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(54) Title: PROCESS FOR PREPARING N-BENZYL-3-HYDROXY-4-SUBSTITUTED-PYRIDIN-2-(1H)-ONES

(57) Abstract: Disclosed herein is a process for preparing N-benzyl-3-hydroxypyridin-2-(1H)-ones that are substituted at the pyridine ring 4-position with a 4-carbamoylpiperazin-1-yl moiety. The process comprises A) reacting 3-hydroxypyridin-2(1 H)-one with a benzylating agent in the presence of a silylating reagent that provides at least 2 equivalents of a silyl protecting group and a proton source; to form a N-benzyl-3-hydroxypyridin-2(1 H)-one; and B) reacting the N-benzyl-3-hydroxypyridin-2(1 H)-one formed in Step (A) with a carbamoylpiperazine, in the presence of a source of formaldehyde and an acid to form the substituted N-benzyl-3-hydroxypyridin-2-(1 H)-one.

PROCESS FOR PREPARING N-BENZYL-3-HYDROXY-4-SUBSTITUTED-PYRIDIN-2-(1H)-ONES

PRIORITY

This Application claims the benefit of priority from United States Provisional Patent Application Serial No. 61/941,540, filed February 19, 2014, the entirety of which is incorporated herein by reference.

FIELD OF THE DISCLOSURE

Disclosed herein is a process for preparing N-benzyl-3-hydroxypyridin-2-(1*H*)-ones that are substituted at the pyridine ring 4-position with a 4-carbamoylpiperazin-1-yl moiety.

DETAILED DISCLOSURE

General Definitions

In this specification and in the claims that follow, reference will be made to a number of terms, which shall be defined to have the following meanings:

All percentages, ratios and proportions herein are by weight, unless otherwise specified. All temperatures are in degrees Celsius (^{o} C) unless otherwise specified.

Throughout the description and claims of this specification the word "comprise" and other forms of the word, such as "comprising" and "comprises," means including but not limited to, and is not intended to exclude, for example, other additives, components, integers, or steps.

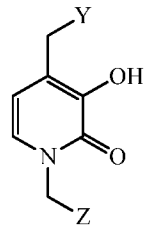
As used in the description and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

The antecedent "about" indicates that the values are approximate. For example the range of "about 1 equivalent (equiv.) to about 50 equivalents" indicates that the values are approximate values. The range of "about 1 equivalent to about 50 equivalents" includes approximate and specific values, e.g., the range includes about 1 equivalent, 1 equivalent, about 50 equivalent and 50 equivalents.

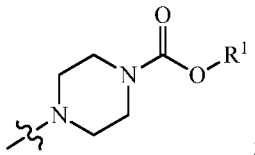
When a range is described, the range includes both the endpoints of the range as well as all numbers in between. For example, "between 1 equiv. and 10 equiv." includes 1 equiv., 10 equiv. and all amounts between 1 equiv. and 10 equiv. Likewise, "from 1 equiv. to 10 equiv." includes 1 equiv., 10 equiv. and all amounts between 1 equiv. and 10 equiv.

COMPOUNDS

The present disclosure provides a process for the preparation of compounds having the general formula:

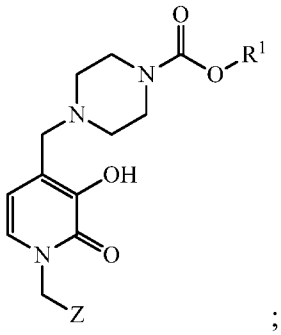


wherein Y is a 4-carbamoylpiperazin-1-yl unit having the formula:



;

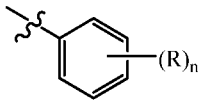
thereby providing a compound having the formula:



;

(I)

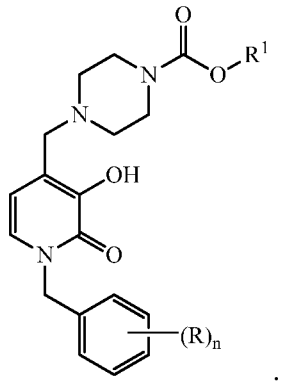
wherein R^1 is defined herein. Z is a substituted or unsubstituted phenyl ring having the formula:



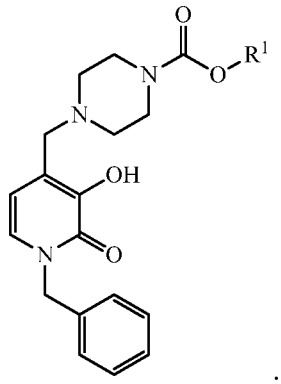
; and

the index n is an integer from 0 to 5.

As such, the compounds that can be prepared by the disclosed process are also represented by the formula:



R units when present represent from 1 to 5 substitutions for a hydrogen atom on the indicated phenyl ring. As such, the index n is an integer from 1 to 5 when one or more substitutions are present. When the index n is 0, R is absent and therefore there are no substitutions for hydrogen and the resulting subgenus is represented by the formula:



R Units

R units are independently chosen from:

i) C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkyl. Non-limiting examples of C_1-C_4 linear alkyl units include methyl (C_1), ethyl (C_2), n-propyl (C_3), n-butyl (C_4), n-pentyl (C_5) and n-hexyl (C_6). Non-limiting examples of C_3-C_6 branched and C_3-C_6 cyclic alkyl units include *iso*-propyl (C_3), cyclopropyl (C_3), *sec*-butyl (C_4), *iso*-butyl (C_4), *tert*-butyl (C_4), cyclobutyl (C_4), *neo*-pentyl (C_5), cyclopentyl (C_5), iso-hexyl (C_6), cyclohexyl (C_6), and the like;

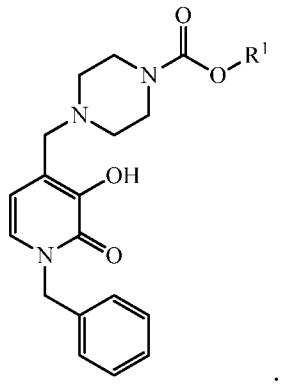
ii) C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkoxy. Non-limiting examples of C_1-C_4 linear alkoxy units include methoxy (C_1), ethoxy (C_2), n-propoxy (C_3), n-butoxy (C_4), n-pentyloxy (C_5) and n-hexyloxy (C_6). Non-limiting examples of C_3-C_6 branched and C_3-C_6 cyclic alkoxy units include *iso*-propoxy (C_3), cyclopropoxy (C_3), *sec*-butoxy (C_4), *iso*-butoxy (C_4), *tert*-

butoxy (C_4), cyclobutoxy (C_4), neopentyloxy (C_5), cyclopentyloxy (C_5), iso-hexyloxy (C_6), cyclohexyloxy (C_6), and the like;

iii) halogen, wherein each R unit comprising a halogen is independently chosen from fluoro, chloro, bromo or iodo; or

iv) cyano.

