalkyl, $(C_5$-$C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkanoyl, hydroxy, hydroxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyloxy, $(C_1$-$C_3)$-alkyloxy-$(C_1$-$C_4)$-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or (C_1-C_6)-alkyl;

R14, R15 are independently of each other H, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted with 1 to 3 groups selected from the list OR17, COOR19 and a 4-, 5- or 6-membered heterocycle;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17;

R16 is (C_1-C_6)-alkyl;

R17 is H or (C_1-C_6)-alkyl;

R18 is H or (C_1-C_6)-alkyl;

R1a, R1b, R1c are independently of each other H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

R2a, R2b, R2c are independently of each other H, F, Cl, Br, (C_1-C_6)-alkyl, (C_1-C_3)-alkyl substituted with COOR19 or CN;

R19 is H or (C_1-C_6)-alkyl;

Y is N or CH;

Z is a bond, O, CR5R5', NR6, C=O, S, SO or SO_2;

R5, R5', R6 are independently of each other H or (C_1-C_4)-alkyl;

R3 is a bond or $(CR7R7')_p$;

p is 0, 1, 2, 3 or 4;

R7, R7' are independently of each other H or (C_1-C_6)-alkyl;

R4 is F, Cl, SF_5, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, OR8, (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, or 5- or 6-membered heteroaryl ring;

wherein the groups (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

R8 is H, (C_1-C_6)-alkyl, hydroxy-(C_1-C_4)-alkyl or (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

In another group of embodiments
the 3-position of the central pyrrolidinone ring has (*R*)-configuration.

In another group of embodiments
X is C-R1a.

In another group of embodiments
X is CH.

In another group of embodiments
A is CR31R33 or NR31.

In another group of embodiments
A is CH_2.

In another group of embodiments

R32 is COOR13, CONR14R15, SO_2R16 or OH.

In another group of embodiments

R32 is COOR13 or CONR14R15.

In another group of embodiments

R14, R15 are independently of each other H, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted with OR17, or (C_3-C_6)-cycloalkyl;

or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;

wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17.

In another group of embodiments

R14, R15 are independently of each other H, (C_1-C_6)-alkyl or (C_1-C_6)-alkyl substituted with OR17.

In another group of embodiments

R16 is CH_3.

In another group of embodiments

R1a, R1c are independently of each other H, F or CH_3.

In another group of embodiments

R1b is H.

In another group of embodiments

R1a is H or F.

In another group of embodiments

R1b and R1c are H.

In another group of embodiments
R2a is H, F or CH_3.

In another group of embodiments
R2b and R2c are H.

In another group of embodiments
R2a, R2b and R2c are H.

In another group of embodiments
Y is N.

In another group of embodiments
Z is O.

In another group of embodiments
R7, R7' are H.

In another group of embodiments
p is 0, 1 or 2.

In another group of embodiments
R4 is (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted with 1 to 3 groups F, (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl or phenyl;
wherein the groups (C_3-C_8)-cycloalkyl and phenyl may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and F.

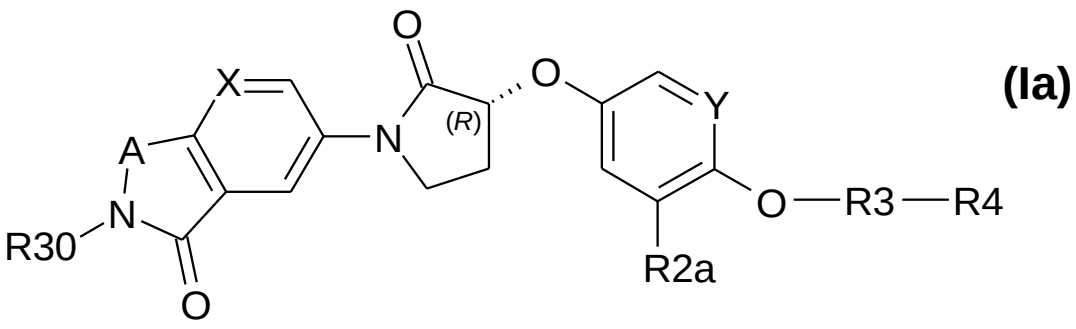
In another group of embodiments
R4 is (C_3-C_6)-cycloalkyl.

In another group of embodiments
R3 is CH_2 or CH_2-CH_2.

In another group of embodiments

R3 is CH_2.

In another group of embodiments the compound of the formula I is a compound of the formula Ia



(Ia)

in which

X is N or C-R1a;

A is CR31R33, NR31, CR31R33-NR31 or CR31=N;

R30 is H or $(CR11R12)_n$-R32;

R31 is H or $(CR11R12)_n$-R32;

R33 is H or $(C_1$-$C_6)$-alkyl;

R11, R12 are independently of each other H or $(C_1$-$C_6)$-alkyl;

n is 0, 1, 2 or 3;

R32 is $(C_1$-$C_6)$-alkyl, COOR13, CONR14R15, $S(O)_mR16$, OH, CN, $(C_3$-$C_8)$-cycloalkyl, 4-, 5- or 6-membered heterocycle or 5- or 6-membered heteroaryl ring;

wherein the groups $(C_3$-$C_8)$-cycloalkyl, 4-, 5- or 6-membered heterocycle, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3

groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyloxy, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or (C_1-C_6)-alkyl;

R14, R15 are independently of each other H, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted with 1 to 3 groups selected from the list OR17, COOR19 and a 4-, 5- or 6-membered heterocycle;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17;

R16 is (C_1-C_6)-alkyl;

R17 is H or (C_1-C_6)-alkyl;

R18 is H or (C_1-C_6)-alkyl;

R1a is H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

R2a is H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

Y is N or CH;

R3 is a bond or $(CR7R7')_p$;

p is 0, 1, 2, 3 or 4;

R7, R7' are independently of each other H or (C_1-C_6)-alkyl;

R4 is (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, OR8, (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;
wherein the groups (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

R8 is H, (C_1-C_6)-alkyl, hydroxy-(C_1-C_4)-alkyl or (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

In another group of embodiments the compound of the formula I is a compound of the formula Ia, in which

X is N or C-R1a;

A is CR31R33, NR31, CR31R33-NR31 or CR31=N;

R30 is H or $(CR11R12)_n$-R32;

R31 is H or $(CR11R12)_n$-R32;

R33 is H or (C_1-C_6)-alkyl;

R11, R12 are independently of each other H or (C_1-C_6)-alkyl;

n is 0, 1, 2 or 3;

R32 is (C_1-C_6)-alkyl, COOR13, CONR14R15, $S(O)_m$R16, OH, CN, (C_3-C_8)-cycloalkyl, 4-, 5- or 6-membered heterocycle or 5- or 6-membered heteroaryl ring;
wherein the groups (C_3-C_8)-cycloalkyl, 4-, 5- or 6-membered heterocycle, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyloxy, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or (C_1-C_6)-alkyl;

R14, R15 are independently of each other H, (C_1-C_6)-alkyl or (C_1-C_6)-alkyl substituted with OR17, or (C_3-C_6)-cycloalkyl;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17;

R16 is (C_1-C_6)-alkyl;

R17 is H or (C_1-C_6)-alkyl;

R18 is H or (C_1-C_6)-alkyl;

R1a is H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

R2a is H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

Y is N or CH;

R3 is a bond or $(CR7R7')_p$;

p is 0, 1, 2, 3 or 4;

R7, R7' are independently of each other H or $(C_1\text{-}C_6)$-alkyl;

R4 is $(C_1\text{-}C_6)$-alkyl, $(C_2\text{-}C_6)$-alkenyl, OR8, $(C_3\text{-}C_8)$-cycloalkyl, $(C_5\text{-}C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;
wherein the groups $(C_3\text{-}C_8)$-cycloalkyl, $(C_5\text{-}C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkanoyl, hydroxy, hydroxy-$(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_3)$-alkyloxy-$(C_1\text{-}C_4)$-alkyl, oxo, F and Cl;

R8 is H, $(C_1\text{-}C_6)$-alkyl, hydroxy-$(C_1\text{-}C_4)$-alkyl or $(C_1\text{-}C_3)$-alkyloxy-$(C_1\text{-}C_4)$-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

In another group of embodiments the compound of the formula I is a compound of the formula Ia, in which

X is C-R1a;

A is CR31R33 or NR31;

R30 is H or $(CR11R12)_n$-R32;

R31 is H or $(CR11R12)_n$-R32;

R33 is H or $(C_1\text{-}C_6)$-alkyl;

R11, R12 are independently of each other H or $(C_1\text{-}C_6)$-alkyl;

n is 0, 1, 2 or 3;

R32 is (C_1-C_6)-alkyl, COOR13, CONR14R15, $S(O)_m$R16, OH, CN, (C_3-C_8)-cycloalkyl, 4-, 5- or 6-membered heterocycle or 5- or 6-membered heteroaryl ring;
wherein the groups (C_3-C_8)-cycloalkyl, 4-, 5- or 6-membered heterocycle, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyloxy, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or (C_1-C_6)-alkyl;

R14, R15 are independently of each other H, (C_1-C_6)-alkyl or (C_1-C_6)-alkyl substituted with OR17, or (C_3-C_6)-cycloalkyl;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17;

R16 is (C_1-C_6)-alkyl;

R17 is H or (C_1-C_6)-alkyl;

R18 is H or (C_1-C_6)-alkyl;

R1a is H or F;

R2a is H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

Y is N or CH;

R3 is a bond or $(CR7R7')_p$;

p is 0, 1, 2, 3 or 4;

R7, R7' are independently of each other H or $(C_1\text{-}C_6)$-alkyl;

R4 is $(C_1\text{-}C_6)$-alkyl, $(C_2\text{-}C_6)$-alkenyl, OR8, $(C_3\text{-}C_8)$-cycloalkyl, $(C_5\text{-}C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;
wherein the groups $(C_3\text{-}C_8)$-cycloalkyl, $(C_5\text{-}C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkanoyl, hydroxy, hydroxy-$(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_3)$-alkyloxy-$(C_1\text{-}C_4)$-alkyl, oxo, F and Cl;

R8 is H, $(C_1\text{-}C_6)$-alkyl, hydroxy-$(C_1\text{-}C_4)$-alkyl or $(C_1\text{-}C_3)$-alkyloxy-$(C_1\text{-}C_4)$-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

In another group of embodiments the compound of the formula I is a compound of the formula Ia, in which

X is C-R1a;

A is CH_2, $CH(C_1\text{-}C_6)$-alkyl or $C((C_1\text{-}C_6)\text{-alkyl})_2$;

R30 is H or $(CR11R12)_n$-R32;

R11, R12 are independently of each other H or $(C_1\text{-}C_6)$-alkyl;

n is 0, 1, 2 or 3;

R32 is (C_1-C_6)-alkyl, COOR13, CONR14R15, $S(O)_m$R16, OH, CN, (C_3-C_8)-cycloalkyl, 4-, 5- or 6-membered heterocycle or 5- or 6-membered heteroaryl ring;
wherein the groups (C_3-C_8)-cycloalkyl, 4-, 5- or 6-membered heterocycle, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyloxy, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or (C_1-C_6)-alkyl;

R14, R15 are independently of each other H, (C_1-C_6)-alkyl or (C_1-C_6)-alkyl substituted with OR17, or (C_3-C_6)-cycloalkyl;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17;

R16 is (C_1-C_6)-alkyl;

R17 is H or (C_1-C_6)-alkyl;

R18 is H or (C_1-C_6)-alkyl;

R1a is H or F;

R2a is H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

Y is N or CH;

R3 is CH_2 or CH_2-CH_2;

R4 is (C_3-C_8)-cycloalkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

In another group of embodiments the compound of the formula I is a compound of the formula Ia, in which

X is CH;

A is CH_2;

R30 CH_2-CONR14R15;

R14 is H or (C_1-C_6)-alkyl

R15 is (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted with OR17, or (C_3-C_6)-cycloalkyl;

R17 is H or (C_1-C_6)-alkyl;

R2a is H or F;

Y is N;

R3 is CH_2 or CH_2-CH_2;

R4 is (C_3-C_8)-cycloalkyl;

or a physiologically acceptable salt thereof.

In another group of embodiments the compound of the formula I is a compound of the formula Ia, in which

X is N or CH;

A is CH_2;

R30 CH_2-$S(O)_m$R16;

m is 0, 1 or 2;

R16 is (C_1-C_6)-alkyl;

R2a is H or F;

Y is N;

R3 is CH_2 or CH_2-CH_2;

R4 is CF_3 or (C_3-C_8)-cycloalkyl;

or a physiologically acceptable salt thereof.

In another embodiment compounds of the formula I are encompassed selected from the list Examples 1-01 to 1-69, 2-01 to 2-66, 3-01 to 3-05, 4-01 to 4-42, 5-01 to 5-06 and 6-01 to 6-04.

In another embodiment compounds of the formula I are encompassed selected from the following list:
Tert-butyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]propanoic acid,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-methyl-3-oxo-isoindolin-1-yl]acetic acid,

methyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]propanoate,

methyl 2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-methyl-3-oxo-isoindolin-1-yl]acetate,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(2-oxotetrahydrofuran-3-yl)isoindolin-1-one,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-methyl-3-oxo-isoindolin-1-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-propyl-isoindolin-1-one,

2-[6-[(3R)-3-[(6-isopropylsulfanyl-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(2-methyltetrazol-5-yl)isoindolin-1-one,

2-[3-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1,1-dimethyl-3-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-isoindolin-2-yl]acetic acid,

methyl 2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-isoindolin-2-yl]acetate,

2-[3-[(3R)-3-[4-(2-cyclopropylacetyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(methylsulfonylmethyl)isoindolin-1-one,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[(2-methyltetrazol-5-yl)methyl]isoindolin-1-one,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(methylsulfinylmethyl)isoindolin-1-one,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(methylsulfanylmethyl)isoindolin-1-one,

2-[6-[(3R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

methyl 2-[6-[(3R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-methyl-isoindolin-1-one,

5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1,2-dihydroindazol-3-one,

2-[6-[(3S)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[5-[(3S)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-indazol-2-yl]-N,N-dimethyl-acetamide,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-indazol-2-yl]-N,N-dimethyl-acetamide,

2-[3-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,

ethyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,

2-tert-butyl-6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-isoindolin-1-one,

methyl 2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate,

methyl 2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,

2-tert-butyl-6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-isoindolin-1-one,

methyl 2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate,

6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(2-hydroxyethyl)isoindolin-1-one,

2-[6-[(3R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

methyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N,1-trimethyl-4-oxo-2,3-dihydroquinazoline-2-carboxamide (Stereomer I),

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N,1-trimethyl-4-oxo-2,3-dihydroquinazoline-2-carboxamide (Stereomer II),

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N,3-trimethyl-4-oxo-quinazoline-2-carboxamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N-dimethyl-4-oxo-3H-quinazoline-2-carboxamide,

N-(2-hydroxyethyl)-N-methyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-1-one,

2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-1-one,

2-[6-[(3R)-3-[[6-(2,4-difluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

N,N-dimethyl-2-[5-oxo-3-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]-7H-pyrrolo[3,4-b]pyridin-6-yl]acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(trifluoromethoxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[[6-(3-cyclopropylpropyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-[[(1R,3S,5S)-3-bicyclo[3.1.0]hexanyl]oxy]-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(2-cyclopropylethyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-fluoro-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-methyl-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethylamino)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-(4-fluorophenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[(6-chloro-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-propanoylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-pentanoylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-(4-butanoylphenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(4-fluorobenzoyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(4-fluorophenoxy)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[(6-fluoro-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-[[(1R,3R,5S)-3-bicyclo[3.1.0]hexanyl]oxy]-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethylsulfanyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[(6-cyclopropylsulfanyl-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(2-cyclopropylacetyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(trifluoromethylsulfanyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2-pyridyloxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-(4-morpholinophenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(1,2,4-triazol-1-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[4-(4-acetylpiperazin-1-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(pentafluoro-λ{6}-sulfanyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2-oxopyrrolidin-1-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-(1,3,4-oxadiazol-2-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2,2,2-trifluoroethoxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-(4-methylthiazol-2-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-[(4-oxothiazol-2-yl)amino]phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[4-(3-isopropyl-1,2,4-oxadiazol-5-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(pyrrolidine-1-carbonyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(1,2,4-triazol-4-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-(4-oxazol-5-ylphenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-pyrazin-2-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[4-(1-ethyltetrazol-5-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(thiadiazol-4-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[3-chloro-4-(trifluoromethoxy)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-thiazol-2-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-[(3-methyl-1,2,4-oxadiazol-5-yl)methoxy]phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(tetrazol-1-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
ethyl 3-[2-chloro-5-[(3R)-1-[2-[2-(dimethylamino)-2-oxo-ethyl]-3-oxo-isoindolin-5-yl]-2-oxo-pyrrolidin-3-yl]oxy-phenyl]propanoate,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-pyrrolidin-1-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[5-bromo-6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(cyclopropanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetic acid,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetic acid,
2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetic acid,
2-[[2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetyl]amino]acetic acid,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(2-oxo-2-pyrrolidin-1-yl-ethyl)isoindolin-1-one,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N-cyclopropyl-2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,
6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,
6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,
2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-diethyl-acetamide,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetamide,
6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(2-oxo-2-pyrrolidin-1-yl-ethyl)isoindolin-1-one,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,
6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,
2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,
2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(2-oxo-2-pyrrolidin-1-yl-ethyl)isoindolin-1-one,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(1H-tetrazol-5-ylmethyl)acetamide,

methyl 2-[[2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetyl]amino]acetate,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-[2-hydroxy-1-(hydroxymethyl)ethyl]acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-bis(2-hydroxyethyl)acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-[(2S)-2,3-dihydroxypropyl]acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-[(2R)-2,3-dihydroxypropyl]acetamide,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetonitrile,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetic acid,

6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[(3-methyloxetan-3-yl)methyl]isoindolin-1-one,

6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-methyl-isoindolin-1-one,
6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-isopropyl-isoindolin-1-one,
6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(3-hydroxypropyl)isoindolin-1-one,
2-[4-fluoro-1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(2,2-dimethylpropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[(6-allyloxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclobutylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(methylsulfinylmethyl)isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(methylsulfanylmethyl)isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(methylsulfinylmethyl)isoindolin-1-one,
6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(methylsulfonylmethyl)isoindolin-1-one,
2-(methylsulfinylmethyl)-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-1-one,
3-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-6-(methylsulfinylmethyl)-7H-pyrrolo[3,4-b]pyridin-5-one,
2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
3-[(3R)-3-[[6-(cyclopropanecarbonyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-6-(methylsulfinylmethyl)-7H-pyrrolo[3,4-b]pyridin-5-one,
6-[(3R)-3-[[6-(cyclopropanecarbonyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(methylsulfinylmethyl)isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropanecarbonyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(methylsulfonylmethyl)isoindolin-1-one

6-[(3R)-3-[4-(cyclopropanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-2-(methylsulfinylmethyl)isoindolin-1-one

3-[(3R)-3-[4-(cyclopropanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-6-(methylsulfinylmethyl)-7H-pyrrolo[3,4-b]pyridin-5-one

3-[(3R)-3-[4-(cyclopropanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-6-(methylsulfonylmethyl)-7H-pyrrolo[3,4-b]pyridin-5-one

6-(methylsulfinylmethyl)-3-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]-7H-pyrrolo[3,4-b]pyridin-5-one,

ethyl 2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetate,

methyl 2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetate,

3-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-6-(methylsulfonylmethyl)-7H-pyrrolo[3,4-b]pyridin-5-one,

6-(methylsulfonylmethyl)-3-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]-7H-pyrrolo[3,4-b]pyridin-5-one,

6-((S)-methanesulfinylmethyl)-3-{(R)-2-oxo-3-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yloxy]-pyrrolidin-1-yl}-6,7-dihydro-pyrrolo[3,4-b]pyridin-5-one,

6-((R)-methanesulfinylmethyl)-3-{(R)-2-oxo-3-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yloxy]-pyrrolidin-1-yl}-6,7-dihydro-pyrrolo[3,4-b]pyridin-5-one,

2-[6-[(3R)-3-[[6-(1-methylcyclopropanecarbonyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[4-(4-fluorobenzoyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,

2-[1-oxo-6-[(3R)-2-oxo-3-(4-thiazol-2-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[[6-(cyclopropanecarbonyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[4-(cyclopropanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,

2-[1-oxo-6-[(3R)-2-oxo-3-(4-pentanoylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[4-(1-methylcyclopropanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[[6-(3-cyclopropylpropanoyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[[6-(3-cyclopropylpropanoyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropanecarbonyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[[6-(1-methylcyclopropanecarbonyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[[6-(5-methylthiazol-2-yl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(4-fluorobenzoyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(cyclopropanecarbonyl)-3-fluoro-phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(3,3-difluorocyclobutanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(5-fluorothiazol-2-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(2,2-difluorocyclopropanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(4,4,4-trifluorobutanoyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetic acid,
N-cyclopropyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N-isopropyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N-methyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N-ethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-(2-oxo-2-pyrrolidin-1-yl-ethyl)-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-1-one,
N,N-diethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide and

2-[2-(azetidin-1-yl)-2-oxo-ethyl]-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-1-one.

In another embodiment compounds of the formula I are encompassed selected from the following list:

Tert-butyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]propanoic acid,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-methyl-3-oxo-isoindolin-1-yl]acetic acid,

methyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]propanoate,

methyl 2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-methyl-3-oxo-isoindolin-1-yl]acetate,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(2-oxotetrahydrofuran-3-yl)isoindolin-1-one,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-methyl-3-oxo-isoindolin-1-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-propyl-isoindolin-1-one,

2-[6-[(3R)-3-[(6-isopropylsulfanyl-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(2-methyltetrazol-5-yl)isoindolin-1-one,

2-[3-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1,1-dimethyl-3-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-isoindolin-2-yl]acetic acid,

methyl 2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-isoindolin-2-yl]acetate,

2-[3-[(3R)-3-[4-(2-cyclopropylacetyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(methylsulfonylmethyl)isoindolin-1-one,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[(2-methyltetrazol-5-yl)methyl]isoindolin-1-one,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(methylsulfinylmethyl)isoindolin-1-one,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(methylsulfanylmethyl)isoindolin-1-one,

2-[6-[(3R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

methyl 2-[6-[(3R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-methyl-isoindolin-1-one,

5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1,2-dihydroindazol-3-one,

2-[6-[(3S)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[5-[(3S)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-indazol-2-yl]-N,N-dimethyl-acetamide,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-indazol-2-yl]-N,N-dimethyl-acetamide,

2-[3-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,

ethyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,

2-tert-butyl-6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-isoindolin-1-one,

methyl 2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate,

methyl 2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,

2-tert-butyl-6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-isoindolin-1-one,

methyl 2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate,

6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(2-hydroxyethyl)isoindolin-1-one,

2-[6-[(3R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

methyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N,1-trimethyl-4-oxo-2,3-dihydroquinazoline-2-carboxamide (Stereomer I),

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N,1-trimethyl-4-oxo-2,3-dihydroquinazoline-2-carboxamide (Stereomer II),

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N,3-trimethyl-4-oxo-quinazoline-2-carboxamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N-dimethyl-4-oxo-3H-quinazoline-2-carboxamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(trifluoromethoxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[[6-(3-cyclopropylpropyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-[[(1R,3S,5S)-3-bicyclo[3.1.0]hexanyl]oxy]-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(2-cyclopropylethyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-fluoro-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-methyl-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethylamino)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-(4-fluorophenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[(6-chloro-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-propanoylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-pentanoylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-(4-butanoylphenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[4-(4-fluorobenzoyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[4-(4-fluorophenoxy)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[(6-fluoro-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-[[(1R,3R,5S)-3-bicyclo[3.1.0]hexanyl]oxy]-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethylsulfanyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[(6-cyclopropylsulfanyl-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[4-(2-cyclopropylacetyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(trifluoromethylsulfanyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2-pyridyloxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-(4-morpholinophenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(1,2,4-triazol-1-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[4-(4-acetylpiperazin-1-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(pentafluoro-λ{6}-sulfanyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2-oxopyrrolidin-1-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-(1,3,4-oxadiazol-2-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2,2,2-trifluoroethoxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-(4-methylthiazol-2-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-[(4-oxothiazol-2-yl)amino]phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[4-(3-isopropyl-1,2,4-oxadiazol-5-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(pyrrolidine-1-carbonyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(1,2,4-triazol-4-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-(4-oxazol-5-ylphenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-pyrazin-2-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[4-(1-ethyltetrazol-5-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(thiadiazol-4-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[3-chloro-4-(trifluoromethoxy)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-thiazol-2-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

N,N-dimethyl-2-[6-[(3R)-3-[4-[(3-methyl-1,2,4-oxadiazol-5-yl)methoxy]phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(tetrazol-1-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

ethyl 3-[2-chloro-5-[(3R)-1-[2-[2-(dimethylamino)-2-oxo-ethyl]-3-oxo-isoindolin-5-yl]-2-oxo-pyrrolidin-3-yl]oxy-phenyl]propanoate,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-pyrrolidin-1-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetic acid,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetic acid,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetic acid,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(2-oxo-2-pyrrolidin-1-yl-ethyl)isoindolin-1-one,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,

N-cyclopropyl-2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,

6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,

6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,

2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-diethyl-acetamide,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetamide,

6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(2-oxo-2-pyrrolidin-1-yl-ethyl)isoindolin-1-one,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,

6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(2-oxo-2-pyrrolidin-1-yl-ethyl)isoindolin-1-one,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetonitrile,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetic acid,

6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[(3-methyloxetan-3-yl)methyl]isoindolin-1-one,

6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-methyl-isoindolin-1-one,

6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-isopropyl-isoindolin-1-one,

6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(3-hydroxypropyl)isoindolin-1-one,

2-[4-fluoro-1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(2,2-dimethylpropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[(6-allyloxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide and

2-[6-[(3R)-3-[[6-(cyclobutylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide.

In another embodiment compounds of the formula I are encompassed selected from the following list:
N,N-Dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2,2,2-trifluoroethoxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[4-fluoro-1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]-N,N-dimethyl-acetamide and
N,N-dimethyl-2-[5-oxo-3-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]-7H-pyrrolo[3,4-b]pyridin-6-yl]acetamide.

In another embodiment compounds of the formula I are encompassed selected from the following list:
N,N-Dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2,2,2-trifluoroethoxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[4-fluoro-1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]-N,N-dimethyl-acetamide and

In another embodiment the compound of the formula I is N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide.

In another embodiment the compound of the formula I is N,N-dimethyl-2-[5-oxo-3-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]-7H-pyrrolo[3,4-b]pyridin-6-yl]acetamide.

In another embodiment compounds of the formula I are encompassed selected from the following list:
2-[6-[(3R)-3-[[6-(2-Cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-fluoro-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide and
2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide.

In another embodiment the compound of the formula I is 2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide.

In another embodiment the compound of the formula I is 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide.

In another embodiment the compound of the formula I is 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-fluoro-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide.

In another embodiment compounds of the formula I are encompassed selected from the following list:

2-[3-[(3R)-3-[[6-(4-Fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,
6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one and
2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide.

In another embodiment the compound of the formula I is 2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide.

In another embodiment the compound of the formula I is 2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide.

In another embodiment compounds of the formula I are encompassed selected from the following list:
2-[1-Oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-(2-oxo-2-pyrrolidin-1-yl-ethyl)-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-1-one and
2-[2-(azetidin-1-yl)-2-oxo-ethyl]-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-1-one.

In another embodiment the compound of the formula I is 2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide.

In another embodiment the compound of the formula I is N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide.

In another embodiment compounds of the formula I are encompassed selected from the following list:
6-(Methylsulfinylmethyl)-3-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]-7H-pyrrolo[3,4-b]pyridin-5-one,
6-(methylsulfonylmethyl)-3-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]-7H-pyrrolo[3,4-b]pyridin-5-one,
6-((S)-methanesulfinylmethyl)-3-{(R)-2-oxo-3-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yloxy]-pyrrolidin-1-yl}-6,7-dihydro-pyrrolo[3,4-b]pyridin-5-one and
6-((R)-methanesulfinylmethyl)-3-{(R)-2-oxo-3-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yloxy]-pyrrolidin-1-yl}-6,7-dihydro-pyrrolo[3,4-b]pyridin-5-one.

In another embodiment the compound of the formula I is 6-(methylsulfonylmethyl)-3-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]-7H-pyrrolo[3,4-b]pyridin-5-one.

Structural elements such as groups, substituents, hetero ring members, numbers or other features, for example alkyl groups, groups like R5, R5', R7, R7' etc., which can occur several times in the compounds of the formula I, can all independently of one another have at each occurrence any of the indicated meanings and can in each case be identical to or different from one another. For example, the alkyl groups in a dialkylamino group can be identical or different.

Herein, the terms "including" and "comprising" are used in their open, non-limiting sense. As used herein, the terms "(C_1-C_6)" and so forth refer to moieties having 1 to 6 carbon atoms and so forth, respectively. Within composed terms like "hydroxy-(C_0-C_4)-alkyl" the option "(C_0)-alkyl refers to a bond (i.e. in this case a directly bound hydroxy group), or in case of an unsubstituted "(C_0)-alkyl" it refers to a hydrogen.

The term "alkyl", as used herein, refers to saturated, monovalent hydrocarbon radicals. The term "alkenyl", as used herein, refers to monovalent hydrocarbon radicals, which

contain at least one carbon-carbon double bond, wherein each double bond can have E- or Z-configuration. The term “alkynyl”, as used herein, refers to monovalent hydrocarbon radicals, which contain at least one carbon-carbon triple bond. The alkyl, alkenyl and alkynyl groups can be linear, i.e. straight-chain, or branched. This also applies when they are part of other groups, for example alkyloxy groups (= alkoxy groups, O-alkyl groups), alkyloxycarbonyl groups or alkyl-substituted amino groups, or when they are substituted. Depending on the respective definition, the number of carbon atoms in an alkyl group can be 1, 2, 3, 4, 5 or 6, or 1, 2, 3, or 4. Examples of alkyl are methyl, ethyl, propyl including n-propyl and isopropyl, butyl including n-butyl, sec-butyl, isobutyl and tert-butyl, pentyl including n-pentyl, 1-methylbutyl, isopentyl, neopentyl and tert-pentyl, hexyl including n-hexyl, 3,3-dimethylbutyl and isohexyl. Double bonds and triple bonds in alkenyl groups and alkynyl groups respectively can be present in any positions. Examples of alkenyl and alkynyl are ethenyl, prop-1-enyl, prop-2-enyl (= allyl), but-2-enyl, 2-methylprop-2-enyl, 3-methylbut-2-enyl, hex-3-enyl, hex-4-enyl, prop-2-ynyl (= propargyl), but-2-ynyl, but-3-ynyl, hex-4-ynyl or hex-5-ynyl. Substituted alkyl groups, alkenyl groups and alkynyl groups can be substituted in any positions, provided that the respective compound is sufficiently stable and is suitable for the desired purpose such as use as a drug substance. The prerequisite that a specific group and a compound of the formula I are sufficiently stable and suitable for the desired purpose such as use as a drug substance, applies in general with respect to the definitions of all groups in the compounds of the formula I.

