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(54) **IMPROVED SYNTHETIC METHODS OF MAKING FUSED HETEROCYCLIC COMPOUNDS AS OREXIN RECEPTOR MODULATORS**

VERBESSERTE SYNTHETISCHE VERFAHREN ZUR HERSTELLUNG VON KONDENSIERTEN HETEROCYCLISCHEN VERBINDUNGEN ALS OREXIN-REZEPTOR-MODULATOREN

PROCÉDÉS SYNTHÉTIQUES AMÉLIORÉS DE PRODUCTION DE COMPOSÉS HÉTÉROCYCLIQUES FUSIONNÉS UTILISÉS EN TANT QUE MODULATEURS DU RÉCEPTEUR DE L'OREXINE

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(73) Proprietor: **Janssen Pharmaceutica N.V.**
2340 Beerse (BE)

(72) Inventors:
- **DEPRÉ, Dominique Paul Michel**
  2340 Beerse (BE)
- **MATCHA, Kiran**
  2340 Beerse (BE)
- **HUYGAERTS, Andy Josephina Joannes**
  2340 Beerse (BE)
- **MOENS, Luc Jozef Raphael**
  2340 Beerse (BE)
- **GALA, Dinesh**
  Raritan, NJ 08869 (US)

(74) Representative: **Carpmaels & Ransford LLP**
One Southampton Row
London WC1B 5HA (GB)

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- **M. A. LETAVIC ET. AL.: "Novel Octahydropyrrolo[3,4-c]pyrroles are Selective Orexin-2 Antagonists: SAR Leading to a Clinical Candidate.", JOURNAL OF MEDICINAL CHEMISTRY, vol. 58, no. 14, 18 June 2015 (2015-06-18) , pages 5620-5636, XP055493378, DOI: 10.1021/acs.jmedchem.5b00742**
- **Mark D. Oldham: "5-0XAZOLIDINONES: KEy INTERMEDIATES TO PEPTIDOMIMETICS WITH LATENT REACTIVITY AND CONFORMATIONAL RESTRICTION", , 1997, XP55734406,**
- **DATABASE Pubchem 26 March 2005 (2005-03-26), XP55734421, Database accession no. CID312674**
- **DATABASE Pubchem 18 December 2015 (2015-12-18), Database accession no. CID101510576**
- **DATABASE Pubchem 20 August 2012 (2012-08-20), Database accession no. CID59486002**

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- **DATABASE Pubchem 18 June 2017 (2017-06-18), Database accession no. CID128564374**
- **DATABASE Pubchem 5 December 2007 (2007-12-05), Database accession no. CID21867682**
- **DATABASE Pubchem 11 July 2005 (2005-07-11), Database accession no. CID1514449**

Description

FIELD OF THE INVENTION

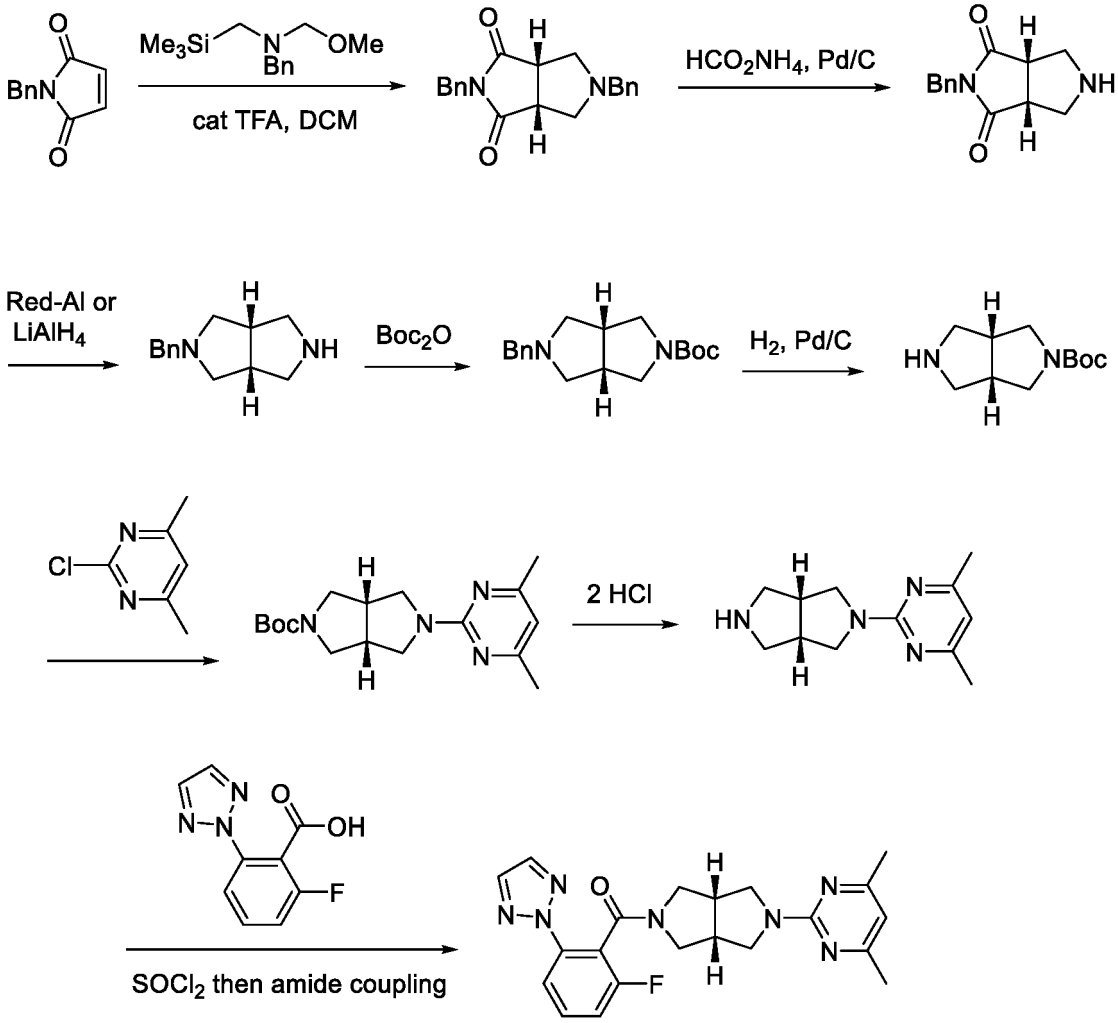
[0001] The present invention relates to the synthesis methods making (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone, a compound useful for modulation of the orexin receptor and for the treatment of disease states, disorders, and conditions mediated by orexin receptor activity.

BACKGROUND OF THE INVENTION

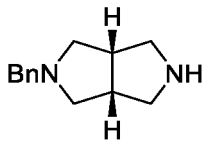
[0002] Orexin (or hypocretin) signaling is mediated by two receptors and two peptide agonists. The two orexin peptides (orexin A and orexin B) herein after referred to as orexins, bind to two high affinity receptors, termed orexin-1 and orexin-2 receptors. The orexin-1 receptor is selective in favor of orexin A, while the orexin-2 receptor binds both orexins with similar affinities. The orexins, are cleavage products of the same gene, prepro orexin. In the central nervous system neurons expressing preproorexin, the precursor from which orexin is produced, are found in the perifornical nucleus, the dorsal hypothalamus and the lateral hypothalamus (C. Peyron et al., J. Neurosci., 1998, 18(23), 9996-10015). Orexinergic cells in these nuclei project to many areas of the brain, extending rostrally to the olfactory bulbs and caudally to the spinal cord (van den Pol, A.N. et al., J. Neuroscience., 1999, 19(8), 3171-3182).

[0003] Substituted diaza-bicyclic compounds have been reported as active central nervous system agents (International Publication No. WO2001081347, November 1, 2001; US2002/0019388, February 14, 2002), α7 acetylcholine receptor modulators (US2005/101602, May 12, 2005; US2005/0065178, March 24, 2005 and Frost et al, Journal of Medicinal Chemistry, 2006, 49(26), 7843-7853), proline transporter inhibitors for the treatment of cognitive impairment (WO2008067121, June 5, 2008) and for improving cognition (WO 2006 124897, November 23, 2006 and US20060258672, November 16, 2006), as androgen receptor ligands for the treatment of androgen receptor associated conditions including cancer (WO2009081197, July 2, 2009), and as histone deacetylase inhibitors for the treatment of cancers, neurodegenerative diseases and autoimmune diseases (WO20060123121, November 23, 2006).

[0004] Among the developed compounds, (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone was found to act as an inhibitor of the orexin-2 receptor and to be useful for the treatment of sleep disorders and major depressive diseases (US 8,653,263 B2). The original synthesis had a linear sequence of eight steps from commercially available 1-benzyl-1*H*-pyrrole-2,5-dione, including four protecting group manipulation steps (scheme below).



[0005] Other multi-step efforts to make the (3aR,6aS)-2-benzyloctahydropyrrolo[3,4-c]pyrrole intermediate,

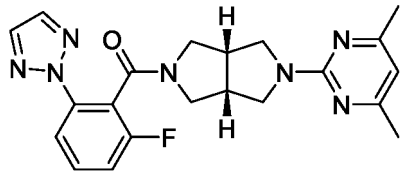


have been reported (Org. Proc. Res. Dev. 2010, 18, 592, and J. Med. Chem. 2015, 58, 5620). However, an improved synthesis was required for economical commercial production of (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone.