One aspect of the disclosure relates to compounds wherein the index n is equal to 0 and therefore R unit substitutions are absent therefore resulting in a subgenus having the formula:



Another aspect of the disclosure relates to compounds wherein the index n is equal to 1. One embodiment of this aspect relates to compounds wherein R is a halogen. The following are non-limiting examples of this embodiment wherein Z units are chosen from 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2-iodophenyl, 3-iodophenyl, and 4-iodophenyl.

In one iteration of this embodiment, Z is 4-chlorophenyl.

Another embodiment of this aspect relates to compounds wherein R is chosen from one or more C_1-C_6 linear alkyl units. Non-limiting examples of this embodiment are Z units chosen from 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 2-(n-propyl)phenyl, 3-(n-propyl)phenyl, 4-(n-propyl)phenyl, 2-(n-butyl)phenyl, 3-(n-butyl)phenyl, 4-(n-butyl)phenyl, 2-(n-pentyl)phenyl, 3-(n-pentyl)phenyl, 4-(n-pentyl)phenyl, 2-(n-hexyl)phenyl, 3-(n-hexyl)phenyl, and 4-(n-hexyl)phenyl.

A further embodiment of this aspect relates to compounds wherein R is chosen from one or more C_3-C_6 branched alkyl units. Non-limiting examples of this embodiment are Z unis chosen from 2-(*iso*-propyl)phenyl, 3-(*iso*-propyl)phenyl, 4-(*iso*-propyl)phenyl, 2-(*iso*-

butyl)phenyl, 3-(*iso*-butyl)phenyl, 4-(*iso*-butyl)phenyl, 2-(*sec*-butyl)phenyl, 3-(*sec*-butyl)phenyl, 4-(*sec*-butyl)phenyl, 2-(*tert*-butyl)phenyl, 3-(*tert*-butyl)phenyl, 4-(*tert*-butyl)phenyl, 2-(*iso*-pentyl)phenyl, 3-(*iso*-pentyl)phenyl, 4-(*iso*-pentyl)phenyl, 2-(*iso*-hexyl)phenyl, 3-(*iso*-hexyl)phenyl, and 4-(*iso*-hexyl)phenyl.

A still further embodiment of this aspect relates to compounds wherein R is chosen from one or more C_1-C_6 linear alkoxy units. Non-limiting examples of this embodiment are Z unis chosen from 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-(n-propoxy)phenyl, 3-(n-propoxy)phenyl, 4-(n-propoxy)phenyl, 2-(n-butoxy)phenyl, 3-(n-butoxy)phenyl, 4-(n-butoxy)phenyl, 2-(n-pentyloxy)phenyl, 3-(n-pentyloxy)phenyl, 4-(n-pentyloxy)phenyl, 2-(n-hexyloxy)phenyl, 3-(n-hexyloxy)phenyl, and 4-(n-hexyloxy)phenyl.

A yet further embodiment of this aspect relates to compounds wherein R is chosen from one or more C_3-C_6 branched alkoxy units. Non-limiting examples of this embodiment are Z unis chosen from 2-(*iso*-propoxy)phenyl, 3-(*iso*-propoxy)phenyl, 4-(*iso*-propoxy)phenyl, 2-(*iso*-butoxy)phenyl, 3-(*iso*-butoxy)phenyl, 4-(*iso*-butoxy)phenyl, 2-(*sec*-butoxy)phenyl, 3-(*sec*-butoxy)phenyl, 4-(*sec*-butoxy)phenyl, 2-(*tert*-butoxy)phenyl, 3-(*tert*-butoxy)phenyl, 4-(*tert*-butoxy)phenyl, 2-(*iso*-pentyloxy)phenyl, 3-(*iso*-pentyloxy)phenyl, 4-(*iso*-pentyloxy)phenyl, 2-(*iso*-hexyloxy)phenyl, 3-(*iso*-hexyloxy)phenyl, and 4-(*iso*-hexyloxy)phenyl.

A further aspect of the disclosure relates to compounds wherein the index n is greater than 1. One embodiment of this aspect relates to compounds wherein R is a halogen. The following are non-limiting examples of this embodiment wherein Z units are chosen from 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2,3,4-trifluorophenyl, 2,3,5-trifluorophenyl, 2,4,6-trifluorophenyl, 3,4,5-trifluorophenyl, 2,3,4,5-tetrafluorophenyl, 2,3,4,6-tetra-fluorophenyl, 2,3,4,5,6-pentafluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2,3,4-trichlorophenyl, 2,3,5-trichlorophenyl, 2,4,6-trichlorophenyl, 3,4,5-trichlorophenyl, 2,3,4,5-tetrachlorophenyl, 2,3,4,6-tetra-chlorophenyl, 2,3,4,5,6-pentachlorophenyl, 2,3-dibromophenyl, 2,4-dibromophenyl, 2,5-dibromophenyl, 2,6-dibromophenyl, 3,4-dibromophenyl, 3,5-dibromophenyl, 2,3,4-tribromophenyl, 2,3,5-tribromophenyl, 2,4,6-tribromophenyl, 3,4,5-tribromophenyl, 2,3,4,5-tetrabromophenyl, 2,3,4,6-tetra-bromophenyl, 2,3,4,5,6-pentabromophenyl, 2,3-diiodophenyl, 2,4-

diiodophenyl, 2,5-diiodophenyl, 2,6-diiodophenyl, 3,4-diiodophenyl, 3,5-diiodophenyl, 2,3,4-triiodophenyl, 2,3,5-triiodophenyl, 2,4,6-triiodophenyl, 3,4,5-triiodophenyl, 2,3,4,5-tetraiodophenyl, 2,3,4,6-tetra-iodophenyl, and 2,3,4,5,6-pentaiodophenyl.

