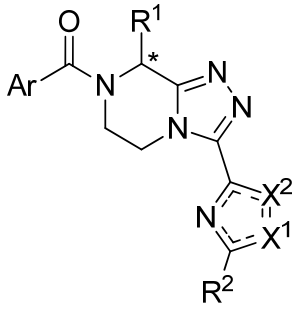
SUMMARY

The ~~invention~~present disclosure 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

R¹ is alkyl, haloalkyl, hydroxyalkyl or alkoxyalkyl, preferably **R¹** is methyl, ethyl, *n*-propyl, hydroxyethyl, methoxyethyl, trifluoromethyl, difluoromethyl or fluoromethyl; more preferably **R¹** is methyl;

R² is alkyl, alkoxyalkyl or haloalkyl, preferably **R²** is methyl, ethyl, methoxymethyl, trifluoromethyl, difluoromethyl, fluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl or 2,2,2-trifluoroethyl; more preferably **R²** is methyl, ethyl, methoxymethyl, trifluoromethyl, difluoromethyl or fluoromethyl; even more preferably **R²** is methyl;

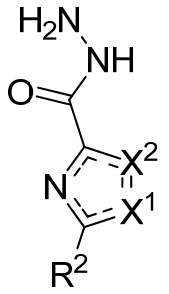
Ar is a phenyl group, optionally substituted by one or more substituent(s) selected from H, halo, alkyl, alkoxy, haloalkyl, nitrile and thiophen-2-yl; preferably **Ar** is a phenyl group, optionally substituted by one or more substituent(s) selected from H, F, Cl, methyl, methoxy, trifluoromethyl, nitrile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

X¹ is N and **X²** is S or O; or **X¹** is S and **X²** is N;

---- represents a single or a double bound depending on **X¹** and **X²**;

said process comprising the following steps:

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

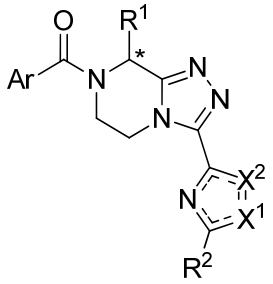


(E)

or a salt or solvate thereof, wherein **X¹**, **X²** and **R²** are as defined above;

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

In one aspect of the present disclosure, there is provided a process of preparing a 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

R¹ is alkyl, haloalkyl, hydroxyalkyl or alkoxyalkyl;

R² is alkyl, alkoxyalkyl or haloalkyl;

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

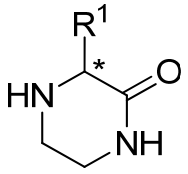
X¹ is N and **X²** is S or O; or **X¹** is S and **X²** is N;

--- represents a single or a double bond depending on **X¹** and **X²**; and

* and the solid line extending from R^1 signify individual enantiomers, excluding racemic mixtures thereof;

said process comprising the following steps:

a) reacting a compound of Formula A:

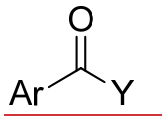


(A)

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

* and the solid line extending from R^{1} signify individual enantiomers, excluding racemic mixtures thereof;

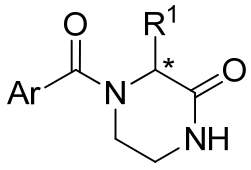
with a compound of Formula B:



(B)

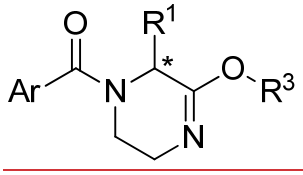
wherein **Ar** is as defined above; and **Y** is hydroxyl or halo;

to obtain a compound of Formula C:



(C)

wherein * and the solid line extending from R^{1} signify individual enantiomers, excluding racemic mixtures thereof 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:



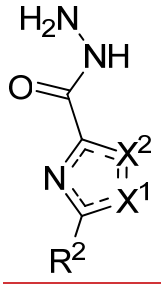
(D)

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

* and the solid line extending from R^1 signify individual enantiomers, excluding racemic mixtures thereof

in the presence of a base; and

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 a solvate thereof.

