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(54) **Title**: PROCESS AND INTERMEDIATES FOR THE PREPARATION OF PRELADENANT AND RELATED COMPOUNDS

(57) **Abstract**: The present invention describes processes for the synthesis of 2-(furan-2-yl)-7-[2-[4-[4-(2-methoxyethoxy)phenyl]piperazin-l-yl] ethyl]-7H-pyrazolo[4,3-e][1,2,4]- triazolo[1,5c] pyrimidin-5-amine (Preladenant) represented by the structure of formula (1), and solvates and salts thereof, especially salts with pharmaceutically acceptable acids. The process of the present invention is useful not only for Preladenant production, but also for the preparation of other biologically active compounds of general formula (17), such as A2a receptor antagonists used for the treatment of central nervous system diseases, among others. The present invention further relates to certain intermediates formed in such processes.

PROCESS AND INTERMEDIATES FOR THE PREPARATION OF PRELADENANT AND RELATED COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to processes for the preparation of substituted 5-amino-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidines, in particular Preladenant and its analogs, and their solvates (e.g., hydrates) and salts with physiologically acceptable acids. The present invention further relates to certain intermediates formed in such processes.

BACKGROUND OF THE INVENTION

Preladenant (also known as SCH-420814) is an adenosine A_{2A} antagonist under development for the treatment of Parkinson's Disease (PD) (Neustadt et al., *Bioorganic & Medicinal Chemistry Letters*, 2007, 17, 1376-1380). Preladenant has high selectivity towards A_{2A} receptor as compared to A_1, A_{2B}, and A_3 receptors, and excellent *in vivo* activity against PD symptoms.

Preladenant and other 5-amino-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]-pyrimidine derivatives are described in PCT international patent publications WO 01/092264, WO 2005/054245 and WO 2005/044819, the contents of each of which are incorporated by reference herein.

WO 01/092264 and WO 2005/054245 disclose processes for preparing 5-amino-2-substituted-pyrazol[4,3-e]-1,2,4-triazolo-[1,5-c]-pyrimidines comprising dehydrative rearrangement of their corresponding intermediate hydrazines. This high-temperature rearrangement reaction of N'-(6-amino-1H-pyrazolo[3,4-d]pyrimidin-4-yl)furan-2-carbohydrazide proceeds in the presence of hexamethyldisilazane and N,O-bis(trimethylsilyl)acetamide at 120° C overnight. The carbazide starting material and the product of this reaction are both insoluble in silicon containing reagents, an obstacle that complicates the process control and the separation and purification of the product. In addition, silicon-containing reagents are very sensitive to hydrolysis and thus the reaction demands special protection from moisture. To overcome this, it was proposed to perform the reaction in DMF at 230° C for 30 min [*Bioorg. Med. Chem.*, 2003, 11, 4161] or to use

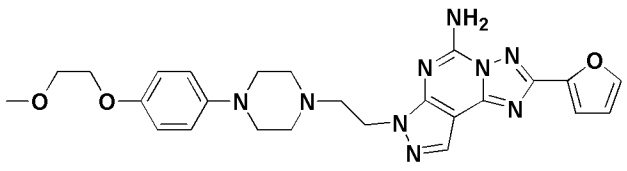
P_2O_5/hexamethyldisiloxane in xylene [JP 2002037787]. However, due to the harsh conditions, the yield of this reaction is varied from 28% to 75%.

WO 2005/044819 describes yet another method for the preparation of Preladenant by reacting alkyl N-4-cyano-1-(2-(4-(4-(2-methoxyethoxy)phenyl)piperazin-1-yl)ethyl)-1H-pyrazol-5-yl formimidate with 2-furoic hydrazide in isobutyric acid at reflux conditions, followed by acid hydrolysis to form 4-(3-(furan-2-yl)-1H-1,2,4-triazol-5-yl)-1-(2-(4-(4-(2-methoxyethoxy)phenyl)piperazin-1-yl)-ethyl)-1H-pyrazol-5-amine, which is subsequently cyclized to Preladenant via a reaction with a cyanating reagent (cyanates or cyanogens halides – the use of which is industrially problematic as these are considered highly toxic, corrosive and hazardous materials).

Thus, the existing methods for manufacturing Preladenant on an industrial scale suffer from unstable yields due to harsh reaction conditions, and the use of problematic reagents, only some of which are commercially available, which possess hazardous properties. Therefore, there continues to be a need in the art for a practical method for making Preladenant, which not only avoids the problems of the existing art, but is also safe, cost effective, and industrially feasible.

SUMMARY OF THE INVENTION

The present invention describes processes for the synthesis of 2-(furan-2-yl)-7-[2-[4-[4-(2-methoxyethoxy)phenyl]piperazin-1-yl]ethyl]-7H-pyrazolo[4,3-e][1,2,4]- triazolo[1,5-c]pyrimidin-5-amine (Preladenant) represented by the structure of formula (1), and solvates and salts thereof, especially salts with pharmaceutically acceptable acids. The present invention further relates to certain intermediates in such processes.



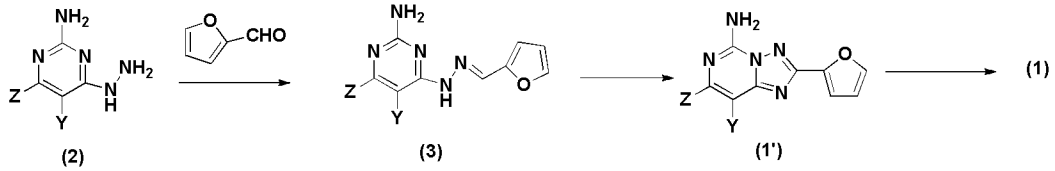
(1)

The process of the present invention comprises the following steps:

(a) coupling of intermediate (2) with furfural to form Schiff base (3);

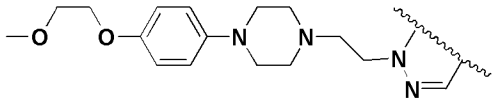
(b) cyclizing compound (3) by Dimroth-type rearrangement to form a compound of formula (1'); and

(c) optionally, converting the compound of formula (1') to a compound of formula (1).

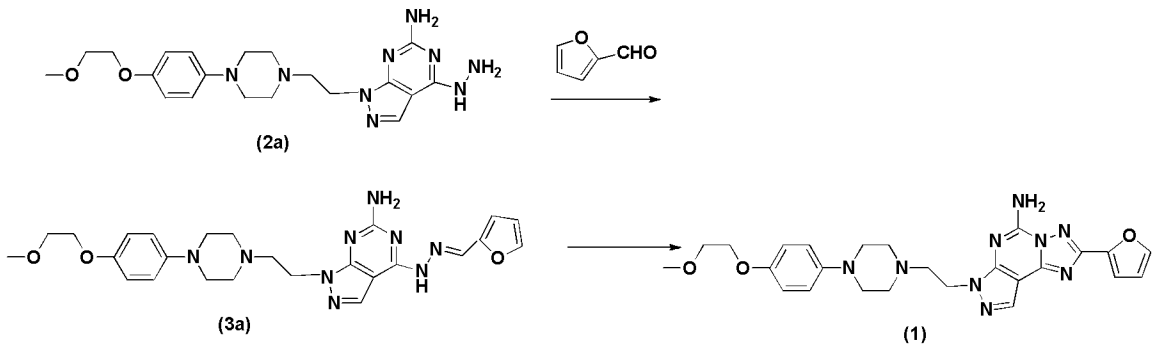


Scheme 1

In one embodiment, Z and Y together represent a group of the formula:



In accordance with this embodiment, 4-hydrazinyl-1-(2-(4-(4-(2-methoxyethoxy)phenyl)piperazin-1-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine, a compound of formula (2a) is coupled with furfural to form a hydrazone of formula (3a), which is subsequently cyclized to directly yield Preladenant of formula (1):



Scheme 2

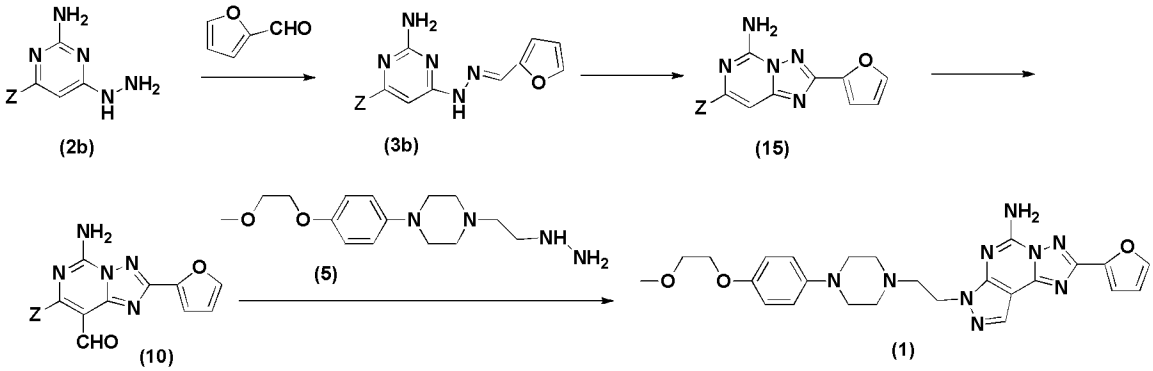
In another embodiment, Z is OH, halogen (Hal) or O-sulfonate and Y is H, and the process comprises the step of:

(a) coupling a compound of formula (2b) with furfural to form a compound formula (3b) wherein Z is OH, halogen or O-sulfonate;

(b) cyclizing compound (3b) to form a compound of formula (15);

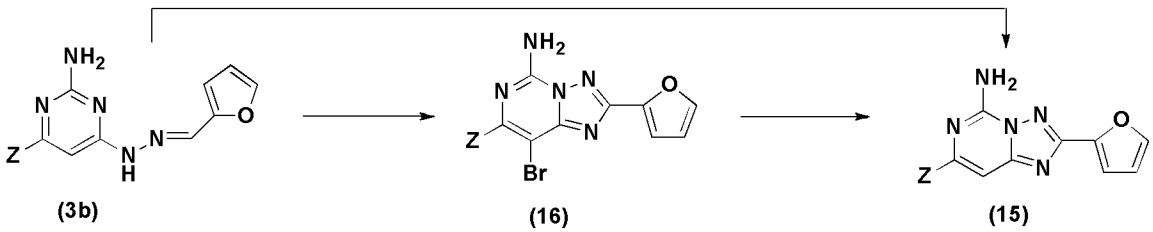
(c) formylating compound (15) to form compound (10); and

(d) reacting the compound of formula (10) with a compound of formula (5) so as to form Preladenant of formula (1).