Another embodiment of this aspect relates to compounds wherein R is a C_1-C_6 linear alkyl. The following are non-limiting examples of this embodiment wherein Z units are chosen from 2,3-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 2,3,4-trimethylphenyl, 2,3,5-trimethylphenyl, 2,4,6-trimethylphenyl, 3,4,5-trimethylphenyl, 2,3,4,5-tetramethylphenyl, 2,3,4,6-tetra-methylphenyl, 2,3,4,5,6-pentamethylphenyl, 2,3-diethylphenyl, 2,4-diethylphenyl, 2,5-diethylphenyl, 2,6-diethylphenyl, 3,4-diethylphenyl, 3,5-diethylphenyl, 2,3,4-triethylphenyl, 2,3,5-triethylphenyl, 2,4,6-triethylphenyl, 3,4,5-triethylphenyl, 2,3,4,5-tetraethylphenyl, 2,3,4,6-tetra-ethylphenyl, 2,3,4,5,6-pentaethylphenyl, 2,3-dibromophenyl, 2,4-dibromophenyl, 2,5-dibromophenyl, 2,6-dibromophenyl, 3,4-dibromophenyl, 3,5-dibromophenyl, 2,3,4-tri(n-propyl)phenyl, 2,3,5-tri(n-propyl)phenyl, 2,4,6-tri(n-propyl)phenyl, 3,4,5-tri(n-propyl)phenyl, 2,3,4,5-tetra(n-propyl)phenyl, 2,3,4,6-tetra-(n-propyl)phenyl, 2,3,4,5,6-penta(n-propyl)phenyl, 2,3-di(n-butyl)phenyl, 2,4-di(n-butyl)phenyl, 2,5-di(n-butyl)phenyl, 2,6-di(n-butyl)phenyl, 3,4-di(n-butyl)phenyl, 3,5-di(n-butyl)phenyl, 2,3,4-tri(n-butyl)-phenyl, 2,3,5-tri(n-butyl)phenyl, 2,4,6-tri(n-butyl)phenyl, 3,4,5-tri(n-butyl)phenyl, 2,3,4,5-tetra(n-butyl)phenyl, 2,3,4,6-tetra(n-butyl)phenyl, and 2,3,4,5,6-penta(n-butyl)phenyl.

A still further aspect of the disclosure relates to compounds wherein the index n is greater than 1 and wherein at least one R is chosen from C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkyl and at least one R is chosen from halogen.

A yet further aspect of the disclosure relates to compounds wherein the index n is greater than 1 and wherein at least one R is chosen from C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkoxy and at least one R is chosen from halogen.

A still yet further aspect of the disclosure relates to compounds wherein the index n is greater than 1 and wherein at least one R is chosen from C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkyl and at least one R is chosen from C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkoxy.

R^1 Units

R^1 units are C_1-C_4 linear or C_3-C_4 branched alkyl. Non-limiting examples of C_1-C_4 linear alkyl units include methyl (C_1), ethyl (C_2), n-propyl (C_3), and n-butyl (C_4). Non-

limiting examples of C_3-C_6 branched alkyl units include *iso*-propyl (C_3), *sec*-butyl (C_4), *iso*-butyl (C_4) and *tert*-butyl (C_4).

In one embodiment R^1 is *tert*-butyl.

In another embodiment R^1 is methyl.

In a further embodiment R^1 is ethyl.

The following are non-limiting examples of compounds that can be prepared by the disclosed process:

Methyl 4-((1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,3-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,4-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,5-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,6-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3,4-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3,5-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,3-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,4-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,5-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,6-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3,4-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3,5-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2-bromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3-bromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(4-bromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,3-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,4-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,5-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,6-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3,4-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3,5-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2-iodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3-iodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(4-iodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,3-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,4-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,5-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,6-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3,4-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3,5-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,3-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,4-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,5-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,6-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3,4-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3,5-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,3-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,4-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,5-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,6-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3,4-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3,5-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2-bromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3-bromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(4-bromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,3-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,4-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,5-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,6-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3,4-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3,5-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2-iodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3-iodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(4-iodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,3-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,4-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,5-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,6-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3,4-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3,5-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(4-fluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,3-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,4-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,5-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,6-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3,4-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3,5-difluorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,3-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,4-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,5-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,6-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3,4-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3,5-dichlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2-bromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3-bromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(4-bromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,3-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,4-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,5-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,6-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3,4-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3,5-dibromobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2-iodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3-iodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(4-iodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,3-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,4-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,5-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,6-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3,4-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3,5-diiodobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2-methylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3-methylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(4-methylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,3-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,4-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,5-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,6-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3,4-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3,5-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2-methoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3-methoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(4-methoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,3-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,4-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,5-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(2,6-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3,4-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Methyl 4-((1-(3,5-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2-methylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3-methylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(4-methylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,3-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,4-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,5-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,6-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3,4-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3,5-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2-methoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3-methoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(4-methoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,3-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,4-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,5-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(2,6-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3,4-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

Ethyl 4-((1-(3,5-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2-methylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3-methylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(4-methylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,3-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,4-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,5-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,6-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3,4-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3,5-dimethylbenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2-methoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3-methoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(4-methoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,3-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,4-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,5-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(2,6-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate;

tert-Butyl 4-((1-(3,4-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate; and

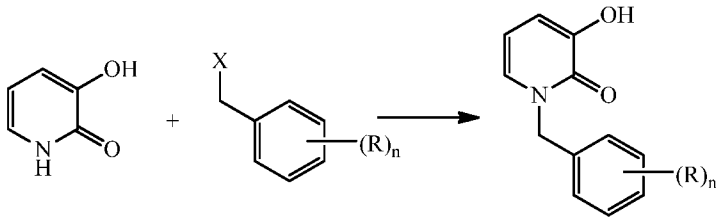
tert-Butyl 4-((1-(3,5-dimethoxybenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate.

PROCESS

The disclosed process is outlined herein below in Scheme I.

