Title: PROCESS FOR THE SYNTHESIS OF SUBSTITUTED UREA COMPOUNDS

Abstract: A process for preparing a substituted urea compound of Formula II or Formula I, or a pharmaceutically acceptable salt or ester thereof, Formula II, Formula I the process comprising the reaction of an intermediate of Formula II or Formula I', Formula II, Formula I with a carbamoyl halide of the formula: RIR2NCl(=0)Hal, in a solvent consisting essentially of pyridine, wherein Hal represents Cl, F or Br, and wherein R1 and R2, R3, V, W, X, Y and Z are as defined herein.
PROCESS FOR THE SYNTHESIS OF SUBSTITUTED UREA COMPOUNDS

The present invention relates to processes for the synthesis of substituted urea compounds and of intermediates useful in the production of such compounds. In particular, though not exclusively, it relates to processes for synthesising certain active pharmaceutical ingredients having a heteroaryl N-carboxamide core, and novel intermediates used in such processes.

Molecules containing urea functional groups are of interest in medicinal chemistry. A common method for their preparation is to convert a first amine component to an isocyanate or activated carbamate, followed by reaction with a second amine component. However, this approach is not available when neither of the amine components is a primary amine. In particular, secondary amines cannot be converted to isocyanates, and secondary carbamates are known to suffer from low reactivity in the required nucleophilic substitution reaction with the second amine component (see Lee et al. (2004) Tetrahedron 60, 3439). Complex or harsh approaches have thus been used in these circumstances, e.g. the aluminium amide approach described by Lee et al. (above).

A number of molecules having fatty acid amide hydrolase (FAAH) inhibitory activity and containing urea groups are disclosed in WO 2010/074588, the entire contents of which, and in particular the details of the compounds claimed therein, are hereby incorporated herein. For example, a subgroup of the compounds disclosed in this document contain an imidazole-1-carboxamide motif. These compounds are generally prepared using an approach comprising carbamoylation of 1H-imidazole derivatives with carbamoyl chlorides. For illustrative purposes, 3-(1-(cyclohexyl(methyl)carbamoyl)-1H-imidazol-4-yl)pyridine-1-oxide, hereinafter sometimes referred to as compound A, is prepared by reaction of the imidazolylpyridine hydrochloride with potassium 2-methylpropan-2-olate in a mixed solvent of tetrahydrofuran (THF) and dimethylformamide (DMF), followed by addition of a catalytic amount of pyridine and N,N-dimethylpyridine-4-amine, this step being followed by addition of cyclohexyl(methyl)carbamic chloride. This mixture is kept at elevated temperature overnight, following which a non-oxidised intermediate can be extracted in low yield. This intermediate is then oxidised to give compound A. A similar approach to urea formation using cyclohexyl(methyl)carbamic chloride is described in Koga et al. (1998) Bioorg. Med. Chem. Lett. 8, 1471. The solvent used for urea formation in this instance is DMF.

The main limitation of the above procedure disclosed in WO 2010/074588 is the very low overall yield. This problem is addressed in WO2012/015324, wherein the ureas of WO2010/074588 are synthesised using an alternative approach based on the reaction of a phenylcarbamate derivative of an N-containing heteroaryl group with a primary or secondary amine. The yield using the phenylcarbamate approach is reported to be much improved, and WO2012/015324 discourages the use of the carbamoyl chloride approach.

Therefore, there exists a need to provide an efficient approach for the formation of substituted ureas, particularly (but not exclusively) those containing an imidazole-1-carboxamide core.

According to one aspect of the present invention, there is provided a process for preparing a substituted urea compound of Formula II or Formula I, or a pharmaceutically acceptable salt or ester thereof,
the process comprising the reaction of an intermediate of Formula II' or Formula I',

with a carbamoyl halide of the formula: RIR2NC(=0)Hal, in a solvent consisting essentially of pyridine,

wherein Hal represents CI, F, I or Br,

wherein R1 and R2 can each be independently selected from H, C120 alkyl, C1 alkoxyl, aryl, heteroaryl, partially or fully saturated heterocyclyl, C3-10 cycloalkyl, aryl C1-4 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-4 alkyl, C1-10 cycloalkyl C1-6 alkyl, Rla, halogen, OH, ORla, OCORla, SH, SRIa, SCORla, NH2, NHRla, NHSO2NH2, NHSO2Rla, NRlaCORlb, NHCORla, NRlaRlb, CORla, CSRIa, CN, COOH, COORla, CONH2, CONHOH, CONHRla, CONHORla, S02Rla, SO2H2, SO2NH2, CONRaRlb, SO2NRlaRlb, wherein Rla and Rib are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or Rla and Rlb, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R1 or R2 is C1-20 alkyl, alkoxyl, aryl, heteroaryl, heterocyclyl, C3-10 cycloalkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, C1-10 cycloalkyl C1-6 alkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from Rlc, halogen, aryl, heteroaryl, heterocyclyl, C1-6 alkoxyl, arylxoy, heteroarylxy, heterocyclyxylxy, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, aryl C1-6 alkoxyl, heteroaryl C1-6 alkoxyl, heterocyclyl C1-6 alkoxyl, C1-6 alkylamino, C1-6 dialkylamino, C1-6 dialkyl, OH, ORlc, OCORlc, SH, SRLc, SCORlc, NH2, N02, NHRlc, NHSO2NH2, NHSO2Rlc, NRlcCORld, NHC(NH)NH2, NHCORlc, NRlcRld, CORlc, CSRLc, CN, COOH, COORlc, CONH2, CONHOH, CONHRlc, CONHORlc, CONRaRld, C(NO)NH2, CONRaRld, S02Rlc, S02H2, S02NRlcRld, wherein Rlc and Rld are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or Rlc and Rld, together with the heteroatom to which they are joined, can form heterocyclyl,
wherein, when the substituent of R1 or R2 is C1-6 alkyl, aryl, heteroaryl, heterocyclyl, C1-6 alkoxy, arilxy, heteroaryloxy, heterocyclyloxy, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, arilxy C1-6 alkyl, heteroaryloxy C1-6 alkyl, heterocyclyloxy C1-6 alkyl, alkyl C1-6 alkyl, alkoxy C1-6 alkyl, aryl C1-6 alkoxy, heteroaryl C1-6 alkoxy, heterocyclyl C1-6 alkoxy, C1-6 alkylamino, C1-6 dialkylamino, C1-6 alkyl or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from Rle, halogen, C1-10 alkyl, OH, ORle, COORle, SH, SRle, SCORle, NH2, NO2, NHRle, NHSO2Nle, NHSO2Rle, NReCORle, NH(NH)NH2, NHCORle, NReRlf, CORle, CSRle, CN, COOH, COORle, CONH2, CONH0H, CONHRle, CONHRle, C(NO)NH2, CONReRlf, S02Rle, S02H, S02NReRlf, wherein Rle and Rlf are independently selected from Ar, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or Rle and Rlf, together with the heteroatom to which they are joined, can form heterocyclyl,

with the exception that R1 and R2 are not both H;

or

R1 and R2, together with the N to which they are attached, can form a heteroaryl or heterocyclyl group, each of which may optionally be substituted with one or more oxygen atoms or one or more groups selected from arilxy, heteroaryloxy, heterocyclyloxy, heteroaryloxy, heterocyclyloxy, R2a, halogen, OH, OR2a, COOR2a, SH, SR2a, SCOR2a, NH2, NO2, NHR2a, NHSO2Nle, NHSO2Rle, R2aCOR2b, NH(NH)NH2, NHCOR2a, NR2aR2b, COR2a, CSR2a, CN, COOH, COOR2a, CONH2, CONH0H, CONHR2a, CONHR2a, C(NO)NH2, CONR2aR2b, S02R2a, S02H, S02NH2, S02NReR2b, wherein R2a and R2b are independently selected from Ar, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R2a and R2b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of the heteroaryl or heterocyclyl formed by R1 and R2 together is arilxy, heteroaryloxy, heterocyclyloxy, C3-8 cycloalkyl, C1-6 alkyl, aryl C1-6 alkyl, heteroaryl CI-6 alkyl, heterocyclyl C1-6 alkyl, C3-8 cycloalkyl C1-6 alkyl, C1-6 alkyl, arilxy, heteroaryloxy, heterocyclyoxy, or a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, hydroxyl, C1-6 alkyl, aryl, heteroaryl, heterocyclyl, C3-8 cycloalkyl, C1-6 alkyl, aryl C1-6 alkyl, heteroaryl CI-6 alkyl, heterocyclyl C1-6 alkyl, C3-8 cycloalkyl C1-6 alkyl, C1-6 alkyl, arilxy, heteroaryloxy, heterocyclyoxy, C3-8 cycloalkyl, aryl C1-6 alkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, C3-8 cycloalkyl C1-6 alkyl, aryl C1-6 alkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, C3-8 cycloalkyl and heterocyclyl, or R2c and R2d, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of the substituent of the heteroaryl or heterocyclyl formed by R1 and R2 together is C1-6 alkyl, aryl, heteroaryl, heterocyclyl, C3-8 cycloalkyl, C1-6 alkyl, arilxy, heteroaryloxy, heterocyclyoxy, C3-8 cycloalkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, C3-8 cycloalkyl C1-6 alkyl, aryl C1-6 alkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, C3-8 cycloalkyl and heterocyclyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or
more groups selected from C\textsubscript{1-4} alkoxy, R2e, halogen, OH, OR2e, OCOR2e, SH, SR2e, SCOR2e, NH\textsubscript{2}, N0 \textsubscript{2}, NHR2e, NHSO\textsubscript{2}NH\textsubscript{2}, NH\textsubscript{2}SO\textsubscript{2}R2e, NR2eCOR2f, NHC(NH)NH\textsubscript{2}, NR2eR2f, NHCOR2e, COR2e, CSR2e, CN, COOH, COOR2e, CONH\textsubscript{2}, CONHOH, CONHHR2e, CONHOR2e, C(NO)NH\textsubscript{2}, CONR2eR2f, SO\textsubscript{2}R2e, S0 \textsubscript{2}H, S0 \textsubscript{2}NH\textsubscript{2}, S0 \textsubscript{2}NR2eR2f, wherein R2e and R2f are independently selected from C\textsubscript{1-6} alkyl, substituted C\textsubscript{1-6} alkyl, aryl, heteroaryl, C\textsubscript{3-8} cycloalkyl and heterocyclyl, or R2e and R2f, together with the heteroatom to which they are joined, can form heterocyclyl;

Ring A is selected from aryl, heteroaryl and heterocyclyl moieties, each of which may optionally be substituted with one or more groups selected from halogen, C\textsubscript{1-4} alkyl, aryl, heteroaryl, heterocyclyl, C\textsubscript{1-6} alkoxy, arloxy, heteroaroyloxy, heterocyclyloxy, Ra, C\textsubscript{1-6} alkyl, OH, ORa, OCORa, SH, SRa, SCORa, NH\textsubscript{2}, N0 \textsubscript{2}, NHRa, NHSO\textsubscript{2}NH\textsubscript{2}, NHSO\textsubscript{2}Ra, NRaCORb, NHCORa, NHC(NH)NH\textsubscript{2}, NRaRb, CORa, CSRa, CN, COOH, COORa, CONH\textsubscript{2}, CONHRa, CONHOH, CONHORa, C(NO)NH\textsubscript{2}, CONR2eRa, S0 \textsubscript{2}Ra, S0 \textsubscript{2}H, S0 \textsubscript{2}NH\textsubscript{2}, S0 \textsubscript{2}NRaRb, wherein Ra and Rb are independently selected from C\textsubscript{1-6} alkyl, substituted C\textsubscript{1-6} alkyl, aryl, heteroaryl, C\textsubscript{3-8} cycloalkyl and heterocyclyl, or Ra and Rb, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when Ring A is substituted with C\textsubscript{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C\textsubscript{1-6} alkoxy, arloxy, heteroaroyloxy, heterocyclyloxy, C\textsubscript{1-6} alkyl, C\textsubscript{3-8} cycloalkyl or is substituted with a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, Rc, C\textsubscript{1-6} alkyl, aryl C\textsubscript{1-6} alkyl, heteroaryl C\textsubscript{1-6} alkyl, heterocyclyl C\textsubscript{1-6} alkyl, OH, ORc, OCORc, SH, SRc, SCORc, NH\textsubscript{2}, N0 \textsubscript{2}, NHrc, NHSO\textsubscript{2}NH\textsubscript{2}, NHSO\textsubscript{2}Rc, NRCORd, NHCORc, NHC(NH)NH\textsubscript{2}, NRcRd, CORc, CSRc, CN, COOH, COORc, CONH\textsubscript{2}, CONHOH, CONHRC, CONHORc, C(NO)NH\textsubscript{2}, CONR2eRd, S0 \textsubscript{2}Rc, S0 \textsubscript{2}H, S0 \textsubscript{2}NH\textsubscript{2}, S0 \textsubscript{2}NRcRd, wherein Rc and Rd are independently selected from C\textsubscript{1-6} alkyl, substituted C\textsubscript{1-6} alkyl, aryl, heteroaryl, C\textsubscript{3-8} cycloalkyl and heterocyclyl, or Rc and Rd, together with the heteroatom to which they are joined, can form heterocyclyl;

V can be N, CH or C-R3, wherein R3 is halogen, C\textsubscript{1-4}alkyl, aryl, heteroaryl, heterocyclyl, C\textsubscript{3-8} cycloalkyl, C\textsubscript{1-6} alkoxy, arloxy, heteroaroyloxy, heterocyclyloxy, R3a, OH, OR3a, SH, SR3a, OCOR3a, SCOR3a, NH\textsubscript{2}, N0 \textsubscript{2}, NHR3a, NHSO\textsubscript{2}NH\textsubscript{2}, NHSO\textsubscript{2}R3a, NR3aCOR3b, NHCOR3a, NHC(NH)NH\textsubscript{2}, NR3aR3b, COR3a, CSR3a, CN, COOH, COOR3a, CONH\textsubscript{2}, CONHOH, CONHHR3a, CONHOR3a, C(NO)NH\textsubscript{2}, CONR3aR3b, S0 \textsubscript{2}R3a, S0 \textsubscript{2}H, S0 \textsubscript{2}NH\textsubscript{2}, S0 \textsubscript{2}NR3aR3b, wherein R3a and R3b are independently selected from C\textsubscript{1-6} alkyl, substituted C\textsubscript{1-6} alkyl, aryl, heteroaryl, C\textsubscript{3-8} cycloalkyl and heterocyclyl, or R3a and R3b, together with the heteroatom to which they are joined, can form heterocyclyl;

wherein, when R3 is C\textsubscript{1-4}alkyl, aryl, heteroaryl, heterocyclyl, C\textsubscript{1-6} alkoxy, arloxy, heteroaroyloxy, heterocyclyloxy, C\textsubscript{1-6} alkyl, C\textsubscript{3-8} cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, aryl, heteroaryl, heterocyclyl, C\textsubscript{1-6} alkoxy, arloxy, heteroaroyloxy, heterocyclyloxy, R3c, C\textsubscript{1-6} alkyl, OH, OR3c, OCOR3c, SH, SR3c, SCOR3c, NH\textsubscript{2}, N0 \textsubscript{2}, NHR3c, NHSO\textsubscript{2}NH\textsubscript{2}, NHSO\textsubscript{2}R3c, NR3cCOR3d, NHCOR3c, NHC(NH)NH\textsubscript{2}, NR3cR3d, COR3c, CSR3c, CN, COOH, COOR3c, CONH\textsubscript{2}, CONHOH, CONHHR3c, CONHOR3c, C(NO)NH\textsubscript{2}, CONR3cR3d, S0 \textsubscript{2}R3c, S0 \textsubscript{2}H, S0 \textsubscript{2}NH\textsubscript{2}, S0 \textsubscript{2}NR3cR3d, wherein R3c and R3d are independently selected from C\textsubscript{1-6}.
alkyl, substituted C<sub>1-6</sub> alkyl, aryl, heteroaryl, C<sub>3-8</sub> cycloalkyl and heterocyclyl, or R<sub>3</sub> and R<sub>3d</sub>, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R<sub>3</sub> is C<sub>1-10</sub> alkyl, aryl, heteroaryl, heterocyclyl, C<sub>1-6</sub> alkoxy, arylloxy, heteroaryloxy, heterocyclyloxy, C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R<sub>3e</sub>, C<sub>1-6</sub> alkyl, OH, OR<sub>3e</sub>, OCOR<sub>3e</sub>, SH, SR<sub>3e</sub>, SCOR<sub>3e</sub>, NH<sub>2</sub>, N<sub>0</sub>, NHR<sub>3e</sub>, NHSO<sub>2</sub>NH<sub>2</sub>, NHSO<sub>2</sub>R<sub>3e</sub>, NR<sub>3e</sub>COR<sub>3f</sub>, NHCOR<sub>3e</sub>, NH(NH)NH<sub>2</sub>, NR<sub>3e</sub>R<sub>3f</sub>, COR<sub>3e</sub>,CSR<sub>3e</sub>,CN, COOH, COOR<sub>3e</sub>, CONH<sub>2</sub>, CONHOH, CONHR<sub>3e</sub>, CONHOR<sub>3e</sub>, C(NO<sub>2</sub>)NH<sub>2</sub>, CONR<sub>3e</sub>R<sub>3f</sub>, S<sub>0</sub> R<sub>3e</sub>, S<sub>0</sub>H, S<sub>0</sub>N<sup>3</sup>, S<sub>0</sub> NR<sub>3e</sub>R<sub>3f</sub>, wherein R<sub>3</sub>e and R<sub>3f</sub> are independently selected from C<sub>1-6</sub> alkyl, substituted C<sub>1-6</sub> alkyl, aryl, heteroaryl, C<sub>3-8</sub> cycloalkyl and heterocyclyl, or R<sub>3</sub>e and R<sub>3f</sub>, together with the heteroatom to which they are joined, can form heterocyclyl;

W can be N, CH or C-R<sub>4</sub>, wherein R<sub>4</sub> is halogen, C<sub>1-10</sub> alkyl, aryl, heteroaryl, heterocyclyl, C<sub>1-6</sub> alkoxy, arylloxy, heteroaryloxy, heterocyclyloxy, C<sub>3-8</sub> cycloalkyl, R<sub>4a</sub>, OH, OR<sub>4a</sub>, SH, SR<sub>4a</sub>, OCOR<sub>4a</sub>, SCOR<sub>4a</sub>, NH<sub>2</sub>, N<sub>0</sub>, NHR<sub>4a</sub>, NHSO<sub>2</sub>NH<sub>2</sub>, NHSO<sub>2</sub>R<sub>4a</sub>, NR<sub>4a</sub>COR<sub>4b</sub>, NHCOR<sub>4a</sub>, NH(NH)NH<sub>2</sub>, NR<sub>4a</sub>R<sub>4b</sub>, COR<sub>4a</sub>, CSR<sub>4a</sub>, CN, COOH, COOR<sub>4a</sub>, CONH<sub>2</sub>, CONHOH, CONHR<sub>4a</sub>, CONHOR<sub>4a</sub>, C(NO<sub>2</sub>)NH<sub>2</sub>, CONR<sub>4a</sub>R<sub>4b</sub>, S<sub>0</sub>R<sub>4a</sub>, S<sub>0</sub>H, S<sub>0</sub>N<sup>3</sup>, S<sub>0</sub>NR<sub>4a</sub>R<sub>4b</sub>, wherein R<sub>4a</sub> and R<sub>4b</sub> are independently selected from C<sub>1-6</sub> alkyl, substituted C<sub>1-6</sub> alkyl, aryl, heteroaryl, C<sub>3-8</sub> cycloalkyl and heterocyclyl, or R<sub>4a</sub> and R<sub>4b</sub>, together with the heteroatom to which they are joined, can form heterocyclyl;

wherein, when R<sub>4</sub> is C<sub>1-10</sub> alkyl, aryl, heteroaryl, heterocyclyl, C<sub>1-6</sub> alkoxy, arylloxy, heteroaryloxy, heterocyclyloxy, C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, aryl, heteroaryl, heterocyclyl, C<sub>1-6</sub> alkoxy, arylloxy, heteroaryloxy, heterocyclyloxy, R<sub>4c</sub>, C<sub>1-10</sub> alkyl, OH, OR<sub>4c</sub>, OCOR<sub>4c</sub>, SH, SR<sub>4c</sub>, SCOR<sub>4c</sub>, NH<sub>2</sub>, N<sub>0</sub>, NHR<sub>4c</sub>, NHSO<sub>2</sub>NH<sub>2</sub>, NHSO<sub>2</sub>R<sub>4c</sub>, NR<sub>4c</sub>COR<sub>4d</sub>, NHCOR<sub>4c</sub>, NH(NH)NH<sub>2</sub>, NR<sub>4c</sub>R<sub>4d</sub>, COR<sub>4c</sub>, CSR<sub>4c</sub>, CN, COOH, COOR<sub>4c</sub>, CONH<sub>2</sub>, CONHOH, CONHR<sub>4c</sub>, CONHOR<sub>4c</sub>, C(NO<sub>2</sub>)NH<sub>2</sub>, CONR<sub>4c</sub>R<sub>4d</sub>, S<sub>0</sub>R<sub>4c</sub>, S<sub>0</sub>H, S<sub>0</sub>N<sup>3</sup>, S<sub>0</sub>NR<sub>4c</sub>R<sub>4d</sub>, wherein R<sub>4c</sub> and R<sub>4d</sub> are independently selected from C<sub>1-6</sub> alkyl, substituted C<sub>1-6</sub> alkyl, aryl, heteroaryl, C<sub>3-8</sub> cycloalkyl and heterocyclyl, or R<sub>4c</sub> and R<sub>4d</sub>, together with the heteroatom to which they are joined, can form heterocyclyl;

wherein, when the substituent of R<sub>4</sub> is C<sub>1-10</sub> alkyl, aryl, heteroaryl, heterocyclyl, C<sub>1-6</sub> alkoxy, arylloxy, heteroaryloxy, heterocyclyloxy, C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R<sub>4e</sub>, CMO alkyl, OH, OR<sub>4e</sub>, OCOR<sub>4e</sub>, SH, SR<sub>4e</sub>, SCOR<sub>4e</sub>, NH<sub>2</sub>, N<sub>0</sub>, NHR<sub>4e</sub>, NHSO<sub>2</sub>NH<sub>2</sub>, NHSO<sub>2</sub>R<sub>4e</sub>, NR<sub>4e</sub>COR<sub>4f</sub>, NHCOR<sub>4e</sub>, NH(NH)NH<sub>2</sub>, NR<sub>4e</sub>R<sub>4f</sub>, COR<sub>4e</sub>,CSR<sub>4e</sub>,CN, COOH, COOR<sub>4e</sub>, CONH<sub>2</sub>, CONHOH, CONHR<sub>4e</sub>, CONHOR<sub>4e</sub>, C(NO<sub>2</sub>)NH<sub>2</sub>, CONR<sub>4e</sub>R<sub>4f</sub>, S<sub>0</sub>R<sub>4e</sub>, S<sub>0</sub>H, S<sub>0</sub>N<sup>3</sup>, S<sub>0</sub>NR<sub>4e</sub>R<sub>4f</sub>, wherein R<sub>4e</sub> and R<sub>4f</sub> are independently selected from C<sub>1-6</sub> alkyl, substituted C<sub>1-6</sub> alkyl, aryl, heteroaryl, C<sub>3-8</sub> cycloalkyl and heterocyclyl, or R<sub>4e</sub> and R<sub>4f</sub>, together with the heteroatom to which they are joined, can form heterocyclyl;

R<sub>5</sub> together with the C to which it is attached, can form a carbonyl group with the double bonds in Formula I rearranged accordingly, or R<sub>5</sub> is selected from H, C<sub>1-6</sub> alkyl, aryl, heteroaryl, heterocyclyl, C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkoxy, arylloxy, heteroaryloxy, heterocyclyloxy, R<sub>5a</sub>, halogen, OH, OR<sub>5a</sub>, SH, SR<sub>5a</sub>, OCOR<sub>5a</sub>, SCOR<sub>5a</sub>, NH<sub>2</sub>,...
N0₂, NHS0₂NΗ₂, NHS0₂R5a, NR5aC0R5b, NHC0R5a, NH(ΗΗ)ΝΗ₂, ΝR5aR5b, COR5a, CSR5a, CN, COOH, COOR5a, CONΗ₂, CONHOH, CONHR5a, CONHR5b, C(ΝΟΗ)ΝΗ₂, CONR5aR5b, SOUR5a, S0₂S0H, NR5aR5b, wherein R5a and R5b are independently selected from C₁₋₆ alkyl, aryl, heteroaryl, C₃₋₈ cycloalkyl and heterocyclyl, or R5a and R5b, together with the heteroatom to which they are joined, can form heterocyclyl.

wherein, when R5 is C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, R5c, C₁₋₆ alkyl, OH, OR5c, OCR5c, SH, SR5c, SCOR5c, NH₂, N0₂, NHR5c, NHS0₂NΗ₂, NHS0₂R5c, NR5cCOR5d, NHC0R5c, NH(ΗΗ)ΝΗ₂, NR5cR5d, COR5c, CSR5c, CN, COOH, COOR5c, CONΗ₂, CONHOH, CONHR5c, CONHR5d, C(ΝΟΗ)ΝΗ₂, CONR5cR5d, S0₂R5c, S0₂H, S0₂NΗ₂, S0₂NR5cR5d, wherein R5c and R5d are independently selected from C₁₋₆ alkyl, substituted C₁₋₆ alkyl, aryl, heteroaryl, C₃₋₈ cycloalkyl and heterocyclyl, or R5c and R5d, together with the heteroatom to which they are joined, can form heterocyclyl.

wherein, when the substituent of R5 is C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, C₁₋₆ cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R5e, C₁₋₆ alkyl, OH, OR5e, OCR5e, SH, SR5e, SCOR5e, NH₂, N0₂, NHR5e, NHS0₂NΗ₂, NHS0₂R5e, NR5eCOR5f, NHC0R5e, NH(ΗΗ)ΝΗ₂, NR5eR5f, COR5e, CSR5e, CN, COOH, COOR5e, CONΗ₂, CONHOH, CONHR5e, CONHR5f, C(ΝΟΗ)ΝΗ₂, CONR5eR5f, S0₂R5e, S0₂H, S0₂NΗ₂, S0₂NR5eR5f, wherein R5e and R5f are independently selected from C₁₋₆ alkyl, substituted C₁₋₆ alkyl, aryl, heteroaryl, C₃₋₈ cycloalkyl and heterocyclyl, or R5e and R5f, together with the heteroatom to which they are joined, can form heterocyclyl.

X can be O (with the double bonds in Formula II rearranged accordingly), N, CH or C-R6, wherein R6 is selected from C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, R6a, halogen, OH, OR6a, SH, SR6a, SCOR6a, CONΗ₂, N0₂, NHR6a, NHS0₂NΗ₂, NHS0₂R6a, NR6aCOR6b, NHC0R6a, NH(ΗΗ)ΝΗ₂, NR6aR6b, COR6a, CSR6a, CN, COOH, COOR6a, CONΗ₂, CONHOH, CONHR6a, CONHR6b, C(ΝΟΗ)ΝΗ₂, CONR6aR6b, S0₂R6a, S0₂H, S0₂NΗ₂, S0₂NR6aR6b, wherein R6a and R6b are independently selected from C₁₋₆ alkyl, substituted C₁₋₆ alkyl, aryl, heteroaryl, C₃₋₈ cycloalkyl and heterocyclyl, or R6a and R6b, together with the heteroatom to which they are joined, can form heterocyclyl.

wherein, when R6 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, and when R6 is C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, C₁₋₆ cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R6c, C₁₋₆ alkyl, C₆ alkynl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, aryl C₁₋₆ alkyl, heterocyclyl Cl₋₆ alkyl, aryl C₁₋₆ alkoxy, heteroaryl Cl₋₆ alkoxy, heterocyclyl C₋₆ alkoxy, OH, OR6c, OCR6c, SH, SR6c, SCOR6c, N0₂, NHR6c, NHS0₂NΗ₂, NH(ΗΗ)ΝΗ₂, NHS0₂R6c, NR6cCOR6d, NHC0R6c, NR6cR6d, COR6c, CSR6c, CN, COOH, COOR6c, CONΗ₂, CONHR6c, CONHR6d, CONHOH, C(ΝΟΗ)ΝΗ₂, CONR6cR6d, S0₂R6c, S0₂H, S0₂NΗ₂, S0₂NR6cR6d, wherein R6c and R6d are independently
selected from C₆ alkyl, substituted C₆ alkyl, aryl, heteroaryl, C₃ cycloalkyl and heterocyclyl, or R6c and R6d, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R6 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, or when the substituent of R6 is C₄ alkyl, C₆ alkynyl, aryl, heteroaryl, heterocyclyl, C₁ₓ₆ alkyl, Cs alkyl, alkoxyl, heterocyclyl, aryl C₆ alkyl, heteroaryl C₁₆ alkyl, aryl Cl₆ alkoxyl, heteroaryl Cl₁₆ alkoxyl, heterocyclyl C₄ alkoxyl, C₃ cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R6e, C₆ alkyl, C₄ alkoxyl, OH, OR6e, OCOR6e, SH, SR6e, SCOR6e, NH₂, N0₂, NHR6e, NHSO₂NH₂, NH(NH)NH₂, NHSO₂R6e, NR6eCOR6f, NHCOR6e, NR6eR6f, COR6e, CSR6e, CN, COOH, COOR6e, CON³¼, CONH₂OH, CONHR6e, CONHOR6e, C(NH)NOH, CNR6eR6f, S0₂R6e, SO₂H, SO₂NH₂, S0₂NR6eR6f, wherein R6e and R6f are independently selected from C₆ alkyl, substituted Cl₆ alkyl, aryl, heteroaryl, C₃ cycloalkyl and heterocyclyl, or R6e and R6f, together with the heteroatom to which they are joined, can form heterocyclyl;

Y can be N, CH or C-R7, wherein R7 is selected from C₆ alkyl, aryl, heteroaryl, heterocyclyl, C₁₆ alkoxyl, aryloxyl, heteroaryloxyl, heterocyclyloxyl, R7a, halogen, OH, OR7a, SH, SR7a, OCOR7a, SCOR7a, NH₂, N0₂, NHR7a, NHSO₂NH₂, NHSO₂R7a, NR7aCOR7b, NHCOR7a, NH(NH)NH₂, NR7aR7b, COR7a, CSR7a, CN, COOH, COOR7a, CON³¼, CONH₂OH, CONHR7a, CONHOR7a, C(NH)NOH, CNR7aR7b, S0₂R7a, S0₂H, S0₂NH₂, S0₂NR7aR7b, wherein R7a and R7b are independently selected from C₆ alkyl, substituted C₆ alkyl, aryl, heteroaryl, C₃ cycloalkyl and heterocyclyl, or R7a and R7b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R7 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, and when R7 is C₆ alkyl, aryl, heteroaryl, heterocyclyl, C₆ alkoxyl, alkoxyl, heteroaryloxyl, heterocyclyloxyl, C₃ cycloalkyl or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R7c, C₆ alkyl, C₁₆ alkoxyl, aryl, heteroaryl, heterocyclyl, C₆ alkoxyl, aryl, heteroaryl, heterocyclyl, C₆ alkoxyl, heteroaryl C₁₆ alkoxyl, heterocyclyl C₁₆ alkoxyl, heteroaryl Cl₆ alkynyl, aryl, heteroaryl, heterocyclyl, C₆ alkoxyl, heteroaryl C₁₆ alkoxyl, heterocyclyl C₁₆ alkoxyl, aryl Cl₆ alkoxyl, heteroaryl Cl₁₆ alkoxyl, heterocyclyl Cl₆ alkoxyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, aryl, heteroaryl, heterocyclyl, aryl C₆ alkyl, heteroaryl C₃₅ alkyl, heterocyclyl C₆ alkyl, C₆ alkoxyl, R7c, C₆ alkyl, OH, OR7e, OCO7e, SH, SR7e, SCOR7e, NH₂, N0₂,
NHR7e, NHS0 2NH2, NHS0 2R7e, NHC(NH)N¼, NR7eCOR7f, NHCOR7e, NR7eR7f, COR7e, CSR7e, CN, COOH, COOR7e, CONH2, CONHOH, CONHR7e, CONHOR7e, C(NOH)NH 2, CONR7eR7f, S0 2R7e, S0 2H, S0 2NH2, S0 2NR7eR7f, wherein R7e and R7f are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R7e and R7f, together with the heteroatom to which they are joined, can form heterocyclyl;

Z can be N, CH or C-R8, wherein R8 is selected from C1-4 alkyl, aryl, heteroaryl, heterocyclyl, C1-6 alkoxy, arloxy, heteroarylkoxy, heterocyclyloxy, R8a, halogen, OH, OR8a, SH, SR8a, OCOR8a, SCOR8a, NH2, N0 2, NHR8a, NHS0 2NH2, NHS0 2R8a, NR8aCOR8b, NHCOR8a, NHC(NH)NH 2, NR8aR8b, COR8a, CSR8a, CN, COOH, COOR8a, CONH2, CONHOH, CONHR8a, CONHOR8a, C(NOH)NH 2, CONR8aR8b, S0 2R8a, S0 2H, S0 2NH2, S0 2NR8aR8b, wherein R8a and R8b are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C1-6 cycloalkyl and heterocyclyl, or R8a and R8b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R8 is C1-6 alkyl, C8e alkyl, aryl, heteroaryl, heterocyclyl, C1-6 alkoxy, aryloxy, heteroarylkoxy, heterocyclyloxy, C3-8 cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R8c, C1-6 alkyl, aryl, heterocyclyl, C1-6 alkoxy, aryloxy, heteroarylkoxy, heterocyclyloxy, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, aryl C1-6 alkoxy, heteroaryl C1-6 alkoxy, heterocyclyl C1-6 alkoxy, OH, OR8c, OCOR8c, SH, SR8c, SCORSc, NH2, N0 2, NHR8c, NHS0 2NH2, NHS0 2R8c, NR8cCOR8d, NHCOR8c, NHC(NH)NH 2, NR8cR8d, COR8c, CSR8c, CN, COOH, COOR8c, CONH2, CONHOH, CONHR8c, CONHOR8c, C(NOH)NH 2, CONR8cR8d, S0 2R8c, S0 2H, S0 2NH2, S0 2NR8cR8d, wherein R8c and R8d are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R8c and R8d, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R8 is C1-6 alkyl, aryl, heteroaryl, heterocyclyl, C1-6 alkoxy, aryloxy, heteroarylkoxy, heterocyclyloxy, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, aryl C1-6 alkoxy, heteroaryl C1-6 alkoxy, heterocyclyl C1-6 alkoxy, C3-8 cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R8c, C1-6 alkyl, OH, OR8e, OCOR8e, SH, SR8e, SCOR8e, NH2, N0 2, NHR8e, NHS0 2NH2, NHS0 2R8e, NR8eCOR8f, NHCOR8e, NHC(NH)N¼, NR8eR8f, COR8e, CSR8e, CN, COOH, COOR8e, CONH2, CONHOH, CONHR8e, CONHOR8e, C(NOH)NH 2, CONR8eR8f, S0 2R8e, S0 2H, S0 2NH2, S0 2NR8eR8f, wherein R8e and R8f are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R8e and R8f, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, at most, two of the atoms or groups denoted X, Y and Z can be N;

wherein, when W is N, the CONR1R2 group may be joined to W instead, with the double bonds in Formula I rearranged accordingly.
Compared to the processes described in the prior art, the process of the present invention provides a surprisingly beneficial approach to the production of ureas of Formulas II or I. By using pyridine as the solvent for the urea formation reaction, a marked improvement in yield (potentially greater than 90%) is achieved. This compares extremely favourably with a yield of around 7% reported in WO20 10/074588 (where pyridine is used in catalytic quantities in a DMF/THF solvent), and a yield of around 50% using the phenylcarbamate approach reported in WO2012/015324. The process of the invention also leads to marked savings (around 50%) in the cost of input materials compared to the phenylcarbamate approach. The simplicity and beneficial results of the process of the present invention are surprising given the processes described previously.

As mentioned above the processes of the present invention are useful for preparing compounds having FAAH inhibitory activity and containing urea groups, and in particular those compounds disclosed in WO 2010/074588, the entire contents of which, and in particular the details of the compounds claimed therein, are hereby incorporated herein by reference. The compounds of WO 2010/074588 may be used in a variety of diseases or conditions in which the endogenous endocannabinoid system is implicated. Such conditions include, for example, pain, such as cancer pain.

The solvent used for the reaction of the intermediate of Formula II or F with the carbamoyl halide consists essentially of pyridine. In the context of the present invention, 'consists essentially of pyridine' means that the solvent used for the reaction comprises at least 10% v/v pyridine together with other, preferably miscible, solvents. Such other solvents may comprise, for example, dichloromethane or dimethylformamide. Further such solvents include isopropyl alcohol, 2-methyltetrahydrofuran, propionitrile or trifluorotoluene. In certain embodiments, the solvent comprises at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, or at least 90% v/v/ pyridine. Allowing the reaction solvent to contain other solvents means that one or both of the reacting species can be introduced in a solvent other than pyridine, provided that the solvent used for the reaction contains enough pyridine to produce an improvement in yield, as demonstrated by the process described herein. The higher the content of pyridine in the solvent, however, the greater the improvement in yield. The purity of the urea produced is also enhanced by the pyridine solvent.

The term \( C_{x,y} \) alkyl as used herein refers to a linear or branched saturated hydrocarbon group containing from x to y carbon atoms. For example, \( C_{1-6} \) alkyl refers to a linear or branched saturated hydrocarbon group containing from 1 to 6 carbon atoms. Examples of \( C_{1-6} \) alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert butyl, n-pentyl, isopentyl, neopentyl and hexyl. Preferably, the hydrocarbon group is linear. The group \( C_{1-6} \) alkyl is preferably \( C_{4-6} \) alkyl. The term \( C_{x,y} \) alkynyl is also used to mean a linear or branched saturated hydrocarbon group containing from x to y carbon atoms and in which a terminal methyl group is further substituted, i.e. so as to render a \( C_{x,y} \) alkyl group.

The term \( C_{x,y} \) alkynyl as used herein refers to a linear or branched hydrocarbon group containing from x to y carbon atoms and at least one carbon-carbon triple bond. For example, \( C_{4-6} \) alkynyl refers to a linear or branched hydrocarbon group containing from 1 to 6 carbon atoms. Examples of \( C_{4-6} \) alkynyl groups include, ethynyl, methylbutynyl (e.g. 3-methyl-1-butynyl), 1,3-butadiynyl and 1,3,5-hexatriynyl.
The term 'aryl' as used herein refers to a C\textsubscript{6}H\textsubscript{12} monocyclic or bicyclic hydrocarbon ring wherein at least one ring is aromatic. Examples of such groups include phenyl, naphthalenyl and tetrahydronaphthalenyl.

The term 'heteroaryl' as used herein refers to a 5-6 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring which monocyclic or bicyclic ring contains 1 to 4 heteroatoms selected from oxygen, nitrogen and sulphur. Examples of such monocyclic aromatic rings include thienyl, furyl, furazanyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, triazinyl, tetrazinyl and the like. Examples of such bicyclic aromatic rings include quinolinyl, isoquinolinyl, quinazolinyl, pteridinyl, cinnolinyl, phthalazinyl, naphthyridinyl, indolyl, isoindolyl, azaindolyl, indoliziny, indazolyl, purinyl, pyrrolopyridyl, furopyridyl, benzofuranyl, isobenzofurany, benzothienyl, benzoimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzoazicdiazolyl, benzothiadiazolyl and imidazopyridyl.

The term 'heteroaryl substituted with one or more oxygen atoms' refers to a heteroaryl ring which has one or more oxygen atoms bonded to the ring. It does not mean that the heteroaryl ring contains one or more oxygen atoms as ring atoms, although in some embodiments, this may be the case. Preferably, the one or more oxygen atoms is bonded to a nitrogen heteroatom in the heteroaryl ring. A heteroaryl substituted with an oxygen atom may contain an N-oxide. An example of a heteroaryl substituted with one or more oxygen atoms is 1-oxidopyridyl in which the pyridyl nitrogen is oxidised.