Scheme 3A

Cyclization of compound (3b) to compound (15) may be carried out directly or by oxidative cyclization/bromination and reduction of an intermediate compound of formula (16):

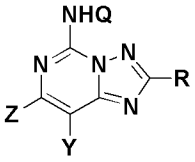


Scheme 3B

In any of the aforementioned embodiments, the step of converting the hydrazine moiety of compound (2) to Schiff base (3) can be performed by any manner known in the art. The step of cyclization of the Schiff base to form the pyrazolopyrimidine moiety is preferably conducted in the presence of an acid or base catalyst which is preferably selected from the group consisting of sodium acetate, acetic anhydride/pyridine, pyridine/pyridinium chloride, bromine in acetic acid and iodobenzenediacetate. Bromine (Br_2) in acetic acid and iodobenzenediacetate are currently preferred reagents for this step. Each possibility represents a separate embodiment of the present invention.

The process of the present invention is useful not only for Preladenant production, but also for the preparation of other biologically active compounds of general formula (17), such as A2a receptor antagonists used for the treatment of central nervous system diseases, among

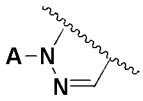
others. Thus, in another embodiment, the present invention provides a process for the preparation of a compound represented by the structure of formula (17):



(17)

or a solvate or salt thereof, wherein

Z and Y together form a group of the formula



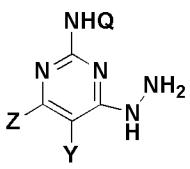
A is H, C_1-C_6 alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl or a C_1-C_6 alkylene-R^a wherein R^a is selected from the group consisting of cycloalkyl, aryl, heterocyclyl and heteroaryl, each of which may optionally be substituted;

R is an unsubstituted or substituted alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl or heteroaryl, preferably furanyl, thienyl, pyridyl, pyridyl N-oxide, oxazolyl, phenyl or pyrrolyl; and

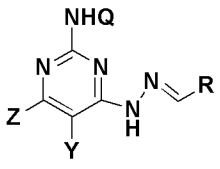
Q is H, an unsubstituted or substituted alkyl, an unsubstituted or subsituted aryl or a nitrogen protecting group;

the process comprising the steps of:

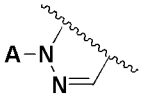
(a) coupling a compound of formula (18) with an aldehyde of formula R-CHO to form a hydrazone of formula (19):



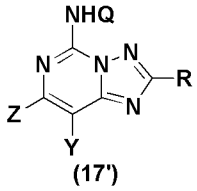
(18)



(19)

wherein Z is OH, halogen or O-sulfonate and Y is H; or Z and Y together form a group of the formula  wherein A is as defined above;

(b) cyclizing compound (19) to form a compound of formula (17') wherein Z and Y are as defined in (a); and

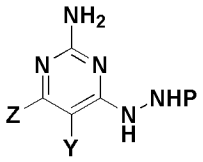


(17')

(c) optionally, when Z is OH, halogen or O-sulfonate and Y is H, further converting the product of step (b) to the compound of formula (17).

The present invention further relates to certain intermediates formed in the aforementioned processes. One novel intermediate is 4-Chloro-1-(2-(4-(4-(2-methoxyethoxy)phenyl)piperazin-1-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine, a compound of formula (6).

Another novel intermediate is a compound of general formula



wherein

P is a nitrogen protecting group, preferably Boc;

Z is OH, Hal or O-sulfonate and;

Y is H is or CHO.

Another novel intermediate is 5-amino-7-chloro-2-(furan-2-yl)-[1,2,4]triazolo[1,5-c]pyrimidine-8-carbaldehyde, a compound of formula (10).

Another novel intermediate is 4-(2-(furan-2-ylmethylene)hydrazinyl)-1-(2-(4-(4-(2-methoxyethoxy)phenyl) piperazin-1-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine, a compound of formula (3a).

In some embodiments, the present invention relates to a Preladenant or a solvate, or salt thereof, wherein the Preladenant is prepared in accordance with the process of the present invention.

In other embodiments, the present invention further relates to a method of treating a neurodegenerative disease, especially Parkinson's Disease (PD), comprising administering to

a subject in need thereof a therapeutically acceptable amount of Preladenant or a solvate, or salt thereof, wherein the Preladenant is prepared in accordance with the process of the present invention.

In other embodiments, the present invention further relates to the use of Preladenant, or a solvate, or salt thereof, prepared in accordance with the process of the present invention for treating a neurodegenerative disease, especially Parkinson's Disease (PD).

Further embodiments and the full scope of applicability of the present invention will become apparent from the detailed description given hereinafter. However, it should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to processes for the synthesis and isolation of 2-(furan-2-yl)-7-[2-[4-[4-(2-methoxyethoxy)phenyl]piperazin-1-yl]ethyl]-7H-pyrazolo[4,3-e] [1,2,4]-triazolo[1,5-c]pyrimidin-5-amine (Preladenant), and solvates (e.g., hydrates) and pharmaceutically acceptable salts thereof, especially salts with pharmaceutically acceptable acids. The process of the invention may further be used to prepare compounds of general formula (17) as further described hereinbelow.

The production method relates to a process for manufacturing compound (1) by coupling compound (2) with furfural and cyclizing the resulting compound (3) to (1) directly or through an intermediate of formula (1') (Scheme 1). Two alternative embodiments of this process are set forth in Schemes 2 and 3. In Scheme 2, a compound of formula (2a) is reacted with furfural and the resulting compound of formula (3a) is cyclized to (1) directly. In Scheme 3A, a compound of formula (2b) is reacted with furfural and the resulting compound of formula (3b) is cyclized to compound (15), which is then formylated to produce a compound of formula (10), which in turn is coupled with a compound of formula (5) to result in (1). Cyclization of compound (3b) to compound (15) may be carried out directly or by oxidative cyclization/bromination and reduction of an intermediate compound of formula (16) (Scheme 3B).

For these reactions, the compound of formula (2) (such as compounds (2a) and (2b)) and furfural are preferably used in about an equimolar amount or in an excessive amount for either of the compounds and the mixture is stirred in an inert solvent under suitable reaction conditions, which can be determined by a person of skill in the art, in the absence or in the presence of an acid or base catalyst, preferably at about room temperature (e.g., about 20°C to 25°C) to about reflux (which temperature will depend on the nature of the solvent), generally for about 0.1 hour to about 1 day, or any period of time there between. The nature of the solvent is not particularly limiting. Some examples include, but are not limited to aromatic hydrocarbons such as benzene, toluene, and xylene; ethers such as diethyl ether, MTBE, diisopropyl ether, tetrahydrofuran (THF), 1,4-dioxane, 1,2-dimethoxyethane, and 1,2-diethoxyethane; halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, and chloroform; alcohols such as methanol, ethanol, 2-propanol, and butanol; N,N-dimethylformamide (DMF), N-methylpyrrolidone (NMP), dimethyl sulfoxide (DMSO), and any mixtures thereof. Each possibility represents a separate embodiment of the present invention. Alcohol (e.g., ethanol) is a currently preferred solvent.

The acid catalyst, if present, can be an inorganic or organic acid such as hydrochloric, hydrobromic, phosphoric, sulfuric, para-toluenesulfonic, methanesulfonic or tungstic acid. Also, polymeric acid resins and the like can be used. The reaction can also be catalyzed by bases, such as piperidine or a phosphate salt (e.g., sodium and potassium phosphate, hydrogen phosphate or dihydrogen phosphate). Microwave irradiation can facilitate this reaction. In such case the reaction proceeds without solvent, using excess of furfural. Each possibility represents a separate embodiment of the present invention.

Chemical Definitions:

An "alkyl" group refers to any saturated aliphatic hydrocarbon, including straight-chain, branched-chain and cyclic alkyl groups (cycloalkyl). In one embodiment, the alkyl group has 1-12 carbons, designated herein as C_1-C_{12}-alkyl. In another embodiment, the alkyl group has 1-6 carbons, designated herein as C_1-C_6-alkyl. In another embodiment, the alkyl group has 1-4, carbons designated herein as C_1-C_4-alkyl. The alkyl group may be unsubstituted or substituted by one or more groups selected from halogen, hydroxy, alkoxy carbonyl, amido, alkylamido, dialkylamido, nitro, amino, alkylamino, dialkylamino, carboxyl, thio thioalkyl, and the like.