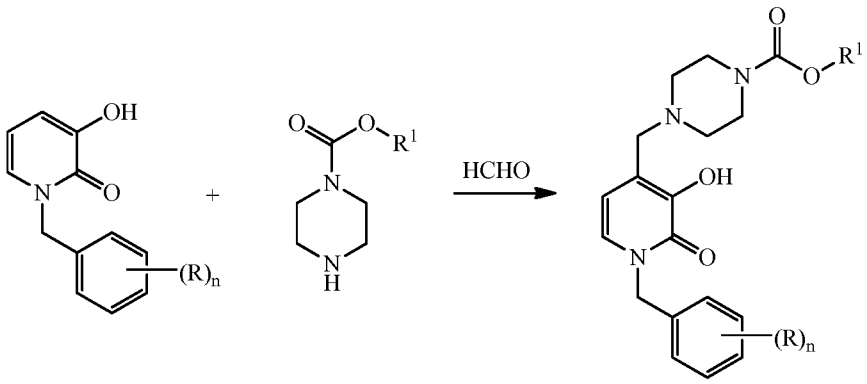
Scheme I

Step A



A-1 **A-2**

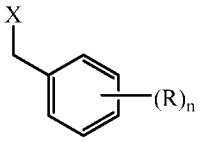
Step B



A-2 **B-1** **B-2**

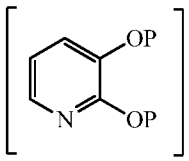
Step A

Step A relates to the benzylation of 3-hydroxypyridin-2(1*H*)-one (2,3-dihydroxy-pyridine) at the pyridin-2(1*H*)-one ring nitrogen with a benzylating agent having the formula:



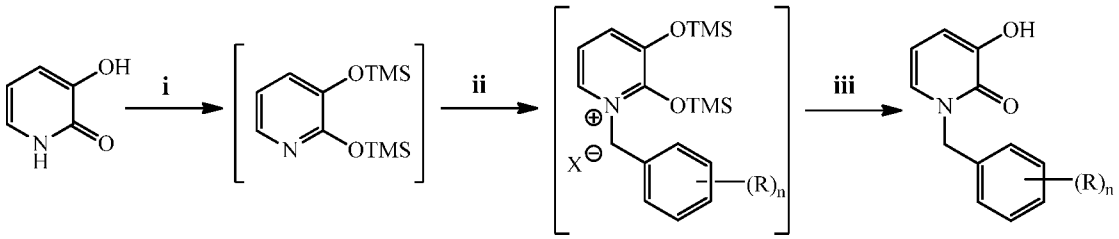
wherein X is a leaving group. Non-limiting examples of leaving groups include chloro, bromo, iodo, tosyl, mesyl and the like. R and the index n are defined herein above.

The reaction depicted in step A is carried out under modified Silyl-Hilbert-Johnson conditions. Without wishing to be limited by theory, the reaction depicted in Step A includes formation of di-silylated intermediate. This di-protected intermediate prevents undesired O-benzylation of the 3-hydroxy and 2-hydroxy units of the pyridine tautomeric form 3-hydroxypyridin-2(1*H*)-one by the benzylating agent **A-1**. The resulting bis-silyl protected intermediate has the formula:



wherein P represents a silyl protecting group. Scheme II below summarizes a non-limiting example of Step A wherein two equivalents of hexamethyldisilazane are used to form intermediate **A-i**.

Scheme II



A-i **A-ii** **A-2**

Step A(i) relates to the addition of at least about 2 equivalents of a silylating reagent to form a bis-O-silyl intermediate or a least one equivalent of a silylating reagent that can provide two equivalents of a silyl protecting group to form an intermediate such as **A-i** as depicted in the example set forth in Scheme II. In one non-limiting example, this intermediate can be formed by the reaction of bis(trimethylsilyl)amine (HMDS) with 3-hydroxypyridin-2(1*H*)-one. As indicated, intermediate **A-i** is not isolated, but is converted to intermediate **A-ii** *in situ* by the addition of reagent **A-1** during step A(ii). Also as indicated in Scheme II, product **A-ii** is also not isolated. Aqueous work-up removes the silyl protecting groups allowing the pyridinium salt **A-ii** to collapse and tautomerize to the

3-hydroxy-pyridin-2(1*H*)-one form and thereby liberate N-benzyl-3-hydroxypyridin-2(1*H*)-ones having the formula **A-2**.

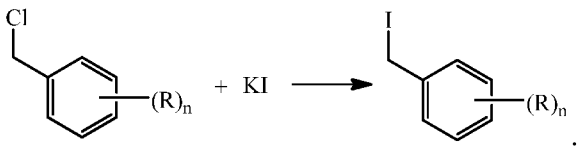
Step A can be conducted with any a silylating reagent in an amount wherein the agent provides two or more equivalents of protecting group. For example, one equivalent of hexamethyldisilazane provides two equivalents of a silyl protecting group. In one embodiment of the disclosed process, hexamethyldisilazane is used as the silylating reagent. Non-limiting examples of silylating reagents include trimethylsilyl chloride, *tert*-butyl dimethylsilyl chloride, trimethylsilylimidazole, N,O-bis(trimethylsilyl)acetamide, N,N'-bis(trimethylsilyl)urea, N,O-bis(trimethylsilyl)trifluoroacetamide, heptamethyldisilazane, 1,1,3,3,-tetramethyl-1,3-divinyl-disilizane, and the like.

Step A is conducted in the presence of a source of proton, *i.e.*, a strong or weak protic acid as well as some salts of strong mineral acids. Typically the acid is present in a catalytic amount. In one embodiment, the source of proton is ammonium sulfate, $(NH_4)_2SO_4$. In another embodiment, the acid is hydroiodic, HI, or hydrobromic acid, HBr. In another embodiment the acid is phosphoric acid, H_3PO_4, or sulfuric acid, H_2SO_4.

Step A can be conducted in the presence of any compatible solvent or mixture of compatible solvents. Non-limiting examples of solvents includes acetonitrile, tetrahydrofuran, dichloromethane, chloroform, 1,2-dichloroethane, 1,1,1-trichloroethane, toluene, m-xylene and mixtures thereof. In one embodiment, acetonitrile is used as the solvent.

In one embodiment of the disclosed process, the reactant **A-1** is activated toward nucleophilic attack by 3-hydroxypyridin-2(1*H*)-one. This is accomplished by replacing the original leaving group X with a leaving group X^1 which is more labile to attack by the 3-hydroxypyridin-2(1*H*)-one nitrogen. In one embodiment, an *in situ* Finkelstein reaction is used to activate the leaving group. A non-limiting example of the formation of an activated benzylating agent is depicted herein below in Scheme III.