The term 'heterocyclyl' refers to a 3-8 (preferably 4-8 and, more preferably, 4-7) membered monocyclic ring or a fused 8-12 membered bicyclic ring which may be saturated or partially unsaturated, which monocyclic or bicyclic ring contains 1 to 4 heteroatoms selected from oxygen, nitrogen, silicon or sulphur. Examples of such monocyclic rings include oxaziridinyl, oxiranyl, dioxiranyl, aziridinyl, pyrrolidinyl, pyridinyl, azetidinyl, pyrazolinyl, oxazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dioxolanyl, dioxany, oxathiylany, oxathanil, dithianil, dihydrofurany, tetrahydrofurany, dihydropran, tetrahydropranly, tetrahydroprimidyl, tetrahydrothiophenyl, tetrahydrothiopyryl, diazepanyl and azepanyl. Examples of such bicyclic rings include indolinyl, isoindolinyl, benzopyranyl, quinuclidinyl, 2,3,4,5-tetrahydro- 1H-3-benzazepine, 4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl, and, tetrahydrosoquinolinyl.

The term 'heterocyclyl substituted with one or more oxygen atoms' refers to a heterocyclyl ring which has one or more oxygen atoms bonded to the ring. It does not mean that the heterocyclyl ring contains one or more oxygen atoms as ring atoms, although in some embodiments, this may be the case. Preferably, the one or more oxygen atoms is bonded to a heteroatom, such as nitrogen or sulphur, in the heterocyclyl ring. An example of a heterocyclyl substituted with one or more oxygen atoms is 1,l-dioxido-1,3-thiazolidinyl.

The terms 'bicyclic ring' and 'fused' in the context of a bicyclic ring refers to two rings which are joined together across a bond between two atoms (e.g. naphthalene), across a sequence of atoms to form a bridge (e.g. quinuclidine) or together at a single atom to form a spiro compound (e.g. 1,4-dioxa-8-aza-spiro[4,5]decane and N,N,3,3-dimethyl-1,5-dioxaaspiro[5,5]undecan-9-yl).
The term 'C<sub>x-y</sub>cycloalkyl' as used herein refers to a saturated hydrocarbon ring of x to y carbon atoms which can be mono, bi or tricyclic. For example, C<sub>3-10</sub>cycloalkyl refers to a saturated mono, bi or tricyclic hydrocarbon ring of 3 to 10 carbon atoms. Examples of C<sub>3-10</sub>cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and adamantyl.

The term 'aryl C<sub>x-y</sub>alkyl' as used herein refers to an aryl group as defined above attached to a C<sub>x-y</sub>alkyl as defined above. For example, aryl C<sub>1-5</sub>alkyl refers to an aryl group attached to a linear or branched saturated hydrocarbon group containing from 1 to 6 carbon atoms. Examples of aryl C<sub>1-6</sub>alkyl groups include benzyl, phenylethyl, phenylpropyl, phenylbutyl, phenylpentyl and phenylhexyl.

The terms 'heteroaryl C<sub>x-y</sub>alkyl', 'heterocyclic C<sub>x-y</sub>alkyl' and 'C<sub>x-y</sub>cycloalkyl C<sub>x-y</sub>alkyl' as used herein refers to a heteroaryl, heterocyclyl or C<sub>x-y</sub>cycloalkyl group as defined above attached to a C<sub>x-y</sub>alkyl as defined above.

The term 'C<sub>x-y</sub>alkoxy' as used herein refers to an -O-C<sub>x-y</sub>alkyl group wherein C<sub>x-y</sub>alkyl is as defined above. Examples of such groups include methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy.

The term 'aryloxy' as used herein refers to an -O-aryl group. Examples of such groups include phenoxy. The terms 'heteroaryloxy' and 'heterocyclyloxy' as used herein refer to an -O-heteroaryl and -O-heterocyclyl group respectively.

The term 'halogen' as used herein refers to a fluorine, chlorine, bromine or iodine atom, unless otherwise specified.

The term 'C<sub>x-y</sub>alkylamino' as used herein refers to a secondary amine group (-NH(R)) of which the R group is selected from a linear or branched saturated hydrocarbon group containing from x to y carbon atoms. Examples of C<sub>x-y</sub>alkylamino groups include methylamino, ethylamino and propylamino.

The term 'C<sub>x-y</sub>dialkylamino' as used herein refers to a tertiary amine group (-NR(R*)) of which the R and R* groups are each independently selected from a linear or branched saturated hydrocarbon group containing from x to y carbon atoms. Examples of C<sub>x-y</sub>dialkylamino groups include dimethylamino, methylethlamino and diethylamino.

The term 'substituted C<sub>i-j</sub>alkyl' used herein with reference to the identity of the various groups identified as R (for example, in the phrase 'wherein R8e and R8f are independently selected from C<sub>1-6</sub>alkyl, substituted C<sub>i-j</sub>alkyl, aryl, heteroaryl, C<sub>1-8</sub>cycloalkyl and heterocyclyl') means that the particular R group (e.g. R1a, R2c, R4d, R5e, etc.) can be substituted with one or more groups selected from R', halogen, OH, OR', SH, SR', OCOR', SCOR', NH<sub>2</sub>, N0<sub>2</sub>, NHR', NHSO<sub>2</sub>, NH<sub>2</sub>CONR', NR'COR', NHC(NH)NH<sub>2</sub>, NHCOR', NR'R', COR', CSR', CN, COOH, COOR', CONH<sub>2</sub>, CONHOR', CONH'COR', CONH'R', CONH'COR', C(NOH)NH<sub>2</sub>, S0<sub>2</sub>R', S0<sub>2</sub>H, S0<sub>2</sub>NH<sub>2</sub>, S0<sub>2</sub>NR'R', wherein R' and R'' are independently selected from C<sub>i-j</sub>alkyl, aryl, heteroaryl, C<sub>3-8</sub>cycloalkyl and heterocyclyl, or R' and R'', together with the heteroatom to which they are joined, can form heterocyclyl.

'Pharmaceutically acceptable salts' of compounds prepared according to the present invention include salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids and salts with basic or
acidic amino acids. Salts with acids may, in particular, be employed in some instances. Exemplary salts include hydrochloride salt, acetate salt, trifluoroacetate salt, methanesulfonate salt, 2-hydroxypropane-1, 2,3-tricarboxylate salt, (2R,3R)-2,3-dihydroxy succinate salt, phosphate salt and oxalate salt. The compound of the present invention may be in either solvate (e.g. hydrate) or non-solvate (e.g. non-hydrate) form. When in a solvate form, additional solvents may be alcohols such as propan-2-01.

Pharmaceutically acceptable esters’ of compounds prepared according to the invention are derivatives in which one or more carboxyl (i.e. -C(O)OH) groups of the said compounds are modified by reaction with an alcoholic moiety U-OH so as to yield -C(0)OU groups, wherein U may be C₃₋₁₄ alkyl (e.g. C₁₋₆ alkyl), aryl, heteroaryl, C₃₋₈ cycloalkyl or combinations thereof.

General methods for the preparation of salts and esters are well known to the person skilled in the art. Pharmaceutical acceptability of salts and esters will depend on a variety of factors, including formulation processing characteristics and in vivo behaviour, and the skilled person would readily be able to assess such factors having regard to the present disclosure.

Where compounds prepared according to the invention exist in different enantiomeric and/or diastereoisomeric forms (including geometric isomerism about a double bond), these compounds may be prepared as isomeric mixtures or racemates, although the invention relates to all such enantiomers or isomers, whether present in an optically pure form or as mixtures with other isomers. Individual enantiomers or isomers may be obtained by methods known in the art, such as optical resolution of products or intermediates (for example chiral chromatographic separation (e.g. chiral HPLC)), or an enantiomeric synthesis approach. Similarly, where compounds prepared according to the invention may exist as alternative tautomeric forms (e.g. keto/enol, amide/imidic acid), the invention relates to preparation of the individual tautomers in isolation, and of mixtures of the tautomers in all proportions.

In particular embodiments of the process of the invention, compounds according to Formula II are prepared.

In an embodiment, when R₁ and R₂ together form piperidinyl in compounds having Formula I, the piperidinyl is not substituted with methyl, dimethyl, ethyl, isopropyl, tert-butyl, methoxycarbonyl, trifluoromethyl, chloro, bromo or benzyl. In another embodiment, R₁ and R₂ together in compounds having Formula I do not form 6,7-dimethoxy-3,4-dihydro-1H-isquinolin-2-yl, 6-methoxy-3,4-dihydro-1H-isquinolin-2-yl, 7-methoxy-3,4-dihydro-1H-isquinolin-2-yl, 7-amino-3,4-dihydro-1H-isquinolin-2-yl, 7-nitro-3,4-dihydro-1H-isquinolin-2-yl, 3,4-dihydro-1H-isquinolin-2-yl, 3,4-dihydro-1H-isquinolin-1-yl, 3,4-dihydro-2H-quinolin-1-yl, pyrrolidin-1-yl, 3,6-dihydro-2H-pyrindin-1-yl, 8-aza-spiro[4.5]dec-8-yl, 1,3-dihydroisindol-2-yl, octahydroisindol-2-yl, 1,2,6-triaza-spiro[2.5]oct-1-en-6-yl or azepan-1-yl. In a further embodiment, when R₁ or R₂ is methyl, the other of R₁ or R₂ is not 4-chlorobutyl, 4-azidobutyl, or 4-isothiocyanatobutyl. In another embodiment, Ring A in compounds having Formula I does not form a pyridine, pyrimidine, substituted pyridine or substituted pyrimidine, when R₁ and R₂, together with the N to which they are attached, form piperidinyl, piperazinyl, substituted piperidinyl or substituted piperazinyl. In a further embodiment, the compound prepared by the process of the invention is not (4-phenyl-1H-imidazol-1-yl)(4-(quinolin-2-ylmethyl)piperazin-1-yl)methanone.
In compounds of Formula II, zero, one or two of the atoms or groups denoted X, Y and Z can be N.

In a particular embodiment, the process of the invention is used to prepare a compound having a formula selected from Formula I or Formula II:

![Chemical Structures]

wherein:

R1 and R2 can each be independently selected from H, Ci.20 alkyl, alkoxy, aryl, heteroaryl, heterocyclyl, C3-10 cycloalkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl Cw alkyl and C2-i0 cycloalkyl Ci-4 alkyl, each of which, with the exception of H, may optionally be substituted with one or more groups selected from halogen, Ci-6 alkyl, aryl, heteroaryl, heterocyclyl, C1-6 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, aryl C1-6 alkyl, heteroaryl Cw alkyl, heterocyclyl C1-6 alkyl, aryl Ci-6 alkoxy, heteroaryl C1-6 alkoxy, heterocyclyl C1-6 alkoxy, amino, C1-6 alkylamino and C1-6 dialkylamino, with the exception that R1 and R2 are not both H, or

R1 and R2, together with the N to which they are attached, can form a heteroaryl or heterocyclyl group, each of which may optionally be substituted with one or more groups selected from hydroxy, aryl, heteroaryl, heterocyclyl, C3-8 cycloalkyl, C1-6 alkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl Cw alkyl, C3-8 cycloalkyl C1-6 alkyl, Ci-6 alkoxy, aryloxy, heteroaryloxy, and heterocyclyloxy, each of which may optionally be substituted with a group selected from halogen, hydroxyl, C1-4 alkyl, aryl, heteroaryl, C1-4 alkoxy, arylxy, heteroaryloxy, aryl C1-4 alkoxy and heteroaryl C1-4 alkoxy, each of which, with the exception of halogen and hydroxyl, may optionally be substituted with C1-4 alkoxy;

Ring A is selected from aryl, heteroaryl and heterocyclyl moiety, each of which may optionally be substituted with one or more groups selected from halogen, hydroxyl, aryl, heteroaryl, heterocyclyl, Cj-6 alkoxy, arylxy, heteroaryloxy and heterocyclyloxy, each of which, with the exception of halogen and hydroxyl, may optionally be substituted with halogen, cyano, amide and carboxylic acid;

V can be N, CH or C-R3, wherein R3 is halogen, aryl, heteroaryl, heterocyclyl or C3-8 cycloalkyl, each of which, with the exception of halogen, may optionally be substituted with halogen;

W can be N, CH or C-R4, wherein R4 is C1-10 alkyl, aryl, heteroaryl, heterocyclyl or C3-8 cycloalkyl, each of which may optionally be substituted with halogen;
R5 is selected from H, C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyl and C₅₋₈ cycloalkyl, each of which, with the exception of H, may optionally be substituted with halogen;

X can be N, CH or C-R₆, wherein R₆ is selected from C₁₋₆ alkyl, aryl, heteroaryl and heterocyclyl, each of which, with the exception of H, may optionally be substituted with one or more groups selected from halogen, hydroxyl, amine, nitro, amide, cyano, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl, heterocyclyl C₁₋₆ alkyl, aryl C₅₋₆ alkoxy, heteroaryl C₅₋₆ alkoxy and heterocyclyl C₅₋₆ alkoxy;

Y can be N, CH or C-R₇, wherein R₇ is selected from C₁₋₆ alkyl, aryl, heteroaryl and heterocyclyl, each of which, with the exception of H, may optionally be substituted with one or more groups selected from halogen, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl, heterocyclyl C₁₋₆ alkyl, aryl C₁₋₆ alkoxy, heteroaryl C₁₋₆ alkoxy and heterocyclyl C₁₋₆ alkoxy, each of which may optionally be substituted with C₁₋₄ alkyl, cyano, amine, amide, halogen, aryl, heteroaryl, heterocyclyl, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl and heterocyclyl C₁₋₆ alkyl;

Z can be N, CH or C-R₈, wherein R₈ is selected from C₁₋₉ alkyl, aryl, heteroaryl, heterocyclyl or C₅₋₉ cycloalkyl, each of which may optionally be substituted with halogen;

or a pharmaceutically acceptable salt or ester thereof;

provided that when R₁ and R₂ together form piperidinyl in compounds having Formula I, the piperidinyl is not substituted with methyl, dimethyl, ethyl, isopropyl, tert-butyl, trifluoromethyl, chloro, bromo or benzyl.

In an embodiment of the invention, the process is used to prepare a compound having Formula I or Formula II:

![Formula I](image)

![Formula II](image)

wherein:

R₁ and R₂ can each be independently selected from H, C₁₋₂₀ alkyl, alkoxy, aryl, heteroaryl, partially or fully saturated heterocyclyl, C₃₋₁₀ cycloalkyl, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl, heterocyclyl C₁₋₆ alkyl, C₂₋₁₀ cycloalkyl C₁₋₆ alkyl, Rla, halogen, OH, ORla, SH, SRLa, OCORla, SCORla, N₃, NRRLa, NRRlaRlb, CORla, CSRLa, CN, COOH, COORla, CONH₂, S₂O₂Rla, S₂₃H, S₂O₂NH₂, CONRLaRlb, S₇N₂RRLaRlb, wherein Rla and
Rib are independently selected from C_{1-6} alkyl, substituted C_{1-4} alkyl, C_{3-8} cycloalkyl and heterocyclyl, and R1a and Rib, together with the adjacent heteroatom, can form heterocyclyl,

wherein, when R1 or R2 is C_{1-4} alkyl (such as C_{1-6} alkyl), alkoxy, aryl, heteroaryl, heterocyclyl, C_{3-8} cycloalkyl (such as C_{3-8} cycloalkyl), aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl, C_{3-8} cycloalkyl C_{1-6} alkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with Rlc, halogen, C_{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C_{3-8} alkoxy, alkoxy, heteroalcohol, heterocyclyloxy, aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl, aryl C_{1-6} alkoxy, heteroaryl C_{1-6} alkoxy, heterocyclyl C_{1-6} alkoxy, C_{1-6} dialkylamino, C_{1-6} dialkylamino, C_{1-6}alkyl, OH, ORlc, OCORlc, SH, SRlc, SCORlc, NH2, NHRlc, NNRlcRlc, CONRlcRlc, SRlc, CN, COOH, COORlc, CONH2, S02Rlc, S03H, S02NH2, CONRlcRlc, wherein Rlc and Rid are independently selected from C_{1-6} alkyl, substituted C_{1-4} alkyl, C_{3-8} cycloalkyl and heterocyclyl, and Rlc and Rid, together with the adjacent heteroatom, can form heterocyclyl,

wherein, when the substituent of R1 or R2 is C_{1-10} alkyl, aryl, heteroaryl, heterocyclyl, C_{3-8} alkoxy, arloxy, heteroalcohol, heterocyclyloxy, aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl, C_{3-8} dialkylamino, C_{1-6} dialkylamino, C_{1-6} alkyl, C_{3-8} cycloalkyl or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with Rle, C_{1-10} alkyl, OH, ORle, OCORle, SH, SRle, SCORle, NH2, NHRle, NNRleRle, CONRleRle, CSRle, CN, COOH, COORle, CONH2, S02Rle, S03H, S02NH2, CONRleRle, S02NRleRle, wherein Rle and Rif are independently selected from C_{1-4} alkyl, substituted C_{1-4} alkyl, C_{3-8} cycloalkyl and heterocyclyl, and Rle and Rif, together with the adjacent heteroatom, can form heterocyclyl, with the exception that R1 and R2 are not both H, or

R1 and R2, together with the N to which they are attached, can form a heteroaryl or heterocyclyl group, each of which may optionally be substituted with one or more groups selected from hydroxy, aryl, heteroaryl, partially or fully saturated heterocyclyl, C_{3-8} cycloalkyl, C_{1-6} alkyl, aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl, C_{3-8} cycloalkyl C_{1-6} alkyl, C_{3-8} alkoxy, C_{3-8} alkyl, arly C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl, C_{3-8} cycloalkyl C_{1-6} alkyl, C_{3-8} alkoxy, heteroalcohol, heterocyclyloxy, R2a, halogen, OH, OR2a, SH, SR2a, OCOR2a, SCOR2a, NH2, NHR2a, NNR2aR2b, COR2a, CSR2a, CN, COOH, COOR2a, CONH2, S02R2a, S03H, S02NH2, CONR2aR2b, wherein R2a and R2b are independently selected from d . . . 6 alkyl, substituted C_{1-6} alkyl, C_{3-8} cycloalkyl and heterocyclyl, and R2a and R2b, together with the adjacent heteroatom, can form heterocyclyl,
wherein, when the substituent of the substituent of the heteroaryl or heterocyclyl of R1 and R2 together is C1,4 alkyl, aryl, heteroaryl, heterocyclyl, C3,5 cycloalkyl, C2,4 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C3,8 cycloalkoxyloxy, aryl C1,4 alkoxy, heteroaryl C1,4 alkoxy, heterocyclyl C1,4 alkoxy, C2,4 cycloalkyl C1,4 alkoxy, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with C1,4 alkoxy, R2e, halogen, OH, OR2e, SH, SR2e, OCOR2e, SCOR2e, NH2, NH2R2e, NR2eR2f, CONR2e, NR2eR2f, CONR2e, OCNH2, S0 2R2e, S0 3H, S0 2NH2, CONR2eR2f, S0 2NR2eR2f, wherein R2e and R2f are independently selected from C1,4 alkyl, substituted C1,6 alkyl, C3,8 cycloalkyl and heterocyclyl, and R2e and R2f, together with the adjacent heteroatom, can form heterocyclyl;

Ring A is selected from aryl, heteroaryl and heterocyclyl moiety, each of which may optionally be substituted with one or more groups selected from halogen, C1,4 alkyl, hydroxy, aryl, heteroaryl, heterocyclyl, C1,6 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, Ra, Cw,9 alkyl, OH, ORa, OCORa, SH, SRa, SCORa, NH2, NH2R, NRaRb, OCNH2, S0 2Ra, S0 3H, S0 2NH2, CONRb, S0 2NRaRb, wherein Ra and Rb are independently selected from C1,6 alkyl, substituted C1,6 alkyl, C3,8 cycloalkyl and heterocyclyl, and Ra and Rb, together with the adjacent heteroatom, can form heterocyclyl,

wherein, when Ring A is substituted with C1,6 alkyl, aryl, heteroaryl, heterocyclyl, C1,6 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C1,6 alkyl, C3,8 cycloalkyl or is substituted with a group containing one or more of these moieties, each of these moieties may optionally be substituted with Rc, C1,4 alkyl, OH, ORc, OCORc, SH, SRC, OCNH2, NH2, NH2R, NRcRd, SCORc, CN, COOH, COORc, CONH2, S0 2Rc, S0 3H, S0 2NH2, CONRcRd, S0 2NRcRd, wherein Rc and Rdc are independently selected from C1,6 alkyl, substituted C1,6 alkyl, C3,8 cycloalkyl and heterocyclyl, and Rc and Rd, together with the adjacent heteroatom, can form heterocyclyl;

V can be N, CH or C-R3, wherein R3 is halogen, C1,10 alkyl, aryl, heteroaryl, heterocyclyl, C3,8 cycloalkyl, C1,6 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, R3a, OH, OR3a, SH, SR3a, OCOR3a, SCOR3a, NH2, NH2R3a, NR3aR3b, OCNH2, S0 2R3a, S0 3H, S0 2NH2, CONR3aR3b, S0 2NR3aR3b, wherein R3a and R3b are independently selected from C1,6 alkyl, substituted C1,6 alkyl, C3,8 cycloalkyl and heterocyclyl, and R3a and R3b, together with the adjacent heteroatom, can form heterocyclyl,

wherein, when R3 is C1,6 alkyl, aryl, heteroaryl, heterocyclyl, C1,6 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C1,6 alkyl, C3,8 cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with aryl, heteroaryl, heterocyclyl, C1,6 alkyl, aryloxy, heteroaryloxy, heterocyclyloxy, R3c, C1,0 alkyl, OH, OR3c, OCOR3c, SH, SR3c, SCOR3c, NH2, NH2R3c, NR3cR3d, OCNH2, SCOR3c, CN, COOH, COOR3c, CONH2, S0 2R3c, S0 3H, S0 2NH2, CONR3cR3d, S0 2NR3cR3d, wherein R3c and R3d are independently selected from C1,6 alkyl, substituted C1,6 alkyl, C3,8 cycloalkyl and heterocyclyl, and R3c and R3d, together with the adjacent heteroatom, can form heterocyclyl,

wherein, when the substituent of R3 is C1,10 alkyl, aryl, heteroaryl, heterocyclyl, C1,6 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C1,6 alkyl, C3,8 cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with R3c, C1,10 alkyl, OH, OR3c, OCOR3c, SH, SR3c, SCOR3c, NH2, NH2R3c, NR3cR3d, OCNH2, SCOR3c, CN, COOH, COOR3c, CONH2, S0 2R3c, S0 3H, S0 2NH2, CONR3cR3d, S0 2NR3cR3d, wherein R3e and R3f are independently selected from Cw,6 alkyl, substituted Cw,6
alkyl, C₃₈ cycloalkyl and heterocyclyl, and R₃e and R₃f, together with the adjacent heteroatom, can form heterocyclyl;

W can be N, CH or C-R₄, wherein R₄ is halogen, C₁₋₁₀ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C₂₋₈ cycloalkyl, R₄a, OH, OR₄a, SH, SR₄a, OCOR₄a, SCOR₄a, NH₂, NHR₄a, NR₄aR₄b, COR₄a, CSR₄a, CN, COOH, COOR₄a, CONH₂, S₀₂R₄a, S₀₂H, S₀₂NH₂, CONR₄aR₄b, S₀₂NR₄aR₄b, wherein R₄a and R₄b are independently selected from C₁₋₆ alkyl, substituted C₁₋₄ alkyl, C₃₋₈ cycloalkyl and heterocyclyl, and R₄a and R₄b, together with the adjacent heteroatom, can form heterocyclyl,

wherein, when R₄ is C₁₋₁₀ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C₁₋₆ alkyl, C₂₋₈ cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, R₄c, C₃₋₈ alkyl, OH, OR₄c, OCOR₄c, SH, SR₄c, SCOR₄c, NH₂, NHR₄c, NR₄cR₄d, COR₄c, CSR₄c, CN, COOH, COOR₄c, CONH₂, S₀₂R₄c, S₀₂H, S₀₂NH₂, CONR₄cR₄d, S₀₂NR₄cR₄d, wherein R₄c and R₄d are independently selected from C₁₋₆ alkyl, substituted C₁₋₆ alkyl, C₃₋₈ cycloalkyl and heterocyclyl, and R₄c and R₄d, together with the adjacent heteroatom, can form heterocyclyl,

wherein, when the substituent of R₄ is C₁₋₁₀ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C₁₋₆ alkyl, C₂₋₈ cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with R₄e, C₁₋₆ alkyl, OH, OR₄e, OCOR₄e, SH, SR₄e, SCOR₄e, NH₂, NHR₄e, NR₄eR₄f, COR₄e, CSR₄e, CN, COOH, COOR₄e, CONH₂, S₀₂R₄e, S₀₂H, S₀₂NH₂, CONR₄eR₄f, S₀₂NR₄eR₄f, wherein R₄e and R₄f are independently selected from C₁₋₆ alkyl, substituted C₁₋₆ alkyl, C₃₋₈ cycloalkyl and heterocyclyl, and R₄e and R₄f, together with the adjacent heteroatom, can form heterocyclyl;

R₅ is selected from H, C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyl, C₂₋₈ cycloalkyl, C₁₋₆ alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, R₅a, halogen, OH, OR₅a, SH, SR₅a, OCOR₅a, SCOR₅a, NH₂, NHR₅a, NR₅aR₅b, COR₅a, CSR₅a, CN, COOH, COOR₅a, CONH₂, S₀₂R₅a, S₀₂H, S₀₂NH₂, CONR₅aR₅b, S₀₂NR₅aR₅b, wherein R₅a and R₅b are independently selected from C₁₋₆ alkyl, substituted C₁₋₆ alkyl, C₂₋₈ cycloalkyl and heterocyclyl, and R₅a and R₅b, together with the adjacent heteroatom, can form heterocyclyl,

wherein, when R₅ is C₁₋₁₀ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C₁₋₆ alkyl, C₂₋₈ cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, R₅c, C₁₋₆ alkyl, OH, OR₅c, OCOR₅c, SH, SR₅c, SCOR₅c, N₅₄, NHR₅c, NR₅cR₅d, COR₅c, CSR₅c, CN, COOH, COOR₅c, CON₅₄, S₀₂R₅c, S₀₂H, S₀₂NH₂, CONR₅cR₅d, S₀₂NR₅cR₅d, wherein R₅c and R₅d are independently selected from C₁₋₆ alkyl, substituted C₁₋₆ alkyl, C₂₋₈ cycloalkyl and heterocyclyl, and R₅c and R₅d, together with the adjacent heteroatom, can form heterocyclyl,

wherein, when the substituent of R₅ is C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C₂₋₈ cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with R₅e, C₁₋₆ alkyl, OH, OR₅e, OCOR₅e, SH, SR₅e, SCOR₅e,
NH₂, NHR₅e, NR₅eR₅f, COR₅e, CSR₅e, CN, COOH, COOR₅e, CONH₂, SO₂R₅e, SO₃H, SO₂NH₃, CONR₅eR₅f, SO₂NR₅eR₅f, wherein R₅e and R₅f are independently selected from Cl₆ alkyl, substituted Cl₆ alkyl, C₃₋₈ cycloalkyl and heterocyclyl, and R₅e and R₅f, together with the adjacent heteroatom, can form heterocyclyl.

X can be N, CH or C-R₆, wherein R₆ is selected from Cl₆ alkyl, aryl, heteroaryl, heterocyclyl, C₃₋₈ alkoxy, aryl, heteroaryl, heterocyclyloxy, R₆a, halogen, OH, OR₆a, SH, SR₆a, OR₆a, SCOR₆a, N₆H₂, NHR₆a, NR₆aR₆b, CONR₆a, CSR₆a, CN, COOH, COOR₆a, CONH₂, SO₂R₆a, SO₃H, SO₂NH₂, CONR₆aR₆b, SO₂NR₆aR₆b, wherein R₆a and R₆b are independently selected from C₁₋₆ alkyl, substituted Cl₆ alkyl, C₃₋₈ cycloalkyl and heterocyclyl, and R₆a and R₆b, together with the adjacent heteroatom, can form heterocyclyl.

wherein, when R₆ is C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyl, C₃₋₈ alkoxy, aryl, heteroaryl, heterocyclyloxy, C₃₋₈ cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with R₆c, Cl₆ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyl, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl, heterocyclyl C₁₋₆ alkyl, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl, heterocyclyl C₁₋₆ alkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with R₆e, Cl₆ alkyl, OH, OR₆e, OCOR₆e, SH, SR₆e, SCOR₆e, N₆H₂, NHR₆e, NR₆eR₆f, CONR₆e, CSR₆e, CN, COOH, COOR₆e, CONH₂, SO₂R₆e, SO₃H, SO₂NH₂, CONR₆eR₆f, SO₂NR₆eR₆f, wherein R₆e and R₆f are independently selected from C₁₋₆ alkyl, substituted Cl₆ alkyl, C₃₋₈ cycloalkyl and heterocyclyl, and R₆e and R₆f, together with the adjacent heteroatom, can form heterocyclyl.

wherein, when the substituent of R₆ is C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, aryl, heteroaryl, heterocyclyloxy, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl, heterocyclyl C₁₋₆ alkyl, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl, heterocyclyl C₁₋₆ alkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with R₆e, Cl₆ alkyl, OH, OR₆e, OCOR₆e, SH, SR₆e, SCOR₆e, N₆H₂, NHR₆e, NR₆eR₆f, CONR₆e, CSR₆e, CN, COOH, COOR₆e, CONH₂, SO₂R₆e, SO₃H, SO₂NH₂, CONR₆eR₆f, SO₂NR₆eR₆f, wherein R₆e and R₆f are independently selected from C₁₋₆ alkyl, substituted Cl₆ alkyl, C₃₋₈ cycloalkyl and heterocyclyl, and R₆e and R₆f, together with the adjacent heteroatom, can form heterocyclyl.

Y can be N, CH or C-R₇, wherein R₇ is selected from C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyl, Cl₆ alkoxy, aryl, heteroaryl, heterocyclyloxy, R₇a, halogen, OH, OR₇a, SH, SR₇a, OCOR₇a, SCOR₇a, N₇H₂, NHR₇a, NR₇aR₇b, CONR₇a, CSR₇a, CN, COOH, CONH₇a, SO₂R₇a, SO₃H, SO₂NH₂, CONR₇aR₇b, SO₂NR₇aR₇b, wherein R₇a and R₇b are independently selected from C₁₋₆ alkyl, substituted Cl₆ alkyl, C₃₋₈ cycloalkyl and heterocyclyl, and R₇a and R₇b, together with the adjacent heteroatom, can form heterocyclyl.

wherein, when R₇ is C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, aryl, heteroaryl, heterocyclyloxy, C₃₋₈ cycloalkyl or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with R₇c, C₆ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyloxy, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl, heterocyclyl C₁₋₆ alkyl, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkoxy, heterocyclyl C₁₋₆ alkoxy, OH, OR₇c, SCOR₇c, NH₂, NHR₇c, NR₇cR₇d, CONR₇c, CSR₇c, CN, COOH, COOR₇c, CONH₂, SO₂R₇c, SO₃H, SO₂NH₂, CONR₇cR₇d.
S0NR7cR7d, wherein R7c and R7d are independently selected from C\textsubscript{1-6} alkyl, substituted C\textsubscript{1-6} alkyl, C\textsubscript{3-8} cycloalkyl and heterocyclyl, and R7c and R7d, together with the adjacent heteroatom, can form heterocyclyl,

wherein, when the substituent of R7 is C\textsubscript{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C\textsubscript{1-6} alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, aryl C\textsubscript{1-6} alkyl, heteroaryl C\textsubscript{1-6} alkyl, heterocyclyl C\textsubscript{1-6} alkyl, aryl C\textsubscript{1-6} alkoxy, heteroaryl C\textsubscript{1-6} alkoxy, heterocyclyl C\textsubscript{1-6} alkoxy, C\textsubscript{3-8} cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with R7e, C\textsubscript{1-6} alkyl, OH, OR7e, OCOR7e, SH, SR7e, SCOR7e, NH\textsubscript{2}, NHR7e, NR7eR7f, COR7e, CSR7e, CN, COOH, COOR7e, CONH\textsubscript{2}, SO\textsubscript{2}R7e, SO\textsubscript{3}H, S0\textsubscript{2}NH\textsubscript{2}, CONR7eR7f, S0\textsubscript{2}NR7eR7f, wherein R7e and R7f are independently selected from C\textsubscript{1-6} alkyl, substituted C\textsubscript{1-6} alkyl, C\textsubscript{3-8} cycloalkyl and heterocyclyl, and R7e and R7f, together with the adjacent heteroatom, can form heterocyclyl;

Z can be N, CH or C-R8, wherein R8 is selected from C\textsubscript{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C\textsubscript{1-6} alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, R8a, halogen, OH, OR8a, SH, SR8a, OCOR8a, SCOR8a, NH\textsubscript{2}, NHR8a, NR8aR8b, COR8a, CSR8a, CN, COOH, COOR8a, CONH\textsubscript{2}, SO\textsubscript{2}R8a, S0\textsubscript{3}H, S0\textsubscript{2}NH\textsubscript{2}, CONR8aR8b, S0\textsubscript{2}NR8aR8b, wherein R8a and R8b are independently selected from C\textsubscript{1-6} alkyl, substituted C\textsubscript{1-6} alkyl, C\textsubscript{3-8} cycloalkyl and heterocyclyl, and R8a and R8b, together with the adjacent heteroatom, can form heterocyclyl,

wherein, when R8 is C\textsubscript{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C\textsubscript{1-6} alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, C\textsubscript{3-8} cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with R8c, C\textsubscript{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C\textsubscript{1-6} alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, aryl C\textsubscript{1-6} alkyl, heteroaryl C\textsubscript{1-6} alkyl, heterocyclyl C\textsubscript{1-6} alkyl, aryl C\textsubscript{1-6} alkoxy, heteroaryl C\textsubscript{1-6} alkoxy, heterocyclyl C\textsubscript{1-6} alkoxy, OH, OR8c, OCOR8c, SH, SR8c, SCOR8c, NH\textsubscript{2}, NHR8c, NR8cR8d, COR8c, CSR8c, CN, COOH, COOR8c, CONH\textsubscript{2}, SO\textsubscript{2}R8c, S0\textsubscript{3}H, S0\textsubscript{2}NH\textsubscript{2}, CONR8cR8d, S0\textsubscript{2}NR8cR8d, wherein R8c and R8d are independently selected from C\textsubscript{1-6} alkyl, substituted C\textsubscript{1-6} alkyl, C\textsubscript{3-8} cycloalkyl and heterocyclyl, and R8c and R8d, together with the adjacent heteroatom, can form heterocyclyl,

wherein, when the substituent of R8 is C\textsubscript{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C\textsubscript{1-6} alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, aryl C\textsubscript{1-6} alkyl, heteroaryl C\textsubscript{1-6} alkyl, heterocyclyl C\textsubscript{1-6} alkyl, aryl C\textsubscript{1-6} alkoxy, heteroaryl C\textsubscript{1-6} alkoxy, heterocyclyl C\textsubscript{1-6} alkoxy, C\textsubscript{3-8} cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with R8e, C\textsubscript{1-6} alkyl, OH, OR8e, OCOR8e, SH, SR8e, SCOR8e, NH\textsubscript{2}, NHR8e, NR8eR8f, COR8e, CSR8e, CN, COOH, COOR8e, CONH\textsubscript{2}, SO\textsubscript{2}R8e, S0\textsubscript{3}H, S0\textsubscript{2}NH\textsubscript{2}, CONR8eR8f, S0\textsubscript{2}NR8eR8f, wherein R8e and R8f are independently selected from C\textsubscript{1-6} alkyl, substituted C\textsubscript{1-6} alkyl, C\textsubscript{3-8} cycloalkyl and heterocyclyl, and R8e and R8f, together with the adjacent heteroatom, can form heterocyclyl;

or a pharmaceutically acceptable salt or ester thereof.

In such an embodiment, the compound may be limited by the following exceptions:

provided that when R1 and R2 together form piperidinyl in compounds having Formula 1, the piperidinyl is not substituted with methyl, dimethyl, ethyl, isopropyl, tert-butyl, trifluoromethyl, chloro, bromo or benzy1,
provided that R1 and R2 together in compounds having Formula I do not form 6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl, 6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl, 7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl, 7-amino-3,4-dihydro-1H-isoquinolin-2-yl, 7-nitro-3,4-dihydro-1H-isoquinolin-2-yl, 3,4-dihydro-1H-isoquinolin-2-yl, 3,4-dihydro-1H-isoquinolin-1-yl, 3,4-dihydro-2H-quinolin-1-yl, pyrrolidin-1-yl, 3,6-dihydro-2H-pyridin-1-yl, 8-aza-spiro[4.5]dec-8-yl, 1,3-dihydroisoindol-2-yl, octahydroisoindol-2-yl, 1,2,6-triaza-spiro[2.5]oct-l-en-6-yl or azepan-1-yl, and/or

provided that Ring A in compounds having Formula I does not form a pyridine, pyrazine, substituted pyridine or substituted pyrazine, when R1 and R2, together with the N to which they are attached, form piperidinyl, piperazinyl, substituted piperidinyl or substituted piperazinyl.