Similarly, the term “alkylene” denotes a bivalent radical. For example, the term “C_1 to C_{12} alkylene” denotes a bivalent radical of 1 to 12 carbons.

A "cycloalkyl" group refers to a non-aromatic mono- or multicyclic ring system. In one embodiment, the cycloalkyl group has 3-10 carbon atoms. In another embodiment, the cycloalkyl group has 5-10 carbon atoms. Examples of monocyclic cycloalkyl groups include cyclopentyl, cyclohexyl, cycloheptyl and the like. The cycloalkyl group can be unsubstituted or substituted with any one or more of the substituents defined above for alkyl. A cycloalkenyl is a cycloalkyl group containing one or more double bonds within the ring.

An “aryl” group refers to an aromatic ring system containing from 6-14 ring carbon atoms. The aryl ring can be monocyclic, bicyclic, tricyclic and the like. Non-limiting examples of aryl groups are phenyl, naphthyl including 1-naphthyl and 2-naphthyl, and the like. The aryl group can be unsubstituted or substituted with any one or more of the substituents defined above for alkyl.

An "alkynyl" group refers to an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond including straight-chain and branched-chain. In one embodiment, the alkynyl group has 2-8 carbon atoms in the chain, designated herein as C_2-C_8-alkynyl. In another embodiment, the alkynyl group has 2-6 carbon atoms in the chain, designated herein as C_2-C_6-alkynyl. Exemplary alkynyl groups include ethynyl, propynyl, butynyl, 3-methylbutynyl, n-pentynyl, heptynyl, octynyl, nonanyl and decynyl. The alkynyl group can be unsubstituted or substituted through available carbon atoms with one or more groups defined hereinabove for alkyl.

The term “heteroaryl” used herein alone or as part of another group refers to a heteroaromatic system containing at least one heteroatom ring wherein the atom is selected from nitrogen, sulfur and oxygen. The heteroaryl contains 5 or more ring atoms. The heteroaryl group can be monocyclic, bicyclic, tricyclic and the like. Also included in this definition are the benzoheterocyclic rings. If nitrogen is a ring atom, the present invention also contemplates the N-oxides of the nitrogen containing heteroaryls. Non-limiting examples of heteroaryls include thienyl, benzothienyl, 1-naphthothienyl, thianthrenyl, furanyl, benzofuranyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indazolyl, purinyl, isoquinolyl, quinolyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, carbolinyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl and the like. A preferred

heteroaryl group is furanyl. The heteroaryl group can be unsubstituted or substituted through available atoms with one or more groups defined hereinabove for alkyl.

The term “heterocyclic ring” or “heterocyclyl” used herein alone or as part of another group refers to a five-membered to eight-membered rings that have 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen, in particular nitrogen, either alone or in conjunction with sulfur or oxygen ring atoms. These five-membered to eight-membered rings can be saturated, fully unsaturated or partially unsaturated, with fully saturated rings being preferred. Preferred heterocyclic rings include piperidinyl, pyrrolidinyl pyrrolinyl, pyrazolinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, piperazinyl, indolinyl, dihydrofuranyl, tetrahydrofuranyl, dihydrothiophenyl, tetrahydrothiophenyl, dihydropyranyl, tetrahydropyranyl, dihydrothiazolyl, and the like. A preferred heterocyclyl group is piperazinyl, which may be substituted. The heterocyclyl group can be unsubstituted or substituted through available atoms with one or more groups defined hereinabove for alkyl.

The term "O-sulfonate" as used herein refers to a group of formula $-OSO_2-R'$ where R' is an alkyl or aryl as defined hereinabove. Preferably, the O-sulfonate group is OMs (mesylate, R'=Me) or OTs (tosylate, R'= C_6H_4-CH_3-p).

The term “solvate” as used herein means a physical association of a compound of the invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. “Solvate” encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates and the like. “Hydrate” is a solvate wherein the solvent molecule is water.

As used herein, the term "nitrogen protecting group" (P) refers to a group which may be attached to a nitrogen atom to protect said nitrogen atom from participating in a reaction and which may be readily removed following the reaction. The nitrogen protecting group can be an acid labile protecting group, a base labile protecting group, or a protecting group that is removable under neutral conditions. Non-limiting examples of nitrogen-protecting groups are silyl protecting groups ($Si(R")_3$ wherein R" is alkyl, aryl, aralkyl etc.), acyl groups such as acetyl ($COCH_3$), benzoyl, 2-bromoacetyl, 4-bromobenzoyl, tert-butylacetyl, carboxaldehyde, 2-chloroacetyl, 4-chlorobenzoyl, α-chlorobutyryl, 4-nitrobenzoyl, o-nitrophenoxyacetyl, phthalyl, pivaloyl, propionyl, trichloroacetyl, and trifluoroacetyl; amide groups such as acetamide and the like; sulfonyl groups such as benzenesulfonyl, and p-toluenesulfonyl;

carbamate groups of the formula -C(O)O-R''' wherein R''' is for example methyl, ethyl, t-butyl, benzyl, phenylethyl, CH_2=CH-CH_2, such as benzyloxycarbonyl (Cbz), tert-butyloxycarbonyl (Boc), p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, and the like. Other suitable nitrogen protecting group include, but are not limited to: benzyl, formyl, phenylsulfonyl, (Fmoc), p-nitrobenzenesulfoethoxycarbonyl propargyloxycarbonyl, picolinyl, prenyl, o-nitrobenzyloxy methyl, 4-methyoxyphenoxymethyl, guaiacolmethyl, siloxymethyl, such as triisopropylsiloxymethyl, 2-cyanoethyoxymethyl, 2-quinolinylmethyl, dichloroacetyl, trichloroacetyl, 2-[4-nitrophenyl]ethylsulfonate, p-methoxy benzyl and trityl. Each possibility represents a separate embodiment of the invention. A currently preferred protecting group is Boc.

Other examples of nitrogen-protecting groups are described by C. B. Reese and E. Haslam, "Protective Groups in Organic Chemistry, "J.G. W. McOmie, Ed. , Plenum Press, New York, NY, 1973, Chapters 3 and 4, respectively, and T. W. Greene and P.G. M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed. , John Wiley and Sons, New York, NY, 1991, Chapters 2 and 3, each of which is incorporated herein by reference.

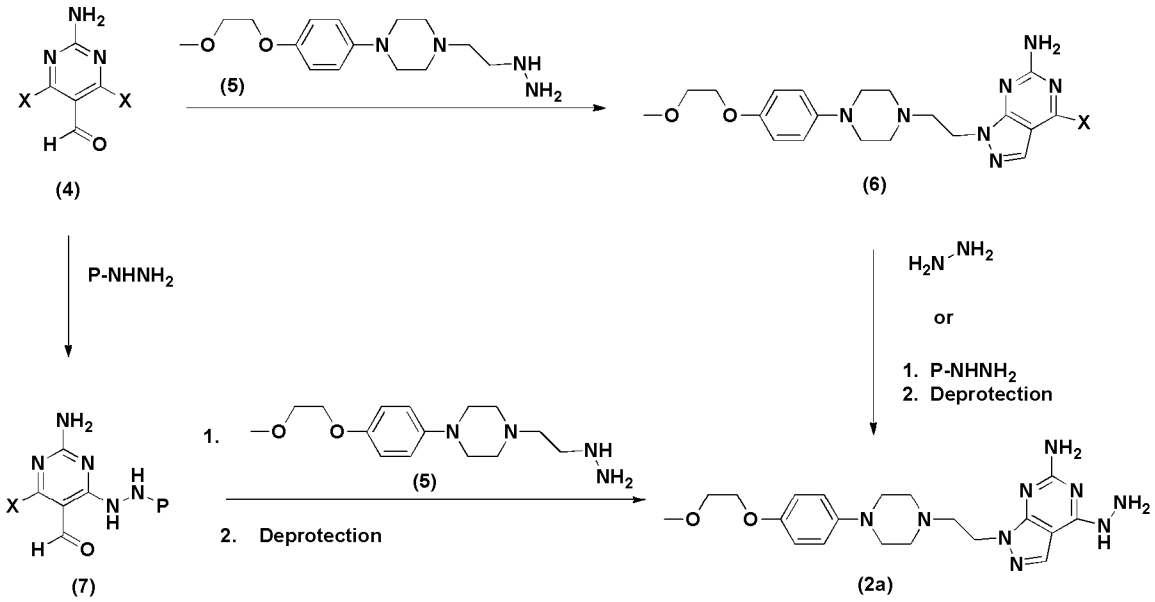
All references cited herein are hereby incorporated by reference in their entirety, as if fully set forth herein.

Several non-limiting embodiments of the present invention will now be presented.

A. Preparation of Preladenant (1) from Compound (2a):

In one embodiment as set forth in Scheme 2, Preladenant of formula (1) is prepared by coupling a compound of formula (2a) with furfural to form a hydrazone (Schiff base) of formula (3a), which is subsequently cyclized to Preladenant of formula (1).