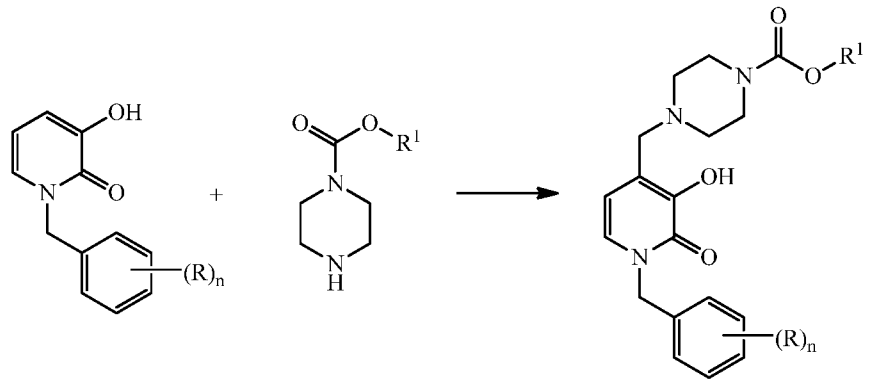
Scheme III



Step B

Step B relates to a Mannich Reaction between the N-benzyl-3-hydroxypyridin-2(1*H*)-one formed in Step A and a 4-carbamoylpiperazine, **B-1**. Step B is depicted in Scheme IV below.

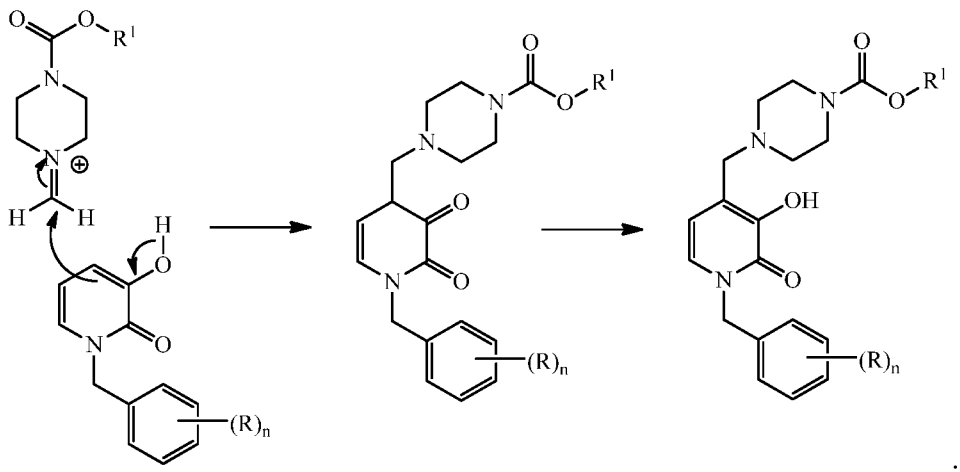
Scheme IV



A-2 **B-1** **B-2**

Without wishing to be limited by theory, Step B of the disclosed process involves the condensation of A-2 with B-1 in the presence of formaldehyde under standard Mannich Reaction conditions. The *in situ* generated imine of **B-1** reacts with intermediate **A-2** according to the proposed Scheme V herein below.

Scheme V



Intermediate A-2 and adduct B-1 are combined together with a source of formaldehyde and a protic acid. The reaction can be conducted at room temperature or at any temperature at or below reflux depending upon the choice of an optional solvent.

The reaction can be conducted in the presence of a compatible solvent. Non-limiting examples of solvents include water, formic acid, acetic acid; alcohols, for example, methanol, ethanol, 2,2,2-trichlorethanol, propanol, isopropanol, butanol, *tert*-butanol, and

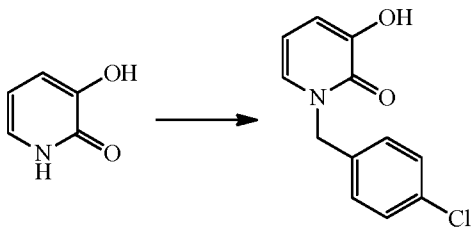
the like; esters, for example, methyl acetate, ethyl acetate, methyl propionate, ethyl propionate, and the like; ethers, for example, diethyl ether, methyl *tert*-butyl ether, tetrahydrofuran, dimethoxyethane, bis(2-methoxyethyl) ether (diglyme), 1,4-dioxane,and the like; alkanes, for example, pentane, isopentane, petroleum ether, hexane, mixtures of hexanes, cyclohexane, heptanes, isoheptane, octane, isooctane, and the like; halogenated solvents, for example, dichloromethane, chloroform, carbon tetrachloride, 1,1-dichloroethane, 1,1,1-trichloroethane, 1,2-dichloroethane, chlorobenzene, and the like; aromatic hydrocarbons, for example, benzene, toluene, 1,2-dimethylbenzene (*ortho*-xylene), 1,3-dimethylbenzene (*meta*-xylene), 1,4-dimetylbenzene (*para*-xylene), nitrobenzene, and the like; dipolar aprotic solvents, for example, acetonitrile, dimethylsulfoxide, *N,N*-dimethylformamide, *N,N*-diethylformamide, *N,N*-dimethylacetamide, *N,N*-diethylacetamide, *N*-methyl-2-pyrrolidinone, carbon disulfide, and hexamethylphosphoramide; and mixtures of one or more solvents.

In one embodiment of the disclosed process the solvent is an alcohol, for example, methanol, ethanol, n-propanol or *iso*-propanol. In one non-limiting example ethanol is used as a solvent. The formulator can choose different alcohols depending upon the desired temperature to which the reaction is heated, for example, the temperature of reflux.

In one embodiment of the disclosed process the source of formaldehyde is a 37% weight percent solution in water. Other reagents which form or release formaldehyde or a formaldehyde equivalent can be used.

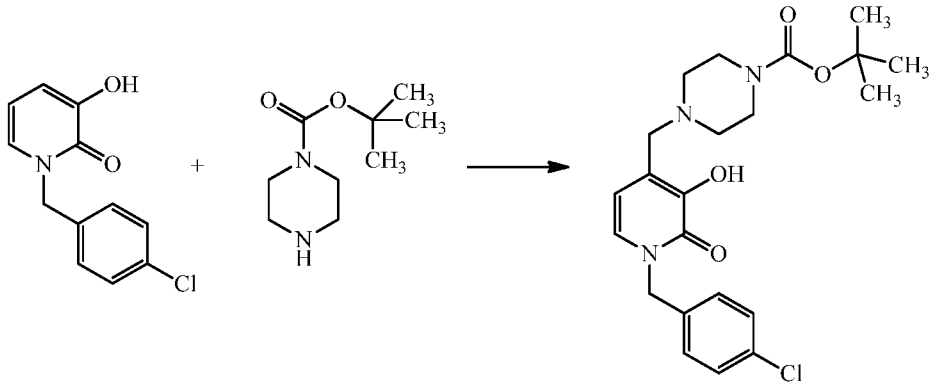
The following is a non-limiting example of the disclosed process as outlined in Scheme VI and depicted in Example 1.