In accordance with a further embodiment of the invention, the process is used for preparing a compound having Formula I or Formula II:

![Diagram](image)

wherein:

R1 and R2 can each be independently selected from H, C\textsubscript{3-10} alkyl, C\textsubscript{6} alkyl, aryl, heteroaryl, partially or fully saturated heterocyclyl, C\textsubscript{3,10} cycloalkyl, aryl C\textsubscript{6} alkyl, heteroaryl C\textsubscript{6} alkyl, heterocyclyl C\textsubscript{1-6} alkyl, C\textsubscript{3,10} cycloalkyl C\textsubscript{1-6} alkyl, Rla, halogen, OH, ORla, SH, SRla, OCORla, SCORla, NH\textsubscript{2}, NRlaRlb, CORla, CSRla, CN, COOH, COORla, CONH\textsubscript{2}, S0\textsubscript{2}Rla, S0\textsubscript{2}H, S0\textsubscript{2}NH\textsubscript{2}, CONRlaRlb, S0\textsubscript{2}NRlaRlb, wherein Rla and Rib are independently selected from C\textsubscript{1-6} alkyl, substituted C\textsubscript{1-6} alkyl, aryl, heteroaryl, C\textsubscript{3,8} cycloalkyl and heterocyclyl, or Rla and Rib, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R1 or R2 is C\textsubscript{1,20} alkyl (such as C\textsubscript{6} alkyl), alkoxy, aryl, heteroaryl, heterocyclyl, C\textsubscript{3,10} cycloalkyl (such as C\textsubscript{3,8} cycloalkyl), aryl C\textsubscript{6} alkyl, heteroaryl C\textsubscript{6} alkyl, heterocyclyl C\textsubscript{1,6} alkyl, C\textsubscript{3,10} cycloalkyl C\textsubscript{6} alkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from Rlc, halogen, aryl, heteroaryl, heterocyclyl, C\textsubscript{6} alkoxycarbonyl, arylcarbonyl, heteroaryloxy, heterocycloxy, aryl C\textsubscript{6} alkyl, heteroaryl C\textsubscript{6} alkyl, heterocyclyl C\textsubscript{6} alkyl, aryl C\textsubscript{6} alkoxycarbonyl, heterocyclyl C\textsubscript{6} alkoxycarbonyl, C\textsubscript{1,6} alkoxy, heterocyclyl C\textsubscript{1,6} alkoxy, C\textsubscript{1,6} alkoxy, C\textsubscript{1,6} dialkylamino, C\textsubscript{1,6} dialkylamino, C\textsubscript{1,6} alkyl, OH, ORlc, OCORlc, SH, SRlc, SCORlc, NH\textsubscript{2}, NO\textsubscript{2}, NRlcRld, CORlc, CSRlc, CN, COOH, COORlc, CONH\textsubscript{2}, S0\textsubscript{2}Rlc, S0\textsubscript{2}H, S0\textsubscript{2}NH\textsubscript{2}, CONRlcRld, S0\textsubscript{2}NRlcRld, wherein Rlc and Rld are independently selected from C\textsubscript{1,6} alkyl,
substituted C₁ᵉ alkyl, aryl, heteroaryl, C₃₋₅ cycloalkyl and heterocyclyl, or Rlc and Rid, together with the
heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R₁ or R₂ is C₁₋₅ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋ᵉ alkoxy, arlyloxy, heteroaryloxy, heterocycloxyloxy, aryl C₁₋₅ alkyl, heteroaryl C₁₋ᵉ alkyl, heterocyclyl C₁₋ᵉ alkyl, aryl C₁₋ᵉ alkoxy, heteroaryl C₁₋ᵉ alkoxy, heterocyclyl C₁₋ᵉ alkoxy, C₁₋ᵉ dialkylamino, C₁₋ᵉ dialkylamino, C₁₋ᵉ alkyl, C₃₋₃ cycloalkyl or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from Rle, halogen, C₁₋₁₀ alkyl, OH, ORle, OCORle, SH, SRle, SCORle, NH₂, N₂, NHRle, NRleRlf, CORle, CSRle, CN, COOH, COORle, CONH₂, S₀₂Rle, S₀₂H, S₀₂NH₂, CONRleRlf, S₀₂NRleRlf, wherein Rle and Rlf are independently selected from C₁₋ᵉ alkyl, substituted C₁₋ᵉ alkyl, aryl, heteroaryl, C₃₋₅ cycloalkyl and heterocyclyl, or Rle and Rlf, together with the heteroatom to which they are joined, can form heterocyclyl,

with the exception that R₁ and R₂ are not both H,

or

R₁ and R₂, together with the N to which they are attached, can form a heteroaryl or heterocyclyl group, each of which may optionally be substituted with one or more oxygen atoms or one or more groups selected from hydroxyl, aryl, heteroaryl, partially or fully saturated heterocyclyl, C₃₋₅ cycloalkyl, Cᵉ₋₁₀ alkyl, aryl Cᵉ₋₁₀ alkyl, heteroaryl Cᵉ₋₁₀ alkyl, heterocyclyl Cᵉ₋₁₀ alkyl, C₁₋ᵉ cycloalkyl Cᵉ₋₁₀ alkyl, Cᵉ₋₁₀ alkoxy, arlyloxy, heteroaryloxy, heterocycloxyloxy, R₂a, halogen, OH, OR₂a, SH, SR₂a, OCOR₂a, SCOR₂a, NH₂, N₂, NHR₂a, NRleRlf, COR₂a, CSR₂a, CN, COOH, COOR₂a, CONH₂, S₀₂R₂a, S₀₂H, S₀₂NH₂, CONR₂aRlf, S₀₂NRleRlf, wherein R₂a and Rlf are independently selected from C₁₋ᵉ alkyl, substituted C₁₋ᵉ alkyl, aryl, heteroaryl, C₃₋₅ cycloalkyl and heterocyclyl, or R₂a and Rlf, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of the heteroaryl or heterocyclyl formed by R₁ and R₂ together is aryl, heteroaryl, heterocyclyl, C₃₋₅ cycloalkyl, Cᵉ₋₁₀ alkyl, aryl Cᵉ₋₁₀ alkyl, heteroaryl Cᵉ₋₁₀ alkyl, heterocyclyl Cᵉ₋₁₀ alkyl, C₃₋₅ cycloalkyl Cᵉ₋₁₀ alkyl, Cᵉ₋₁₀ alkoxy, arlyloxy, heteroaryloxy, heterocycloxyloxy, C₃₋₅ cycloalkyoxy, aryl Cᵉ₋₁₀ alkoxy, heteroaryl Cᵉ₋₁₀ alkoxy, heterocyclyl Cᵉ₋₁₀ alkoxy, C₃₋₅ cycloalkyl Cᵉ₋₁₀ alkoxy, R₂c, OR₂c, SH, SR₂c, OCOR₂c, SCOR₂c, NH₂, N₂, NHR₂c, NRleRlf, COR₂c, CSR₂c, CN, COOH, COOR₂c, CONH₂, S₀₂R₂c, S₀₂H, S₀₂NH₂, CONR₂cRlf, S₀₂NRleRlf, wherein R₂c and Rlf are independently selected from C₁₋ᵉ alkyl, substituted C₁₋ᵉ alkyl, aryl, heteroaryl, C₃₋₅ cycloalkyl and heterocyclyl, or R₂c and Rlf, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of the substituent of the heteroaryl or heterocyclyl formed by R₁ and R₂ together is C₁₋ᵉ alkyl, aryl, heteroaryl, heterocyclyl, C₃₋₅ cycloalkyl, Cᵉ₋₁₀ alkoxy, arlyloxy, heteroaryloxy, heterocycloxyloxy, C₃₋₅ cycloalkylxyloxy, aryl Cᵉ₋₁₀ alkoxy, heteroaryl Cᵉ₋₁₀ alkoxy, heterocyclyl Cᵉ₋₁₀ alkoxy, C₃₋₅ cycloalkyl Cᵉ₋₁₀ alkoxy, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from C₁₋ᵉ alkoxy, R₂c, halogen, OH, OR₂c, SH, SR₂c, OCOR₂c, SCOR₂c, NH₂, N₂,
NHR2e, NR2eR2f, NHCOR2e, COR2e, CSR2e, CN, COOH, COOR2e, CONH, S0 2R2e, S0 2H, S0 2NH2, CONR2eR2f, S0 2NR2eR2f, wherein R2e and R2f are independently selected from Ci, alkyl, substituted Ci, alkyl, aryl, heteroaryl, C3, cycloalkyl and heterocyclyl, or R2e and R2f, together with the heteroatom to which they are joined, can form heterocyclyl;

Ring A is selected from aryl, heteroaryl and heterocyclyl moieties, each of which may optionally be substituted with one or more groups selected from halogen, Ci, alkyl, hydroxyl, aryl, heteroaryl, heterocyclyl, C3, alkoxycarbonyl, aryloxy, heteroaryloxy, heterocyclyloxy, Ra, Ci, alkyl, OH, ORa, OCORa, SH, SRa, SCORA, NH2, N0 3 NRa, NRaRb, CORa, CSRa, CN, COOH, COORa, CON3a, CONH, CONHORa, S0 2 Ra, S0 3 H, S0 2 NH2, CONRaRb, S0 2 NRaRb, wherein Ra and Rb are independently selected from Ci, alkyl, substituted Ci, alkyl, aryl, heteroaryl, C3, cycloalkyl and heterocyclyl, or Ra and Rb, together with the heteroatom to which they are joined, can form heterocyclyl;

wherein, when Ring A is substituted with Ci, alkyl, aryl, heteroaryl, heterocyclyl, Ci, alkoxycarbonyl, aryloxy, heteroaryloxy, heterocyclyloxy, Ci, alkyl, C3, cycloalkyl or is substituted with a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, Rc, Ci, alkyl, aryl, heteroaryl, heterocyclyl, heterocyclyloxy, R3a, OH, OR3a, SH, SR3a, OCO3a, SCOR3a, NH2, N0 3 NR3a, NR3aRb, COR3a, CSR3a, CN, COOH, COOR3a, CONH3a, S0 2 R3a, S0 3 H, S0 2 NH2, CONR3aRb, S0 2 NR3aRb, wherein R3a and R3b are independently selected from Ci, alkyl, substituted Ci, alkyl, aryl, heteroaryl, C3, cycloalkyl and heterocyclyl, or R3a and R3b, together with the heteroatom to which they are joined, can form heterocyclyl;

V can be N, CH or C-R3, wherein R3 is halogen, Ci, alkyl, aryl, heteroaryl, heterocyclyl, C3, cycloalkyl, Ci, alkoxycarbonyl, aryloxy, heteroaryloxy, heterocyclyloxy, R3a, OH, OR3a, SH, SR3a, OCO3a, SCOR3a, NH2, N0 3 NR3a, NR3aR3b, COR3a, CSR3a, CN, COOH, COOR3a, CONH3a, S0 2 R3a, S0 3 H, S0 2 NH2, CONR3aRb, S0 2 NR3aR3b, wherein R3a and R3b are independently selected from Ci, alkyl, substituted Ci, alkyl, aryl, heteroaryl, C3, cycloalkyl and heterocyclyl, or R3a and R3b, together with the heteroatom to which they are joined, can form heterocyclyl;

wherein, when R3 is Ci, alkyl, aryl, heteroaryl, heterocyclyl, Ci, alkoxycarbonyl, aryloxy, heteroaryloxy, heterocyclyloxy, Ci, alkyl, C3, cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, aryl, heteroaryl, heterocyclyl, Ci, alkoxycarbonyl, aryloxy, heteroaryloxy, heterocyclyloxy, R3c, Ci, alkyl, OH, OR3c, SH, SR3c, OCO3c, SCOR3c, NH2, N0 3 NR3c, NR3cR3d, COR3c, CSR3c, CN, COOH, COOR3c, CONH3c, S0 2 R3c, S0 3 H, S0 2 NH2, CONR3cR3d, S0 2 NR3cR3d, wherein R3c and R3d are independently selected from Ci, alkyl, substituted Ci, alkyl, aryl, heteroaryl, C3, cycloalkyl and heterocyclyl, or R3c and R3d, together with the heteroatom to which they are joined, can form heterocyclyl;

wherein, when the substituent of R3 is Ci, alkyl, aryl, heteroaryl, heterocyclyl, Ci, alkoxycarbonyl, aryloxy, heteroaryloxy, heterocyclyloxy, Ci, alkyl, C3, cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R3e, Ci, alkyl, OH, OR3e, SCOR3e, NH2, N0 3 NR3e, NR3eR3f, COR3e, CSR3e, CN, COOH, COOR3e, CONH3e, S0 2 R3e, S0 3 H, S0 2 NH2, CONR3eR3f, S0 2 NR3eR3f, wherein R3e and R3f are independently
selected from C_1-6 alkyl, substituted C_1-6 alkyl, aryl, heteroaryl, C_3-8 cycloalkyl and heterocyclyl, or R3e and R3f, together with the heteroatom to which they are joined, can form heterocyclyl;

W can be N, CH or C-R4, wherein R4 is halogen, C_1-10 alkyl, aryl, heteroaryl, heterocyclyl, C_1-6 alkoxyl, arloxy, heteroaryloxy, heterocyclyloxy, C_1-8 cycloalkyl, R4a, OH, OR4a, SH, SR4a, COR4a, SCOR4a, NH_2, N_2-R4a, NHR4a, NR4aR4b, COR4a, CSR4a, CN, COOH, COOR4a, CONH_2, S0_2-R4a, S0_2-NH_2, CONR4aR4b, S0_2-NR4aR4b, wherein R4a and R4b are independently selected from C_1-6 alkyl, substituted C_1-6 alkyl, aryl, heteroaryl, C_3-8 cycloalkyl and heterocyclyl, or R4a and R4b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R4 is C_1-10 alkyl, aryl, heteroaryl, heterocyclyl, C_1-6 alkoxyl, arloxy, heteroaryloxy, heterocyclyloxy, C_1-6 alkyl, C_3-8 cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, aryl, heteroaryl, heterocyclyl, C_1-6 alkoxyl, arloxy, heteroaryloxy, heterocyclyloxy, R4c, Ci.io alkyl, OH, OR4c, OCR4c, SH, SR4c, COR4c, NH_2, N_2-R4c, NHR4c, NR4cR4d, COR4c, CSR4c, CN, COOH, COOR4c, CONH_2, S0_2-R4c, S0_2-NH_2, S0_2-NR4cR4d, wherein R4c and R4d are independently selected from C_1-6 alkyl, substituted C_1-6 alkyl, aryl, heteroaryl, C_3-8 cycloalkyl and heterocyclyl, or R4c and R4d, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R4 is C_1-40 alkyl, aryl, heteroaryl, heterocyclyl, C_1-6 alkoxyl, arloxy, heteroaryloxy, heterocyclyloxy, C_1-6 alkyl, C_3-8 cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R4e, C_1-jo alkyl, OH, OR4e, OCR4e, SH, SR4e, COR4e, NH_2, N_2-R4e, NHR4e, NR4eR4f, COR4e, CSR4e, CN, COOH, COOR4e, CONH_2, S0_2-R4e, S0_2-NH_2, S0_2-NR4eR4f, wherein R4e and R4f are independently selected from C_1-6 alkyl, substituted C_1-6 alkyl, aryl, heteroaryl, C_3-8 cycloalkyl and heterocyclyl, or R4e and R4f, together with the heteroatom to which they are joined, can form heterocyclyl,

R5 is selected from H, C_1-6 alkyl, aryl, heteroaryl, heterocyclyl, C_3-8 cycloalkyl, C_1-6 alkoxyl, arloxy, heteroaryloxy, heterocyclyloxy, R5a, halogen, OH, OR5a, SH, SR5a, OCR5a, SCOR5a, NH_2, N_2-R5a, NHR5a, NR5aR5b, COR5a, CSR5a, CN, COOH, COOR5a, CONH_2, S0_2-R5a, S0_2-NH_2, S0_2-NR5aR5b, wherein R5a and R5b are independently selected from C_1-6 alkyl, substituted C_1-6 alkyl, aryl, heteroaryl, C_3-8 cycloalkyl and heterocyclyl, or R5a and R5b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R5 is C_1-6 alkyl, aryl, heteroaryl, heterocyclyl, C_1-6 alkoxyl, arloxy, heteroaryloxy, heterocyclyloxy, C_1-6 alkyl, C_3-8 cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, aryl, heteroaryl, heterocyclyl, C_1-6 alkoxyl, arloxy, heteroaryloxy, heterocyclyloxy, R5c, C_1-6 alkyl, OH, OR5c, OCR5c, SH, SR5c, SCOR5c, NH_2, N_2-R5c, NHR5c, NR5cR5d, COR5c, CSR5c, CN, COOH, COOR5c, CONH_2, S0_2-R5c, S0_2-NH_2, S0_2-NR5cR5d, wherein R5c and R5d are independently selected from C_1-6 alkyl, substituted C_1-6 alkyl, aryl, heteroaryl, C_3-8 cycloalkyl and heterocyclyl, or R5c and R5d, together with the heteroatom to which they are joined, can form heterocyclyl,
wherein, when the substituent of R5 is C1-6 alkyl, aryl, heteroaryl, heterocyclyl, C3-6 alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, C3-8 cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R5e, C1-6 alkyl, OH, OR5e, CONR5e, SH, SR5e, SCOR5e, NH2, N0-2, NHR5e, NR5eR5f, OR5e, CSR5e, CN, COOH, CONR5e, CONH2, S02R5e, S02H, S02NH2, CONR5eR5f, S02NR5eR5f, wherein R5e and R5f are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R5e and R5f, together with the heteroatom to which they are joined, can form heterocyclyl;

X can be N, CH or C-R6, wherein R6 is selected from C1-6 alkyl, aryl, heteroaryl, heterocyclyl, C1-6 alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, R6a, halogen, OH, 0R6a, SH, SR6a, SCOR6a, SCOR6a, NH2, N0-2, NHR6a, NR6aR6b, COR6a, C6R6a, CN, COOH, COOR6a, CONH2, S02R6a, S02H, S02NH2, CONR6aR6b, S02NR6aR6b, wherein R6a and R6b are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R6a and R6b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R6 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, and when R6 is C1-6 alkyl, aryl, heteroaryl, heterocyclyl, C1-6 alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, C3-8 cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R6c, C1-6 alkyl, C1-6 alkynyl, aryl, heteroaryl, heterocyclyl, C1-6 alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, aryl C1-6 alkyl, heterocyclyl C1-6 alkyl, aryl C1-6 alkoxy, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, OH, OR6c, OCOR6c, SH, SR6c, SCOR6c, NH2, N0-2, NHR6c, NR6cR6d, COR6c, CSR6c, CN, COOH, COOR6c, CONH2, CONOH, C(NO)NH2, S02R6c, S02H, S02NH2, CONR6cR6d, S02NR6cR6d, wherein R6c and R6d are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R6c and R6d, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R6 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, or when the substituent of R6 is C1-6 alkyl, C1-6 alkynyl, aryl, heteroaryl, heterocyclyl, C1-6 alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, aryl C1-6 alkyl, heterocyclyl C1-6 alkyl, aryl C1-6 alkoxy, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R6e, C1-6 alkyl, C1-6 alkoxy, OH, OR6e, OCOR6e, SH, SR6e, SCOR6e, NH2, N0-2, NHR6e, NR6eR6f, COR6e, CSR6e, CN, COOH, COOR6e, CONH2, C(NO)NH2, S02R6e, S02H, S02NH2, CONR6eR6f, S02NR6eR6f, wherein R6e and R6f are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R6e and R6f, together with the heteroatom to which they are joined, can form heterocyclyl;

Y can be N, CH or C-R7, wherein R7 is selected from C1-6 alkyl, aryl, heteroaryl, heterocyclyl, C1-6 alkoxy, arloxy, heteroaryloxy, heterocyclyloxy, R7a, halogen, OH, OR7a, SH, SR7a, OCOR7a, SCOR7a, NH2, N0-2, NHR7a, NR7aR7b, COR7a, CSR7a, CN, COOH, COOR7a, CONH2, S02R7a, S02H, S02NH2, CONR7aR7b, S02NR7aR7b, wherein R7a and R7b are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl,
heteroaryl, C₆₋₄ cycloalkyl and heterocyclyl, or R⁷a and R⁷b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R⁷ is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, and when R⁷ is C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyl, C₃₋₄ alkoxy, arylalkoxy, heteroalkoxy, heterocyclyloxy, C₃₋₈ cycloalkyl or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R⁷c, C₁₋₆ alkyl, C₁₋₆ alkenyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, arylalkoxy, heteroalkoxy, heterocyclyloxy, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl, heterocyclyl C₁₋₆ alkyl, aryl C₁₋₆ alkoxy, heteroaryl C₁₋₆ alkoxy, heterocyclyl C₁₋₆ alkoxy, OH, 07c, OCOR⁷c, SH, SR⁷c, SCOR⁷c, NH₂, NO₂, NHR⁷c, NR⁷cR⁷d, COR⁷c, CSR⁷c, CN, COOH, COOR⁷c, CONH₂, (NOH)NH₂, S0₂R⁷c, S0₂H, CONR⁷cR⁷d, S0₂NR⁷cR⁷d, wherein R⁷c and R⁷d are independently selected from C₁₋₆ alkyl, substituted C₁₋₆ alkyl, aryl, heteroaryl, C₃₋₄ cycloalkyl and heterocyclyl, or R⁷c and R⁷d, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R⁷ is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, or when the substituent of R⁷ is C₁₋₆ alkyl, C₁₋₆ alkenyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, arylalkoxy, heteroalkoxy, heterocyclyloxy, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl, heterocyclyl C₁₋₆ alkyl, aryl C₁₋₆ alkoxy, heteroaryl C₁₋₆ alkoxy, heterocyclyl C₁₋₆ alkoxy, C₃₋₄ cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, aryl, heteroaryl, heterocyclyl, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl, heterocyclyl C₁₋₆ alkyl, R⁷e, C₁₋₆ alkyl, OH, OR⁷e, OCOR⁷e, SH, SR⁷e, SCOR⁷e, NH₂, NO₂, NHR⁷e, NR⁷eR⁷f, COR⁷e, CSR⁷e, CN, COOH, COOR⁷e, CONH₂, (NOH)NH₂, S0₂R⁷e, S0₂H, S0₂NR⁷eR⁷f, wherein R⁷e and R⁷f are independently selected from C₁₋₆ alkyl, substituted C₁₋₆ alkyl, aryl, heteroaryl, C₃₋₄ cycloalkyl and heterocyclyl, or R⁷e and R⁷f, together with the heteroatom to which they are joined, can form heterocyclyl;

Z can be N, CH or C-R⁸, wherein R⁸ is selected from C₂₋₁₀ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₄ alkoxy, arylalkoxy, heteroalkoxy, heterocyclyloxy, R⁸a, halogen, OH, OR⁸a, SH, SR⁸a, OCOR⁸a, SCOR⁸a, NH₂, NO₂, NHR⁸a, NR⁸aR⁸b, COR⁸a, CSR⁸a, CN, COOH, COOR⁸a, CONH₂, S0₂R⁸a, S0₂H, S0₂NH₂, CONR⁸aR⁸b, S0₂NR⁸aR⁸b, wherein R⁸a and R⁸b are independently selected from C₁₋₆ alkyl, substituted C₁₋₆ alkyl, aryl, heteroaryl, C₃₋₄ cycloalkyl and heterocyclyl, or R⁸a and R⁸b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R⁸ is C₁₋₅ alkyl, C₁₋₁₀ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, arylalkoxy, heteroalkoxy, heterocyclyloxy, C₃₋₈ cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R⁸c, C₁₋₄ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₆ alkoxy, arylalkoxy, heteroalkoxy, heterocyclyloxy, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl, heterocyclyl C₁₋₄ alkyl, aryl C₁₋₆ alkoxy, heteroaryl C₁₋₆ alkoxy, heterocyclyl C₁₋₆ alkoxy, OH, OR⁸c, OCOR⁸c, SH, SR⁸c, SCOR⁸c, NH₂, NO₂, NHR⁸c, NR⁸cR⁸d, COR⁸c, CSR⁸c, CN, COOH, COOR⁸c, CONH₂, SO₂R⁸c, S0₂H, S0₂NH₂, CONR⁸cR⁸d, S0₂NR⁸cR⁸d, wherein R⁸c and R⁸d are independently selected from C₁₋₄ alkyl, substituted C₁₋₆ alkyl, aryl, heteroaryl, C₃₋₄ cycloalkyl and heterocyclyl, or R⁸c and R⁸d, together with the heteroatom to which they are joined, can form heterocyclyl,
wherein, when the substituent of $R_8$ is $C_{1-6}$ alkyl, aryl, heteroaryl, heterocyclyl, $C_{1-6}$ alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, aryl $C_{1-6}$ alkyl, heteroaryl $C_{1-6}$ alkyl, heterocyclyl $C_{1-6}$ alkyl, aryl $C_6$ alkoxy, heteroaryl $C_{1-6}$ alkoxy, heterocyclyl $C_{3-8}$ cycloalkyl, or is a group containing one or more of these moieties; each of these moieties may optionally be substituted with one or more groups selected from halogen, $R_8e$, $C_{1-6}$ alkyl, OH, OR$R_8e$, OCOR$R_8e$, SH, SR$R_8e$, SCOR$R_8e$, NH$_2$, N$O_2$, NHR$R_8e$, NR$R_8e$R$R_8f$, COR$R_8e$, CSR$R_8e$, CN, COR, CON$R_8e$, COOH, C(OH)$_2$R$R_8e$, CON$\tilde{\gamma}$, S$O_2$R$R_8e$, S$O$H, S$O_2$NH$_2$, CONR$R_8e$R$R_8f$, S$O_2$NR$R_8e$R$R_8f$, wherein $R_8e$ and $R_8f$ are independently selected from $C_{1-6}$ alkyl, substituted $C_{1-6}$ alkyl, aryl, heteroaryl, $C_{3-8}$ cycloalkyl and heterocyclyl, or $R_8e$ and $R_8f$, together with the heteroatom to which they are joined, can form heterocyclyl;

wherein, at most, two of the atoms or groups denoted X, Y and Z can be N;

wherein, when $W$ is N, the CONR$R_1$R$R_2$ group may be joined to $W$ instead, with the double bonds in Formula I rearranged accordingly;

or a pharmaceutically acceptable salt or ester thereof.

In such an embodiment, the compound may be limited by the following exceptions:

provided that when R$1$ and R$2$ together form piperidinyl in compounds having Formula I, the piperidinyl is not substituted with methyl, dimethyl, ethyl, isopropyl, tert-butyl, methoxycarbonyl, trifluoromethyl, chloro, bromo or benzyl,

provided that R$1$ and R$2$ together in compounds having Formula I do not form 6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl, 6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl, 7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl, 7-amino-3,4-dihydro-1H-isoquinolin-2-yl, 7-nitro-3,4-dihydro-1H-isoquinolin-2-yl, 3,4-dihydro-1H-isoquinol[2,3-$a$]pyridin-1-yl, 3,4-dihydro-1H-isoquinol[2,3-$a$]pyridin-1-yl, pyrrolidin-1-yl, 3,6-dihydro-2H-pyridin-1-yl, 8-aza-spiro[4,5]dec-8-yl, 1,3-dihydrosoindol-2-yl, octahydrosoindol-2-yl, 1,2,6-triaza-spiro[2.5]oct-1-en-6-yl or azepan-1-yl, and/or

provided that Ring A in compounds having Formula I does not form a pyridine, pyrimidine, substituted pyridine or substituted pyrimidine, when R$1$ and R$2$, together with the N to which they are attached, form piperidinyl, piperazinyl, substituted piperidinyl or substituted piperazinyl.

In the preceding embodiments, and in those which follow, it will be appreciated that the process used for preparing the specified groups of compounds of Formula II and Formula I employs an intermediate of Formula IF or Formula I' having a corresponding structure in which the -CONR$R_1$R$R_2$ group of Formula II or Formula I is replaced by H.

Preferably, the compound prepared by the process of the invention has a formula selected from Formula I, Formula IIa, Formula Iib, Formula Iie and Formula lid.
Also preferably, the compound of Formula II or Formula I has a formula selected from Formula Ia, Formula IIa, Formula lib, Formula Ile and Formula lid.

and the intermediate of Formula II or Formula I has a corresponding structure in which the -CONR1R2 group of Formula IIa-d or Formula Ia is replaced by the H of Formula II' or Formula I'. In particular embodiments, the compound has the Formula IIa, wherein the intermediate of Formula II' has a corresponding structure in which the -CONR1R2 group of Formula IIa is replaced by H.
In one embodiment of the invention, R1 is preferably selected from H and C_{1-4} alkyl. More preferably, R1 is selected from H and C_{1-3} alkyl, even more preferably, R1 is selected from H, methyl and ethyl and most preferably, R1 is selected from H and methyl.

R2 is preferably selected from C_{1-4} alkyl, aryl, heteroaryl, heterocyclyl, C_{3-10} cycloalkyl, aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl and C_{3-10} cycloalkyl C_{1-6} alkyl, each of which may be substituted or unsubstituted. Preferably, the aryl, heteroaryl, heterocyclyl and C_{3-10} cycloalkyl (including in aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl and C_{3-10} cycloalkyl C_{1-6} alkyl) have a 6 membered monocyclic ring structure. More preferably, the aryl, heteroaryl, heterocyclyl and C_{3-10} cycloalkyl (including in aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl and C_{3-10} cycloalkyl C_{1-6} alkyl) are selected from phenyl, cyclohexyl, phenyl C_{1-6} alkyl and cyclohexyl C_{1-6} alkyl, each of which can be substituted or unsubstituted. Preferably, the C_{1-6} alkyl of each of aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl and C_{3-10} cycloalkyl C_{1-6} alkyl is a linear alkyl.

Alternatively, R2 can be selected from aryl, heteroaryl, heterocyclyl, aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl and heterocyclyl C_{1-6} alkyl, each of which may be substituted or unsubstituted and wherein the aryl, heteroaryl and heterocyclyl (including in aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl and heterocyclyl C_{1-6} alkyl) have a bicyclic ring structure, preferably, a 10 membered bicyclic ring structure. More preferably, R2 is selected from naphthalenyl and naphthalenyl C_{1-6} alkyl.

Each of the aryl, heteroaryl, heterocyclyl and C_{3-10} cycloalkyl groups of R2 (including in aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl and C_{3-10} cycloalkyl C_{1-6} alkyl) can be substituted with one or more halogens.

Alternatively, each of the aryl, heteroaryl, heterocyclyl and C_{3-10} cycloalkyl groups (including in aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl and C_{3-10} cycloalkyl C_{1-6} alkyl) can be substituted with C_{1-4} alkoxy or aryloxy. Preferably, the C_{1-4} alkoxy is methoxy or ethoxy. Preferably, the aryloxy is monocyclic aryloxy and, more preferably, phenoxy.

In a preferred embodiment, R1 is selected from H and C_{1-4} alkyl, and R2 is selected from aryl, heteroaryl, heterocyclyl, C_{3-10} cycloalkyl, aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl and C_{3-10} cycloalkyl C_{1-6} alkyl, each of which may be substituted or unsubstituted. More preferably, R1 is selected from H, methyl and ethyl, and R2 is selected from aryl, heteroaryl, heterocyclyl, and C_{3-10} cycloalkyl each of which may be substituted or unsubstituted. More preferably, R1 is methyl. More preferably, R2 is selected from aryl, heteroaryl, heterocyclyl, and C_{5-8} cycloalkyl each of which are monocyclic and may be substituted or unsubstituted. More preferably still, R2 is selected from saturated heterocyclyl, and C_{5-8} cycloalkyl each of which are monocyclic and may be substituted or unsubstituted. When R2 is a monocyclic C_{5-8} cycloalkyl, it is preferably unsubstituted. Preferably, R2 is a cyclohexyl, such as an unsubstituted cyclohexyl. When R2 is a monocyclic saturated heterocyclyl, the heterocyclyl ring preferably contains a single heteroatom. Preferably, the heteroatom is a nitrogen or oxygen atom. More preferably, the heterocyclyl is six membered, such as a piperidinyl or tetrahydropyranyl group. If the heteroatom is an oxygen atom, the heterocyclyl is preferably unsubstituted. If the heteroatom is a nitrogen atom, the nitrogen heteroatom may be substituted or unsubstituted. If the nitrogen heteroatom is substituted, it is preferably substituted with a group selected from C_{1-6} alkyl, aryl, heteroaryl,
heterocyclyl, C3-, cycloalkyl, aryl C6 alkyl, heteroaryl C6 alkyl, heterocyclyl C1-6 alkyl and C3,2 alkyl, each of which may be substituted or unsubstituted. More preferably, the nitrogen heteroatom is substituted with a group selected from C1-6 alkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-4 alkyl and C5-8 cycloalkyl C1-4 alkyl. More preferably, the nitrogen heteroatom is substituted with a group selected from aryl C1-4 alkyl and heteroaryl C1-4 alkyl, wherein the aryl and heteroaryl are monocyclic and, preferably, six membered. Preferably, the nitrogen heteroatom is substituted with a group selected from phenyl C1-2 alkyl and pyridyl C1-2 alkyl. Preferably, the heteroatom in the said heterocyclyl group is at the 4 position relative to the position of attachment of the heterocyclyl group R2 to the urea nitrogen. When R1 and R2 are as defined in this paragraph, the compound preferably has the formula IIa. Preferably, when R1 and R2 are as defined in this paragraph, R6 is a substituted or unsubstituted aryl or heteroaryl and, preferably, a substituted or unsubstituted monocyclic aryl or heteroaryl. The monocyclic aryl or heteroaryl is preferably six membered. In one embodiment, R6 is a substituted or unsubstituted aryl (such as phenyl) and, preferably, unsubstituted. In another embodiment, R6 is a substituted or unsubstituted heteroaryl and, preferably, substituted or unsubstituted pyridyl. In one embodiment, the heteroaryl is substituted with an oxygen atom. For example, the nitrogen heteroatom of pyridyl may be substituted with an oxygen atom so that it is oxidised, i.e. an N-oxide is formed.

It has been found that compounds with the selection of R1 and R2 in the preceding paragraph show relatively high specificity for FAAH. Further, compounds in which R2 is heterocyclyl, such as piperidinyl or tetrahydropyranyl, have been found to be relatively metabolically stable.

In an alternative embodiment, R2 is preferably C2-6 alkyl. More preferably, R2 is C3-6 alkyl and, more preferably still, R2 is C4-12 alkyl. Preferably, the alkyl in a linear alkyl.

In a preferred embodiment, R1 is selected from H and CM alkyl, and R2 is C2-20 alkyl.

In various embodiments, when R1 is: H or C1-4 alkyl; H or C1-3 alkyl; H, methyl or ethyl; H or methyl; or methyl, R2 can be selected from C1-6 alkoxy, aryl, heteroaryl, partially or fully saturated heterocyclyl, C3-8 cycloalkyl, aryl C1-4 alkyl, heterocyclyl C1-6 alkyl, heterocyclyl C1-6 alkyl, C3-8 cycloalkyl C1-6 alkyl, halogen, OH, ORla, OCORla, SH, SRLa, SCORla, NH2, NHRla, NHSO2NH2, NSO2Rla, NRlaCORlb, NHCORla, NNRlaRlb, CORla, CSRla, CN, COOH, COORla, CONH2, CONHOH, CONHRIa, CONHORla, SO3Rla, SO3H, SO2NH2, CONRlaRlb, S02NRlaRlb, wherein Rla and Rlb are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or Rla and Rlb, together with the heteroatom to which they are joined, can form heterocyclyl, wherein R2 can be substituted or unsubstituted.

Alternatively, in other embodiments, when R1 is: H and C1-4 alkyl; H and C1-3 alkyl; H, methyl and ethyl; H and methyl; or methyl, R2 can be selected from aryl, heteroaryl, partially or fully saturated heterocyclyl, C3-10 cycloalkyl, aryl C1-4 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-4 alkyl, C3-10 cycloalkyl C1-6 alkyl, wherein R2 can be substituted or unsubstituted.

In a preferred embodiment, R1 and R2, together with the N to which they are attached, form a heterocyclyl group which may be substituted or unsubstituted. Preferably, the heterocyclyl is a 5 or 6 membered monocyclic ring and, more preferably, a 5 membered monocyclic ring. In certain embodiments, the said heterocyclyl contains one
or two, preferably 1, additional heteroatoms (i.e. in addition to the N). These additional heteroatoms may be, for example, N, O and/or S. Preferably, the heterocycl is oxazolidinyl. Preferably, the oxygen atom in the oxazolidinyl is at the 3 position relative to the urea nitrogen. Preferably, the oxazolidinyl is substituted with one, two or three methyl or ethyl groups. More preferably, the oxazolidinyl is substituted with two methyl or ethyl groups. More preferably still, the oxazolidinyl is substituted with two methyl groups on the same carbon atom. More preferably, the oxazolidinyl is 4,4-dimethyl-3-yl. When R1 and R2 are as defined in this paragraph, the compound preferably has the formula Ia or Ila. Preferably, when R1 and R2 are as defined in this paragraph and the compound has the formula Ila, R6 is a substituted or unsubstituted aryl and, more preferably, phenyl. When R1 and R2 are as defined in this paragraph and the compound has the formula la, ring A is preferably an unsubstituted or substituted benzo moiety.

Compounds having R1 and R2 as defined in the preceding paragraph have been found to be relatively potent inhibitors of FAAH. They have also been found to have relatively high specificity for FAAH.

In an alternative embodiment, R1 and R2, together with the N to which they are attached, form a heterocycl group which may be substituted or unsubstituted. Preferably, the heterocycl is a 5 or 6 membered monocyclic ring and, more preferably, a 6 membered monocyclic ring. Preferably, R1 and R2 together form morpholino, piperazinyl oxazolidinyl, pyrrolidinyl or piperidinyl. More preferably, R1 and R2 together form morpholino or piperazinyl.

Preferably, the heterocycl of R1 and R2 together is substituted with C1-4 alkyl, aryl, heteroaryl, C3-8 cycloalkyl aryl C3-8 alkyl, heteroaryl C1-6 alkyl, aryloxy, heteroaryloxy, aryl C1-6 alkoxy and heteroaryl C1-6 alkoxy, each of which may optionally be substituted with one or more halogens or C1-4 alkyl groups. Preferably, the substituent aryl, heteroaryl or C3-8 cycloalkyl is a 5 or 6 membered monocyclic ring. More preferably, the heterocycl of R1 and R2 together is substituted with aryl, aryl C1-6 alkyl and aryloxy, each of which may optionally be substituted with one or more halogen. More preferably still, the heterocycl of R1 and R2 together is substituted with phenyl, phenyl C1-6 alkyl or phenoxy, each of which may optionally be substituted with one or more halogen,

Alternatively, the heterocycl of R1 and R2 together may be substituted with a heteroaryl or heteroaryl C1-6 alkyl. In one embodiment, the heteroaryl has a bicyclic ring structure, for example, benzodioxolymethyl. Alternatively, the heteroaryl may be monocyclic, for example, pyridyl.

In another alternative, the heterocycl of R1 and R2 together may be substituted with a C3-8 cycloalkyl. Preferably, the C3-8 cycloalkyl is a monocyclic cycloalkyl such as cyclohexyl.

In one embodiment, the heterocycl of R1 and R2 together can be 1,4-dioxa-8-azaspiro[4.5]dec-8-yl, dimethyloxazolidinyl, methylpiperazinyl, benzyloxyphenylpiperazinyl, tolyloxypiperidinyl, pyrrolidinyl C1-4 alkyl piperidinyl, pyridylpiperidinyl, pyridloxadiazol-5-ylpiperidinyl or benzoxypiperidinyl.

In one embodiment, the heterocycl of R1 and R2 together is piperidinyl substituted with phenoxy or phenyl C1-4 alkoxy and wherein the phenyl may optionally be substituted with halogen.

In one embodiment of the invention, when V is C-R3, R3 is H or halogen.
In another embodiment of the invention, when W is C-R4, R4 is selected from H and aryl. Preferably, R4 is selected from H and phenyl. More preferably, R4 is H.

In the compound prepared according to the invention, ring A is preferably a substituted or unsubstituted monocyclic aryl or heteroaryl moiety and, more preferably, a monocyclic aryl moiety. Preferably, ring A is a substituted or unsubstituted benzo moiety. When the monocyclic aryl of ring A is substituted, the substituent is one or more of halogen, Cl, alkyl or aryl which can optionally be substituted with one or more of halogen, cyano, carboxylic acid or amide. Preferably, the substituent aryl is monocyclic aryl and, more preferably, phenyl. In a preferred embodiment, the compound, having ring A as defined in this paragraph, has formula Ia.

In one embodiment, ring A is substituted with a moiety selected from C1-6 alkoxy, C1-6 alkyl, and C6-alkyl-CO-C6 alkyl, wherein the C1-6 alkoxy, C1-6 alkyl, or C6-alkyl-CO-C6 alkyl is substituted with a moiety selected from aryl, heteroaryl, heterocyclyl, and C3-10 cycloalkyl, wherein each of these moieties may optionally be substituted with aryl, heteroaryl, heterocyclyl, C3-10 cycloalkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, and C3-10 cycloalkyl C1-6 alkyl. Preferably, ring A is substituted with a C1-6 alkyl-CO-C6 alkyl, wherein the C6-alkyl-CO-C6 alkyl is substituted with a moiety selected from aryl, heteroaryl, heterocyclyl, and C3-10 cycloalkyl, wherein each of these moieties may optionally be substituted with aryl, heteroaryl, heterocyclyl, C3-10 cycloalkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, and C3-10 cycloalkyl C1-6 alkyl. Preferably, the C6-alkyl-CO-C6 alkyl is substituted with a heterocyclyl, more preferably, a monocyclic heterocyclyl, more preferably still, a heterocyclyl containing one or two nitrogen heteroatoms, even more preferably, a six membered heterocyclyl, and most preferably, piperazine. Preferably, the C1-6 alkoxy, C1-6 alkyl, or C6-alkyl-CO-C6 alkyl is linear. Preferably, compounds as described in this paragraph are of formula Ia.

In another embodiment, ring A is substituted with one or more groups selected from halogen, Cl, alkyl, C1-6 alkoxy, OH, ORa, OCORa, SH, SRa, SCORa, NH2, N02, NHRa, NHSO2Ra, NHC(OR)NH2, NHCORa, NH(NH)NH2, NRaRb, CORa, CSRa, CN, COOH, COORa, CONH2, CONHRA, CONHOH, CONHORa, C(NO)NH2, CONRArb, S02Ra, S02H, S02NH2, S02NRaRb, wherein Ra and Rb are C1-6 alkyl. Preferably, ring A is substituted with one or more groups selected from halogen, OH, SH, NH2, N02, NH(NH)NH2, CN, COOH, CONH2, CONHOH, C(NO)NH2, S02H, and S02NH2. More preferably, ring A is substituted with one or more groups selected from halogen, OH, NH2, N02, NH(NH)NH2, CN, COOH, CONH2, CONHOH, C(NO)NH2, S02H, and S02NH2. Preferably, compounds as described in this paragraph are of formula Ia.

Preferably, in the compound prepared according to the invention, R5 is H or halogen, and, more preferably, R5 is H.

In one embodiment, R5 together with the ring carbon to which it is attached, does not form a carbonyl group. The compound is of Formula II as indicated above.