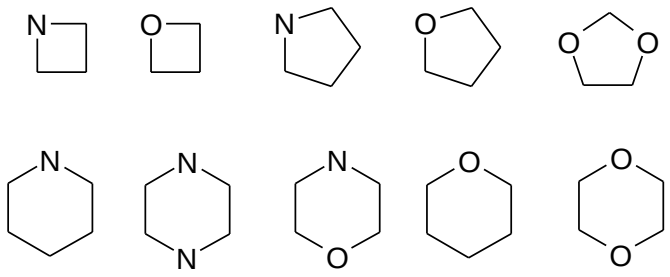
Independently of one another and independently of any other substituents, alkyl groups, divalent alkyl groups, alkenyl groups, alkynyl groups, cycloalkyl groups and heterocycloalkyl groups are optionally substituted by one or more fluorine substituents which can be located in any positions, i.e., the said groups can be unsubstituted by fluorine substituents or substituted by fluorine substituents, for example by 1, 2 or 3, by 1 or 2, or by 1 fluorine substituents. Examples of fluorine-substituted said groups are trifluoromethyl, difluoromethyl and fluoromethyl.

The term “alkanediyl” or “alkylene”, as used herein, refers to saturated, divalent hydrocarbon radicals. The term “alkenediyl”, as used herein, refers to divalent hydrocarbon radicals, which contain at least one carbon-carbon double bond, wherein each double bond can have E- or Z-configuration. The term “alkynediyl”, as used herein,

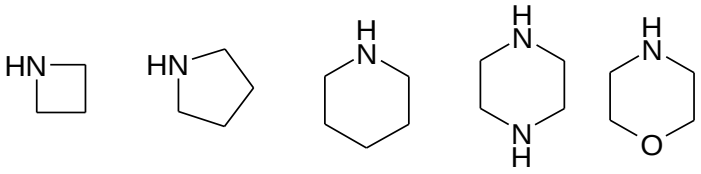
refers to divalent hydrocarbon radicals, which contain at least one carbon-carbon triple bond. As far as applicable, the preceding explanations regarding alkyl, alkenyl and alkynyl groups apply correspondingly to alkanediyl, alkenediyl and alkynediyl groups, which thus can likewise be linear and branched. Examples of divalent alkyl groups are -CH_2- (= methylene), -CH_2-CH_2-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -$CH(CH_3)$-CH_2-, -CH_2-$CH(CH_3)$-, -$C(CH_3)_2$-CH_2- and -CH_2-$C(CH_3)_2$-.

The term “cycloalkyl”, as used herein, unless otherwise indicated, refers to a monovalent radical of a saturated hydrocarbon ring system, which is monocyclic. In a monocyclic cycloalkyl group the number of ring carbon atoms can be for example 3, 4, 5, 6, 7 or 8. In one embodiment of the invention, the number of ring carbon atoms in a cycloalkyl group, independently of the number of ring carbon atoms in any other cycloalkyl group is 3, 4, 5 or 6, in another embodiment 3 or 4, in another embodiment 3, in another embodiment 5 or 6, in another embodiment 5, in another embodiment 6. Examples of cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term “heterocycle”, as used herein, unless otherwise indicated, refers to a cycloalkyl as defined above, in which 1, 2, 3 or 4 carbon atoms are replaced by nitrogen or oxygen atoms, provided that the heterocycloalkyl system is stable and suitable as a subgroup for the desired purpose of the compound of the formula I such as use as a drug substance. Depending on the definition of the respective heterocyclic group, in one embodiment of the invention the number of ring heteroatoms which can be present in a heterocyclic group, independently of the number of ring heteroatoms in any other heterocyclic group, is 1 or 2, in another embodiment 2, in another embodiment 1, wherein the ring heteroatoms can be identical or different. The heterocycloalkyl group can be attached by any ring carbon atom or saturated ring nitrogen atom, with the exception of spiro- or bridgehead atoms.

Exemplary monocyclic heterocycloalkyl groups are derived from, but not limited to, the ring systems azetidine, oxetane, pyrrolidine, tetrahydrofuran, 1,3-dioxolane, piperidine, piperazine, morpholine, tetrahydropyran or 1,4-dioxane:



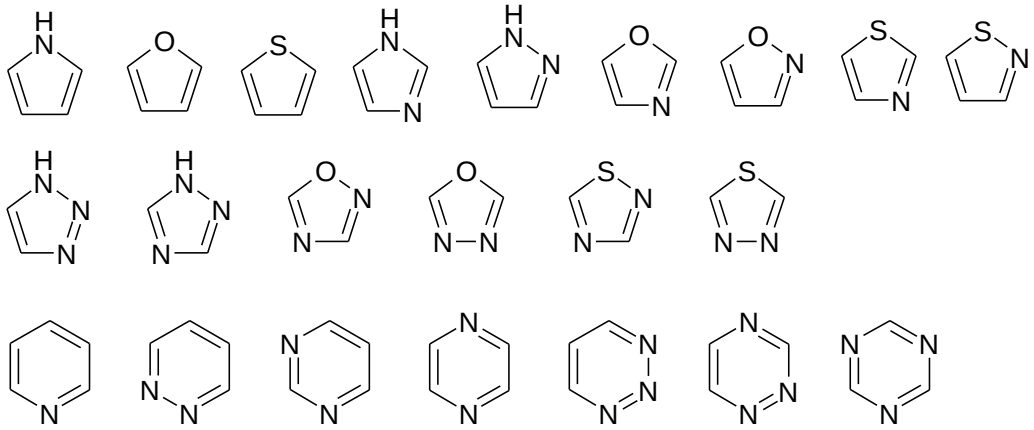
In one embodiment monocyclic heterocycloalkyl groups are derived from azetidine, pyrrolidine, piperidine, piperazine or morpholine:



The term “aryl”, as used herein, refers to a radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl.

The term “heteroaryl” as used herein, refers to a radical derived from a fully unsaturated monocyclic ring system, in which 1, 2 or 3 carbon atoms are replaced by heteroatoms. The ring heteroatoms are generally chosen from N, O and S, wherein N includes ring nitrogen atoms which carry a hydrogen atom or a substituent as well as ring nitrogen atoms which do not carry a hydrogen atom or a substituent. Ring heteroatoms can be located in any position, provided that the heterocyclic system is stable and suitable as a subgroup for the desired purpose of the compound of the formula I such as use as a drug substance. Heteroaryl radicals are derived from 5-membered or 6-membered monocyclic rings.

Exemplary heteroaryl systems are derived from, but not limited to, the following ring systems: pyrrole, furan, thiophene, imidazole, pyrazole, oxazole (= [1,3]oxazole), isoxazole (= [1,2]oxazole), thiazole (= [1,3]thiazole), isothiazole (= [1,2]thiazole), [1,2,3]triazole, [1,2,4]triazole, [1,2,4]oxadiazole, [1,3,4]oxadiazole, [1,2,4]thiadiazole, [1,3,4]thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, [1,2,3]triazine, [1,2,4]triazine or [1,3,5]triazine:



Groups like phenyl and residues of aromatic heterocycles which are optionally substituted by one or more substituents, can be unsubstituted or substituted, for example by 1, 2 or 3, or by 1 or 2, or by 1, identical or different substituents which can be located in any positions. Aromatic nitrogen heterocycles which in the parent ring system carry a hydrogen atom on a ring nitrogen atom in a 5-membered ring, such as a pyrrole or imidazole ring, for example, can be substituted on ring carbon atoms and/or on such ring nitrogen atoms. In one embodiment of the invention, substituents on such ring nitrogen atoms are chosen from (C_1-C_4)-alkyl groups, i.e. such ring nitrogen atoms in aromatic heterocycles carry a hydrogen atom or a (C_1-C_4)-alkyl substituent. When it is stated with respect to ring nitrogen atoms in aromatic heterocycles and any other heterocycles that they can carry a hydrogen atom or a substituent, such ring nitrogen atoms either carry a hydrogen atom or a substituent or they do not carry a hydrogen atom or substituent. Ring nitrogen atoms which carry a hydrogen atom or a substituent, occur in a nitrogen-containing aromatic 5-membered ring as is present in pyrrole or imidazole for example, and in a non-aromatic ring including a saturated ring. Ring nitrogen atoms which do not carry a hydrogen atom or a substituent unless they are present in positively charged form, including any further ring nitrogen atoms in addition to ring nitrogen atoms which carry a hydrogen atom or a substituent, occur in an aromatic ring as is present in thiazole, imidazole or pyridine, for example, and in a non-aromatic ring in which they are part of a double bond, and they occur as ring nitrogen atoms via which a ring is bonded. Suitable ring nitrogen atoms in aromatic heterocycles in the compounds of the formula I, such as the ring nitrogen atom in a pyridine ring, can in general also be present as N-oxide or as quaternary salt, for example as N-(C_1-C_4)-alkyl salt such as N-methyl salt, wherein in one embodiment of the invention the counter

anion in such quaternary salt is a physiologically acceptable anion which is derived from an acid that forms a physiologically acceptable salt.

In monosubstituted phenyl groups, the substituent can be located in the 2-position, the 3-position or the 4-position. In disubstituted phenyl groups, the substituents can be located in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl groups, the substituents can be located in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position or 3,4,5-position.

Ring heteroatoms can be located in any positions, provided that the heterocyclic system is known in the art and is stable and suitable as a subgroup for the desired purpose of the compound of the formula I such as use as a drug substance. In one embodiment of the invention, two ring oxygen atoms cannot be present in adjacent ring positions of any heterocycle, in another embodiment two ring heteroatoms chosen from oxygen and sulfur cannot be present in adjacent ring positions of any heterocycle. Substituents on heterocyclic groups can be located in any positions. For example, in a pyridin-2-yl group substituents can be located in the 3-position and/or 4-position and/or 5-position and/or 6-position, in a pyridin-3-yl group substituent can be located in the 2-position and/or 4-position and/or 5-position and/or 6-position, in a pyridin-4-yl group substituents can be located in the 2-position and/or 3-position and/or 5-position and/or 6-position.

When an oxo group is bonded to a carbon atom, it replaces two hydrogen atoms on a carbon atom of the parent system. Thus, if a CH_2 group in a chain or a ring is substituted by oxo, i.e. by a doubly bonded oxygen atom, it becomes a CO group. Evidently, an oxo group cannot occur as a substituent on a carbon atom in an aromatic ring such as in a phenyl group, for example.

The present invention includes all stereoisomeric forms of the compounds of the formula I and their salts and solvates. With respect to each chiral center, independently of any other chiral center, the compounds of the formula I can be present in S configuration or substantially S configuration, or in R configuration or substantially R configuration, or as a mixture of the S isomer and the R isomer in any ratio. The invention includes all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all

ratios. Thus, compounds according to the invention which can exist as enantiomers can be present in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, and in the form of mixtures of the two enantiomers in all ratios including racemates. In the case of a E/Z isomerism, or cis/trans isomerism, for example on double bonds or rings such as cycloalkyl rings, the invention includes both the E form and Z form, or the cis form and the trans form, as well as mixtures of these forms in all ratios. In one embodiment of the invention, a compound which can occur in two or more stereoisomeric forms is a pure, or substantially pure, individual stereoisomer. The preparation of individual stereoisomers can be carried out, for example, by separation of a mixture of isomers by customary methods, for example by chromatography or crystallization, by the use of stereochemically uniform starting materials in the synthesis, or by stereoselective synthesis. Optionally, a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at the stage of the compound of the formula I or at the stage of a starting material or an intermediate during the synthesis. The present invention also includes all tautomeric forms of the compounds of the formula I and their salts and solvates.

In case the compounds of the formula I contain one or more acidic and/or basic groups, i.e. salt-forming groups, the invention also includes their corresponding physiologically or toxicologically acceptable salts, i.e. non-toxic salts, in particular their pharmaceutically acceptable salts.

The present invention furthermore includes all solvates of compounds of the formula I, for example hydrates or adducts with alcohols such as (C_1-C_4)-alkanols, active metabolites of the compounds of the formula I, and also prodrugs and derivatives of the compounds of the formula I which in vitro may not necessarily exhibit pharmacological activity but which in vivo are converted into pharmacologically active compounds, for example esters or amides of carboxylic acid groups.

The compounds of the present invention can be widely combined with other pharmacologically active compounds, such as all drugs mentioned in the Rote Liste 2014, e.g. all antidiabetics mentioned in the Rote Liste 2014, chapter 12, all weight-reducing agents or appetite suppressants mentioned in the Rote Liste 2014, chapter 06,

all lipid-lowering agents mentioned in the Rote Liste 2014, chapter 58, all antihypertensives mentioned in the Rote Liste 2014 chapter 17, all nephroprotectives mentioned in the Rote Liste, or all diuretics mentioned in the Rote Liste 2014, chapter 36.

The active ingredient combinations can be applied either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present in one pharmaceutical preparation. When administered separately, administration may occur simultaneously or sequentially, in any order. The amount of the compound of the invention and the other pharmaceutically active ingredient(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. The administration of the combination may be concomitantly in: (1) a unitary pharmaceutical composition including all pharmaceutically active ingredients; or (2) separate pharmaceutical compositions each including at least one of the pharmaceutically active ingredients. Alternatively, the combination may be administered separately in a sequential manner wherein one treatment agent is administered first and the other second or vice versa. Such sequential administration may be close in time or remote in time.

Most of the active ingredients mentioned hereinafter are disclosed in the USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2014.

Therapeutic agents which are suitable for combinations include, for example, antidiabetic agents such as:

Insulin and insulin derivatives, for example: insulin glargine (e.g. Lantus®), higher than 100U/mL concentrated insulin glargine, e.g. 270 - 330U/mL of insulin glargine or 300U/mL of insulin glargine (as disclosed in EP 2387989), insulin glulisine (e.g. Apidra®), insulin detemir (e.g. Levemir®), insulin lispro (e.g. Humalog®, Liprolog®), insulin degludec (e.g. DegludecPlus®, IdegLira (NN9068)), insulin aspart and aspart formulations (e.g. NovoLog®), basal insulin and analogues (e.g. LY2605541, LY2963016, NN1436), PEGylated insulin lispro (e.g. LY-275585), long-acting insulins (e.g. NN1436, Insumera (PE0139), AB-101, AB-102, Sensulin LLC), intermediate-acting insulins (e.g. Humulin®N, Novolin®N), fast-acting and short-acting insulins (e.g. Humulin®R, Novolin®R, Linjeta® (VIAject®), PH20 insulin, NN1218, HinsBet®), premixed

insulins, SuliXen®, NN1045, insulin plus Symlin®, PE-0139, ACP-002 hydrogel insulin, and oral, inhalable, transdermal and buccal or sublingual insulins (e.g. Exubera®, Nasulin®, Afrezza®, insulin tregopil, TPM-02 insulin, Capsulin®, Oral-lyn®, Cobalamin® oral insulin, ORMD-0801, Oshadi oral insulin, NN1953, NN1954, NN1956, VIAtab®). Also suitable are those insulin derivatives which are bonded to albumin or another protein by a bifunctional linker.

Glucagon-like-peptide 1 (GLP-1), GLP-1 analogues, and GLP-1 receptor agonists, for example: lixisenatide (e.g. Lyxumia®), exenatide (e.g. exendin-4, rExendin-4, Byetta®, Bydureon®, exenatide NexP), liraglutide (e.g. Victoza®), semaglutide, taspoglutide, albiglutide, dulaglutide, ACP-003, CJC-1134-PC, GSK-2374697, PB-1023, TTP-054, langlenatide (HM-11260C), CM-3, GLP-1 Eligen, AB-201, ORMD-0901, NN9924, NN9926, NN9927, Nodexen, Viador-GLP-1, CVX-096, ZYOG-1, ZYD-1, ZP-3022, CAM-2036, DA-3091, DA-15864, ARI-2651, ARI-2255, exenatide-XTEN (VRS-859), exenatide-XTEN + Glucagon-XTEN (VRS-859 + AMX-808) and polymer-bound GLP-1 and GLP-1 analogues.

Dual GLP-1/GIP agonists (e.g. RG-7697 (MAR-701), MAR-709, BHM081, BHM089, BHM098).
Dual GLP-1/glucagon receptor agonists (e.g. BHM-034, OAP-189 (PF-05212389, TKS-1225), TT-401/402, ZP2929, LAPS-HMOXM25, MOD-6030).
Dual GLP-1/gastrin agonists (e.g. ZP-3022).

Other suitable combination partners are:

Further gastrointestinal peptides such as peptide YY 3-36 (PYY3-36) or analogues thereof and pancreatic polypeptide (PP) or analogues thereof.

Glucagon receptor agonists or antagonists, glucose-dependent insulinotropic polypeptide (GIP) receptor agonists or antagonists, ghrelin antagonists or inverse agonists, xenin and analogues thereof.

Dipeptidyl peptidase-IV (DPP-4) inhibitors, for example: alogliptin (e.g. Nesina®, Kazano®), linagliptin (e.g. Ondero®, Trajenta®, Tradjenta®, Trayenta®), saxagliptin (e.g.

Onglyza®, Komboglyze XR®), sitagliptin (e.g. Januvia®, Xelevia®, Tesavel®, Janumet®, Velmetia®, Juvisync®, Janumet XR®), anagliptin, teneligliptin (e.g. Tenelia®), trelagliptin, vildagliptin (e.g. Galvus®, Galvumet®), gemigliptin, omarigliptin, evogliptin, dutogliptin, DA-1229, MK-3102, KM-223, KRP-104, PBL-1427, Pinoxacin hydrochloride, and Ari-2243.

Sodium-dependent glucose transporter 2 (SGLT-2) inhibitors, for example: canagliflozin, dapagliflozin, remogliflozin, remogliflozin etabonate, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, ertugliflozin, EGT-0001442, LIK-066, SBM-TFC-039, and KGA-3235 (DSP-3235).
Dual inhibitors of SGLT-2 and SGLT-1 (e.g. LX-4211, LIK066).
SGLT-1 inhibitors (e.g. LX-2761, KGA-3235) or SGLT-1 inhibitors in combination with anti-obesity drugs such as ileal bile acid transfer (IBAT) inhibitors (e.g. GSK-1614235 + GSK-2330672).

Biguanides (e.g. metformin, buformin, phenformin).

Thiazolidinediones (e.g. pioglitazone, rosiglitazone), glitazone analogues (e.g. lobeglitazone).

Peroxisome proliferator-activated receptors (PPAR-)(alpha, gamma or alpha/gamma) agonists or modulators (e.g. saroglitazar (e.g. Lipaglyn®), GFT-505), or PPAR gamma partial agonists (e.g. Int-131).

Sulfonylureas (e.g. tolbutamide, glibenclamide, glimepiride, Amaryl®, glipizide) and meglitinides (e.g. nateglinide, repaglinide, mitiglinide).

Alpha-glucosidase inhibitors (e.g. acarbose, miglitol, voglibose).

Amylin and amylin analogues (e.g. pramlintide, Symlin®).

G-protein coupled receptor 119 (GPR119) agonists (e.g. GSK-1292263, PSN-821, MBX-2982, APD-597, ARRY-981, ZYG-19, DS-8500, HM-47000, YH-Chem1).

GPR40 agonists (e.g. TUG-424, P-1736, P-11187, JTT-851, GW9508, CNX-011-67, AM-1638, AM-5262).

GPR120 agonists and GPR142 agonists.

Systemic or low-absorbable TGR5 (GPBAR1 = G-protein-coupled bile acid receptor 1) agonists (e.g. INT-777, XL-475, SB756050).

Other suitable combination partners are:

Diabetes immunotherapeutics, for example: oral C-C chemokine receptor type 2 (CCR-2) antagonists (e.g. CCX-140, JNJ-41443532), interleukin 1 beta (IL-1ß) antagonists (e.g. AC-201), or oral monoclonal antibodies (MoA) (e.g. methalozamide, VVP808, PAZ-320, P-1736, PF-05175157, PF-04937319).

Anti-inflammatory agents for the treatment of the metabolic syndrome and diabetes, for example: nuclear factor kappa B inhibitors (e.g. Triolex®).

Adenosine monophosphate-activated protein kinase (AMPK) stimulants, for example: Imeglimin (PXL-008), Debio-0930 (MT-63-78), R-118.

Inhibitors of 11-beta-hydroxysteroid dehydrogenase 1 (11-beta-HSD-1) (e.g. LY2523199, BMS770767, RG-4929, BMS816336, AZD-8329, HSD-016, BI-135585).

Activators of glucokinase (e.g. PF-04991532, TTP-399 (GK1-399), GKM-001 (ADV-1002401), ARRY-403 (AMG-151), TAK-329, TMG-123, ZYGK1).

Inhibitors of diacylglycerol O-acyltransferase (DGAT) (e.g. pradigastat (LCQ-908)), inhibitors of protein tyrosine phosphatase 1 (e.g. trodusquemine), inhibitors of glucose-6-phosphatase, inhibitors of fructose-1,6-bisphosphatase, inhibitors of glycogen phosphorylase, inhibitors of phosphoenol pyruvate carboxykinase, inhibitors of glycogen synthase kinase, inhibitors of pyruvate dehydrogenase kinase.

Modulators of glucose transporter-4, somatostatin receptor 3 agonists (e.g. MK-4256).

One or more lipid lowering agents are also suitable as combination partners, for example: 3-hydroxy-3-methylglutaryl-coenzym-A-reductase (HMG-CoA-reductase) inhibitors such as simvastatin (e.g. Zocor®, Inegy®, Simcor®), atorvastatin (e.g. Sortis®, Caduet®), rosuvastatin (e.g. Crestor®), pravastatin (e.g. Lipostat®, Selipran®), fluvastatin (e.g. Lescol®), pitavastatin (e.g. Livazo®, Livalo®), lovastatin (e.g. Mevacor®, Advicor®), mevastatin (e.g. Compactin®), rivastatin, cerivastatin (Lipobay®), fibrates such as bezafibrate (e.g. Cedur® retard), ciprofibrate (e.g. Hyperlipen®), fenofibrate (e.g. Antara®, Lipofen®, Lipanthyl®), gemfibrozil (e.g. Lopid®, Gevilon®), etofibrate, simfibrate, ronifibrate, clinofibrate, clofibride, nicotinic acid and derivatives thereof (e.g. niacin, including slow release formulations of niacin), nicotinic acid receptor 1 agonists (e.g. GSK-256073), PPAR-delta agonists, acetyl-CoA−acetyltransferase (ACAT) inhibitors (e.g. avasimibe), cholesterol absorption inhibitors (e.g. ezetimibe, Ezetrol®, Zetia®, Liptruzet®, Vytorin®, S-556971), bile acid-binding substances (e.g. cholestyramine, colesevelam), ileal bile acid transport (IBAT) inhibitors (e.g. GSK-2330672, LUM-002), microsomal triglyceride transfer protein (MTP) inhibitors (e.g. lomitapide (AEGR-733), SLx-4090, granotapide), modulators of proprotein convertase subtilisin/kexin type 9 (PCSK9) (e.g. alirocumab (REGN727/SAR236553), AMG-145, LGT-209, PF-04950615, MPSK3169A, LY3015014, ALD-306, ALN-PCS, BMS-962476, SPC5001, ISIS-394814, 1B20, LGT-210, 1D05, BMS-PCSK9Rx-2, SX-PCK9, RG7652), LDL receptor up-regulators, for example liver selective thyroid hormone receptor beta agonists (e.g. eprotirome (KB-2115), MB07811, sobetirome (QRX-431), VIA-3196, ZYT1), HDL-raising compounds such as: cholesteryl ester transfer protein (CETP) inhibitors (e.g. anacetrapib (MK0859), dalcetrapib, evacetrapib, JTT-302, DRL-17822, TA-8995, R-1658, LY-2484595, DS-1442), or dual CETP/PCSK9 inhibitors (e.g. K-312), ATP-binding cassette (ABC1) regulators, lipid metabolism modulators (e.g. BMS-823778, TAP-301, DRL-21994, DRL-21995), phospholipase A2 (PLA2) inhibitors (e.g. darapladib, Tyrisa®, varespladib, rilapladib), ApoA-I enhancers (e.g. RVX-208, CER-001, MDCO-216, CSL-112), cholesterol synthesis inhibitors (e.g. ETC-1002), lipid metabolism modulators (e.g. BMS-823778, TAP-301, DRL-21994, DRL-21995) and omega-3 fatty acids and derivatives thereof (e.g. icosapent ethyl (AMR101), Epanova®, AKR-063, NKPL-66, PRC-4016, CAT-2003).

Other suitable combination partners are one or more active substances for the treatment of obesity, such as for example:
Bromocriptine (e.g. Cycloset®, Parlodel®), phentermine and phentermine formulations or combinations (e.g. Adipex-P, Ionamin, Qsymia®), benzphetamine (e.g. Didrex®), diethylpropion (e.g. Tenuate®), phendimetrazin (e.g. Adipost®, Bontril®), bupropion and combinations (e.g. Zyban®, Wellbutrin XL®, Contrave®, Empatic®), sibutramine (e.g. Reductil®, Meridia®), topiramat (e.g. Topamax®), zonisamid (e.g. Zonegran®), tesofensine, opioid antagonists such as naltrexone (e.g. Naltrexin®, naltrexone + bupropion), cannabinoid receptor 1 (CB1) antagonists (e.g. TM-38837), melanin-concentrating hormone (MCH-1) antagonists (e.g. BMS-830216, ALB-127158(a)), MC4 receptor agonists and partial agonists (e.g. AZD-2820, RM-493), neuropeptide Y5 (NPY5) or NPY2 antagonists (e.g. velneperit, S-234462), NPY4 agonists (e.g. PP-1420), beta-3-adrenergic receptor agonists, leptin or leptin mimetics, agonists of the 5-hydroxytryptamine 2c (5HT2c) receptor (e.g. lorcaserin, Belviq®), pramlintide/metreleptin, lipase inhibitors such as cetilistat (e.g. Cametor®), orlistat (e.g. Xenical®, Calobalin®), angiogenesis inhibitors (e.g. ALS-L1023), betahistidin and histamine H3 antagonists (e.g. HPP-404), AgRP (agouti related protein) inhibitors (e.g. TTP-435), serotonin re-uptake inhibitors such as fluoxetine (e.g. Fluctine®), duloxetine (e.g. Cymbalta®), dual or triple monoamine uptake inhibitors (dopamine, norepinephrine and serotonin re-uptake) such as sertraline (e.g. Zoloft®), tesofensine, methionine aminopeptidase 2 (MetAP2) inhibitors (e.g. beloranib), and antisense oligonucleotides against production of fibroblast growth factor receptor 4 (FGFR4) (e.g. ISIS-FGFR4Rx) or prohibitin targeting peptide-1 (e.g. Adipotide®).

Moreover, combinations with drugs for influencing high blood pressure, chronic heart failure or atherosclerosis, for example: nitric oxide donors, AT1 antagonists or angiotensin II (AT2) receptor antagonists such as telmisartan (e.g. Kinzal®, Micardis®), candesartan (e.g. Atacand®, Blopress®), valsartan (e.g. Diovan®, Co-Diovan®), losartan (e.g. Cosaar®), eprosartan (e.g. Teveten®), irbesartan (e.g. Aprovel®, CoAprovel®), olmesartan (e.g. Votum®, Olmetec®), tasosartan, azilsartan (e.g. Edarbi®), dual angiotensin receptor blockers (dual ARBs), angiotensin converting enzyme (ACE) inhibitors, ACE-2 activators, renin inhibitors, prorenin inhibitors, endothelin converting enzyme (ECE) inhibitors, endothelin receptor (ET1/ETA) blockers, endothelin antagonists, diuretics, aldosterone antagonists, aldosterone synthase inhibitors, alpha-

blockers, antagonists of the alpha-2 adrenergic receptor, beta-blockers, mixed alpha-/beta-blockers, calcium antagonists, calcium channel blockers (CCBs), nasal formulations of the calcium channel blocker diltiazem (e.g. CP-404), dual mineralocorticoid/CCBs, centrally acting antihypertensives, inhibitors of neutral endopeptidase, aminopeptidase-A inhibitors, vasopeptide inhibitors, dual vasopeptide inhibitors such as neprilysin-ACE inhibitors or neprilysin-ECE inhibitors, dual-acting AT receptor-neprilysin inhibitors, dual AT1/ETA antagonists, advanced glycation end-product (AGE) breakers, recombinant renalase, blood pressure vaccines such as anti-RAAS (renin-angiotensin-aldosteron-system) vaccines, AT1- or AT2-vaccines, drugs based on hypertension pharmacogenomics such as modulators of genetic polymorphisms with antihypertensive response, thrombocyte aggregation inhibitors, and others or combinations thereof are suitable.

In another aspect, this invention relates to the use of a compound according to the invention or a physiologically acceptable salt thereof combined with at least one of the active substances described above as a combination partner, for preparing a medicament which is suitable for the treatment or prevention of diseases or conditions which can be affected by binding to the GPR119 and modulating its activity. This is preferably a disease in the context of the metabolic syndrome, particularly one of the diseases or conditions listed above, most particularly diabetes or obesity or complications thereof.

The use of the compounds according to the invention, or a physiologically acceptable salt thereof, in combination with one or more active substances may take place simultaneously, separately or sequentially.

The use of the compound according to the invention, or a physiologically acceptable salt thereof, in combination with another active substance may take place simultaneously or at staggered times, but particularly within a short space of time. If they are administered simultaneously, the two active substances are given to the patient together; if they are used at staggered times, the two active substances are given to the patient within a period of less than or equal to 12 hours, but particularly less than or equal to 6 hours.

Consequently, in another aspect, this invention relates to a medicament which comprises compounds according to the invention or a physiologically acceptable salt of such a compound and at least one of the active substances described above as combination partners, optionally together with one or more inert carriers and/or diluents.

The compounds according to the invention, or physiologically acceptable salt or solvate thereof, and the additional active substance to be combined therewith may both be present together in one formulation, for example a tablet or capsule, or separately in two identical or different formulations, for example as so-called kit-of-parts.

