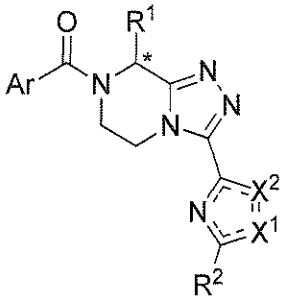
SUMMARY

In a first aspect of the present disclosure, there is provided a process of preparing chiral *N*-acyl-(3-substituted)-(8-substituted)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine of general Formula I:



(I)

or solvates thereof, wherein

R^1 is alkyl, haloalkyl, hydroxyalkyl or alkoxyalkyl;

R^2 is alkyl, alkoxyalkyl or haloalkyl;

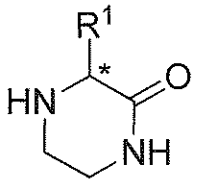
Ar is a phenyl group, optionally substituted by one or more substituent(s) selected from H, halo, alkyl, alkoxy, haloalkyl, nitrile and thiophen-2-yl;

X^1 is N and **X**^{2} is S or O; or **X**^{1} is S and **X**^{2} is N;

=== represents a single or a double bound depending on **X**^{1} and **X**^{2};

said process comprising the following steps:

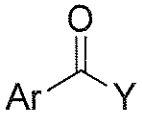
a) reacting a compound of Formula A:



(A)

wherein **R**^{1} is as defined above;

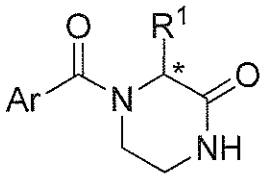
with a compound of Formula B:



(B)

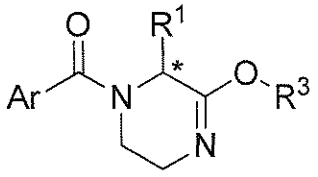
wherein **Ar** is as defined above; and **Y** is hydroxyl or halo;

to obtain a compound of Formula C:



(C)

b) converting the compound of Formula C with a tri(C1-C2 alkyl)oxonium salt, a (C1-C2)alkylsulfate, a (C1-C2)chloroformate or $PCl_5/POCl_3$/(C1-C2)hydroxyalkyl, so as to obtain a compound of Formula D:

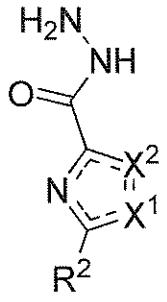


(D)

wherein **Ar** and $\mathbf{R^1}$ are as defined above, and $\mathbf{R^3}$ is C1-C2 alkyl;

in the presence of a base;

c) reacting the compound of Formula D with a compound of Formula E

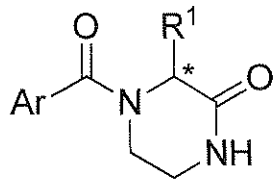


(E)

or a salt or solvate thereof, wherein $\mathbf{X^1}$, $\mathbf{X^2}$ and $\mathbf{R^2}$ are as defined above;

so as to obtain a compound of Formula I or solvate thereof.

In a second aspect of the present disclosure, there is provided a compound of Formula C:



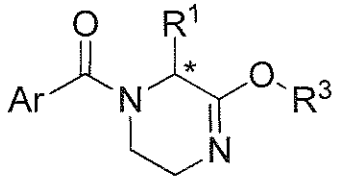
(C)

or solvates thereof, wherein

$\mathbf{R^1}$ is alkyl, haloalkyl, hydroxyalkyl or alkoxyalkyl;

Ar is a phenyl group, optionally substituted by one or more substituent(s) selected from H, halo, alkyl, alkoxy, haloalkyl, nitrile and thiophen-2-yl.

In a third aspect of the present disclosure, there is provided a compound of Formula D:



(D)

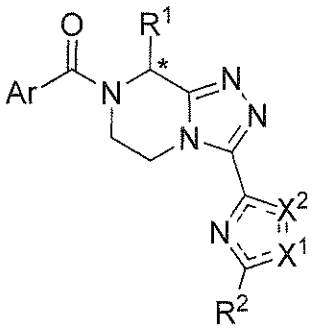
or solvates thereof, wherein

$\mathbf{R^1}$ is alkyl, haloalkyl, hydroxyalkyl or alkoxyalkyl;

$\mathbf{R^3}$ is C1-C2 alkyl;

Ar is a phenyl group, optionally substituted by one or more substituent(s) selected from H, halo, alkyl, alkoxy, haloalkyl, nitrile and thiophen-2-yl.

The present disclosure also relates to a process of preparing chiral *N*-acyl-(3-substituted)-(8-substituted)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine of general Formula I:



(I)

or solvates thereof, wherein

$\mathbf{R^1}$ is alkyl, haloalkyl, hydroxyalkyl or alkoxyalkyl, preferably $\mathbf{R^1}$ is methyl, ethyl, *n*-propyl, hydroxyethyl, methoxyethyl, trifluoromethyl, difluoromethyl or fluoromethyl; more preferably $\mathbf{R^1}$ is methyl;

$\mathbf{R^2}$ is alkyl, alkoxyalkyl or haloalkyl, preferably $\mathbf{R^2}$ is methyl, ethyl, methoxymethyl, trifluoromethyl, difluoromethyl, fluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl or 2,2,2-trifluoroethyl; more preferably $\mathbf{R^2}$ is methyl, ethyl, methoxymethyl, trifluoromethyl, difluoromethyl or fluoromethyl; even more preferably $\mathbf{R^2}$ is methyl;