Scheme VI



1

Reagents and conditions: (i) HMDS, $(NH_4)SO_4$; CH_3CN; reflux, 4 hr;
(ii) KI, 4-chlorobenzyl chloride.



1 2 3

Reagents and conditions: HCHO (aq.), AcOH, EtOH; 50 ^{O}C, 18 hr.

EXAMPLE 1

tert-Butyl 4-((1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate (3)

Preparation of 1-(4-chlorobenzyl)-3-hydroxypyridin-2(1*H*)-one (**1**): to a nitrogen purged 1-L round bottom flask equipped with a mechanical stirrer, upright condenser, and thermometer was charged 3-hydroxypyridin-2(1*H*)-one [2,3-dihydroxypyridine] (40.0 g, 0.36 mol, 1 equiv.) [CAS No. 16867-04-2], ammonium sulfate (2.4 g, 0.02 mol, 0.05 equiv.) and acetonitrile (200 mL, 5 parts v/w). The resulting suspension was stirred at room temperature. Hexamethyldisilazane (116.2 g, 0.72 mol, 2 equiv.) is added dropwise. The resulting suspension was heated to reflux for 4 hours. The solution was then cooled to room temperature followed by the addition of a solution of 4-chlorobenzyl chloride (63.8 g, 0.4 mol, 1.1 equiv.) in acetonitrile (40 mL, 1 part v/w). Potassium iodide (59.8 g, 0.36 mol, 1 equiv.) is then added. The solution was then brought to reflux for 16 hours. The solution was cooled to 5 °C and water (240 mL) was slowly added over 15 minutes. The reaction mixture was allowed to warm to room temperature and stirring was continued for 2 hours. The solution was filtered under vacuum and rinsed with water (360 mL). The filter cake is then washed with methyl *tert*-butyl ether (360 mL). The resulting green-brown solid is vacuum dried to afford 63.5 g (86.2%) of the desired product. ^{1}H NMR (DMSO-*d*6) δ ppm 7.4 (d, 2H), 7.3 (d, 1H), 7.2 (d, 2H), 6.7 (d, 1H), 6.1 (t, 1H), and 5.1 (s, 2H).

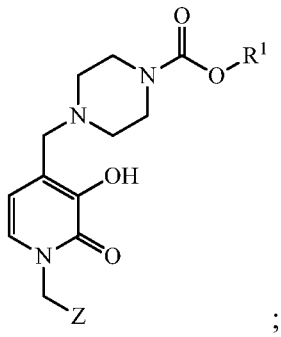
Preparation of *tert*-butyl 4-((1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate (**3**): to a nitrogen purged 2-L round

bottom flask equipped with a mechanical stirrer, upright condenser, and thermometer was charged 1-(4-chlorobenzyl)-3-hydroxypyridin-2(1*H*)-one (**1**) (50.0 g, 0.21 mol, 1 equiv.), *tert*-butyl piperazine-1-carboxylate, (**2**) (79.0 g, 0.42 mol, 2 equiv.) [CAS No. 57260-71-6] and ethanol (750 mL, 15 parts v/w). The solution was stirred and 37% aqueous formaldehyde (34.7 mL, 0.47 mol, 2.2 equiv.) and acetic acid (36.4 mL, 0.64 mol, 3 equiv.) were added and the solution stirred for 1 hour after which the reaction solution was heated to 50 °C for 18 hours. The reaction mixture was then cooled below room temperature and filtered under vacuum. The resulting solid was rinsed with ethanol (250 mL) and dried under a stream of nitrogen to afford 77.2 g (83.9%) of the desired product. ^{1}H NMR (DMSO-*d6*) δ ppm 7.4 (d, 2H), 7.3 (d, 2H), 7.2 (d, 1H), 6.2 (d, 1H), 5.1 (s, 2H), 3.4-3.2 (m partly under brs water peak, 6H), 2.3 (m, 4H), 1.4 (s, 9H).^{13}C NMR (DMSO-*d6*) [observed] δ ppm 157.24, 153.77, 144.36, 136.33, 132.15, 129.67, 128.48, 126.86, 124.56, 107.01, 78.74, 54.68, 52.49, 50.64, 43.48, and 28.03.

Other advantages which are obvious and which are inherent to the invention will be evident to one skilled in the art.

WHAT IS CLAIMED IS:

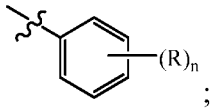
1. A process for preparing a compound having the formula:



;

(I)

wherein Z is a substituted or unsubstituted phenyl ring having the formula:



;

the index n is an integer from 0 to 5;

when the index n is an integer form 1 to 5 then R represents from 1 to 5 independently chosen substitutions for hydrogen; when the index n is equal to 0, R is absent; each R is independently chosen from:

i) C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkyl;

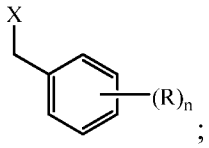
ii) C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkoxy;

iii) halogen; and

iv) cyano;

R^1 is C_1-C_4 linear or C_3-C_4 branched alkyl; comprising,

A) reacting 3-hydroxypyridin-2(1*H*)-one with a benzylating agent having the formula:

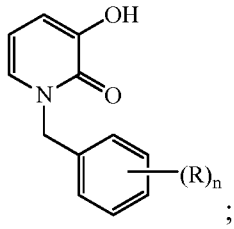


;

X is a leaving group;

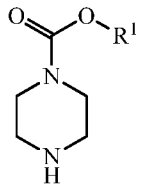
in the presence of a silylating reagent that provides at least 2 equivalents of a silyl protecting group and a proton source;

to form a N-benzyl-3-hydroxypyridin-2(1*H*)-one having the formula:



; and

B) reacting the N-benzyl-3-hydroxypyridin-2(1*H*)-one formed in Step (A) with a compound having the formula:



;

in the presence of a source of formaldehyde and an acid to form the compound having Formula (I).