Compounds according to the invention can be administered to animals, in particular to mammals including humans, as pharmaceuticals by themselves, in mixtures with one another, or in the form of pharmaceutical compositions. The administration can be carried out orally, for example in the form of tablets, film-coated tablets, sugar-coated tablets, granules, hard and soft gelatin capsules, solutions including aqueous, alcoholic and oily solutions, juices, drops, syrups, emulsions or suspensions, rectally, for example in the form of suppositories, or parenterally, for example in the form of solutions for subcutaneous, intramuscular or intravenous injection or infusion, in particular aqueous solutions.

Suitable pharmaceutical compositions for oral administration may be in the form of separate units, for example capsules, cachets, lozenges or tablets, each of which contains a defined amount of the compound of formula I; as powders or granules; as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact. The compositions are generally produced by uniform and homogeneous mixing of the active ingredient with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or molding a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets can be produced by tableting the compound in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one (or more)

surfactant(s)/dispersant(s) in a suitable machine. Molded tablets can be produced by molding the compound, which is in powder form and has been moistened with an inert liquid diluent, in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration comprise lozenges which contain a compound of formula I with a flavoring, typically sucrose, and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

Coated formulations and coated slow-release formulations, especially acid- and gastric juice-resistant formulations, also belong within the framework of the invention. Suitable coatings resistant to gastric juice comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Pharmaceutical compositions suitable for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing a compound of formula I with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

Pharmaceutical compositions suitable for parenteral administration comprise preferably sterile aqueous preparations of a compound of formula I, which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions of the invention generally contain 0.1 to 5% by weight of the active compound.

Other suitable administration forms are, for example, percutaneous or topical administration, for example in the form of ointments, creams, tinctures, sprays, powders or transdermal therapeutic systems, or inhalative administration, for example in the form of nasal sprays or aerosol mixtures, or forms such as microcapsules, implants or rods.

Pharmaceutical compositions suitable for topical use on the skin are preferably in the form of ointment, cream, lotion, paste, spray, aerosol or oil. The carriers used may be petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active ingredient is generally present in a concentration of 0.1 to 15% by weight of the composition, for example 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal uses may be in the form of single patches which are suitable for long-term close contact with the patient's epidermis. Such patches suitably contain the active ingredient in an aqueous solution which is buffered where appropriate, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active ingredient concentration is about 1% to 35%, preferably about 3% to 15%. A particular option is for the active ingredient to be released by electrotransport or iontophoresis as described, for example, in Pharmaceutical Research, 2(6): 318 (1986).

Compounds according to the invention can additionally be used in systems for local drug delivery, for example in coated stents for preventing or reducing in-stent restenosis or by applying them locally by means of a catheter. The appropriate administration form depends, among others, on the disease to be treated and on its severity.

The dosing of compounds according to the invention to achieve the desirable therapeutic effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.3 mg to 100 mg (typically from 3 mg to 50 mg) per day and per kilogram of body weight, for example 3-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.3 mg to 1.0 mg/kg, which can suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, 0.1 ng to 100 mg, typically 1 ng to 100 mg, per milliliter. Single doses may contain, for example, 1 mg to 10 g of the active ingredient. Thus, ampoules for injections may contain, for example, from 1 mg to 100 mg, and orally administrable single-dose formulations, for example tablets or capsules, may contain, for example, from 1.0 to 1000 mg, typically from 10 to 600 mg. For prevention and/or treatment of the abovementioned conditions, the compounds of the formula I themselves may be used as the compound, but they are

preferably present with a compatible carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain 0.05% to 95% by weight of the active ingredient. Other pharmaceutically active substances may likewise be present, including other compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Another subject of the present invention are processes for the preparation of the compounds of the formula I and their salts and solvates, by which the compounds are obtainable and which are outlined in the following.

Abbreviations

Abbreviations within this document have their common meanings unless defined otherwise herein. An exemplary list of abbreviations used, can be found below.

Abbreviation	**Meaning**
Ac	acetyl
amu	atomic mass unit
atm	atmosphere (pressure unit, 101325 Pa)
Boc_2O	di-tert-butyl-dicarbonate
BSA	bovine serum albumin
cAMP	cyclic adenosine monophosphate
cat.	catalyst / catalyzed
CDI	carbonyl diimidazole
dba	dibenzylideneacetone
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIPEA	diisopropyl-ethyl-amine
DMAP	4-dimethylaminopyridine
DMEM	Dulbecco's modified eagle medium
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppf	diphenylphosphinoferrocene
EA	ethyl acetate
EC_{50}	concentration causing 50% of the maximal response
EDCI	ethyl dimethylaminopropyl carbodiimide

Abbreviation	Meaning
ESI	electrospray ionization
FA	formic acid
FCS	fetal calf serum
GPR119	G-protein coupled receptor 119
h	hour(s)
Hal	halogen (atom)
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*‘,*N*’-tetramethyl-uronium hexafluorophosphate
HBSS	Hank's buffered salt solution
HEK 293	human embryonic kidney 293
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoric acid triamide
HOBt	1-hydroxy-benzotriazole
HPLC	high pressure liquid chromatography
HTRF	homogenous time-resolved fluorescence
IBMX	1-methyl-3-(2-methylpropyl)-7H-purine-2,6-dione
LCMS	liquid chromatography coupled mass spectroscopy
LG	leaving group
MeCN	methyl cyanide (acetonitrile)
min	minute(s)
MS	mass spectroscopy
MTBE	methyl tert.-butyl ether
NMP	*N*-methyl pyrrolidin-2-one
NMR	nuclear magnetic resonance (spectrum)
PBS	phosphate buffered saline
PE	petroleum ether
PMBCl	para-methoxybenzyl chloride
R_t	retention time
RT	room temperature
SGC	silica gel chromatography
SiO_2	silica gel (for chromatography)
TBAF	tetra-n-butylammonium fluoride
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TM	transition metal
TMS	tetramethylsilane
$TMSCHN_2$	trimethylsilyldiazomethane
Ts	para-tolylsulfonyl
UV	ultraviolet (spectrum)

Synthetic Methods

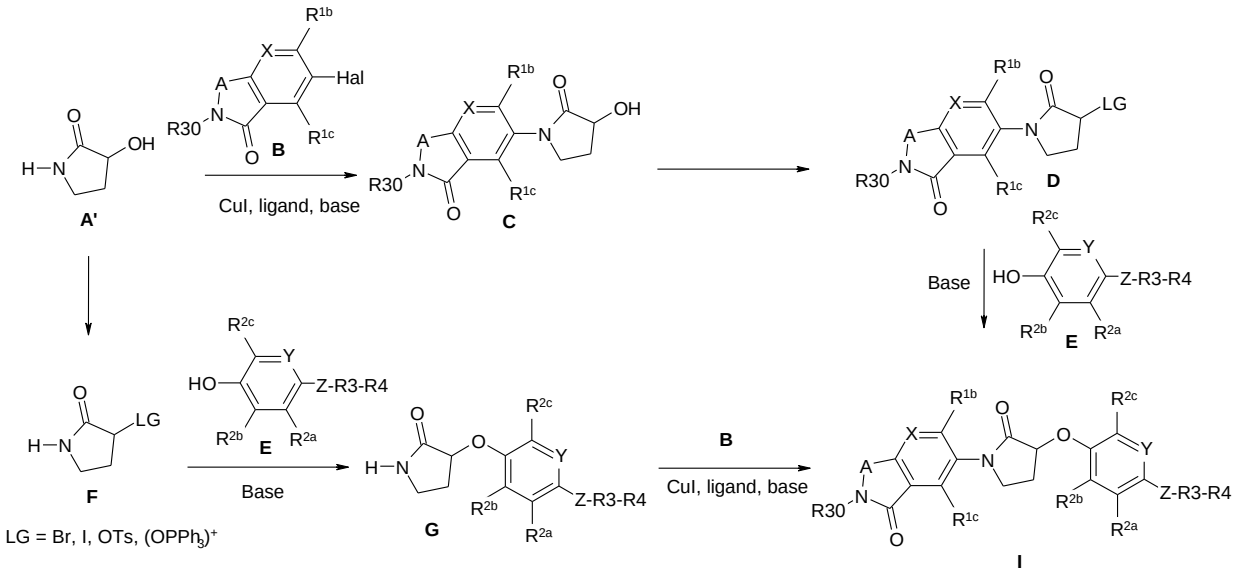
Variables in the formulae of the schemes represent moieties as defined above unless other meanings are given.

Detailed descriptions of the Typical Procedures to which reference is made in this section can be found in the Examples section.

Compounds of the invention having the formula I may be prepared by combining known synthetic procedures. In a first method 3-hydroxy-pyrrolidin-2-one (A') (commercially available as racemic mixture and in both enantiomeric forms) is coupled with bicyclic aryl halides B (typically Hal is Br or I) to provide intermediates C. An example for suitable coupling conditions (CuI, *N*,*N*'-dimethyl-ethane-1,2-diamine, cesium carbonate) can be found in the Typical Procedure 1. Conversion of the hydroxy group in C to a suitable leaving group (LG is for example Br, I, OTs or $OPPh_3^+$) can be accomplished with various well known reagents (e.g. PPh_3/I_2, PPh_3/CBr_4, PPh_3/DIAD or $TsCl/NEt_3$) providing the intermediates D, which may be isolated or may be reacted without isolation with hydroxy-aryl building blocks of type E using an appropriate base (e.g. Na_2CO_3, K_2CO_3, Cs_2CO_3 or NaH). For example the conditions in the Typical Procedure 3 may be applied to couple intermediates C and E to provide compounds I.

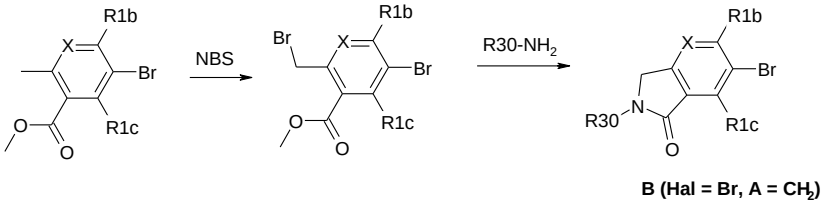
A second method of synthesizing compounds I starts with a pyrrolidin-2-one substituted with a leaving group (LG) in 3-position (structures F), which may be prepared by reacting A' with the reagents mentioned above. Other procedures for making structures F are known (e.g. base-promoted cyclization of 2,4-dibromo-butyramide). Intermediates F may be isolated or generated in situ to react with hydroxy-aryls E (typically in the presence of a base as described above) to provide intermediates G. As a final step, for example copper-catalyzed coupling with aryl halides B provides the desired compounds I (Scheme 1).

Scheme 1.



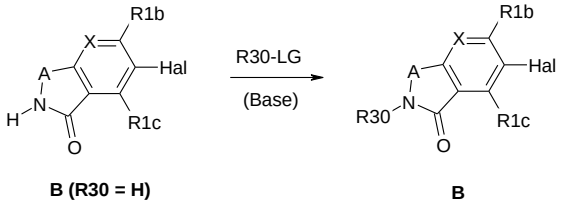
Isoindolinones B (Hal = Br, A = CH_2) may be prepared by reaction of 5-bromo-2-bromomethyl-benzoic acid methyl esters (X = C-R1a) or 5-bromo-2-bromomethyl-nicotinic acid methyl esters (X = N) with amines R30-NH_2 (Scheme 2a).

Scheme 2a.



Alkylation of N-unsubstituted isoindolinones B (R30 = H), for example with R30-LG under the exemplary conditions given in Typical Procedure 2, gives access to further intermediates B as illustrated in Scheme 2b.

Scheme 2b.



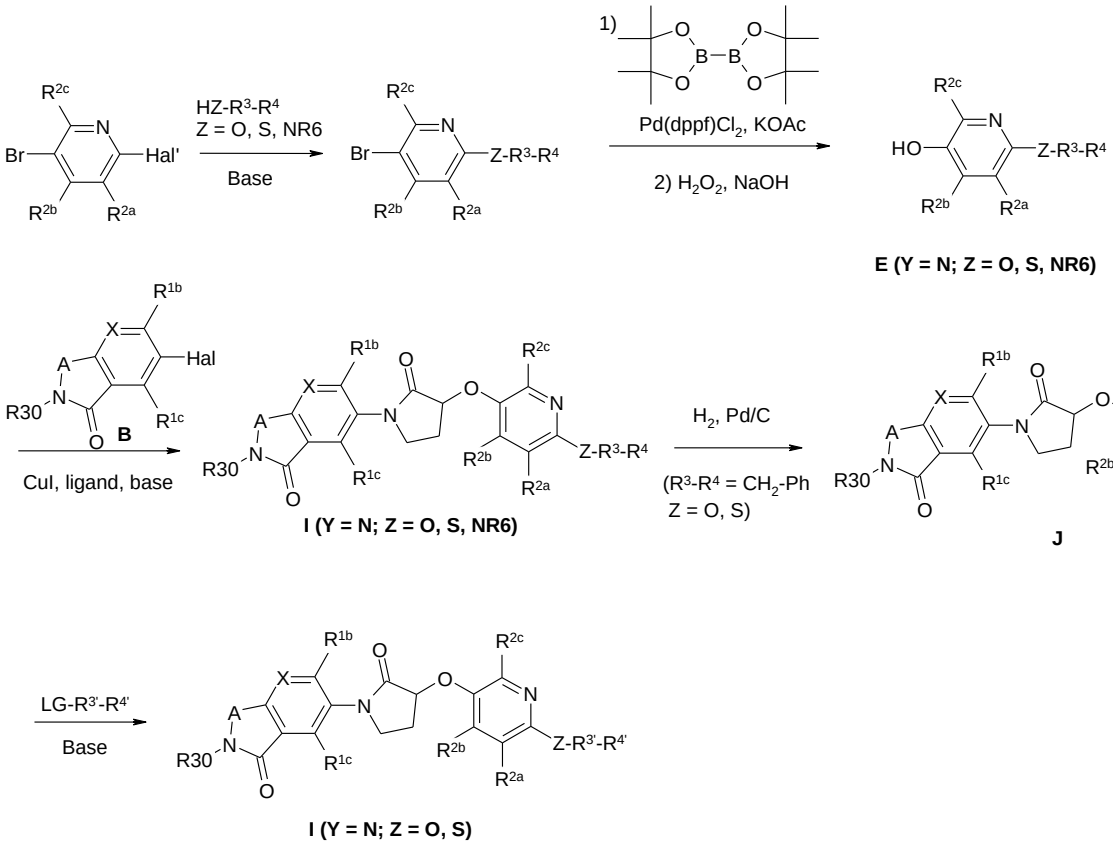
Certain compounds I (Y = N; Z = O, S, NR6) may be prepared by coupling aryl halides B with hydroxy-pyridines E (Y = N; Z = O, S, NR6). Said hydroxy-pyridines E may be

prepared by displacement of a halide (F, Cl, Br or I) in the 2-position of 5-bromo-2-halo-pyridines, which are substituted with R^{2a}, R^{2b} and R^{2c}, using nucleophiles of the type $HZ\text{-}R^3\text{-}R^4$ (Z = O, S, NR6) followed by conversion of the 5-bromo-substituent to a hydroxy group (e.g. by oxidation of a boronate group introduced by palladium catalyzed coupling with bis-pinacolato-diboron). See Typical Procedure 6 for exemplary conditions for the nucleophilic displacement reaction, Typical Procedures 5 for examples of boronate-oxidation conditions, Typical Procedure 4 for an example of conditions to install a boronate group and Scheme 3 for illustration of the overall method.

A benzyl group ($R^3\text{-}R^4 = CH_2\text{-}Ph$) in compounds I (Y = N, Z = O, S) may be cleaved for example by hydrogenolysis to provide intermediates J, which may be alkylated by $LG\text{-}R^{3'}\text{-}R^{4'}$, $R^{3'}$ and $R^{4'}$ being defined like R^3 and R^4 respectively, to yield compounds I (Y = N; Z = O, S).

For example, the structure J may be a 2-hydroxy-pyridine (Z = O), which may be alkylated under Mitsunobu-conditions (PPh_3/DIAD; see for example Typical Procedure 3) starting with alcohols $HO\text{-}R^{3'}\text{-}R^{4'}$. Triphenylphosphine may be introduced into the reaction as polymer. DIAD may be replaced by other azodicarboxylates (e.g. DEAD). Alternatively, structures J may be reacted with alkyl halides as exemplified in Typical Procedure 10.

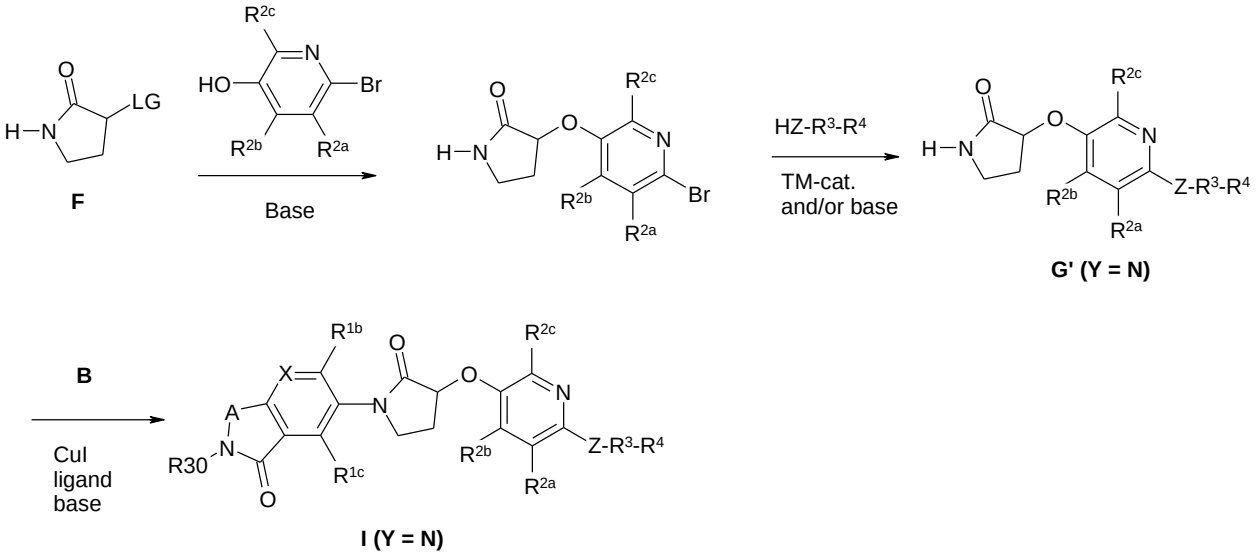
Scheme 3.



Certain other compounds of the invention may be prepared by reaction of hydroxy-pyrrolidinones C with 6-bromo-pyridin-3-ols under Mitsunobu-conditions and subsequent transition metal catalyzed replacement of the Br-atom by Z-R^3-R^4.

Variation of the order of the steps in the synthetic sequence provides further methods to prepare compounds I. For example intermediates F may be reacted with 6-bromo-pyridin-3-ols and subsequently the bromo-substituent may be exchanged for Z-R^3-R^4 to provide intermediates G (Y = N). In a last step, coupling with aryl halides B again provides compounds I (Y = N) as illustrated in Scheme 4.

Scheme 4.



Other derivatives of formula I (e.g. with R30 = CH_2COOH) can be obtained by cleaving the ester functionality in structures I (R30 = $CH_2COO(C_1\text{-}C_6)$-alkyl) for example using the conditions described in Typical Procedures 7a, 7b and 7c. Still other compounds I (R30 = $CH_2CONR14R15$) are provided by the reaction of said acids with amines of the structure HNR14R15 using for example EDCI as coupling reagent (see Typical Procedure 9 for exemplary conditions).

Analytical Methods

Examples were characterized by standard analytical methods. This includes at least two methods (e.g. selected from HPLC, MS, ^{1}H-NMR). In particular, MS and HPLC data were obtained by combined analytical HPLC/MS (LCMS). For example the following LCMS methods were used.

Method A

Column: Waters UPLC BEH C18 2.1*50 mm, 1.7 µm; mobile phase: (H_2O + 0.05% FA) : (MeCN + 0.035% FA) 98:2 (0 min) to 5:95 (2 min) to 5:95 (2.6 min) to 95:5 (2.7 min) to 95:5 (3 min); flow rate: 0.9 mL/min; column temperature: 55°C; ionization method: ES^+; UV wavelength: 220 nm.

Method B

Column: Waters XBridge C18 4.6*50 mm, 2.5 µm; mobile phase: (H_2O + 0.1% FA) : (MeCN + 0.1% FA) 97:3 (0 min) to 40:60 (3.5 min) to 2:98 (4 min) to 2:98 (5 min) to

97:3 (5.2 min) to 97:3 (6.5 min); flow rate: 0.9 mL/min; column temperature: 55°C; ionization method: ES^+; UV wavelength: 220 nm.

Method C

Column: Waters UPLC BEH C18 2.1*50 mm, 1.7 µm; mobile phase: (H_2O + 0.05% FA) : (MeCN + 0.035% FA) 95:5 (0 min) to 5:95 (2 min) to 5:95 (2.6 min) to 95:5 (2.7 min) to 95:5 (3 min); flow rate: 0.9 mL/min; column temperature: 55°C; ionization method: ES^+; UV wavelength: 220 nm.

Method D

Column: Waters UPLC BEH C18 2.1*50 mm, 1.7 µm; mobile phase: (H_2O + 0.1% FA) : MeCN + 0.08% FA) 95:5 (0 min) to 5:95 (1.1 min) to 5:95 (1.7 min) to 95:5 (1.8 min) to 95:5 (2 min); flow rate: 0.9 mL/min; column temperature: 55°C; ionization method: ES^+; UV wavelength: 220 nm.

Method E

Column: Waters UPLC BEH C18 2.1*50 mm; 1.7 µm; mobile phase: (H_2O + 0.05% FA) : (MeCN + 0.035% FA) 95:5 (0 min) to 5:95 (1.1 min) to 5:95 (1.7 min) to 95:5 (1.8 min) to 95:5 (2 min); flow rate: 0.9 mL/min; column temperature: 55°C; ionization method: ES^+; UV wavelength: 220 nm.

In general, HPLC data is represented by the retention time (R_t; in min); MS data is given as the observed mass number (m/z) of the ion $[M+H]^+$ (if present) and ^{1}H-NMR data is reported by lists of chemical shifts δ (in ppm vs. TMS) of the observed signals (the number of hydrogen atoms was determined using the area under the respective signal; signal multiplicity is characterized as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplets, q = quartet, m = multiplet, br = broad; coupling constants *J* are given in Hertz (Hz)). Deuterated solvents were used for NMR spectroscopy.

Examples

The following examples are particular embodiments of the invention. They partially illustrate the scope of the invention without limiting it.

Abbreviations and chemical symbols have their usual and customary meanings unless otherwise indicated.

The examples were prepared, isolated and analyzed by the procedures and methods given. Alternatively they may be prepared by the general synthetic methods detailed

above. Further variations of the synthetic procedures may be proposed by a person skilled in the art.

When example compounds containing a basic group were purified by preparative HPLC on reversed phase column material and, as customary, the eluent was a gradient mixture of water and acetonitrile containing trifluoroacetic acid (TFA), they were obtained in part in the form of their addition salt with TFA, depending on the details of the workup such as evaporation or lyophilization conditions. In the names of the example compounds and their structural formulae any such TFA present is not specified.

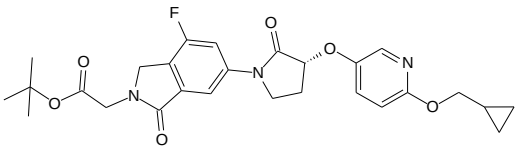
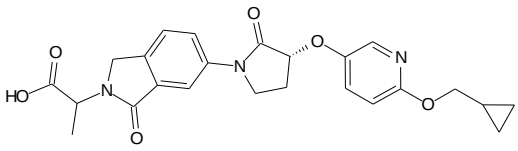
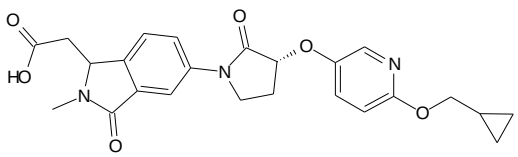
Preparation of Examples 1

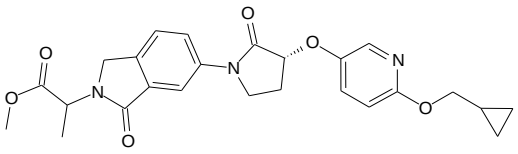
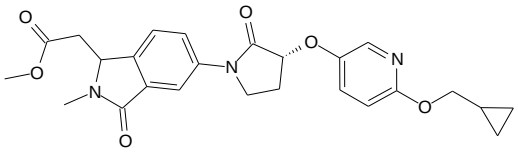
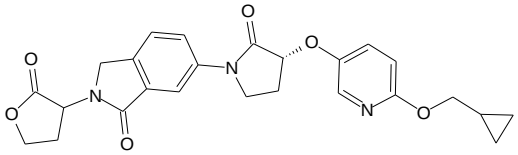
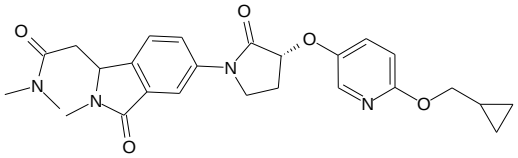
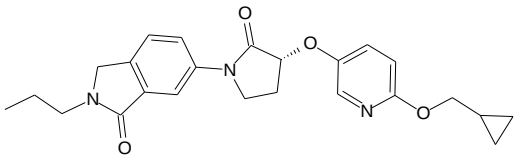
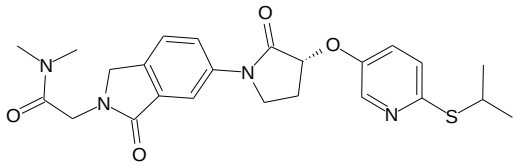
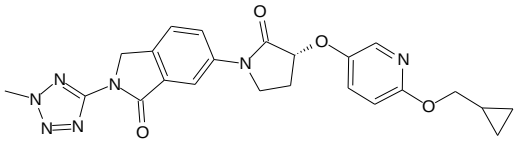
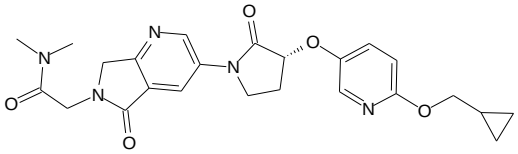
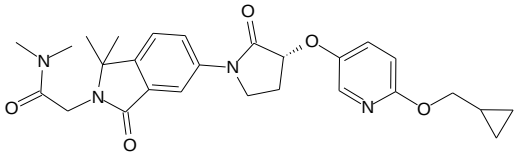
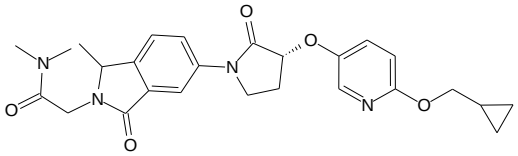
Example 1-01 (Typical Procedure 1)

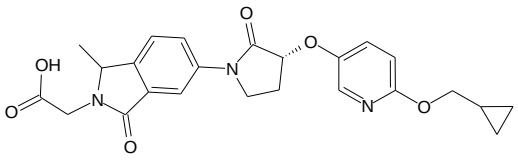
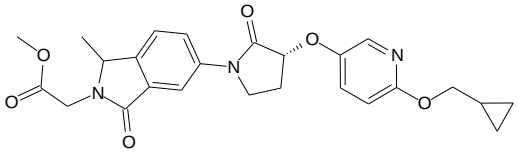
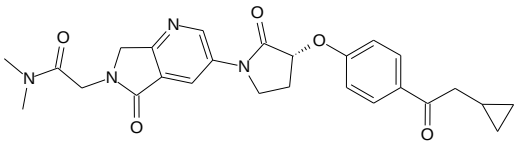
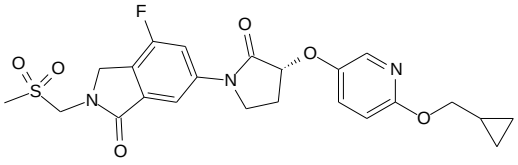
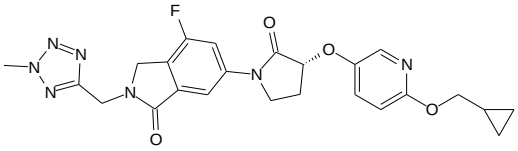
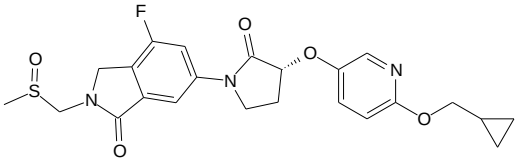
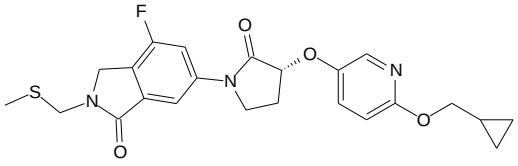
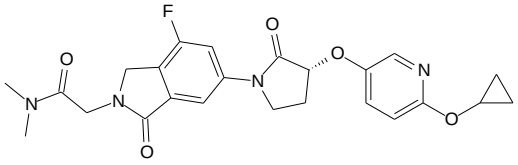
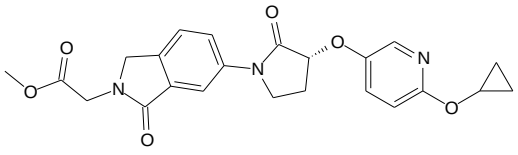
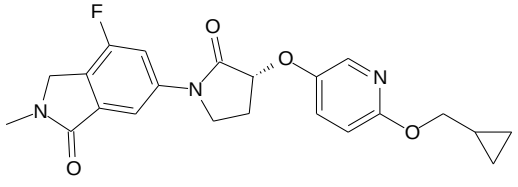
To a mixture of tert-butyl 2-(6-bromo-4-fluoro-1-oxoisoindolin-2-yl)acetate (50 mg), (R)-3-((6-(cyclopropylmethoxy)pyridin-3-yl)oxy)pyrrolidin-2-one (43 mg) and 1,4-dioxane (3 mL) was added *N*,*N*'-dimethyl-ethane-1,2-diamine (128 mg) and cesium carbonate (71 mg). The mixture was purged for 5 minutes with a flow of argon and CuI (17 mg) was added. The mixture was heated at 100°C for 1 hour. After cooling to RT, insoluble material was removed by filtration and the filtrate concentrated. The residue was purified by preparative HPLC to provide example 1-01.