Compound (2a) can be prepared according to the method disclosed in US 6,630,475, the contents of which are incorporated by reference herein. Alternatively, compound (2a) can be synthesized according to the following scheme (Scheme 4):



Scheme 4

In Scheme 4, X is a halogen (e.g., F, Cl, Br or I, preferably Cl) or O-sulfonate, and P is a nitrogen protecting group as defined herein.

Non-limiting examples of the intermediates (4)-(7) and their preparation are provided in the Examples section.

Compound (2a) is then reacted with furfural to produce a compound of formula (3a), which undergoes cyclization and Dimroth-type rearrangement to form the compound of the formula (1). Usually, Dimroth-type rearrangements proceed under acid, base or heat catalyzed conditions [L. Kürti, B. Czakó. Strategic applications of named reactions in organic synthesis. Elsevier, 2005, p.144-145], for example, using sodium acetate [*Journal of the Korean Chemical Society*, 2010, 54, (6), 841]; acetic anhydride/pyridine [*Sci Pharm.* 2010, 78, 1–12; *Acta Chim. Slov.* 2005, 52, 429–434]; pyridine/pyridinium chloride [*J. Chem. Soc.*, Perkin Trans. 1, 1999, 1333–1337]; iodobenzenediacetate (IBA) [*European Journal of Medicinal Chemistry*, 2003, 38, 533-536; *European Journal of Medicinal Chemistry*, 2004, 39, 1073–1077; *European Journal of Medicinal Chemistry*, 2007, 42, 868-872]. The contents of each of the aforementioned references are incorporated by reference herein.

While any of the aforementioned methods can be applied to the synthesis of Preladenant (1), it has now been surprisingly found that this reaction proceeds with good yield of the desired compound (1) by bromine assistance, which plays a role of oxidant and catalyst for rearrangement. The reaction may be carried out in, e.g., glacial acetic acid

preferably at about room temperature (e.g., about 20°C to 25°C) to about reflux, generally for about 0.1 hour to about 24 hours, or any period of time there between. Sodium or potassium acetate can be added as facilitating additives. Another preferred reagent for the oxidation reaction is iodobenzenediacetate.

Compound (1) can be separated from the reaction mixture as a free base or in the form of a salt with physiologically acceptable acids.

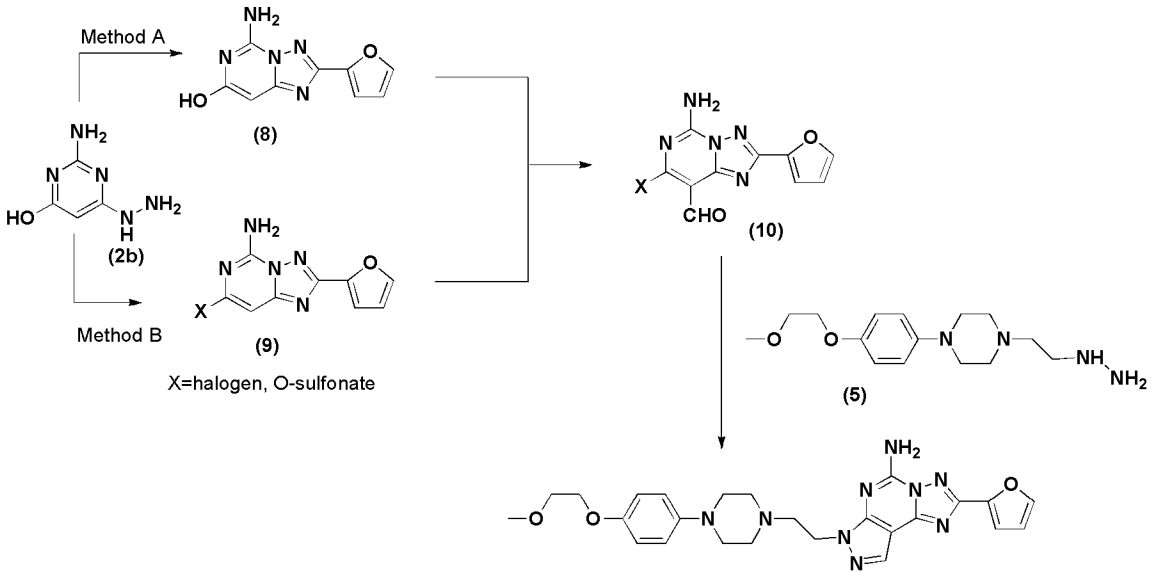
This method is economically advantageous on an industrial scale over the methods in the prior art, due to the fewer number of stages and the simplicity of execution.

B. Preparation of Preladenant from (1) Compound (2b):

In another embodiment as set forth in Scheme 3A, Preladenant of formula (1) is prepared by coupling a compound of formula (2b) with furfural to form a hydrazone (Schiff base) of formula (3b), which is subsequently cyclized to form compound (15), formylated to form compound (10) and coupled with compound (5) to form Preladenant of formula (1).

Compound (2b) (Z=OH) can be prepared by any known method, such as the methods described in US 2009/008237, WO 2010/006032 or *Journal of Medicinal Chemistry*, 1992, 35(20), 3678-85, the contents of each of which are incorporated by reference herein. Alternatively, compound (2b) (Z=OH) can be synthesized by reacting commercially available 2-amino-6-chloropyrimidin-4-ol with monoprotected hydrazine, such as Boc-hydrazine, followed by deprotection of the resulting compound to form compound of formula (2b).

Transformation of compound (2b) to compound of formula (10) may be achieved by two alternative methods, hereinafter designated Method A and B, shown generally in Scheme 5, and in further detail in Schemes 6 (Method A) and 7 (Method B).



Scheme 5

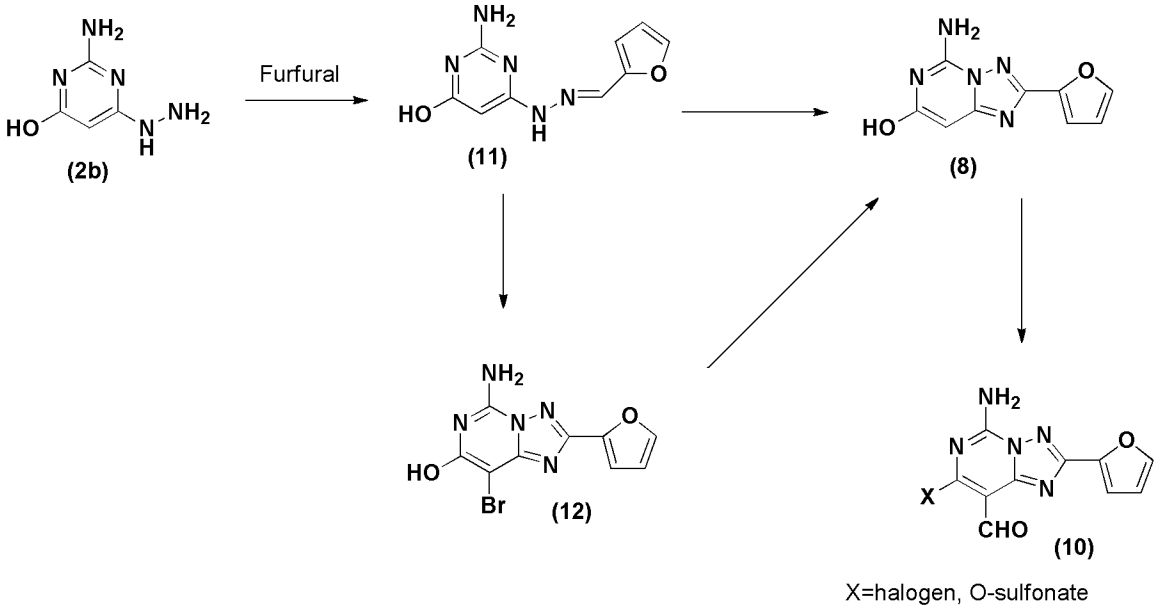
Method A:

Method A comprises the following steps (Scheme 6):

a) reacting hydrazine (2b) with furfural to form hydrazone (11);

b) cyclization of compound (11) to form compound (8) directly (for example by reaction with iodobenzenediacetate (IBA)), or by oxidative cyclization/ bromination (e.g., with Br_2/AcOH) and reduction (e.g., with H_2, Pd/C) of intermediate compound (12); and

c) halogenation/O-sulfonylation and formylation of compound (8) to form compound (10). For example, compound (8) may be converted to the corresponding compound (10) by reaction with $POCl_3$/DMF.