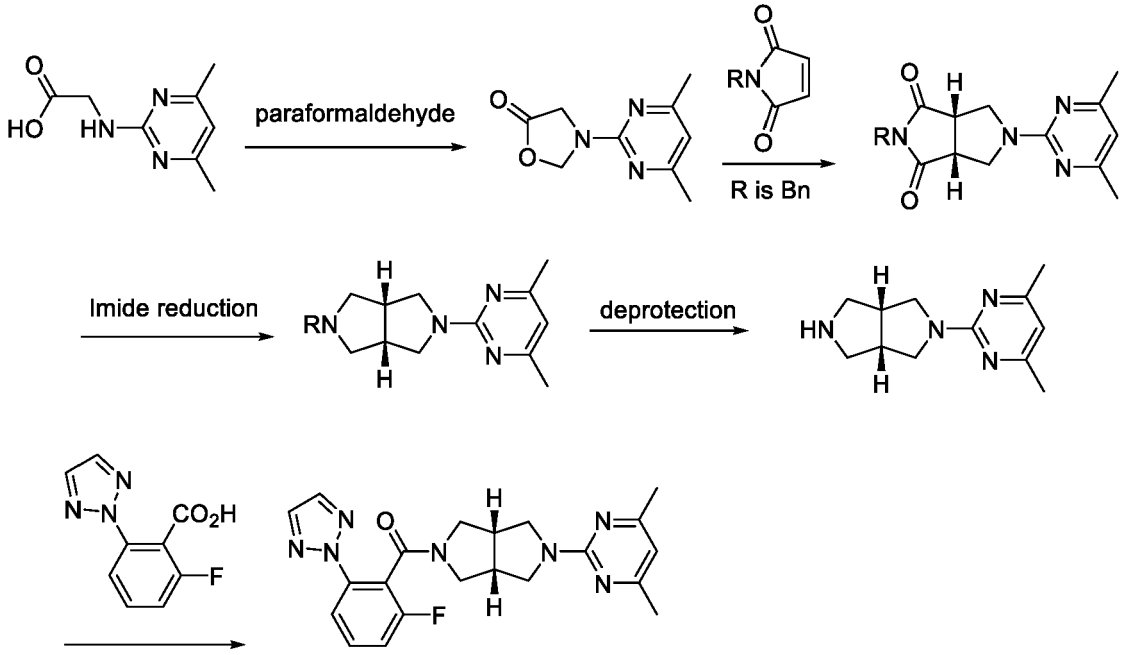
[0006] It is an object of the invention to provide a process for preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone utilizing fewer protecting group steps and a shorter overall reaction sequence in order to reduce cost of manufacturing.

SUMMARY OF THE INVENTION

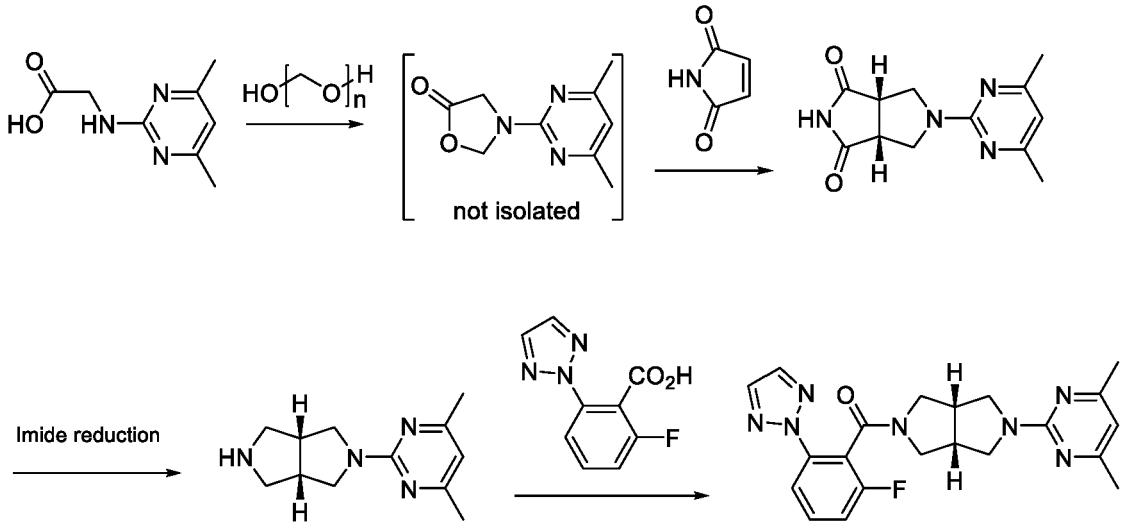
[0007] The invention comprises a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone



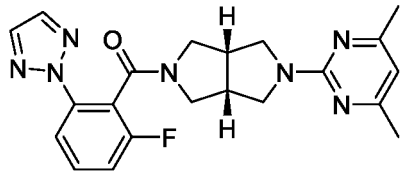
[0008] Wherein early installation of the 4,6-dimethylpyrimid-2-yl group obviates the need for three protecting group manipulation steps, reducing the linear sequence from commercially available 1-benzyl-1*H*-pyrrole-2,5-dione to four steps.



[0009] In other embodiments of the invention, protecting groups are eliminated altogether, and the linear sequence from commercially available 1*H*-pyrrole-2,5-dione is reduced to as few as three steps.

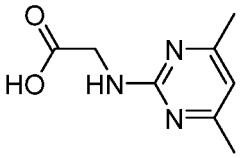


[0010] The invention comprises a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexshydropyrrolo[3,4-c]pyrrol-2(1*H*)-Y1)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

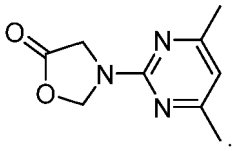


said process comprising step described below:

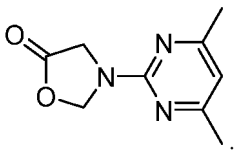
a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,



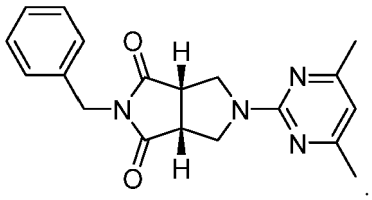
wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



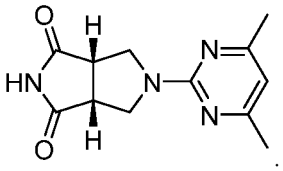
[0011] The invention further comprises a compound which is 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one,



[0012] The invention further comprises a compound which is (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione,

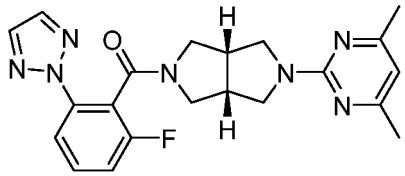


[0013] The invention further comprises a compound which is (3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione,



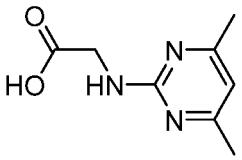
DETAILED DESCRIPTION OF THE INVENTION

[0014] The invention comprises a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

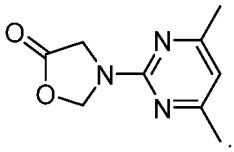


said process comprising step described below:

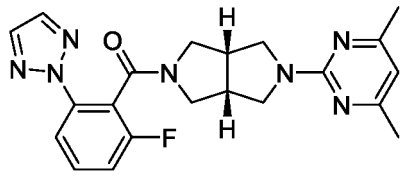
a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,



wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one

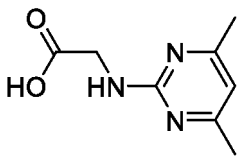


[0015] Another embodiment of the invention is a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

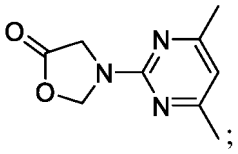


said process comprising the steps described below:

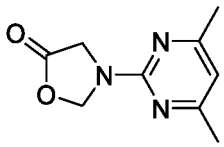
a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,



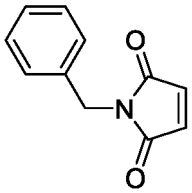
wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



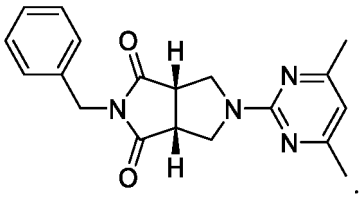
b) Reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



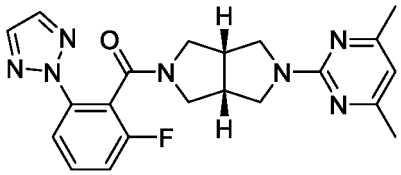
with 1-benzyl-1H-pyrrole-2,5-dione



at a temperature greater than 250 °C to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole- 1,3(2*H*,3a*H*)-dione

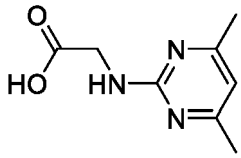


[0016] Another embodiment of the invention is a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-y])hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3 -triazol-2-yl)phenyl)methanone

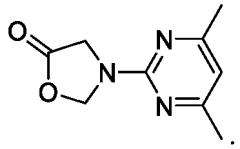


said process comprising the steps described below:

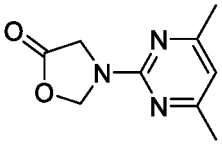
a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,



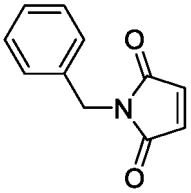
wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



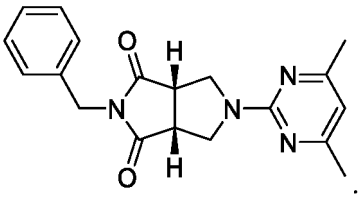
b) Reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



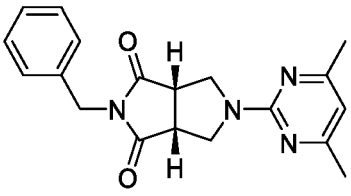
with 1-benzyl-1H-pyrrole-2,5-dione



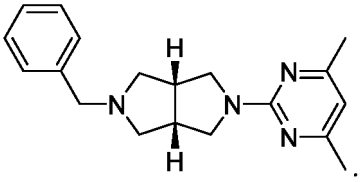
at a temperature greater than 250 °C to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole- 1,3(2*H*,3a*H*)-dione



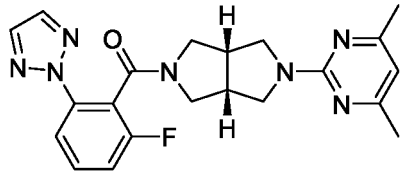
c) reduction of (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole

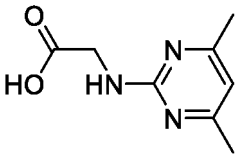


[0017] Another embodiment of the invention is a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

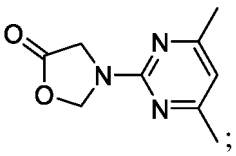


said process comprising the steps described below:

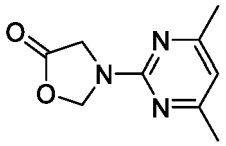
a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,



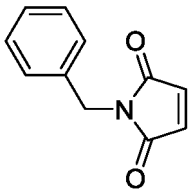
wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



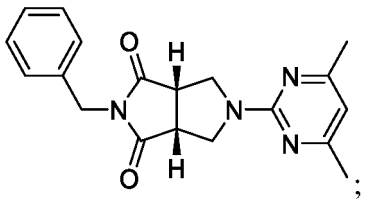
b) Reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



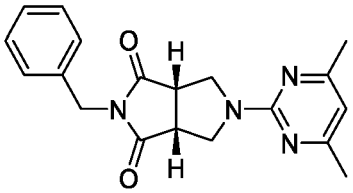
with 1-benzyl-1H-pyrrole-2,5-dione



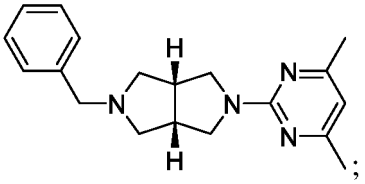
at a temperature greater than 250 °C to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



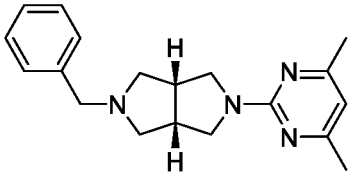
c) reduction of (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



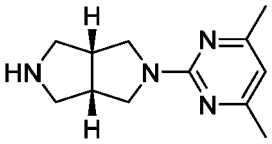
to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



d) deprotection of (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3 ,4-c]pyrrole

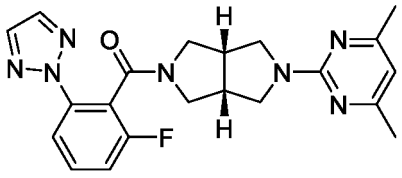


to form (3a*R*,6a*S*)-2-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



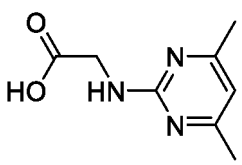
by means of 10% (w/w) Pd/C and ammonium formate.