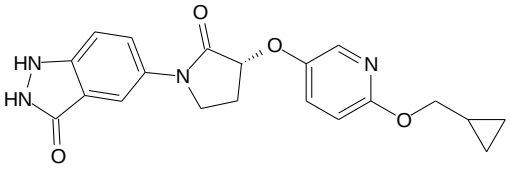
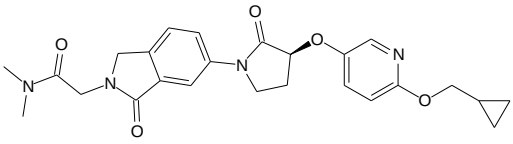
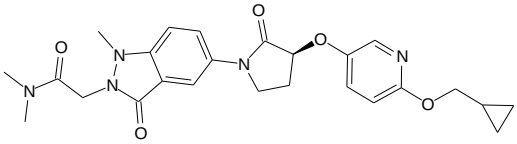
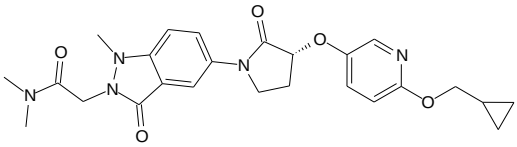
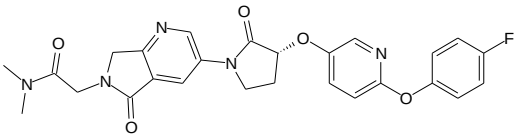
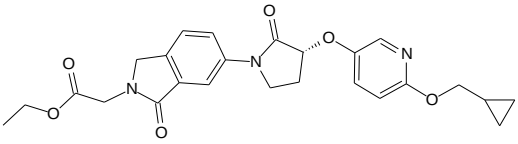
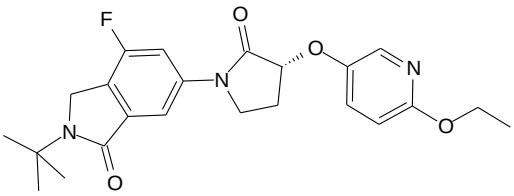
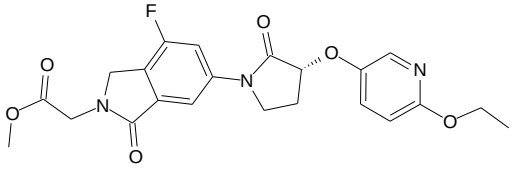
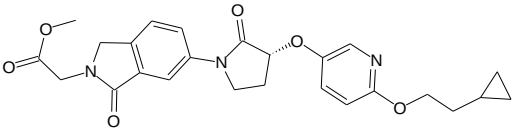
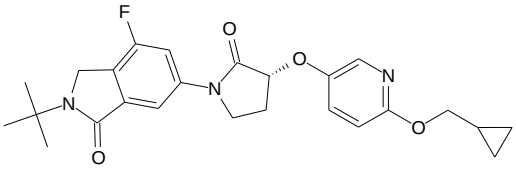
Following essentially the Typical Procedure 1, the Examples 1 in Table 1 were prepared using the respective aryl bromides and 3-substituted pyrrolidinones.

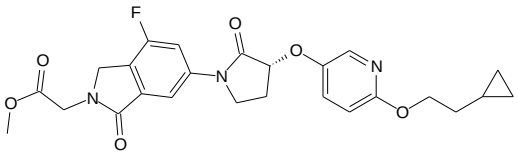
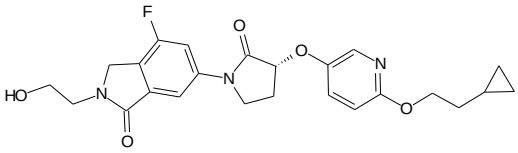
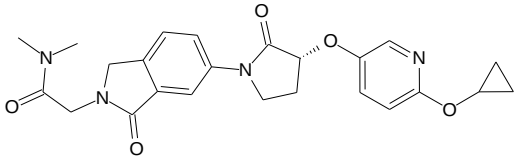
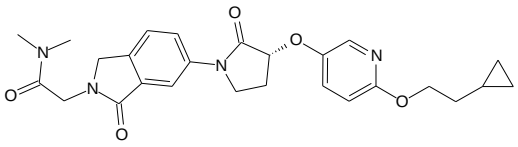
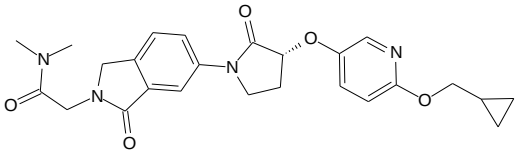
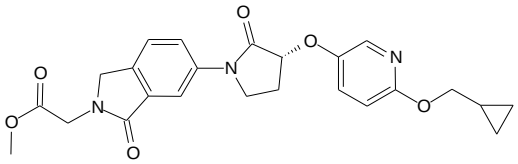
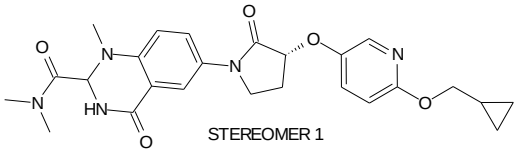
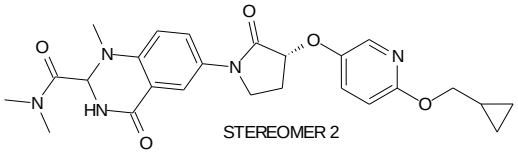
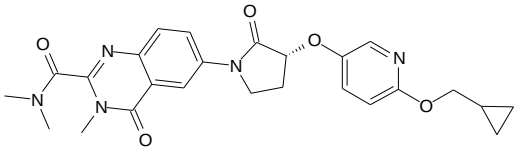
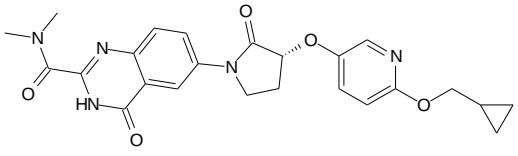
Table1.

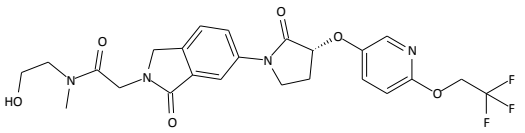
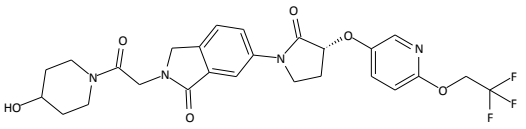
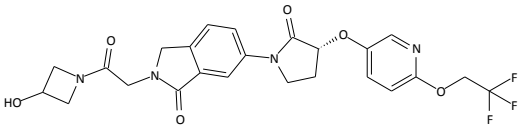
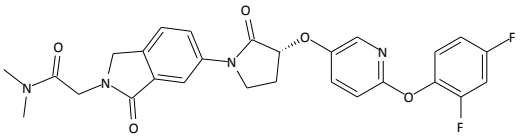
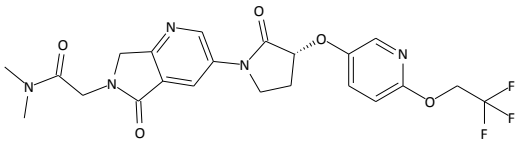
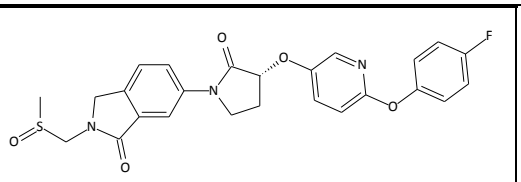
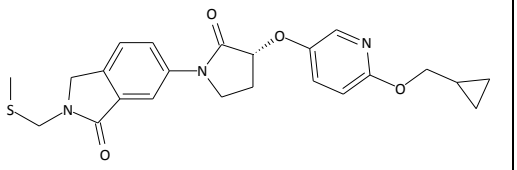
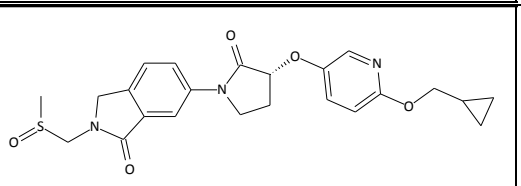
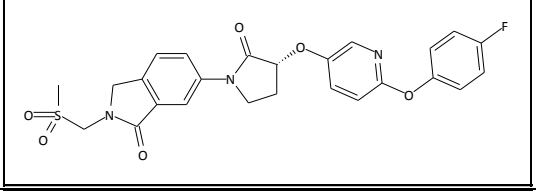
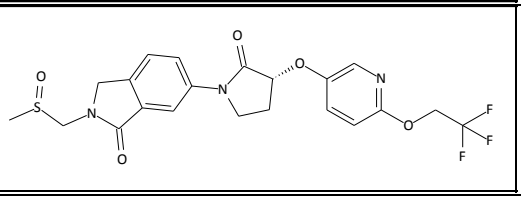
Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
1-01		A	1.89	512.3
1-02		A	1.60	452.2
1-03		A	1.53	452.1

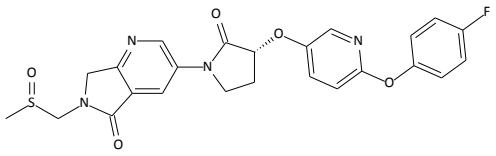
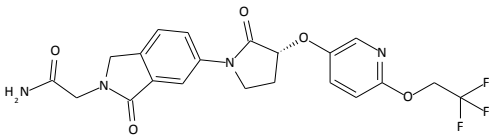
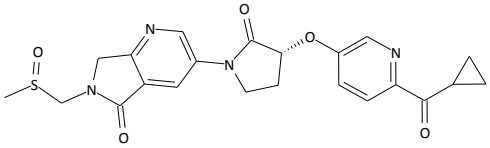
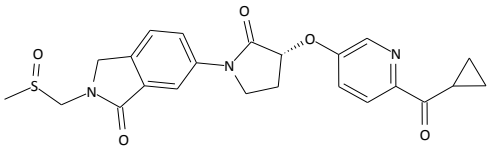
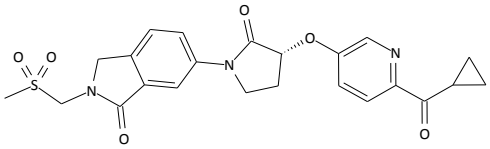
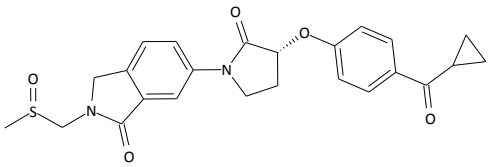
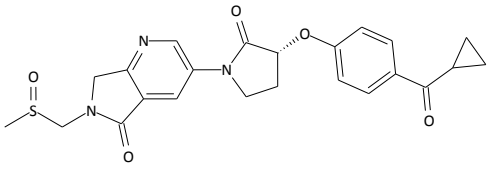
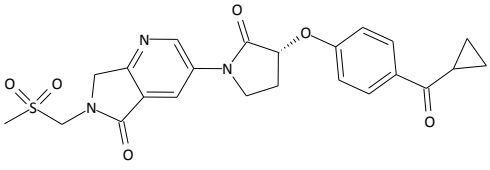
Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
1-04		A	1.70	466.2
1-05		A	1.65	466.2
1-06		A	1.63	464.3
1-07		A	1.60	479.4
1-08		A	1.75	422.1
1-09		A	1.62	469.3
1-10		A	1.68	462.4
1-11		A	1.52	466.3
1-12		A	1.68	493.4
1-13		B	3.95	479.4

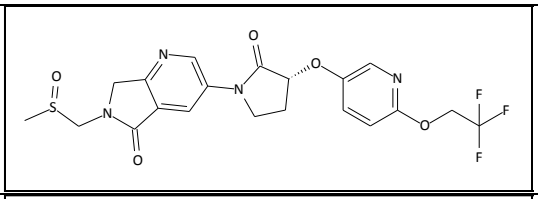
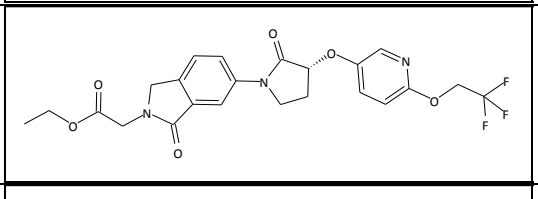
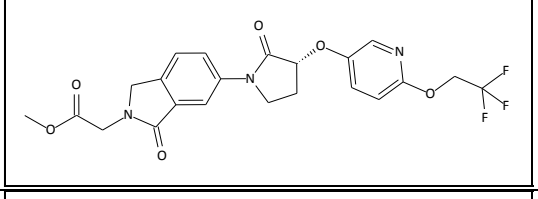
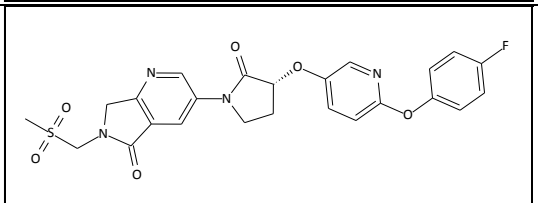
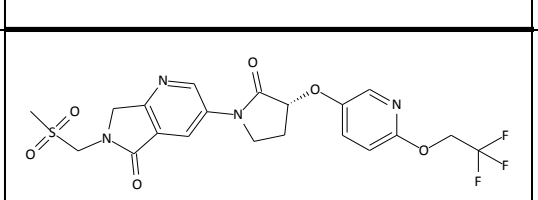
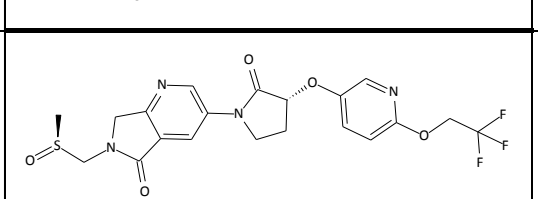
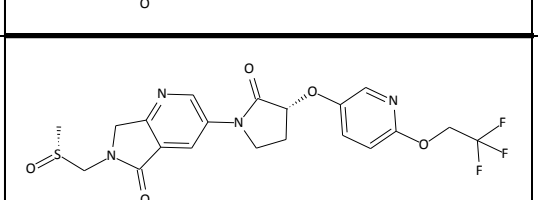
Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
1-14		B	3.95	452.3
1-15		A	1.74	466.3
1-16		C	1.71	477.2
1-17		A	1.68	490.3
1-18		A	1.67	494.4
1-19		A	1.56	474.3
1-20		A	1.81	458.2
1-21		A	1.53	469.2
1-22		A	1.50	438.2
1-23		A	1.67	412.1

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
1-24		A	1.45	381.1
1-25		A	1.59	465.4
1-26		A	1.58	480.3
1-27		A	1.58	480.3
1-28		C	1.74	506.1
1-29		A	1.70	466.1
1-30		A	1.83	428.3
1-31		A	1.65	444.2
1-32		A	1.77	466.2
1-33		A	1.91	454.2

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
1-35		A	1.84	484.1
1-36		A	1.72	456.3
1-37		A	1.40	451.2
1-38		A	1.66	479.2
1-39		A	1.58	465.3
1-40		A	1.65	452.3
1-41	 STEREOMER 1	A	1.60	480.3
1-42	 STEREOMER 2	A	1.60	480.3
1-43		C	1.83	478.1
1-44		A	1.72	464.2

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
1-45		C	1.58	523.1
1-46		C	1.60	549.1
1-47		C	1.57	521.1
1-48		C	1.64	523.2
1-49		C	1.51	494.2
1-50		C	1.55	496.1
1-51		C	1.72	440.1
1-52		C	1.5	456.2
1-53		C	1.64	512.1
1-54		C	1.55	484.0

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
1-55		C	1.49	497.1
1-56		C	1.53	465.1
1-57		C	1.30	453.2 (ESI-)
1-58		C	1.39	454.2
1-59		C	1.48	470.2
1-60		C	1.45	453.1
1-61		C	1.37	454.1
1-62		C	1.50	470.1

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
1-63		C	1.53	483.1
1-64		C	1.73	494.1
1-65		C	1.68	480.1
1-66		C	1.57	513.1
1-67		C	1.57	501.1
1-68		C	1.49	485.2
1-69		C	1.49	485.2

The reaction of (*R*)-3-[6-(2-cyclopropyl-methoxy)-pyridin-3-yloxy]-pyrrolidin-2-one with 2-(5-bromo-1-methyl-3-oxo-1H-indazol-2(3H)-yl)-N,N-dimethylacetamide according to Typical Procedure 1 provided a crude mixture, which was separated by HPLC (column: Chiralcel OD-H/126, 4.6*250 mm; mobile phase: EtOH/MeOH 1:1 with 0.1% TFA; flow rate: 1.0 mL/min; column temperature: 30°C; UV wavelength: 224 nm) to provide examples 1-41 (R_t = 5.00 min), 1-26 (R_t = 6.89 min), 1-27 (R_t = 7.78 min) and 1-42 (R_t = 12.46 min).

Occasionally carboxylic acids (e.g. Examples 1-03 and 1-14, respectively) were obtained as additional products from the reaction mixture due to (partial) ester hydrolysis (for example in the reaction of methyl 2-(6-bromo-1-oxoisoindolin-2-yl)propanoate and methyl 2-(5-bromo-1-methyl-3-oxoisoindolin-2-yl)acetate, respectively, with (*R*)-3-[6-(2-cyclopropyl-methoxy)-pyridin-3-yloxy]-pyrrolidin-2-one according to Typical Procedure 1). The carboxylic acids obtained, can be converted to methyl esters (e.g. Examples 1-05 and 1-15, respectively) by dissolving the respective acid in DCM (5 mL/mmol) and methanol (0.5 mL/mmol) and addition of $TMSCHN_2$ (1.5 equiv.). After the gas evolution has ceased, the reaction mixture is evaporated to provide the desired methyl ester.

Preparation of 3-Substituted Pyrrolidin-2-ones

(*R*)-3-[6-(4-Fluoro-phenoxy)-pyridin-3-yloxy]-pyrrolidin-2-one (Typical Procedure 3)

A mixture of THF (200 mL) and DCM (100 mL) under argon was added triphenylphosphine (polymer, 1.8 mmol/g, 20 g). Diisopropyl azodicarboxylate (8.87 g) was added. After 5 minutes (*S*)-3-hydroxy-pyrrolidin-2-one (3.1 g) and 6-(4-fluoro-phenoxy)-pyridin-3-ol (6.0 g) were added. After 30 minutes the mixture was filtered and the filtrate concentrated. The residue was purified by chromatography (SiO_2; DCM/MeOH 15:1) to provide the title compound. MS ESI^+: m/z = 289 $[M+H]^+$.

6-(4-Fluoro-phenoxy)-pyridin-3-ol

A mixture of 6-bromo-pyridin-3-ol (8.0 g), 4-fluorophenol (15.5 g) and cesium carbonate (30 g) was heated to 170°C for 6 hours. After the mixture reached room temperature, it was distributed between water and MTBE. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography (SiO_2; EA/heptane 1:1.5) to provide the subtitle compound. MS ESI^+: m/z = 206 $[M+H]^+$.

(*R*)-3-[6-(2-Cyclopropyl-ethoxy)-pyridin-3-yloxy]-pyrrolidin-2-one

A mixture of (*S*)-3-hydroxy-pyrrolidin-2-one (0.79 g), 6-(2-cyclopropyl-ethoxy)-pyridin-3-ol (1.4 g), triphenylphosphine (2.25 g), DCM (30 mL) and THF (20 mL) was added DIAD (1.74 g). After 2 days the mixture was filtered and the filtrate was evaporated. The residue was purified by SGC (eluent: EA/MeOH 9:1) to provide the title compound. MS ESI^+: m/z = 263 $[M+H]^+$.

6-(2-Cyclopropyl-ethoxy)-pyridin-3-ol (Typical Procedure 4)

A mixture of 5-bromo-2-(2-cyclopropyl-ethoxy)-pyridine (2.2 g), bis(pinacolato)diboron (2.54 g) and 1,4-dioxane (15 mL) was purged with argon. Potassium acetate (2.68 g) and Pd(dppf)Cl_2 (0.35 g) were added. The mixture was irradiated in a microwave instrument for 1 hour at 80°C. After the mixture reached room temperature, it was distributed between water and EA. The organic phase was dried (Na_2SO_4) and concentrated to obtain the crude boronate.

Typical Procedure 5

The crude boronate from above was dissolved in THF (50 mL) and NaOH (40% in water, 10 mL) and H_2O_2 (30% in water, 3 mL) were added. After 3 hours the mixture was neutralized and extracted with EA. The organic phase was dried (Na_2SO_4) and concentrated to provide the subtitle compound. MS ESI$^+$: m/z = 180 $[M+H]^+$.

5-Bromo-2-(2-cyclopropyl-ethoxy)-pyridine (Typical Procedure 6)

A mixture of 2-cyclopropyl-ethanol (4.1 g) and DMF (15 mL) under argon was treated with NaH (60% in mineral oil, 0.45 g). After 4 hours 5-bromo-2-fluoro-pyridine (3.0 g) was added at 0°C. After 4 hours at room temperature, the mixture was distributed between water and EA. The organic phase was washed twice (water), dried (Na_2SO_4) and concentrated. The residue was purified by chromatography (SiO_2; EA/heptane 1:4) to provide the subtitle compound. MS ESI$^+$: m/z = 242 $[M+H]^+$.

(R)-3-((6-Ethoxypyridin-3-yl)oxy)pyrrolidin-2-one

The procedures described above for (*R*)-3-[6-(2-cyclopropyl-ethoxy)-pyridin-3-yloxy]-pyrrolidin-2-one were followed substituting ethanol for 2-cyclopropyl-ethanol to provide the title compound. MS ESI$^+$: m/z = 223 $[M+H]^+$.

(*R*)-3-[6-(2-Cyclopropyl-methoxy)-pyridin-3-yloxy]-pyrrolidin-2-one

A mixture of (*S*)-3-hydroxy-pyrrolidin-2-one (3.00 g), 6-(2-cyclopropyl-methoxy)-pyridin-3-ol (4.90 g), triphenylphosphine (polymer, 8.56 g), DCM (30 mL) and THF (50 mL) was added DIAD (6.60 g) keeping the reaction temperature below 30°C. After 12 hours the mixture was filtered and the filtrate was evaporated. The residue was purified by SGC (eluent: EA/MeOH 9:1) to provide the title compound. MS ESI$^+$: m/z = 249 $[M+H]^+$.

6-Cyclopropylmethoxy-pyridin-3-ol

A mixture of 5-bromo-2-cyclopropylmethoxy-pyridine (8.00 g), bis(pinacolato)diboron (8.91 g) and 1,4-dioxane (53 mL) was purged with argon. Potassium acetate (3.44 g) and Pd(dppf)Cl_2 (2.57 g) were added and the mixture heated to 100°C for 1 hour by

microwave irradiation. The mixture was filtered and the filtrate diluted with EA, washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by SGC (eluent: EA/heptane 1:6) to provide the crude boronate. MS ESI^+: m/z = 276 $[M+H]^+$. The boronate was dissolved in THF (60 mL). Aqueous NaOH (5 M) was added at 0°C. Hydrogen peroxide (30% in water, 30 mL) was added slowly. The mixture was allowed to warm to RT and stirred for 4 hours. The mixture was extracted with MTBE. The aqueous phase was adjusted to pH 3-4 by addition of diluted HCl and extracted with EA. The organic phase was dried (Na_2SO_4) and concentrated to provide the subtitle compound. MS ESI^+: m/z = 166 $[M+H]^+$.

5-Bromo-2-cyclopropylmethoxy-pyridine

To a mixture of 2-cyclopropyl-methanol (6.15 g) and DMF (12 mL) was added NaH (60% in mineral oil, 1.5 g) at 0°C. After stirring for 4 hours at RT the mixture was diluted with DMF (5 mL) and 5-bromo-2-fluoro-pyridine (6.00 g) was slowly added keeping the reaction temperature below 30°C. After 30 minutes at RT the mixture was heated to 130°C for 1 hour by microwave irradiation. After cooling to RT, the mixture was diluted with EA and washed with water (3 times). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by SGC to provide the subtitle compound. MS ESI^+: m/z = 228 $[M+H]^+$.

(*R*)-3-[6-(2-Cyclopropoxy)-pyridin-3-yloxy]-pyrrolidin-2-one

Typical Procedure 3 was followed. Reaction of 6-cyclopropoxy-pyridin-3-ol and (*S*)-3-hydroxy-pyrrolidin-2-one provided the title compound. MS ESI^+: m/z = 235 $[M+H]^+$.

6-Cyclopropoxy-pyridin-3-ol

A mixture of 5-bromo-2-cyclopropoxypyridine (Milestone Pharmtech, 500 mg) in THF (10 mL) was cooled (-78°C) and n-BuLi (2.5 M in toluene, 1.49 mL) was added dropwise within 10 minutes. After 20 minutes trimethyl borate (429 µL) was added. After 2 hours peracetic acid (32% in AcOH, 786 µL) was added dropwise. After 10 minutes the reaction temperature was changed to 0°C. After 1 hour the mixture was poured into aqueous $NaHSO_3$-solution (5%, 5 mL). The mixture was extracted with EA. The organic phase was dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography (silica gel, heptane to EA/heptane 2:3) to provide the subtitle compound. MS ESI^+: m/z = 152 $[M+H]^+$.

(*R*)-3-(6-Methylsulfanyl-pyridin-3-yloxy)-pyrrolidin-2-one (Typical Procedure 8)

A mixture of (*R*)-3-(6-bromo-pyridin-3-yloxy)-pyrrolidin-2-one (0.8 g), sodium methanethiolate (327 mg) and DMF (15 mL) was heated to 100°C for 15 minutes. After the mixture reached room temperature, it was distributed between water and EA. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by preparative HPLC to provide the title compound. MS ESI$^+$: m/z = 225 $[M+H]^+$.

(*R*)-3-(6-Bromo-pyridin-3-yloxy)-pyrrolidin-2-one

Typical Procedure 3 was followed. Reaction of (*S*)-3-hydroxy-pyrrolidin-2-one with 6-bromo-pyridin-3-ol provided the subtitle compound. MS ESI$^+$: m/z = 257 $[M+H]^+$.

(*R*)-3-(6-Isopropylsulfanyl-pyridin-3-yloxy)-pyrrolidin-2-one

Typical Procedure 8 was followed. Reaction of (*R*)-3-(6-bromo-pyridin-3-yloxy)-pyrrolidin-2-one with sodium 2-propanethiolate provided the title compound. MS ESI$^+$: m/z = 253 $[M+H]^+$.

(R)-3-(4-(2-Cyclopropylacetyl)phenoxy)pyrrolidin-2-one

A solution of 2-cyclopropyl-1-(4-hydroxyphenyl)ethanone (1.1 g), (S)-3-hydroxypyrrolidin-2-one (947 mg), PPh_3 (2.78 g) and DIAD (2.15 g) in THF (5 mL) was stirred at 4°C for 15 hours. The reaction mixture was diluted with EA (200 mL), and washed with water (100 mL x 2) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with DCM/MeOH = 50:1 to provide the title compound. MS ESI$^+$: m/z = 260 $[M+H]^+$.

2-Cyclopropyl-1-(4-hydroxyphenyl)ethanone

To a solution of 1-(4-(tert-butyldimethylsilyloxy)phenyl)-2-cyclopropylethanone (3.8 g) in THF (50 mL) was added a solution of TBAF (6.65 g) in THF (10 mL). The reaction mixture was stirred for 4 hours at RT. The solvent was removed under reduced pressure and the residue was dissolved in EA (100 mL), washed with HCl (0.5 N, 20 mL), brine (20 mL) and dried over Na_2SO_4. The residue was purified by column chromatography on silica gel eluting with DCM/MeOH = 200:1 to provide the subtitle compound. MS ESI$^+$: m/z = 177 $[M+H]^+$.

1-(4-(Tert-butyldimethylsilyloxy)phenyl)-2-cyclopropylethanone

To a solution of (4-bromophenoxy)(tert-butyl)dimethylsilane (3.15 g) in THF (20 mL) was added a solution of t-BuLi (6.8 mL) dropwise at -78°C. The reaction mixture was stirred for 20 minutes at -78°C and then a solution of 2-cyclopropyl-N-methoxy-N-

methylacetamide (1.3 g) in dry THF (5 mL) was added slowly. The reaction mixture was allowed to warm to RT and stirred for 4 hours. The reaction mixture was poured into water (100 mL) and the volatiles were removed under reduced pressure. The aqueous phase was extracted with EA (50 mL x 3). The organic phase was washed with brine and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to provide the subtitle compound. MS ESI^+: m/z = 291 $[M+H]^+$.

(4-Bromophenoxy)(tert-butyl)dimethylsilane

To a solution of 4-bromophenol (5.0 g) in DMF (25 mL) was added tert-butylchlorodimethylsilane (5.0 g) and imidazole (5.0 g) in portions at RT. The mixture was stirred for 3 hours and then poured into water (200 mL). The mixture was extracted with Et_2O (80 mL x 3). The organic phase was washed with water (30 mL x 4), HCl (1 N, 30 mL), saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL).The organic phase was dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to provide the subtitle compound.

2-Cyclopropyl-N-methoxy-N-methylacetamide

To a stirred solution of 2-cyclopropylacetic acid (1.0 g) in DCM (30 mL) was added CDI (1.86 g) at room temperature. The mixture was stirred for 2 hours at RT and then O,N-dimethylhydroxylamine hydrochloride (1.07 g) was added. The reaction mixture was stirred for 20 hours at RT. The reaction mixture was poured into water (100 mL) and then extracted with DCM (30 mL x 3). The organic phase was washed with water (50 mL), HCl (1 N, 30 mL), saturated aqueous $NaHCO_3$ (30 mL) and dried over Na_2SO_4. After filtration the solvent was removed under reduced pressure to provide the subtitle compound.

(R)-3-[6-(2,2,2-Trifluoro-ethoxy)-pyridin-3-yloxy]-pyrrolidin-2-one

Following Typical Procedure 3, reaction of 6-(2,2,2-trifluoroethoxy)pyridin-3-ol with (S)-3-hydroxy-pyrrolidin-2-one provided the title compound. MS ESI^+: m/z = 277 $[M+H]^+$.