Scheme 6

Method B:

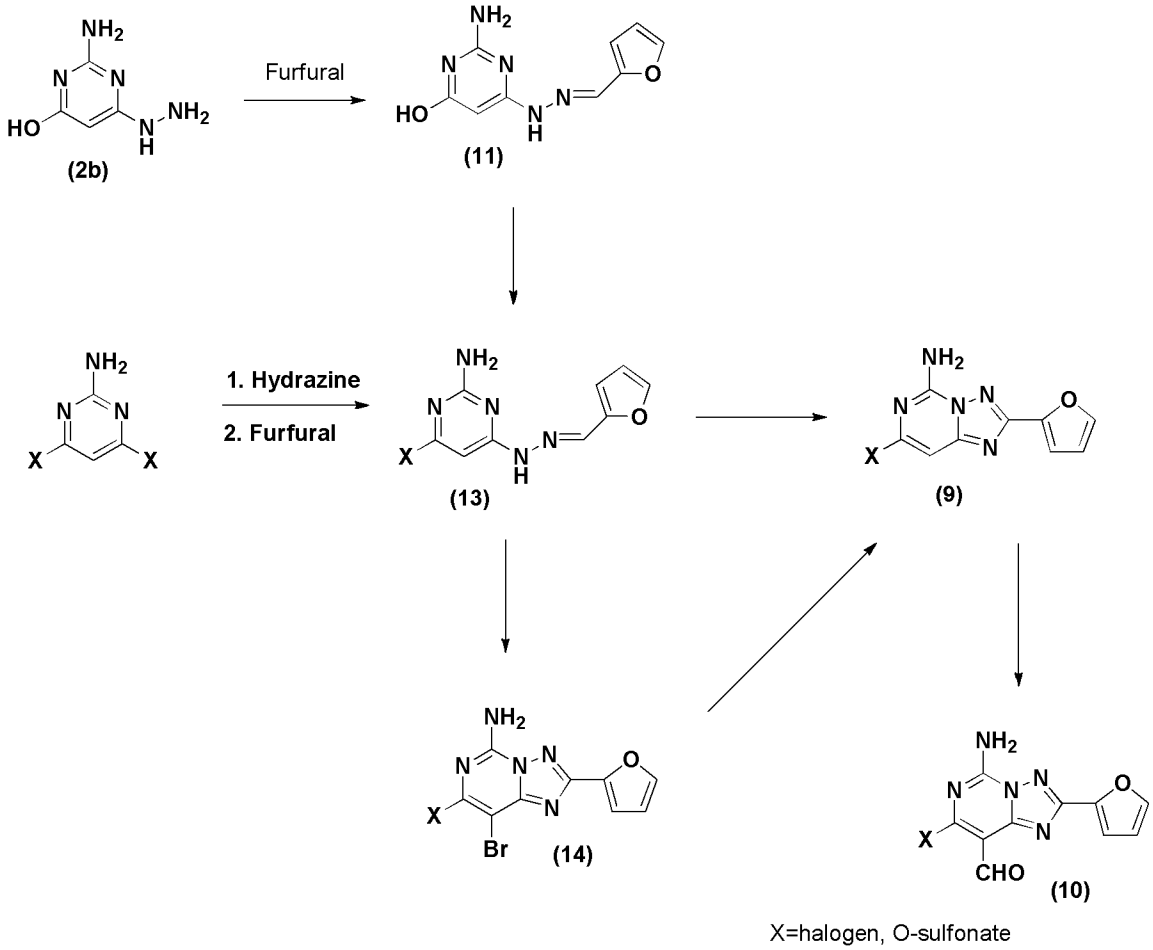
Method B comprises the following steps (Scheme 7):

a) reacting hydrazine (2b) with furfural to form hydrazone (11),

b) halogenation or O-sulfonylation of hydrazone (11) by an appropriate reagent (e.g., a chlorination agent such as thionyl chloride or phosphorus oxychloride) to form compound (13). Alternatively, compound (13) can be prepared from commercially available 4,6-dichloropyrimidin-2-amine or a similar compound wherein X is a halogen or O-sulfonate, by sequential reactions with hydrazine and furfural,

c) cyclization of compound (13) to form compound (9) (for example by reaction with iodobenzenediacetate (IBA)), or by oxidative cyclization/bromination (e.g., with Br_2/AcOH) and reduction (e.g., with H_2, Pd/C) of intermediate compound (14); and

d) formylation of compound (9) to form compound (10). For example, compound (9) may be converted to the corresponding compound (10) by reaction with $POCl_3$/DMF.



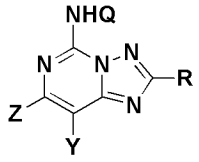
Scheme 7

Reaction of compound (2b) with furfural followed by cyclization and Dimroth-type rearrangement of compounds (11) or (13) may be performed in accordance with the conditions set forth for conversion of compound (2a) to (3a) to (1) as described hereinabove.

The process of the present invention may further comprise the conversion of Preladenant to a salt, preferably with pharmaceutically or physiologically acceptable acids. The term "salt" encompasses both basic and acid addition salts, including but not acid addition salts with salts with amine nitrogens. Furthermore, the term includes salts that form by standard acid-base reactions with basic groups (such as amino groups) and organic or inorganic acids. Such acids include, but are not limited to, hydrochloric, hydrofluoric, trifluoroacetic, sulfuric, phosphoric, acetic, succinic, citric, lactic, maleic, fumaric, palmitic, cholic, pamoic, mucic, D-glutamic, D-camphoric, glutaric, phthalic, tartaric, lauric, stearic, salicylic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic, and like acids. Each possibility represents a separate embodiment of the present invention.

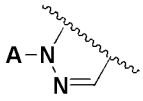
C. Preparation of Compounds of formula (17)

The process of the invention is unexpectedly advantageous over the processes described in the prior art (e.g. WO 01/092264, WO 2005/054245 and WO 2005/044819). The high overall yield, mild reaction conditions and available reagents make this approach industrially useful not only for Preladenant production, but also for the preparation of other biologically active compounds of general formula (17), such as A2a receptor antagonists used for the treatment of central nervous system diseases, among others.



(17)

wherein Z and Y together form a group of the formula



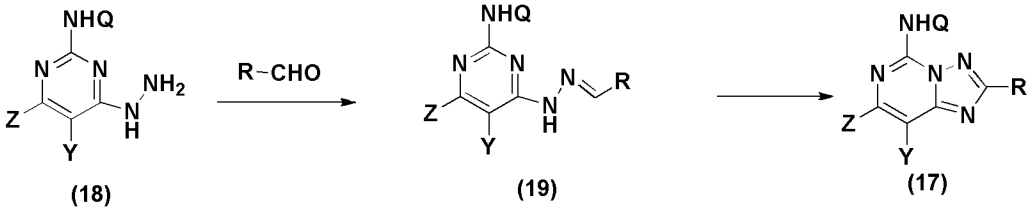
wherein A is H, C_1-C_6 alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl or a C_1-C_6 alkylene-R^a wherein R^a is selected from the group consisting of cycloalkyl, aryl, heterocyclyl and heteroaryl, each of which may optionally be substituted, or A is any substituent as described, for example, in WO 01/092264, WO 2005/054245 and WO 2005/044819, the contents of each of which are incorporated by reference herein;

R is an unsubstituted or substituted alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl or heteroaryl, for example furanyl, thienyl, pyridyl, pyridyl N-oxide, oxazolyl, phenyl, pyrrolyl etc.; and

Q is H, an unsubstituted or substituted alkyl, an unsubstituted or subsituted aryl, a nitrogen protecting group, etc.

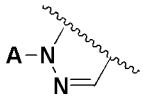
Additional examples of compounds which may be made by the novel processes of the present invention are SCH-58261 (5-Amino-7-(2-phenylethyl)-2-(2-furyl)-pyrazolo(4,3-e)-1,2,4-triazolo(1,5-c)pyrimidine), SCH-442,416 (2-(2-furyl)-7-[3-(4-methoxyphenyl)propyl]-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-amine), and the compounds described in Müller et al. *Recent Pat CNS Drug Discov.* 2007 Jan;2(1):1-21, the contents of each of which are incorporated by reference herein.

The process is described in Scheme 8:



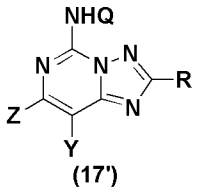
Scheme 8

The process comprises the steps of:

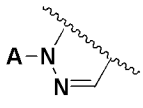
(a) coupling a compound of formula (18) with an aldehyde R-CHO to form a hydrazone of formula (19), wherein Z is OH, halogen or O-sulfonate and Y is H; or Z and Y together form a group of the formula 

wherein A is as defined above;

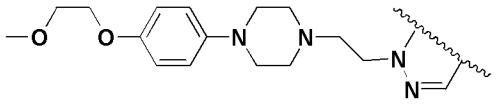
(b) cyclizing compound (19) to form a compound of formula (17') wherein Z and Y are as defined in (a); and



(c) optionally, when Z is OH, halogen or O-sulfonate and Y is H, further converting the product of step (b) to the compound of formula (17).

In one embodiment of formula (17), 

represents:



Reaction of compound (18) with the aldehyde R-CHO followed by cyclization and Dimroth-type rearrangement of compound (19) may be performed in accordance with the conditions set forth for conversion of compound (2a) to (3a) to (1), or of compound (2b) to (3b) to (1), or any variations thereof, as set forth in Schemes 1-7 above.

The principles of the present invention are demonstrated by means of the following non-limiting examples.

EXAMPLES

Specific compounds which are representative of this invention were prepared as per the following examples and reaction sequences; the examples and the schemes depicting the reaction sequences are offered by way of illustration, to aid in the understanding of the invention and should not be construed to limit in any way the invention set forth in the claims which follow thereafter.

No attempt has been made to optimize the yields obtained in any of the reactions. Unless otherwise noted, the materials used in the examples were obtained from readily available commercial suppliers or synthesized by standard methods known to one skilled in the art of chemical synthesis.