In another embodiment, X is not O. The compound is of Formula II as indicated above.
In compounds having Formula II, when $X$ is $C$-$R_6$, $R_6$ is preferably a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl. Preferably, the aryl $R_6$ is phenyl or naphthalenyl. More preferably, the aryl $R_6$ is phenyl. Preferably, the aryl $R_6$ is substituted with one or more groups selected from halogen, $C_{1-4}$ alkoxy, hydroxyl, amide, nitro, aryl, heterocyclyl, heteroaryl, heterocyclyl, aryloxy, each of which may be substituted or unsubstituted. Preferably, the aryl substituent of $R_6$ is phenyl which may be substituted or unsubstituted. When $R_6$ is defined as in this paragraph, the compound of Formula II is preferably an imidazole (i.e. $X$ is CH or C-$R_6$, $Y$ is N, and $Z$ is CH or C-$R_8$) or a 1,2,3-triazole (i.e. $X$ is CH or C-$R_6$, $Y$ is N, and $Z$ is N). More preferably, the compound has formula Ila.

Alternatively, $R_6$ is preferably H, halogen or aryl and, more preferably, H. When $R_6$ is defined as in this paragraph, the compound of Formula II is preferably a pyrazole (i.e. $X$ is CH or C-$R_6$, $Y$ is CH or C-$R_7$, and $Z$ is N).

In one embodiment of the invention, when $Y$ is C-$R_7$, $R_7$ is selected from aryl or heteroaryl, each of which can be substituted or unsubstituted. Preferably, the aryl and heteroaryl are monocyclic. Preferably, the aryl or heteroaryl is substituted with one or more halogens. In a preferred embodiment of the invention, $R_7$ is substituted or unsubstituted aryl. When $R_7$ is defined as in this paragraph, the compound of Formula II is preferably a pyrazole (i.e. $X$ is CH or C-$R_6$, $Y$ is CH or C-$R_7$, and $Z$ is N) or a 1,2,4-triazole (i.e. $X$ is N, $Y$ is CH or C-$R_7$, and $Z$ is N).

In one embodiment, when $Y$ is C-$R_7$, $R_7$ is H.

In another embodiment of the invention, when $Z$ is C-$R_8$, $R_8$ is selected from H and aryl. Preferably, $R_8$ is selected from H and phenyl. More preferably, $R_8$ is H.

In one embodiment of the invention, $R_6$ is a group selected from aryl, heteroaryl, heterocyclyl, $C_{3-10}$ cycloalkyl, wherein the $R_6$ group is substituted with a group selected from $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxy $C_{1-6}$ alkyl, and $C_{0-6}$ alkyl-CO-$C_{0-6}$ alkyl, wherein the $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxy $C_{1-6}$ alkyl, or $C_{0-6}$ alkyl-CO-$C_{0-6}$ alkyl group is substituted with a group selected from aryl, heteroaryl, heterocyclyl, and $C_{3-10}$ cycloalkyl. Preferably, $R_6$ is a group selected from aryl, heteroaryl, heterocyclyl, $C_{3-10}$ cycloalkyl, wherein the $R_6$ group is substituted with a group selected from $C_{1-6}$ alkoxy and $C_{1-6}$ alkoxy $C_{1-6}$ alkyl, wherein the $C_{1-6}$ alkoxy or $C_{1-6}$ alkoxy $C_{1-6}$ alkyl group is substituted with a group selected from aryl, heteroaryl, heterocyclyl, and $C_{3-10}$ cycloalkyl. Preferably, $R_6$ is a group selected from aryl, heteroaryl, heterocyclyl, $C_{3-10}$ cycloalkyl, wherein the $R_6$ group is substituted with a group selected from $C_{1-6}$ alkoxy and $C_{1-6}$ alkoxy $C_{1-6}$ alkyl, wherein the $C_{1-6}$ alkoxy or $C_{1-6}$ alkoxy $C_{1-6}$ alkyl group is substituted with a heterocyclyl. More preferably, $R_6$ is an aryl which is substituted with a group selected from $C_{1-6}$ alkoxy and $C_{1-6}$ alkoxy $C_{1-6}$ alkyl, wherein the $C_{1-6}$ alkoxy or $C_{1-6}$ alkoxy $C_{1-6}$ alkyl group is substituted with a heterocyclyl. More preferably still, $R_6$ is an aryl which is substituted with $C_{1-6}$ alkoxy, wherein the $C_{1-6}$ alkoxy is substituted with a heterocyclyl.

Preferably, $R_6$ is an aryl or heteroaryl. Preferably, $R_6$ has a monocyclic ring structure such as a monocyclic aryl or heteroaryl. In one embodiment, $R_6$ has a six membered ring structure such as phenyl or pyridyl.

Preferably, the $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxy $C_{1-6}$ alkyl or $C_{0-6}$ alkyl-CO-$C_{0-6}$ alkyl is linear.
Preferably, the substituent of the C$_{1-6}$ alkoxy or C$_{1-6}$ alkyl is monocyclic. Preferably, the substituent of the C$_{6}$ alkoxy or C$_{6}$ alkoxy C$_{6}$ alkyl is six membered. Preferably, the substituent of the C$_{1-6}$ alkoxy or C$_{6}$ alkoxy C$_{1-6}$ alkyl is heterocyclic. Preferably, the heterocyclic is fully saturated. Preferably, the heterocyclic contains one or two heteroatoms such as nitrogen or oxygen. Preferably, the heterocyclic contains at least one nitrogen heteroatom. In one embodiment, the heterocyclic is piperidinyl, piperazinyl, or tetrahydropyranyl. In this embodiment, the compound preferably is of formula IIa.

In one embodiment, when W is N, the CONR1R2 group may not be joined to W instead. In this embodiment, the compound is of Formula I as indicated above.

**Formula I and IIa**

In compounds having formula I and, in particular, compounds having formula la, ring A is preferably a substituted or unsubstituted aryl or heteroaryl moiety. More preferably, ring A is a substituted or unsubstituted monocyclic aryl or heteroaryl moiety. More preferably still, ring A is a substituted or unsubstituted six-membered aryl or heteroaryl moiety. Most preferably, ring A is a substituted or unsubstituted monocyclic aryl such as a benzo moiety.

When ring A is substituted, the substituent may be one or more groups selected from halogen, OH, C$_{1-4}$ alkyl, C$_{1-4}$ alkoxy, SH, NH$_2$, NO$_2$, CN, COOH, CONH$_2$, CONOH, benzyloxyaminocarbonyl, S0$_2$H, S0$_2$NH$_2$, aryl, heteroaryl, heterocyclyl, and C$_{3-8}$ cycloalkyl. When the substituent is C$_{1-4}$ alkyl, aryl, heteroaryl, heterocyclyl, or C$_{3-8}$ cycloalkyl, each of these moieties may optionally be substituted with one or more groups selected from halogen, OH, SH, NH$_2$, NO$_2$, CN, COOH, CONH$_2$, S0$_2$H, S0$_2$NH$_2$, d$_2$ alkyl, C$_{1-3}$ alkoxy and benzyl.

Preferably, the substituent of ring A is one or more groups selected from halogen, OH, C$_{1-3}$ alkyl, C$_{1-3}$ alkoxy, NH$_2$, NO$_2$, CN, COOH, CONH$_2$, monocyclic aryl, monocyclic heteroaryl, monocyclic heterocyclyl, and C$_{5-8}$ cycloalkyl. When the substituent is C$_{1-3}$ alkyl, monocyclic aryl, monocyclic heteroaryl, monocyclic heterocyclyl, or C$_{5-8}$ cycloalkyl, each of these moieties may optionally be substituted with one or more groups selected from halogen, CN, COOH, CONH$_2$, and C$_{1-3}$ alkoxy.

More preferably, the substituent of ring A is one or more groups selected from halogen, OH, C$_{1-2}$ alkyl, C$_{1-2}$ alkoxy, and phenyl. When the substituent is C$_{1-2}$ alkyl or phenyl, each of these moieties may optionally be substituted with one or more groups selected from halogen, CN, COOH, CONH$_2$, and Cl$_{1-3}$ alkoxy.

In a preferred embodiment of compounds having formula I and, in particular, compounds having formula la, R1 and R2, together with the N to which they are attached, form a heterocyclyl group which may be substituted or unsubstituted. Preferably, the heterocyclyl is a 5 or 6 membered monocyclic ring, more preferably, a 6 membered monocyclic ring. In certain embodiments, the said heterocyclyl contains one or two, preferably 1, additional heteroatoms (i.e. in addition to the N). These additional heteroatoms may be, for example, N, O and/or S. In one embodiment, the heterocyclyl is morpholino. In an alternative embodiment, the heterocyclyl is piperazinyl. In other embodiments, the said heterocyclyl contains no additional heteroatoms (i.e. it contains a single N atom).
one embodiment, the heterocyclyl is piperidinyl. Where the heterocyclyl is substituted, it is preferably substituted with an aryl or an aryl C1-4 alkyl, wherein the aryl is preferably monocyclic and more preferably phenyl. The alkyl is preferably linear. More preferably, the heterocyclyl is substituted with an aryl or an aryl C1-2 alkyl, wherein the aryl is preferably monocyclic and more preferably phenyl.

In a preferred embodiment of compounds having formula I and, in particular, compounds having formula Ia, R1 is selected from H and C1-4 alkyl, and R2 is selected from aryl, heteroaryl, heterocyclyl, C3-10 cycloalkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl and C3-10 cycloalkyl C1-6 alkyl, each of which may be substituted or unsubstituted. In one embodiment, R1 is selected from H, methyl and ethyl, and R2 is selected from aryl, heteroaryl, heterocyclyl, and C5-8 cycloalkyl, each of which are monocyclic and may be substituted or unsubstituted. More preferably, R1 is selected from H and methyl. In one embodiment, R1 is methyl. In an alternative embodiment, R1 is H. More preferably, R2 is selected from saturated heterocyclyl, and C5-8 cycloalkyl, each of which are monocyclic and may be substituted or unsubstituted. When R2 is a monocyclic C5-8 cycloalkyl, it is preferably unsubstituted. Preferably, R2 is a cyclopentyl or cyclohexyl. More preferably, R2 is a cyclohexyl, such as an unsubstituted cyclohexyl. When R2 is a monocyclic saturated heterocyclyl, the heterocyclyl ring preferably contains a single heteroatom. More preferably, the heterocyclyl is six membered, such as a piperidinyl or tetrahydropyranyl group. The nitrogen heteroatom may be substituted or unsubstituted.

In an alternative embodiment, R1 is selected from H, methyl and ethyl, and R2 is selected from aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, and C5-8 cycloalkyl C1-6 alkyl, each of which are monocyclic and may be substituted or unsubstituted. More preferably, R2 is aryl C1-6 alkyl in which the aryl is monocyclic and may be substituted or unsubstituted. More preferably still, R2 is aryl C1-6 alkyl in which the aryl is monocyclic and may be substituted or unsubstituted and the C1-6 alkyl is linear. Even more preferably, R2 is phenyl C1-6 alkyl which may be substituted or unsubstituted and the C1-6 alkyl is linear. In one embodiment, the phenyl is unsubstituted.

In an alternative embodiment, R1 is selected from H, methyl and ethyl, and R2 is C1-4 alkyl substituted with a group selected from aryl C1-4 alkoxy, heteroaryl C1-4 alkoxy, heterocyclyl C1-4 alkoxy, and C5-8 cycloalkyl C1-4 alkoxy, each of which are monocyclic and may be substituted or unsubstituted. Preferably, R2 is substituted C1-3 alkyl. In one embodiment, R2 is substituted C1-3 alkyl. Preferably, the substituent of R2 is aryl C1-4 alkoxy in which the aryl is monocyclic and may be substituted or unsubstituted. More preferably still, the substituent of R2 is aryl C1-4 alkoxy in which the aryl is monocyclic and may be substituted or unsubstituted and the C1-4 alkoxy is linear. Even more preferably, the substituent of R2 is phenyl C1-4 alkoxy which may be substituted or unsubstituted and the C1-4 alkoxy is linear. In one embodiment, the substituent of R2 is aryl C1-3 alkoxy in which the aryl is monocyclic (e.g. phenyl) and may be substituted or unsubstituted and the C1-3 alkoxy is linear. In some embodiments, the phenyl is unsubstituted.

In yet another embodiment of compounds having formula I and, in particular, compounds having formula la, R1 is selected from H and C1-4 alkyl, and R2 is selected from heterocyclyl which may be substituted or unsubstituted. Preferably, R1 is H, methyl or ethyl, and R2 is a bicyclic heterocyclyl which may be substituted or unsubstituted. More preferably, R1 is H or methyl, and R2 is a bicyclic heterocyclyl which may be substituted or unsubstituted, wherein one of the rings of the heterocyclyl contains two oxygen atoms. In one embodiment, R2 is 3,3-dimethyl-1,5-dioxaspiro[5.5]undec-9-yl.
In an alternative preferred embodiment of compounds having formula I and, in particular, compounds having formula Ia, R1 is selected from H and C₁₋₄ alkyl, and R2 is C₂₋₉ alkyl. More preferably, R1 is H, methyl or ethyl and more preferably still, R1 is H or methyl. Preferably, R2 is C₃₋₁₆ alkyl, wherein the alkyl is a linear alkyl. More preferably, R2 is C₄₋₁₄ alkyl, wherein the alkyl is a linear alkyl.

**Formula Ila**

In a preferred embodiment of compounds having Formula Ila, R1 is selected from H and C₁₋₄ alkyl, and R2 is selected from C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyl. C₃₋₁₀ cycloalkyl, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl, heterocyclyl C₁₋₆ alkyl and C₃₋₁₀ cycloalkyl C₁₋₄ alkyl, each of which may be substituted or unsubstituted. More preferably, R1 is selected from H, methyl and ethyl, and R2 is selected from aryl, heteroaryl, heterocyclyl, and C₄₋₁₀ cycloalkyl each of which may be substituted or unsubstituted. More preferably, R1 is methyl. More preferably, R2 is selected from aryl, heteroaryl, heterocyclyl, and C₅₋₈ cycloalkyl each of which are monocyclic and may be substituted or unsubstituted. More preferably still, R2 is selected from aryl such as phenyl, saturated heterocyclyl, and C₅₋₈ cycloalkyl each of which are monocyclic and may be substituted or unsubstituted. When R2 is a monocyclic C₅₋₈ cycloalkyl (i.e. cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl) or aryl, it is preferably unsubstituted. Preferably, R2 is a cyclohexyl, such as an unsubstituted cyclohexyl. When R2 is a monocyclic saturated heterocyclyl, the heterocyclyl ring preferably contains a single heteroatom, such as nitrogen or oxygen. More preferably, the heterocyclyl is six membered, such as a piperidinyl or tetrahydropyranyl group. In one embodiment, the heteroatom is a nitrogen heteroatom which may be substituted or unsubstituted. Preferably, the heteroatom in the said heterocyclyl group is at the 4-position relative to the position of attachment of the heterocyclyl group R2 to the urea nitrogen. In one embodiment, the nitrogen atom is substituted with monocyclic aryl (preferably phenyl) C₁₋₃ alkyl; preferably, the nitrogen atom is substituted with benzyl or phenylethyl; and, more preferably, the nitrogen atom is substituted with benzyl.

In an alternative preferred embodiment of compounds having Formula Ila, R1 and R2, together with the N to which they are attached, form a heterocyclyl group which may be substituted or unsubstituted. Preferably, the heterocyclyl is a 5 or 6 membered monocyclic ring and, more preferably, a 5 membered monocyclic ring. In certain embodiments, the said heterocyclyl contains one or two, preferably 1, additional heteroatoms (i.e. in addition to the N). These additional heteroatoms may be, for example, N, 0 and/or S. Preferably, the heterocyclyl is oxazolidinyl. Preferably, the oxygen atom in the oxazolidinyl is at the 3 position relative to the urea nitrogen. Preferably, the oxazolidinyl is substituted with one, two or three methyl or ethyl groups. More preferably, the oxazolidinyl is substituted with two methyl or ethyl groups. More preferably still, the oxazolidinyl is substituted with two methyl groups on the same carbon atom. More preferably, the oxazolidinyl is 4,4-dimethylxazolidin-3-yl.

In yet another preferred embodiment of compounds having formula Ila, R1 and R2, together with the N to which they are attached, form a heterocyclyl group which may be substituted or unsubstituted. Preferably, the heterocyclyl is a 5 or 6 membered monocyclic ring, more preferably, a 6 membered monocyclic ring. In certain embodiments, the said heterocyclyl contains one or two, preferably 1, additional heteroatoms (i.e. in addition to
the N). These additional heteroatoms may be, for example, N, O and/or S. In one embodiment, the heterocyclyl is morpholino. In an alternative embodiment, the heterocyclyl is piperazinyl. In other embodiments, the said heterocyclyl contains no additional heteroatoms (i.e. it contains a single N atom). In one embodiment, the heterocyclyl is piperadiny. Where the heterocyclyl is substituted, it is preferably substituted with aryl, aryl C_{1-4}
alkyl, C_{5-6} cycloalkyl, or C_{6} cycloalkyl C_{1-4} alkyl, wherein the aryl is preferably monocyclic and more preferably phenyl, and the cycloalkyl is preferably cyclohexyl. The alkyl is preferably linear. In one embodiment, the heterocyclyl is substituted with an aryl or an aryl C_{1-4} alkyl (preferably C_{1-2} alkyl), wherein the aryl is preferably monocyclic and more preferably phenyl. The aryl may optionally be substituted with one or more halogen atoms.

In compounds having formula IIa, R5 is preferably selected from H, C_{1-4} alkyl, aryl, heteroaryl, heterocyclyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, R5a, halogen, OH, OR5a, SH, SR5a, OCOR5a, SCOR5a, NH_{2}, NO_{2}, NHR5a, NR5aR5b, COR5a, CSR5a, CN, COOH, COOR5a, CONH_{2}, SOR5aR5b, wherein R5a and R5b are independently selected from C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl, and R5a and R5b, together with the heteroatom to which they are joined, can form heterocyclyl. More preferably, R5 is selected from H, C_{1-4} alkyl, aryl, heteroaryl, heterocyclyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, halogen, OH, SH, NH_{2}, NO_{2}, CN, COOH, CONH_{2}, SOR5, SOR_{5} OH, SOR_{5} NH_{2}. More preferably still, R5 is selected from H, C_{3-8} alkyl, aryl, heteroaryl, heterocyclyl, C_{1-4} cycloalkyl, C_{1-4} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, halogen, OH, SH, NH_{2}, NO_{2}, CN, COOH, CONH_{2}, SOR_{5}, SOR_{5} OH, wherein the aryl, heteroaryl, heterocyclyl and C_{3-8} cycloalkyl groups are monocyclic. Even more preferably, R5 is selected from H, C_{1-3} alkyl, aryl, heteroaryl, heterocyclyl, C_{3-8} cycloalkyl, halogen, OH, NH_{2}, COOH and CONH_{2}, wherein the aryl, heteroaryl, heterocyclyl and C_{3-8} cycloalkyl groups are monocyclic. More preferably still, R5 is selected from H, C_{1-2} alkyl and halogen. Even more preferably, R5 is selected from H and halogen such as F, Cl and Br. In one embodiment, R5 is H.

In compounds having formula IIa, R6 is preferably selected from aryl, heteroaryl, heterocyclyl and C_{3-8} cycloalkyl, each of which may be substituted or unsubstituted. More preferably, R6 is selected from aryl and heteroaryl each of which may be substituted or unsubstituted. In one embodiment, the heteroaryl contains one heteroatom, e.g. an oxygen or nitrogen atom. Preferably, the aryl or heteroaryl is monocyclic. More preferably, the aryl or heteroaryl is a six membered monocyclic ring, for example, phenyl or pyridyl. In one embodiment, the heteroaryl contains a nitrogen atom which is substituted with an oxygen atom such as oxidoypyridyl. In another embodiment, R6 is unsubstituted monocyclic aryl such as phenyl, or monocyclic aryl such as phenyl substituted with one or more groups selected from halogen, C_{1-2} alkoxy (optionally substituted with one or more halogen atoms), or OH.

In one embodiment, R6 is unsubstituted or substituted 2-oxo-2,3-dihydro-1H-benzo[d]imidazolyl.

When R6 is substituted, the substituent is preferably one or more groups selected from halogen, C_{3-8} alkoxy, aryl, heteroaryl, heterocyclyl, OH, CN, CONH_{2}, NH_{2}, heterocyclyl C_{1-4} alkoxy, aryl C_{1-4} alkoxy, heteroaryl C_{1-4} alkoxy, NO_{2}, SOR_{5}, SOR_{5} OH, C(NO)OHNH_{2}, CONOH, 2H-tetrazol-5-yl, dimethylamino, benzylamino, methylsulfonyl, morpholinosulfonyl and piperidinylsulfonyl. The piperidinylsulfonyl may optionally be substituted with arylmethoxy (preferably benzoxy) or OH. Preferably, the aryl, heteroaryl and heterocyclyl are monocyclic. In one embodiment, the aryl, heteroaryl and heterocyclyl are six-membered monocyclic rings. In a particular
embodiment in which R6 is monocyclic aryl, it may optionally be substituted with one or more groups selected from halogen, OH, C1,3 alkoxy (preferably C1,2 alkoxy), aryl (e.g. a monocyclic aryl such as phenyl), heteroaryl (e.g. monocyclic heteroaryl containing one or two nitrogen atoms, or one oxygen atom), heterocyclyl (e.g. piperazinyl, piperadiny1 or morpholino) C1,3 alkoxy (preferably C1,2 alkoxy), aryl (e.g. monocyclic aryl such as phenyl) C1,3 alkoxy (preferably C1,3 alkoxy), CONH2, NH2, NO2, OCHF2, S0,2 NH2, morpholinosulfonyl and C(NOH)NH2.

In another embodiment in which R6 is monocyclic aryl, it may optionally be substituted with one or more groups selected from halogen, OH, methoxy, phenyl, pyridyl, pyrazinyl, pyranyl, piperazinylmethoxy, piperadiny1methoxy, morpholinemethoxy, benzox1y, CONH2, NH2, NO2, OCHF2, S0,2 NH2, morpholinosulfonyl and C(NOH)NH2.

In one embodiment when R6 is monocyclic aryl such as phenyl, the substituent of R6 is aryl, preferably monocyclic aryl such as phenyl, which may be substituted or unsubstituted. Where it is substituted, preferably it is substituted with CONH2.

When the substituent of R6 is C1,4 alkoxy, aryl, heteroaryl, heterocyclyl, heterocyclyl C1,4 alkoxy, aryl C1,4 alkoxy, heteroaryl C1,4 alkoxy or S0,3, each of these moieties may optionally be substituted with one or more groups selected from halogen, OH, C1,3 alkoxy (which may be substituted with one or more halogen), CONH2, CN, NCH3CH3, NHCOCH3, methylhydroxybutyl, and methy1hydroxybutynyl.

In compounds having formula Ilia, R8 is preferably selected from H, C1,5 alkyl, aryl, heteroaryl, heterocyclyl, C3,5 cycloalkyl, C1,6 alkoxy, ar1oxy, heteroaryloxy, heterocyclyloxy, R8a, halogen, OH, OR8a, SH, SR8a, OCSR8a, SCOR8a, NH2, NO2, NR8aR8b, COR8a, CSR8a, CN, COOH, COOR8a, CONH2, S0,2 R8a, S0,3 H, S0,2 NH2, CONR8aR8b, S0,2 NR8aR8b, wherein R8a and R8b are independently selected from C1,6 alkyl, aryl, heteroaryl, C3,5 cycloalkyl and heterocyclyl, and R8a and R8b, together with the heteroatom to which they are joined, can form heterocyclyl. More preferably, R8 is selected from H, C1,6 alkyl, aryl, heteroaryl, heterocyclyl, C3,5 cycloalkyl, C1,6 alkoxy, ar1oxy, heteroaryloxy, heterocyclyloxy, halogen, OH, SH, NH2, NO2, CN, COOH, CONH2, S0,3 H, S0,2 NH2. More preferably still, R8 is selected from H, C1,4 alkyl, aryl, heteroaryl, heterocyclyl, C3,5 cycloalkyl, C1,4 alkoxy, ar1oxy, heteroaryloxy, heterocyclyloxy, halogen, OH, SH, NH2, NO2, CN, COOH, CONH2, S0,3 H, S0,2 NH2, wherein the aryl, heteroaryl, heterocyclyl and C3,5 cycloalkyl groups are monocyclic. Even more preferably, R8 is selected from H, C1,3 alkyl, aryl, heteroaryl, heterocyclyl, C3,5 cycloalkyl, halogen, OH, NH2, COOH and CONH2, wherein the aryl, heteroaryl, heterocyclyl and C3,5 cycloalkyl groups are monocyclic. More preferably still, R8 is selected from H, C1,2 alkyl, halogen and monocyclic aryl such as phenyl. Even more preferably, R8 is selected from H, C1,2 alkyl, and halogen such as F, Cl and Br. More preferably still, R8 is selected from H and halogen such as F, Cl and Br. In one embodiment, R8 is H.

In one embodiment of compounds having formula Ilia, R1 is selected from H and C1,4 alkyl,

R2 is selected from aryl, heteroaryl, heterocyclyl, C3,5 cycloalkyl, aryl C1,6 alkyl, heteroaryl C1,6 alkyl, heterocyclyl C1,6 alkyl and C3,10 cycloalkyl C1,6 alkyl, each of which may optionally be substituted with one or more groups selected from R2a, halogen, OH, OR2a, OGOR2a, SH, SR2a, SCOR2a, NH2, NHR2a, NHS0,2 NH2,
NHS0 2R2a, NR2aCOR2b, NHC(NH)NH 2, NCOR2a, NR2aR2b, COR2a, CSR2a, CN, COOH, COOR2a, 
CONH 2, CONHOH, CONHR2a, CONHOR2a, C(NO)H)NH 2, S0 2R2a, S0 3H, S0 2NH2, CONR2aR2b, 
S0 2NR2aR2b, wherein R2a and E12b are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, 
heteroaryl, C13-8 cycloalkyl and heterocycl, or R2a and R2b, together with the heteroatom to which they are 
joined, can form heterocycl, 

wherein, when the substituent of R2 is C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl, 
heterocycl or a group containing one or more of these moieties, each of these moieties may optionally be 
substituted with one or more groups selected from R2c, halogen, OH, OR2c, OCOR2c, SH, SR2c, SCOR2c, NH2, 
NHR2c, NHS0 2NH2, NHS0 2R2c, NR2cCOR2d, NHC(NH)NH 2, NHCOR2c, NR2cR2d, COR2c, CSR2c, CN, 
COOH, COOR2c, CONH2, CONHOH, CONHR2c, CONHOR2c, C(NO)H)NH 2, S0 2R2c, S0 3H, S0 2NH2, 
CONR2cR2d, S0 2NR2cR2d, wherein R2c and R2d are independently selected from Ci6 alkyl, substituted Ci6 
alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocycl, or R2c and R2d, together with the heteroatom to which they 
are joined, can form heterocycl, 

R5 is selected from H, R5a, halogen, OH, OR5a, OCOR5a, SH, SR5a, SCOR5a, NH2, NHR5a, NHS0 2NH2, 
NHS0 2R5a, NR5aCOR5b, NHC(NH)NH 2, NHSOR5a, NR5aR5b, COR5a, CSR5a, CN, COOH, COOR5a, 
CONH2, CONHOH, CONHR5a, CONHOR5a, C(NO)H)NH 2, S0 2R5a, S0 3H, S0 2NH2, CONR5aR5b, 
S0 2NR5aR5b, wherein R5a and R5b are independently selected from Ci6 alkyl, substituted Ci6 alkyl, aryl, 
heteroaryl, C3-8 cycloalkyl and heterocycl, or R5a and R5b, together with the heteroatom to which they are 
joined, can form heterocycl, 

R6 is selected from aryl, heteroaryl, heterocycl, C3-10 cycloalkyl, each of which may optionally be substituted 
with one or more groups selected from R6a, halogen, OH, OR6a, OCOR6a, SH, SR6a, SCOR6a, NO 2, NH2, 
NHR6a, NHS0 2NH2, NHS0 2R6a, NR6aCOR6b, NHC(NH)NH 2, NHCOR6a, NR6aR6b, COR6a, CSR6a, CN, 
COOH, COOR6a, CONH2, CONHOH, CONHR6a, CONHOR6a, C(NO)H)NH 2, S0 2R6a, S0 3H, S0 2NH2, 
CONR6aR6b, S0 2NR6aR6b, wherein R6a and R6b are independently selected from Ci6 alkyl, substituted Ci6 
alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocycl, or R6a and R6b, together with the heteroatom to which they 
are joined, can form heterocycl, and wherein, when R6 is heteroaryl or heterocycl, each of these moieties may 
optionally be substituted with one or more oxygen atoms, 

wherein, when the substituent of R6 is Ci6 alkyl, substituted Ci6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl, 
heterocycl or a group containing one or more of these moieties, each of these moieties may optionally be 
substituted with one or more groups selected from R6c, halogen, OH, OR6c, OCOR6c, SH, SR6c, SCOR6c, NH2, 
NHR6c, NHS0 2NH2, NHS0 2R6c, NR6cCOR6d, NHC(NH)NH 2, NHCOR6c, NR6cR6d, COR6c, CSR6c, CN, 
COOH, COOR6c, CONH2, CONHOH, CONHR6c, CONHOR6c, C(NO)H)NH 2, S0 2R6c, S0 3H, S0 2NH2, 
CONR6cR6d, S0 2NR6cR6d, wherein R6c and R6d are independently selected from Ci6 alkyl, substituted Ci6 
alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocycl, or R2c and R2d, together with the heteroatom to which they 
are joined, can form heterocycl, and wherein, when the substituent of R6 is heteroaryl or heterocycl, each of 
these moieties may optionally be substituted with one or more oxygen atoms, and
R8 is selected from H, R8a, halogen, OH, OR8a, SH, SR8a, SCOR8a, NH2, NHSO, NHSO2, R8a, NR8aCOR8b, NHC(\(\text{NOH}\))NH2, NHCOR8a, NR8aR8b, COR8a, CSR8a, CN, COOH, CON8a, CONH2, CONHOH, CONHR8a, CONHOR8a, C(NO)NH2, S02R8a, S02H, S02NH2, CONR8aR8b, S02NR8aR8b, wherein R8a and R8b are independently selected from C1-5 alkyl, substituted Ci6 alkyl, aryl, heteroaryl, C5-8 cycloalkyl and heterocyclyl, or R8a and R8b, together with the heteroatom to which they are joined, can form heterocyclyl.

In the above embodiment, preferably, R1 is selected from H, methyl and ethyl, and R2 is selected from aryl, heteroaryl, heterocyclyl, and C5-10 cycloalkyl each of which may be substituted or unsubstituted. More preferably, R1 is methyl. More preferably, R2 is selected from aryl, heteroaryl, heterocyclyl, and C5-8 cycloalkyl each of which are monocyclic and may be substituted or unsubstituted. More preferably still, R2 is selected from heterocyclyl, and C5-8 cycloalkyl each of which are monocyclic and may be substituted or unsubstituted. Preferably, the heterocyclyl is fully saturated. When R2 is a monocyclic C5-8 cycloalkyl (i.e. cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl), it is preferably unsubstituted. In one embodiment, R2 is a cyclopentyl or a cyclohexyl, such as an unsubstituted cyclopentyl or unsubstituted cyclohexyl. When R2 is a monocyclic saturated heterocyclyl, the heterocyclyl ring preferably contains a single heteroatom, such as nitrogen or oxygen. Preferably, the heterocyclyl is six membered, such as a piperidinyl or tetrahydropyranly group. Preferably, the heteroatom in the said heterocyclyl group is at the 4-position relative to the position of attachment of the heterocyclyl group R2 to the urea nitrogen. In one embodiment, the heteroatom is a nitrogen heteroatom which may be substituted or unsubstituted.

In a particular embodiment, the nitrogen atom is substituted with a group selected from CN, CONH2, C(NO)NH2, S02-C14 alkyl, S02-aryl (optionally substituted with a C14 alkyl or C14 haloalkyl, such as trifluoromethyl), CO-heteroaryl (optionally substituted with a heteroaryl or halogen), CO-C14 alkyl, COO-C14 alkyl, C14 alkyl (optionally substituted with OH, CN, COOH), aryl C13 alkyl, heteroaryl C13 alkyl such as piperidinyl C13 alkyl (optionally substituted with COO-C13 alkyl), heterocyclyl C13 alkyl, aryl, heteroaryl (optionally substituted with one or more halogens such as chlorine), and heterocyclyl. Preferably, the nitrogen atom is substituted with a group selected from CN, CONH2, C(NO)NH2, S02-C14 alkyl, S02-aryl (optionally substituted with a C14 haloalkyl, such as trifluoromethyl), CO-monocyclic heteroaryl (optionally substituted with a monocyclic heteroaryl or halogen), CO-C14 alkyl, COO-C14 alkyl, C14 alkyl (optionally substituted with OH, CN, COOH), monocyclic aryl C13 alkyl, monocyclic heterocyclyl C13 alkyl such as piperidinyl C13 alkyl (optionally substituted with COO-C13 alkyl), monocyclic heterocyclyl C13 alkyl, monocyclic aryl, monocyclic heteroaryl (optionally substituted with one or more halogens such as chlorine), and monocyclic heterocyclyl. More preferably, the nitrogen atom is substituted with a group selected from CN, C14 alkyl (optionally substituted with OH, CN, COOH), monocyclic aryl C13 alkyl, and monocyclic heterocyclyl C13 alkyl (preferably piperidinyl C13 alkyl). More preferably still, the nitrogen atom is substituted with a group selected from C14 alkyl (optionally substituted with OH, CN, COOH), monocyclic aryl C13 alkyl, and monocyclic heteroaryl C13 alkyl (preferably piperidinyl C13 alkyl).
In one embodiment, the nitrogen atom is substituted with monocyclic aryl (preferably phenyl) \( C \), alkyl; preferably, the nitrogen atom is substituted with benzyl or phenylethyl; and, more preferably, the nitrogen atom is substituted with benzyl.

In one embodiment R5 is H, halogen, OH or \( C_{1,4} \) alkyl. Preferably, R5 is H.

In another embodiment, R6 is selected from aryl, heteroaryl, and heterocyclyl, each of which may be substituted or unsubstituted. Preferably, R6 is selected from monocyclic aryl (such as phenyl), monocyclic heteroaryl (such as pyridyl), and heterocyclyl, each of which may be substituted or unsubstituted. In one embodiment, R6 is an unsubstituted aryl. When R6 is a substituted aryl, it is preferably substituted with one or more groups selected from halogen, \( R_{6a} \), OH, OR, NH, NH\(_2\), NO\(_2\), NH\(_2\)NH, \( R_{6a} \), NR\(_6a\), R\(_6b\), C(NO\(_2\))NH\(_2\), COR\(_6a\), COOH, COOR\(_6a\), CONH\(_2\), CONHOH, S0\(_2\)R\(_6a\), S0\(_2\)NR\(_6a\)R\(_6b\), wherein R\(_6a\) and R\(_6b\) are independently selected from Ci, alkyl, substituted \( C_{1,6} \) alkyl, aryl, heteroaryl, \( C_{3,8} \) cycloalkyl and heterocyclyl,

wherein, when the substituent of R6 is Ci, alkyl, substituted \( C_{1,6} \) alkyl, aryl, heteroaryl, \( C_{3,8} \) cycloalkyl, heterocyclyl or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from OR\(_6c\), OH, and CONH\(_2\), wherein R\(_6c\) and R\(_6d\) are independently selected from Ci, alkyl, substituted \( C_{1,6} \) alkyl, aryl, heteroaryl, \( C_{3,8} \) cycloalkyl and heterocyclyl, and wherein, when the substituent of R6 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms.

Preferably, when R6 is a substituted aryl, it is substituted with one or more groups selected from halogen, OH, \( C_{1,4} \) alkoxy, CON\(_4\), C(NO\(_2\))NH\(_2\), CONHOH, S0\(_2\)-C\(_{1,4}\) alkyl, heterocyclyl (optionally substituted with an oxygen atom), and aryl (optionally substituted with CONH\(_2\)). In one embodiment, R6 may be substituted with one or more groups selected from 5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl, 3-carbamoylphenyl, 2H-tetrazol-5-yl, \( C_{1,4} \) alkoxy, halogen, OH, CONHOH.

When R6 is a heterocyclyl, it is preferably substituted with an oxygen atom. The substituent of R6 may be 2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl or 2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl.

When R6 is a heteroaryl, it is preferably unsubstituted or substituted with an oxygen atom. For example, the heterocyclyl may contain an N-oxide. In one embodiment, R6 is pyridyl or pyridyl oxide.

In another embodiment, R8 is H, halogen, OH or \( C_{1,4} \) alkyl. Preferably, R8 is H.

**Formula IIb**

In a preferred embodiment of compounds having Formula IIb, R1 is selected from H and \( C_{1,4} \) alkyl, and R2 is selected from aryl, heteroaryl, heterocyclyl, \( C_{3,10} \) cycloalkyl, aryl \( C_{1,4} \) alkyl, heteroaryl \( C_{1,6} \) alkyl, heterocyclyl \( C_{3,8} \) alkyl and \( C_{3,10} \) cycloalkyl Ci, alkyl, each of which may be substituted or unsubstituted. More preferably, R1 is selected from H, methyl and ethyl, and R2 is selected from aryl, heteroaryl, heterocyclyl, and \( C_{4,10} \) cycloalkyl each
of which may be substituted or unsubstituted. More preferably, R1 is methyl. More preferably, R2 is selected from aryl, heteroaryl, heterocyclyl, and C_{5-8} cycloalkyl each of which are monocyclic and may be substituted or unsubstituted. More preferably still, R2 is monocyclic aryl such as phenyl and may be substituted or unsubstituted. When R2 is substituted, the substituent may be aryl, C_{14} alkoxy, aryl C_{w} alkoxy or arlyloxy.

Preferably, the substituent of R2 is aryl, C_{M} alkoxy, aryl C_{14} alkoxy or arlyloxy, wherein the aryl is monocyclic and more preferably, phenyl.

When R2 is a monocyclic C_{5-8} cycloalkyl or aryl, it is preferably unsubstituted. Preferably, R2 is a cyclohexyl, such as an unsubstituted cyclohexyl. When R2 is a monocyclic saturated heterocyclyl, the heterocyclyl ring preferably contains a single heteroatom, such as nitrogen or oxygen. More preferably, the heterocyclyl is six membered, such as a piperidinyl or tetrahydropyranyl group. In one embodiment the heteroatom is a nitrogen heteroaryl which may be substituted or unsubstituted. Preferably, the heteroatom in the said heterocyclyl group is at the 4 position relative to the position of attachment of the heterocyclyl group R2 to the urea nitrogen. In one embodiment, the nitrogen atom is substituted with monocyclic aryl (preferably phenyl) C_{M} alky.

In an alternative preferred embodiment of compounds having formula lib, R1 and R2, together with the N to which they are attached, form a heterocyclyl group which may be substituted or unsubstituted. Preferably, the heterocyclyl is a 5 or 6 membered monocyclic ring and, more preferably, a 5 membered monocyclic ring. In certain embodiments, the said heterocyclyl contains one or two, preferably 1, additional heteroatoms (i.e. in addition to the N). These additional heteroatoms may be, for example, N, O and/or S. Preferably, the heterocyclyl is oxazolidinyl. Preferably, the oxygen atom in the oxazolidinyl is at the 3 position relative to the urea nitrogen. Preferably, the oxazolidinyl is substituted with one, two or three methyl or ethyl groups. More preferably, the oxazolidinyl is substituted with two methyl or ethyl groups. More preferably still, the oxazolidinyl is substituted with two methyl groups on the same carbon atom. More preferably, the oxazolidinyl is 4,4-dimethyloxazolidin-3-yl.