(R)-3-[6-(2,4-Difluoro-phenoxy)-pyridin-3-yloxy]-pyrrolidin-2-one

Following Typical Procedure 3, reaction of 6-(2,4-difluoro-phenoxy)-pyridin-3-ol with (S)-3-hydroxy-pyrrolidin-2-one provided the title compound. MS ESI^+: m/z = 307 $[M+H]^+$.

6-(2,4-Difluoro-phenoxy)-pyridin-3-ol

Following Typical Procedures 4 and 5a, conversion of 5-bromo-2-(2,4-difluoro-phenoxy)-pyridine to the boronate and oxidation provided the subtitle compound. MS ESI$^+$: m/z = 224 $[M+H]^+$.

5-Bromo-2-(2,4-difluoro-phenoxy)-pyridine

A mixture of 2,5-dibromo-pyridine (24.0 g), 2,4-difluoro-phenol (26.4 g) and K_2CO_3 (42.0 g) in DMF (300 mL) was stirred at 150°C overnight. After cooling to room temperature, the mixture was diluted with water (600 mL), extracted with ethyl acetate (400 mL x 3), washed with water (800 mL) and dried over anhydrous Na_2SO_4. The crude product was purified by silica gel chromatography (petrol ether) to provide the subtitle compound. MS ESI$^+$: m/z = 286 $[M+H]^+$.

Preparation of Aryl Bromides

Tert-butyl 2-(6-bromo-4-fluoro-1-oxoisoindolin-2-yl)acetate (Typical Procedure 2)

To a mixture of 6-bromo-4-fluoroisoindolin-1-one (500 mg), tert-butyl 2-bromoacetate (424 mg) and DMF (10 mL) at 0°C was added NaH (104 mg, 60% in mineral oil). The mixture was allowed to warm to RT and stirred for 2 hours. The mixture was partitioned between water and EA. The organic layer was dried (Na_2SO_4) and concentrated. The residue obtained was purified by SGC (heptane/EA 5:1) to provide the title compound. MS ESI$^+$: m/z = 344 $[M+H]^+$.

6-Bromo-4-fluoroisoindolin-1-one

A mixture of 6-bromo-2-(tert-butyl)-4-fluoroisoindolin-1-one (2.9 g) and TFA (12 mL) was heated to 130°C by microwave irradiation for 2 hours. The mixture was cooled to RT and neutralized with aqueous sodium carbonate followed by extraction with EA. The organic layer was dried (Na_2SO_4) and concentrated to provide the subtitle compound. MS ESI$^+$: m/z = 230 $[M+H]^+$.

Using essentially the Typical Procedure 2 the following compounds were obtained:

6-Bromo-2-propylisoindolin-1-one from 6-bromo-isoindolin-1-one and propyl iodide;

Methyl 2-(6-bromo-1-oxoisoindolin-2-yl)acetate from 6-bromo-isoindolin-1-one and methyl 2-bromoacetate;

Ethyl 2-(6-bromo-1-oxoisoindolin-2-yl)acetate from 6-bromo-isoindolin-1-one and ethyl 2-bromoacetate;

2-(6-Bromo-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide from 6-bromo-isoindolin-1-one and 2-bromo-N,N-dimethyl-acetamide;

6-Bromo-4-fluoro-2-methyl-2,3-dihydro-isoindol-1-one from 6-bromo-4-fluoroisoindolin-1-one and methyl iodide;

6-Bromo-4-fluoro-2-(2-methyl-2H-tetrazol-5-ylmethyl)-2,3-dihydro-isoindol-1-one from 6-bromo-4-fluoroisoindolin-1-one and 5-chloromethyl-2-methyl-2H-tetrazole;

6-Bromo-4-fluoro-2-methylsulfanylmethyl-2,3-dihydro-isoindol-1-one from 6-bromo-4-fluoroisoindolin-1-one and (iodomethyl)(methyl)sulfane;

(6-Bromo-4-fluoro-1-oxo-1,3-dihydro-isoindol-2-yl)-acetic acid methyl ester from 6-bromo-4-fluoroisoindolin-1-one and methyl 2-bromoacetate;

2-(6-Bromo-4-fluoro-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide from 6-bromo-4-fluoroisoindolin-1-one and 2-bromo-N,N-dimethyl-acetamide;

2-(3-Bromo-5-oxo-5H-pyrrolo[3,4-b]pyridin-6(7H)-yl)-N,N-dimethylacetamide from 3-bromo-6,7-dihydro-pyrrolo[3,4-b]pyridin-5-one and 2-bromo-N,N-dimethyl-acetamide;

2-(5-Bromo-1, 1-dimethyl-3-oxoisoindolin-2-yl)-N, N-dimethylacetamide from 6-bromo-3,3-dimethyl-2,3-dihydro-isoindol-1-one and 2-bromo-N,N-dimethyl-acetamide;

2-(5-Bromo-1-methyl-3-oxoisoindolin-2-yl)-N,N-dimethylacetamide from 6-bromo-3-methyl-2,3-dihydro-isoindol-1-one and 2-bromo-N,N-dimethyl-acetamide;

Methyl 2-(5-bromo-1-methyl-3-oxoisoindolin-2-yl)acetate from 6-bromo-3-methyl-2,3-dihydro-isoindol-1-one and methyl 2-bromoacetate.

6-Bromo-4-fluoro-2-methanesulfonylmethyl-2,3-dihydro-isoindol-1-one

A mixture of 6-bromo-4-fluoro-2-methylsulfanylmethyl-2,3-dihydro-isoindol-1-one (31 mg) and methanol (0.5 mL) was added water (0.5 mL) and Oxone (67 mg) and stirred for 4 hours. The reaction mixture was distributed between water and EA. The organic layer was dried (Na_2SO_4) and concentrated to provide the title compound. MS ESI^+: m/z = 322 $[M+H]^+$.

6-Bromo-4-fluoro-2-methanesulfinylmethyl-2,3-dihydro-isoindol-1-one

A mixture of 6-bromo-4-fluoro-2-methylsulfanylmethyl-2,3-dihydro-isoindol-1-one (105 mg) and DCM (5 mL) was added MCPBA (63 mg) at -20°C and stirred for 30 minutes. The reaction mixture was diluted with EA (15 mL) and heptane (5 mL), extracted with aqueous sodium bicarbonate (2 x) and washed with brine. The organic layer was dried (Na_2SO_4) and concentrated to provide the title compound. MS ESI^+: m/z = 306 $[M+H]^+$.

6-Bromo-2-(tert-butyl)-4-fluoroisoindolin-1-one

A mixture of compound A (14 g), dodecanoic peroxyanhydride (13.7 g) and 1,2-dichloroethane (100 mL) was heated to reflux for 3 hours. The volatiles were removed and the residue purified by SGC (heptane/EA 87:13) to provide the title compound. MS ESI^+: m/z = 286 $[M+H]^+$.

Compound A

To a mixture of N-(4-bromo-2-fluorobenzyl)-2-methylpropan-2-amine (50.5 g) and DCM (400 mL) was added bis(trichloromethyl) carbonate (57.6 g). DIPEA (168 mL) was added dropwise at 0°C. After 1 hour the mixture was evaporated and the residue slurried with heptane. Solids were removed by filtration and the filtrate was concentrated. The residue was dissolved in MeCN (500 mL) and added potassium O-ethyl carbonodithioate (31.1 g). After 3 hours insoluble material was removed by filtration and the filtrate concentrated. The residue obtained was purified by SGC (heptane/EA 9:1) to provide the subtitle compound. MS ESI^+: m/z = 408 $[M+H]^+$.

N-(4-Bromo-2-fluorobenzyl)-2-methylpropan-2-amine

A mixture of 4-bromo-2-fluorobenzaldehyde (46.2 g), methanol (400 mL) and molecular sieves (4Å) was allowed to stand for 3 hours and then cooled to 0°C. 2-Methylpropan-2-amine (47.8 mL) was added. After 5 hours sodium borohydride (9.32 g) was added in portions. After 2 hours the volatiles were removed and the residue partitioned between water and EA. The organic layer was dried (Na_2SO_4) and concentrated to provide the subtitle compound. MS ESI^+: m/z = 260 $[M+H]^+$.

6-Bromo-3-methylisoindolin-1-one

To a solution of tert-butyl 5-bromo-1-methyl-3-oxoisoindoline-2-carboxylate (2.0 g) in DCM (100 mL) was added TFA (3.2 g) at 0°C. The reaction mixture was stirred at RT for 2 hours. The resulting mixture was partitioned between water and ethyl acetate, and the phases were separated. The organic phase was washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the resulting residue was purified by column chromatography (silica gel, PE/EA = 8:1) to provide the title compound. MS ESI^+: m/z = 226 $[M+H]^+$.

Tert-butyl 5-bromo-1-methyl-3-oxoisoindoline-2-carboxylate

To a solution of tert-butyl 6-bromo-1-oxoisoindoline-2-carboxylate (25.0 g) in THF (240 mL) was added NaHMDS (44.1 mL, 2 M in THF) at -78°C. The reaction solution was stirred at -78°C for 1 hour. MeI (11.4 g) was added dropwise. The reaction solution was stirred at -78°C for 2 hours, allowed to warm to RT and stirred for 1 hour. After the

reaction was complete, 80 mL of water was added and the solution was extracted with EA (250 mL x 3). The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by column chromatography (silica gel, EA/PE = 1:40) to provide the subtitle compound. MS ESI^+: m/z = 270 $[M+H-tBu]^+$. Also obtained was 5-bromo-1,1-dimethyl-3-oxo-1,3-dihydro-isoindole-2-carboxylic acid tert-butyl ester. MS ESI^+: m/z = 284 $[M+H-tBu]^+$.

Tert-butyl 6-bromo-1-oxoisoindoline-2-carboxylate

To a mixture of 6-bromo-2,3-dihydro-isoindol-1-one (10.0 g), DMAP (11.5 g) and THF (100 mL), $(Boc)_2O$ (15.4 g) was added and the mixture was stirred at room temperature for 12 hours. The resulting yellow mixture was partitioned between water and ethyl acetate, and the phases were separated. The organic phase was washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the resulting residue was purified by column chromatography (silica gel, PE/EA = 15:1) to provide the subtitle compound. MS ESI^+: m/z = 256 $[M+H-tBu]^+$.

6-Bromo-3, 3-dimethylisoindolin-1-one

To a solution of 5-bromo-1,1-dimethyl-3-oxo-1,3-dihydro-isoindole-2-carboxylic acid tert-butyl ester (1.2 g) in DCM (50 mL) was added TFA (1.7 g) at 0°C. The reaction mixture was stirred at RT for 2 hours. The resulting mixture was partitioned between water and ethyl acetate, and the phases were separated. The organic phase was washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the resulting residue was purified by column chromatography (silica gel, PE/EA = 7:1) to provide the title compound. MS ESI^+: m/z = 240 $[M+H-tBu]^+$.

Methyl 2-(6-bromo-1-oxoisoindolin-2-yl)propanoate

To a mixture of methyl 2-aminopropanoate hydrochloride (1.5 g) and MeOH (50 mL) was added TEA (2.2 g) and methyl 5-bromo-2-(bromomethyl)benzoate (3.0 g) at RT. The mixture was heated to reflux with stirring for 5 hours. After cooling to RT, the reaction mixture was evaporated in vacuo. The residue was purified by column chromatography on silica gel eluting with EA/PE = 1: 5 to provide the title compound. MS ESI^+: m/z = 298 $[M+H]^+$.

Methyl 2-(5-bromo-2-methylisoindolin-1-yl)acetate

To a solution of 6-bromo-2-methylisoindolin-1-one (10.1 g) in THF (250 mL) was added LDA (33.5 mL, 2 M in THF) at -20°C. The mixture was stirred at 0°C for 30 minutes and then methyl 2-bromoacetate (10.3 g) was added at 0°C. The mixture was allowed to warm to RT and stirred for 20 hours. The mixture was poured into water (300 mL) and then extracted with EA (200 mL x 3). The combined organic phases were washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the obtained residue was purified by column chromatography on silica gel eluting with EA/PE = 1:3 to provide the title compound. MS ESI^+: m/z = 298 $[M+H]^+$.

6-Bromo-2-methylisoindolin-1-one

Methyl 5-bromo-2-(bromomethyl)benzoate (23 g) was added to methylamine (300 mL, 30% alcoholic solution). The mixture was heated to reflux with stirring for 5 hours. The reaction mixture was cooled to RT and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel eluting with EA/PE = 1:1 to provide the subtitle compound. MS ESI^+: m/z = 226 $[M+H]^+$.

6-Bromo-2-(2-oxotetrahydrofuran-3-yl)isoindolin-1-one

To a mixture of 3-amino-dihydrofuran-2(3H)-one hydrobromide (5.85 g) and MeOH (100 mL) was added TEA (6.5 g) and methyl 5-bromo-2-(bromomethyl)benzoate (9.0 g). The mixture was heated under reflux for 5 hours. The mixture was cooled to RT and the solvent was removed by evaporation under reduced pressure. The residue was dissolved in EA (100 mL) and washed with brine (10 mL). The organic phase was dried over Na_2SO_4. After filtration and evaporation of the solvent, the obtained residue was purified by column chromatography on silica gel eluting with DCM/MeOH = 99:1 to provide the title compound. MS ESI^+: m/z = 296 $[M+H]^+$.

2-(5-Bromo-2-methyl-3-oxoisoindolin-1-yl)-N,N-dimethylacetamide

To a suspension of 2-(5-bromo-2-methyl-3-oxoisoindolin-1-yl)acetic acid (1.2 g) in DCM (50 mL) was added DIPEA (1.64 g), EDCI (1.22 g) and HOBt (856 mg). The mixture was stirred for 30 minutes at RT and then dimethylamine (4.2 mL, 2 M in THF) was added. The mixture was stirred for 20 hours at 25-30°C. The reaction mixture was poured into water (20 mL). The organic phase was separated. After concentration, the residue was purified by column chromatography on silica gel eluting with DCM/MeOH = 99:1 to provide the title compound. MS ESI^+: m/z = 311 $[M+H]^+$.

2-(5-Bromo-2-methyl-3-oxoisoindolin-1-yl)acetic acid

To a solution of methyl 2-(5-bromo-2-methyl-3-oxoisoindolin-1-yl)acetate (1.3 g) in THF (20 mL) was added NaOH (349 mg in 5 mL water) at RT. The mixture was stirred for 4 hours. The volatiles were removed in vacuo and the aqueous phase was neutralized by adding HCl (1 N) to pH = 2. The precipitate was collected by filtration and dried to provide the subtitle compound. MS ESI$^+$: m/z = 284 $[M+H]^+$.

6-Bromo-2-(2-methyl-2H-tetrazol-5-yl)isoindolin-1-one

A mixture of methyl 5-bromo-2-methylbenzoate (3.8 g), 2-methyl-2H-tetrazol-5-amine (5.0 g) and MeOH (20 mL) was heated at reflux overnight. The solution was concentrated and the crude material was purified by chromatography (hexane/EA = 1:1) to provide the title compound. MS ESI$^+$: m/z = 294 $[M+H]^+$.

5-Bromo-1H-indazol-3(2H)-one

A mixture of methyl 5-bromo-2-fluorobenzoate (2.0 g), hydrazine monohydrate (4.25 mL) and ethanol (10 mL) was heated to 110°C by microwave irradiation for 45 minutes. After cooling to RT, the mixture was evaporated and the residue purified by preparative HPLC to provide the title compound. MS ESI$^+$: m/z = 213 $[M+H]^+$.

2-(5-Bromo-1-methyl-3-oxo-1H-indazol-2(3H)-yl)-N,N-dimethylacetamide

To a mixture of 5-bromo-1-methyl-1H-indazol-3(2H)-one (1.28 g) and DME (10 mL) was added NaOMe (300 mg). After 1 hour, 2-bromo-N,N-dimethyl-acetamide (985 mg) was added. After 2 days the volatiles were removed and the residue purified by preparative HPLC to provide the title compound. MS ESI$^+$: m/z = 312 $[M+H]^+$.

5-Bromo-1-methyl-1H-indazol-3(2H)-one

A mixture of methyl 5-bromo-2-fluorobenzoate (2.0 g), methyl hydrazine (1.84 mL) and ethanol (8 mL) was stirred at RT for 2 hours. The residue obtained after evaporation of the reaction mixture was partitioned between water and EA. The organic phase was washed with water (2 x), dried over Na_2SO_4, and concentrated to provide the subtitle compound. MS ESI$^+$: m/z = 227 $[M+H]^+$.

6-Bromo-4-fluoro-2-(2-hydroxyethyl)isoindolin-1-one

To a mixture of methyl 2-(6-bromo-4-fluoro-1-oxoisoindolin-2-yl)acetate (0.4 g) and methanol (5 mL) was added $NaBH_4$ (150 mg) at 0°C. The mixture was allowed to warm

to RT and stirred for 3 hours. Evaporation of the volatiles gave a crude product that was used without further purification.

6-Bromo-N,N,3-trimethyl-4-oxo-3,4-dihydroquinazoline-2-carboxamide

To a DMF (5 mL) solution of 6-bromo-N,N-dimethyl-4-oxo-3,4-dihydroquinazoline-2-carboxamide (220 mg) and K_2CO_3 (135 mg) was added MeI (140 mg). The mixture was stirred for 1 hour at RT and partitioned between water (100 mL) and EA (50 mL x 3). The organic layers were combined, washed with water and brine, dried over $MgSO_4$, filtered and evaporated. The crude was purified by chromatography on silica gel (PE/EA = 1:2) to provide the title compound. MS ESI^+: m/z = 310 $[M+H]^+$.

6-Bromo-N,N-dimethyl-4-oxo-3,4-dihydroquinazoline-2-carboxamide

To a DMF (15 mL) solution of 6-bromo-4-oxo-3,4-dihydroquinazoline-2-carboxylic acid (1.2 g), HATU (2.04 g) and DIPEA (1.16 g) was added dimethylamine hydrochloride (436 mg). The mixture was stirred for 2 hours at RT and partitioned between water (100 mL) and EA (50 mL x 3). The organic layers were combined, washed with water and brine, dried over $MgSO_4$, filtered and evaporated. The crude was purified by chromatography on silica gel (PE/EA = 1:2) to provide the title compound. MS ESI^+: m/z = 296 $[M+H]^+$.

6-Bromo-4-oxo-3,4-dihydroquinazoline-2-carboxylic acid

To a solution of ethyl 6-bromo-4-oxo-3,4-dihydroquinazoline-2-carboxylate (3.0 g) in THF (30 mL) and H_2O (8 mL) was added $LiOH*H_2O$ (1.7 g). After the mixture was stirred for 30 minutes at RT, the reaction was concentrated and added water (30 mL), the pH was adjusted to 2 with 1 M HCl. The resulting precipitate was filtered and washed with water to provide the subtitle compound. MS ESI^+: m/z = 269 $[M+H]^+$.

Ethyl 6-bromo-4-oxo-3,4-dihydroquinazoline-2-carboxylate

A mixture of 2-amino-5-bromobenzoic acid (5.0 g) and ethyl cyanoformate (2.3 g) was added 4 M HCl in dioxane (30 mL). The mixture was stirred for 3 hours at 85°C. The mixture was concentrated and washed with water (20 mL) and EA (20 mL) to provide the subtitle compound. MS ESI^+: m/z = 297 $[M+H]^+$.

2-(6-Bromo-1-oxo-1,3-dihydro-isoindol-2-yl)-N-(2-hydroxy-ethyl)-N-methyl-acetamide

To a mixture of DIPEA (1.18 g), 2-(methylamino)ethanol (2.75 g) and DCM (50 mL) at 0°C, was added dropwise 2-(6-bromo-1-oxoisoindolin-2-yl)acetyl chloride (2.64 g) in

DCM (20 mL). The mixture was stirred 30 minutes at 0°C. The cooling bath was removed. After 2 hours the mixture was concentrated and the residue distributed between ethyl acetate and HCl (1 N). After separation, the organic phase was washed with HCl (1 N) and brine, dried over Na_2SO_4 and concentrated to provide the title compound. MS ESI^+: m/z = 327 $[M+H]^+$.

In a similar manner, 6-bromo-2-[2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-2,3-dihydro-isoindol-1-one and 6-bromo-2-[2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-2,3-dihydro-isoindol-1-one were obtained from 2-(6-bromo-1-oxoisoindolin-2-yl)acetyl chloride and 3-hydroxy-azetidine and 4-hydroxy-piperidine, respectively.

2-(6-Bromo-1-oxoisoindolin-2-yl)acetyl chloride

To a mixture of 2-(6-bromo-1-oxoisoindolin-2-yl)acetic acid (2.4 g) and DCM (20 mL) at 0°C was added oxalyl chloride (2.26 g). After 1 hour the mixture was concentrated. The crude product was co-evaporated with toluene twice and used without further purification.

2-(6-Bromo-1-oxoisoindolin-2-yl)acetic acid

A mixture of 2-(6-bromo-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide (50 g), sodium hydroxide (10 M, 150 mL) and methanol (500 mL) was heated to reflux for 8 hours and then kept at room temperature for 48 hours. The mixture was diluted with water (1 L) and made acidic by addition of HCl (conc.). The precipitate was collected by filtration, washed with water and dried under vacuum to provide the subtitle compound. MS ESI^+: m/z = 270 $[M+H]^+$.

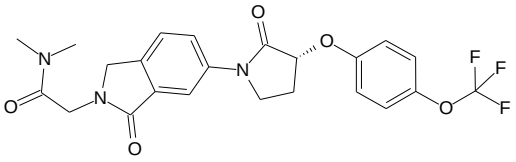
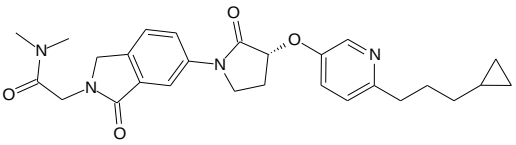
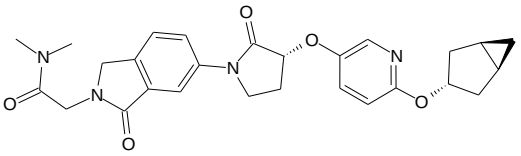
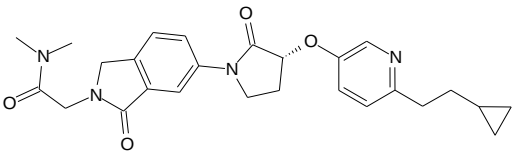
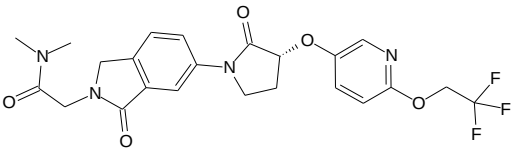
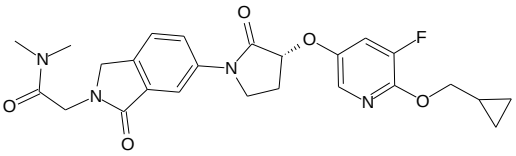
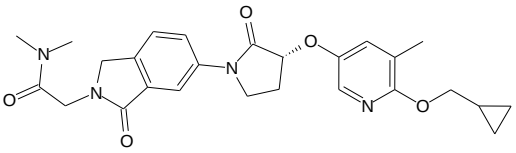
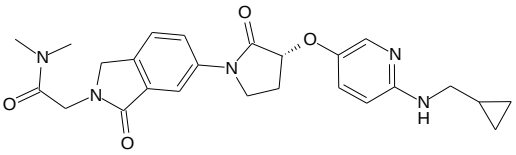
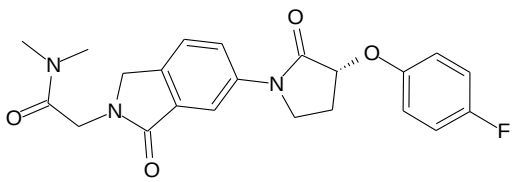
Preparation of Examples 2

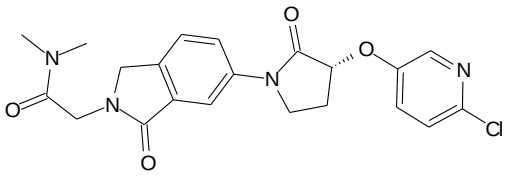
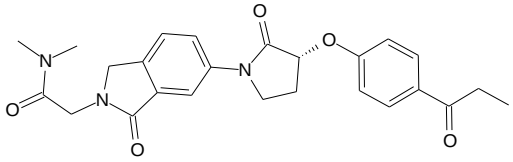
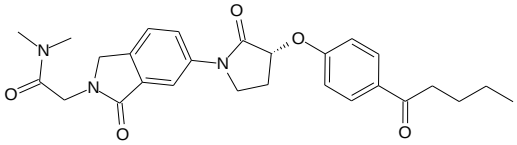
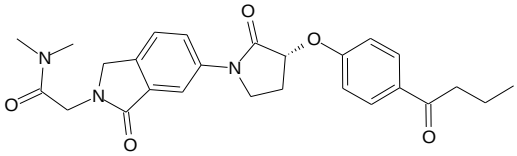
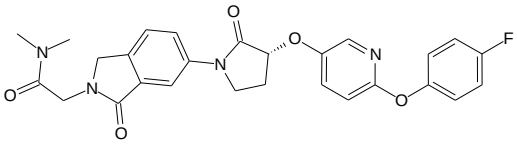
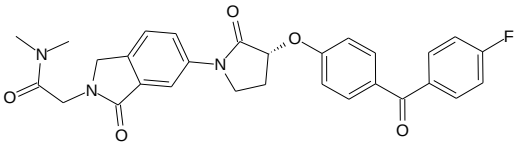
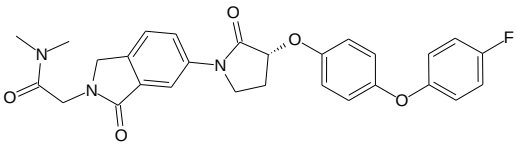
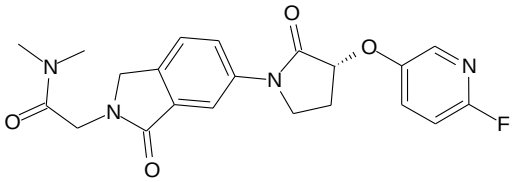
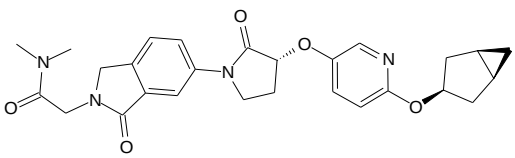
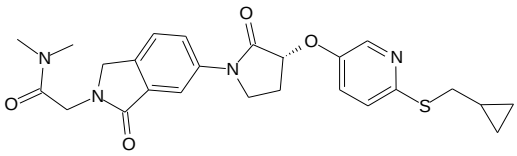
Example 2-01

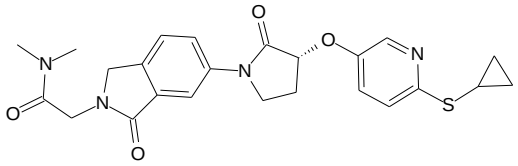
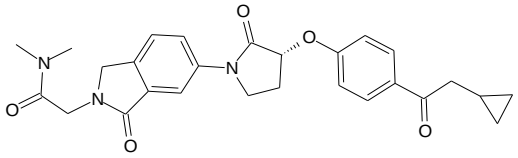
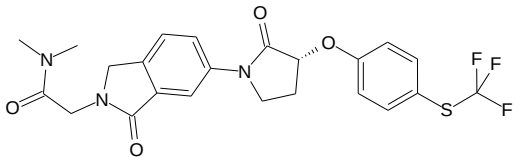
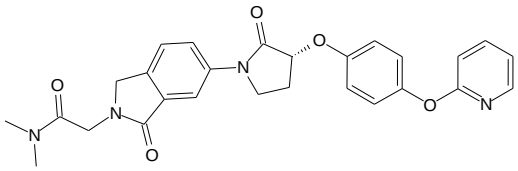
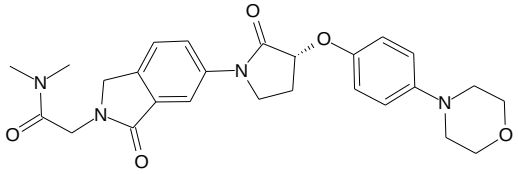
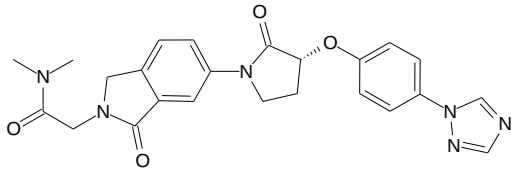
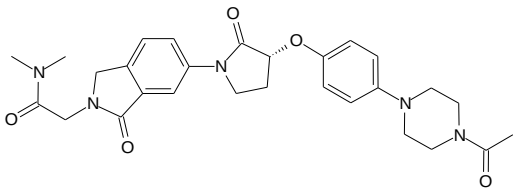
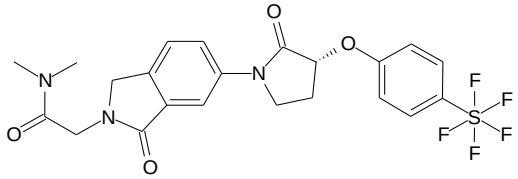
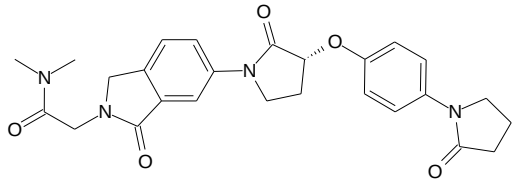
A mixture of triphenyl-phosphine (polymer, 2.3 mmol/g, 165 mg), DEAD (68 mg) and DCM (6 mL) was stirred at 0°C for 15 minutes. (S)-2-(6-(3-hydroxy-2-oxopyrrolidin-1-yl)-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide (100 mg) and 4-trifluoromethoxy-phenol (57 mg) were added. The mixture was allowed to warm to RT and stirred for 12 hours. Insoluble material was filtered off and the filtrate was concentrated to provide a residue, which was purified by preparative HPLC to provide Example 2-01.