According to the present ~~invention~~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.

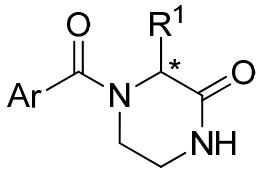
In one ~~embodiment~~example, the process does not use any protecting group.

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

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

The ~~invention~~present disclosure also refers to synthesis of chiral intermediates.

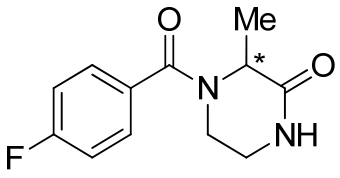
In one ~~embodiment~~example, the process provides chiral compounds of Formula C:



(C)

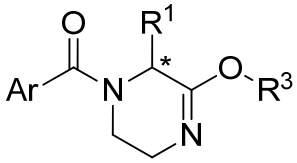
or solvates thereof, wherein **R**[1] and **Ar** are as defined above.

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



(C-b2)

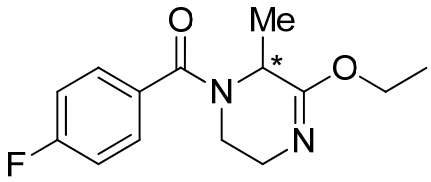
The ~~invention~~present disclosure also refers to compounds of Formula D:



(D)

or solvates thereof, wherein **R**[1], **R**[3] and **Ar** are as defined above.

In one preferred ~~embodiment~~example, 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 ~~invention~~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.

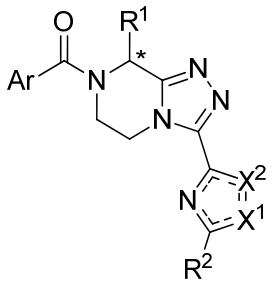
DETAILED DESCRIPTION

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

CLAIMS

1. A process of preparing a 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 an unsubstituted phenyl group or a phenyl group~~, optionally~~ substituted by one or more substituent(s) selected from the group consisting of ~~H,~~ halo, alkyl, alkoxy, haloalkyl, nitrile, and thiophen-2-yl;

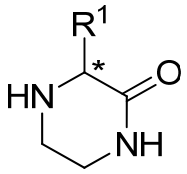
X^1 is N and **X^2** is S or O; or **X^1** is S and **X^2** is N;

--- represents a single or a double bo~~u~~nd depending on **X^1** and **X^2**; and

* and the solid line extending from R^1 signify individual enantiomers, excluding racemic mixtures thereof;

said process comprising the following steps:

a) reacting a compound of Formula A:

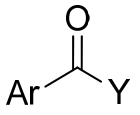


(A)

wherein **R^1** is as defined above and

* and the solid line extending from R^1 signify individual enantiomers, excluding racemic mixtures thereof;

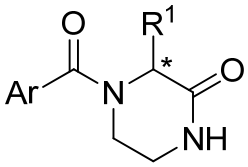
with a compound of Formula B:



(B)

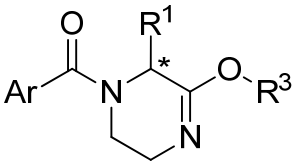
wherein **Ar** is as defined above; and **Y** is hydroxyl or halo;

to obtain a compound of Formula C:



(C)

wherein * and the solid line extending from R^1 signify individual enantiomers, excluding racemic mixtures thereof 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:



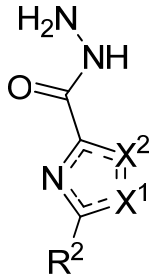
(D)

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

* and the solid line extending from R^1 signify individual enantiomers, excluding racemic mixtures thereof

in the presence of a base; and

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 a solvate thereof.

2. The process according to claim **1** proceeding with the retention of stereochemistry with respect to the starting material.

3. The process according to ~~anyone of~~ claim **1** ~~and 2~~, wherein the reaction of each step is carried out at room temperature~~under controlled mild experimental conditions~~.