Preparation of starting materials:

2-amino-4,6-dihydroxypyrimidine is commercially available or can be prepared starting from diethyl malonate and guanidine hydrochloride or nitrate (both commercially available) by condensation in basic conditions (sodium methylate) [*Journal of Organic Chemistry*, 1975, 40(25), 3713-16; *Henan Huagong*, (5), 14-15; 2000; *Shiyou Huagong Yingyong*, 26(1), 23-25; 2007; *Xinan Minzu Daxue Xuebao, Ziran Kexueban*, 34(1), 134-136; 2008; *Bioorganic & Medicinal Chemistry Letters,* 2007, 17(23), 6610-6614;; *Bioorganic & Medicinal Chemistry*, 2003, 11(19), 4161-4169.

2-amino-4, 6-dichloropyrimidine-5-carboxaldehyde can be prepared from 2-amino-4,6-dihydroxypyrimidine, according to the procedures disclosed in WO 01/092264 or RU2380417.

Tert-butyl carbazate (mono Boc-hydrazine) is commercially available or can be prepared, according to *JACS*, 1957, 79, 98-101; *Helvetica Chimica Acta,* 1950, 44, 2151-3; *Organic Syntheses*, 1964, 44, 20-5; *Zhurnal Organicheskoi Khimii*, 13(12), 1977, 2531-5; *Tetrahedron Letters*, 1991, 32(26), 3079-82; WO 01/040163; CN1580040; *Bioorganic & Medicinal Chemistry Letters*, 2006, 16(4), 978-983; AND CN101823986.

1-(4-(2-methoxyethoxy)phenyl)piperazine is commercially available or can be prepared according to *Bioorganic & Medicinal Chemistry Letters*, 2007, 17, 1659–1662.

2-(4-(4-(2-Methoxyethoxy)phenyl)piperazin-1-yl)ethanol and 1-(2-chloroethyl)-4-(4-

(2-methoxyethoxy)phenyl)piperazine can be prepared from 1-(4-(2-methoxyethoxy)phenyl)-piperazine, according to *Bioorganic & Medicinal Chemistry Letters*, 2009, 19, 967–971.

1-(2-hydrazinylethyl)-4-(4-(2-methoxyethoxy)phenyl)piperazine (5) can be prepared from 1-(2-chloroethyl)-4-(4-(2-methoxyethoxy)phenyl)piperazine by reaction with tert-butyl carbazate, following by acidic removal of Boc-protecting group and separation of the desired compound (5) as a hydrochloride salt.

Alternately, 1-(2-hydrazinylethyl)-4-(4-(2-methoxyethoxy)phenyl)piperazine (5) can be prepared from 2-(4-(4-(2-methoxyethoxy)phenyl)piperazin-1-yl)ethanol by mesylation or tosylation, reaction of the formed sulfonate with tert-butyl carbazate, following by acidic removal of the Boc-protecting group and separation of the desired compound (5) as an hydrochloride salt.

The contents of each of the aforementioned references are incorporated by reference in its entirety herein.

EXAMPLE 1. Preparation of Preladenant via compound (2a)

a). Preparation of intermediate (6, X = Cl)

1-(2-hydrazinylethyl)-4-(4-(2-methoxyethoxy)phenyl)piperazine (5) (1.0 eq.) and sodium carbonate (1.1 eq.) were added to acetonitrile (40 mL) and stirred at 25-30° C. A solution of 2-amino-4,6-dichloropyrimidine-5-carboxaldehyde (4) (1 eq.) in acetonitrile (15 mL) was added. The reaction mixture was heated to 80° C and stirred with periodic TLC or HPLC monitoring. After completion of the reaction (16 h), the mixture was cooled to 20-25° C, filtered and concentrated under reduced pressure. The crude product is pure enough for use in the next step or it can be purified by chromatography.

b). Preparation of 4-hydrazinyl-1-(2-(4-(4-(2-methoxyethoxy)phenyl)piperazin-1-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine (2a)

Crude intermediate (6) obtained from the previous step (a) was mixed with excess of hydrazine hydrate and the mixture was stirred at 80° C for 2 h. After completion of the reaction (using TLC or HPLC control) the mixture was extracted with ethyl acetate, washed with water and brine. Organic extracts were concentrated under reduced pressure and the

residue was purified by crystallization from an appropriate solvent or by chromatography to form yellowish solids of compound (2a).

c). Preparation of 4-(2-(furan-2-ylmethylene)hydrazinyl)-1-(2-(4-(4-(2-methoxy-ethoxy)phenyl)piperazin-1-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine (3a)

To a stirred solution of hydrazine (2a) (1.6 g, 1eq.) in ethanol (70 ml) were added water (350 ml) containing K_2HPO_4 (663 mg, 1eq.) followed by furfural (0.38 ml, 1eq.) and the resulting mixture was heated to 80°C for 16 h. The reaction progress was monitored by TLC. After completion of the reaction, the ethanol was distilled off under vacuum to obtain a residue, which was mixed with water (5 ml) and extracted with DCM (3 x 20 ml). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to obtain crude product (3a). The crude product was washed with MTBE (5 ml), dried in vacuum and transferred to the next step without purification.

d). Preparation of Preladenant (1)

To a stirred solution of compound (3a) (1.0 eq.) obtained from the previous step (c) in DCM (200 ml) was added iodobenzenediacetate (IBA) (1.12g, 1.1 eq.) and the resulting solution was stirred at rt for 2 h. The reaction progress was monitored by TLC. After completion of the reaction, the mixture was washed with water (20 ml), the organic layer was separated, dried over Na_2SO_4 filtered and evaporated to obtain a crude product (1.8 g crude), which was purified by column chromatography using 0-5% methanol in DCM as an eluent or by crystallization.

Final purification: preladenant (400 mg) was mixed with solution of MTBE: ethanol (9: 1) (10 ml) and stirred for 1 h, filtered and washed with MTBE to afford 350 mg of pure preladenant with HPLC purity >98%.

EXAMPLE 2. Preparation of Preladenant via compound (2a)

a). Preparation of tert-butyl 2-(6-amino-1-(2-(4-(4-(2-methoxyethoxy) phenyl) piperazin-1-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazine carboxylate

1-(2-hydrazinylethyl)-4-(4-(2-methoxyethoxy)phenyl)piperazine (5) hydrochloride (1.0 eq.) and sodium carbonate (1.1 eq.) were added to acetonitrile (40 mL) and stirred at 25-30° C. After stirring at this temperature for 30 hours, a solution of tert-butyl 2-(2-amino-6-

chloro-5-formylpyrimidin-4-yl)hydrazine carboxylate (7) (1 eq.) in acetonitrile (15 mL) was added. The reaction mixture was then heated to 80° C and stirred with periodic TLC or HPLC control. After completion of the reaction (3-5 h), the reaction mixture was cooled down to 20-25° C, filtered and concentrated under reduced pressure. The crude product is pure enough for use in the next step or it can be purified by chromatography.

b). Preparation of 4-hydrazinyl-1-(2-(4-(4-(2-methoxyethoxy)phenyl)piperazin-1-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine (2a)

Crude tert-butyl 2-(6-amino-1-(2-(4-(4-(2-methoxyethoxy)phenyl)piperazin-1-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)hydrazine carboxylate from the previous example (a) was dissolved in a mixture of methanol-methylene chloride (1:1) and treated with 1.25M HCl in methanol. The mixture was stirred at room temperature overnight. After completion of the reaction (monitoring was by TLC or HPLC control) the mixture was neutralized by slow addition of ammonium hydroxide to pH 10-11. The mixture was filtered, concentrated under reduced pressure and the residue was purified by crystallization from an appropriate solvent or by chromatography to form yellowish solids of compound (2a).

c). Preparation of 4-(2-(furan-2-ylmethylene)hydrazinyl)-1-(2-(4-(4-(2-methoxy-ethoxy)phenyl)piperazin-1-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine (3a)

To a stirred solution of furfural (1.2 eq.) in 50 ml MeOH was added hydrazine (2a) from the previous example (b) (1 eq.) at room temperature. The reaction was stirred for 3-4 h. The progress of the reaction was monitored by TLC or HPLC. If the reaction was not completed by this time, the mixture was heated to reflux for an additional 1-2 h. After the reaction was completed, the mixture was concentrated under reduced pressure and the residue was purified by crystallization from an appropriate solvent or by chromatography to form solids of compound (3a).

d). Preparation of Preladenant (1)

A solution of Br_2 (2.2 equiv) in glacial AcOH (10 ml) was slowly added to a suspension of anhydrous sodium acetate (NaOAc) (1.5 g) and the hydrazone (3a) (1.0 equiv) in glacial AcOH (20 mL), and the mixture was stirred at room temperature for an additional 30–60 min. The progress of the reaction was monitored by TLC or HPLC. The reaction was quenched by pouring into ice-cooled 0.5 N aqueous NaOH solution (50 ml). With vigorous stirring, the mixture was agitated for 30–60 min. The product was collected by filtration,

washed several times with water, water-acetonitrile (1:1), and dried at 65 to 75° C under vacuum for about 24 h to give compound (1) with purity >98% (HPLC). The product can be recrystallized from an appropriate solvent or chromatographed. Pure product was obtained as white to off-white powder or crystal in 83% yield (purity > 99.5%).

EXAMPLE 3. Preparation of Preladenant via 2-amino-6-hydrazinylpyrimidin-4-ol (2b)

a). Preparation of 2-amino-6-hydrazinylpyrimidin-4-ol (2b)

2-Amino-6-hydrazinylpyrimidin-4-ol (2b) can be prepared from commercially available 2-amino-6-chloropyrimidin-4-ol, according to WO 2010/006032 or, preferably, via formation of tert-butyl 2-(2-amino-6-hydroxypyrimidin-4-yl)hydrazinecarboxylate.