[0018] Another embodiment of the invention is a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

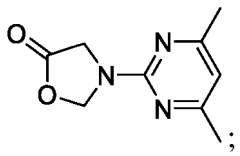


said process comprising the steps described below:

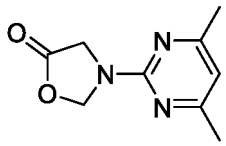
a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,



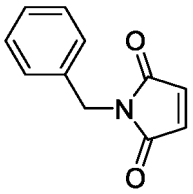
wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



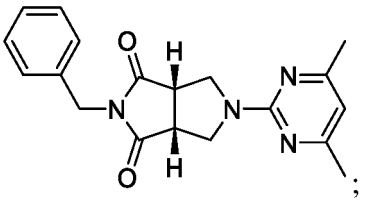
b) Reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



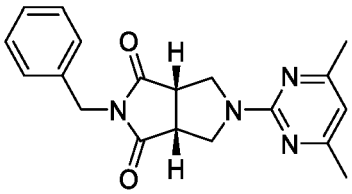
with 1-benzyl-1H-pyrrole-2,5-dione



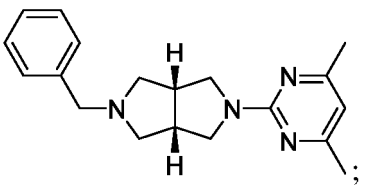
at a temperature greater than 250 °C to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole- 1,3(2*H*,3a*H*)-dione



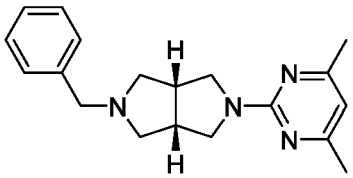
c) reduction of (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



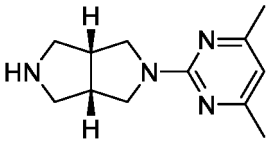
to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



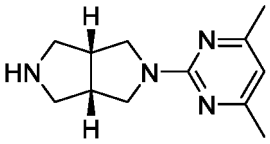
d) deprotection of (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



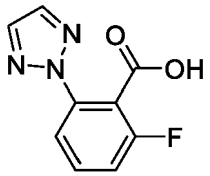
to form (3a*R*,6a*S*)-2-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



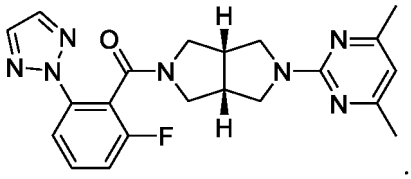
by means of 10% (w/w) Pd/C and ammonium formate;
e) Amidation of (3a*R*,6a*S*)-2-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



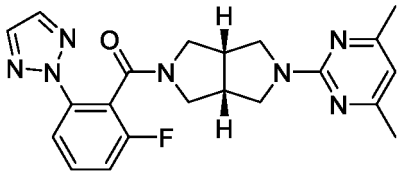
with 2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)benzoic acid



by means of $SOCl_2$ to form (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

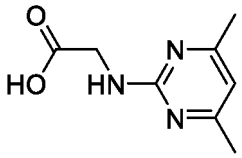


[0019] Another embodiment of the invention is a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-y])hexahydropyrrolo[3,4-c]pyrro]-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3 -triazol-2-yl)phenyl)methanone

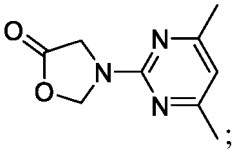


said process comprising the steps described below:

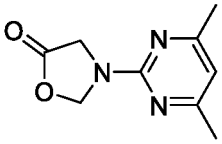
a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,



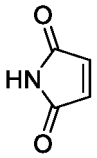
wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



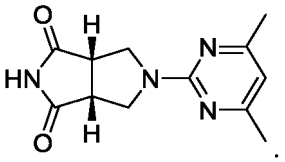
b) Reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



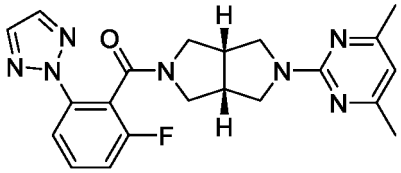
with 1*H*-pyrrole-2,5-dione



at a temperature greater than 250 °C to form (3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione

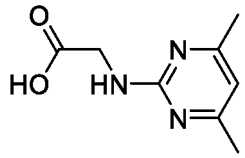


[0020] Another embodiment of the invention is a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

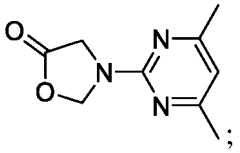


said process comprising the steps described below:

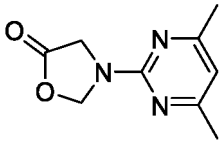
a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,



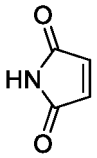
wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



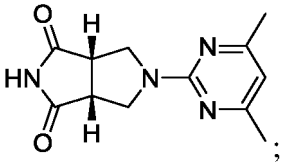
b) reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



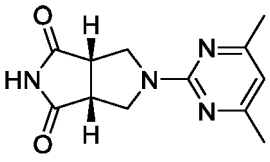
with 1*H*-pyrrole-2,5-dione



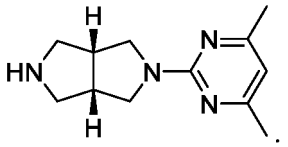
at a temperature greater than 250 °C to form (3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



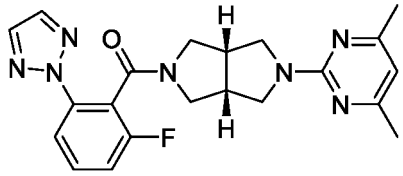
c) reduction of (3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole- 1,3(2*H*,3a*H*)-dione



to form (3a*R*,6a*S*)-2-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole

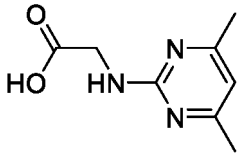


[0021] Another embodiment of the invention is a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1 ,2,3 -triazol-2-yl)phenyl)methanone

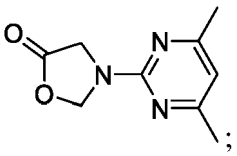


said process comprising the steps described below:

a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,

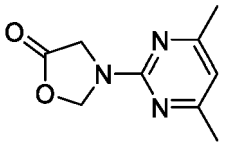


wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one

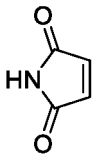


;

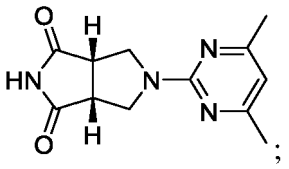
b) reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



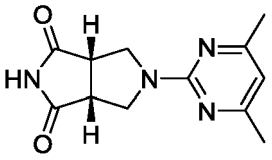
with 1*H*-pyrrole-2,5-dione



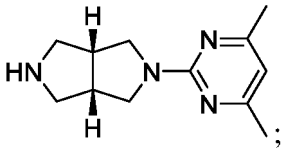
at a temperature greater than 250 °C to form (3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



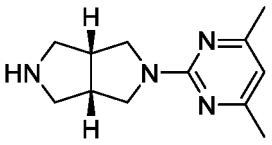
c) reduction of (3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole- 1,3(2*H*,3a*H*)-dione



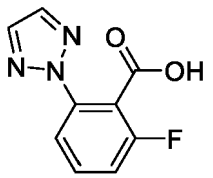
to form (3a*R*,6a*S*)-2-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



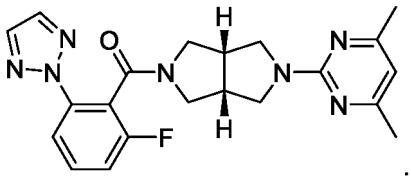
e) Amidation of (3a*R*,6a*S*)-2-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



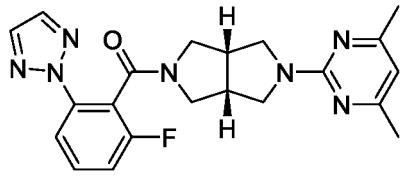
with 2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)benzoic acid



by means of $SOCl_2$ to form (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexaliydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

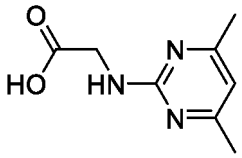


[0022] Another embodiment of the invention is a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

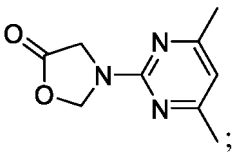


said process comprising the steps described below:

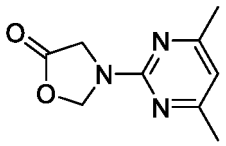
a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,



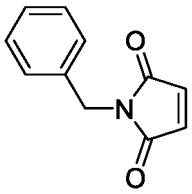
wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one


;

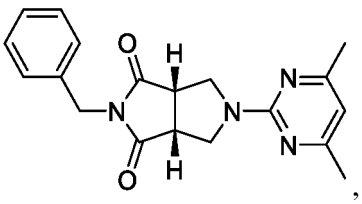
b) Reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



with 1-benzyl-1H-pyrrole-2,5-dione

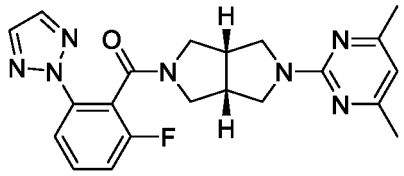


at a temperature greater than 250 °C to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole- 1,3(2*H*,3a*H*)-dione


,

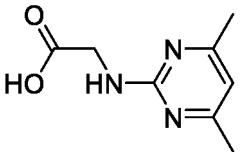
wherein said 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one is not isolated prior to reaction with said 1-benzyl-1H-pyrrole-2,5-dione.