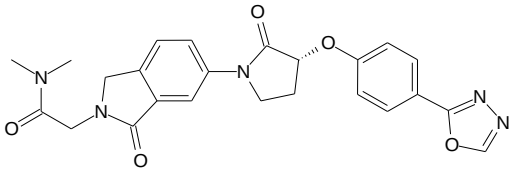
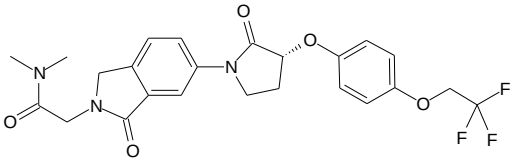
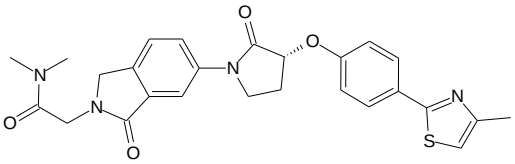
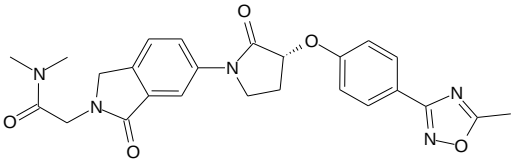
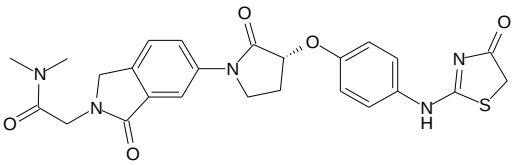
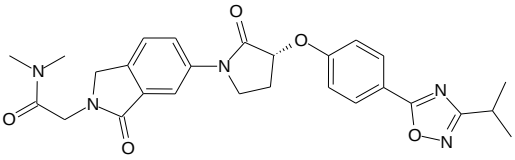
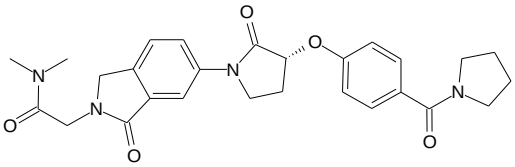
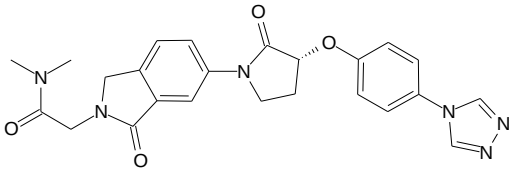
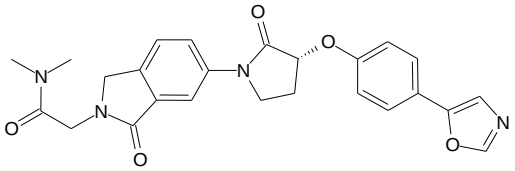
Following essentially this procedure the Examples 2 in Table 2 were obtained by reacting (S)-2-(6-(3-hydroxy-2-oxopyrrolidin-1-yl)-1-oxoisoindolin-2-yl)-N,N-dimethyl-acetamide with the respective phenol or hydroxy-pyridine. DEAD may be substituted by DIAD. DCM may be substituted by THF, or a mixture of both solvents.

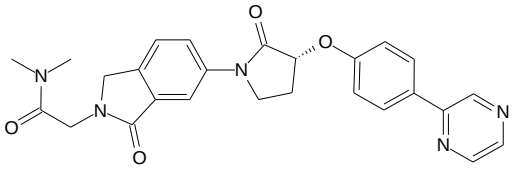
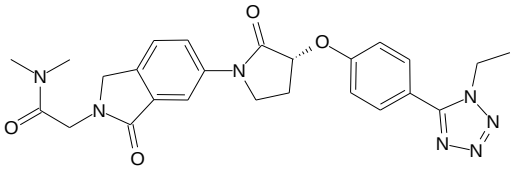
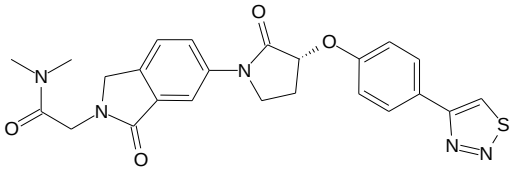
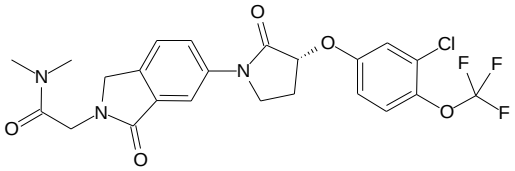
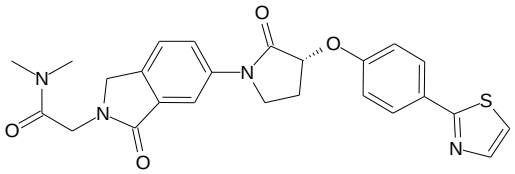
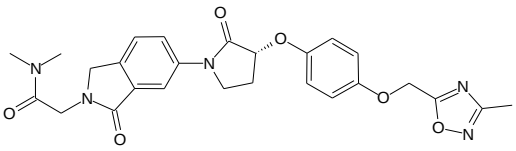
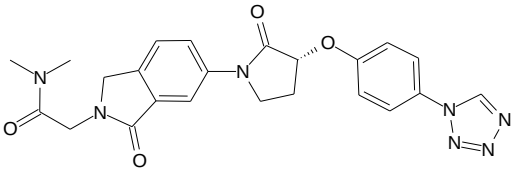
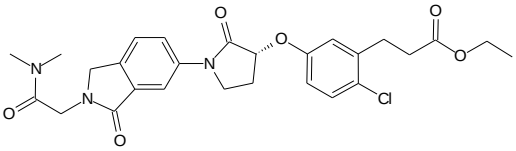
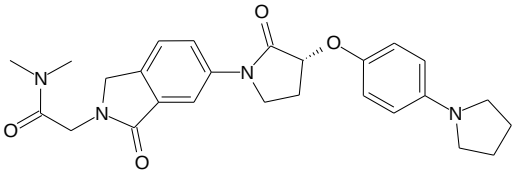
Table 2.

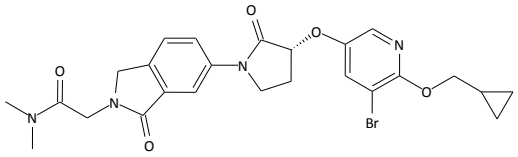
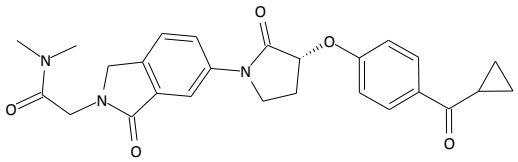
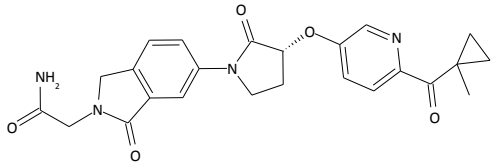
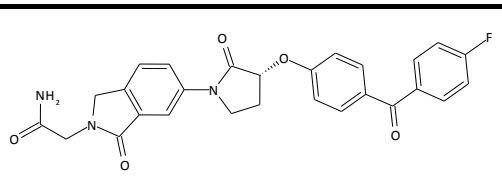
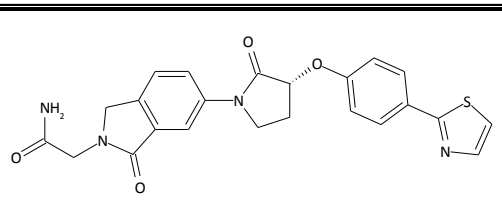
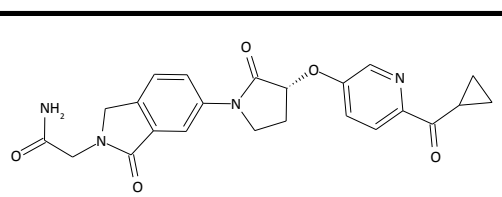
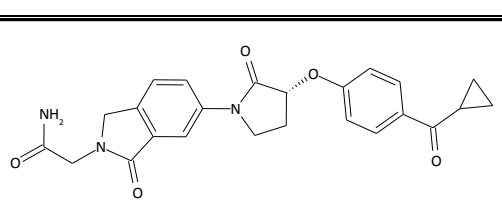
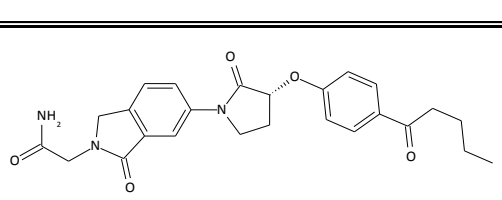
Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
2-01		A	1.68	478.1
2-02		A	1.40	477.4
2-03		A	1.74	491.4
2-04		A	1.32	463.3
2-05		A	1.65	493.3
2-06		A	1.70	483.2
2-07		A	1.72	479.4
2-08		A	1.17	464.3
2-09		A	1.61	412.2

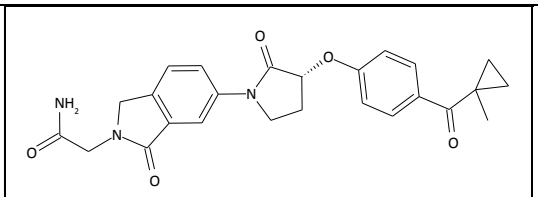
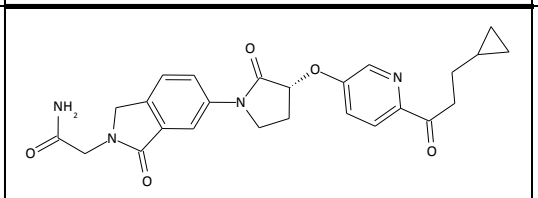
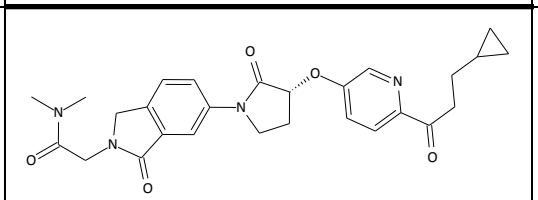
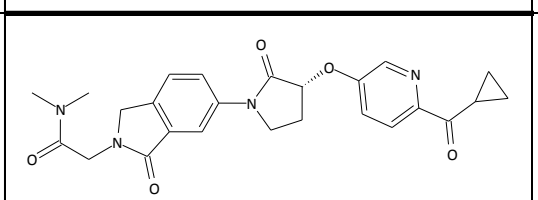
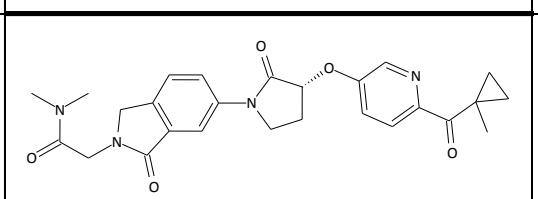
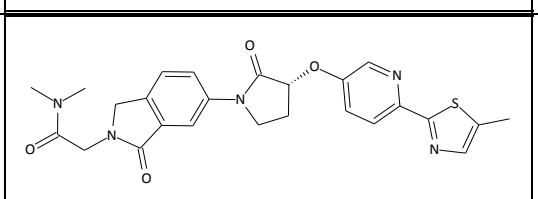
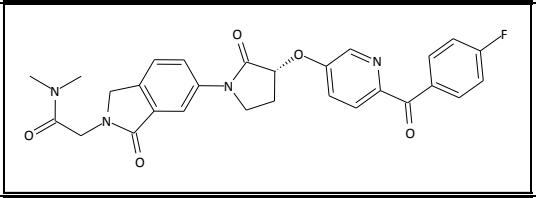
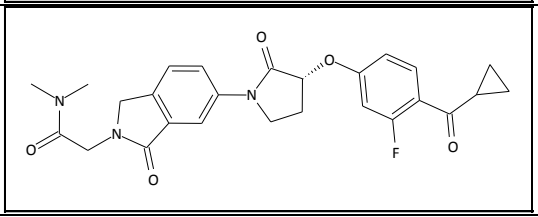
Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
2-10		A	1.51	429.1
2-11		A	1.49	450.1
2-12		A	1.68	478.2
2-13		A	1.58	464.1
2-14		A	1.61	505.1
2-15		A	1.66	516.1
2-16		A	1.75	504.1
2-17		A	1.27	413.1
2-18		A	1.71	491.3
2-19		A	1.64	481.3

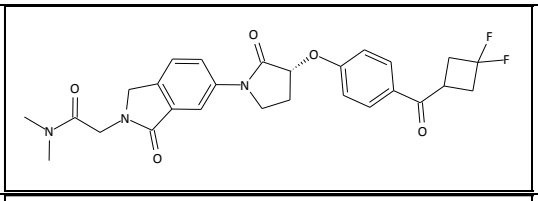
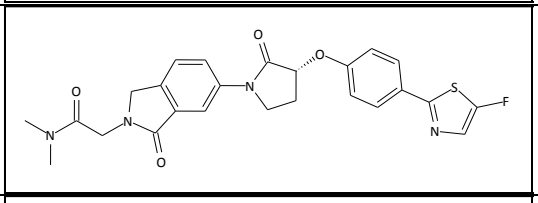
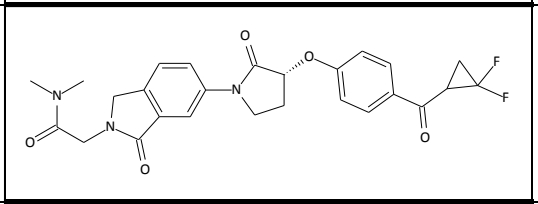
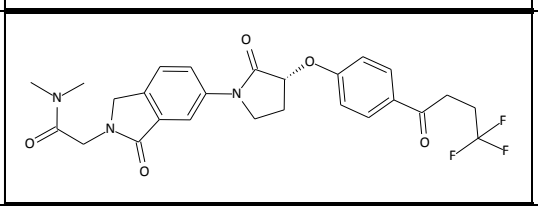
Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
2-20		A	1.51	467.3
2-21		A	1.61	476.3
2-22		A	1.79	494.3
2-23		A	1.58	487.3
2-24		A	1.35	479.3
2-25		A	1.35	461.3
2-26		A	1.32	520.3
2-27		A	1.76	520.3
2-28		A	1.39	477.3

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
2-29		A	1.37	462.3
2-30		A	1.68	492.3
2-31		A	1.63	491.3
2-32		A	1.53	476.2
2-33		A	1.35	508.3
2-34		A	1.73	504.3
2-35		A	1.43	491.3
2-36		A	1.24	461.3
2-37		A	1.47	461.3

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
2-38		A	1.46	472.3
2-39		A	1.44	490.3
2-40		A	1.53	478.2
2-41		A	1.81	512.2
2-42		A	1.57	477.2
2-43		A	1.52	506.3
2-44		A	1.38	462.3
2-45		A	1.77	528.3
2-46		A	1.35	463.4

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
2-47		C	1.76	543.0
2-48		C	1.50	462.2
2-49		C	1.43	449.1
2-50		C	1.58	488.1
2-51		C	1.43	449.1
2-52		C	1.36	435.1
2-53		C	1.42	434.1
2-54		C	1.60	450.2

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
2-55		C	1.50	448.1
2-56		C	1.56	463.2
2-57		C	1.63	491.2
2-58		C	1.44	463.2
2-59		C	1.51	477.2
2-60		C	1.55	492.2
2-61		C	1.62	517.2
2-62		C	1.56	480.3

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
2-63		C	1.64	512.2
2-64		C	1.63	495.3
2-65		C	1.56	498.3
2-66		C	1.63	518.3

Preparation of (S)-2-(6-(3-Hydroxy-2-oxopyrrolidin-1-yl)-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide

Typical Procedure 1 was followed to react 2-(6-bromo-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide with (S)-3-hydroxy-pyrrolidin-2-one to provide the title compound. MS ESI^+: m/z = 318 $[M+H]^+$.

Preparation of Phenols/Hydroxy-pyridines

6-Butylsulfanyl-pyridin-3-ol

Typical Procedure 4 was followed to convert 5-bromo-2-butylsulfanyl-pyridine into the corresponding boronate.

Typical Procedure 5a: The crude boronate (1.03 g) was mixed with THF/water (1:3, 10 mL) and sodium perborate tetrahydrate (1.0 g) was added. After 1 hour the mixture was adjusted to pH 5-6 by addition of HCl (0.1 M) and extracted three times with EA. The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. The residue was separated by preparative HPLC to provide the title compound. MS ESI^+: m/z = 184 $[M+H]^+$.

5-Bromo-2-butylsulfanyl-pyridine

A mixture of 5-bromo-2-chloro-pyridine (2.0 g), 1-butanethiol (1.3 mL), cesium carbonate (4.5 g) and DMF (5 mL) was heated to 60°C for 3 hours. The mixture was diluted with water and extracted three times with EA. The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated to provide the subtitle compound. MS ESI^+: m/z = 246 $[M+H]^+$.

6-(Cyclopropylmethylthio)pyridin-3-ol

Typical Procedures 4 and 5a were followed to convert 5-bromo-2-(cyclopropylmethylthio)pyridine to the title compound. MS ESI^+: m/z = 182 $[M+H]^+$.

5-Bromo-2-(cyclopropylmethylthio)pyridine

To a solution of 5-bromopyridine-2-thiol (3.9 g) in THF (100 mL) was added NaH (1.24 g) at 0°C and the mixture was stirred at 0°C for 30 minutes. Then (bromomethyl)cyclopropane (2.79 g) was added. The mixture was allowed to warm to RT and stirred for 6 hours. The mixture was poured into ice water (200 mL) and extracted with EA (100 mL x 3). The combined organic phases were washed with brine (50 mL) and then dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by SGC (eluent: PE) to provide the subtitle compound. MS ESI^+: m/z = 244 $[M+H]^+$.

6-(Cyclopropylthio)pyridin-3-ol

Typical Procedures 4 and 5a were followed to convert 5-bromo-2-(cyclopropylthio)pyridine to the title compound. MS ESI^+: m/z = 168 $[M+H]^+$.

5-Bromo-2-(cyclopropylthio)pyridine

To a suspension of NaH (60% in mineral oil, 2.40 g) in THF (100 mL) was added dropwise cyclopropanethiol (160 mL, 0.25 M in Et_2O) at 0°C. After stirring for 30 minutes, 5-bromo-2-fluoropyridine (3.52 g) was added in portions at 0°C and then warmed to RT slowly. The reaction mixture was stirred at RT overnight. The reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude product was obtained and used in next step without further purification. MS ESI^+: m/z = 230 $[M+H]^+$.

6-Cyclopropylmethoxy-5-fluoro-pyridin-3-ol

Following Typical Procedures 4 and 5a, conversion of 5-bromo-2-cyclopropylmethoxy-3-fluoro-pyridine to the boronate and oxidation with $NaBO_3$ provided the title compound. MS ESI^+: m/z = 184 $[M+H]^+$.

5-Bromo-2-cyclopropylmethoxy-3-fluoro-pyridine

Following Typical Procedure 6, reaction of 5-bromo-2,3-difluoro-pyridine with cyclopropyl-methanol provided the subtitle compound. MS ESI^+: m/z = 246 $[M+H]^+$.

6-Cyclopropylmethoxy-5-methyl-pyridin-3-ol

Following Typical Procedures 4 and 5a, conversion of 5-bromo-2-cyclopropylmethoxy-3-methyl-pyridine to the boronate and oxidation with $NaBO_3$ provided the title compound. MS ESI^+: m/z = 180 $[M+H]^+$.

5-Bromo-2-cyclopropylmethoxy-3-methyl-pyridine

Following Typical Procedure 6, reaction of 5-bromo-2-fluoro-3-methyl-pyridine with cyclopropyl-methanol provided the subtitle compound. MS ESI^+: m/z = 242 $[M+H]^+$.

6-(2,2,2-Trifluoroethoxy)pyridin-3-ol

Following Typical Procedures 4 and 5a, conversion of 5-bromo-2-(2,2,2-trifluoroethoxy) pyridine to the boronate and oxidation with $NaBO_3$ provided the title compound. MS ESI^+: m/z = 194 $[M+H]^+$.

5-Bromo-2-(2, 2, 2-trifluoroethoxy) pyridine

Following Typical Procedure 6, reaction of 5-bromo-2-fluoro-pyridine with 2,2,2-trifluoroethanol provided the subtitle compound. MS ESI^+: m/z = 256 $[M+H]^+$.

6-(Cyclopropylmethylamino)pyridin-3-ol

Following Typical Procedures 4 and 5a, conversion of 5-bromo-N-(cyclopropylmethyl)pyridin-2-amine to the boronate and oxidation with $NaBO_3$ provided the title compound. MS ESI^+: m/z = 165 $[M+H]^+$.

5-Bromo-N-(cyclopropylmethyl)pyridin-2-amine

To a seal tube was added 5-bromo-2-fluoropyridine (1.57 g), cyclopropylmethanamine (632 mg), DIPEA (2.3 g), and DMSO (5 mL). The resultant mixture was heated under microwave irradiation at 120°C for 2 hours. The reaction mixture was diluted with EA (100 mL), and washed with water (30 mL x 3) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to obtain the crude product (1.82 g), which was used without further purification.

6-((1R,3r,5S)-Bicyclo[3.1.0]hexan-3-yloxy)pyridin-3-ol

To a stirred solution of 2-((1R,3r,5S)-bicyclo[3.1.0]hexan-3-yloxy)-5-bromopyridine (2.10 g) in THF (37 mL) at -78°C was added n-butyl lithium (6.2 mL, 2.5 M in hexane) dropwise and the resulting mixture was allowed to stir at -78°C for 45 minutes. Trimethyl borate (9.5 mL) was added via syringe and the resulting mixture was stirred for an additional 2 hours. The mixture was allowed to warm to room temperature. Water (300 mL) and $NaBO_3$ (3.93 g) were added. The mixture was stirred at room temperature overnight. The reaction mixture was poured into water (100 mL) and extracted with EtOAc (100 mL x 3). The organic phase was dried over sodium sulphate and concentrated to give a crude, which was purified by column chromatography on silica gel eluting with hexane/EA = 8:2 to provide the title compound. MS ESI^+: m/z = 192 $[M+H]^+$.

2-((1R,3r,5S)-Bicyclo[3.1.0]hexan-3-yloxy)-5-bromopyridine

Sodium hydride (730 mg, 60% in mineral oil) was added to a solution of (1R,3r,5S)-bicyclo[3.1.0]hexan-3-ol (2.69 g) in dry DMF (55 mL). The mixture was stirred for 30 minutes at room temperature. 5-Bromo-2-fluoropyridine (1.50 g) was added and the reaction mixture was stirred at 80°C for 5 hours. After cooling to RT, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (100 mL x 3). The organic phase was dried over sodium sulphate and concentrated. The crude was utilized for the next step without further purification.

6-((1S,3S,5R)-Bicyclo[3.1.0]hex-3-yloxy)-pyridin-3-ol

Following Typical Procedures 4 and 5a, conversion of 2-((1S,3S,5R)-bicyclo[3.1.0]hex-3-yloxy)-5-bromo-pyridine to the boronate and oxidation with $NaBO_3$ provided the title compound. MS ESI^+: m/z = 192 $[M+H]^+$.

2-((1S,3S,5R)-Bicyclo[3.1.0]hex-3-yloxy)-5-bromo-pyridine

To a mixture of 5-bromo-pyridin-2-ol (1.42 g), (1R,3r,5S)-bicyclo[3.1.0]hexan-3-ol (1.0 g) and triphenylphosphine (2.67 g) in THF (30 mL) at room temperature was added diisopropyl azodicarboxylate (2.06 g) dropwise under N_2. The reaction mixture was stirred at 55°C for two days under N_2. The reaction mixture was cooled to room temperature, and concentrated under vacuum. The residue was purified by silica gel chromatography (hexane to hexane/ethyl acetate 9:1) to provide the title compound. MS ESI^+: m/z = 254 $[M+H]^+$.

6-(2-Cyclopropylethyl)pyridin-3-ol

A mixture of 2-(2-cyclopropylethyl)-5-(4-methoxybenzyloxy)pyridine (2.5 g) in TFA (20 mL) was heated under reflux for 30 minutes. The reaction mixture was concentrated and the crude residue was purified by silica gel chromatography eluting with petroleum ether/EtOAc (1:1) to provide the title compound. MS ESI$^+$: m/z = 164 $[M+H]^+$.

2-(2-Cyclopropylethyl)-5-(4-methoxybenzyloxy)pyridine

To a mixture of 2-(cyclopropylethynyl)-5-(4-methoxybenzyloxy)pyridine (2.7 g) in MeOH (20 mL) was added Raney-Ni (270 mg) under N_2 atmosphere. The mixture was stirred at room temperature after exchanging the nitrogen for a H_2 atmosphere for 20 minutes. Filtration through a pad of celite and evaporation of the solvent provided the subtitle compound. MS ESI$^+$: m/z = 284 $[M+H]^+$.

2-(Cyclopropylethynyl)-5-(4-methoxybenzyloxy)pyridine

To a round-bottomed flask was added 2-bromo-5-(4-methoxybenzyloxy)pyridine (4.0 g), ethynylcyclopropane (904 mg), Pd(dppf)Cl_2 (787 mg), CuI (200 mg), Et_3N (2.8 g) and DMF (10 mL). The reaction mixture was stirred at 60°C under N_2 atmosphere overnight. After the reaction was complete, the residue was diluted with ethyl acetate (200 mL), washed with water (50 mL x 2), and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude residue was purified by chromatography (silica gel, PE/EA = 4:1) to provide the subtitle compound. MS ESI$^+$: m/z = 280 $[M+H]^+$.

6-(3-Cyclopropylpropyl)pyridin-3-ol

To a solution of 2-(3-cyclopropylpropyl)-5-(4-methoxybenzyloxy)pyridine (800 mg) in EtOH (10 mL) was added TFA (3 mL). The mixture was stirred at RT for 4 hours. The crude obtained after evaporation was purified by chromatography (silica gel, PE/EA = 1:1) to provide the title compound. MS ESI$^+$: m/z = 178 $[M+H]^+$.

2-(3-Cyclopropylpropyl)-5-(4-methoxybenzyloxy)pyridine

To a round-bottomed flask was added 2-(3-cyclopropyl-prop-1-ynyl)-5-(4-methoxy-benzyloxy)-pyridine (820 mg), Raney-Ni (200 mg), and EtOH (10 mL). The reaction mixture was stirred under an hydrogen atmosphere at RT for 15 minutes. The reaction mixture was filtered and the filtrate evaporated to provide the subtitle compound. MS ESI$^+$: m/z = 298 $[M+H]^+$.

2-(3-Cyclopropyl-prop-1-ynyl)-5-(4-methoxy-benzyloxy)-pyridine

To a solution of 2-ethynyl-5-(4-methoxy-benzyloxy)-pyridine (2.19 g) in THF (20 mL) was added n-BuLi (4.51 mL, 2.5 M in hexane) at -78°C over 30 minutes. The resulting mixture was stirred at 0°C for 10 minutes and then re-cooled to -78°C. HMPA (2.4 g) was added, and the mixture was stirred at -78°C for 30 minutes. (Bromomethyl)cyclopropane (1.24 g) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The combined organic layers were washed with water (50 mL x 3) and brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel eluting with EA/PE = 1:6 to provide the subtitle compound. MS ESI$^+$: m/z = 294 $[M+H]^+$.

2-Ethynyl-5-(4-methoxy-benzyloxy)-pyridine

To a 100 mL round-bottomed flask was added 5-(4-methoxybenzyloxy)-2-((trimethylsilyl)ethynyl)pyridine (2.89 g), K_2CO_3 (1.28 g), and MeOH (30 mL). The reaction mixture was stirred at room temperature for 2 hours. The formed precipitate was filtered off and the solid was washed with MeOH (5 mL x 3) to provide the subtitle compound. MS ESI$^+$: m/z = 240 $[M+H]^+$.

5-(4-Methoxybenzyloxy)-2-((trimethylsilyl)ethynyl)pyridine

To a solution of 2-bromo-5-(4-methoxybenzyloxy)pyridine (3.0 g) in DMF (30 mL) was added ethynyltrimethylsilane (1.2 g), Pd(dppf)Cl_2 (373 mg), CuI (98 mg), and Et_3N (2.8 mL). After the addition, the mixture was stirred at 70°C for 4 hours. After cooling to RT, the reaction mixture was diluted with water (30 mL) and extracted with EA (50 mL x 3). The combined organic layers were washed with water (50 mL x 3) and brine (50 mL), dried over Na_2SO_4 and concentrated. The crude was purified by column chromatography on silica gel eluting with EA/PE = 1:10 to provide the subtitle compound. MS ESI$^+$: m/z = 312 $[M+H]^+$.

5-Bromo-6-(cyclopropylmethoxy)pyridin-3-ol

To a solution of 3-bromo-2-(cyclopropylmethoxy)-5-iodopyridine (12.5 g) in dry THF (300 mL) was added *i*-PrMgCl*LiCl (30 mL) dropwise at 0°C. The mixture was stirred at 0°C for 20 min and then $B(OMe)_3$ (5.5 g) was added at 0°C. The mixture was allowed to warm to r.t. and stirred for 3 h. The mixture was quenched by the addition of brine (50 mL). The organic phase was separated and the aqueous phase was extracted with EA (50 mL x 3). The organic phases were combined and the solvent was removed under reduced pressure. The residue was treated according Typical Procedure 5a to obtain the title compound. MS ESI$^+$: m/z = 244 $[M+H]^+$.

3-Bromo-2-(cyclopropylmethoxy)-5-iodopyridine

To a suspension of NaH (60% in mineral oil, 4.32 g) in THF (300 mL) was added cyclopropylmethanol (5.83 g) at 0°C and the mixture was stirred for 30 min at 0°C. A solution of 3-bromo-2-fluoro-5-iodopyridine (16.3 g) in THF (50 mL) was added to the suspension at 0°C. The suspension was allowed to warm to r.t. and stirred for 18 h. The suspension was poured into ice water and then extracted with EA (200 mL x 3). The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by SGC (eluent: PE) to give the subtitle compound. MS ESI^+: m/z = 354 $[M+H]^+$.

Preparation of Examples 3

Example 3-01 (Typical Procedure 7a)

A mixture of (R)-tert-butyl 2-(6-(3-((6-(cyclopropylmethoxy)pyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-4-fluoro-1-oxoisoindolin-2-yl)acetate (23 mg), TFA (1 mL) and DCM (1.5 mL) was stirred for 1 hour. Evaporation of the volatiles provided Example 3-01.