A mixture of 2-amino-6-chloropyrimidin-4-ol (1 eq.) and tert-butyl carbazate (1.2 eq.) in 25 ml of acetonitrile was heated to reflux with TLC or HPLC control. After reaction completion (3-5 h), the mixture was concentrated under reduced pressure and the residue was dissolved in methanol and treated by 1.25M HCl in methanol. The mixture was stirred at room temperature overnight. After reaction completion the mixture was neutralized with ammonium hydroxide to pH 10-11, diluted with water, cooled to 5°C, and stirred at this temperature for 2-4 h. The precipitate which separated was collected by filtration, washed with water followed by ethanol and dried to give a white solid (86% yield), mp 313-315 ° C.

b). Preparation of 2-amino-6-(2-(furan-2-ylmethylene)hydrazinyl)pyrimidin-4-ol (11)

Compound (11) was prepared from compound (2b) according to the procedure from Example 1 (c).

c). Preparation of 5-amino-2-(furan-2-yl)-[1,2,4]triazolo[1,5-c]pyrimidin-7-ol (8)

To a solution of the Schiff's base (11) (10 mmol) in methanol (10 mL) was added iodobenzenediacetate (IBA) (11 mmol) and the mixture was stirred for 1-2 h at room temperature. The solid separated was filtered off and washed with methanol. The resulting compound was pure enough for using in the next step.

d). Preparation of 5-amino-7-chloro-2-(furan-2-yl)-[1,2,4]triazolo[1,5-c]pyrimidine-8-carbaldehyde (10)

6.0 ml of dry DMF was slowly added to 26.0 ml of $POCl_3$ keeping the temperature at 0-5° C. 7.26 g of compound (8) was added to this mixture portion wise. The mixture was heated to 100° C and stirred at this temperature under TLC or HPLC monitoring. After reaction completion (4-6 h) the mixture was cooled to room temperature and poured into a mixture of 150 mL of water and 100 g of ice. The water solution was heated to 45-50° C and stirred for 1-2 h. The suspension was cooled to 3-5° C and stirred at this temperature overnight. The solids were filtered off and dried, yielding of compound (10).

e). Preparation of compound (1)

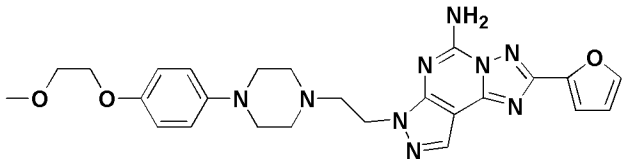
The mixture of compound (10) (1 eq.) and compound (5) (1 eq.) in 200 ml of acetonitrile was heated at reflux till reaction completion (TLC or HPLC control). The mixture was concentrated under reduced pressure to ~40-50 ml, cooled to room temperature and 25-30 ml of water was added. The mixture was stirred at 3-5°C overnight and filtered. The product was collected by filtration, washed several times with water, water-acetonitrile (1:1), and dried at 65 to 75°C in vacuum for about 24 h to give a compound (1) with purity >98% (HPLC).

While the present invention has been particularly described, persons skilled in the art will appreciate that many variations and modifications can be made. Therefore, the invention is not to be construed as restricted to the particularly described embodiments, and the scope and concept of the invention will be more readily understood by reference to the claims, which follow.

CLAIMS

What is claimed is:

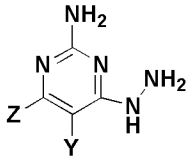
1. A process for the preparation of 2-(furan-2-yl)-7-[2-[4-[4-(2-methoxyethoxy)-phenyl]piperazin-1-yl]ethyl]-7H-pyrazolo[4,3-e][1,2,4]-triazolo[1,5-c]pyrimidin-5-amine (Preladenant), represented by the structure of formula (1):



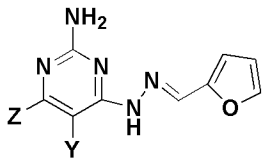
(1)

or a solvate or salt thereof, the process comprising the steps of:

(a) coupling a compound of formula (2) with furfural to form a hydrazone of formula (3):

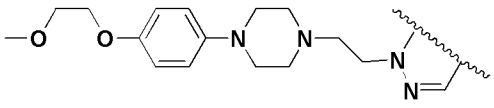


(2)



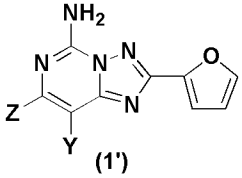
(3)

;

wherein Z and Y together represent  ; or

wherein Z is OH, halogen or O-sulfonate and Y is H;

(b) cyclizing compound (3) to form a compound of formula (1'):



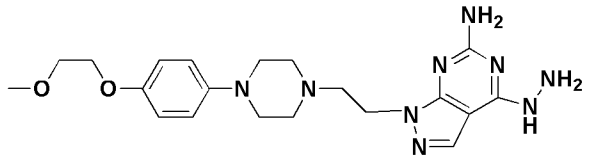
(1')

; and

(c) optionally, when Z is OH, halogen or O-sulfonate and Y is H, further converting the product of step (b) to Preladenant of formula (1).

2. The process according to claim 1, wherein step (b) is carried out in the presence of an acid or base catalyst, preferably wherein the catalyst is selected from sodium acetate, acetic anhydride/pyridine, pyridine/pyridinium chloride, bromine in acetic acid and iodobenzenediacetate.

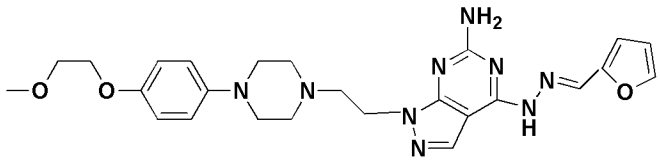
3. The process according to claim 1, wherein in the compound of formula (2) is 4-hydrazinyl-1-(2-(4-(4-(2-methoxyethoxy)phenyl)piperazin-1-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine, represented by the structure of formula (2a)



(2a)

4. The process according to claim 3, comprising the steps of

(a) coupling a compound of formula (2a) with furfural to form a hydrazone of formula (3a):



(3a)

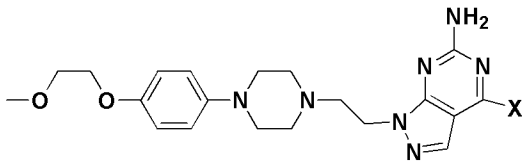
; and

(b) cyclizing compound (3a) to form Preladenant of formula (1).

5. The process according to claim 4, wherein the cyclization step is carried out in the presence of an acid or base catalyst, preferably wherein the catalyst is selected from sodium acetate, acetic anhydride/pyridine, pyridine/pyridinium chloride, bromine in acetic acid and iodobenzenediacetate.

6. The process according to claim 3 or 4, wherein the compound of formula (2a) is prepared by a process comprising the steps of:

(i) reacting a compound of formula (6)

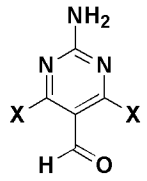


(6)

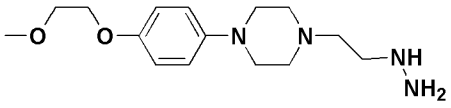
wherein X is a halogen or O-sulfonate, preferably wherein X is Cl, with hydrazine (H_2N-NH_2) or an N-protected derivative thereof of formula H_2N-NHP wherein P is an amino protecting group; and

(ii) optionally, when a protected hydrazine of formula H_2N-NHP is used, removing the protecting group P to form a compound of formula (2a).

7. The process according to claim 6, wherein the compound of formula (6) is prepared by coupling a compound of formula (4) with a compound of formula (5):



(4)

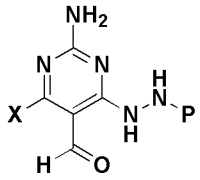


(5)

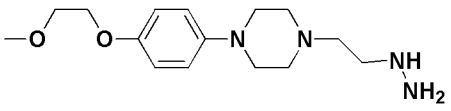
wherein each X is independently a halogen or O-sulfonate, preferably wherein each X is Cl.

8. The process according to claim 3 or 4, wherein the compound of formula (2a) is prepared by a process comprising the steps of:

(i) reacting a compound of formula (7) with a compound of formula (5)



(7)

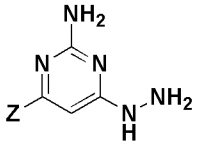


(5)

wherein X is a halogen or O-sulfonate, preferably wherein X is Cl; and P is a nitrogen protecting group; and

(ii) removing the nitrogen protecting group.

9. The process according to claim 1, wherein the compound of formula (2) is represented by the structure of formula (2b):

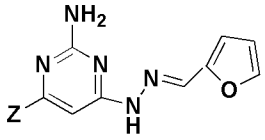


(2b)

wherein Z is OH, halogen or O-sulfonate.