[0023] Another embodiment of the invention is a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

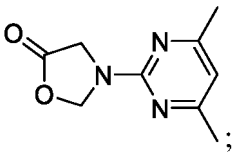


said process comprising the steps described below:

a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,

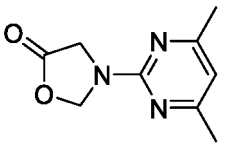


wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one

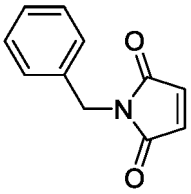


;

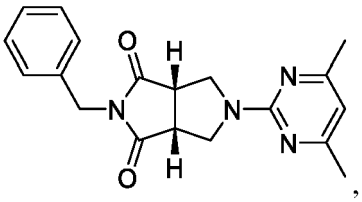
b) Reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



with 1-benzyl-1H-pyrrole-2,5-dione



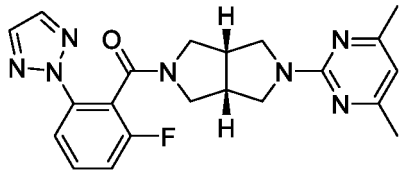
at a temperature greater than 250 °C to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



,

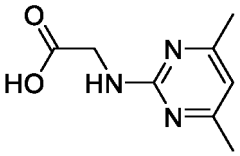
wherein said 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one is isolated prior to reaction with said 1-benzyl-1H-pyrrole-2,5-dione.

[0024] Another embodiment of the invention is a process of preparing (((3a*R*,6a*S*)-5-(4,6-dirnethylpyrimidin-2-y])hexahydropyrrolo[3,4-c]pyrro]-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

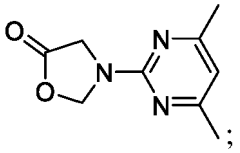


said process comprising the steps described below:

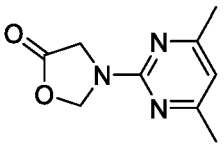
a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,



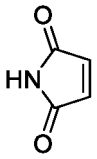
wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one


;

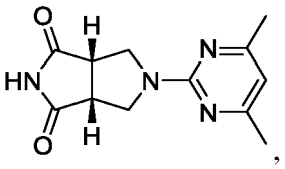
b) Reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



with 1*H*-pyrrole-2,5-dione

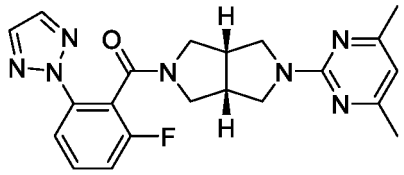


at a temperature greater than 250 °C to form (3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione


,

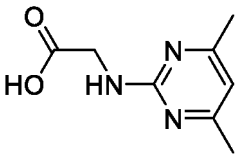
wherein said 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one is not isolated prior to reaction with said 1-benzyl-1H-pyrrole-2,5-dione.

[0025] Another embodiment of the invention is a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-y])hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1 ,2,3 -triazol-2-yl)phenyl)methanone

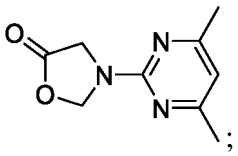


said process comprising the steps described below:

a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,

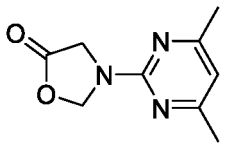


wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one

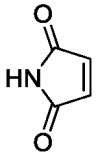


;

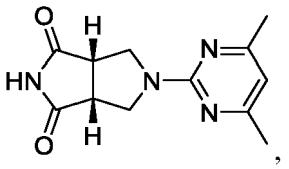
b) Reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



with 1*H*-pyrrole-2,5-dione

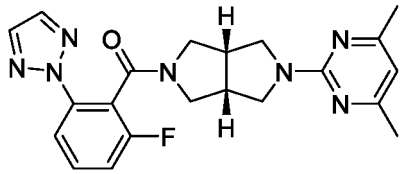


at a temperature greater than 250 °C to form (3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



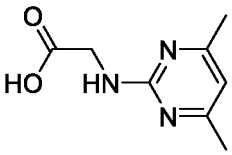
wherein said 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one is isolated prior to reaction with said 1-benzyl-1H-pyrrole-2,5-dione.

[0026] Another embodiment of the invention is a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

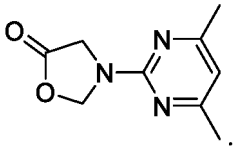


said process comprising the steps described below:

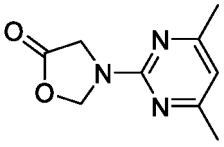
a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,



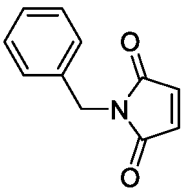
wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



b) Reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one

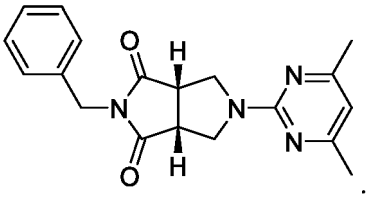


with 1-benzyl-1H-pyrrole-2,5-dione

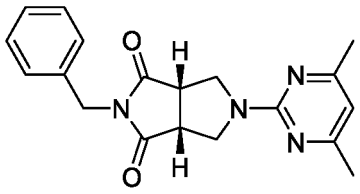


at a temperature greater than 250 °C to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrro-

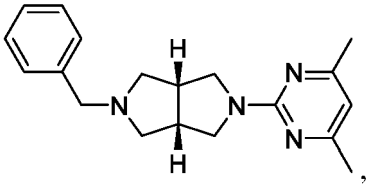
lo[3,4-c]pyrrole- 1,3(2*H*,3a*H*)-dione



c) reduction of (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione

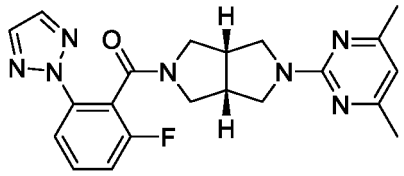


to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



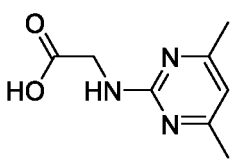
wherein said reduction comprises the use of one or more reagents selected from the group consisting of $NaBH_4$, PMHS, TMDS, Et_3SiH, Red-Al, and BH_3.

[0027] Another embodiment of the invention is a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

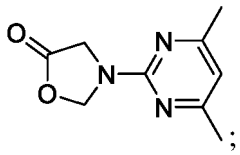


said process comprising the steps described below:

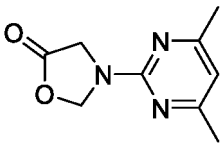
a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,



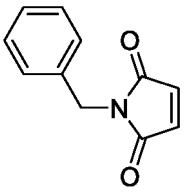
wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



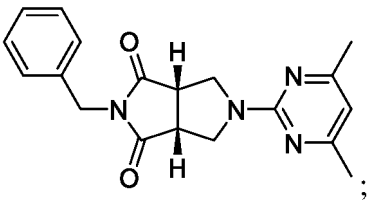
b) Reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



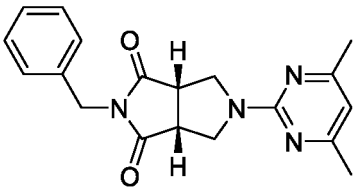
with 1-benzyl-1H-pyrrole-2,5-dione



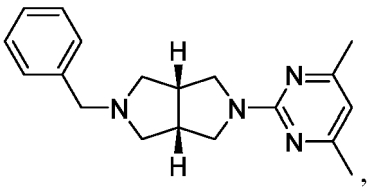
at a temperature greater than 250 °C to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole- 1,3(2H,3aH)-dione



c) reduction of (3aR,6aS)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3 ,4-c]pyrrole-1 ,3(2*H*,3a*H*)-dione

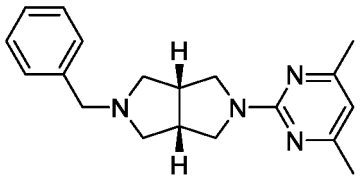


to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole

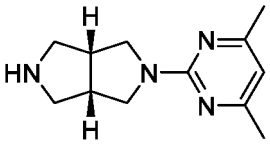


wherein said reduction comprises the use of one or more reagents selected from the group consisting of $NaBH_4$, PMHS, TMDS, Et_3SiH, Red-Al, and BH_3;

d) deprotection of (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3 ,4-c]pyrrole

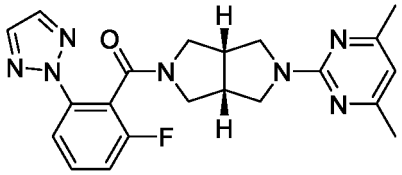


to form (3a*R*,6a*S*)-2-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



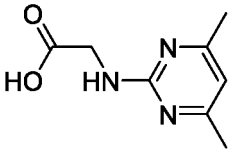
by means of 10% (w/w) Pd/C and ammonium formate.