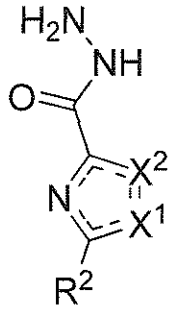
Ar is a phenyl group, optionally substituted by one or more substituent(s) selected from H, halo, alkyl, alkoxy, haloalkyl, nitrile and thiophen-2-yl; preferably **Ar** is a phenyl group, optionally substituted by one or more substituent(s) selected from H, F, Cl, methyl, methoxy, trifluoromethyl, nitrile and thiophen-2-yl; more preferably **Ar** is a phenyl group substituted by H or F;

$\mathbf{X^1}$ is N and $\mathbf{X^2}$ is S or O; or $\mathbf{X^1}$ is S and $\mathbf{X^2}$ is N;

$\overline{\overline{}}$ represents a single or a double bound depending on $\mathbf{X^1}$ and $\mathbf{X^2}$;

said process comprising the following steps:

c) reacting the compound of Formula D with a compound of Formula E:



(E)

or a salt or solvate thereof, wherein $\mathbf{X^1}$, $\mathbf{X^2}$ and $\mathbf{R^2}$ are as defined above;

so as to obtain a compound of Formula I or solvate thereof.

According to the present disclosure, the reaction of each step is carried out under controlled mild experimental conditions. Especially, the reaction is carried out at a temperature equal to or below boiling point of the organic solvent, preferably at room temperature.

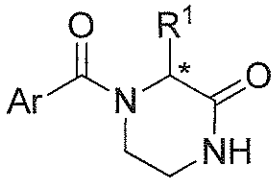
In one embodiment, the process does not use any protecting group.

In one embodiment, the process proceeds with the retention of stereochemistry with respect to the starting material.

The process according to the present disclosure preferably provides the *(R)*-enantiomer of compounds of Formula I.

The present disclosure also refers to synthesis of chiral intermediates.

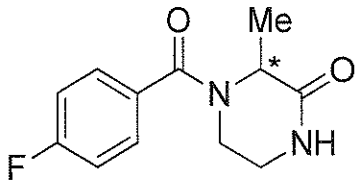
In one embodiment, the process provides chiral compounds of Formula C:



(C)

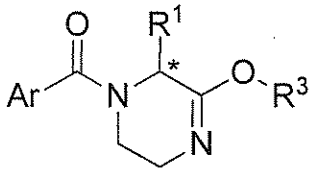
or solvates thereof, wherein $\mathbf{R^1}$ and **Ar** are as defined above.

In one preferred embodiment, compound C has Formula C-b2:



(C-b2)

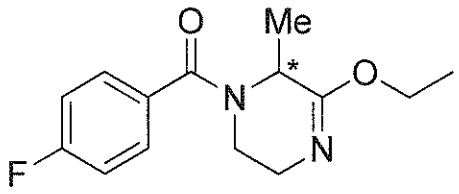
The present disclosure also refers to compounds of Formula D:



(D)

or solvates thereof, wherein $\mathbf{R^1}$, $\mathbf{R^3}$ and **Ar** are as defined above.

In one preferred embodiment, compound D has Formula D-1:



(D-1)

Preferred compounds of Formula C and Formula D are those wherein the stereoisomer obtained is the *(R)*-enantiomer.

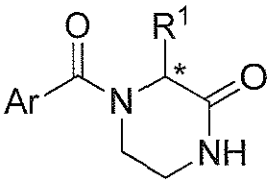
The present disclosure also relates to the use of the compounds provided by the process or solvate thereof, for the manufacture of a medicament, a pharmaceutical composition or a pharmaceutically active ingredient.

DETAILED DESCRIPTION

Process

The invention relates to a novel chiral synthesis of *N*-acyl-(3-substituted)-(8-substituted)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine compounds avoiding use of protection/deprotection steps and thus, allowing achieving high chiral purity while

10. A compound of Formula C:



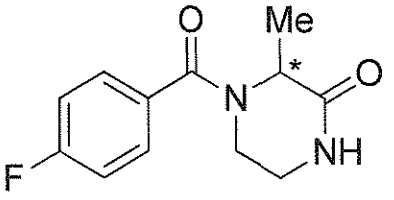
(C)

or solvates thereof, wherein

$\mathbf{R^1}$ is alkyl, haloalkyl, hydroxyalkyl or alkoxyalkyl;

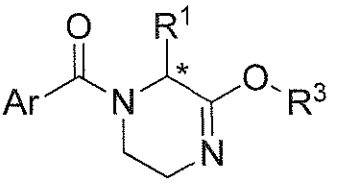
Ar is a phenyl group, optionally substituted by one or more substituent(s) selected from H, halo, alkyl, alkoxy, haloalkyl, nitrile and thiophen-2-yl.

11. The compound of claim **10** having Formula C-b2:



(C-b2)

12. A compound of Formula D:



(D)

or solvates thereof, wherein

$\mathbf{R^1}$ is alkyl, haloalkyl, hydroxyalkyl or alkoxyalkyl;

$\mathbf{R^3}$ is C1-C2 alkyl;

Ar is a phenyl group, optionally substituted by one or more substituent(s) selected from H, halo, alkyl, alkoxy, haloalkyl, nitrile and thiophen-2-yl.