In yet another preferred embodiment of compounds having formula lib, R1 and R2, together with the N to which they are attached, form a heterocyclyl group which may be substituted or unsubstituted. Preferably, the heterocyclyl is a 5 or 6 membered monocyclic ring, more preferably, a 6 membered monocyclic ring. In certain embodiments, the said heterocyclyl contains one or two, preferably 1, additional heteroatoms (i.e. in addition to the N). These additional heteroatoms may be, for example, N, O and/or S. In one embodiment, the heterocyclyl is morpholino. In an alternative embodiment, the heterocyclyl is piperazinyl. In other embodiments, the said heterocyclyl contains no additional heteroatoms (i.e. it contains a single N atom). In one embodiment, the heterocyclyl is piperadiny. Where the heterocyclyl is substituted, it is preferably substituted with aryl, aryl C_{14} alkyl, C_{5-6} cycloalkyl, or C_{5-6} cycloalkyl C_{1-4} alkyl, wherein the aryl is preferably monocyclic and more preferably phenyl, and the cycloalkyl is preferably cyclohexyl. The alkyl is preferably linear. In one embodiment, the heterocyclyl is substituted with an aryl or an aryl C_{14} alkyl (preferably C_{1-2} alkyl), wherein the aryl is preferably monocyclic and more preferably phenyl. The aryl may optionally be substituted with one or more halogen.

In compounds having formula lib, R5 is preferably selected from H, C_{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C_{1-8} cycloalkyl, C_{1-8} alkoxy, arlyloxy, heteroaryloxy, heterocyclyloxy, R5a, halogen, OH, OR5a, SH, SR5a, OCOR5a, SCOR5a, NH_{2}, N0_{2}, NHR5a, NR5aR5b, COR5a, CSR5a, CN, COOH, COOR5a, CONH_{2}, S0_{2}R5a, S0_{2}H,
S0₂NH₂, CONR₅aR₅b, S0₂NR₅aR₅b, wherein R₅a and R₅b are independently selected from C₃₋₅ alkyl, aryl, heteroaryl, C₃₋₅ cycloalkyl and heterocyclyl, and R₅a and R₅b, together with the heteroatom to which they are joined, can form heterocyclyl. More preferably, R₅ is selected from H, C₁₋₅ alkyl, aryl, heteroaryl, heterocyclyl, C₃₋₅ cycloalkyl, C₁₋₅ alkoxycarbonyl, aryloxy, heteroaryloxy, heterocyclyloxy, halogen, OH, SH, NH₂, N0₂, CN, COOH, CONH₂, SO₃H, S0₂NH₂. More preferably still, R₅ is selected from H, C₁₋₅ alkyl, aryl, heteroaryl, heterocyclyl, C₃₋₅ cycloalkyl, C₁₋₅ alkoxycarbonyl, aryloxy, heteroaryloxy, heterocyclyloxy, halogen, OH, SH, NH₂, N0₂, CN, COOH, CONH₂, SO₃H, S0₂NH₂, wherein the aryl, heteroaryl, heterocyclyl and C₅₋₈ cycloalkyl groups are monomorphic. Even more preferably, R₅ is selected from H, C₁₋₅ alkyl, aryl, heteroaryl, heterocyclyl, C₅₋₈ cycloalkyl, halogen, OH, NH₂, COOH and CONH₂, wherein the aryl, heteroaryl, heterocyclyl and C₅₋₈ cycloalkyl groups are monomorphic. More preferably still, R₅ is selected from H, C₁₋₂ alkyl and halogen. Even more preferably, R₅ is selected from H and halogen such as F, Cl and Br. In one embodiment, R₅ is H.

In compounds having formula lib, R₆ is preferably selected from H, C₁₋₅ alkyl, aryl, heteroaryl, heterocyclyl, C₃₋₅ cycloalkyl, C₁₋₅ alkoxycarbonyl, aryloxy, heteroaryloxy, heterocyclyloxy, R₆a, halogen, OH, OR₆a, SH, SR₆a, OCOR₆a, SCOR₆a, NH₂, N0₂, NHR₆a, NR₆aR₆b, COR₆a, CSR₆a, CN, COOH, COOR₆a, CONH₂, S0₂R₆a, S0₂H, S0₂N₃, CONR₆aR₆b, S0₂NR₆aR₆b, wherein R₆a and R₆b are independently selected from C₁₋₅ alkyl, aryl, heteroaryl, C₃₋₅ cycloalkyl and heterocyclyl, and R₆a and R₆b, together with the heteroatom to which they are joined, can form heterocyclyl. More preferably, R₆ is selected from H, C₁₋₅ alkyl, aryl, heteroaryl, heterocyclyl, C₃₋₅ cycloalkyl, C₁₋₅ alkoxycarbonyl, aryloxy, heteroaryloxy, heterocyclyloxy, halogen, OH, SH, NH₂, N0₂, CN, COOH, CONH₂, SO₃H, S0₂NH₂. More preferably still, R₆ is selected from H, C₁₋₅ alkyl, aryl, heteroaryl, heterocyclyl, C₅₋₈ cycloalkyl, C₁₋₅ alkoxycarbonyl, aryloxy, heteroaryloxy, heterocyclyloxy, halogen, OH, SH, NH₂, N0₂, CN, COOH, CONH₂, SO₃H, S0₂NH₂, wherein the aryl, heteroaryl, heterocyclyl and C₅₋₈ cycloalkyl groups are monomorphic. Even more preferably, R₆ is selected from H, C₁₋₅ alkyl, aryl, heteroaryl, heterocyclyl, C₅₋₈ cycloalkyl, halogen, OH, NH₂, COOH and CONH₂, wherein the aryl, heteroaryl, heterocyclyl and C₅₋₈ cycloalkyl groups are monomorphic. More preferably still, R₆ is selected from H, C₁₋₂ alkyl and halogen. Even more preferably, R₆ is selected from H and halogen such as F, Cl and Br. In one embodiment, R₆ is H.

In compounds having formula lib, R₇ is preferably selected from aryl, heteroaryl, heterocyclyl and C₃₋₅ cycloalkyl each of which may be substituted or unsubstituted. More preferably, R₇ is selected from aryl and heteroaryl each of which may be substituted or unsubstituted. In one embodiment, the heteroaryl contains one heteroatom, e.g. an oxygen or nitrogen atom. Preferably, the aryl or heteroaryl is monocyclic. More preferably, the aryl or heteroaryl is a six membered monocyclic ring. In one embodiment, the heteroaryl contains a nitrogen atom which is substituted with an oxygen atom such as oxidopyridyl. In another embodiment, R₇ is unsubstituted monocyclic aryl such as phenyl, or monocyclic aryl such as phenyl substituted with one or more groups selected from halogen, C₁₋₂ alkoxycarbonyl (optionally substituted with one or more halogen), or OH. In a particular embodiment, R₇ is unsubstituted monocyclic aryl such as phenyl.

When R₇ is substituted, the substituent is preferably one or more groups selected from halogen, C₁₋₄ alkoxycarbonyl, aryloxy, heteroaryloxy, OH, CONH₂, NH₂, heterocyclyl C₁₋₄ alkoxycarbonyl, aryloxy, heteroaryloxy, C₁₋₄ alkoxycarbonyl, N0₂, S0₂NH₂, S0₂, C(NO)NH₂ and morpholinosulfonyl. Preferably, the aryl, heteroaryl and heterocyclyl are monocyclic. In one embodiment, the aryl, heteroaryl and heterocyclyl are six membered monocyclic rings. In a
particular embodiment in which R7 is monocyclic aryl, it may optionally be substituted with aryl or heteroaryl, each of which are monocyclic.

Formula lie

5 In a preferred embodiment of compounds having Formula He, R1 is selected from H and C1-4 alkyl, and R2 is selected from aryl, heteroaryl, heterocyclyl, C3-10 cycloalkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-5 alkyl and C3-10 cycloalkyl C1-6 alkyl, each of which may be substituted or unsubstituted. More preferably, R1 is selected from H, methyl and ethyl, and R2 is selected from aryl, heteroaryl, heterocyclyl, and C3-10 cycloalkyl each of which may be substituted or unsubstituted. More preferably, R1 is methyl. More preferably, R2 is selected from aryl, heteroaryl, heterocyclyl, and C5-8 cycloalkyl each of which are monocyclic and may be substituted or unsubstituted. More preferably still, R2 is selected from aryl such as phenyl, saturated heterocyclyl, and C5-8 cycloalkyl each of which are monocyclic and may be substituted or unsubstituted. When R2 is a monocyclic C5-4 cycloalkyl or aryl, it is preferably unsubstituted. Preferably, R2 is a cyclohexyl, such as an unsubstituted cyclohexyl. When R2 is a monocyclic saturated heterocyclyl, the heterocyclyl ring preferably contains a single heteroatom such as nitrogen or oxygen. More preferably, the heterocyclyl is six membered, such as a piperidinyl or tetrahydropyranyl group. In one embodiment, the heteroatom is a nitrogen heteroatom which may be substituted or unsubstituted. Preferably, the heteroatom in the said heterocyclyl group is at the 4 position relative to the position of attachment of the heterocyclyl group R2 to the urea nitrogen. In one embodiment, the nitrogen atom is substituted with monocyclic aryl (preferably phenyl C1-3 alkyl).

10 In an alternative preferred embodiment of compounds having Formula lie, R1 and R2, together with the N to which they are attached, form a heterocyclyl group which may be substituted or unsubstituted. Preferably, the heterocyclyl is a 5 or 6 membered monocyclic ring and, more preferably, a 5 membered monocyclic ring. In certain embodiments, the said heterocyclyl contains one or two, preferably 1, additional heteroatoms (i.e. in addition to the N). These additional heteroatoms may be, for example, N, O and/or S. Preferably, the heterocyclyl is oxazolidinyl. Preferably, the oxygen atom in the oxazolidinyl is at the 3 position relative to the urea nitrogen. Preferably, the oxazolidinyl is substituted with one, two or three methyl or ethyl groups. More preferably, the oxazolidinyl is substituted with two methyl or ethyl groups. More preferably still, the oxazolidinyl is substituted with two methyl groups on the same carbon atom. More preferably, the oxazolidinyl is 4,4-dimethyloxazolidin-3-yl.

15 In yet another preferred embodiment of compounds having formula lie, R1 and R2, together with the N to which they are attached, form a heterocyclyl group which may be substituted or unsubstituted. Preferably, the heterocyclyl is a 5 or 6 membered monocyclic ring, more preferably, a 6 membered monocyclic ring. In certain embodiments, the said heterocyclyl contains one or two, preferably 1, additional heteroatoms (i.e. in addition to the N). These additional heteroatoms may be, for example, N, O and/or S. In one embodiment, the heterocyclyl is morpholino. In an alternative embodiment, the heterocyclyl is piperazinyl. In other embodiments, the said heterocyclyl contains no additional heteroatoms (i.e. it contains a single N atom). In one embodiment, the heterocyclyl is piperadiny1. Where the heterocyclyl is substituted, it is preferably substituted with aryl, aryl C1-4
alkyl, C₅₋₆ cycloalkyl, or C₃₋₆ cycloalkyl Cₛ₋₄ alkyl, wherein the aryl is preferably monocyclic and more preferably phenyl, and the cycloalkyl is preferably cyclohexyl. The alkyl is preferably linear. In one embodiment, the heterocyclyl is substituted with an aryl or an aryl Cᵣ₋₄ alkyl (preferably C₁₋₂ alkyl), wherein the aryl is preferably monocyclic and more preferably phenyl. The aryl may optionally be substituted with one or more halogen.

In compounds having formula (I), R₅ is preferably selected from H, C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyl, C₃₋₆ cycloalkyl, C₆₋₁₀ alkoxy, arylxoy, heteroaryloxy, heterocyclyloxy, R₅a, halogen, OH, OR₅a, SH, SR₅a, OCOOR₅a, SCOR₅a, NR₂, NR₅aR₅b, COR₅a, SR₅a, CN, COOH, CONR₅aR₅b, SO₂R₅a, SO₂NR₅aR₅b, wherein R₅a and R₅b are independently selected from C₁₋₄ alkyl, aryl, heteroaryl, C₃₋₅ cycloalkyl and heterocyclyl, and R₅a and R₅b, together with the heteroatom to which they are joined, can form heterocyclyl. More preferably, R₅ is selected from H, C₁₋₄ alkyl, aryl, heteroaryl, heterocyclyl, C₃₋₈ cycloalkyl, C₁₋₆ alkoxy, arylxoy, heteroaryloxy, heterocyclyloxy, halogen, OH, SH, NH₂, N(OH)₂, CN, COOH, CONH₂, SO₃H, S(O)₂NH₂. More preferably still, R₅ is selected from H, C₁₋₄ alkyl, aryl, heteroaryl, heterocyclyl, C₁₋₈ cycloalkyl, C₁₋₆ alkoxy, arylxoy, heteroaryloxy, heterocyclyloxy, halogen, OH, SH, NH₂, N(OH)₂, CN, COOH, CONH₂, SO₂H, S(O)₂NH₂, wherein the aryl, heteroaryl, heterocyclyl and C₃₋₈ cycloalkyl groups are monocyclic.

Even more preferably, R₅ is selected from H, C₁₋₃ alkyl, aryl, heteroaryl, heterocyclyl, C₃₋₈ cycloalkyl, halogen, OH, NH₂, COOH and CONH₂, wherein the aryl, heteroaryl, heterocyclyl and C₃₋₈ cycloalkyl groups are monocyclic. More preferably still, R₅ is selected from H, C₁₋₂ alkyl and halogen. Even more preferably, R₅ is selected from H and halogen such as F, Cl and Br. In one embodiment, R₅ is H.

In compounds having formula (I), R₆ is preferably selected from aryl, heteroaryl, heterocyclyl and C₃₋₅ cycloalkyl each of which may be substituted or unsubstituted. More preferably, R₆ is selected from aryl and heteroaryl each of which may be substituted or unsubstituted. In one embodiment, the heteroaryl contains one heteroatom, e.g. an oxygen or nitrogen atom. Preferably, the aryl or heteroaryl is monocyclic. More preferably, the aryl or heteroaryl is a six membered monocyclic ring. In one embodiment, the heteroaryl contains a nitrogen atom which is substituted with an oxygen atom such as oxidopyridyl. In another embodiment, R₆ is unsubstituted monocyclic aryl such as phenyl, or monocyclic aryl such as phenyl substituted with one or more groups selected from halogen, C₁₋₂ alkoxy (optionally substituted with one or more halogen), or OH. In a preferred embodiment, R₆ is unsubstituted aryl and, preferably, a monocyclic aryl such as phenyl.

When R₆ is substituted, the substituent is preferably one or more groups selected from halogen, C₁₋₄ alkoxy, aryl, heteroaryl, heterocyclyl, OH, CONH₂, NH₂, heterocyclyl C₁₋₄ alkoxy, aryl C₁₋₄ alkoxy, heteroaryl C₁₋₄ alkoxy, N(OH)₂, S(O)₂NH₂, C(NO)H₂ and morpholinosulfonyl. Preferably, the aryl, heteroaryl and heterocyclyl are monocyclic. In one embodiment, the aryl, heteroaryl and heterocyclyl are six membered monocyclic rings. In a particular embodiment in which R₆ is monocyclic aryl, it may optionally be substituted with one or more groups selected from halogen, OH, C₁₋₃ alkoxy, aryl (e.g. a monocyclic aryl such as phenyl), heteroaryl (e.g. monocyclic heteroaryl containing one or two nitrogen atoms, or one oxygen atom), heterocyclyl (e.g. piperaziny1, piperadiny1 or morpholino) C₁₋₃ alkoxy, aryl (e.g. monocyclic aryl such as phenyl) C₁₋₃ alkoxy, CONH₂, NH₂, N(OH)₂, OCH₂, S(O)₂NH₂, morpholinosulfonyl and C(NO)H₂.
In one embodiment when R6 is monocyclic aryl such as phenyl, the substituent of R6 is aryl, preferably monocyclic aryl such as phenyl, which may be substituted or unsubstituted. Where it is substituted, preferably it is substituted with CONH₂.

When the substituent of R6 is C₁₋₄ alkoxy, aryl, heteroaryl, heterocyclyl, heterocyclyl C₁₋₄ alkoxy, aryl C₁₋₄ alkoxy, heteroaryl C₁₋₄ alkoxy or S₀₂, each of these moieties may optionally be substituted with one or more groups selected from halogen, OH, C₁₋₃ alkoxy (which may be substituted with one or more halogen), CONH₂, CN, NCH₂CH₂, NHCOCH₃, methylhydroxybutyl, and methylhydroxybutynyl.

**Formula lid**

In a preferred embodiment of compounds having Formula lid, R₁ is selected from H and C₁₋₄ alkyl, and R₂ is selected from aryl, heteroaryl, heterocyclyl, C₁₋₄ cycloalkyl, aryl C₁₋₄ alkyl, heteroaryl C₁₋₄ alkyl, heterocyclyl C₁₋₆ alkyl and C₁₋₄ cycloalkyl C₁₋₆ alkyl, each of which may be substituted or unsubstituted. More preferably, R₁ is selected from H, methyl and ethyl, and R₂ is selected from aryl, heteroaryl, heterocyclyl, and C₁₋₄ cycloalkyl each of which may be substituted or unsubstituted. More preferably, R₁ is methyl. More preferably, R₂ is selected from aryl, heteroaryl, heterocyclyl, and C₁₋₄ cycloalkyl each of which are monocyclic and may be substituted or unsubstituted. More preferably still, R₂ is selected from aryl such as phenyl, saturated heterocyclyl, and C₁₋₄ cycloalkyl each of which are monocyclic and may be substituted or unsubstituted. Even more preferably, R₂ is aryl, such as phenyl, which is monocyclic and may be substituted or unsubstituted. When R₂ is substituted, the substituent is preferably one or more halogen.

In one embodiment, R₂ is a cyclohexyl, such as an unsubstituted cyclohexyl. When R₂ is a monocyclic saturated heterocyclyl, the heterocyclyl ring preferably contains a single heteroatom such as nitrogen or oxygen. More preferably, the heterocyclyl is six membered, such as a piperidinyli or tetrahydropyranyl group. In one embodiment, the heteroatom is a nitrogen heteroatom which may be substituted or unsubstituted. Preferably, the heteroatom in the said heterocyclyl group is at the 4 position relative to the position of attachment of the heterocyclyl group R₂ to the urea nitrogen. In one embodiment, the nitrogen atom is substituted with monocyclic aryl (preferably phenyl) C₁₋₃ alkyl.

In an alternative preferred embodiment of compounds having Formula lid, R₁ and R₂, together with the N to which they are attached, form a heterocyclyl group which may be substituted or unsubstituted. Preferably, the heterocyclyl is a 5 or 6 membered monocyclic ring and, more preferably, a 5 membered monocyclic ring. In certain embodiments, the said heterocyclyl contains one or two, preferably 1, additional heteroatoms (i.e. in addition to the N). These additional heteroatoms may be, for example, N, O and/or S. Preferably, the heterocyclyl is oxazolidinyl. Preferably, the oxygen atom in the oxazolidinyl is at the 3 position relative to the urea nitrogen. Preferably, the oxazolidinyl is substituted with one, two or three methyl or ethyl groups. More preferably, the oxazolidinyl is substituted with two methyl or ethyl groups. More preferably still, the oxazolidinyl is substituted with two methyl groups on the same carbon atom. More preferably, the oxazolidinyl is 4,4-dimethyloxazolidin-3-yl.
In yet another preferred embodiment of compounds having formula lid, R1 and R2, together with the N to which they are attached, form a heterocyclyl group which may be substituted or unsubstituted. Preferably, the heterocyclyl is a 5 or 6 membered monocyclic ring, more preferably, a 6 membered monocyclic ring. In certain embodiments, the said heterocyclyl contains one or two, preferably 1, additional heteroatoms (i.e. in addition to the N). These additional heteroatoms may be, for example, N, O and/or S. In one embodiment, the heterocyclyl is morpholino. In an alternative embodiment, the heterocyclyl is piperazinyl. In other embodiments, the said heterocyclyl contains no additional heteroatoms (i.e. it contains a single N atom). In one embodiment, the heterocyclyl is piperdinyl. Where the heterocyclyl is substituted, it is preferably substituted with aryl, aryl C<sub>1-4</sub> alkyl, C<sub>5-6</sub> cycloalkyl, or C<sub>5-6</sub> cycloalkyl C<sub>1-4</sub> alkyl, wherein the aryl is preferably monocylic and more preferably phenyl, and the cycloalkyl is preferably cyclohexyl. The alkyl is preferably linear. In one embodiment, the heterocyclyl is substituted with an aryl or an aryl C<sub>1-4</sub> alkyl (preferably C<sub>1-2</sub> alkyl), wherein the aryl is preferably monocylic and more preferably phenyl. The aryl may optionally be substituted with one or more halogens.

In compounds having formula lid, R5 is preferably selected from H, C<sub>1-6</sub> alkyl, aryl, heteroaryl, heterocyclyl, C<sub>3-8</sub> cycloalkyl, C<sub>6</sub> alkoxy, arylloxy, heteroaryloxy, heterocyclyloxy, R5a, halogen, OH, OR5a, SH, SR5a, OCOR5a, SCOR5a, NH<sub>2</sub>, N<sub>0</sub><sub>2</sub>, NHR5a, NR5aR5b, COR5a, CSR5a, CN, COOH, COOR5a, CON<sub>3</sub>, SO<sub>2</sub>R5a, SO<sub>2</sub>H, SO<sub>2</sub>NH<sub>2</sub>, CONR5aR5b, SO<sub>2</sub>NH<sub>2</sub>, wherein R5a and R5b are independently selected from C<sub>1-6</sub> alkyl, aryl, heteroaryl, C<sub>3-4</sub> cycloalkyl, C<sub>6</sub> alkoxy, arylloxy, heteroaryloxy, heterocyclyloxy, halogen, OH, SH, NH<sub>2</sub>, N<sub>0</sub><sub>2</sub>, CN, COOH, CONH<sub>2</sub>, SO<sub>3</sub>H, SO<sub>2</sub>NH<sub>2</sub>. More preferably still, R5 is selected from H, C<sub>1-4</sub> alkyl, aryl, heteroaryl, heterocyclyl, C<sub>3-5</sub> cycloalkyl, C<sub>1-4</sub> alkoxy, arylloxy, heteroaryloxy, heterocyclyloxy, halogen, OH, SH, NH<sub>2</sub>, N<sub>0</sub><sub>2</sub>, CN, COOH, CONH<sub>2</sub>, SO<sub>3</sub>H, SO<sub>2</sub>NH<sub>2</sub>, wherein the aryl, heteroaryl, heterocyclyl and C<sub>5-9</sub> cycloalkyl groups are monocylic. Even more preferably, R5 is selected from H, C<sub>1-3</sub> alkyl, aryl, heteroaryl, heterocyclyl, C<sub>5-9</sub> cycloalkyl, halogen, OH, NH<sub>2</sub>, COOH and CONH<sub>2</sub>, wherein the aryl, heteroaryl, heterocyclyl and C<sub>5-9</sub> cycloalkyl groups are monocylic. More preferably still, R5 is selected from H, C<sub>1-4</sub> alkyl and halogen. Even more preferably, R5 is selected from H and halogen such as F, Cl and Br. In one embodiment, R5 is H.

In compounds having formula lid, R7 is preferably selected from aryl, heteroaryl, heterocyclyl and C<sub>3-8</sub> cycloalkyl each of which may be substituted or unsubstituted. More preferably, R7 is selected from aryl and heteroaryl each of which may be substituted or unsubstituted. In one embodiment, the heteroaryl contains one heteroatom, e.g. an oxygen or nitrogen atom. Preferably, the aryl or heteroaryl is monocylic. More preferably, the aryl or heteroaryl is a six membered monocyclic ring. In one embodiment, the heteroaryl contains a nitrogen atom which is substituted with an oxygen atom such as oxidopyridyl. In another embodiment, R7 is unsubstituted monocylic aryl such as phenyl, or monocyclic aryl such as phenyl substituted with one or more groups selected from halogen, C<sub>1-4</sub> alkoxy (optionally substituted with one or more halogen), or OH.

When R7 is substituted, the substituent is preferably one or more groups selected from halogen, C<sub>1-4</sub> alkoxy, aryl, heteroaryl, heterocyclyl, OH, CONH<sub>2</sub>, NH<sub>2</sub>, heterocyclyl C<sub>1-4</sub> alkoxy, aryl C<sub>1-4</sub> alkoxy, heteroaryl C<sub>1-4</sub> alkoxy, N<sub>0</sub><sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>3</sub> C(NOH)NH<sub>2</sub> and morpholinosulfonyl. Preferably, the aryl, heteroaryl and heterocyclyl are monocylic. In one embodiment, the aryl, heteroaryl and heterocyclyl are six membered monocyclic rings. In a
particular embodiment in which R7 is monocyclic aryl, it may optionally be substituted with one or more groups selected from halogen, OH, C\textsubscript{1-3} alkoxy, aryl (e.g. a monocyclic aryl such as phenyl), heteroaryl (e.g. monocyclic heteroaryl containing one or two nitrogen atoms, or one oxygen atom), heterocyclyl (e.g. piperazinyl, piperadinylo or morpholino) C\textsubscript{1-3} alkoxy, aryl (e.g. monocyclic aryl such as phenyl) C\textsubscript{1-3} alkoxy, C\textsubscript{0}NH\textsubscript{2}, NH\textsubscript{2}, N\textsubscript{0}, OCH\textsubscript{2}, S\textsubscript{0}-NH\textsubscript{2}, morpholinosulfonyl and C(NO\textsubscript{3})NH\textsubscript{2}. In one embodiment when R7 is monocyclic aryl such as phenyl, the substituent of R7 is aryl (e.g. monocyclic aryl such as phenyl) C\textsubscript{1-3} alkoxy.

When the substituent of R7 is C\textsubscript{1-4} alkoxy, aryl, heteroaryl, heterocyclyl, heterocyclyl C\textsubscript{1-4} alkoxy, aryl C\textsubscript{1-4} alkoxy, heteroaryl C\textsubscript{1-4} alkoxy or S\textsubscript{0}, each of these moieties may optionally be substituted with one or more groups selected from halogen, OH, C\textsubscript{1-3} alkoxy (which may be substituted with one or more halogen), CONH\textsubscript{2}, CN, NCH\textsubscript{3}CH\textsubscript{3}, NHC0CH\textsubscript{3}, methylhydroxybutyl, and methylhydroxybutynyl

In an alternative embodiment of the process of the invention, a compound is prepared having Formula I or Formula II:

![Formula I and II](image)

wherein R1, R2, R5, ring A, V, W, X, Y and Z are as defined above;

or a pharmaceutically acceptable salt or ester thereof;

provided that Ring A in compounds having Formula I does not form pyridine, pyrimidine, substituted pyridine or substituted pyrimidine, when R1 and R2, together with the N to which they are attached, form piperidinyl, piperazinyl, substituted piperidinyl or substituted piperazinyl,

provided that Ring A is not unsubstituted benzo, hydroxybenzo, phenoxybenzo, fluorochlorobenzo, chlorobenzo, bromobenzo, nitrobenzo, aminobenzo, cyanobenzo, methylbenzo, trifluoromethylbenzo, trifluoromethylchlorobenzo, phenylketobenzo, phenylhydroxymethylbenzo, cyclohexylthiobenzo, methoxycarbonylbenszo or methoxygenbenzo,

provided that when R1 or R2 is methyl, the other of R1 or R2 is not 4-chlorobutyl, 4-azidobutyl, or 4-isothiocyanatobutyl, and/or

provided that the compound is not (4-phenyl-1H-imidazol-1-yl)(4-(quinolin-2-ylmethyl)piperazin-1-yl)methanone.
In a particularly preferred embodiment, the compound has the Formula Ila, and the intermediate of Formula II has a corresponding structure in which the -CONR1R2 group of Formula Ila is replaced by the H of Formula II'.

In such an embodiment, the compound may, for example, be of Formula Ila, wherein:

R1 is selected from H and C1-4 alkyl,

R2 is selected from C1-6 alkyl, aryl, heteroaryl, heterocyclyl, C3-10 cycloalkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl and C3-10 cycloalkyl C1-6 alkyl, each of which may optionally be substituted with one or more groups selected from R2a, halogen, OH, OR2a, OCOR2a, SH, SR2a, SCOR2a, NH2, NHR2a, NHSO2R2a, NR2aCOR2b, NHC(NH)NH2, NHCOR2a, NR2aR2b, COR2a, CSR2a, CN, COOH, COOR2a, CONH2, CONHOH, CONHR2a, CONHOR2a, C(NO)NH2, S02R2a, S02H, S02NH2, CONR2aR2b, S02NR2aR2b, wherein R2a and R2b are independently selected from C6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R2a and R2b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R2 is C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl, heterocyclyl or a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from R2c, halogen, OH, OR2c, OCOR2c, SH, SR2c, SCOR2c, NH2, NHR2c, NHSO2NH2, NR2cCOR2d, NHC(NH)NH2, NHCOR2c, NR2cR2d, COR2c, CSR2c, CN, COOH, COOR2c, CONH2, CONHOH, CONHR2c, CONHOR2c, C(NO)NH2, S02R2c, S02H, S02NH2, CONR2cR2d, S02NR2cR2d, wherein R2c and R2d are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R2c and R2d, together with the heteroatom to which they are joined, can form heterocyclyl,

R5 is selected from H, R5a, halogen, OH, OR5a, OCOR5a, SH, SR5a, SCOR5a, NH2, NHR5a, NHSO2NH2, NR5aCOR5b, NHC(NH)NH2, NHCOR5a, NR5aR5b, COR5a, CSR5a, CN, COOH, COOR5a, CONH2, CONHOH, CONHR5a, CONHOR5a, C(NO)NH2, S02R5a, S02H, S02NH2, CONR5aR5b, S02NR5aR5b, wherein R5a and R5b are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R5a and R5b, together with the heteroatom to which they are joined, can form heterocyclyl,

R6 is selected from aryl, heteroaryl, heterocyclyl, C3-10 cycloalkyl, each of which may optionally be substituted with one or more groups selected from R6a, halogen, OH, OR6a, OCOR6a, SH, SR6a, SCOR6a, N02, NH2, NHR6a, NHSO2NH2, NR6aCOR6b, NHC(NH)NH2, NHCOR6a, NR6aR6b, COR6a, CSR6a, CN, COOH, COOR6a, CONH2, CONHOH, CONHR6a, CONHOR6a, C(NO)NH2, S02R6a, S02H, S02NH2, CONR6aR6b, S02NR6aR6b, wherein R6a and R6b are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R6a and R6b, together with the heteroatom to which they are joined, can form heterocyclyl, and wherein, when R6 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms,
wherein, when the substituent of R6 is C1-4 alkyl, substituted C1-4 alkyl, aryl, heteroaryl, C3-8 cycloalkyl, heterocyclyl or a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from R6c, halogen, OH, OR6c, OCOR6c, SH, SR6c, SCOR6c, NH2, NHR6c, NHSO2NH2, NHSO2R6c, NR6cCOR6d, NHC(NH)NH2, NHCOR6c, NR6cR6d, COR6c, CSR6c, CN, COOH, COOR6c, CONH2, CONHOH, CONHR6c, CONHOR6c, C(NO)NH2, S0,R6c, S0,SH, S0,NH2, CONR6cR6d, S0,R6cR6d, wherein R6c and R6d are independently selected from C1-4 alkyl, substituted C1-4 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R2c and R2d, together with the heteroatom to which they are joined, can form heterocyclyl, and wherein, when the substituent of R6 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, and

R8 is selected from H, R8a, halogen, OH, OR8a, OCOR8a, SH, SR8a, SCOR8a, NH2, NHR8a, NHSO2N4, NHSO2R8a, NR8aCOR8b, NHC(NH)NH2, NHCOR8a, NR8aR8b, COR8a, CSR8a, CN, COOH, COOR8a, CONH2, CONHOH, CONHR8a, CONHOR8a, C(NO)NH2, S0,R8a, S0,SH, S0,NH2, CONR8aR8b, S0,NR8aR8b, wherein R8a and R8b are independently selected from C1-4 alkyl, substituted C1-4 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R8a and R8b, together with the heteroatom to which they are joined, can form heterocyclyl.

In particular instances of this preferred embodiment, R1 may be selected from H, methyl and ethyl, and R2 may be selected from aryl, heteroaryl, heterocyclyl, and C3-10 cycloalkyl, each of which may be substituted or unsubstituted. R2 may, for example, be selected from fully saturated heterocyclyl, and C5-8 cycloalkyl, each of which are monocyclic and may be substituted or unsubstituted. By way of further example, R2 may be an unsubstituted cyclopentyl or unsubstituted cyclohexyl. As an alternative example, R2 may be a fully saturated heterocyclyl, wherein the heterocyclyl ring contains a single heteroatom, such as nitrogen or oxygen. In such embodiments, the heterocyclyl R2 may be six membered and the heteroatom in the said heterocyclyl group may be at the 4-position relative to the position of attachment of the heterocyclyl group R2 to the urea nitrogen. In particular embodiments, the heteroatom in heterocyclyl R2 may be a nitrogen heteroatom, which may be substituted with a group selected from CN, CONH2, C(NO)NH2, S0,C1-4 alkyl, S0,aryl, CO-heteroaryl, CO-C1-4 alkyl, COO-C1-4 alkyl, COO-aryl, C1-4 alkyl, aryl C1-4 alkyl, heteroaryl C1-3 alkyl, heterocyclyl C1-4 alkyl, aryl, heteroaryl, and heterocyclyl, wherein the C1-4 alkyl may optionally be substituted with OH, CN, COOH, the S0, aryl may optionally be substituted with a C1-4 alkyl or C1-4 haloalkyl, the CO-heteroaryl may optionally be substituted with a heteroaryl or halogen, the heteroaryl C1-3 alkyl may optionally be substituted with COO-C1-3 alkyl, and the heteroaryl may optionally be substituted with one or more halogens. For example, the nitrogen heteroatom in heterocyclyl R2 may be substituted with phenyl C1-3 alkyl.

In particular embodiments of the process of the invention, R6 may be selected from monocyclic aryl, monocyclic heteroaryl, and heterocyclyl, each of which may be substituted or unsubstituted. For example, R6 may be a substituted aryl, wherein said aryl may be substituted with one or more groups selected from halogen, R6a, OH, OR6a, NH2, N02, NHC(NH)NH2, NHR6a, NR6aR6b, C(NO)NH2, COR6a, COOH, COOR6a, CONH2, CONHOH, S0,R6a, S0,NR6aR6b, wherein R6a and R6b are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl.
wherein, when the substituent of R6 is C1-6 alkyl, substituted C1-6 alky1, aryl, heteroaryl, C3-8 cycloalkyl, heterocyclyl or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from OR6c, OH, and CONH2, wherein R6c is selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, and wherein, when the substituent of R6 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms.

In certain embodiments wherein R6 is a substituted aryl, R6 may be substituted with one or more groups selected from halogen, OH, N02, C1-4 alkoxy, CONH2, C(NOH)NH2, CONHOH, S02C1-4 alkyl, heterocyclyl, and aryl, wherein the heterocyclyl substituent on R6 may optionally be substituted with an oxygen atom and the aryl substituent on R6 may optionally be substituted with CONH2.

In certain embodiments wherein R6 is a heterocyclyl, R6 is optionally substituted with an oxygen atom. Similarly, in certain embodiments wherein R6 is a monocyclic heteroaryl, R6 is optionally substituted with an oxygen atom.

In particular embodiments of the process of the invention, R8 is H. In certain embodiments, R5 is H. In certain examples of the process of the invention, R5 and R8 are both H.

In a particular group of embodiments, the present invention provides a process for preparing a substituted urea of Formula IIa, or a pharmaceutically acceptable salt or ester thereof, as described above, the process comprising the reaction of an imidazolyl intermediate of Formula II’ having a structure corresponding with Formula IIa in which the -CONR1R2 group of Formula IIa is replaced by the H of Formula II’,

with a carbamoyl halide of the formula: RIR2NC(=O)Hal,

wherein R8 is H;

R1 and R2 can each be independently selected from H, C1-20 alkyl, C1-6 alkoxy, aryl, heteroaryl, partially or fully saturated heterocyclyl, C3-10 cycloalkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl and C3-10 cycloalkyl-C1-6 alkyl, each of which may be optionally substituted, or R1 and R2, together with the N to which they are attached, can form a heteroaryl or heterocyclyl group, each of which may optionally be substituted, or R1 and R2 can each be independently selected from Rla, halogen, OH, ORla, OCORla, SH, SRla, SCORla, NH2, NRla, NHSO2NH2, NHSO2Rla, NRlaCORla, NHCORla, NRlaRlb, CORla, CSRla, CN, COOH, COORla, CONH2, CONHOH, CONHRLa, CONHORla, S02Rla, S02H, S02NH2, CONH2Rlb, S02NRlaRlb, wherein Rla and Rlb are independently selected from optionally substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or Rla and Rlb, together with the heteroatom to which they are joined, can form heterocyclyl,

with the exception that R1 and R2 are not both H;

R5 is selected from H, C1-6 alkyl, aryl, heteroaryl, heterocyclyl, C3-8 cycloalkyl, C1-6 alkoxy, arloxy, heteroarylalkoxy, heterocyclyloxy, R5a, halogen, OH, OR5a, SH, SR5a, OCOR5a, SCOR5a, NH2, N02, NR5a, NHSO2NH2, NHSO2R5a, NR5aCOR5b, NHCOR5a, NH(NH)NH2, NR5aR5b, COR5a, CSR5a, CN, COOH,
COOR5a, CONH₂, CONHOH, CONHR5a, CONHOR5a, C(NO)NH₂, CONR5aR5b, S₀₂R5a, S₀₂H, S₀₂N₃H₂, S₀₂NR₅aR₅b, wherein R₅a and R₅b are independently selected from Cᵢ₋₆ alkyl, substituted Cᵢ₋₆ alkyl, aryl, heteroaryl, C₃₋₈ cycloalkyl and heterocyclyl, or R₅a and R₅b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R₅ is Cᵢ₋₆ alkyl, aryl, heteroaryl, heterocyclyl, Cᵢ₋₆ alkyl, C₃₋₈ cycloalkyl, or a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, aryl, heteroaryl, heterocyclyl, Cᵢ₋₆ alkyl, aryl, heteroaryl, heterocyclyl, R₅c, Cᵢ₋₆ alkyl, OH, OR₅c, CONR₅c, CONH₂, NH₂, NØ₂, NH₅R₅e, NHS₀₂NH₂, NHS₀₂R₅c, NR₅cCOR₅d, NHCOR₅c, NHC(NH)NH₂, NR₅cR₅d, COR₅c, CSR₅c, CN, COOH, COOR₅c, CONH₂, CONHOR₅c, CONHOR₅c, C(NO)NH₂, CONR₅cR₅d, S₀₂R₅c, S₀₂N₃H₂, S₀₂NR₅cR₅d, wherein R₅c and R₅d are independently selected from Cᵢ₋₆ alkyl, substituted Cᵢ₋₆ alkyl, aryl, heteroaryl, C₃₋₈ cycloalkyl and heterocyclyl, or R₅c and R₅d, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R₅ is Cᵢ₋₆ alkyl, aryl, heteroaryl, heterocyclyl, Cᵢ₋₆ alkyl, aryl, heteroaryl, heterocyclyl, R₆a, halogen, OH, OR₆a, SH, SR₆a, OCOR₆a, SCOR₆a, NH₂, NØ₂, NHR₆a, NHSO₂NH₂, NH₂NR₆a, SR₆aCOR₆b, NHCOR₆a, NHCOR₆a, NHC(NH)NH₂, NR₆aR₆b, COR₆a, CSR₆a, CN, COOH, COOR₆a, CONH₂, CONHOR₆a, CONHOR₆a, C(NO)NH₂, CONR₆aR₆b, S₀₂R₆a, S₀₂H, S₀₂NH₂, S₀₂NR₆aR₆b, wherein R₆a and R₆b are independently selected from Cᵢ₋₆ alkyl, substituted Cᵢ₋₆ alkyl, aryl, heteroaryl, C₃₋₈ cycloalkyl and heterocyclyl, or R₆a and R₆b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R₆ is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, and when R₆ is Cᵢ₋₆ alkyl, aryl, heteroaryl, heterocyclyl, Cᵢ₋₆ alkyl, aryl, heteroaryl, heterocyclyl, R₆c, halogen, OH, OR₆c, SH, SR₆c, SCOR₆c, NH₂, NØ₂, NHR₆c, NHSO₂NH₂, NHCOR₆c, NR₆cCOR₆d, NHCOR₆c, NR₆cR₆d, COR₆c, CSR₆c, CN, COOH, COOR₆c, CONH₂, CONHOR₆c, CONHOR₆c, CONH₂, CONHOR₆c, CONR₆cR₆d, S₀₂R₆c, S₀₂H, S₀₂NH₂, S₀₂NR₆cR₆d, wherein R₆c and R₆d are independently selected from Cᵢ₋₆ alkyl, aryl, heteroaryl, C₃₋₈ cycloalkyl and heterocyclyl, or R₆c and R₆d, together with the heteroatom to which they are joined, can form heterocyclyl,
alkyl, substituted C\textsubscript{1-6} alkyl, aryl, heteroaryl, C\textsubscript{2-8} cycloalkyl and heterocyclyl, or R\textsubscript{6c} and R\textsubscript{6d}, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R\textsubscript{6} is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, or when the substituent of R\textsubscript{6} is C\textsubscript{1-6} alkyl, C\textsubscript{1-6} alkenyl, aryl, heteroaryl, heterocyclyl, C\textsubscript{1-6} alkoxy, aryl oxy, heteroaryl oxy, heterocyclyl oxy, aryl C\textsubscript{1-6} alkyl, heteroaryl C\textsubscript{1-6} alkyl, heterocyclyl C\textsubscript{1-6} alkyl, aryl C\textsubscript{1-6} alkoxy, heteroaryl C\textsubscript{1-6} alkoxy, heterocyclyl C\textsubscript{1-6} alkoxy, C\textsubscript{2-8} cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R\textsubscript{6e}, C\textsubscript{1-6} alkyl, C\textsubscript{1-4} alkoxy, OH, OR\textsubscript{6e}, OCOR\textsubscript{6e}, SH, SR\textsubscript{6e}, SCOR\textsubscript{6e}, N\textsubscript{0\textsubscript{2}}, NR\textsubscript{6e}R\textsubscript{6f}, COR\textsubscript{6e}, CSR\textsubscript{6e}, CN, COOH, COOR\textsubscript{6e}, CONH\textsubscript{2}, CONHOH, CONHR\textsubscript{6e}, CONCOR\textsubscript{6e}, CONeCOR\textsubscript{6e}, SO\textsubscript{2}R\textsubscript{6e}, SO\textsubscript{3}H, S\textsubscript{0}2NR\textsubscript{6e}R\textsubscript{6f}, wherein R\textsubscript{6e} and R\textsubscript{6f} are independently selected from Cl-β alkyl, substituted C\textsubscript{1-6} alkyl, aryl, heteroaryl, C\textsubscript{2-8} cycloalkyl and heterocyclyl, or R\textsubscript{6e} and R\textsubscript{6f}, together with the heteroatom to which they are joined, can form heterocyclyl.