[0028] Another embodiment of the invention is a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

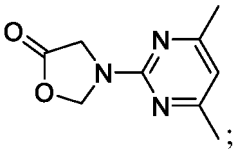


said process comprising the steps described below:

a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,

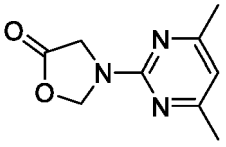


wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one

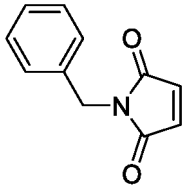


;

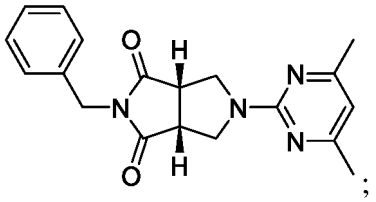
b) Reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



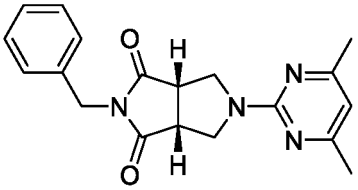
with 1-benzyl-1H-pyrrole-2,5-dione



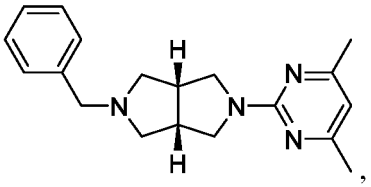
at a temperature greater than 250 °C to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole- 1,3(2*H*,3a*H*)-dione



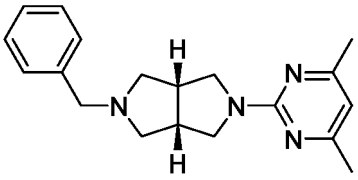
c) reduction of (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



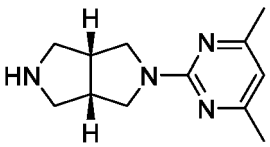
to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



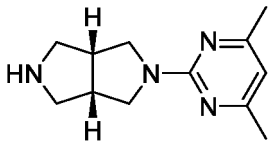
wherein said reduction comprises the use of one or more reagents selected from the group consisting of $NaBH_4$, PMHS, TMDS, Et_3SiH, Red-Al, and BH_3;
d) deprotection of (3aR,6aS)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3 ,4-c]pyrrole



to form (3aR,6aS)-2-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole

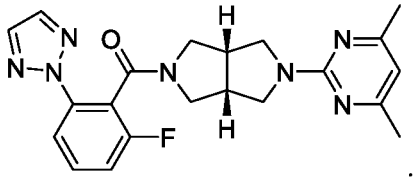


by means of 10% (w/w) Pd/C and ammonium formate;
e) Amidation of (3a*R*,6a*S*)-2-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole

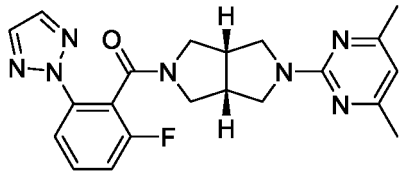


with 2-fluoro-6-(2H-1,2,3-triazol-2-yl)benzoic acid

by means of $SOCl_2$ to form (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

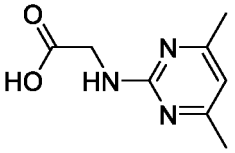


[0029] Another embodiment of the invention is a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

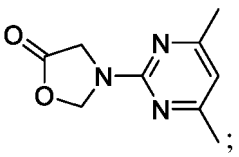


said process comprising the steps described below:

a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,

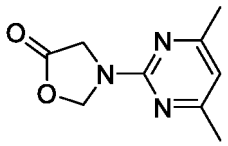


wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one

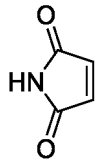


;

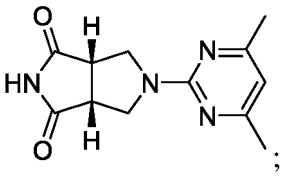
b) reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



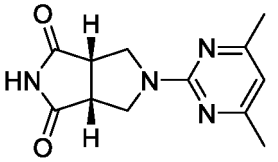
with 1*H*-pyrrole-2,5-dione



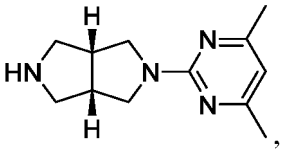
at a temperature greater than 250 °C to form (3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



c) reduction of (3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole- 1,3(2*H*,3a*H*)-dione

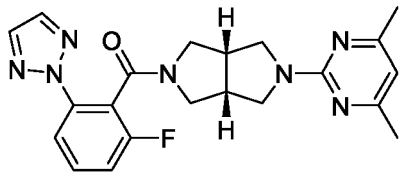


to form (3a*R*,6a*S*)-2-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



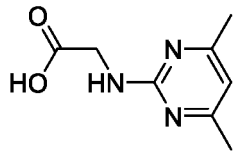
wherein said reduction comprises the use of one or more reagents selected from the group consisting of $NaBH_4$, PMHS, TMDS, Et_3SiH, Red-Al, and BH_3.

[0030] Another embodiment of the invention is a process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

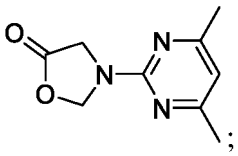


said process comprising the steps described below::

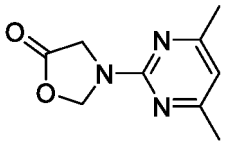
a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,



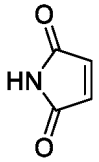
wherein said oxazolidination is characterized by the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



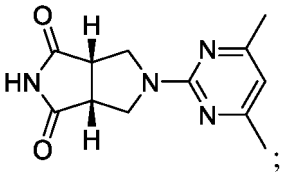
b) reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



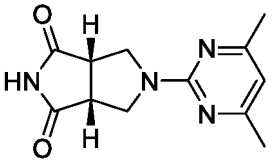
with 1*H*-pyrrole-2,5-dione



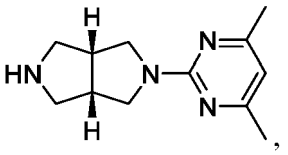
at a temperature greater than 250 °C to form (3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



c) reduction of (3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole- 1,3(2*H*,3a*H*)-dione

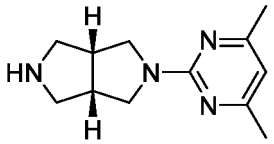


to form (3a*R*,6a*S*)-2-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole

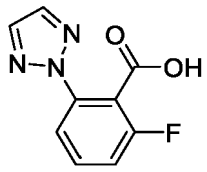


wherein said reduction comprises the use of one or more reagents selected from the group consisting of $NaBH_4$, PMHS, TMDS, Et_3SiH, Red-Al, and BH_3.

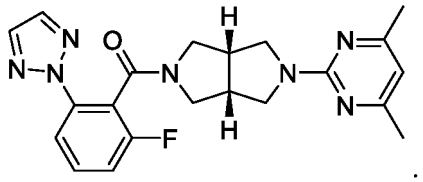
e) Amidation of (3a*R*,6a*S*)-2-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



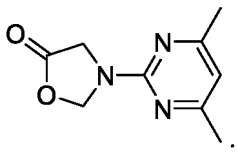
with 2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)benzoic acid



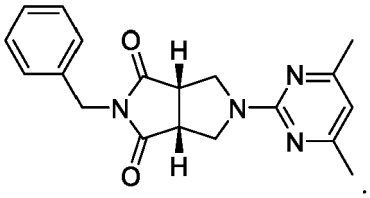
by means of $SOCl_2$ to form (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone



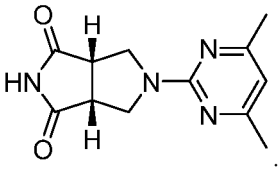
[0031] Another embodiment of the invention is a compound which is 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



[0032] Another embodiment of the invention is a compound which is (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



[0033] Another embodiment of the invention is a compound which is (3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione

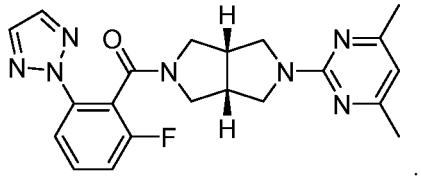


[0034] The invention may be more fully appreciated by reference to the following description, including the following glossary of terms and the concluding examples.

[0035] As used herein, the terms "including", "containing" and "comprising" are used herein in their open, non-limiting sense.

DEFINITIONS

[0036] The term "(((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone" means



[0037] Any formula given herein is intended to represent compounds having structures depicted by the structural formula as well as certain variations or forms.

[0038] Products of the chemical reactions described in this specification may be reacted directly with additional reagents or may be separated prior to subsequent reaction. The term "isolated" means the partial or complete separation of a reaction product from other materials in the reaction vessel. These other materials include, but are not limited to solvents, unreacted starting material, reagents used in the reaction, side-products, impurities and the products of reagents used in the reaction.

[0039] The term "preparing" means synthesizing by means of chemical processes.

[0040] Additionally, any formula given herein is intended to refer also to hydrates, solvates, and polymorphs of such compounds, and mixtures thereof, even if such forms are not listed explicitly.

[0041] Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, respectively. Such isotopically labeled compounds are useful in metabolic studies (preferably with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques [such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT)] including drug or substrate tissue distribution assays, or in radioactive treatment of patients. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

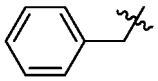
[0042] Those skilled in the art will recognize that compounds and reagents used in the reactions of the invention may exist as salts. The invention contemplates the use of all salts of any compound used in a reaction exemplified herein.

[0043] Examples of salts include, without limitation, sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycolates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

[0044] When a compound or reagent used in a reaction of the invention contains a basic nitrogen, a salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, boric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, phenylacetic acid, propionic acid, stearic acid, lactic acid, ascorbic acid, maleic acid, hydroxymaleic acid, isethionic acid, succinic acid, valeric acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, oleic acid, palmitic acid, lauric acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as mandelic acid, citric acid, or tartaric acid, an amino acid, such as aspartic acid, glutaric acidor glutamic acid, an aromatic acid, such as benzoic acid, 2-acetoxybenzoic acid, naphthoic

acid, or cinnamic acid, a sulfonic acid, such as laurylsulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, any compatible mixture of acids such as those given as examples herein, and any other acid and mixture thereof that are regarded as equivalents or acceptable substitutes in light of the ordinary level of skill in this technology.

[0045] Those skilled in the art will recognize many reagents may be used for the removal a benzyl protecting group



and reagents used in such removal are both diverse and known to the skilled practitioner. The invention contemplates the use of all common means of benzyl group removal, including those described in Protective Groups in Organic Synthesis, by T. W. Green, and P. G. M. Wuts, Wiley-Interscience, New York, 1999, 579-580, 744-747.

[0046] Examples of deprotective reagents include, but are not limited to, ammonium formate in the presence of a palladium catalyst, hydrogen gas in the presense of a palladium catalyst, formic acid, formic acid-triethylamine mixture, sodium formate, potassium formate, cyclohexene, or cyclohexadiene.

[0047] Exemplary reactions useful in methods of the invention will now be described by reference to the illustrative synthetic schemes for their general preparation below and the specific examples that follow. Those skilled in the art will recognize that reactions may be performed in any suitable solvent. Those skilled in the art will also recognize that, except where specifically limited, reactions may be performed at a wide range of temperatures. Unless otherwise specified, reactions may be performed between the melting point and the reflux temperature of the solvent, and preferably between 0 °C and the reflux temperature of the solvent. Reactions may be heated employing conventional heating or microwave heating. Reactions may also be conducted in sealed pressure vessels above the normal reflux temperature of the solvent.