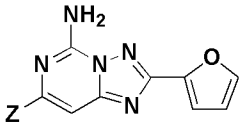
10. The process according to claim 9, comprising the steps of:

(a) coupling a compound of formula (2b) with furfural to form a hydrazone of formula (3b):



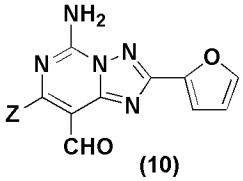
(3b) ;

(b) cyclizing compound (3b) to form a compound of formula (15):



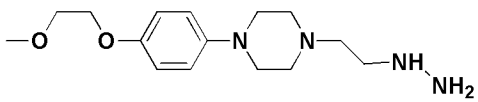
(15) ;

(c) formylating compound (15) to form compound (10):



(10) ; and

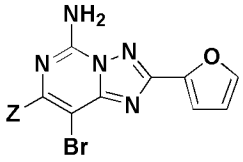
(d) reacting the compound of formula (10) with a compound of formula (5)



(5)

so as to form Preladenant of formula (1).

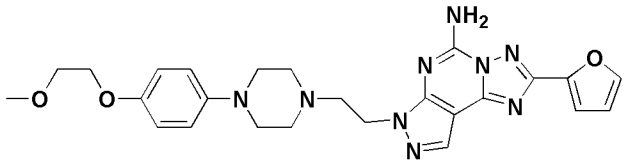
11. The process according to claim 10, wherein the cyclization of compound (3b) to compound (15) is carried out directly or by oxidative cyclization/bromination and reduction of an intermediate compound of formula (16)



(16)

12. The process according to claim 11, wherein the cyclization step is carried out in the presence of an acid or base catalyst preferably, wherein the catalyst is selected from sodium acetate, acetic anhydride/pyridine, pyridine/pyridinium chloride, bromine in acetic acid and iodobenzenediacetate.

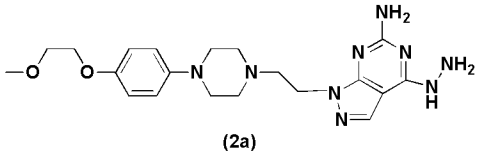
13. A process for the preparation of 2-(furan-2-yl)-7-[2-[4-[4-(2-methoxyethoxy)-phenyl]piperazin-1-yl]ethyl]-7H-pyrazolo[4,3-e][1,2,4]-triazolo[1,5-c]pyrimidin-5-amine (Preladenant), represented by the structure of formula (1):



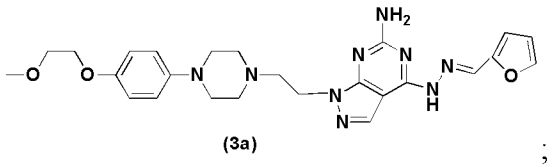
(1)

or a solvate or salt thereof, the process comprising the steps of:

(a) coupling a compound of formula (2a) with furfural to form a hydrazone of formula (3a)



(2a)



(3a)

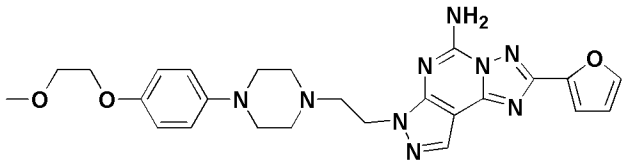
;

and

(b) cyclizing compound (3a) to form Preladenant of formula (1).

14. The process according to claim 13, wherein step (b) is carried out in the presence of an acid or base catalyst, preferably wherein the catalyst is selected from sodium acetate, acetic anhydride/pyridine, pyridine/pyridinium chloride, bromine in acetic acid and iodobenzenediacetate.

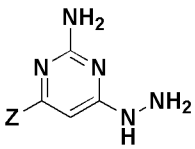
15. A process for the preparation of 2-(furan-2-yl)-7-[2-[4-[4-(2-methoxyethoxy)-phenyl]piperazin-1-yl]ethyl]-7H-pyrazolo[4,3-e][1,2,4]-triazolo[1,5-c]pyrimidin-5-amine (Preladenant), represented by the structure of formula (1)



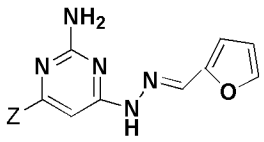
(1)

or a solvate or salt thereof, the process comprising the steps of:

(a) coupling a compound of formula (2b) with furfural to form a hydrazone of formula (3b):

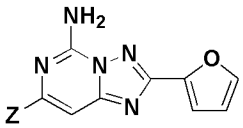


(2b)



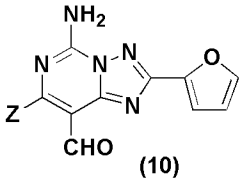
(3b) ;

(b) cyclizing compound (3b) to form a compound of formula (15):



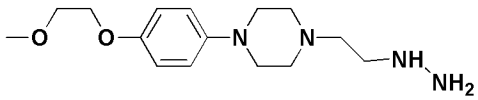
(15) ;

(c) formylating compound (15) so as to form compound (10):



(10) ; and

(d) reacting the compound of formula (10) with a compound of formula (5)



(5)

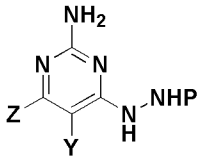
so as to form Preladenant of formula (1).

16. The process according to claim 15, wherein the cyclization step is carried out in the presence of an acid or base catalyst preferably, wherein the catalyst is selected from sodium acetate, acetic anhydride/pyridine, pyridine/pyridinium chloride, bromine in acetic acid and iodobenzenediacetate.

17. The process according to any one of the preceding claims, further comprising the step of converting Preladenant into a pharmaceutically acceptable salt thereof, preferably a salt with a physiologically acceptable acid.

18. 4-Chloro-1-(2-(4-(4-(2-methoxyethoxy)phenyl)piperazin-1-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine.

19. A compound of general formula



wherein P is a nitrogen protecting group, preferably Boc; Z is OH, halogen or O-sulfonate; and Y is H is or CHO.

20. 5-Amino-7-chloro-2-(furan-2-yl)-[1,2,4]triazolo[1,5-c]pyrimidine-8-carbaldehyde .

21. 4-(2-(furan-2-ylmethylene)hydrazinyl)-1-(2-(4-(4-(2-methoxyethoxy)phenyl) piperazin-1-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-6-amine (3a).

22. Preladenant or a salt or solvate thereof, which is prepared in accordance with the process of any of claims 1 to 17.

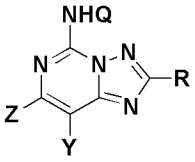
23. A method of treating a neurodegenerative disease comprising administering to a subject in need thereof a therapeutically acceptable amount of Preladenant or a solvate or salt thereof, wherein the Preladenant is prepared in accordance with the process of any of claims 1 to 17.

24. The method according to claim 23, wherein the neurodegenerative disease is Parkinson's Disease.

25. Use of Preladenant, or a solvate or salt thereof, prepared in accordance with the process of any of claims 1 to 17, for treating a neurodegenerative disease.

26. The use of claim 25, wherein the neurodegenerative disease is Parkinson's Disease.

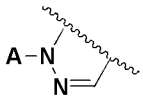
27. A process for the preparation of a compound represented by the structure of formula (17):



(17)

or a solvate or salt thereof, wherein

Z and Y together form a group of the formula



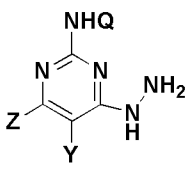
A is H, C_1-C_6 alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl or a C_1-C_6 alkylene-R^a wherein R^a is selected from the group consisting of cycloalkyl, aryl, heterocyclyl and heteroaryl, each of which may optionally be substituted;

R is an unsubstituted or substituted alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl or heteroaryl, preferably furanyl, thienyl, pyridyl, pyridyl N-oxide, oxazolyl, phenyl or pyrrolyl; and

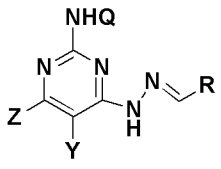
Q is H, an unsubstituted or substituted alkyl, an unsubstituted or subsituted aryl or a nitrogen protecting group;

the process comprising the steps of:

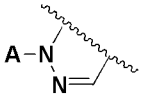
(a) coupling a compound of formula (18) with an aldehyde of formula R-CHO to form a hydrazone of formula (19):



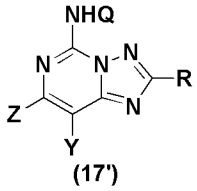
(18)



(19)

wherein Z is OH, halogen or O-sulfonate and Y is H; or Z and Y together form a group of the formula  wherein A is as defined above;

(b) cyclizing compound (19) to form a compound of formula (17') wherein Z and Y are as defined in (a); and



(17')

(c) optionally, when Z is OH, halogen or O-sulfonate and Y is H, further converting the product of step (b) to the compound of formula (17).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2012/050100

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 497/14 (2012.01)
USPC - 544/252
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 31/519; C07D 497/14 (2012.01)
USPC - 514/259.31, 267, 275; 544/251, 252, 262, 263, 297, 323, 334

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Orbit, STN, PubChem, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/0099061 A1 (NEUSTADT et al) 25 July 2002 (25.07.2002) entire document	18
A	US 2006/0149060 A1 (KUO et al) 06 July 2006 (06.07.2006) entire document	1-27
A	US 2003/0212080 A1 (MATASI et al) 13 November 2003 (13.11.2003) entire document	1-27
A	US 2006/0009504 A1 (HEIMBECHER et al) 12 January 2006 (12.01.2006) entire document	1-27
A	US 2007/0238726 A1 (BLAKE et al) 11 October 2007 (11.10.2007) entire document	1-27

☐ 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 August 2012	17 AUG 2012
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. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)