In certain embodiments of the process of the invention, for example in the particular group of embodiments mentioned immediately above for the preparation of compounds of Formula Ila, R1 and R2 are not both methyl. In particular embodiments, when R1 or R2 is methyl, the other of R1 or R2 is not 4-chlorobutyl, 4-azidobutyl, or 4-isothiocyanatobutyl. In an embodiment, the substituted urea is not (4-phenyl-1H-imidazol-1-yl)(4-(quinolin-2-yl)methyloxazepin-1-yl)methanone.

R1 and R2 may, especially in the particular group of embodiments mentioned immediately above for the preparation of compounds of Formula Ila, optionally be substituted in the manner set out in claim 1 of WO 2010/074588 A2. In particular, in preferred embodiments, when R1 or R2 is Cl\textsubscript{1-6} alkyl, alkoxy, aryl, heteroaryl, heterocyclyl, C\textsubscript{2-10} cycloalkyl, aryl C\textsubscript{1-6} alkyl, heteroaryl Cl\textsubscript{1-6} alkyl, heterocyclyl C\textsubscript{1-6} alkyl, C\textsubscript{2-13} cycloalkyl Cl\textsubscript{1-6} alkyl, C\textsubscript{1-6} alkoxy, aryl oxy, heteroaryl oxy, heterocyclyl oxy, aryl C\textsubscript{1-6} alkyl, heteroaryl C\textsubscript{1-6} alkoxy, heterocyclyl C\textsubscript{1-6} alkoxy, C\textsubscript{2-8} cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from Rlc, halogen, aryl, heteroaryl, heterocyclyl, C\textsubscript{1-6} alkoxy, aryl oxy, heteroaryl oxy, heterocyclyl oxy, aryl C\textsubscript{1-6} alkyl, heteroaryl C\textsubscript{1-6} alkoxy, heterocyclyl C\textsubscript{1-6} alkoxy, aryl C\textsubscript{1-6} alkoxy, heteroaryl C\textsubscript{1-6} alkoxy, heterocyclyl C\textsubscript{1-6} alkoxy, C\textsubscript{1-6} alkenyl amine, C\textsubscript{1-6} dialkyl amine, C\textsubscript{1-6} alkyl amine, OH, ORlc, OCORlc, SH, SRlc, SCORlc, NH\textsubscript{2}, N\textsubscript{0\textsubscript{2}}, NRlcRlc, NHSO\textsubscript{2}NH\textsubscript{2}, NH\textsubscript{2}SO\textsubscript{2}Rlc, NRlcCORld, NHSO\textsubscript{2}NH\textsubscript{2}, NH\textsubscript{2}SO\textsubscript{2}Rlc, NRlcCORld, NHSO\textsubscript{2}NH\textsubscript{2}, NHSO\textsubscript{2}Rlc, NRlcCORld, CONH\textsubscript{2}, CONRlc, CN, COOH, COORlc, CONH\textsubscript{2}, CONHRlc, CONCORlc, CONHNRlc, CONeNRlc, SO\textsubscript{2}Rlc, SO\textsubscript{3}H, S\textsubscript{0}2NRlcRlc, wherein Rlc and Rld are independently selected from C\textsubscript{1-6} alkyl, substituted C\textsubscript{1-6} alkyl, aryl, heteroaryl, C\textsubscript{2-8} cycloalkyl and heterocyclyl, or Rlc and Rld, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R1 or R2 is C\textsubscript{1-10} alkyl, aryl, heteroaryl, heterocyclyl, C\textsubscript{1-6} alkoxy, aryl oxy, heteroaryl oxy, heterocyclyl oxy, aryl C\textsubscript{1-6} alkyl, heteroaryl C\textsubscript{1-6} alkyl, heterocyclyl C\textsubscript{1-6} alkyl, aryl C\textsubscript{1-6} alkoxy, heteroaryl C\textsubcript{1-6} alkoxy, heterocyclyl C\textsubscript{1-6} alkoxy, C\textsubscript{1-6} alkenyl amine, C\textsubscript{1-6} dialkyl amine, C\textsubscript{1-6} alkyl amine, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from Rlc, halogen, C\textsubscript{1-10} alkyl, OH, ORlc, OCORlc, SH, SRlc, SCORlc, NH\textsubscript{2}, N\textsubscript{0\textsubscript{2}}, NRlcRlc, NHSO\textsubscript{2}NH\textsubscript{2}, NHSO\textsubscript{2}Rlc, NRlcCORld, NHSO\textsubscript{2}NH\textsubscript{2}, NH\textsubscript{2}SO\textsubscript{2}Rlc, NRlcCORld, CONH\textsubscript{2}, CONRlc, CN, COOH, COORlc, CONH\textsubscript{2}, CONHRlc, CONCORlc, CONHNRlc, CONeNRlc, SO\textsubscript{2}Rlc, SO\textsubscript{3}H, S\textsubscript{0}2NRlcRlc, wherein Rlc and Rld are independently selected from C\textsubscript{1-6} alkyl, substituted C\textsubscript{1-6} alkyl, aryl, heteroaryl, C\textsubscript{2-8} cycloalkyl and heterocyclyl, or Rlc and Rld, together with the heteroatom to which they are joined, can form heterocyclyl,
S Office 12, S Office 14RlRlf, wherein Rle and Rlf are independently selected from C1. alkyl, substituted C1. alkyl, aryl, heteroaryl, C3<b>g</b>cycloalkyl and heterocyclyl, or Rle and Rlf, together with the heteroatom to which they are joined, can form heterocyclyl,
or R1 and R2, together with the N to which they are attached, can form a heteroaryl or heterocyclyl group, each of which may optionally be substituted with one or more oxygen atoms or one or more groups selected from aryl, heteroaryl, partially or fully saturated heterocyclyl, C3<b>g</b>cycloalkyl, C1. alkyl, aryl Cw alkyl, heteroaryl Ci. alkyl, heterocyclyl Cw alkyl, C3<b>g</b>cycloalkyl Ci. alkyl, C1. alkyl alkox, arlyoxy, heteroaryloxy, heterocyclyloxy, R2a, halogen, OH, OR2a, OCOR2a, SH, SR2a, SCOR2a, NH2, NO2, NHR2a, NHSO2NH2, NHSO2R2a, MR2aCOR2b, NHC(NH)NH2, NHCOR2a, NR2aR2b, COR2a, CSR2a, CN, COOH, COOR2a, CONH2, CONHOH, CONHR2a, CONHR2b, C(NO)NH2, CON2aR2b, S02R2a, S03H, S02NH2, S02NR2aR2b, wherein R2a and R2b are independently selected from Ci. alkyl, substituted Ci. alkyl, aryl, heteroaryl, C3<b>g</b>cycloalkyl and heterocyclyl, or R2a and R2b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of the heteroaryl or heterocyclyl formed by R1 and R2 together is aryl, heteroaryl, heterocyclyl, C3<b>g</b>cycloalkyl, Ci. alkyl, aryl C1. alkyl, heteroaryl Ci. alkyl, heterocyclyl Ci. alkyl, cycloalkyl Ci. alkyl, alkox, arlyoxy, heteroaryloxy, heterocyclyloxy, or a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, hydroxyl, Ci. alkyl, aryl, heteroaryl, heterocyclyl, C3<b>g</b>cycloalkyl, Ci. alkyl, arlyoxy, heteroaryloxy, heterocyclyloxy, aryl C1. alkyl, heteroaryl C1. alkyl, heterocyclyl Ci. alkyl, cycloalkyl Ci. alkyl, alkox, arlyoxy, heteroaryloxy, heterocyclyloxy, R2c, OR2c, OCOR2c, SH, SR2c, SCOR2c, NH2, NO2, NHR2c, NHSO2NH2, NHSO2R2c, NR2cCOR2d, NHC(NH)NH2, NHCOR2c, NR2cR2d, COR2c, CSR2c, CN, COOH, COOR2c, CONH2, CONHOH, CONHR2c, CON2aR2c, C(NO)NH2, CON2aR2d, S02R2c, S03H, S02NH2, S02NR2cR2d, wherein R2c and R2d are independently selected from Ci. alkyl, substituted Ci. alkyl, aryl, heteroaryl, C3<b>g</b>cycloalkyl and heterocyclyl, or R2c and R2d, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of the substituent formed by R1 and R2 together is C1. alkyl, aryl, heteroaryl, heterocyclyl, C3<b>g</b>cycloalkyl, Ci. alkyl, alkox, arlyoxy, heteroaryloxy, heterocyclyloxy, C3<b>g</b>cycloalkyl, alkox, arlyoxy, heteroaryloxy, heterocyclyloxy, aryl Ci. alkyl, heteroaryl Ci. alkyl, heterocyclyl Ci. alkyl, cycloalkyl Ci. alkyl, alkox, arlyoxy, heteroaryloxy, heterocyclyloxy, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from Cw alkyl, R2e, halogen, OH, OR2e, OCOR2e, SH, SR2e, SCOR2e, N4, N02, NHR2e, NHSO2NH2, NHSO2R2e, NHC(NH)NH2, NR2eR2f, NHCOR2e, NR2eR2f, COR2e, CSR2e, CN, COOH, COOR2e, CONH2, CONHOH, CONHR2e, CON2aR2e, C(NO)NH2, CON2aR2f, S02R2e, S03H, S02NH2, S02NR2eR2f, wherein R2e and R2f are independently selected from Ci. alkyl, substituted Ci. alkyl, aryl, heteroaryl, C3<b>g</b>cycloalkyl and heterocyclyl, or R2e and R2f, together with the heteroatom to which they are joined, can form heterocyclyl.

In certain embodiments of the process of the invention for the preparation of compounds of Formula II, and especially in the particular group of embodiments mentioned immediately above for the preparation of compounds of Formula Ila, the urea compound of Formula II has the following features:
R1 is selected from H and C_{14} alkyl.

R2 is selected from aryl, heteroaryl, heterocyclyl, C_{3-10} cycloalkyl, aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl and C_{3-10} cycloalkyl C_{1-6} alkyl, each of which may optionally be substituted with one or more groups selected from R2a, halogen, OH, OR2a, OCOR2a, SH, SR2a, SCOR2a, NH2, NHR2a, NHSO_{2}R2a, NR2aCOR2b, NH(NH)NH_{2}, NHCOR2a, NR2aR2b, COR2a, CSR2a, CN, COOH, COOR2a, CONH2, CONHOH, CONHR2a, C(NOH)NH_{2}, S_{0}R2a, S_{0}H, S_{0}NH_{2}, CONR2aR2b, S_{0}^{2}NR2aR2b, wherein R2a and R2b are independently selected from C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl, or R2a and R2b, together with the heteroatom to which they are joined, can form heterocyclyl.

wherein, when the substituent of R2 is C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl, heterocyclyl or a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from R2c, halogen, OH, OR2c, OCOR2c, SH, SR2c, SCOR2c, NH2, NHR2c, NHSO_{2}NH_{2}, NHSO_{2}R2c, NR2cCOR2d, NH(NH)NH_{2}, NHCOR2c, NR2cR2d, COR2c, CSR2c, CN, COOH, COOR2c, CONH2, CONHOH, CONHR2c, C(NOH)NH_{2}, S_{0}R2c, S_{0}H, S_{0}NH_{2}, CONR2cR2d, S_{0}^{2}NR2cR2d, wherein R2c and R2d are independently selected from C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl, or R2c and R2d, together with the heteroatom to which they are joined, can form heterocyclyl.

R5 is selected from H, R5a, halogen, OH, OR5a, OCOR5a, SH, SR5a, SCOR5a, NH2, NHR5a, NHSO_{2}NH_{2}, NHSO_{2}R5a, NR5aCOR5b, NH(NH)NH_{2}, NHCOR5a, NR5aR5b, COR5a, CSR5a, CN, COOH, COOR5a, CONH2, CONHOH, CONHR5a, C(NOH)NH_{2}, S_{0}R5a, S_{0}H, S_{0}NH_{2}, CONR5aR5b, S_{0}^{2}NR5aR5b, wherein R5a and R5b are independently selected from C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl, or R5a and R5b, together with the heteroatom to which they are joined, can form heterocyclyl.

R6 is selected from aryl, heteroaryl, heterocyclyl, C_{3-10} cycloalkyl, each of which may optionally be substituted with one or more groups selected from R6a, halogen, OH, OR6a, OCOR6a, SH, SR6a, SCOR6a, NH2, NHR6a, NHSO_{2}NH_{2}, NHSO_{2}R6a, NR6aCOR6b, NH(NH)NH_{2}, NHCOR6a, NR6aR6b, COR6a, CSR6a, CN, COOH, COOR6a, CONH2, CONHOH, CONHR6a, C(NOH)NH_{2}, S_{0}R6a, S_{0}H, S_{0}NH_{2}, CONR6aR6b, S_{0}^{2}NR6aR6b, wherein R6a and R6b are independently selected from C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl, or R6a and R6b, together with the heteroatom to which they are joined, can form heterocyclyl.

wherein, when R6 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, and

wherein, when the substituent of R6 is C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl, heterocyclyl or a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from R6c, halogen, OH, OR6c, OCOR6c, SH, SR6c, SCOR6c, NH2, NHSO_{2}NH_{2}, NHSO_{2}R6c, NR6cCOR6d, NH(NH)NH_{2}, NHCOR6c, NR6cR6d, COR6c, CSR6c, CN, COOH, COOR6c, CONH2, CONHOH, CONHR6c, C(NOH)NH_{2}, S_{0}R6c, S_{0}H, S_{0}NH_{2}, CONR6cR6d, S_{0}^{2}NR6cR6d, wherein R6c and R6d are independently selected from C_{1-6} alkyl, substituted C_{1-6}
alkyl, aryl, heteroaryl, C₃₋₈ cycloalkyl and heterocyclyl, or R₂c and R₂d, together with the heteroatom to which they are joined, can form heterocyclyl, and wherein, when the substituent of R₆ is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms.

In such embodiments, R₁ may be selected from H, methyl and ethyl, with R₂ selected from aryl, heteroaryl, heterocyclyl, and C₃₋₁ₒ cycloalkyl, each of which may be substituted or unsubstituted.

In particular, R₂ may be selected from fully saturated heterocyclyl and C₃₋₈ cycloalkyl, each of which are monocyclic and may be substituted or unsubstituted. Preferably, R₂ is an unsubstituted cyclopentyl or unsubstituted cyclohexyl.

Alternatively in such embodiments, R₂ may be a fully saturated heterocyclyl, wherein the heterocyclyl ring contains a single heteroatom, such as nitrogen or oxygen. Such heterocyclyl may be six membered, the heteroatom in the said heterocyclyl group preferably being at the 4-position relative to the position of attachment of the heterocyclyl group R₂ to the urea nitrogen. The said heteroatom at the 4-position may be a nitrogen heteroatom which is substituted with a group selected from CN, CONH₂, C(NOH)NH₂, S0₂-C₄₋₆ alkyl, S0₂-aryl, CO-heteroaryl, CO-C₁₄ alkyl, COO-C₁₄ alkyl, C₁₄ alkyl, aryl C₁₃ alkyl, heteroaryl C₁₃ alkyl, heterocyclyl C₁₃ alkyl, aryl, heteroaryl, and heterocyclyl, wherein the C₁₄ alkyl may optionally be substituted with OH, CN, COOH, the S0₂-aryl may optionally be substituted with a C₄₋₆ alkyl or C₁₄ haloalkyl, the CO-heteroaryl may optionally be substituted with a heteroaryl or halogen, the heteroaryl C₁₃ alkyl may optionally be substituted with COO-C₁₃ alkyl, and the heteroaryl may optionally be substituted with one or more halogens. In certain such embodiments, the said nitrogen heteroatom is substituted with phenyl C₁₃ alkyl.

In particular embodiments, and especially in the particular group of embodiments mentioned immediately above for the preparation of compounds of Formula Ila, R₆ is selected from monocyclic aryl, monocyclic heteroaryl, and heterocyclyl, each of which may be substituted or unsubstituted. In such embodiments, R₆ may be a substituted aryl, wherein said aryl is substituted with one or more groups selected from halogen, R₆a, OH, OR₆a, NH₂, NO₂, NH(NH)NH₂, NHR₆a, NRR₆aR₆b, C(NOH)NH₂, COR₆a, COOH, COOR₆a, CONH₂, CONHOH, S0₂R₆a, S0₂NRR₆aR₆b, wherein R₆a and R₆b are independently selected from C₁₋₆ alkyl, substituted C₁₋₆ alkyl, aryl, heteroaryl, C₃₋₈ cycloalkyl and heterocyclyl,

wherein, when the substituent of R₆ is C₁₋₆ alkyl, substituted C₁₋₆ alkyl, aryl, heteroaryl, C₃₋₈ cycloalkyl, heterocyclyl or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from 0R₆c, OH, and CONH₂, wherein R₆c is selected from C₁₋₆ alkyl, substituted C₁₋₆ alkyl, aryl, heteroaryl, C₃₋₈ cycloalkyl and heterocyclyl, and wherein, when the substituent of R₆ is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms. In particular, R₆ may be a substituted aryl which is substituted with one or more groups selected from halogen, OH, C₁₋₆ alkoxy, CONH₂, C(NOH)NH₂, CONHOH, S0₂-C₁₋₆ alkyl, heterocyclyl, and aryl, wherein the heterocyclyl may optionally be substituted with an oxygen atom and the aryl may optionally be substituted with CONH₂.
In alternative embodiments, R6 is a heterocycl which is substituted with an oxygen atom. In yet further embodiments, R6 is a monocyclic heteroaryl (such as pyridyl) which is substituted with an oxygen atom (i.e. N-oxidopyridyl).

In preferred embodiments, Hal in the carbamoyl halide used in the process of the invention represents CI.

In preferred embodiments of the process of the invention, both R1 and R2 in the carbamoyl halide are other than Hal.

In particular embodiments, including in the particular group of embodiments mentioned immediately above for the preparation of compounds of Formula IIa, R1 is C1-3 alkyl, preferably C1-10 alkyl, more preferably C3-6 alkyl, such as methyl. In particular embodiments, the said alkyl is unsubstituted.

In certain embodiments, including in the particular group of embodiments mentioned immediately above for the preparation of compounds of Formula IIa, R2 is C3-10 cycloalkyl, preferably C3-8 cycloalkyl, such as cyclohexyl. In particular embodiments, the said cycloalkyl is unsubstituted.

In particular embodiments, including in the particular group of embodiments mentioned immediately above for the preparation of compounds of Formula IIa, R5 is H. In certain embodiments, including in the particular group of embodiments mentioned immediately above for the preparation of compounds of Formula IIa, R6 is heteroaryl. Said heteroaryl R6 may be six-membered. For example, R6 may be pyridyl, such as 2-pyridyl, 3-pyridyl or 4-pyridyl (and particularly 3-pyridyl). In such embodiments, the urea of Formula II may be subjected to a further step of N-oxidation of the pyridine (or other heteroaryl) R6. In particular, the N-oxidation may be conducted using a peroxyacid, such as peracetic acid.

In a preferred embodiment of the present invention, the process of the invention is used for the preparation of 3-(1-(cyclohexyl(methyl))carbamoyl-1H-imidazol-4-yl)pyridine 1-oxide (compound A). In another embodiment, the process of the invention is used for the preparation of 3-cyclohexyl-N-methyl-4-(pyridin-3-yl)-1H-imidazole-1-carboxamide.

In particular embodiments of the process of the invention, the carbamoyl halide is a carbamoyl chloride, prepared by subjecting an amine R1R2NH to carbamoylation using a phosgene reagent, such as triphosgene.

Such a carbamoylation step may be conducted in dichloromethane, in the presence of a base, such as a carbonate salt (e.g. Na).

In certain embodiments, the carbamoyl chloride is not isolated before addition to the intermediate of Formula II’ or Formula II’. It will be appreciated that the intermediate of Formula II’ or Formula II’ is preferably presented in solution in pyridine in these embodiments. In such embodiments, a ‘telescoped’ or one-pot process may be achieved, which can lead to further enhancements in overall urea product yield.

In particular embodiments of the process of the invention, the intermediate of Formula II’ has a structure according to Formula i;
wherein $R_5$ and $R_6$ are as defined above.

In such embodiments, the intermediate of Formula i may in particular be prepared from a mercaptoimidazole having the structure:

![Formula i](image)

wherein $R_5$ and $R_6$ are as defined above, or an imidazolethione tautomer thereof, using Raney nickel or a nitrate oxidation step (e.g. using a sodium nitrite/nitric acid mixture). An analogous desulphurisation step is described, for example, in Ganellin et al. ((1995), J. Med. Chem. 38, 17) and La Mattina ((1983) J. Heterocyclic Chem. 20, 533). This step may, for example, be conducted in water.

The intermediate of Formula i, especially when produced as described above may, in preferred embodiments, be presented in solution in a solvent, in particular an organic solvent. The solvent may then be chosen so as to enhance the downstream transformation of the intermediate. Thus, in a preferred embodiment, the intermediate of Formula i is transferred to a solution in pyridine, such that it may more readily be used in the process described above. An aspect of the present invention therefore provides an intermediate of Formula i in solution in an organic solvent, wherein Formula i is as defined above. Appropriate solvents include pyridine, isopropyl alcohol, 2-methyltetrahydrofuran, dichloromethane, propionitrile or trifluorotoluene (or mixtures of these solvents, optionally in combination with other common organic solvents used in chemical synthesis).

In turn, where the mercaptoimidazole or imidazolethione tautomer thereof has $R_5$ as $H$, it may be prepared by treatment of an aminoketone of Formula ii:

![Formula ii](image)

wherein $R_6$ is as defined above, or a salt thereof, with thiocyanate. The thiocyanate may, for example, be an isothiocyanate, such as potassium isothiocyanate. This step may, for example, be conducted in water.
In an alternative embodiment, the intermediate of Formula i, wherein R5 is H, may be prepared by formylation of an aminoketone of Formula ii:

\[
\begin{align*}
\text{O} & \quad \text{NH}_2 \\
\text{R}_6
\end{align*}
\]

Formula ii

wherein R6 is as defined above, or a salt thereof, followed by reaction of the -NHCHO derivative so formed with an ammonium salt. The formylation may be conducted using an appropriate formyl anhydride, such as aceticformic anhydride, and may for example be conducted in a non-polar solvent such as dichloromethane. The ammonium salt may be organic, such as ammonium acetate, and this reaction may be conducted, for example, in a non-polar solvent such as toluene. This reaction may be aided by addition of para-toluene-sulphonic acid, such that a tosylate salt of the intermediate of Formula i is obtained.

In embodiments, the aminoketone or salt of Formula ii is prepared by acid hydrolysis of an azirine derivative of formula iii

\[
\begin{align*}
\text{R}_6 & \quad \text{N} \\
\end{align*}
\]

Formula iii

wherein R6 is as defined in claim 33. The acid hydrolysis may, for example, be conducted using concentrated HCl, for example in an alcohol/water solvent (such as ethanol/water). The azirine derivative may have reduced stability, and should only be presented in solution, preferably an acidic solution.

The azirine derivative of formula iii may be prepared by subjecting a ketoxime tosylate derivative of formula iv:

\[
\begin{align*}
\text{\text{\_\_O\text{Ts}}} & \quad \text{N} \\
\text{R}_6
\end{align*}
\]

Formula iv

wherein R6 is as defined above and OTs represents toluenesulphonate, to treatment with a base. The base may be organic or inorganic. The organic base may, for example, be an alkoxide salt, such as potassium or sodium t-butoxide, ethoxide or methoxide. Suitable inorganic bases include potassium phosphate and potassium carbonate.

The treatment with base may for instance be conducted in an alcoholic solvent, such as t-butanol or methanol, or in an ether solvent such as methyl-t-butyl ether. The inorganic bases may, for example, be presented in dichloromethane.
It will be appreciated by one skilled in the art that the sequence of steps from the ketoxime tosylate to the aminoketone is a form of the Neber rearrangement. Such a reaction sequence is known, for example from Ganellin et al. (1995) and La Martina (1983) referred to above.

In certain embodiments, the ketoxime tosylate of Formula iv is prepared from the corresponding ketoxime: R6C(=N-OH)CH, wherein R6 is as defined above, by reaction with tosyl chloride. Such a reaction may be conducted, for example, using pyridine as solvent.

In embodiments of the process of the invention which include the steps of preparation of the ketoxime tosylate (Formula iv) from the corresponding ketoxime, preparation of the aminoketone (Formula ii) from the azirine derivative, it is preferred that R6 represents an aryl or heteroaryl group, as defined herein.

In certain embodiments, the ketoxime R6C(=N-OH)CH, is prepared from the corresponding acetyl derivative of R6: R6-C(=O)CH3, wherein R6 is as defined above, by reaction thereof with hydroxylamine. This reaction may take place, for example, in an alcoholic solvent such as methanol (optionally with water). An acetate salt, such as sodium acetate, is preferably also used.

In an alternative embodiment, the intermediate of Formula i may be prepared from the acetyl derivative of R6 (R6-C(=O)CH3) by bromination (for example using HBr, optionally in acetic acid) to R6-C(=O)CH2Br, followed by treatment with diformylamide (or its sodium salt) to yield the di-formyl derivative of the aminoketone of Formula ii (i.e. the -N(CHO)(CHO) derivative). This may be readily converted to the formyl derivative, which may then be converted to the intermediate of Formula i by reaction with an ammonium salt, as described above.

As a further alternative, the bromoacetyl derivative R6-C(=O)CH2Br may be treated with an aminating reagent (such as hexamethylenetetramine) to produce the aminoketone of Formula ii.

The present invention also provides a process for preparing an intermediate of Formula i, the process comprising the reaction of an aminoketone of Formula ii, as defined above, or a salt thereof, with thiocyanate, to produce the mercaptoimidazole or imidazolethione tautomer thereof defined above, then the use of Raney nickel or a nitrate oxidation step (e.g. using a sodium nitrite/nitric acid mixture), so as to yield the intermediate of Formula i in solution in a solvent, such as an organic solvent. Preferred solvents include pyridine, IPA (isopropyl alcohol), 2-methyltetrahydrofuran, dichloromethane, propionitrile or trifluorotoluene (or mixtures thereof, optionally in combination with other organic solvents commonly used in chemical synthesis). If the intermediate of Formula i is produced in an organic solvent other than pyridine, it is preferred that a step of solvent exchange is then carried out, such that a pyridine solution is produced.

In a second aspect, the present invention provides a process for the preparation of an aminoketone of Formula ii:

![Formula ii](image)
or a salt thereof, wherein R₆ is as defined above, the process comprising the tosylation of the corresponding ketoxime: R₆C(=N-OH)CH₃, using tosyl chloride in the presence of a first base and in a solvent comprising a Cᵢ₋ₓ alcohol, followed by treatment of the resulting ketoxime tosylate, without isolation, with a second base in a solvent comprising a Cₓ alcohol to yield the corresponding azirine derivative of Formula iii:

![Formula iii](image)

followed by acid hydrolysis of the azirine derivative to yield the aminoketone or salt of Formula ii.

According to the second aspect, the first base, employed during the tosylation step, is preferably a butoxide salt, such as sodium t-butoxide. The solvent used in the tosylation step preferably comprises butanol, such as t-butanol, optionally together with methyl-t-butyl ether. In a preferred embodiment, the base and alcoholic solvent are added to the ketoxime, followed by addition of the tosyl chloride in portions. This approach reduces the potentially disadvantageous exothermicity of the tosylation step. The second base, employed during the production of the azirine derivative, may in particular be a methoxide salt, such as sodium methoxide. This weaker base is more appropriate for the azirine formation. Advantageously, the solvent used during the production of the azirine derivative may be methanol.

The process according to the second aspect is suitable for a 'telescoped' or One-pot approach to synthesis of the aminoketone of Formula ii from the ketoxime. In such a process, there is no need to isolate the ketoxime tosylate before subjecting it to a Neber rearrangement. Such an approach can lead to an improvement in yield of the aminoketone, and a reduction in the overall reaction time and utilisation of reactor capacity. A yield of aminoketone of 90% has been obtained via this process. The non-telescoped process might typically be expected to yield aminoketone at around 70-85%.

According to the second aspect, the resulting aminoketone of Formula ii may be used to prepare an intermediate of Formula i as defined above, by means of the steps described above.

In a third aspect, there is provided a process for preparing an aminoketone of Formula ii:

![Formula ii](image)

or a salt thereof, wherein R₆ is as defined above, the process comprising the reaction of the corresponding acetyl derivative of R₆: R₆-CH(=0)CH₃, with hydroxylamine in a solvent consisting essentially of pyridine, followed by tosylation of the resulting ketoxime, without isolation thereof, using tosyl chloride, followed by treatment of the
resulting ketoxime tosylate with a base in a solvent comprising a Ci. alcohol, to produce the corresponding azirine derivative of Formula iii:

\[
\begin{align*}
R_6 & \quad N \\
\end{align*}
\]

Formula iii

followed by acid hydrolysis of the azirine derivative to yield the aminoketone or salt of Formula ii.

In the third aspect, the reaction between the acetyl derivative and hydroxylamine is conducted in a solvent consisting essentially of pyridine (the meaning of which is the same as defined above in connection with the first aspect). By employing pyridine as solvent (e.g. instead of an alcohol), the resulting ketoxime is obtained in a pyridine solution which can be used directly in the subsequent step (tosylation). This avoids the need for an isolation step (filtration and drying etc.), thereby allowing a telescoped synthesis of the aminoketone and decreasing process time and cost.

Pyridinium salts (e.g. pyridinium HCl when hydroxylamine HCl is used) present in the mixture obtained from the ketoxime preparation step have no detrimental effect on the next steps.

The preferred features of the first aspect, particularly in terms of the definition of R6, are equally preferred in the third aspect. Thus, R6 is in particular embodiments is an optionally substituted aryl or heteroaryl group.

In certain embodiments of the first, second and third aspects, the base used in the conversion of the ketoxime tosylate (Formula iv) to the azirine (Formula iii) comprises 1,8-diazabicyclo[5.4.0]undec-7-ene (hereinafter referred to as DBU).

In certain embodiments of the processes of the invention, when the ketoxime tosylate is converted, via the azirine, to the aminoketone, inorganic salt formation is encountered. Such inorganic salts may, for example, arise from the alkali metal alkoxide used for the azirine formation and the HCl used for hydrolysis of the azirine. These inorganic salts can pose problems when trying to isolate the aminoketone by precipitation from an organic solvent such as methanol or ethanol. The inorganic salts have low solubility in the said organic solvent, and hence can be retained on the filter with the aminoketone. Surprisingly, by using DBU, efficient conversion of the ketoxime tosylate can be achieved, yet the salts of DBU which are produced are soluble in e.g. methanol or ethanol and hence can be washed from the aminoketone product. DBU thus leads to a process which yields a high purity aminoketone product, but without the need for a precipitation/filtration step to remove inorganic salt impurities (e.g. by employing MTBE). Other organic bases were tested and were found not to be capable of conversion of the ketoxime tosylate to a useful degree.

In a fourth aspect, there is provided a process for preparing an azirine derivative of Formula iii
Formula iii

wherein R6 is as defined above, the process comprising subjecting a ketoxime tosylate of Formula iv:

\[
\begin{array}{c}
\text{OTs} \\
\text{R}_6
\end{array}
\]

Formula iv

to treatment with a base, wherein the base comprises DBU.

The advantages of using DBU for the conversion of the ketoxime tosylate to the azirine are discussed above in connection with the preceding aspects. In particular, the use of DBU avoids the production of inorganic salts as by-products which have to be removed from downstream products derived from the azirine.

In an embodiment of the fourth aspect, there is provided a process for preparing an aminoketone of Formula ii

\[
\begin{array}{c}
\text{NH}_2 \\
\text{R}_6
\end{array}
\]

Formula ii

wherein an azirine derivative of Formula iii prepared according to the fourth aspect is subjected to acid hydrolysis.

In another aspect the present invention provides a substituted urea of Formula II or Formula I as defined above, or a pharmaceutically acceptable salt or ester thereof, obtained or obtainable by the processes of the invention as defined above.

Based on the processes of the invention, a number of novel intermediates may be formed which are of use in the synthesis of substituted ureas. Such novel intermediates are also an aspect of the present invention.

In another aspect of the present invention, there is provided a substituted urea compound of Formula II or Formula I as defined above, obtained or obtainable by the process of the first aspect of the invention or by a process in which the process of any of the second, third or fourth aspects is comprised.

In a particular embodiment of this aspect, the substituted urea compound which is obtained or obtainable is 3-(1-(cyclohexyl(methyl)carbamoyl)-1H-imidazol-4-yl)pyridine 1-oxide (compound A). In another embodiment, the substituted urea compound which is obtained or obtainable is N-cyclohexyl-N-methyl-4-(pyridin-3yl)-1H-imidazole-1-carboxamide.
The present invention will now be described in more detail by way of example only, with reference to the appended Figures, as follows:

Figure 1, which shows a $^1$H NMR spectrum of a ketoxxime R6C(=N-OH)CH$_3$ used in the process of the invention;

Figure 2, which shows a $^3$C NMR spectrum of a ketoxxime R6C(=N-OH)CH$_3$ used in the process of the invention (peaks at 151.2, 149.5, 146.7, 133, 132.6, 123.5, 11.4ppm);

Figure 3, which shows a $^1$H NMR spectrum of a ketoxxime tosylate corresponding to the ketoxxime of Figures 1 and 2;

Figure 4, which shows a $^3$C NMR spectrum of a ketoxxime tosylate corresponding to the ketoxxime of Figures 1 and 2 (peaks at 162.8, 151.9, 147.5, 145.7, 134.6, 131.7, 130.1, 129.3, 128.6, 123.9, 21.2, 14ppm):

Figure 5, which shows a $^1$H NMR spectrum of an aminoketone of Formula ii, produced from the ketoxxime tosylate of Figures 3 and 4;

Figure 6, which shows a $^3$C NMR spectrum of an aminoketone of Formula ii, produced from the ketoxxime tosylate of Figures 3 and 4 (peaks at 192.2, 152.4, 147.8, 137.9, 130, 125, 45, lppm);

Figure 7, which shows a $^1$H NMR spectrum of a mercaptoimidazole produced from the aminoketone of Figures 5 and 6;

Figure 8, which shows a $^3$C NMR spectrum of a mercaptoimidazole produced from the aminoketone of Figures 5 and 6 (peaks at 162.3, 148.1, 145.3, 130.9, 126.1, 124.5, 123.8, 113.5ppm);

Figure 9, which shows a $^1$H NMR spectrum of an intermediate of Formula i produced from the mercaptoimidazole of Figures 7 and 8;

Figure 10, which shows a $^1$C NMR spectrum of an intermediate of Formula i produced from the mercaptoimidazole of Figures 7 and 8 (peaks at 147.1, 145.8, 136.6, 131.3, 130.4, 123.7, 113.9ppm);

Figure 11, which shows $^1$H (a) and $^3$C (b) NMR spectra of a compound of Formula II (N-cyclohexyl-N-methyl-4-(pyridin-3yl)-IH-imidazole-I-carboxamide) (peaks at 151.0, 148.5, 146.7, 139.2, 137.3, 132.4, 129.0, 123.6, 113.9, 57.6, 31.4, 30.0, 25.4, 25.2) prepared by means of the process of the invention; and

Figure 12, which shows $^1$H (a) and $^3$C (b) NMR spectra of an imidazolylpyridine phenyl carbamate derivative (peaks at 149.7, 149.0, 146.9, 146.9, 140.8, 137.9, 132.7, 129.9, 128.4, 127.2, 123.6, 120.9, 112.8) which can be used to prepare a compound of Formula II.

The Examples which follow illustrate the processes of the present invention by reference to synthesis of the compound N-cyclohexyl-N-methyl-4-(pyridin-3yl)-IH-imidazole-I-carboxamide and its intermediates. NMR
spectra of the various intermediates and products were recorded at 20°C, on a Bruker 400 MHz DPX spectrometer with solvent (DMSO) used as internal standard.

Example 1. Preparation of 2-amino-1-pyridin-3-yl-ethanone.2HCl

1.1 Preparation of 1-pyridin-3-yl-ethanone oxime

3-Acetylpyridine (1.0wt, 1.00eq) is charged into the reactor followed by MeOH (6.0 vol). Hydroxylamine hydrochloride (0.69wt, 1.20 eq) is charged into the reactor. Heat the reaction mixture to reflux and stir for not less than one hour. Charge Sodium Acetate (1.09wt, 1.61 eq) and stir at reflux for not less than one hour. Cool the mixture to 10°C in approximately 3 hours and stir at that temperature for not less than one hour. The suspension is filtered and the reactor/cake washed with cold MeOH (1.0 vol). The resultant filtrate is distilled under vacuum at not more than 60°C to ~1.5vol. Water (6.0 vol) is added and the temperature adjusted to 10°C. After stirring the slurry at 10°C for not less than two hours, the suspension is filtered and the cake washed with cold water (2.0 vol). The cake, comprising the pyridyl oxime, is dried under vacuum.

The purity of the product was ascertained by HPLC, with identity confirmable by NMR (see Figures 1 and 2).

The yield was consistently around 88-95% in several production runs.

1.2 Preparation of 1-pyridin-3-yl-ethanone oxime O-tosylate

Pyridyl Oxime (1.0wt, 1.00eq) is charged into the reactor followed by Pyridine (3.7 vol). Cool the reaction mixture to 5°C. Add slowly tosyl chloride (1.54wt, 1.10eq). Stir at 25°C until reaction complete. Charge the reaction mixture, maintaining the temperature below 10°C, into distilled water (23.0 vol) at 0°C. Stir the slurry at 10°C for not less than two hours. The suspension is filtered and the reactor/cake washed with cold water (5.0 vol). The cake, comprising the ketoxime tosylate, is dried under vacuum at 40°C.

The purity of the product was ascertained by HPLC, with identity confirmable by NMR (see Figures 3 and 4).

The yield was consistently around 87-95% in several production runs.