Example 3-02 (Typical Procedure 7b)

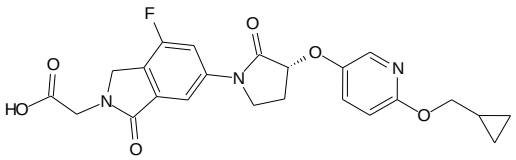
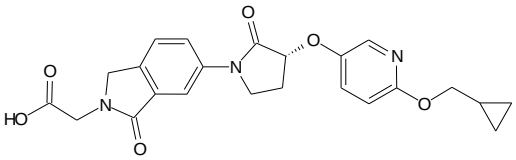
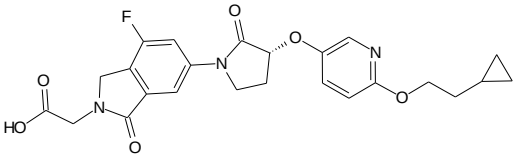
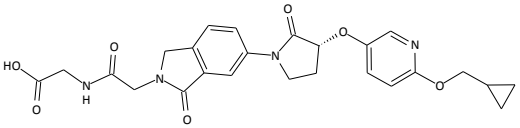
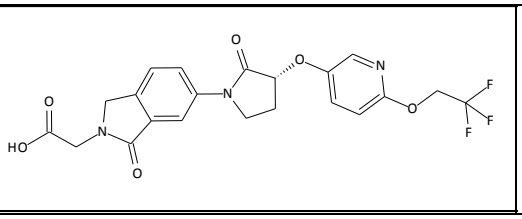
A mixture of (R)-ethyl 2-(6-(3-((6-(cyclopropylmethoxy)pyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-1-oxoisoindolin-2-yl)acetate (10 mg) and THF/MeOH/H_2O/DIPEA (2:2:1:1, 0.5 mL) was heated by microwave irradiation to 120°C for 1 hour. Example 3-02 (containing residual amounts of DIPEA) was obtained by evaporation of the volatiles.

Example 3-03 (Typical Procedure 7c)

A mixture of (R)-methyl 2-(6-(3-((6-(2-cyclopropylethoxy)pyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-4-fluoro-1-oxoisoindolin-2-yl)acetate (750 mg), LiOH (1.16 mL, 2 M in water) and THF (20 mL) was stirred for 2 hours. The reaction mixture was acidified with HCl (2 M) and extracted with EA. The organic layer was dried over Na_2SO_4, and concentrated to provide Example 3-03.

Table 3.

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
3-01		A	1.62	456.2
3-02		C	1.56	438.2
3-03		A	1.87	470.2
3-04		C	1.52	495.2
3-05		C	1.58	466.1

Preparation of Examples 4

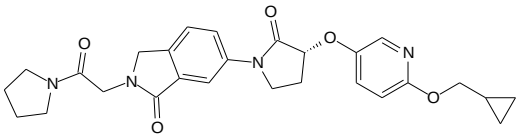
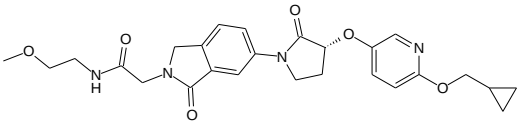
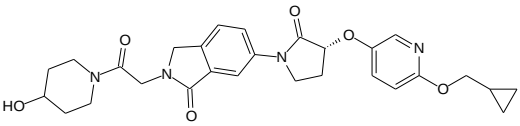
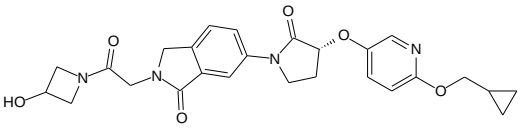
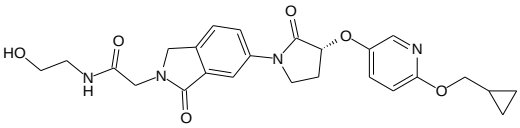
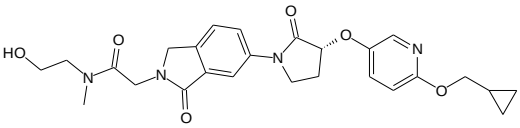
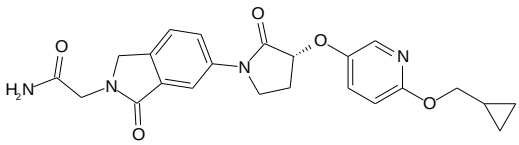
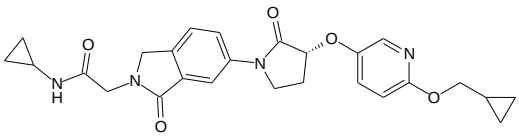
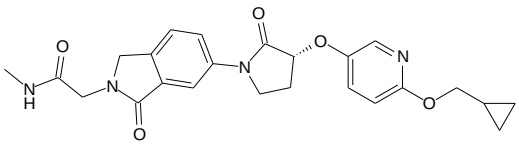
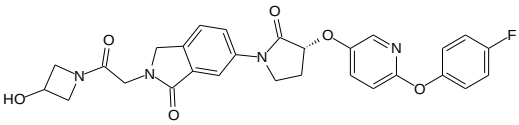
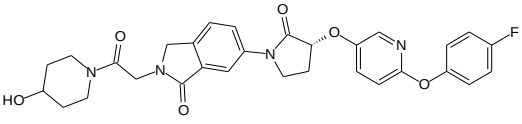
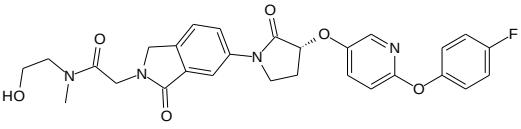
Example 4-01 (Typical Procedure 9)

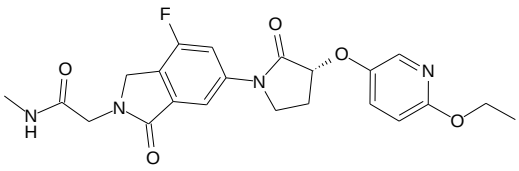
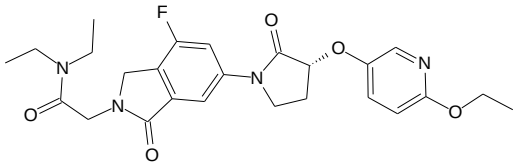
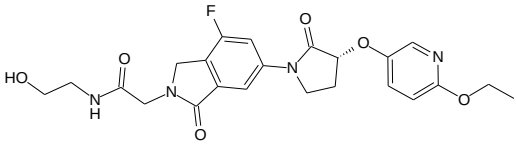
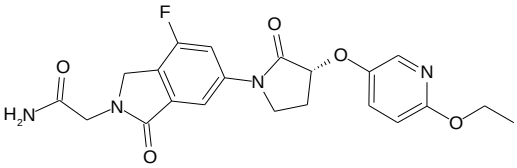
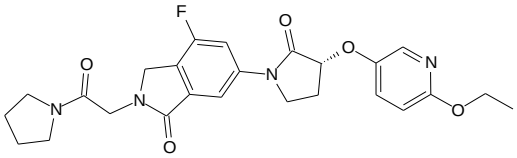
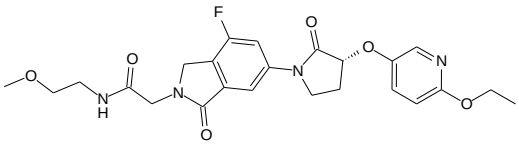
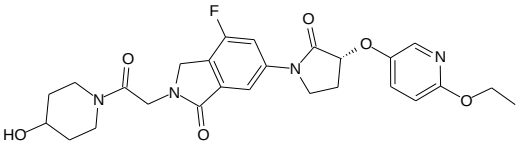
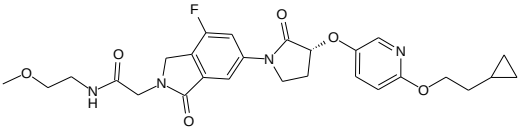
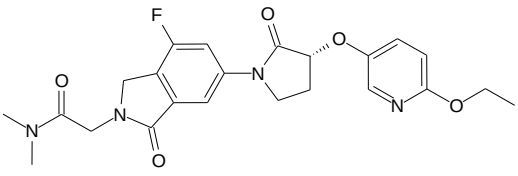
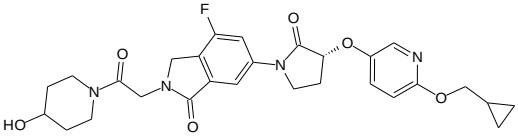
To a mixture of (R)-2-(6-(3-((6-(cyclopropylmethoxy)pyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-1-oxoisoindolin-2-yl)acetic acid (100 mg), DIPEA (40 µL) and DMF (2 mL) was added EDCI (44 mg) and HOBt (31 mg). After 10 minutes pyrrolidine (16 mg) was added. After 2 hours the mixture was separated by preparative HPLC to provide Example 4-01.

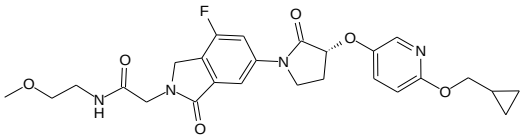
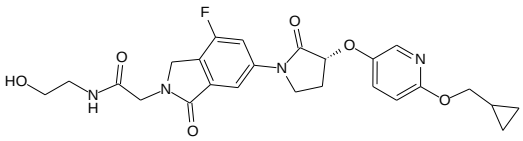
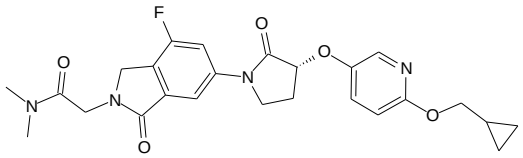
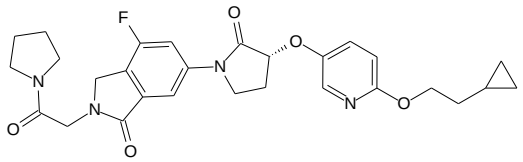
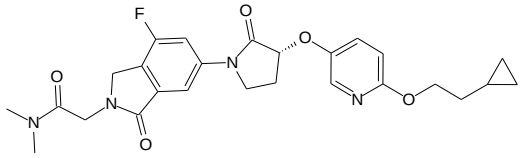
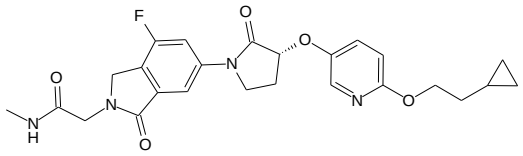
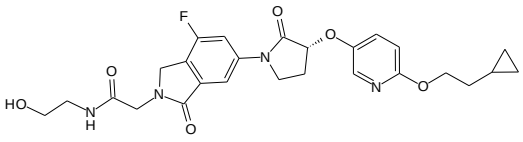
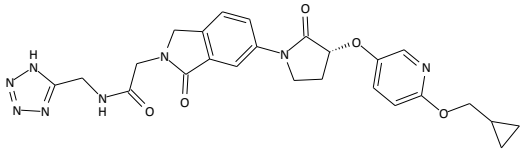
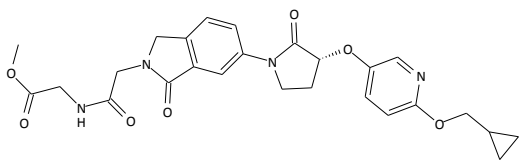
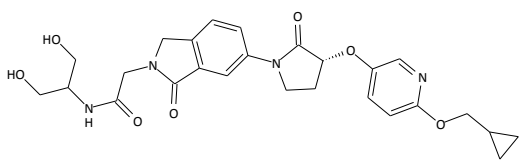
Following essentially this procedure the Examples 4 in Table 4 were obtained by coupling of the appropriate carboxylic acid with the respective amine.

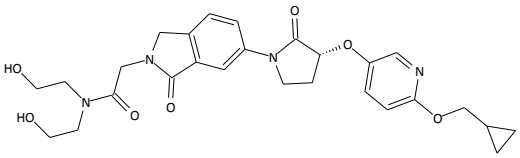
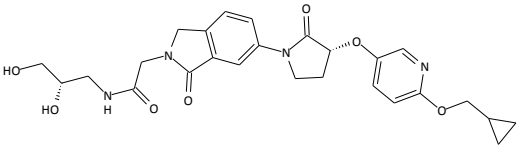
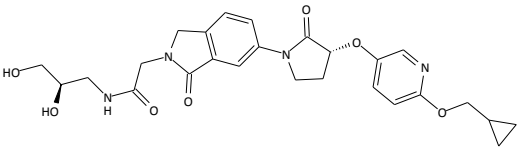
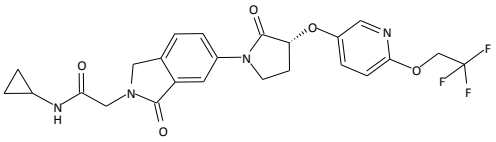
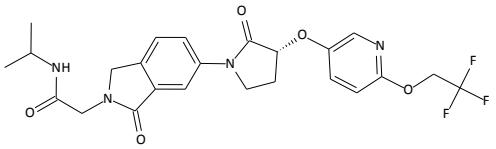
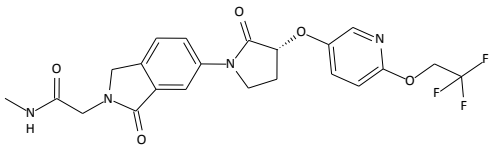
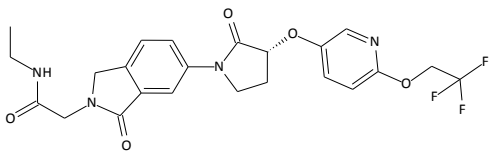
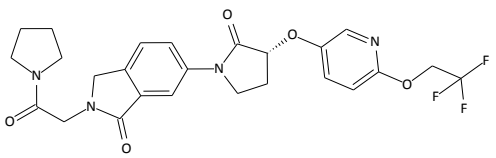
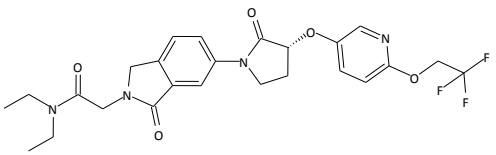
Table 4.

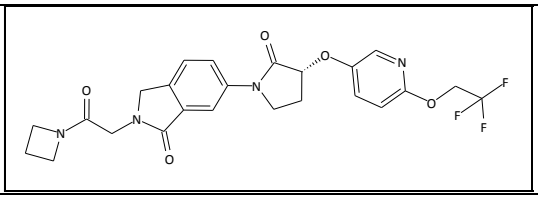
Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
4-01		A	1.73	491.2
4-02		A	1.68	495.2
4-03		A	1.64	521.2
4-04		A	1.62	537.3 ESI-: [M-H+FA]-
4-05		A	1.60	481.2
4-06		A	1.63	495.2
4-07		A	1.61	437.1
4-08		A	1.70	477.2
4-09		A	1.65	451.1
4-10		C	1.57	533.1
4-11		C	1.60	561.1
4-12		C	1.58	535.1

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
4-13		A	1.50	443.2
4-14		A	1.68	485.3
4-15		A	1.44	473.2
4-16		B	3.33	429.2
4-17		A	1.61	483.2
4-18		A	1.53	487.3
4-19		A	1.50	513.2
4-20		A	1.74	527.3
4-21		A	1.55	457.2
4-22		A	1.61	539.4

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
4-23		A	1.64	513.4
4-24		A	1.55	499.3
4-25		A	1.64	483.2
4-26		A	1.92	523.3
4-27		A	1.88	497.3
4-28		A	1.85	483.3
4-29		A	1.80	513.3
4-30		C	1.54	519.3
4-31		C	1.60	509.3
4-32		C	1.48	511.3

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
4-33		C	1.50	525.3
4-34		C	1.48	511.3
4-35		C	1.48	511.3
4-36		n.a.	n.a.	n.a.
4-37		n.a.	n.a.	n.a.
4-38		C	1.56	479.1
4-39		C	1.61	493.1
4-40		C	1.64	519.2
4-41		C	1.7	521.17

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
4-42		C	1.6	505.2

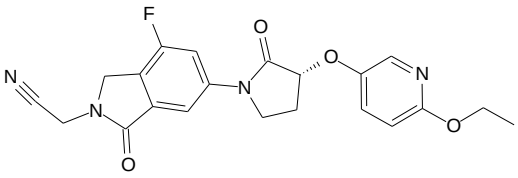
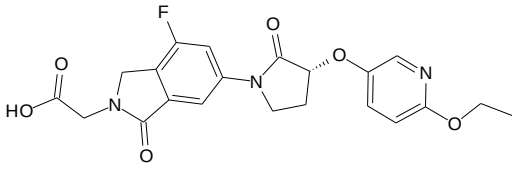
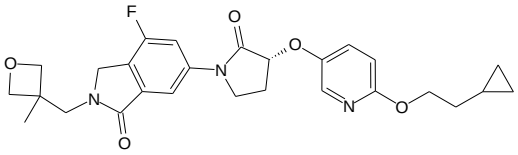
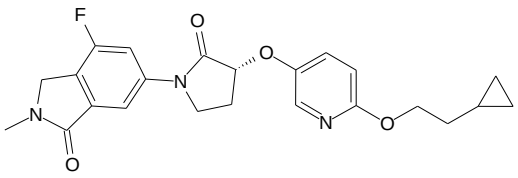
Preparation of Examples 5

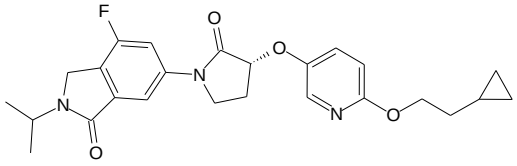
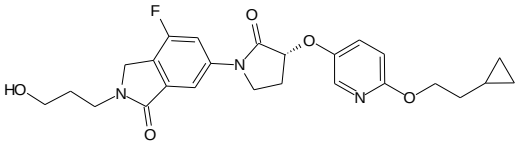
Example 5-01

Following Typical Procedure 2, (R)-6-(3-((6-ethoxypyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-4-fluoroisoindolin-1-one was reacted with 2-bromoacetonitrile to provide Example 5-01. Similarly the other Examples 5 in Table 5 were obtained by alkylation of the appropriate N-unsubstituted isoindolinone and the respective alkyl bromide or iodide.

Example 5-02 was obtained by adding water to the reaction mixture promoting the saponification of the primary reaction product ({6-[(R)-3-(6-ethoxy-pyridin-3-yloxy)-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-1,3-dihydro-isoindol-2-yl}-acetic acid methyl ester).

Table 5.

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
5-01		A	1.63	411.2
5-02		A	1.52	430.2
5-03		A	1.62	496.3
5-04		A	1.93	426.2

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
5-05		A	2.04	454.3
5-06		A	1.75	470.3

(R)- 6-(3-((6-Ethoxypyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-4-fluoroisoindolin-1-one

A mixture of (R)-2-(tert-butyl)-6-(3-((6-ethoxypyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-4-fluoroisoindolin-1-one (1.6 g) and TFA (5 mL) was heated by microwave irradiation to 130°C for 1 hour. After cooling to RT, the reaction mixture was evaporated. Residual TFA was removed by co-evaporation with toluene (3 x 30 mL) to provide the title compound. MS ESI^+: m/z = 372 $[M+H]^+$.

6-{(R)-3-[6-(2-Cyclopropyl-ethoxy)-pyridin-3-yloxy]-2-oxo-pyrrolidin-1-yl}-4-fluoro-2,3-dihydro-isoindol-1-one

Following Typical Procedure 1, (R)-3-((6-(cyclopropylethoxy)pyridin-3-yl)oxy)pyrrolidin-2-one was reacted with 6-bromo-4-fluoroisoindolin-1-one to provide the title compound. MS ESI^+: m/z = 412 $[M+H]^+$.

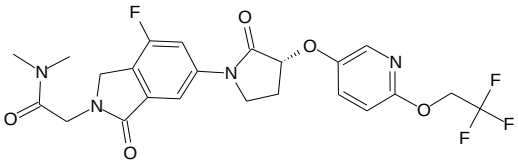
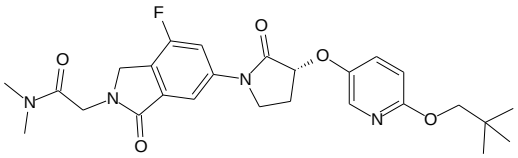
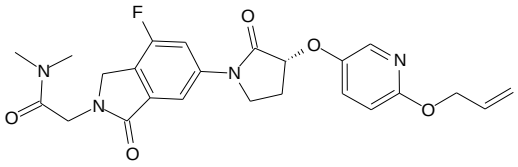
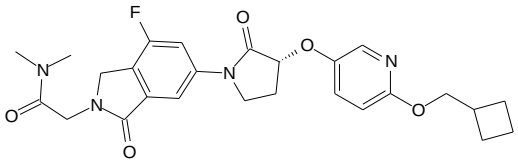
Preparation of Examples 6

Example 6-01 (Typical Procedure 10)

A mixture of (R)-2-(4-fluoro-6-(3-((6-hydroxypyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide (90 mg), 2-bromo-1,1,1-trifluoroethane (34 mg), potassium carbonate (58 mg) and DMF (3 mL) was heated to 130°C for 1 hour. The reaction mixture was filtered and separated by preparative HPLC to provide Example 6-01.

Similarly the other Examples 6 in Table 6 were obtained by alkylating (R)-2-(4-fluoro-6-(3-((6-hydroxypyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide with the respective alkyl bromide.

Table 6.

Example	Structure	LCMS Method	R_t [min]	ESI^+ m/z [amu]
6-01		A	1.66	511.2
6-02		A	1.81	499.5
6-03		A	1.59	469.3
6-04		A	1.76	497.3

(R)-2-(4-Fluoro-6-(3-((6-hydroxypyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide

A mixture of (R)-2-(6-(3-((6-(benzyloxy)pyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-4-fluoro-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide (2.2 g), Pd/C (452 mg, 10%) and methanol (50 mL) was stirred under an atmosphere of hydrogen (1 atm) for 8 hours. The catalyst was filtered off and the filtrate concentrated. The crude was purified by SGC (DCM/MeOH 9:1) to provide the title compound. MS ESI^+: m/z = 429 $[M+H]^+$.

(R)-2-(6-(3-((6-(benzyloxy)pyridin-3-yl)oxy)-2-oxopyrrolidin-1-yl)-4-fluoro-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide

Following Typical Procedure 1, (R)-3-((6-(benzyloxy)pyridin-3-yl)oxy)pyrrolidin-2-one was reacted with 2-(6-bromo-4-fluoro-1-oxoisoindolin-2-yl)-N,N-dimethylacetamide to provide the subtitle compound. MS ESI^+: m/z = 519 $[M+H]^+$.

(*R*)-3-(6-Benzyloxy-pyridin-3-yloxy)-pyrrolidin-2-one

Following the sequence described for (*R*)-3-[6-(2-cyclopropyl-ethoxy)-pyridin-3-yloxy]-pyrrolidin-2-one, the subtitle compound was prepared from phenyl-methanol, 5-bromo-2-fluoro-pyridine and (*S*)-3-hydroxy-pyrrolidin-2-one. MS ESI^+: m/z = 285 $[M+H]^+$.

Pharmacological Utility

The biological activity of the compounds of the invention may be demonstrated by known in vitro assays. Examples include in vitro cellular assays for recombinant and non-recombinant GPR119 as described in the following.

Functional Cellular Assays Measuring GPR119-mediated cAMP Release

Compounds of the invention, which are agonists of GPR119, were characterized by functional assays measuring the cAMP response of HEK-293 cell lines stably expressing recombinant GPR119 from man, mouse or rat, or by using a hamster cell line HIT-T15 expressing GPR119 endogenously. The cAMP content was determined using a kit based on homogenous time-resolved fluorescence (HTRF) from Cisbio Corp. (cat. no. 62AM4PEC). For preparation, cells were split into T175 culture flasks and grown to near confluency in medium (DMEM / 10% FCS for HEK-293 cells, and F-12K medium / 10% horse serum / 2.5% FCS for HIT-T15 cells, respectively). Medium was then removed and cells washed with PBS lacking calcium and magnesium ions, followed by proteinase treatment with accutase (Sigma-Aldrich, cat. no. A6964). Detached cells were washed and resuspended in assay buffer (1 x HBSS; 20 mM HEPES, 0.1% BSA, 2 mM IBMX) and cellular density determined. They were then diluted to 400000 cells/mL and 25 µL-aliquots dispensed to the wells of 96-well plates. For measurement, 25 µL of test compound in assay buffer was added and incubated for 30 minutes at room temperature. After addition of HTRF reagents diluted in lysis buffer, the plates were incubated for 1 hour, followed by measuring the fluorescence ratio at 665 vs. 620 nm. Potency of the agonists was quantified by determining the concentrations that caused 50% of the maximal response/activation (EC_{50}). See Table 7 for exemplary data obtained using the cell line expressing human GPR119.

Compounds of the invention show EC_{50} values typically in the range of about 0.001 to 100 µM, preferably from about 0.001 to 10 µM, more preferably from about 0.001 to 1 µM and most preferably from about 0.001 to 0.3 µM.

Table 7.

Example	EC_{50} [µM]	Example	EC_{50} [µM]	Example	EC_{50} [µM]	Example	EC_{50} [µM]	Example	EC_{50} [µM]
1-01	0.089	1-41	2.030	2-11	0.267	2-50	0.102	4-18	0.381
1-02	2.030	1-42	0.366	2-12	0.044	2-51	0.126	4-19	0.297
1-03	10.900	1-43	0.449	2-13	0.075	2-52	0.207	4-20	0.062
1-04	0.540	1-44	0.276	2-14	0.085	2-53	0.130	4-21	0.222

1-05	0.313	1-45	0.179	2-15	0.066	2-54	0.038	4-22	0.088
1-06	0.151	1-46	0.184	2-16	0.047	2-55	0.207	4-23	0.157
1-07	1.900	1-47	0.218	2-17	9.360	2-56	0.034	4-24	0.266
1-08	1.050	1-48	0.073	2-18	0.074	2-57	0.050	4-25	0.080
1-09	0.163	1-49	0.106	2-19	0.047	2-58	0.251	4-26	0.048
1-10	0.267	1-50	0.064	2-20	0.233	2-59	0.330	4-27	0.046
1-11	0.202	1-51	0.057	2-21	0.072	2-60	0.097	4-28	0.049
1-12	29.400	1-52	0.124	2-22	0.041	2-61	0.106	4-29	0.157
1-13	0.237	1-53	0.098	2-23	0.261	2-62	0.059	4-30	0.749
1-14	4.440	1-54	0.066	2-24	21.000	2-63	0.098	4-31	0.153
1-15	0.221	1-55	0.106	2-25	12.000	2-64	0.038	4-32	0.448
1-16	0.360	1-56	0.051	2-26	1.060	2-65	0.125	4-33	0.598
1-17	0.030	1-57	1.120	2-27	0.160	2-66	0.052	4-34	0.541
1-18	0.065	1-58	0.680	2-28	1.470	3-01	1.050	4-35	0.556
1-19	0.071	1-59	0.451	2-29	3.390	3-02	0.443	4-36	0.562
1-20	0.046	1-60	0.147	2-30	0.082	3-03	0.087	4-37	0.232
1-21	0.346	1-61	0.516	2-31	0.343	3-04	0.807	4-38	0.131
1-22	0.242	1-62	0.139	2-32	0.268	3-05	0.544	4-39	0.205
1-23	0.695	1-63	0.104	2-33	2.210	4-01	0.106	4-40	0.043
1-24	14.300	1-64	0.027	2-34	0.084	4-02	0.144	4-41	0.040
1-25	0.441	1-65	0.052	2-35	8.660	4-03	0.206	4-42	0.039
1-26	14.200	1-66	0.163	2-36	32.800	4-04	0.197	5-01	0.067
1-27	0.488	1-67	0.081	2-37	0.862	4-05	0.249	5-02	6.080
1-28	0.976	1-68	0.143	2-38	0.808	4-06	0.281	5-03	2.530
1-29	0.015	1-69	0.131	2-39	27.000	4-07	0.163	5-04	1.240
1-30	>100	2-01	0.106	2-40	0.337	4-08	0.168	5-05	5.040
1-31	0.065	2-02	0.056	2-41	0.470	4-09	0.107	5-06	0.609
1-32	0.063	2-03	0.054	2-42	0.117	4-10	0.208	6-01	0.077
1-33	8.510	2-04	0.156	2-43	1.500	4-11	0.218	6-02	0.126
1-35	0.019	2-05	0.062	2-44	14.700	4-12	0.297	6-03	0.064
1-36	0.142	2-06	0.082	2-45	1.510	4-13	0.326	6-04	0.035
1-37	1.040	2-07	0.115	2-46	6.370	4-14	0.288	empty	empty
1-38	0.035	2-08	2.120	2-47	0.090	4-15	0.547	empty	empty
1-39	0.060	2-09	0.739	2-48	0.202	4-16	0.271	empty	empty
1-40	0.044	2-10	2.070	2-49	0.424	4-17	0.191	empty	empty

Based on the demonstrated ability of the compounds of the invention to activate GPR119 it is predicted that said compounds are useful for treatment of diseases and/or prevention of conditions which are modulated by GPR119.

Especially, the compounds of the invention may be useful to treat GPR119-related diseases and/or prevent GPR119-mediated conditions in humans.

The compounds of the invention are especially suitable for the treatment and/or prevention of:

1a) Disorders of fatty acid metabolism and glucose utilization disorders

1b) Disorders in which insulin resistance is involved

2) Diabetes mellitus, especially type 2 diabetes mellitus, including the prevention of the sequelae associated therewith. Particular aspects in this context are:

- a) Improvement of hyperglycemia
- b) Improvement of insulin resistance
- c) Improvement of glucose tolerance
- d) Protection of pancreatic beta cells
- e) Improvement of beta cell function
- f) Prevention of micro- and macrovascular disorders, such as
  - a. Retinopathy
  - b. Atherosclerosis
  - c. Nephropathy and microalbuminuria
  - d. Neuropathy
- g) Chronic low grade inflammation

3) Various other conditions which may be associated with the metabolic syndrome or the syndrome X, such as

- a) Increased abdominal girth
- b) Obesity
- c) Liver disorders
  - a. Fatty liver
  - b. Steatosis
  - c. Steatohepatitis
  - d. Cirrhosis
- d) Dyslipidemia (e.g. hypertriglyceridemia, hypercholesterolemia, hyperlipoproteinemia and/or low HDL)
- e) Insulin resistance
- f) Hypercoagulability
- g) Hyperuricemia
- h) Thromboses, hypercoagulable and prothrombotic states (arterial and venous)

i) High blood pressure

j) Endothelial dysfunction

k) Heart failure, for example (but not limited to) following myocardial infarction, hypertensive heart disease or cardiomyopathy

4) Cardiovascular diseases, for example (but not limited to) myocardial infarction and stroke

5) Bone-related diseases and disorders characterized by redcued bone mass, such as:

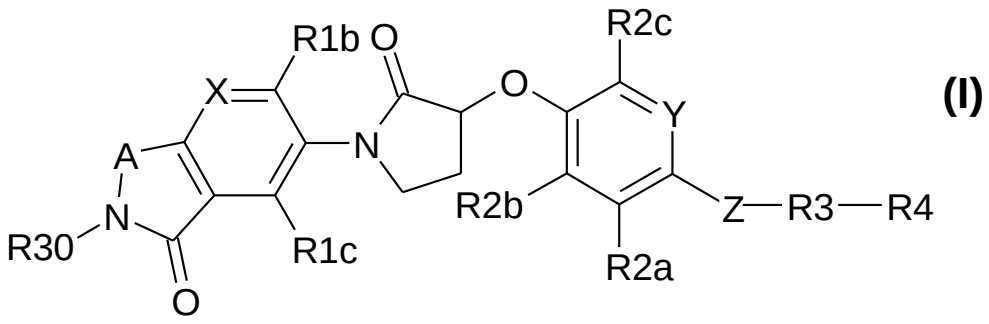
a) Osteoporosis

b) Rheumatoid arthritis

c) Osteoarthritis.