ABBREVIATIONS

[0048] Herein and throughout the specification, the flowing abbreviations may be used.

Abbreviation	Term
acac	acetylacetonate
Bn	benzyl
BOC	tert-Butylcarbamoyl
DCM	dichloromethane
DMSO	dimethylsulfoxide
EtOAc, or EA	ethyl Acetate
EtOH	ethanol
Et_3SiH	triethylsilane
HOAc	acetic Acid
HPLC	high-performance liquid chromatography
KHMDS	potassium hexamethyldisilylamide
MTBE	methyl tert-butyl ether
MeOH	methanol
OAc	acetate
PMHS	Poly(methylhydrosiloxane)
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
TBAF	tetrabutylammonium fluoride
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran

(continued)

Abbreviation	Term
TMDS	1,1,3,3-tetramethyldisiloxane
UPLC	ultra-pressure liquid chromatography

EXAMPLES

[0049] In obtaining the compounds described in the examples below and the corresponding analytical data, the following experimental and analytical protocols were followed unless otherwise indicated.

[0050] Unless otherwise stated, reaction mixtures were stirred at room temperature (rt) under a nitrogen atmosphere. Where mixtures, solutions, and extracts were "concentrated", they were typically concentrated under reduced pressure. Reactions under microwave irradiation conditions were carried out in a Biotage Initiator or CEM Discover instrument.

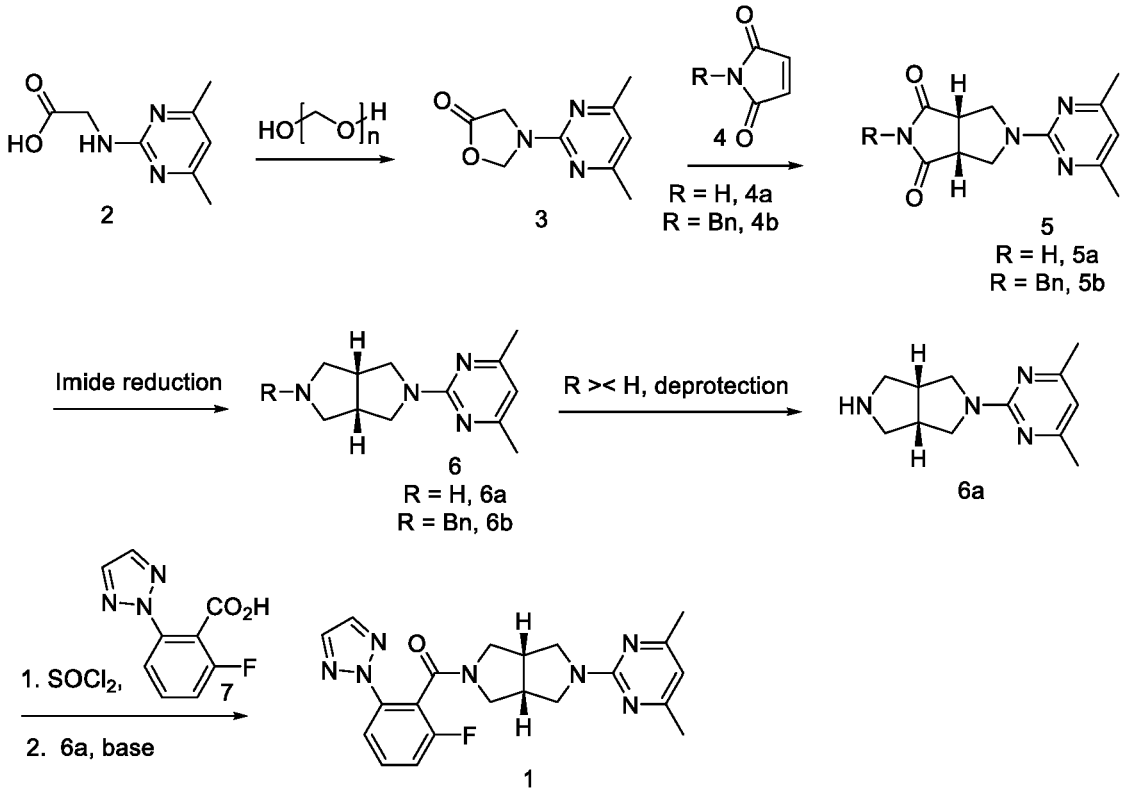
[0051] Normal-phase flash column chromatography (FCC) was performed on silica gel (SiO_2) using prepackaged cartridges, eluting with the indicated solvents.

[0052] Mass spectra (MS) were obtained on either Bruker QTOF, Waters QTOF Ultima instruments using electrospray ionization (ESI) in positive mode unless otherwise indicated, or on a Waters GC-TOF using electronic impact (EI). Calculated (calcd.) mass corresponds to the exact mass.

[0053] Nuclear magnetic resonance (NMR) spectra were obtained on Bruker spectrometers. The format of the ^1H NMR data below is: chemical shift in ppm downfield of the tetramethylsilane reference (multiplicity, coupling constant J in Hz, integration).

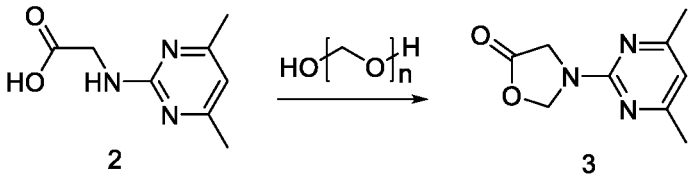
[0054] Chemical names were generated using ChemDraw Ultra 6.0.2 (CambridgeSoft Corp., Cambridge, MA) or ACD/Name Version 9 (Advanced Chemistry Development, Toronto, Ontario, Canada).

GENERAL SCHEME



Example 1: Formation of compound **3** from compound **2**

[0055]



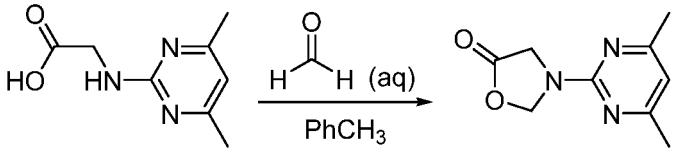
2 3

Example 1a: batch mode in toluene using paraformaldehyde with isolation

[0056] To a 10L jacketed reactor were added compound **2** (496.10 g) and toluene (7.44 L). The reaction mixture was heated to 65 °C and subsequently charged with paraformaldehyde (1.2 equiv, 98.65 g). While stirring with a strong nitrogen flow, conversion was followed up by FTIR. After 23 hours reaction stalled. More paraformaldehyde (0.45 equiv, 36.99 g) was charged. After 20 hours reaction was complete according to FTIR. The reaction mixture was filtered to remove unreacted **2** and leftovers of paraformaldehyde. The mother liquor was distilled to dryness to give compound **3** (528.97 g, yield: 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (s, 1H), 5.64 (s, 2H), 4.27 (s, 2H), 2.33 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (C), 167.95 (2 x C), 158.76 (CO), 111.78 (CH), 80.29 (CH_2), 45.01 (CH_2), 24.0 (2 x CH_3). High resolution MS (EI, *m/z):* calcd for $C_9H_{11}N_3O_2$ $(M)^{+\cdot}$: 193.0851; found: 193.0847. mp.130-135 °C (dec.).

Example 1b: alternative Synthesis - with aqueous solution of formaldehyde

[0057]

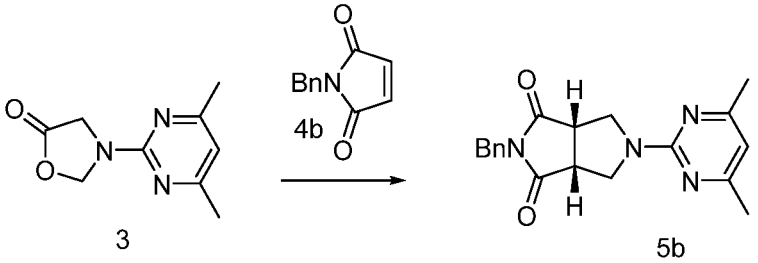


2 3

[0058] A reactor of 25 mL was charged with compound **2** (500 mg), toluene (5 mL) and aqueous solution of formaldehyde (13.31 mol/L, 4 equiv) at room temperature. To the reactor was attached a Dean-Stark apparatus and the solution was heated to 120 °C. After 1h the reaction mixture became a homogeneous solution from a heterogeneous mixture and it was cooled to 25 °C. The content of the reactor was transferred to a separating funnel and diluted with ethyl acetate (30 mL). The organic layer was washed with water and brine solution followed by drying on $MgSO_4$. Removal of solvent in vacuo provided product **3** in 80% yield.

Example 2: Formation of compound **5b** (R = Bn) from compound **3**

[0059]



3 5b

Example 2a: Screening in toluene under various flow mode conditions

[0060] A solution of compound **3** and compound **4b** (1 equiv each) in toluene (4L/mole) was delivered to the flow set up by a syringe pump (Isco 250D).

[0061] The solution was preheated in a coil of 1.7 mm id. and the reaction took place in a coil of 4 mm i.d with a length and flow rate to reach a residence time of 5 minutes. The reaction temperature was controlled by a heat-exchanger. The preheating unit, and reactor coil were all made from stainless steel and placed in the heat-exchanger to obtain a uniform reaction temperature. The process pressure was adjusted at 10 bar above vapour pressure of toluene with a

back pressure regulator (Swagelock). At the outlet the reaction mixture was cooled in a stainless steel tube in tube (id. of 1.7mm) to 60 °C and depressurized to atmospheric pressure before UPLC analysis. A fast temperature screening demonstrates the reaction does not occur before 200 °C and needs a temperature above 250 °C (see chart below). The kinetics are very fast at 300 °C (< 2min) and the product is stable for at least 5 min.

°C	% in-situ yield **(5b)** or % unconverted **(3, 4b)**		
	3	**4b**	**5b**
25	98	2	--
200	97	2	1
250	74	2	21
300	5	--	78
350	5	--	80

Example 2b: Reaction kinetics with 1.5 equiv compound **4b**

[0062] A second series of experiments using the same device than the one described in example 2a shows that the reaction is complete in about 4 minutes at 275 °C, and in less than 2 minutes at 300 °C. The compound **5b** is stable under these conditions at 300 °C for at least 5 minutes (see charts below).