1.3 Preparation of 2-amino-1-pyridin-3-yl-ethanone.2HCl

To a solution of Potassium tert-Butoxide (0.448wt, 1.00eq) in Methanol (4.5vol) was charged slowly a solution of Ketoxxime Tosylate (1.0wt, 1.00eq) in Methanol (4.5vol) maintaining the temperature below 10°C. Heat the reaction mixture to 25°C. Stir at 25°C for not less than two hours. Charge MTBE (3.0vol) to the reaction mixture. Cool the mixture to 10°C, stir for 1 hour and filter the suspension while transferring the solution to a different
reactor. Wash the cake and reactor with MTBE (0.5vol) and combine with the filtrate. Charge slowly to the organic layer a solution of 4N HCl (2.58 vol) maintaining the temperature below 10°C. Concentrate the solution under vacuum until ~1.5vol.

For conversion of the resulting azirine derivative, charge cone HCl to the slurry and stir at 80°C for 3 hours. Concentrate under vacuum until ~1vol. Charge into the reactor distilled water (1.0 vol) and heat to 50°C. Filter through activated charcoal and wash with distilled water (1.0 vol). Concentrate the aqueous layer under vacuum until -1.0 vol. Charge Ethanol (5.0 vol) and continue concentration until -1.0vol. Charge Ethanol (10.0 vol) and heat to reflux. Stir at reflux for 0.5 hour and cool to 5°C. Stir the slurry at 5°C for not less than two hours. The suspension is filtered and the reactor/cake washed with cold Ethanol (1.0 vol). The cake, comprising the aminoketone, is dried under vacuum.

The purity of the product was ascertained by HPLC, with identity confirmable by NMR (see Figures 5 and 6). The yield was consistently around 77-85% in several production runs.

Example 2. Preparation of 2-amino-1-pyridin-3-yl-ethanone,2HCl from ketoxime via telescoped process of the invention

This process demonstrates that tosylation of the ketoxime may be performed in alcohol, thereby avoiding the isolation of the tosylate before driving the reaction towards the Neber rearrangement.

A run of the reaction was performed in methanol using 2.2, equiv of t.BuOK to advance not only the completion of the tosylation but, due to the excess, also to take part in the azirine formation. The tosylate formed and it reacted toward the azirine.

In another run, t.BuOH was used as solvent. Tosylation was driven to completion and the following Neber rearrangement was successful to give the expected aminoketone.

At a larger scale replication of this process, the sequence of addition of the reactant and the nature of the base becomes more important. It was determined that t.BuONa/MTBE in t.BuOH is efficient for tosylation of the oxime but is less favourable for the Neber rearrangement. Therefore the Neber rearrangement is preferably conducted in a MeOH/MeONa system.

A preferable approach for a one-pot tosylation and Neber rearrangement according to the present invention is to conduct the tosylation in t.BuOH using t.BuONa/MTBE so that the oxime sodium salt is formed initially, to which the tosyl chloride is added in portions to maintain the temperature around 20-22 degC. The Neber reaction then preferably uses NaOMe/MeOH as base. Upon subsequent hydrolysis of the azirine, an isolated yield of 90% of aminoketone has been achieved without the isolation of the intermediate ketoxime tosylate.
Example 3. Preparation of 3-(1H-imidazol-4-yl)-pyridine, an intermediate of Formula i

3.1 Preparation of mercaptoimidazole/imidazolethione intermediate

The aminoketone 2-amino-1-pyridin-3-yl-ethanone.2HCl (1.0 wt; 1.00eq) is charged into the reactor followed by deionized water (3.0 vol). Potassium Thiocyanate (0.535wt; 1.15 eq) is charged into the reactor. Heat the reaction mixture to 90°C and stir for not less than 30 minutes. Cool the mixture to 15°C and stir at that temperature for not less than 30 minutes. The suspension is filtered and the reactor/cake washed with cold deionized water (1.0 vol). The wet cake is added portion wise to a solution of sodium bicarbonate (0.563 wt; 1.40eq) in deionized water (7.0 vol) at 30°C. The suspension is stirred at 30°C until no gas evolution is observed and the slurry is cooled to 15°C. After stirring at 15°C for 1 hour, the suspension is filtered and the reactor/cake washed with deionized water (2.0 vol). The cake, comprising the mercaptoimidazole 4-(pyridin3-yl)-1H-imidazole-2(3H)-thione, is dried under vacuum.

The purity of the product was ascertained by HPLC, with identity confirmable by NMR (see Figures 7 and 8). The yield was consistently around 71-79% in several production runs.

3.2 Preparation of 3-(1H-imidazol-4-yl)-pyridine

4-(Pyridin-3-yl)-1H-imidazole-2(3H)-thione from 3.1 above (1.0 wt; 1.00eq) is charged into the reactor followed by deionized water (8 vol). Sodium nitrite (0.58wt; 1.5 eq) is charged into the reactor. Cool the reaction mixture to 5°C. Add slowly 65% Nitric Acid (1.97 vol; 5eq). The lines and reactor are rinsed with deionized water (2 vol). Heat the reaction mixture to 35°C during one hour and stir for not less than 6 hours maintaining the temperature. In some embodiments, the reaction mixture may be heated to 85°C (e.g. over 3 hours, with stirring for a further 2 hours). Cool the mixture to 15°C and charge slowly Sodium Carbonate (2.0 wt) (an alternative base is, for example, NaOH). The solution is then heated to 30°C and saturated with Sodium Chloride (2 wt). To the aqueous layer is charged Isopropanol (4 vol). After stirring for not less than 30 minutes (during which, in some embodiments, the temperature may be increased, for example to 55/60°C), phases are separated, to the aqueous layer Sodium Chloride (2 wt) is charged and the extraction of the aqueous layer is repeated 1 time with IPA (4 vol) and 1 time with IPA (2 vol) (an alternative solvent is, for example, 2-methyl tetrahydrofuran). The mixture is concentrated under vacuum to 2 vol.

The purity of the product was ascertained by HPLC, with identity confirmable by NMR (see Figures 9 and 10). The yield was consistently around 84-92% in several production runs.

An important feature of this part of the process is that it allows the production of an intermediate of Formula i in solution in a chosen solvent. Thus, it is possible to isolate the intermediate of Formula i in pyridine so that it may be readily be used in the process of the first aspect of the invention, or in an alternative solvent (IPA in the present example) which may readily be exchanged with pyridine, as described below, or mixed with sufficient pyridine to provide the required solvent 'consisting essentially of pyridine', as defined in accordance with the present invention. Particular alternative solvents which may be mixed with pyridine in this manner include 2-methyltetrahydrofuran, dichloromethane, propionitrile and trifluorotoluene.
Example 4. Preparation of (N-cyclohexyl-N-methyl-4-(pyridin-3yl)-1H-imidazole-1-carboxamide), a compound of Formula II

4.1 Carbamoyl chloride formation
To a solution of Triphosgene (0.80wt; 0.48eq) in DCM (6.0 vol) at 10°C was slowly added a solution of N-Methylcyclohexylamine (0.83wt; 1.3eq) in DCM (3.2 vol). Sodium carbonate (1.55wt; 2.6 eq) was charged and the reaction mixture heated to 25°C. After 3 hours the suspension is filtered and the reactor/cake washed with DCM (1 vol) to produce a solution of N-cyclohexyl-N-methyl carbamoyl chloride.

4.2 Urea formation
The IPA solution of imidazolylpyridine from 3.2 is concentrated under vacuum to 2 vol. Pyridine is charged (4 vol) and concentration continued until 2 vol. The solution is filtered and the concentration is repeated two times more until 3 vol. To the resulting pyridine solution of the imidazolylpyridine (3.0vol; 1.00eq) at 25°C is charged the DCM solution of the carbamoyl chloride from 4.1 above. The mixture is heated to 50°C while distilling. After 30 minutes at 50°C, the reaction mixture is heated to 90°C in 1 hour continuing the distillation. The mixture is stirred at 90°C for not less than 1 hour. Cool the mixture to 45°C in 3 hours. To the suspension is then added Isopropanol (5.2 vol) and after 30 minutes stirring at 45°C the mixture is cooled to 0°C in 2 hours. After stirring at 0°C for not less than 2 hours the suspension is filtered and the reactor/cake washed with cold Isopropanol (1.5 vol), deionized water (10.0 vol) and cold Isopropanol (1.5 vol). The cake, comprising the compound of Formula II, is dried under vacuum.

The purity of the product was ascertained by HPLC, with identity confirmable by NMR (see Figure 11). The yield was consistently around 86-92% in several production runs.

The urea described in this Example has been produced by the process of the invention in batches of more than 12kg, with purity of 99.8% (by HPLC). At kg production levels, the overall yield of urea (based on starting from the aminoketone and the R1R2NH amine) is up to approximately 40-60%, and may be improved further. In terms of process efficiency, the use of the process of the invention has the potential to significantly reduce the cost of production of the ureas of Formulae I and II, for example by around 75%.

Example 5. 3-(1-(cyclohexyl(methyl)carbamoyl-1H-imidazol-4-yl)pyridine 1-oxide (compound A)
To a solution of N-cyclohexyl-N-methyl-4-(pyridin-3-yl)-1H-imidazole-1-carboxamide in dichloromethane at 25°C was added peracetic acid (38%; the concentration is not critical, and may be varied) in a single portion. The reaction mixture was then maintained at 25°C for at least 20 h, whereupon the reaction was washed four times with water (in some embodiments, the water for the extraction step may be supplemented with a small amount (e.g. 1%) of acetic acid, which helps to promote product solubility in the DCM). The dichloromethane solution was then filtered prior to diluting with 2-propanol. Dichloromethane (50%) was then distilled off under atmospheric pressure, whereupon, 2-propanol was charged at the same rate as the distillate was collected. The distillation was continued until >90% of the dichloromethane was collected. The resulting suspension was then cooled to 20°C and aged for at least 30 min. prior to cooling to 0°C and aging for a further 60 min. The reaction mixture was then filtered and the product washed with additional 2-propanol, before drying at 50°C under vacuum to afford the title compound as an off-white crystalline solid.

The purity of the product was ascertained by HPLC, with identity confirmable by NMR. The yield was consistently >80% in several production runs.

Example 6. Preparation of (N-cyclohexyl-N-methyl-4-(pyridin-3yl)-1H-imidazole-1-carboxamide) via phenyl carbamate intermediate (Reference Example)

6.1 Preparation of phenyl carbamate

3-(1H-Imidazol-4-yl)-pyridine (1) was reacted with phenyl chloroformate (7) in hexane (0.1 mmol), in DCM (0.1 mmol), or preferably in saturated NaHCO₃ (0.1 mmol). Upscale to 10 mmol revealed that phenyl chloroformate can hydrolyse in aqueous NaHCO₃ and 1.5 equiv excess was required to reach improved yield. In toluene (0.689 mmol) the product was isolated in reasonable yield. The structure was confirmed by NMR (Figure 12) and LCMS (96% purity). Solid NaHCO₃ in THF improved the yield to 99.1% (10 mmol).

Using 2-propanol without any additional base (0.68 mmol) surprisingly resulted in complete conversion of 3-(1H-imidazol-4-yl)-pyridine (1) to the phenyl carbamate HCl salt (8) in 93.2%. Scale up to 10 mmol gave similar results (93.6% yield; 25 mmol 94.9%).
In order to check the base's melting point the phenyl carbamate base was synthesised from the 3-(1H-imidazol-4-yl)-pyridine (1) and diphenyl carbonate (9) in refluxing 2-Me THF (melting point: 153-155°C). Similar results were obtained when using toluene (1 mmol), xylene (1 mmol).

A reaction path is shown below. In the reaction of phenyl carbamate as HCl (8) or base (2) conditions were sought wherein the formation of 3-(1H-imidazol-4-yl)-pyridine (1; route a) is significantly lessened or suppressed.
Compound 8 was reacted with 10 in the presence of triethylamine in THF at 25°C (7.763 mmol; 38.9%). The same reaction can be carried out using DCM as solvent, in THF:water 1:1, in THF:sat aq. NaHCO3, in AcOH/H2O creating a buffered environment; in THF using KI as catalyst, in THF and activated charcoal, in 2-propanol, in THF/MgO system, in MeCN/MgCl2 system, in MeCN/ZnCl2 system, in DCM/THF/ZnCl2 system, in DCM/ZnCl2 system, in toluene/TEA, in THF/CuBr system, in trimethyl orthoformate as solvent, in THF/KH2PO4 system, in toluene/sat aq. NaHCO3 system, in THF/DBU system, in THF/EtMgCl system.

Example 7. Preparation of aminoketone via alternative telescoped route and using DBU

![Chemical structure diagram]

The use of solvents other than pyridine (e.g. methanol) for the first step means that the ketoxime may need to be isolated before tosylation can take place (the latter reaction being particularly favourable in pyridine as solvent). The use of pyridine as solvent for the first step works well, with pyridine acting as a scavenger of HCl. Since the oxime formation generates 1 eq. of water, this should be removed (azeotropic distillation) prior to adding TsCl.

In a typical example, 10g of acetylpyridine is mixed with 60ml of pyridine and the mixture os cooled to 5 °C. Hydroxylamine HCl (6.02g) is added and the mixture heated to 65 °C. After distillation under vacuum, the mixture is cooled to 0 °C. Tosyl Cl (18.9g) is added and the mixture is stirred overnight. The mixture is added to ice/water and stirred. The solid ketoxime tosylate product is filtered and washed with water, then dried under vacuum to obtain a light pink solid (19.6g, molar yield 82%). Identity was confirmed by NMR.

For the next step, Neber rearrangement and production of aminoketone, a typical example is as follows. The pyridine ketoxime tosylate (18.8g) in MeOH (150ml) are charged. DBU (11.6ml) is added, maintaining the temperature below 20 °C. The mixture is stirred at 25 °C until the reaction is complete (orange solution). The reaction is cooled to 0-5 °C and quenched with 4N HCl (48.6 ml), maintaining temperature below 20 °C. The mixture is concentrated under vacuum and concentrated HCl is added (44.7g). The mixture is stirred at 85 °C for 2 hours. The mixture is concentrated under vacuum and water (37.6ml) is added. After decoloriation (charcoal), and filtration, the solution is concentrated and ethanol is charged, with stirring at 65 °C for 1 hour. After cooling to room temperature, the solid aminoketone product is filtered and washed with ethanol, then dried under vacuum. A light yellow solid (76 % molar yield) was obtained. Identity was confirmed by NMR.

Example 8. Larger-scale production of aminoketone

The primary objective of this Example is to manufacture and demonstrate a cost-effective pilot scale process for 100kg Aminoketone Dihydrochloride.

Step 1:
Batch size: ~50kg of 3-acetylpyridine
Expected quantity range: 89 kg to 98 kg of Ketoxime Tosylate
Expected molar yield: 75 - 82%
Expected quality range: NLT (Not Lower Than) 92% by NMR

8.1.1 Process Outline

3-Acetylpyridine (1.0wt, 1.00eq) and pyridine (6vol) are mixed together and cooled to 5°C. Hydroxylamine hydrochloride (0.60wt, 1.05eq) is slowly added and the mixture heated to 65°C. After 1.5 hour at 65°C the mixture is concentrated under vacuum until 2vol of distillates are collected. The mixture is cooled to 0°C and tosyl chloride (1.89wt, 1.20eq) is added in portions. After stirring 12 hours at room temperature the reaction mixture is slowly added to deionized water (18vol) maintaining the temperature between 15°C and 25°C. After stirring for 2 hour at 10°C the suspension is filtered and washed with deionized water (10vol). The material is dried under vacuum at NMT (Not More Than) 35°C under nitrogen bleed.

8.1.1 Process Detail

1. In reactor A charge 3-Acetylpyridine (1.0 kg) to a reactor
2. Charge Pyridine (6.0 L)
3. Cool the reaction mixture to a temperature between 0°C and 5°C
4. Charge Hydroxylamine Hydrochloride (0.60 kg) maintaining the temperature below 10°C (addition is slightly exothermic)
5. Heat the reaction mixture to a temperature between 65°C and 70°C
6. Stir at a temperature between 65°C and 70°C for NLT 1.5 hour
7. Concentrate under vacuum until the volume of distillates is ~2L
8. Cool the reactor contents to a temperature between 0°C and 5°C
9. Add slowly Tosyl Chloride (1.89 kg) maintaining the temperature below 10°C (addition is slightly exothermic)
10. Heat to a temperature between 20°C and 25°C in NLT 1.5hr
11. Stir at a temperature between 20°C and 25°C for NLT 12 hours
12. In reactor B charge Deionized water (18 L)
13. Cool the contents of reactor B to a temperature between 10°C and 15°C.
14. Transfer the content of reactor A to reactor B at a rate that the temperature in reactor B is between 15°C and 25°C (the addition is exothermic and good temperature control is important to achieve good product precipitation).

15. Rinse reactor A and lines with Pyridine (0.5 L) while transferring to reactor B.

16. Adjust temperature between 10°C and 15°C and stir for NLT 2 hours.

17. Filter and wash reactor and cake with Deionized water (10 L).

18. Dry under vacuum at a temperature between 30°C and 35°C, under nitrogen sweep until content of deionized water by KF (Karl Fischer) is NMT 1.0%.

8.2.1 Process Detail

The mixture mixture of Ketoxime Tosylate (1.0wt, 1.00eq) and Methanol (8vol) is slowly added DBU (0.62vol, 1.2eq) maintaining the temperature below 20°C. The mixture is stirred at r.t. until reaction complete. The mixture is cooled to 0/5°C and quenched with 4N HCl solution (2.58vol, 3.0eq) maintaining the temperature below 20°C.

The reaction mixture is concentrated to 1.5vol under vacuum followed by cone. HCl (2vol, 7.0eq) addition. The mixture is heated up to 85/90°C and stirred for 2 hours. The mixture is then concentrated under vacuum to ~1.5vol followed by deionized water (1vol) addition. The mixture temperature is adjusted to 50°C and filtered through charcoal cartridge to remove color. The reactor and filter are washed with deionized water (1vol). and the mixture concentrated under vacuum to ~1.5vol. Ethanol (5vol) is charged and the mixture concentrated again to ~1.5vol. Ethanol (10vol) is charged and the slurry stirred at 65°C for 1 hour. After cooling to r.t. the suspension is filtered and washed with EtOH (1vol). The material is dried under vacuum at NMT 45°C until LOD < 1.0%.

8.2.1 Process Detail

Appearance: Light beige/pinkish crystalline solid
KF: 0.14%

The molar yield is up to 82 %, with purity of >92% confirmed by NMR.
1. Charge Methanol (8 L)
2. Charge Ketoxime Tosylate (1.0 kg)
3. Add slowly DBU (0.62 vol) maintaining the temperature below 20°C (addition is slightly exothermic, with time the suspension becomes an orange solution)
4. Adjust reaction mixture temperature between 20°C and 25°C and stir for NLT 2.5 hours
5. Cool the reaction mixture to a temperature between 0°C and 5°C
6. Add slowly a solution of 4N HCl (2.58 L) maintaining the temperature below 20°C (addition is exothermic. The solution color goes darker. Process maximum volume ~12vol)
7. Concentrate under vacuum until ~1.5vol at a temperature NMT 60°C (at the end of distillation dark brown slurry should be observed. Process minimum volume ~1.5vol)
8. Charge 37% HCl (2.0 L) to the slurry
9. Heat the mixture to a temperature between 85°C and 90°C
10. Stir at a temperature between 85°C and 90°C for approximately 2 hours
11. Concentrate under vacuum until ~1.5vol at a temperature NMT 60°C (Note 4)
12. Charge deionized water (1.0 L)
13. Adjust temperature between 55°C and 50°C
14. Filter the solution, maintaining the temperature NLT 40°C, through an activated charcoal cartridge while transferring the solution to a different reactor
15. Rinse reactor, filter and lines with distilled deionized water (1.0 L) maintaining the temperature NLT 40°C
16. Concentrate under vacuum until ~1.5 vol at a temperature NMT 60°C
17. Charge Ethanol (5.0 L) and continue distillation until ~1.5 vol (ethanol used was 95% grade)
18. Charge Ethanol (10.0 L)
19. Heat the slurry to a temperature between 77°C and 83°C (reflux should be observed)
20. Stir at a temperature between 77°C and 83°C ~30minutes
21. Cool to a temperature between 20°C and 25°C
22. Stir at a temperature between 20°C and 25°C for NLT 2 hours
23. Filter and wash reactor and cake with Ethanol (1.0 L) (wet product density is 0.36)
24. Dry under vacuum at a temperature between 40°C to 45°C, under nitrogen sweep until LOD NMT (Loss on drying not more than) 1.0% (usually the product is dried in 20 hours)

8.2.3 Results
The yield is up to 76%, with purity of up to 99.7% confirmed by NMR.

Example 9. Preparation of additional ureas of Formula I and II using process of the invention

9.1: Alternative imidazole derivatives used for producing urea

N-cyclohexyl-(4-methoxyphenyl)-N-methyl-1H-imidazole-1-carboxanfde
In a 5ml vessel charge 4-(4-methoxyphenyl)-1H-imidazole (0.2 g, 1.148 mmol) and Pyridine (1 ml). Charge cyclohexyl(methyl)carbamic chloride (0.242 g, 1.378 mmol). Heat to 90°C and stir for NLT 1hr. After 1.5hr reaction is not complete by TLC. Charge additional cyclohexyl(methyl)carbamic chloride (0.121 g, 0.689 mmol) and continue heating. After 2.5hr concentrate to dryness. Charge Isopropanol (5.00 ml) and water (1.000 ml). Stir for 30 min at r.t. and filter. Wash the cake with water (2.000 ml) and Isopropanol (2.000 ml). A white solid was obtained. After drying under vacuum at 45°C 0.205g (64% molar yield; purity >95%) were obtained.

$^{13}$C NMR (150 MHz, CDCl$_3$, 20°C) δ: 159.1, 151.4, 142, 136.8, 126.4, 125.8, 114, 112.1, 57.5, 55.3, 31.3, 30, 25.4, 25.2

N-cyclohexyl-4-(3,5-dinitrophenyl)-N-methyl-1H-imidazole-1-carboxamide

In a 5ml vessel charge 4-(3,5-dinitrophenyl)-1H-imidazole (0.2 g, 0.854 mmol) and Pyridine (1 ml). Charge cyclohexyl(methyl)carbamic chloride (0.180 g, 1.025 mmol). Heat to 90°C and stir for NLT 1hr. After 1.5hr reaction is not complete by TLC. Charge additional cyclohexyl(methyl)carbamic chloride (0.090 g, 0.512 mmol) and continue heating. Concentrate to dryness. Charge Isopropanol (5.00 ml) and water (3.00 ml). Stir for 30 min at room temperature. Filter and wash with water (2.000 ml) and Isopropanol (2.000 ml). A dark yellow solid was obtained. Purification by preparative TLC affords a light yellow solid 0.123g (37% molar yield; purity >95%) after drying.

$^{13}$C NMR (150 MHz, DMSO, 20°C) δ: 150.3, 148.7, 138.6, 136.9, 136.9, 124.2, 118.1, 116.2, 56.8, 31.4, 28.9, 25.1, 24.8

9.2 Non-imidazole structures (Reference example)

This illustrates that the processes of the invention are not limited to the production of ureas based on imidazole scaffolds.

1-benzyl-3-cyclohexyl-1,3-dimethylurea

In a 25ml reactor charge N-methyl-1-phenylmethanamine (1.5 g, 12.38 mmol) and Pyridine (5.25 ml). Charge cyclohexyl(methyl)carbamic chloride (2.75 g, 14.85 mmol). Heat to 95°C After 1hr a dark mixture is obtained. After 2.5hr at 95°C heating was stopped. Adjust pH to 7-8 by adding sat. solution of sodium bicarb. Concentrate to dryness. Add water (19.50 ml) and extract 3x with CH$_2$Cl$_2$ (15.00 ml). Dry with magnesium sulfate, filter and concentrate to dryness. The mixture was purified in a silica plug and decolorizing charcoal. After concentration to dryness orange oil was obtained 2.7g (84% molar yield; purity >95%) were obtained.

$^{13}$C NMR (150 MHz, CDCl$_3$, 20°C) δ: 165.6, 138.3, 128.5, 127.5, 127, 57, 54.5, 36.8, 30.7, 30.1, 25.9, 25.7

N-cyclohexyl-N-methylpiperidine-1-carboxamide
In a 25mL reactor charge:piperidine (1.5 g, 17.62 mmol) and Pyridine (5.25 ml).
Charge cyclohexyl(methyl)carbamic chloride (3.91 g, 21.14 mmol)
Heat to 95°C
After 1hr a dark suspension is obtained
After 2.5hr at 95°C heating was stopped and pH adjusted to 7-8 by adding sat. solution of sodium bicarb.
Concentrate to dryness
Add water (19.50 ml) and extract 3x with CH₂Cl₂ (15.00 ml)
Dry with magnesium sulfate, the mixture was passed in a silica plug
The yellow solution was concentrated to dryness
1.7g (43% molar yield; purity >95%) of an yellow oily residue were obtained
\[ ^13 \text{C NMR (150 MHz, CDCl}_3, 20^\circ \text{C)} \delta: 165.3, 56.7, 48.1, 30.8, 30.1, 26, 25.7, 25.7, 24.8 \]

9.3 Alternative carbamoyl chlorides used to produce ureas

**N-benzyl-N-methyl-4-(pyridin-3-yl)-1 H-imidazole-1-carboxamide**

To 3-(1H-imidazol-4-yl)pyridine (0.5 g, 3.44 mmol) and Pyridine (2.5 ml) charge benzyl(methyl)carbamic chloride (0.759 g, 4.13 mmol).

The reaction mixture was heated to 90°C and stir for 1hr.

Sample for TLC. Still starting material, more carbamoyl chloride (0.3g, were added. The mixture was stirred for 1hr and the reaction conversion was checked by TLC (DCM/MeOH, 9:1). No starting material left. The reaction was cooled to room temperature and the pyridine was removed.

The mixture was diluted with sat NaHCO₃ and DCM. The biphasic mixture was separated. The aqueous layer was washed with DCM.

The combined organic layers were washed with sat NaHCO₃, dried over Na₂SO₄, concentrated to dryness. A dark brown solid (1.13g) was obtained.

The product was purified by column chromatography on silica gel (eluent: EtOAc then DCM/MeOH 94:6).

A brown solid (0.91 g) was obtained in 81% molar yield; purity >95%.

\[ ^13 \text{C NMR (150 MHz, CDCl}_3, 20^\circ \text{C)} \delta: 151.6, 148.5, 146.6, 139.4, 137.5, 135.1, 132.5, 129.2, 128.9, 128.3, 127.4, 123.6, 113.9, 54.2, 36.5 \]

**Piperidin-1-yl(4-(pyridin-3-yl)-1 H-imidazol-1 -yQmethanone**

To 3-(1H-imidazol-4-yl)pyridine (0.5 g, 3.44 mmol) and Pyridine (2.5 ml) charge benzyl(methyl)carbamic chloride (0.759 g, 4.13 mmol).

The reaction mixture was heated to 90°C and stir for 1hr.

Sample for TLC. Still starting material, more carbamoyl chloride (0.3g, were added. The mixture was stirred for 1hr and the reaction conversion was checked by TLC (DCM/MeOH, 9:1). No starting material left. The reaction was cooled to room temperature and the pyridine was removed.

The mixture was diluted with sat NaHCO₃ and DCM. The biphasic mixture was separated. The aqueous layer was washed with DCM. The combined organic layers were washed with sat NaHCO₃, dried over Na₂SO₄, concentrated to dryness. MTBE was added followed by heptane. A pale yellow solid precipitated. The solid was collected.

After drying, 414mg of expected product was obtained as yellow solid in 46.9 % molar yield; purity >95%.

\[ ^13 \text{C NMR (150 MHz, CDCl}_3, 20^\circ \text{C)} \delta: 150.4, 148.5, 146.7, 139.3, 137.3, 132.4, 129, 123.6, 113.9, 47.7, 25.8, 24.1 \]
N,N-diethyl-4-(pyridin-3-yl)-1H-imidazole-1-carboxamide

Charge 3-(1H-imidazol-4-yl)pyridine (0.5 g, 3.44 mmol) and Pyridine (2.5 ml). Charge diethylcarbamic chloride (0.467 g, 3.44 mmol).

The reaction mixture was heated to 90°C and stirred for 1hr. Sample for TLC. Still starting material, more carbamoyl chloride (0.3g) was added. The mixture was stirred for 1h and the reaction conversion was checked by TLC (DCM/MeOH, 9:1). No starting material left. The reaction was cooled to room temperature and the pyridine was removed.

The mixture was diluted with sat NaHCO₃ and DCM. The biphasic mixture was separated. The aqueous layer was washed with DCM.

The combined organic layers were washed with sat NaHCO₃, dried over Na₂SO₄, concentrated to dryness. Yellow oil (0.835mg) was obtained in 94% molar yield; purity >95%

¹³C NMR (150 MHz, CDCl₃, 20°C) δ: 150.8, 148.5, 146.7, 139.3, 137, 132.4, 129, 123.6, 113.8, 42.8, 13.2

(2-methylpyrrolidin-1-yl)(4-(pyridin-3-yl)-1H-imidazol-1-yl)methanone

Charge 3-(1H-imidazol-4-yl)pyridine (0.3 g, 2.067 mmol) and Pyridine (1.5 ml). Charge 2-methylpyrrolidin-1-carbonyl chloride (0.305 g, 2.067 mmol).

The reaction mixture was heated to 90°C and stirred for 1hr. Sample for TLC. Still starting material, more carbamoyl chloride (0.3g) was added. The mixture was stirred for 1h and the reaction conversion was checked by TLC (DCM/MeOH, 9:1). No starting material left. The reaction was cooled to room temperature and was diluted with water, then sat NaHCO₃ and DCM. The biphasic mixture was separated. The aqueous layer was washed with DCM. The combined organic layers were washed with sat NaHCO₃, dried over Na₂SO₄, concentrated to dryness. Brownish oil (621 mg) was obtained.

The product was purified by column chromatography on silica gel (eluent EtOAc then DCM/MeOH 9:1). An oily material (500mg) was obtained in 80% molar yield; purity >95%

¹³C NMR (150 MHz, CDCl₃, 20°C) δ: 149.3, 148.5, 146.7, 139.1, 137, 132.5, 129.1, 123.6, 113.6, 55.8, 50.2, 33.1, 25.1, 19.5

9.4 Examination of pyridine level used in solvent for urea formation

The goal of this Example was to identify if the method of the invention for the preparation of N-cyclohexyl-N-methyl-4-(pyridin-3yl)-1H-imidazole-1-carboxamide (compound of Formula II) could be carried out in different proportions of solvent/pyridine. Thus a matrix was developed where 4 solvents were going to be tested at different ratios (25; 50 and 75% of pyridine). Below are presented the results under the different conditions (yields are molar yield).

<table>
<thead>
<tr>
<th>% Pyridine</th>
<th>2-Methyltetrahydrofuran</th>
<th>Trifluorotoluene</th>
<th>Dichloromethane</th>
<th>Propionitrile</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>Purity: 100% Yield: 86% Rx Time: 2hr</td>
<td>Purity: 100% Yield: 86% Rx Time: &lt;2hr</td>
<td>Purity: 100% Yield: 85% Rx Time: &lt;2hr</td>
<td>Purity: 100% Yield: 82% Rx Time: 2hr</td>
</tr>
<tr>
<td>50</td>
<td>Purity: 100% Yield: 80% Rx Time: &gt;2hr</td>
<td>Purity: 100% Yield: 83% Rx Time: &gt;2hr</td>
<td>Purity: 100% Yield: 77% Rx Time: &gt;2hr</td>
<td>Purity: 100% Yield: 71% Rx Time: &gt;2hr</td>
</tr>
<tr>
<td>25</td>
<td>Purity: 100% Yield: 56% Rx Time: &gt;2hr</td>
<td>Purity: 100% Yield: 51% Rx Time: &gt;2hr</td>
<td>Purity: 100% Yield: 63.3% Rx Time: &gt;2hr</td>
<td>Purity: 100% Yield: 59.2% Rx Time: &gt;2hr</td>
</tr>
</tbody>
</table>

Standard procedure
In a tube reactor charge:
3-(1H-imidazol-4-yl)pyridine (1 g, 6.89 mmol), Pyridine (1 ml), DCM (3.00 ml) and cyclohexyl(methyl)carbamic chloride (1.529 g, 8.27 mmol). Heat to 85°C until reaction is complete.
Charge Isopropanol (8.00 ml) and stir at room temperature during NLT 3hr. Filter and wash with water (8.00 ml) and Isopropanol (4.00 ml). Dry under vacuum.

As a general conclusion from data analysis, reduced quantities of pyridine present in the reaction mixture (eg. 25%) lead to the reaction time being longer and yields lower, sometimes due to lower conversion. However the quality is not affected, even at 25% pyridine. It was demonstrated as well that the reaction can be performed without impact on yield and time if ratio of non-pyridine solvent present in reaction mixture is not higher than 25%.

Within the scope of this Example it was also studied the effect of the base catalyst used in the urea formation. Alternatives to pyridine were selected (Triethylamine, Hunig's base and DBU) to be tested in a standard procedure. In all cases the reaction affords the expected product. In the 3 cases problems in the stirring of the reaction were found and in the triethylamine case the quality is affected. The table below summarizes the results:

<table>
<thead>
<tr>
<th>Base</th>
<th>Purity</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triethylamine</td>
<td>84.6%</td>
<td>72%</td>
</tr>
<tr>
<td>Hunig's base</td>
<td>100%</td>
<td>58%</td>
</tr>
<tr>
<td>DBU</td>
<td>100%</td>
<td>77%</td>
</tr>
</tbody>
</table>

The results reported in Examples 9.1 to 9.4 illustrate the general applicability of the processes of the invention in the preparation of ureas of Formula I and II, and the relevant intermediate compounds defined herein. They also illustrate the degree to which the processes described in the other Examples may be varied within the extent of the claims and yet still provide beneficial results.

All documents cited herein are hereby incorporated herein by way of reference in their entirety.
Claims

1. A process for preparing a substituted urea compound of Formula II or Formula I, or a pharmaceutically acceptable salt or ester thereof, the process comprising the reaction of an intermediate of Formula II' or Formula I',

with a carbamoyl halide of the formula: RIR2NC(=0)Hal, in a solvent consisting essentially of pyridine,

wherein Hal represents Cl, F, I or Br,

wherein R1 and R2 can each be independently selected from H, C1-2 alkyl, C1-6 alkoxy, aryl, heteroaryl, partially or fully saturated heterocyclic, C3-8 cycloalkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, C3-10 cycloalkyl C1-6 alkyl, Rla, halogen, OH, ORla, OCORla, SH, SRla, SCORla, NH2, NHRla, NHSO2NH2, NHSO2Rla, NRlaCORlb, NHCORla, NRlaRlb, CORla, CSRla, CN, COOH, COORla, CONH2, CONHOH, CONHRla, CONHORla, S0,Rla, S0,H, S0,NH2, S0,NRlaRlb, S0,NRlaRlb, wherein Rla and Rib are independently selected from C1-4 alkyl, substituted C1-4 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or Rla and Rib, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R1 or R2 is C1-20 alkyl, alkoxy, aryl, heteroaryl, heterocyclyl, C3-10 cycloalkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, C3-10 cycloalkyl C1-6 alkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from Rlc, halogen, aryl, heteroaryl, heterocyclyl, C1-8 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, aryl C1-6 alkoxy, heteroaryl C1-6 alkoxy, heterocyclyl C1-6 alkoxy, C1-6 alkylamino, C1-6 dialkylamino, C1-6 alkyl, OH, ORlc, OCORlc, SH, SRlc, SCORlc, NH2, NO2, NHRlc, NHSO2NH2, NHSO2Rlc, NRlcCORld, NH(NH)NH2, NHCORlc, NRlcRld, CORlc, CSRlc, CN, COOH,
COORlc, CONH₂, CONHOH, CONHRlc, CONHORlc, C(NO)NH₂, CONRlcRld, S⁻Rlc, S⁻H, S⁻NH₂, S⁻₂NRlcRld, wherein Rlc and Rld are independently selected from C₆₋₆ alkyl, substituted C₄₋₆ alkyl, aryl, heteroaryl, C₃₋₈ cycloalkyl and heterocyclyl, or Rlc and Rld, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R₁ or R₂ is Cᵢ₋ᵢ₆ alkyl, aryl, heteroaryl, heterocyclyl, C₆₋₆ alkoxyl, arylxoy, heteroarylxy, heterocyclyloxy, aryl C₆₋₆ alkyl, heteroaryl C₆₋₆ alkyl, heterocyclyl C₆₋₆ alkyl, aryl C₆₋₆ alkoxyl, heteroaryl C₆₋₆ alkoxyl, heterocyclyl C₆₋₆ alkoxyl, C₆₋₆ alkyamino, C₆₋₆ dialkyamino, C₆₋₆ cycloalkyl or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from Rle, halogen, Cᵢ₋₁₀ alkyl, ORle, OCORle, SH, SRle, SCORle, NH₂, N₀₂, NHRle, NHSO₂NH₂, NHSO₂Rle, NRleCORlc, NHSO₂Rle, NRleRl, CORle, CSRle, CN, COOH, COORle, CON₄₂, CONHOH, CONHRle, CONHORle, C(NO)NH₂, CONRlcRlf, S₀₂Rle, S₀₂H, S₀₂NH₂, S₀₂NRleRlf, wherein Rle and Rlf are independently selected from C₁₋₆ alkyl, substituted C₁₋₆ alkyl, aryl, heteroaryl, C₃₋₈ cycloalkyl and heterocyclyl, or Rle and Rlf, together with the heteroatom to which they are joined, can form heterocyclyl,

with the exception that R₁ and R₂ are not both H;

or

R₁ and R₂, together with the N to which they are attached, can form a heteroaryl or heterocyclyl group, each of which may optionally be substituted with one or more oxygen atoms or one or more groups selected from aryl, heteroaryl, partially or fully saturated heterocyclyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyl, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl, heterocyclyl C₁₋₆ alkyl, C₃₋₈ cycloalkyl C₁₋₆ alkyl, C₁₋₆ alkoxyl, arylxoy, heteroarylxy, heterocyclyloxy, R₂a, halogen, OH, OR₂a, OCOR₂a, SH, SR₂a, SCOR₂a, NH₂, N₀₂, NHR₂a, NHSO₂NH₂, NHSO₂R₂a, NR₂aCOR₂b, NHSO₂R₂a, NR₂aR₂b, COR₂a, CSR₂a, CN, COOH, COOR₂a, CON₂H₂, CONHOH, CONHR₂a, CONHOR₂a, C(NO)NH₂, CONR₂aR₂b, S₀₂R₂a, S₀₂H, S₀₂NH₂, S₀₂NR₂aR₂b, wherein R₂a and R₂b are independently selected from C₁₋₆ alkyl, substituted C₁₋₆ alkyl, aryl, heteroaryl, C₃₋₈ cycloalkyl and heterocyclyl, or R₂a and R₂b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of the heteroaryl or heterocyclyl formed by R₁ and R₂ together is aryl, heteroaryl, heterocyclyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyl, aryl C₁₋₆ alkyl, heteroaryl C₁₋₆ alkyl, heterocyclyl C₁₋₆ alkyl, C₃₋₈ cycloalkyl C₁₋₆ alkyl, C₁₋₆ alkoxyl, arylxoy, heteroarylxy, heterocyclyloxy, or a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, hydroxyl, C₁₋₆ alkyl, aryl, heteroaryl, heterocyclyl, C₃₋₈ cycloalkyl, C₁₋₆ alkoxyl, arylxoy, heteroarylxy, heterocyclyloxy, C₃₋₈ cycloalkylxoy, aryl C₁₋₆ alkoxyl, heteroaryl C₁₋₆ alkoxyl, heterocyclyl C₁₋₆ alkoxyl, C₃₋₈ cycloalkyl C₁₋₆ alkoxyl, R₂c, OR₂c, OCOR₂c, SH, SR₂c, SCOR₂c, NH₂, N₀₂, NHR₂c, NHSO₂NH₂, NHSO₂R₂c, NR₂cCOR₂d, NHC(NH)NH₂, NHCOR₂c, NR₂cR₂d, COR₂c, CSR₂c, CN, COOH, COOR₂c, CON₂H₂, CONHOH, CONHR₂c, CONHOR₂c, C(NO)NH₂, CONR₂cR₂d, S₀₂R₂c, S₀₂H, S₀₂NH₂, S₀₂NR₂cR₂d, wherein R₂c and R₂d are independently selected from C₁₋₆ alkyl, substituted C₁₋₆ alkyl, aryl, heteroaryl, C₃₋₈ cycloalkyl and heterocyclyl, or R₂c and R₂d, together with the heteroatom to which they are joined, can form heterocyclyl,
wherein, when the substituent of the substituent of the heteroaryl or heterocyclyl formed by R1 and R2 together is C1-6 alkyl, aryl, heteroaryl, heterocyclyl, C3-8 cycloalkyl, C1-6 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C3-8 cycloalkyloxy, aryl C3-8 alkoxy, heteroaryl C1-4 alkoxy, heterocyclyl C1-4 alkoxy, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from C1-4 alkoxy, R2e, halogen, OH, OR2e, OCO2e, SH, SR2e, SCOR2e, NH2, N02, NHR2e, NHSO2NH2, NHSO2R2e, NR2eCOR2f, NHC(=NH)NH2, NR2eR2f, NHCOR2e, COR2e, CSR2e, CN, COOH, COOR2e, CONH2, CONH20H, CONHR2e, CONH20R2e, C(NO)NH2, CONR2eR2f, S02R2e, S02H, S02NH2, S02NR2eR2f, whereby R2e and R2f are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R2e and R2f, together with the heteroatom to which they are joined, can form heterocyclyl;