2. The process according to Claim 1, wherein R^1 is chosen from methyl, ethyl and *tert*-butyl.

3. The process according to Claim 1, wherein R^1 is *tert*-butyl.

4. The process according to any one of Claims 1 to 3, wherein R is halogen.

5. The process according to any one of Claims 1 to 4, wherein Z is chosen from 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2-iodophenyl, 3-iodophenyl, and 4-iodophenyl.

6. The process according to any one of Claims 1 to 3, wherein Z is 4-chlorophenyl.

7. The process according to any one of Claims 1 to 3, wherein R is C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkyl.

8. The process according to any one of Claims 1 to 3, Z is chosen from 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethylphenyl, 3-ethylphenyl, 4-

ethylphenyl, 2-(n-propyl)phenyl, 3-(n-propyl)phenyl, 4-(n-propyl)phenyl, 2-(n-butyl)phenyl, 3-(n-butyl)phenyl, 4-(n-butyl)phenyl, 2-(n-pentyl)phenyl, 3-(n-pentyl)phenyl, 4-(n-pentyl)phenyl, 2-(n-hexyl)phenyl, 3-(n-hexyl)phenyl, and 4-(n-hexyl)phenyl

9. The process according to any one of Claims 1 to 3, Z is chosen from 2-(*iso*-propyl)phenyl, 3-(*iso*-propyl)phenyl, 4-(*iso*-propyl)phenyl, 2-(*iso*-butyl)phenyl, 3-(*iso*-butyl)phenyl, 4-(*iso*-butyl)phenyl, 2-(*sec*-butyl)phenyl, 3-(*sec*-butyl)phenyl, 4-(*sec*-butyl)phenyl, 2-(*tert*-butyl)phenyl, 3-(*tert*-butyl)phenyl, 4-(*tert*-butyl)phenyl, 2-(*iso*-pentyl)phenyl, 3-(*iso*-pentyl)phenyl, 4-(*iso*-pentyl)phenyl, 2-(*iso*-hexyl)phenyl, 3-(*iso*-hexyl)phenyl, and 4-(*iso*-hexyl)phenyl.

10. The process according to any one of Claims 1 to 3, wherein R is C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkoxy.

11. The process according to any one of Claims 1 to 3, wherein Z is chosen from 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-(n-propoxy)phenyl, 3-(n-propoxy)phenyl, 4-(n-propoxy)phenyl, 2-(n-butoxy)phenyl, 3-(n-butoxy)phenyl, 4-(n-butoxy)phenyl, 2-(n-pentyloxy)phenyl, 3-(n-pentyloxy)phenyl, 4-(n-pentyloxy)phenyl, 2-(n-hexyloxy)phenyl, 3-(n-hexyloxy)phenyl, and 4-(n-hexyloxy)phenyl.

12. The process according to any one of Claims 1 to 3, wherein Z is chosen from 2-(*iso*-propoxy)phenyl, 3-(*iso*-propoxy)phenyl, 4-(*iso*-propoxy)phenyl, 2-(*iso*-butoxy)phenyl, 3-(*iso*-butoxy)phenyl, 4-(*iso*-butoxy)phenyl, 2-(*sec*-butoxy)phenyl, 3-(*sec*-butoxy)phenyl, 4-(*sec*-butoxy)phenyl, 2-(*tert*-butoxy)phenyl, 3-(*tert*-butoxy)phenyl, 4-(*tert*-butoxy)phenyl, 2-(*iso*-pentyloxy)phenyl, 3-(*iso*-pentyloxy)phenyl, 4-(*iso*-pentyloxy)phenyl, 2-(*iso*-hexyloxy)phenyl, 3-(*iso*-hexyloxy)phenyl, and 4-(*iso*-hexyloxy)phenyl.

13. The process according to any one of Claims 1 to 3, wherein Z is chosen from 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2,3,4-trifluorophenyl, 2,3,5-trifluorophenyl,

2,4,6-trifluorophenyl, 3,4,5-trifluorophenyl, 2,3,4,5-tetrafluorophenyl, 2,3,4,6-tetra-fluorophenyl, 2,3,4,5,6-pentafluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2,3,4-trichlorophenyl, 2,3,5-trichlorophenyl, 2,4,6-trichlorophenyl, 3,4,5-trichlorophenyl, 2,3,4,5-tetrachlorophenyl, 2,3,4,6-tetra-chlorophenyl, 2,3,4,5,6-pentachlorophenyl, 2,3-dibromophenyl, 2,4-dibromophenyl, 2,5-dibromophenyl, 2,6-dibromophenyl, 3,4-dibromophenyl, 3,5-dibromophenyl, 2,3,4-tribromophenyl, 2,3,5-tribromophenyl, 2,4,6-tribromophenyl, 3,4,5-tribromophenyl, 2,3,4,5-tetrabromophenyl, 2,3,4,6-tetra-bromophenyl, 2,3,4,5,6-pentabromophenyl, 2,3-diiodophenyl, 2,4-diiodophenyl, 2,5-diiodophenyl, 2,6-diiodophenyl, 3,4-diiodophenyl, 3,5-diiodophenyl, 2,3,4-triiodophenyl, 2,3,5-triiodophenyl, 2,4,6-triiodophenyl, 3,4,5-triiodophenyl, 2,3,4,5-tetraiodophenyl, 2,3,4,6-tetraiodophenyl, and 2,3,4,5,6-pentaiodophenyl.

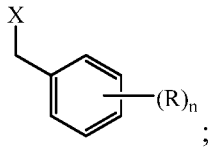
14. The process according to any one of Claims 1 to 3, wherein Z is chosen from 2,3-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethyl-phenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 2,3,4-trimethylphenyl, 2,3,5-trimethyl-phenyl, 2,4,6-trimethylphenyl, 3,4,5-trimethylphenyl, 2,3,4,5-tetramethylphenyl, 2,3,4,6-tetra-methylphenyl, 2,3,4,5,6-pentamethylphenyl, 2,3-diethylphenyl, 2,4-diethylphenyl, 2,5-diethylphenyl, 2,6-diethylphenyl, 3,4-diethylphenyl, 3,5-diethylphenyl, 2,3,4-triethylphenyl, 2,3,5-triethylphenyl, 2,4,6-triethylphenyl, 3,4,5-triethylphenyl, 2,3,4,5-tetraethylphenyl, 2,3,4,6-tetra-ethylphenyl, 2,3,4,5,6-pentaethylphenyl, 2,3-dibromophenyl, 2,4-dibromo-phenyl, 2,5-dibromophenyl, 2,6-dibromophenyl, 3,4-dibromophenyl, 3,5-dibromophenyl, 2,3,4-tribromophenyl, 2,3,5-tri(n-propyl)phenyl, 2,4,6-tri(n-propyl)phenyl, 3,4,5-tri(n-propyl)phenyl, 2,3,4,5-tetra(n-propyl)phenyl, 2,3,4,6-tetra-(n-propyl)phenyl, 2,3,4,5,6-penta(n-propyl)phenyl, 2,3-di(n-butyl)phenyl, 2,4-di(n-butyl)phenyl, 2,5-di(n-butyl)phenyl, 2,6-di(n-butyl)phenyl, 3,4-di(n-butyl)phenyl, 3,5-di(n-butyl)phenyl, 2,3,4-tri(n-butyl)-phenyl, 2,3,5-tri(n-butyl)phenyl, 2,4,6-tri(n-butyl)phenyl, 3,4,5-tri(n-butyl)phenyl, 2,3,4,5-tetra(n-butyl)phenyl, 2,3,4,6-tetra(n-butyl)phenyl, and 2,3,4,5,6-penta(n-butyl)phenyl