Temperature: 275°C			
min	% in-situ yield (**5b**) or % unconverted (**3**, **4b**)		
	3	**4b**	**5b**
0	100	100	0
1	46	50	54
1.5	27	35	66
2	17	28	77
2.5	11	23	83
3	7	19	85
4	3	15	89
5	2	13	90

Temperature: 300°C			
min	% in-situ yield (**5b**) or % unconverted (**3**, **4b**)		
	3	**4b**	**5b**
0	100	100	0
1	4	16	86
1.5	1	11	88
2	1	10	88
2.5	0	9	88
3	0	8	88
3.5	0	8	88
4	0	7	88

Example 2c: flow mode in toluene with isolation

[0063] A solution of compound **3** (1 mole) and compound **4b** (1.5 or 1.25 equiv) in toluene (4L/mole) was pumped throught the flow system described in the example 2a with a flow such as to reach the desired time at the desired temperature described in the table below. After cooling, the solution was collected, partially evaporated under reduced

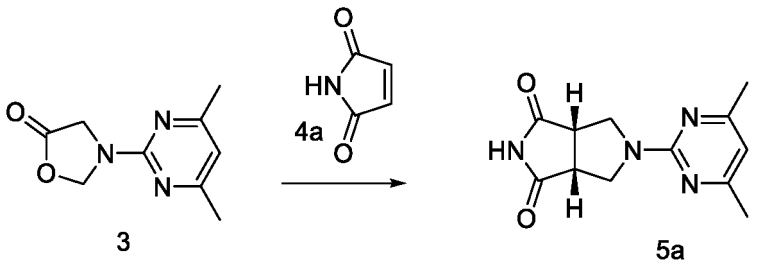
pressure to a final concentration of 0.8L/mole and crystallized at 0 °C for 5 hours. The solid (compound **5b**) was filtered, washed and dried.

Temperature (°C)	Residence time (min)	Equiv **4b**	% in-situ yield **5b**	% isolated yield **5b**
275	6	1.5	87.1	82.2
300	3.5	1.5	87.9	73.8
275	6	1.25	92.1	80.7
300	3.5	1.25	89.1	78.2

[0064] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.29 (m, 2H), 7.22-7.26 (m, 3H), 6.35 (s, 1H), 4.62 (s, 2H), 4.41-4.44 (m, 2H), 3.56-3.62 (m, 2H), 3.42-3.44 (m, 2H), 2.288 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.18 (2 x CO), 167.36 (2 x C), 161.08 (C), 135.58 (C), 128.74 (2 x CH), 128.55 (2 x CH), 127.98 (CH), 110.47 (CH), 48.88(2 x CH_2), 44.61 (2 x CH), 42.85 (CH_2), 24.08 (2 x CH_3). High resolution MS (ES, *m/z*): calcd for $C_{19}H_{21}N_4O_2$ $(M + H)^+$: 337.1665; found: 337.1666. m.p. = 162 °C.

Example 3: Formation of compound **5a** from compound **3** and compound **4a**

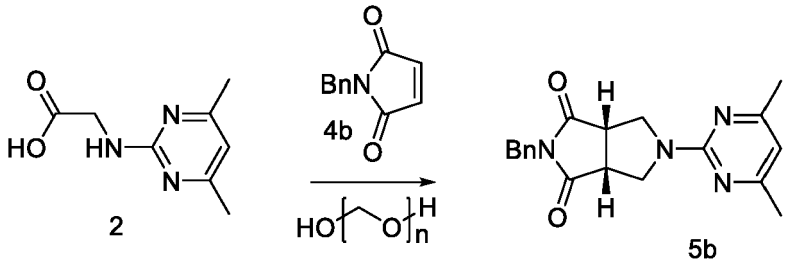
[0065]



[0066] 1.00 g (5.18 mmol) of compound **3,** 777 mg (7.76 mmol) of compound **4a** and 12 ml of toluene-ds were placed in a microwave vial. The vial was sealed and heated to 250 °C for about an hour before being cooled to room temperature. NMR analysis of the reaction mixture using 1,3,5-trimethoxybenzene as internal standard reveals that the compound **5a** was formed in 45% yield. The compound **5a** was isolated and purified as a solid by flash chromatography. ^{1}H NMR (400MHz, METHANOL-d_4) δ = 6.47 (s, 1H), 4.83 (br s, 1H), 4.29 (d, *J*=10.1 Hz, 2H), 3.59 - 3.47 (m, 4H), 2.29 (s, 6H). ^{13}C NMR (101MHz, METHANOL-d_4) δ = 182.26 (2 x C), 169.15 (2 x C), 162.62 (C), 111.33 (CH), 50.04 (2 x CH_2), 47.24 (2 x CH), 23.91 (2 x CH_3). High resolution MS (ES, *m/z*): calcd for $C_{12}H_{15}N_4O_2$ $(M + H)^+$: 247.1195; found: 247.1189.

Example 4: Formation of compound **5b** from compound **2**

[0067]



Example 4a: one-pot reaction in microwave (MW) vial

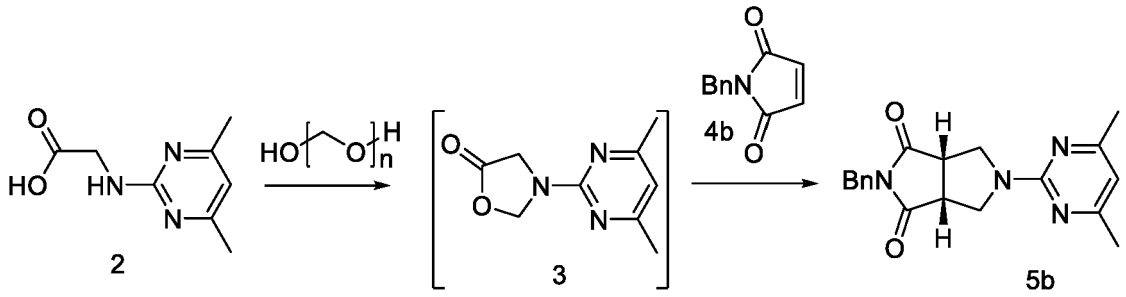
[0068] To a microwave vial (10 mL) were added compound **2** (250 mg), compound **4b,** paraformaldehyde and toluene-ds and 1,4-dichlorobenzene (51 mg, 0.25 equiv); the amounts of compound **4b,** paraformaldehyde and toluene-ds are

reported in the table below. The tube was sealed with a cap, placed in a Biotage microwave oven and heated to 250 °C for 1h while stirring. After 1h the reaction vial was cooled to room temperature and a sample was analyzed by ^{1}H NMR to calculate the in-situ yield. Following are the results of different experiments.

S. No	Equiv **4b**	Equiv paraformaldehyde	Toluene-d_8 (L/kg)	% in-situ yield **5b**
1	1	1.5	16	81
2	1.25	1.5	16	84
3	1.5	1.5	16	91
4	1	1.5	12	69
5	1	1.5	8	58
6	1	1.2	16	71

Example 4b: one-pot reaction in flow mode

[0069]



[0070] A mixed suspension of compound **2** (1 mole), paraformaldehyde (1.3 mole/mole) and compound **4b** (1.4 mole/mole) in toluene (4 L/mole) was delivered to a flow set up by a syringe pump (Isco 250D).

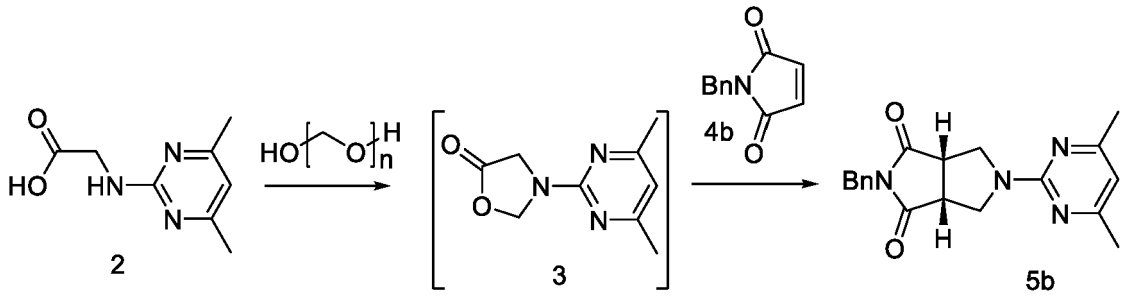
[0071] The suspension was preheated in a coil (1.7 mm id.) and a telescoped reaction took place in a coil (1.7 mm i.d) with a length defined by the desired residence time and flow rates. The temperature for the first reaction (formation of compound **3**) was controlled by a first heat-exchanger and the temperature for the second reaction formation of compound **5b**) was controlled by a second heat-exchanger. The preheating unit, and reactor coils were all made from stainless steel and placed in two heated zones to obtain a uniform reaction temperature. The process pressure was adjusted at 10 bar above vapour pressure of toluene with a back pressure regulator (Swagelock). At the outlet the reaction mixture was cooled in a stainless steel tube in tube with id. of 1.7mm to 60 °C and depressurized to atmospheric pressure. The product was diluted and analyzed by UPLC.

[0072] The conversion of compound **2** into compound **5b** is reported in the table.

Step 1		Step 2		% Yield relative to compound **2**		
T-°C	min	T-°C	min	Comp.**3**	Comp.**2**	Comp.**5b**
180	8	300	3.4	0	0	54.2
180	6	300	2.6	0.2	0.2	54.9
180	4	300	1.7	1.1	2.9	42.0
160	8	300	3.4	0	0	62.1
160	6	300	2.6	0	0	62.6
160	4	300	1.7	1.1	0.8	53.3
200	4	300	2.6	0.1	0.1	60.8
200	6	300	1.7	1	0.8	50.7

Example 4c: one-pot reaction in batch-flow mode

[0073]



[0074] A suspension of compound **2** (1 mole), paraformaldehyde (1.5 equiv) and compound **4b** (1.4 mole/mole) in toluene (4 L/mole) was heated in a closed vessel to 85 °C (0.5 bar overpressure) and stirred for two hours to reach complete conversion of **2** into **3** (see table below). After cooling, the resulting solution (25 °C) was dried over $MgSO_4$. Then used in the next step.