Ring A is selected from aryl, heteroaryl and heterocyclyl moieties, each of which may optionally be substituted with one or more groups selected from halogen, C1-6 alkyl, aryl, heteroaryl, heterocyclyl, C1-6 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, Ra, C1-6 alkyl, OH, ORa, OCORa, SH, SRa, SCORa, NH2, N02, NHRa, NHSO2NH2, NHSO2Ra, NRaCORa, NHCORa, NHC(=NH)NH2, NRaRb, CORa, CSRa, CN, COOH, COORa, CONH2, CONH20a, CONH20Ra, C(NO)NH2, CONRaRb, S02Ra, S02H, S02NH2, S02NRaRb, whereby Ra and Rb are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or Ra and Rb, together with the heteroatom to which they are joined, can form heterocyclyl;

wherein, when Ring A is substituted with C1-6 alkyl, aryl, heteroaryl, heterocyclyl, C1-6 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C1-6 alkyl, C3-8 cycloalkyl or is substituted with a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, Rc, C1-6 alkyl, aryl C3-8 alkoxy, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl, OH, ORc, OCOc, SH, SRC, SCORc, NH2, N02, NHRc, NHSO2NH2, NHSO2Rc, NRcCORd, NHCORc, NHC(=NH)NH2, NRcRd, CORc, CSRc, CN, COOH, COORc, CONH2, CONH20c, CONH20Rc, CNH20Ra, CONH20Rc, C(NO)NH2, CONRcRd, S02Rc, S02H, S02NH2, S02NRcRd, whereby Rc and Rd are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C1-6 cycloalkyl and heterocyclyl, or Rc and Rd, together with the heteroatom to which they are joined, can form heterocyclyl;

V can be N, CH or C-R3, wherein R3 is halogen, Cno alkyl, aryl, heteroaryl, heterocyclyl, C3-8 cycloalkyl, C1-6 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, R3a, OH, OR3a, SH, SR3a, OCO3a, SCOR3a, NH2, N02, NHSO2NH2, NHSO2R3a, NR3aCOR3b, NHCOR3a, NHC(=NH)NH2, NR3aR3b, COR3a, CSR3a, CN, COOH, COOR3a, CONH2, CONH203a, CONH20R3a, CONH20R3a, C(NO)NH2, CONR3aR3b, S02R3a, S02H, S02NH2, S02NR3aR3b, whereby R3a and R3b are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R3a and R3b, together with the heteroatom to which they are joined, can form heterocyclyl;

wherein, when R3 is Cno alkyl, aryl, heteroaryl, heterocyclyl, C1-6 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C1-6 alkyl, C3-8 cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, aryl, heteroaryl, heterocyclyl, C1-6 alkyl, aryloxy, heteroaryloxy, heterocyclyloxy, R3c, C1-6 alkyl, OH, OR3c, OCO3c, SH,
SR3c, SCOR3c, N¾, N 0 2 NHR3c, NHS0 N H , NHS0 R3c, NR3cCOR3d, NHCOR3c, NHC(NH)NH2, NR3cR3d, COR3c, CSR3c, CN, COOH, COOR3c, CONH2, CONH0H, CONHR3c, CONHR3c, C(NO)NH2, CONR3cR3d, S0 2R3c, S0 2NH2, S0 2NR3cR3d, wherein R3c and R3d are independently selected from C 1 6 alkyl, substituted C 1 6 alkyl, aryI, heteroaryl, C 3 8 cycloalkyl and heterocyclyl, or R3c and R3d, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R3 is C 1 4 alkyl, aryI, heteroaryl, heterocyclyl, C 1 6 alkoxyo, aryloxy, heteroaryloxy, heterocyclyloxy, C 1 6 alkyl, C 3 8 cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R3e, Ci i o alkyl, OH, OR3e, OCO3e, SH, SR3e, SCOR3e, NH2, N 0 2 NHR3e, NHR3e, NHC(NH)NH2, CONHR3e, C(NO)NH2, CONR3eR3f, S0 2R3e, S0 2H, S0 2N 0 2, S0 2NR3eR3f, wherein R3e and R3f are independently selected from C 1 6 alkyl, substituted C 1 6 alkyl, aryI, heteroaryl, C 3 8 cycloalkyl and heterocyclyl, or R3e and R3f, together with the heteroatom to which they are joined, can form heterocyclyl;

W can be N, CH or C-R4, wherein R4 is halogen, C 0 alkyl, aryI, heteroaryl, heterocyclyl, C 1 6 alkoxyo, aryloxy, heteroaryloxy, heterocyclyloxy, C 3 8 cycloalkyl, R4a, OH, OR4a, SH, SR4a, OCO4a, SCOR4a, NH2, N 0 2 NHR4a, NHR4a, NHS0 2NH2, NR4aCOR4b, NHCOR4a, NHC(NH)NH2, NR4aR4b, OR4a, CSR4a, CN, COOH, COOR4a, CONH2, CONH0H, CONHR4a, CONHR4a, C(NO)NH2, CONR4aR4b, S0 2R4a, S0 2H, S0 2N 0 2, S0 2NR4aR4b, wherein R4a and R4b are independently selected from C 1 6 alkyl, substituted C 1 6 alkyl, aryI, heteroaryl, C 3 8 cycloalkyl and heterocyclyl, or R4a and R4b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R4 is Ci i o alkyl, aryI, heteroaryl, heterocyclyl, C 1 6 alkoxyo, aryloxy, heteroaryloxy, heterocyclyloxy, C 1 6 alkyl, C 3 8 cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, aryI, heteroaryl, heterocyclyl, Ci i o alkoxyo, aryloxy, heteroaryloxy, heterocyclyloxy, R4c, Ci i o alkyl, OH, OR4c, OCO4c, SH, SR4c, SCOR4c, NH2, N 0 2 NHR4c, NHR4c, NHC(NH)NH2, NR4cR4d, OR4c, CSR4c, CN, COOH, COOR4c, CONH2, CONH0H, CONHR4c, CONHR4c, C(NO)NH2, CONR4cR4d, S0 2R4c, S0 2H, S0 2N 0 2, S0 2NR4cR4d, wherein R4c and R4d are independently selected from C 1 6 alkyl, substituted C 1 6 alkyl, aryI, heteroaryl, C 3 8 cycloalkyl and heterocyclyl, or R4c and R4d, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R4 is C 1 4 alkyl, aryI, heteroaryl, heterocyclyl, C 1 6 alkoxyo, aryloxy, heteroaryloxy, heterocyclyloxy, Ci i o alkyl, C 3 8 cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R4e, Ci i o alkyl, OH, OR4e, OCO4e, SH, SR4e, SCOR4e, NH2, N 0 2 NHR4e, NHR4e, NHC(NH)NH2, NR4eR4f, OR4e, CSR4e, CN, COOH, COOR4e, CONH2, CONH0H, CONHR4e, CONHR4e, C(NO)NH2, CONR4eR4f, S0 2R4e, S0 2H, S0 2N 0 2, S0 2NR4eR4f, wherein R4e and R4f are independently selected from Ci i o alkyl, substituted C 1 6 alkyl, aryI, heteroaryl, C 3 8 cycloalkyl and heterocyclyl, or R4e and R4f, together with the heteroatom to which they are joined, can form heterocyclyl;
R5 together with the C to which it is attached, can form a carbonyl group with the double bonds in Formula I rearranged accordingly, or R5 is selected from H, C_{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, R5a, halogen, OH, OR5a, SH, SR5a, OCOR5a, SCOR5a, NH2, N02, NHR5a, NHS02NH2, NHS02R5a, NR5aCOR5b, NHCOR5a, NH(NH)NH2, NR5aR5b, COR5a, CSR5a, CN, COOH, COOR5a, CONH2, CONHOR5a, CONHOR5a, CONH(NH)NH2, CONR5aR5b, S02R5a, SO3H, S02NH2, S02NR5aR5b, wherein R5a and R5b are independently selected from C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl, or R5a and R5b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R5 is C_{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C_{3-8} cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, aryl, heteroaryl, heterocyclyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, R5c, C_{1-6} alkyl, OH, OR5c, OCOR5c, SH, SR5c, SCOR5c, NH2, N02, NHR5c, NHS02NH2, NHS02R5c, NR5cCOR5d, NHCOR5c, NH(NH)NH2, NR5cR5d, COR5c, CSR5c, CN, COOH, COOR5c, CONH2, CONHOR5c, CONHOR5c, CONH(NH)NH2, CONR5cR5d, S02R5c, S02JH, S02NH2, S02NR5cR5d, wherein R5c and R5d are independently selected from C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl, or R5c and R5d, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R5 is C_{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C_{3-8} cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R5e, C_{1-6} alkyl, OH, OR5e, OCOR5e, SH, SR5e, SCOR5e, NH2, N02, NHR5e, NHS02NH2, NHS02R5e, NR5eCOR5f, NHCOR5e, NH(NH)NH2, NR5eR5f, COR5e, CSR5e, CN, COOH, COOR5e, CONH2, CONHOR5e, CONH(NH)NH2, CONR5eR5f, S02R5e, S02JH, S02NH2, S02NR5eR5f, wherein R5e and R5f are independently selected from C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl, or R5e and R5f, together with the heteroatom to which they are joined, can form heterocyclyl;

X can be O (with the double bonds in Formula II rearranged accordingly), N, CH or C-R6, wherein R6 is selected from C_{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, R6a, halogen, OH, OR6a, SH, SR6a, OCOR6a, SCOR6a, NH2, N02, NHR6a, NHS02NH2, NHS02R6a, NR6aCOR6b, NHCOR6a, NH(NH)NH2, NR6aR6b, COR6a, CSR6a, CN, COOH, COOR6a, CONH2, CONHOR6a, CONH(NH)NH2, CONR6aR6b, S02R6a, S02JH, S02NH2, S02NR6aR6b, wherein R6a and R6b are independently selected from C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, heteroaryl, C_{3-8} cycloalkyl and heterocyclyl, or R6a and R6b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R6 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, and when R6 is C_{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C_{3-8} cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R6c, C_{1-6} alkyl, C_{1-6} alkylnyl, aryl, heteroaryl, heterocyclyl, C_{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkyl, heterocyclyl C_{1-6} alkyl, aryl C_{1-6} alkyl, heteroaryl C_{1-6} alkoxy, heterocyclyl C_{1-6} alkoxy, OH, OR6c,
0C0R6c, SH, SR6c, SC0R6c, NH2, N0, NHR6c, NHS0, NHC(NH)NH2, NHS0, NR6c, NR6c0R6d, NHC0R6c, NR6cR6d, C0R6c, CN, COOH, COOR6c, CONH2, CONHR6c, CONHOR6c, CONHOH, C(NO)NH2, CONR6cR6d, S0, S0H, S0, S02H, S0, NR6cR6d, wherein R6c and R6d are independently selected from Ci, alkyl, substituted C1-C6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R6c and R6d, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R6 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, or when the substituent of R6 is C1-C6 alkyl, C1-C6 alkynyl, aryl, heteroaryl, heterocyclyl, C1-C6 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, aryl C1-C6 alkyl, heteroaryl C1-C6 alkyl, heterocyclyl C1-C6 alkyl, aryl C1-C6 alkoxy, heteroaryl C1-C6 alkoxy, C3-8 cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R6e, C1-C6 alkyl, C1-C6 alkoxy, OH, OR6e, OCOR6e, SH, SR6e, SCOR6e, NH2, N0, NHR6e, NHS0, NH2, NHC(NH)NH2, NHS0, NR6e, NR6eCOR6f, NHCOR6e, NR6eR6f, OR6e, CSR6e, CN, COOH, COOR6e, CONH2, CONHOH, CONHR6e, CONHOR6e, C(NO)NH2, CONR6eR6f, S0, S0H, S0, S02H, S0, NR6eR6f, wherein R6e and R6f are independently selected from Ci, alkyl, substituted C1-C6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R6e and R6f, together with the heteroatom to which they are joined, can form heterocyclyl;

Y can be N, CH or C-R7, wherein R7 is selected from C1-C6 alkyl, aryl, heteroaryl, heterocyclyl, C1-C6 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, R7a, halogen, OH, OR7a, SH, SR7a, OCOR7a, SCOR7a, NH2, N0, NHR7a, NHS0, NH2, NHS0, R7a, NR7aCOR7b, NHCOR7a, NHC(NH)NH2, NR7aR7b, OR7a, CSR7a, CN, COOH, COOR7a, CONH2, CONHOH, CONHR7a, CONHOR7a, C(NO)NH2, CONR7aR7b, S0, S0H, S0, S02H, S0, NR7aR7b, wherein R7a and R7b are independently selected from C1-C6 alkyl, substituted C1-C6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R7a and R7b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when R7 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, and when R7 is C1-C6 alkyl, aryl, heteroaryl, heterocyclyl, C1-C6 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, C3-8 cycloalkyl or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R7c, C1-C6 alkyl, C1-C6 alkoxy, aryl, heteroaryl, heterocyclyl, C1-C6 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, aryl C1-C6 alkyl, heteroaryl C1-C6 alkyl, heterocyclyl C1-C6 alkyl, aryl C1-C6 alkoxy, heteroaryl C1-C6 alkoxy, heterocyclyl C1-C6 alkoxy, OH, 07c, OCOR7c, SH, SR7c, SCOR7c, NH2, N0, NHR7c, NHS0, NH2, NHC(NH)NH2, NHS0, R7c, NR7cCOR7d, NHCOR7c, NR7cR7d, OR7c, CSR7c, CN, COOH, COOR7c, CONH2, CONHR7c, CONHOR7c, CONHOH, C(NO)NH2, CONR7cR7d, S0, R7c, S0H, S0, S02H, S0, NR7cR7d, wherein R7c and R7d are independently selected from C1-C6 alkyl, substituted C1-C6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, or R7c and R7d, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R7 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, or when the substituent of R7 is C1-C6 alkyl, C1-C6 alkoxy, aryl, heteroaryl, heterocyclyl, C1-C6 alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, aryl C1-C6 alkyl, heteroaryl C1-C6 alkyl, heterocyclyl C1-C6 alkyl, aryl C1-C6 alkoxy, heteroaryl C1-C6 alkoxy, heterocyclyl C1-C6 alkoxy, C3-8 cycloalkyl, or
is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, aryl, heteroaryl, heterocyclyl, aryl C\textsubscript{i} alkyl, heteroaryl C\textsuperscript{\alpha} alkyl, heterocyclyl C\textsubscript{w} alkyl, C\textsubscript{1-4} alkoxy, R\textsubscript{7}e, C\textsubscript{1-6} alkyl, OH, OR\textsubscript{7}e, O\textsubscript{COR\textsubscript{7}e}, SH, SR\textsubscript{7}e, SC\textsubscript{OR\textsubscript{7}e}, NH\textsubscript{2}, N\textsubscript{0}, N\textsubscript{HR\textsubscript{7}e}, N\textsubscript{H3}0\textsubscript{2}NH\textsubscript{2}, N\textsubscript{H3}0\textsubscript{2}R\textsubscript{7}e, N\textsubscript{HC(NH)NH\textsubscript{2}}, N\textsubscript{R\textsubscript{7}e}C\textsubscript{OR\textsubscript{7}f}, N\textsubscript{HCOR\textsubscript{7}e}, N\textsubscript{R\textsubscript{7}e}R\textsubscript{7}f, COR\textsubscript{7}e, CSR\textsubscript{7}e, CN, COOH, CO\textsubscript{OR\textsubscript{7}e}, CONH\textsubscript{2}, CON\textsubscript{OH}, CON\textsubscript{HR\textsubscript{7}e}, GON\textsubscript{HR\textsubscript{7}e}, C(N\textsubscript{OH})NH\textsubscript{2}, CON\textsubscript{R\textsubscript{7}e}R\textsubscript{7}f, S\textsubscript{0}2R\textsubscript{7}e, S\textsubscript{0}2H, S\textsubscript{0}2NR\textsubscript{7}eR\textsubscript{7}f, wherein R\textsubscript{7}e and R\textsubscript{7}f are independently selected from C\textsubscript{1-6} alkyl, aryl, heteroaryl, C\textsubscript{3-8} cycloalkyl and heterocyclyl, or R\textsubscript{7}e and R\textsubscript{7}f, together with the heteroatom to which they are joined, can form heterocyclyl.

Z can be N, CH or C-R\textsubscript{8}, wherein R\textsubscript{8} is selected from C\textsubscript{1-10} alkyl, aryl, heteroaryl, heterocyclyl, C\textsubscript{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, R\textsubscript{8a} halogen, OH, OR\textsubscript{8a}, SH, SR\textsubscript{8a}, O\textsubscript{COR\textsubscript{8a}}, SC\textsubscript{OR\textsubscript{8a}}, NH\textsubscript{2}, N\textsubscript{0}, N\textsubscript{HR\textsubscript{8a}}, N\textsubscript{H3}0\textsubscript{2}NH\textsubscript{2}, N\textsubscript{H3}0\textsubscript{2}R\textsubscript{8a}, NR\textsubscript{8a}COR\textsubscript{8b}, NH\textsubscript{COR\textsubscript{8a}}, NH\textsubscript{C(NH)NH\textsubscript{2}}, NR\textsubscript{8a}R\textsubscript{8b}, COR\textsubscript{8a}, CSR\textsubscript{8a}, CN, COOH, CO\textsubscript{OR\textsubscript{8a}}, CONH\textsubscript{2}, CON\textsubscript{OH}, CON\textsubscript{HR\textsubscript{8a}}, CON\textsubscript{HR\textsubscript{8a}}, C(N\textsubscript{OH})NH\textsubscript{2}, CON\textsubscript{R\textsubscript{8a}}R\textsubscript{8b}, S\textsubscript{0}2R\textsubscript{8a}, S\textsubscript{0}2H, S\textsubscript{0}2NR\textsubscript{8a}R\textsubscript{8b}, wherein R\textsubscript{8a} and R\textsubscript{8b} are independently selected from C\textsubscript{1-6} alkyl, substituted C\textsubscript{1-6} alkyl, aryl, heteroaryl, C\textsubscript{3-8} cycloalkyl and heterocyclyl, or R\textsubscript{8a} and R\textsubscript{8b}, together with the heteroatom to which they are joined, can form heterocyclyl.

wherein, when R\textsubscript{8} is C\textsubscript{1-6} alkyl, C\textsubscript{1-4} alkoxy, MR\textsubscript{8}, aryl, heteroaryl, heterocyclyl, C\textsubscript{3-8} cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R\textsubscript{8c}, C\textsubscript{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C\textsubscript{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, R\textsubscript{8a}, halogen, OH, OR\textsubscript{8a}, SH, SR\textsubscript{8a}, O\textsubscript{COR\textsubscript{8a}}, SC\textsubscript{OR\textsubscript{8a}}, NH\textsubscript{2}, N\textsubscript{0}, N\textsubscript{HR\textsubscript{8a}}, N\textsubscript{H3}0\textsubscript{2}NH\textsubscript{2}, N\textsubscript{H3}0\textsubscript{2}R\textsubscript{8a}, NR\textsubscript{8a}COR\textsubscript{8b}, NH\textsubscript{COR\textsubscript{8a}}, NH\textsubscript{C(NH)NH\textsubscript{2}}, NR\textsubscript{8a}R\textsubscript{8b}, COR\textsubscript{8a}, CSR\textsubscript{8a}, CN, COOH, CO\textsubscript{OR\textsubscript{8a}}, CONH\textsubscript{2}, CON\textsubscript{OH}, CON\textsubscript{HR\textsubscript{8a}}, CON\textsubscript{HR\textsubscript{8a}}, C(N\textsubscript{OH})NH\textsubscript{2}, CON\textsubscript{R\textsubscript{8a}}R\textsubscript{8b}, S\textsubscript{0}2R\textsubscript{8a}, S\textsubscript{0}2H, S\textsubscript{0}2NR\textsubscript{8a}R\textsubscript{8b}, wherein R\textsubscript{8a} and R\textsubscript{8b} are independently selected from C\textsubscript{1-6} alkyl, substituted C\textsubscript{1-6} alkyl, aryl, heteroaryl, C\textsubscript{3-8} cycloalkyl and heterocyclyl, or R\textsubscript{8c} and R\textsubscript{8d}, together with the heteroatom to which they are joined, can form heterocyclyl.

wherein, when the substituent of R\textsubscript{8} is C\textsubscript{1-6} alkyl, aryl, heteroaryl, heterocyclyl, C\textsubscript{1-6} alkoxy, aryloxy, heteroaryloxy, heterocyclyloxy, aryl C\textsubscript{1-6} alkyl, heteroaryl C\textsubscript{1-6} alkyl, heterocyclyl C\textsubscript{w} alkyl, aryl C\textsubscript{1-6} alkoxy, heteroaryl C\textsubscript{1-6} alkoxy, heterocyclyl C\textsubscript{1-6} alkoxy, C\textsubscript{3-8} cycloalkyl, or is a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from halogen, R\textsubscript{8e}, C\textsubscript{1-6} alkyl, OH, OR\textsubscript{8e}, O\textsubscript{COR\textsubscript{8e}}, SH, SR\textsubscript{8e}, SC\textsubscript{OR\textsubscript{8e}}, NH\textsubscript{2}, N\textsubscript{0}, N\textsubscript{HR\textsubscript{8e}}, N\textsubscript{H3}0\textsubscript{2}NH\textsubscript{2}, N\textsubscript{H3}0\textsubscript{2}R\textsubscript{8e}, NR\textsubscript{8e}COR\textsubscript{8f}, NH\textsubscript{COR\textsubscript{8e}}, N\textsubscript{HC(NH)NH\textsubscript{2}}, NR\textsubscript{8e}R\textsubscript{8f}, COR\textsubscript{8e}, CSR\textsubscript{8e}, CN, COOH, CO\textsubscript{OR\textsubscript{8e}}, CON\textsubscript{H\textsubscript{2}}, CON\textsubscript{OH}, CON\textsubscript{HR\textsubscript{8e}}, CON\textsubscript{HR\textsubscript{8e}}, C(N\textsubscript{OH})NH\textsubscript{2}, CON\textsubscript{R\textsubscript{8e}}R\textsubscript{8f}, S\textsubscript{0}2R\textsubscript{8e}, S\textsubscript{0}2H, S\textsubscript{0}2NR\textsubscript{8e}R\textsubscript{8f}, wherein R\textsubscript{8e} and R\textsubscript{8f} are independently selected from C\textsubscript{1-6} alkyl, substituted C\textsubscript{1-6} alkyl, aryl, heteroaryl, C\textsubscript{3-8} cycloalkyl and heterocyclyl, or R\textsubscript{8e} and R\textsubscript{8f}, together with the heteroatom to which they are joined, can form heterocyclyl.

wherein, at most, two of the atoms or groups denoted X, Y and Z can be N.
wherein, when W is N, the CONR1R2 group may be joined to W instead, with the double bonds in Formula I rearranged accordingly.

2. The process according to claim 1, wherein the compound of Formula II or Formula I has a formula selected from Formula Ila, Formula lib, Formula lie, Formula lid, and Formula la.

and wherein the intermediate of Formula II\(\Gamma\) or Formula I\(\Gamma\) has a corresponding structure in which the -CONR1R2 group of Formula Ila-d or Formula la is replaced by H.
3. A process according to claim 1 or claim 2, wherein the compound has the Formula Ia, and wherein the intermediate of Formula II' has a corresponding structure in which the -CONR1R2 group of Formula Iia is replaced by H.

4. The process according to claim 3, wherein the compound is of Formula Ila, and wherein:

R1 is selected from H and C1-4 alkyl,

R2 is selected from C1-6 alkyl, aryl, heteroaryl, heterocyclyl, C3-6 cycloalkyl, aryl C1-6 alkyl, heteroaryl C1-6 alkyl, heterocyclyl C1-6 alkyl and C1,4 cycloalkyl Ci-6 alkyl, each of which may optionally be substituted with one or more groups selected from R2a, halogen, OH, OR2a, OCOR2a, SH, SR2a, SCOR2a, NH2, NHR2a, NHSO2R2a, NHR2aCOR2b, NHC(NH)NH2, NHCOR2a, NR2aR2b, COR2a, CSR2a, CN, COOH, COOR2a, CONH2, CONHOH, CONHR2a, CONHOR2a, C(NO)HNH2, SO2R2a, SO3H, SO2NH2, CONR2aR2b, SO2NR2aR2b, wherein R2a and R2b are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C1-6 cycloalkyl and heterocyclyl, or R2a and R2b, together with the heteroatom to which they are joined, can form heterocyclyl,

wherein, when the substituent of R2 is Ci-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C1-6 cycloalkyl, heterocyclyl or a group containing one or more of these moieties, each of these moieties may optionally be substituted with one or more groups selected from R2c, halogen, OH, OR2c, OCOR2c, SH, SR2c, SCOR2c, NH2, NHR2c, NHSO2R2c, NHR2cCOR2d, NHC(NH)NH2, NHCOR2c, NR2cR2d, COR2c, CSR2c, CN, COOH, COOR2c, CONH2, CONHOH, CONHR2c, CONHOR2c, C(NO)HNH2, SO2R2c, SO3H, SO2NH2, CONR2cR2d, SO2NR2cR2d, wherein R2c and R2d are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C1-6 cycloalkyl and heterocyclyl, or R2c and R2d, together with the heteroatom to which they are joined, can form heterocyclyl,

R5 is selected from H, R5a, halogen, OH, OR5a, OCOR5a, SH, SR5a, SCOR5a, NH2, NHR5a, NHSO2NH2, NHSO2R5a, NR5aCOR5b, NHC(NH)NH2, NHCOR5a, NR5aR5b, COR5a, CSR5a, CN, COOH, COOR5a, CONH2, CONHOH, CONHR5a, CONHOR5a, C(NO)HNH2, SO2R5a, SO3H, SO2NH2, CONR5aR5b, SO2NR5aR5b, wherein R5a and R5b are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C1-6 cycloalkyl and heterocyclyl, or R5a and R5b, together with the heteroatom to which they are joined, can form heterocyclyl,

R6 is selected from aryl, heteroaryl, heterocyclyl, C1-6 cycloalkyl, each of which may optionally be substituted with one or more groups selected from R6a, halogen, OH, OR6a, OCOR6a, SH, SR6a, SCOR6a, N02, NH3, NHR6a, NHSO2NH2, NHSO2R6a, NR6aCOR6b, NHC(NH)NH2, NHCOR6a, NR6aR6b, COR6a, CSR6a, CN, COOH, COOR6a, CONH2, CONHOH, CONHR6a, CONHOR6a, C(NO)HNH2, SO2R6a, SO3H, SO2NH2, CONR6aR6b, SO2NR6aR6b, wherein R6a and R6b are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C1-6 cycloalkyl and heterocyclyl, or R6a and R6b, together with the heteroatom to which they are joined, can form heterocyclyl, and wherein, when R6 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms,
wherein, when the substituent of R6 is C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C2-8 cycloalkyl, heterocyclyl or a group containing one or more of these moieties, each or more of these moieties may optionally be substituted with one or more groups selected from R6c, halogen, OH, OR6c, OCOR6c, SH, SR6c, SCOR6c, NH2, NHR6c, NHS02NH2, NHS02R6c, NR6cCOR6d, NHC(NH)N¼, NHCOR6c, NR6cR6d, COR6c, CSR6c, CN, COOH, COOR6c, CONH2, CONHOH, CONHRC6c, CONH(R)NH2, S02R6c, S03H, S02NH2, CONR6cR6d, S02NR6cR6d, wherein R6c and R6d are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C2-8 cycloalkyl and heterocyclyl or R6c and R6d, together with the heteroatom to which they are joined, can form heterocyclyl, and wherein, when the substituent of R6 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms, and

R8 is selected from H, R5a, halogen, OH, OR5a, OCOR5a, SH, SR5a, SCOR5a, NH2, NHR5a, NHS02NH2, NHS02R5a, NR5aCOR5b, NHC(NH)N¼, NHCOR5a, NR5aR5b, COR5a, CSR5a, CN, COOH, COOR5a, CONH2, CONHOH, CONHRC5a, CONH(R)NH2, C(NOH)NH2, S02R5a, S03H, S02NH2, CONR5aR5b, S02NR5aR5b, wherein R5a and R5b are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C2-8 cycloalkyl and heterocyclyl, or R5a and R5b, together with the heteroatom to which they are joined, can form heterocyclyl.

5. The process according to claim 4, wherein R1 is selected from H, methyl and ethyl, and R2 is selected from aryl, heteroaryl, heterocyclyl, and C3-10 cycloalkyl each of which may be substituted or unsubstituted.

6. The process according to claims 4 or 5, wherein R2 is selected from fully saturated heterocyclyl and C5-8 cycloalkyl, each of which are monocyclic and may be substituted or unsubstituted.

7. The process according to claim 6, wherein R2 is an unsubstituted cyclopentyl or unsubstituted cyclohexyl.

8. The process according to claim 6, wherein R2 is a fully saturated heterocyclyl, and wherein the heterocyclyl ring contains a single heteroatom, such as nitrogen or oxygen.

9. The process according to claim 8, wherein the heterocyclyl R2 is six membered and the heteroatom in the said heterocyclyl group is at the 4-position relative to the position of attachment of the heterocyclyl group R2 to the urea nitrogen.

10. The process according to claim 9, wherein the heteroatom in heterocyclyl R2 is a nitrogen heteroatom which is substituted with a group selected from CN, CONH2, C(NOH)NH2, S02C1-4 alkyl, S02aryl, CO-heteroaryl, CO-C1-8 alkyl, COO-C1-8 alkyl, COO-aryl, C1-4 alkyl, aryl C1-3 alkyl, heteroaryl C1-3 alkyl, heterocyclyl C1-3 alkyl, aryl, heteroaryl, and heterocyclyl, wherein the C1-4 alkyl may optionally be substituted with OH, CN, COOH, the S02-aryl may optionally be substituted with a C1-4 alkyl or C1-4 haloalkyl, the CO-heteroaryl may optionally be substituted with a heteroaryl or halogen, the heteroaryl C1-3 alkyl may optionally be substituted with COO-C1-3 alkyl, and the heteroaryl may optionally be substituted with one or more halogens.

11. The process according to claim 10, wherein the nitrogen heteroatom is substituted with phenyl C1-3 alkyl.
12. The process according to any one of claims 4 to 11, wherein R6 is selected from monocyclic aryl, monocyclic heteroaryl, and heterocyclyl, each of which may be substituted or unsubstituted.

13. The process according to claim 12, wherein R6 is a substituted aryl, and wherein said aryl is substituted with one or more groups selected from halogen, R6a, OH, OR6a, N¾, N0 2, NH2, CONH2, CONHOH, S02R6a, S02NR6aR6b, C(NOH)NH2, COR6a, COOH, COOR6a, CON¾, CONHOH, S02R6a, S02NR6aR6b, wherein R6a and R6b are independently selected from C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, wherein, when the substituent of R6 is C1-6 alkyl, substituted C1-6 alkyl, aryl, heteroaryl, C3-8 cycloalkyl, heterocyclyl or is a group containing one or more of these moieties, each of these moieties: may optionally be substituted with one or more groups selected from OR6c, OH, and CONH2, wherein R6c is selected from C1-6 alkyl, substituted C1-4 alkyl, aryl, heteroaryl, C3-8 cycloalkyl and heterocyclyl, and wherein, when the substituent of R6 is heteroaryl or heterocyclyl, each of these moieties may optionally be substituted with one or more oxygen atoms.

14. The process according to claim 13, wherein R6 is a substituted aryl which is substituted with one or more groups selected from halogen, OH, N0 2, C1-4 alkoxy, CON¾, C(NOH)NH2, CONHOH, S02C-C1-4 alkyl, heterocyclyl, and aryl, wherein the heterocyclyl may optionally be substituted with an oxygen atom and the aryl may optionally be substituted with CONH2.

15. The process according to claim 12, wherein R6 is a heterocyclyl which is optionally substituted with an oxygen atom.

16. The process according to claim 12, wherein R6 is a monocyclic heteroaryl which is optionally substituted with an oxygen atom.

17. The process according to any of claims 3 to 16, wherein R8 is H.

18. The process according to any of claims 3 to 17, wherein R5 is H.

19. The process according to any preceding claim, wherein Hal in the carbamoyl halide having the formula RIR2NC(=0)Hal represents Cl.

20. A process according to any of claims 1 to 3, wherein in the carbamoyl halide having the formula RIR2NC(=0)Hal, both of R1 and R2 are other than H.

21. A process according to any of claims 1 to 3, wherein R1 is C1-20 alkyl.

22. A process according to any of claims 1 to 3, wherein R2 is C3-10 cycloalkyl.

23. A process according to any of claims 1 to 3, wherein R6 is heteroaryl.

24. A process according to claim 23, wherein R6 is pyridyl.
25. A process according to claim 24, wherein the urea of Formula IIa is subjected to a further step of N-oxidation of the pyridine R6.

26. A process according to claim 25, wherein the N-oxidation is conducted using a peroxycacid, such as peracetic acid.

27. A process according to claim 25 or claim 26, for the preparation of 3-(1-(cyclohexyl(methyl)carbamoyl)-1H-imidazol-4-yl)pyridine 1-oxide.

28. A process according to any preceding claim, wherein the carbamoyl halide is a carbamoyl chloride, prepared by subjecting an amine R1R2NH to carbamoylation using a phosgene reagent, such as triphosgene.

29. A process according to claim 28, wherein the carbamoylation is conducted in dichloromethane, in the presence of a base.

30. A process according to claim 28 or claim 29, wherein the carbamoyl chloride is not isolated before addition of the intermediate of Formula II' or Formula I'.

31. A process according to any preceding claim, wherein the intermediate of Formula II' has a structure according to Formula i:

\[
\begin{align*}
\text{Formula i} \\
\text{wherein } R5 \text{ and } R6 \text{ are as defined according to any preceding claim.}
\end{align*}
\]

32. A process according to claim 31, wherein the intermediate of Formula i is prepared from a mercaptoimidazole having the structure:

\[
\begin{align*}
\text{Formula ii} \\
\text{wherein } R5 \text{ and } R6 \text{ are as defined in claim 31, or an imidazolethione tautomer thereof, using Raney nickel or a sodium nitrite/nitric acid mixture.}
\end{align*}
\]

33. A process according to claim 32, wherein the mercaptoimidazole or imidazolethione tautomer thereof has R5 as H, and is prepared by treatment of an aminoketone of Formula ii:
wherein R₆ is as defined in claim 32, or a salt thereof, with thiocyanate.

34. A process according to claim 31, wherein the intermediate of Formula i, wherein R₅ is H, is prepared by formylation of an aminoketone of Formula ii:

wherein R₆ is as defined in claim 31, or a salt thereof, followed by reaction of the -NHCHO derivative so formed with an ammonium salt.

35. A process according to claim 33, wherein the aminoketone or salt of Formula ii is prepared by acid hydrolysis of an azirine derivative of formula iii:

wherein R₆ is as defined in claim 33.

36. A process according to claim 35, wherein the azirine derivative of formula iii is prepared by subjecting a ketoxime tosylate derivative of formula iv:

wherein R₆ is as defined in claim 35 and OT₅ represents toluenesulphonate, to treatment with a base.

37. A process according to claim 36, wherein the ketoxime tosylate of Formula iv is prepared from the corresponding ketoxime: R₆C(=N-OH)CH₂ wherein R₆ is as defined in claim 36, by reaction with tosyl chloride.
38. A process according to claim 37, wherein the ketoxime R6C(=N-OH)CH3 is prepared from
the corresponding acetyl derivative of R6: R6-C(=0)CH3, wherein R6 is as defined in claim 37, by reaction thereof
with hydroxylamine.

39. A process for the preparation of an aminoketone of Formula ii:

\[
\begin{align*}
\text{O} & \\
R_6 & \\
\text{NH}_2
\end{align*}
\]

Formula ii

or a salt thereof, wherein R6 is as defined according to any preceding claim, the process comprising the tosylation
of the corresponding ketoxime: R6C(=N-OH)CH3, using tosyl chloride in the presence of a first base and in a
solvent comprising a C1-6 alcohol, followed by treatment of the resulting ketoxime tosylate, without isolation, with
a second base in a solvent comprising a C1-6 alcohol to yield the corresponding azirine derivative of Formula iii:

\[
\begin{align*}
\text{R}_6 & \\
\text{N} & \\
\end{align*}
\]

Formula iii

followed by acid hydrolysis of the azirine derivative to yield the aminoketone or salt of Formula ii.

40. A process according to claim 39, wherein the first base, employed during the tosylation step, is a butoxide
salt, such as sodium t-butoxide.

41. A process according to claim 39 or 40, wherein the solvent used in the tosylation step comprises butanol,
such as t-butanol, optionally together with methyl-t-butyl ether.

42. A process according to any of claims 39 to 41, wherein the base and alcoholic solvent are added to the
ketoxime, followed by addition of the tosyl chloride in portions.

43. A process according to any of claims 39 to 42, wherein the second base, employed during the production of
the azirine derivative, is a methoxide salt, such as sodium methoxide.

44. A process according to any of claims 39 to 43, wherein the solvent used during the production of the azirine
derivative is methanol.

45. A process according to any of claims 39 to 44, wherein the resulting aminoketone of Formula ii is used to
prepare an intermediate of Formula i according to claim 31, by means of the steps of claims 32 and 33, or claim
34.

46. A process for preparing an aminoketone of Formula ii:
or a salt thereof, wherein R6 is as defined according to any preceding claim, the process comprising the reaction of the corresponding acetyl derivative of R6: R6-C(=O)CH3, with hydroxylamine in a solvent consisting essentially of pyridine, followed by tosylation of the resulting ketoxime, without isolation thereof, using tosyl chloride, followed by treatment of the resulting ketoxime tosylate with a base in a solvent comprising a C6 alcohol, to produce the corresponding azirine derivative of Formula iii:

followed by acid hydrolysis of the azirine derivative to yield the aminoketone or salt of Formula ii.

47. A process according to claim 46, wherein the base used in the conversion of the ketoxime tosylate to the azirine is DBU.

48. A process according to claim 36 or claim 39, wherein the base used in the conversion of the ketoxime tosylate to the azirine is DBU.

49. A process for preparing an azirine derivative of Formula iii

wherein R6 is as defined according to any preceding claim, the process comprising subjecting a ketoxime tosylate of Formula iv:

to treatment with a base, wherein the base comprises DBU.
50. A process for preparing an aminoketone of Formula ii

\[ R_5 \text{O} \backslash \text{NH}_2 \]

Formula ii

wherein an azirine derivative of Formula iii prepared according to claim 49 is subjected to acid hydrolysis,

51. A substituted urea compound of Formula II or Formula I as defined in claim 1, obtained or obtainable by the process of any of claims 1 to 38, or by a process in which a process according to any of claims 39 to 50 is comprised.
Figure 11b
Figure 12a