Claims:

1. A compound of the formula I



(I)

in which

X is N or C-R1a;

A is CR31R33, NR31, CR31R33-NR31 or CR31=N;

R30 is H or $(CR11R12)_n$-R32;

R31 is H or $(CR11R12)_n$-R32;

R33 is H or $(C_1$-$C_6)$-alkyl;

R11, R12 are independently of each other H or $(C_1$-$C_6)$-alkyl;

n is 0, 1, 2 or 3;

R32 is $(C_1$-$C_6)$-alkyl, COOR13, CONR14R15, $S(O)_m$R16, OH, CN, $(C_3$-$C_8)$-cycloalkyl, $(C_5$-$C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;

wherein the groups (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyloxy, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or (C_1-C_6)-alkyl;

R14, R15 are independently of each other H, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted with 1 to 3 groups selected from the list OR17, COOR19 and a 4-, 5- or 6-membered heterocycle;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17;

R16 is (C_1-C_6)-alkyl;

R17 is H or (C_1-C_6)-alkyl;

R18 is H or (C_1-C_6)-alkyl;

R1a, R1b, R1c are independently of each other H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

R2a, R2b, R2c are independently of each other H, F, Cl, Br, (C_1-C_6)-alkyl, (C_1-C_3)-alkyl substituted with COOR19 or CN;

R19 is H or (C_1-C_6)-alkyl;

Y is N or CH;

Z is a bond, O, CR5R5', NR6, C=O, S, SO or SO_2;

R5, R5', R6 are independently of each other H or (C_1-C_4)-alkyl;

R3 is a bond or $(CR7R7')_p$;

p is 0, 1, 2, 3 or 4;

R7, R7' are independently of each other H or (C_1-C_6)-alkyl;

R4 is F, Cl, SF_5, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, OR8, (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, or 5- or 6-membered heteroaryl ring;

wherein the groups (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

R8 is H, (C_1-C_6)-alkyl, hydroxy-(C_1-C_4)-alkyl or (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

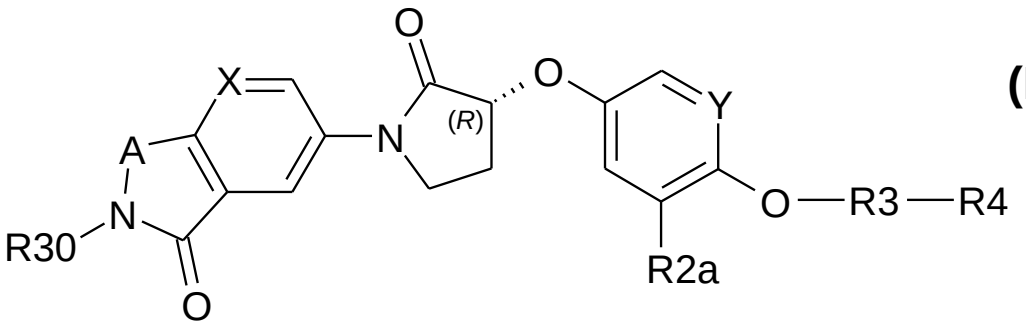
2. A compound of the formula I as claimed in claim 1, wherein

the 3-position of the pyrrolidinone ring has (*R*)-configuration.

3. A compound of the formula I as claimed in claim 1 or 2, wherein

Z is O.

4. A compound of the formula I as claimed in any of claims 1 to 3, which is a compound of the formula Ia



(Ia)

in which

X is N or C-R1a;

A is CR31R33, NR31, CR31R33-NR31 or CR31=N;

R30 is H or $(CR11R12)_n$-R32;

R31 is H or $(CR11R12)_n$-R32;

R33 is H or $(C_1$-$C_6)$-alkyl;

R11, R12 are independently of each other H or $(C_1$-$C_6)$-alkyl;

n is 0, 1, 2 or 3;

R32 is $(C_1$-$C_6)$-alkyl, COOR13, CONR14R15, $S(O)_mR16$, OH, CN, $(C_3$-$C_8)$-cycloalkyl, 4-, 5- or 6-membered heterocycle or 5- or 6-membered heteroaryl ring;

wherein the groups (C_3-C_8)-cycloalkyl, 4-, 5- or 6-membered heterocycle, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyloxy, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or (C_1-C_6)-alkyl;

R14, R15 are independently of each other H, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted with 1 to 3 groups selected from the list OR17, COOR19 and a 4-, 5- or 6-membered heterocycle;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17.

R16 is (C_1-C_6)-alkyl;

R17 is H or (C_1-C_6)-alkyl;

R18 is H or (C_1-C_6)-alkyl;

R1a is H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

R2a is H, F, Cl, Br, (C_1-C_6)-alkyl or CN;

Y is N or CH;

R3 is a bond or $(CR7R7')_p$;

p is 0, 1, 2, 3 or 4;

R7, R7' are independently of each other H or (C_1-C_6)-alkyl;

R4 is (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, OR8, (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;
wherein the groups (C_3-C_8)-cycloalkyl, (C_5-C_8)-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, hydroxy, hydroxy-(C_1-C_4)-alkyl, (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl, oxo, F and Cl;

R8 is H, (C_1-C_6)-alkyl, hydroxy-(C_1-C_4)-alkyl or (C_1-C_3)-alkyloxy-(C_1-C_4)-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

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

R14, R15 are independently of each other H, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl substituted with OR17, or (C_3-C_6)-cycloalkyl;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list (C_1-C_4)-alkyl and OR17.

6. A compound of the formula I as claimed in claim 5, wherein

X is C-R1a;

A is CR31R33 or NR31;

R30 is H or $(CR11R12)_n$-R32;

R31 is H or $(CR11R12)_n$-R32;

R33 is H or $(C_1$-$C_6)$-alkyl;

R11, R12 are independently of each other H or $(C_1$-$C_6)$-alkyl;

n is 0, 1, 2 or 3;

R32 is $(C_1$-$C_6)$-alkyl, COOR13, CONR14R15, $S(O)_m$R16, OH, CN, $(C_3$-$C_8)$-cycloalkyl, 4-, 5- or 6-membered heterocycle or 5- or 6-membered heteroaryl ring;
wherein the groups $(C_3$-$C_8)$-cycloalkyl, 4-, 5- or 6-membered heterocycle, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkanoyl, hydroxy, hydroxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyloxy, $(C_1$-$C_3)$-alkyloxy-$(C_1$-$C_4)$-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or $(C_1$-$C_6)$-alkyl;

R14, R15 are independently of each other H, $(C_1$-$C_6)$-alkyl or $(C_1$-$C_6)$-alkyl substituted with OR17, or $(C_3$-$C_6)$-cycloalkyl;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list $(C_1$-$C_4)$-alkyl and OR17.

R16 is $(C_1$-$C_6)$-alkyl;

R17 is H or $(C_1$-$C_6)$-alkyl;

R18 is H or $(C_1$-$C_6)$-alkyl;

R1a is H or F;

R2a is H, F, Cl, Br, $(C_1$-$C_6)$-alkyl or CN;

Y is N or CH;

R3 is a bond or $(CR7R7')_p$;

p is 0, 1, 2, 3 or 4;

R7, R7' are independently of each other H or $(C_1$-$C_6)$-alkyl;

R4 is $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, OR8, $(C_3$-$C_8)$-cycloalkyl, $(C_5$-$C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl or 5- or 6-membered heteroaryl ring;
wherein the groups $(C_3$-$C_8)$-cycloalkyl, $(C_5$-$C_8)$-bicycloalkyl, 4-, 5- or 6-membered heterocycle, phenyl, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkanoyl, hydroxy, hydroxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_3)$-alkyloxy-$(C_1$-$C_4)$-alkyl, oxo, F and Cl;

R8 is H, $(C_1$-$C_6)$-alkyl, hydroxy-$(C_1$-$C_4)$-alkyl or $(C_1$-$C_3)$-alkyloxy-$(C_1$-$C_4)$-alkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

7. A compound of the formula Ia as claimed in claim 5 or 6, wherein

X is C-R1a;

A is CH_2, $CH(C_1\text{-}C_6)$-alkyl or $C((C_1\text{-}C_6)\text{-alkyl})_2$;

R30 is H or $(CR11R12)_n$-R32;

R11, R12 are independently of each other H or $(C_1\text{-}C_6)$-alkyl;

n is 0, 1, 2 or 3;

R32 is $(C_1\text{-}C_6)$-alkyl, COOR13, CONR14R15, $S(O)_mR16$, OH, CN, $(C_3\text{-}C_8)$-cycloalkyl, 4-, 5- or 6-membered heterocycle or 5- or 6-membered heteroaryl ring;
wherein the groups $(C_3\text{-}C_8)$-cycloalkyl, 4-, 5- or 6-membered heterocycle, 5- or 6-membered heteroaryl ring may be optionally substituted with 1 to 3 groups selected from the list $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkanoyl, hydroxy, hydroxy-$(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_6)$-alkyloxy, $(C_1\text{-}C_3)$-alkyloxy-$(C_1\text{-}C_4)$-alkyl, oxo, F and Cl;

m is 0, 1 or 2;

R13 is H or $(C_1\text{-}C_6)$-alkyl;

R14, R15 are independently of each other H, $(C_1\text{-}C_6)$-alkyl or $(C_1\text{-}C_6)$-alkyl substituted with OR17, or $(C_3\text{-}C_6)$-cycloalkyl;
or R14 and R15 form together with the N-atom to which they are attached, a 4-, 5- or 6-membered heterocycle, optionally containing an additional heteroatom selected from the list O, S and NR18;
wherein the 4-, 5- or 6-membered heterocycle may be optionally substituted with 1 to 3 groups selected from the list $(C_1\text{-}C_4)$-alkyl and OR17;

R16 is $(C_1$-$C_6)$-alkyl;

R17 is H or $(C_1$-$C_6)$-alkyl;

R18 is H or $(C_1$-$C_6)$-alkyl;

R1a is H or F;

R2a is H, F, Cl, Br, $(C_1$-$C_6)$-alkyl or CN;

Y is N or CH;

R3 is CH_2 or CH_2-CH_2;

R4 is $(C_3$-$C_8)$-cycloalkyl;

wherein at each occurrence the hydrogen atoms of alkyl groups may be partially or fully replaced by fluorine atoms;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

8. A compound of the formula Ia as claimed in claims 5 to 7, wherein

X is CH;

A is CH_2;

R30 CH_2-CONR14R15;

R14 is H or $(C_1$-$C_6)$-alkyl;

R15 is $(C_1$-$C_6)$-alkyl or $(C_1$-$C_6)$-alkyl substituted with OR17, or $(C_3$-$C_6)$-cycloalkyl;

R17 is H or (C_1-C_6)-alkyl;

R2a is H or F;

Y is N;

R3 is CH_2 or CH_2-CH_2;

R4 is (C_3-C_8)-cycloalkyl;

or a physiologically acceptable salt thereof.

9. A compound selected from the list:

Tert-butyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]propanoic acid,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-methyl-3-oxo-isoindolin-1-yl]acetic acid,

methyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]propanoate,

methyl 2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-methyl-3-oxo-isoindolin-1-yl]acetate,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(2-oxotetrahydrofuran-3-yl)isoindolin-1-one,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-methyl-3-oxo-isoindolin-1-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-propyl-isoindolin-1-one,

2-[6-[(3R)-3-[(6-isopropylsulfanyl-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(2-methyltetrazol-5-yl)isoindolin-1-one,

2-[3-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1,1-dimethyl-3-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-isoindolin-2-yl]acetic acid,

methyl 2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-isoindolin-2-yl]acetate,

2-[3-[(3R)-3-[4-(2-cyclopropylacetyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(methylsulfonylmethyl)isoindolin-1-one,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[(2-methyltetrazol-5-yl)methyl]isoindolin-1-one,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(methylsulfinylmethyl)isoindolin-1-one,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(methylsulfanylmethyl)isoindolin-1-one,

2-[6-[(3R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

methyl 2-[6-[(3R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-methyl-isoindolin-1-one,

5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1,2-dihydroindazol-3-one,

2-[6-[(3S)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[5-[(3S)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-indazol-2-yl]-N,N-dimethyl-acetamide,

2-[5-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-methyl-3-oxo-indazol-2-yl]-N,N-dimethyl-acetamide,

2-[3-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,

ethyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,

2-tert-butyl-6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-isoindolin-1-one,

methyl 2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate,

methyl 2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,

2-tert-butyl-6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-isoindolin-1-one,

methyl 2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetate,

6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(2-hydroxyethyl)isoindolin-1-one,

2-[6-[(3R)-3-[[6-(cyclopropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

methyl 2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetate,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N,1-trimethyl-4-oxo-2,3-dihydroquinazoline-2-carboxamide (Stereomer I),

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N,1-trimethyl-4-oxo-2,3-dihydroquinazoline-2-carboxamide (Stereomer II),

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N,3-trimethyl-4-oxo-quinazoline-2-carboxamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-N,N-dimethyl-4-oxo-3H-quinazoline-2-carboxamide,

N-(2-hydroxyethyl)-N-methyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-1-one,
2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-1-one,
2-[6-[(3R)-3-[[6-(2,4-difluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[5-oxo-3-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]-7H-pyrrolo[3,4-b]pyridin-6-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(trifluoromethoxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(3-cyclopropylpropyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-[[(1R,3S,5S)-3-bicyclo[3.1.0]hexanyl]oxy]-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(2-cyclopropylethyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-fluoro-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-methyl-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethylamino)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-(4-fluorophenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[(6-chloro-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-propanoylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-pentanoylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-(4-butanoylphenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[4-(4-fluorobenzoyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[4-(4-fluorophenoxy)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[(6-fluoro-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-[[(1R,3R,5S)-3-bicyclo[3.1.0]hexanyl]oxy]-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethylsulfanyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[(6-cyclopropylsulfanyl-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[4-(2-cyclopropylacetyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(trifluoromethylsulfanyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2-pyridyloxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

N,N-dimethyl-2-[6-[(3R)-3-(4-morpholinophenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(1,2,4-triazol-1-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[4-(4-acetylpiperazin-1-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(pentafluoro-λ{6}-sulfanyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2-oxopyrrolidin-1-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

N,N-dimethyl-2-[6-[(3R)-3-[4-(1,3,4-oxadiazol-2-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2,2,2-trifluoroethoxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

N,N-dimethyl-2-[6-[(3R)-3-[4-(4-methylthiazol-2-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-[(4-oxothiazol-2-yl)amino]phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[4-(3-isopropyl-1,2,4-oxadiazol-5-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(pyrrolidine-1-carbonyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(1,2,4-triazol-4-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-(4-oxazol-5-ylphenoxy)-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-pyrazin-2-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[4-(1-ethyltetrazol-5-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(thiadiazol-4-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[3-chloro-4-(trifluoromethoxy)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-thiazol-2-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[4-[(3-methyl-1,2,4-oxadiazol-5-yl)methoxy]phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(tetrazol-1-yl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
ethyl 3-[2-chloro-5-[(3R)-1-[2-[2-(dimethylamino)-2-oxo-ethyl]-3-oxo-isoindolin-5-yl]-2-oxo-pyrrolidin-3-yl]oxy-phenyl]propanoate,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-(4-pyrrolidin-1-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[5-bromo-6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[4-(cyclopropanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetic acid,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetic acid,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetic acid,

2-[[2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetyl]amino]acetic acid,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(2-oxo-2-pyrrolidin-1-yl-ethyl)isoindolin-1-one,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,

N-cyclopropyl-2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,

6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,

6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,

2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-diethyl-acetamide,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetamide,

6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(2-oxo-2-pyrrolidin-1-yl-ethyl)isoindolin-1-one,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,

6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-methoxyethyl)acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(2-oxo-2-pyrrolidin-1-yl-ethyl)isoindolin-1-one,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(1H-tetrazol-5-ylmethyl)acetamide,

methyl 2-[[2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetyl]amino]acetate,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-[2-hydroxy-1-(hydroxymethyl)ethyl]acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-bis(2-hydroxyethyl)acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-[(2S)-2,3-dihydroxypropyl]acetamide,

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-[(2R)-2,3-dihydroxypropyl]acetamide,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetonitrile,

2-[6-[(3R)-3-[(6-ethoxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]acetic acid,

6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-[(3-methyloxetan-3-yl)methyl]isoindolin-1-one,

6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-methyl-isoindolin-1-one,

6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-isopropyl-isoindolin-1-one,

6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-2-(3-hydroxypropyl)isoindolin-1-one,

2-[4-fluoro-1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(2,2-dimethylpropoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[(6-allyloxy-3-pyridyl)oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[[6-(cyclobutylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(methylsulfinylmethyl)isoindolin-1-one,

6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(methylsulfanylmethyl)isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(methylsulfinylmethyl)isoindolin-1-one,
6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(methylsulfonylmethyl)isoindolin-1-one,
2-(methylsulfinylmethyl)-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-1-one,
3-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-6-(methylsulfinylmethyl)-7H-pyrrolo[3,4-b]pyridin-5-one,
2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
3-[(3R)-3-[[6-(cyclopropanecarbonyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-6-(methylsulfinylmethyl)-7H-pyrrolo[3,4-b]pyridin-5-one,
6-[(3R)-3-[[6-(cyclopropanecarbonyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(methylsulfinylmethyl)isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropanecarbonyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-(methylsulfonylmethyl)isoindolin-1-one
6-[(3R)-3-[4-(cyclopropanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-2-(methylsulfinylmethyl)isoindolin-1-one
3-[(3R)-3-[4-(cyclopropanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-6-(methylsulfinylmethyl)-7H-pyrrolo[3,4-b]pyridin-5-one
3-[(3R)-3-[4-(cyclopropanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-6-(methylsulfonylmethyl)-7H-pyrrolo[3,4-b]pyridin-5-one
6-(methylsulfinylmethyl)-3-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]-7H-pyrrolo[3,4-b]pyridin-5-one,
ethyl 2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetate,
methyl 2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetate,
3-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-6-(methylsulfonylmethyl)-7H-pyrrolo[3,4-b]pyridin-5-one,
6-(methylsulfonylmethyl)-3-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]-7H-pyrrolo[3,4-b]pyridin-5-one,

6-((S)-methanesulfinylmethyl)-3-{(R)-2-oxo-3-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yloxy]-pyrrolidin-1-yl}-6,7-dihydro-pyrrolo[3,4-b]pyridin-5-one,
6-((R)-methanesulfinylmethyl)-3-{(R)-2-oxo-3-[6-(2,2,2-trifluoro-ethoxy)-pyridin-3-yloxy]-pyrrolidin-1-yl}-6,7-dihydro-pyrrolo[3,4-b]pyridin-5-one,
2-[6-[(3R)-3-[[6-(1-methylcyclopropanecarbonyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[4-(4-fluorobenzoyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
2-[1-oxo-6-[(3R)-2-oxo-3-(4-thiazol-2-ylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(cyclopropanecarbonyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[4-(cyclopropanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
2-[1-oxo-6-[(3R)-2-oxo-3-(4-pentanoylphenoxy)pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[4-(1-methylcyclopropanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(3-cyclopropylpropanoyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(3-cyclopropylpropanoyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropanecarbonyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[[6-(1-methylcyclopropanecarbonyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[6-[(3R)-3-[[6-(5-methylthiazol-2-yl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(4-fluorobenzoyl)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(cyclopropanecarbonyl)-3-fluoro-phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(3,3-difluorocyclobutanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[4-(5-fluorothiazol-2-yl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

2-[6-[(3R)-3-[4-(2,2-difluorocyclopropanecarbonyl)phenoxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(4,4,4-trifluorobutanoyl)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetic acid,
N-cyclopropyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N-isopropyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N-methyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N-ethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
2-(2-oxo-2-pyrrolidin-1-yl-ethyl)-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-1-one,
N,N-diethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide and
2-[2-(azetidin-1-yl)-2-oxo-ethyl]-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-1-one;

or a pharmaceutically acceptable salt thereof.

10. A compound as claimed in claim 9 selected from the list

N,N-Dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,
N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[4-(2,2,2-trifluoroethoxy)phenoxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide and
2-[4-fluoro-1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]-N,N-dimethyl-acetamide;

or a pharmaceutically acceptable salt thereof.

11. A compound as claimed in claim 10, which is

N,N-dimethyl-2-[1-oxo-6-[(3R)-2-oxo-3-[[6-(2,2,2-trifluoroethoxy)-3-pyridyl]oxy]pyrrolidin-1-yl]isoindolin-2-yl]acetamide,

or a pharmaceutically acceptable salt thereof.

12. A compound as claimed in claim 9 selected from the list

2-[6-[(3R)-3-[[6-(2-Cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-fluoro-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one,
6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-methyl-acetamide,
2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide and
2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-4-fluoro-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)acetamide;

or a pharmaceutically acceptable salt thereof.

13. A compound as claimed in claim 12, which is

2-[6-[(3R)-3-[[6-(2-cyclopropylethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

or a pharmaceutically acceptable salt thereof.

14. A compound as claimed in claim 12, which is

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

or a pharmaceutically acceptable salt thereof.

15. A compound as claimed in claim 12, which is

2-[6-[(3R)-3-[[6-(cyclopropylmethoxy)-5-fluoro-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

or a pharmaceutically acceptable salt thereof.

16. A compound as claimed in claim 9 selected from the list

2-[3-[(3R)-3-[[6-(4-Fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl]-N,N-dimethyl-acetamide,
2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,
6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(3-hydroxyazetidin-1-yl)-2-oxo-ethyl]isoindolin-1-one,

6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-2-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]isoindolin-1-one and
2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide;

or a pharmaceutically acceptable salt thereof.

17. A compound as claimed in claim 16, which is
2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N,N-dimethyl-acetamide,

or a pharmaceutically acceptable salt thereof.

18. A compound as claimed in claim 16, which is

2-[6-[(3R)-3-[[6-(4-fluorophenoxy)-3-pyridyl]oxy]-2-oxo-pyrrolidin-1-yl]-1-oxo-isoindolin-2-yl]-N-(2-hydroxyethyl)-N-methyl-acetamide,

or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising at least one compound as claimed in any of claims 1 to 18 or a physiologically acceptable salt of any of them, for use as a pharmaceutical.

20. A pharmaceutical composition as claimed in claim 19, comprising additionally one or more active ingredients selected from the list:
Insulin and insulin derivatives, GLP-1, GLP-1 analogues and GLP-1 receptor agonists, polymer bound GLP-1 and GLP-1 analogues, dual GLP-1/GIP agonists, dual GLP-1/glucagon receptor agonists, PYY3-36 or analogues thereof, pancreatic polypeptide or analogues thereof, glucagon receptor agonists or antagonists, GIP receptor agonists or antagonists, ghrelin antagonists or inverse agonists, xenin and analogues thereof, DDP-

IV inhibitors, SGLT-2 inhibitors, dual SGLT-2/SGLT-1 inhibitors, biguanides, thiazolidinediones, PPAR agonists, PPAR modulators, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, amylin and amylin analogues, GPR119 agonists, GPR40 agonists, GPR120 agonists, GPR142 agonists, TGR5 agonists, AMPK stimulants, AMPK activators, inhibitors of 11-beta-HSD, activators of glucokinase, inhibitors of DGAT, inhibitors of protein tyrosine phosphatase 1, inhibitors of glucose-6-phosphatase, inhibitors of fructose-1,6-bisphosphatase, inhibitors of glycogen phosphorylase, inhibitors of phosphoenol pyruvate carboxykinase, inhibitors of glycogen synthase kinase, inhibitors of pyruvate dehydrogenase kinase, CCR-2 antagonists, modulators of glucose transporter-4, somatostatin receptor 3 agonists, HMG-CoA-reductase inhibitors, fibrates, nicotinic acid and derivatives thereof, nicotinic acid receptor 1 agonists, , ACAT inhibitors, cholesterol absorption inhibitors, bile acid-binding substances, IBAT inhibitors, MTP inhibitors, modulators of PCSK9, LDL receptor up-regulators (liver selective thyroid hormone receptor beta agonists), HDL-raising compounds, lipid metabolism modulators, PLA2 inhibitors, ApoA-I enhancers, cholesterol synthesis inhibitors, omega-3 fatty acids and derivatives thereof, active substances for the treatment of obesity, CB1 receptor antagonists, MCH-1 antagonists, MC4 receptor agonists and partial agonists, NPY5 or NPY2 antagonists, NPY4 agonists, beta-3 adrenergic receptor agonists, leptin or leptin mimetics, 5HT2c receptor agonists, lipase inhibitors, angiogenesis inhibitors, H3 antagonists, AgRP inhibitors, triple monoamine uptake inhibitors, MetAP2 inhibitors, antisense oligonucleotides against production of fibroblast growth factor receptor 4 or prohibitin targeting peptide-1, drugs for influencing high blood pressure, chronic heart failure or atherosclerosis, angiotensin II receptor antagonists, dual angiotensin receptor blockers (ARB), angiotensin converting enzyme (ACE) inhibitors, angiotensin converting enzyme 2 (ACE-2) activators, , renin inhibitors, prorenin inhibitors, endothelin converting enzyme (ECE) inhibitors, endothelin receptor blockers, endothelin antagonists, diuretics, aldosterone antagonists, aldosterone synthase inhibitors, alpha-blockers, antagonists of the alpha-2 adrenergic receptor, beta-blockers, mixed alpha-/beta-blockers, calcium antagonists/calcium channel blockers (CBBs), dual mineralocorticoid/CCBs, centrally acting antihypertensives, inhibitors of neutral endopeptidase, aminopeptidase-A inhibitors, vasopeptide inhibitors, dual vasopeptide inhibitors, neprilysin-ACE inhibitors, neprilysin-ECE inhibitors, dual-acting Angiotensin (AT) receptor-neprilysin inhibitors, dual AT1/ endothelin-1 (ETA) antagonists, advanced glycation end-product breakers, recombinant renalase, blood pressure vaccines, anti-RAAS vaccines, AT1- or AT2-

vaccines, modulators of genetic polymorphisms with antihypertensive response and thrombocyte aggregation inhibitors.

21. A pharmaceutical composition as claimed in claim 19, comprising additionally metformin.

22. A pharmaceutical composition as claimed in claim 19, comprising additionally at least one DPP-IV inhibitor.

23. A pharmaceutical composition as claimed in claim 22, wherein the DPP-IV inhibitor is selected from the list alogliptin, linagliptin, saxagliptin, sitagliptin, anagliptin, teneligliptin, trelagliptin, vildagliptin, gemigliptin, omarigliptin, evogliptin and dutogliptin.

24. A pharmaceutical composition as claimed in claim 19, comprising additionally at least one SGLT-2 inhibitor.

25. A pharmaceutical composition as claimed in claim 24, wherein the SGLT-2 inhibitor is selected from the list canagliflozin, dapagliflozin, remogliflozin, remogliflozin etabonate, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin and ertugliflozin.

26. A pharmaceutical composition as claimed in claim 19, comprising additionally at least one GPR40 agonist.

27. A pharmaceutical composition as claimed in claim 26, wherein the GPR40 agonist is selected from the list TUG-424, P-1736, P-11187, JTT-851, GW9508, CNX-011-67, AM-1638 and AM-5262.

28. A pharmaceutical composition as claimed in claim 19, comprising additionally ezetimibe.

29. A pharmaceutical composition as claimed in claim 19, comprising additionally at least one HMG-CoA reductase inhibitor.

30. A pharmaceutical composition as claimed in claim 29, wherein the HMG-CoA reductase inhibitor is selected from the list simvastatin, atorvastatin, rosuvastatin, pravastatin, fluvastatin, pitavastatin, lovastatin, mevastatin, rivastatin and cerivastatin.

31. A pharmaceutical composition as claimed in claim 19, comprising additionally at least one PPAR agonist or PPAR modulator.

32. A pharmaceutical composition as claimed in claim 31, wherein the PPAR agonist or PPAR modulator is saroglitazar.

33. A pharmaceutical composition as claimed in claim 31, wherein the PPAR agonist or PPAR modulator is selected from the list pioglitazone, rosiglitazone and lobeglitazone.

34. A pharmaceutical composition as claimed in claim 19, comprising additionally acarbose.

35. A compound of the formula I as claimed in any of claims 1 to 18 for use as a pharmaceutical.

36. A compound of the formula I as claimed in any of claims 1 to 18 for the prevention and/or treatment of diabetes, obesity, dyslipidemia and related disorders.

37. A compound of the formula I as claimed in any of claims 1 to 18 for the prevention and/or treatment of diabetes.

38. A compound of the formula I as claimed in any of claims 1 to 18 for the prevention and/or treatment of obesity.

39. A compound of the formula I as claimed in any of claims 1 to 18 for the prevention and/or treatment of dyslipidemia.

40. A compound of the formula I as claimed in any of claims 1 to 18 for prevention and/or treatment of a disease associated with the GPR119.

41. Use of at least one compound of formula I as claimed in any of claims 1 to 18 for the manufacture of a medicament for treating diabetes, obesity or dyslipidemia.

42. Use of at least one compound of formula I as claimed in any of claims 1 to 18 and of at least one other compound useful for treating diabetes, obesity, dyslipidemia or high blood pressure for the manufacture of a medicament for treating diabetes, obesity, dyslipidemia or high blood pressure.

43. The use as claimed in claim 42 wherein the medicament is to be administered simultaneously.

44. The use as claimed in claim 42 wherein the medicament is to be administered sequentially.