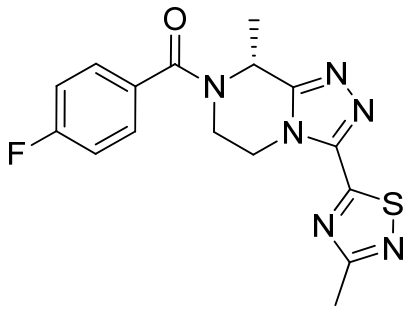
4. The process according to claim 1~~anyone of claims 1 to 3~~, wherein the amide coupling reaction step a) is carried out in an organic solvent at a temperature equal to or below boiling point of the organic solvent.

5. The process according to claim 1~~anyone of claims 1 to 4~~, wherein the process does not use any protecting group.

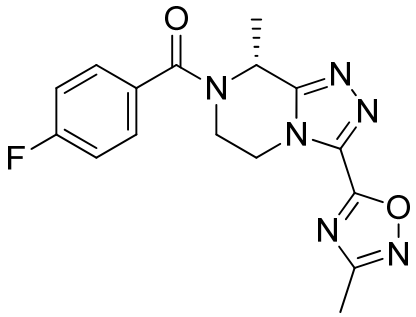
6. The process according to claim 1~~anyone of claims 1 to 5~~, wherein the base in step b) is selected from the group consisting of sodium carbonate, sodium bicarbonate, potassium carbonate ~~or~~and cesium carbonate.

7. The process according to claim 1~~anyone of claims 1 to 6~~, wherein the compound of Formula I is the *(R)*-enantiomer.

8. The process according to claim 1~~anyone of claims 1 to 7~~, wherein the compound of Formula I is



9. The process according to claim 1~~anyone of claims 1 to 7~~, wherein the compound of Formula I is



10. The process of claim 1, wherein the reaction of step b) is carried out in an organic solvent at a temperature equal to or below boiling point of the organic solvent.

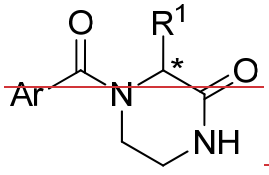
11. The process of claim 1, wherein the reactions of steps a) and b) are carried out in dichloromethane.

12. The process of claim 11, wherein the reactions of steps a) and b) are carried out at room temperature.

13. The process of claim 1, wherein the reaction of step c) is carried out at a temperature between 50 °C and 135 °C.

14. The process of claim 1, wherein the reaction of step c) is carried out at a temperature between 50 °C and 90 °C.

~~**10.** A compound of Formula C:~~



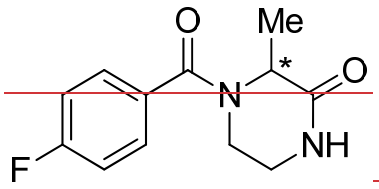
~~(C)~~

~~or solvates thereof, wherein~~

~~**R**^{1} is alkyl, haloalkyl, hydroxyalkyl or alkoxyalkyl;~~

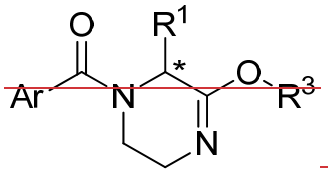
~~**Ar** is a phenyl group, optionally substituted by one or more substituent(s) selected from H, halo, alkyl, alkoxy, haloalkyl, nitrile and thiophen-2-yl;.~~

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



(C-b2)

12. A compound of Formula D:



(D)

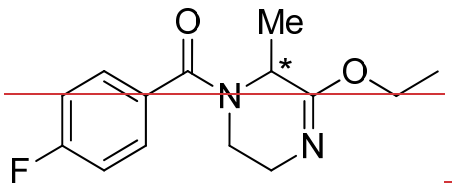
or solvates thereof, wherein

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

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.

13. The compound of claim **12** having Formula D-1:



(D-1)

14. The compound according to anyone of claims **10** to **13**, wherein the stereoisomer obtained is the *(R)* enantiomer.