15. The process according to any one of Claims 1 to 3, wherein at least one R is chosen from C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkyl and at least one R is chosen from halogen.

16. The process according to any one of Claims 1 to 3, wherein at least one R is chosen from C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkoxy and at least one R is chosen from halogen.

17. The process according to any one of Claims 1 to 3, wherein at least one R is chosen from C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkyl and at least one R is chosen from C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkoxy.

18. The process according to any of Claims 1 to 17, wherein the benzylating agent has the formula:



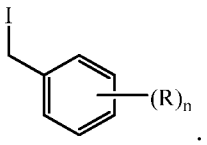
; and

the leaving group X is chosen from chloro, bromo, iodo, tosyl, and mesyl.

19. The process according to any of Claims 1 to 18, wherein the leaving group X is chloro.

20. The process according to any of Claims 1 to 19, wherein the original benzylating agent is converted to an activated benzylating agent.

21. The process according to any of Claims 1 to 20, wherein the activated benzylating agent has the formula:



.

22. The process according to any of Claims 1 to 21, wherein the number of equivalents of silylating reagent in Step (A) is from at least 2 to about 4.

23. The process according to any of Claims 1 to 22, wherein the number of equivalents of silylating reagent in Step (A) is from at least 2 to about 3.

24. The process according to any of Claims 1 to 23, wherein the number of equivalents of silylating reagent in Step (A) is from at least 2 to about 2.5.

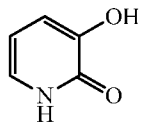
25. The process according to any of Claims 1 to 24, wherein the number of equivalents of silylating reagent in Step (A) is 2.

26. The process according to any of Claims 1 to 25, wherein the proton source in Step (A) is ammonium sulfate.

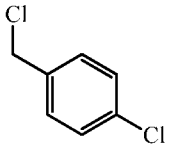
27. The process according to any of Claims 1 to 26, wherein the source of formaldehyde is an aqueous solution of formaldehyde.

28. A process for preparing *tert*-butyl 4-((1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate, comprising,

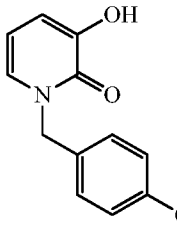
A) reacting 3-hydroxypyridin-2(1*H*)-one having the formula:



with 4-chlorobenzyl chloride having the formula:

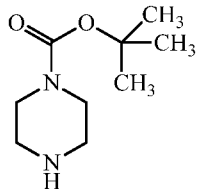


in the presence of two equivalents of a silylating reagent, a proton source and potassium iodide to form 1-(4-chlorobenzyl)-3-hydroxypyridin-2(1*H*)-one having the formula:



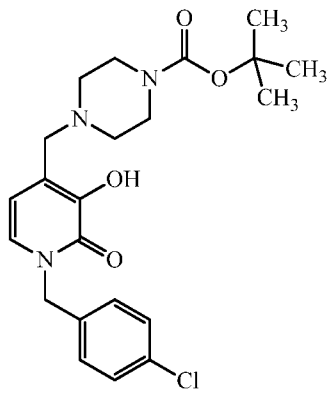
; and

B) reacting 1-(4-chlorobenzyl)-3-hydroxypyridin-2(1*H*)-one with *tert*-butyl piperazine-1-carboxylate having the formula:



;

in the presence of aqueous formaldehyde and an a protic acid to form *tert*-butyl 4-((1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate having the formula:



.

29. The process according to Claim 28, wherein the silylating reagent is hexamethyldisilazane.

30. The process according to Claim 28, wherein the proton source in Step (A) is ammonium sulfate.

31. The process according to Claim 28, wherein the protic acid in Step (B) is acetic acid.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/16243

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/497; C07D 401/06 (2015.01)
CPC - A61K 31/4412; A61K 31/496; C07D 401/14; C07D 401/06; C07D 213/69
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8)- A61K 31/497; C07D 401/06 (2015.01)
CPC- A61K 31/4412; A61K 31/496; C07D 401/14; C07D 401/06; C07D 213/69

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/253.12; 544/360 Patents and NPL (classification, keyword; search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Databases: Google Scholar, Google Patent, PatBase
Search terms used: tert-butyl 4-((1-(4-chlorobenzyl)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-1-carboxylate, process, synthesis, preparation,3-hydroxypyridin-2-one, benzylating, N-boc-piperazine, formaldehyde, acid

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	US 2013/0158010 A1 (Shalwitz et al.) 20 June 2013 (20.06.2013) para [0142], [0239]-[0254], [0427]-[0431], Table I.	1-4, 6, 11, 13 ---------- 7-10, 12, 14-17, 28-31
Y	US 8,323,671 B2 (Wu et al.) 04 December 2012 (04.12.2012) Table 1 No. 10-15 and 22-24; col 18, ln 25-40.	7-10, 12, 15-17
Y	WO 2007/150011 A2 (Duffy et al.) 27 December 2007 (27.12.2007) Example 40.	14
Y	US 4,508,898 A (Ogilvie) 02 April 1985 (02.04.1985) col 3, ln 40-60.	28-31
A	US 8,309,537 B2 (Gardner et al.) 13 November 2012 (13.11.2012) col 12, ln 35-col 17, ln 30.	1-4, 6-17 and 28-31

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 April 2015 (06.04.2015)	01 MAY 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/16243

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5 and 18-27
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.