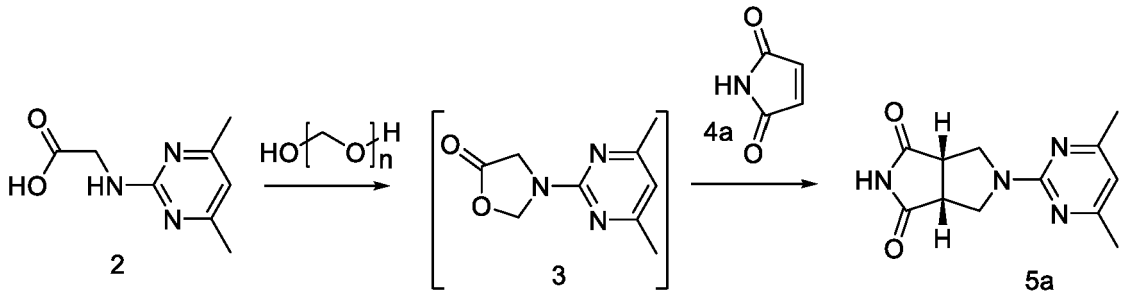
Condition	UPLC (mol rel./ in situ Y)	
	Cpd **3**	Cpd **2**
0 min at 85°C	43 **(44)**	57 **(58.9)**
13 min	91.9 **(95.2)**	5.7 **(5.9)**
80 min	96.5 **(102.2)**	1.3 **(1.4)**
105 min	96.4 **(101.4)**	1.2 **(1.3)**
$MgSO_4$ dried solution	**91.4**	**1**

[0075] The obtained solution of compound **3** was delivered to the flow set up by a syringe pump (Isco 250D). The suspension was preheated in a coil (1.7 mm id.) and the reaction took place in a coil (1.7mm i.d) with a length defined by the desired residence time of 3 minutes and flow rates. The reactions temperature was controlled at 300 °C by a heat-exchanger. The preheating unit, and reactor coil were all made from stainless steel and placed in the heat-exchanger to obtain a uniform reaction temperature. The process pressure was adjusted at 10 bar above vapour pressure of toluene with a back pressure regulator (Swagelock). At the outlet the reaction mixture was cooled in a stainless steel tube in tube (id. of 1.7mm) to 60 °C and depressurized to admospheric pressure. The compound **5b** was obtained in 66% yield.

[0076] Reaction in chlorobenzene gave the compound **5b** in similar yield as in toluene.

Example 5: Formation of compound **5a** from compound **2** and compound **4a**

[0077]

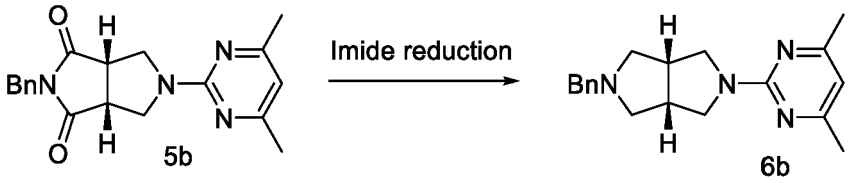


[0078] 250 mg (1.38 mmol) of compound **2, 62** mg (2.07 mmol) of paraformaldehyde, 207 mg (2.07 mmol) of compound **4a** and 4 ml of toluene-ds were placed in a microwave vial. The vial was sealed and heated to 250 °C for about an hour

before being cooled to room temperature. NMR analysis of the reaction mixture using 1,3,5-trimethoxybenzne as internal standard reveals that the compound **5a** was formed in 28% yield. The compound **5a** was isolated and purified as a solid by flash chromatography.

Example 6: Formation of compound **6b** (R = Bn) from compound **5b** (R = Bn)

[0079]



Example 6a: reduction with $NaBH_4$ + BF_3-THF

[0080] A 1-L reactor was charged with compound **5b** (75 g), $NaBH_4$ (19.4 g, 2.25 equiv) and THF (375 mL). The reaction mixture was heated to 50 °C while stirring. To this was added BF_3·THF (78.1 mL, 3.1 equiv) over 2h (Caution: very exothermic in the beginning and the intensity is reduced over the time while addition proceeds). After complete addition of BF_3·THF, the reaction was continued for 1h. Methanol (108 mL, 12 equiv) was slowly added to the reaction mixture over 2.5h. After stirring for additional 12h, solvents (THF and trimethyl borate) were distilled off to reduce the volume to 1/3 and water (560 mL) followed by aqueous NaOH (47.2 mL, 4 equiv, 18.8 M) were slowly added so that pH of the reaction mixture reached ~9.6. To this was added MTBE (225 mL) and aqueous phase was discarded after phase separation. Some MTBE was distilled off (150 mL) and ethanol (203 mL) was charged to the reactor followed by further distillation removed more MTBE. After the distillation, reaction mixture was cooled to 30 °C and was seeded with some product and waited for 30 min to get the crystallization started. Once the crystallization started, water (450 mL) was added over 4h and the reaction mixture was then cooled to 10 °C. After stirring for additional 6h the solids were filtered off using sinter funnel and the wet product was dried in oven at 50 °C for 12h. The product compound **5** (63.3 g, 91% yield) was obtained was as an off white solid. ^{1}H NMR (600MHz, DMSO-d_6) δ = 7.32 - 7.25 (m, 4H), 7.24 - 7.19 (m, 1H), 6.37 (s, 1H), 3.67 (dd, *J*=8.1, 11.5 Hz, 2H), 3.55 (s, 2H), 3.38 (dd, *J*=3.4, 11.3 Hz, 2H), 2.88 - 2.81 (m, 2H), 2.60 (dd, *J*=7.0, 9.3 Hz, 2H), 2.43 (dd, *J*=3.0, 9.4 Hz, 2H), 2.21 (s, 6H). ^{13}C NMR (DMSO-d_6) δ: 166.4, 160.3, 139.1, 128.3, 128.1, 126.7, 108.3, 60.0, 58.8, 52.3, 41.0, 23.7. mp: 80°C. High resolution MS (ES, *m/z):* calcd for $C_{19}H_{25}N_4$ $(M+H)^+$: 309.2079; found: 309.2080.

Example 6b: reduction with $NaBH_4$+ H_2SO_4

[0081] A 500-ml reactor was charged with compound **5b** (30 g), $NaBH_4$ (14.5 g, 4.2 equiv) and THF (210 mL). The reaction mixture was heated to 50 °C while stirring. To this was added H_2SO_4 (10.5 mL, 2.1 equiv) over 2 h (Caution: very exothermic in the beginning and the intensity is reduced over the time while addition proceeds). After the addition of H_2SO_4 complete, the reaction was continued for 0.5 h. Methanol (73 mL, 20 equiv) was slowly added to the reaction mixture over 2 h. After stirring for additional 12 h, solvents (THF and trimethylborate) were distilled off to reduce the volume to 1/3 and water (120 mL) followed by aqueous NaOH (2.4 mL, 0.5 equiv, 18.8 M) were slowly added so that pH of the reaction mixture reached ~9.6. To this was added MTBE (210 mL) and aqueous phase was discarded after phase separation. Some MTBE was distilled off (150 mL) and ethanol (69 mL) was charged to the reactor followed by further distillation removed more MTBE. After the distillation, reaction mixture was cooled to 30 °C and was seeded with some product and waited for 30 min to get the crystallization started. Once the crystallization started, water (207 mL) was added over 4 h and the reaction mixture was then cooled to 10 °C. After stirring for additional 6 h the solids were filtered off using sinter funnel and the wet product was dried in oven at 50 °C for 12 h. The product compound **6b** (23.7 g, 82% yield) was obtained was as an off white solid.

Example 6c: reduction with BH_3-THF

[0082] A 100-mL reactor was charged with compound **5b** (10 g) and THF (60 mL). The reaction mixture was cooled to 10 °C while stirring. To this was added BH_3·THF (89.2 mL, 3 equiv, 1 M in THF) over 1 h. After stirring for 3 days at that temperature, methanol (60 mL) was added over 2 h and then the temperature was raised to 40 °C and stirred for 24 h. All the solvent was removed in vacuo and the crude material was dissolved in ethyl acetate and water. After phase separation, the organic layer was concentrated in vacuo to give the desired product **6b** (9 g, 98% yield).

Example 6d: reduction with Red-Al

[0083] A 25-ml reactor was charged with compound **5b** (500 mg) and toluene (4 mL). The reaction mixture was heated to 60 °C while stirring. In another reactor both Red-Al (1.45 mL, 3 equiv, 60% solution in toluene) and toluene (5 mL) were heated to 60 °C while stirring. The hot Red-Al solution was then added to the above hot solution of compound **5b** over 5 min. The reaction temperature was then raised 100 °C and stirred for 2 h. After cooling to 20 °C, aqueous NaOH solution was added dropwise and stirred for 2 h. Phase separation followed by removal of solvent in vacuo afforded compound **6b** (480 mg, 56.7 mass% by assay, 59% yield).

Example 6e: reduction with silanes (table)

Reduction with $B(C_6F_5)_3$/TMDS procedure:

[0084] A 50-ml reactor was charged with compound **5b** (2 g), 1,1,3,3-tetramethyldisiloxane (TMDS - 6.3 mL, 6 equiv) and toluene (20 mL). The reaction mixture was heated to 60 °C while stirring. To this was added a solution of $B(C_6F_5)_3$ (152 mg, 5 mol%) in toluene (1 mL) and temperature was raised to 100 °C. After stirring for 1 h, the reaction mixture was cooled to 25 °C and contents were transferred to a round bottom flask. Removal of solvents in vacuo provided crude compound **6b** (2.07 g, 88.6% assay, 95% yield).

Reduction with silanes screening (catalyst/hydride source):

[0085] Following the above described procedure various catalysts and silane reagents were used to reduce the compound **5b** (500 mg) to **6b.**

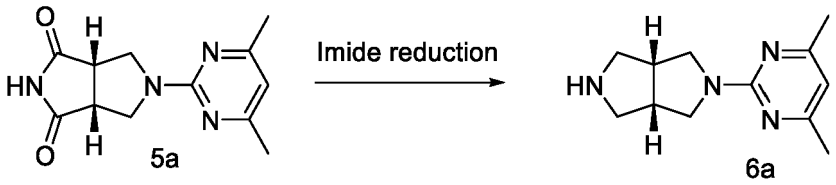
S. No.	Catalyst (mol%)	Silane (equiv)	**6b** (LC relative area%)
1	$B(C_6F_5)_3$ (1)	TMDS (5)	0
2	$B(C_6F_5)_3$ (2)	TMDS (5)	42
3	$B(C_6F_5)_3$ (3)	TMDS (5)	89
4	$B(C_6F_5)_3$ (4)	TMDS (5)	99
5	$B(C_6F_5)_3$ (5)	TMDS (5)	99
6	$Fe_3(CO)_{12}$ (5)	TMDS (5)	38
7	H_2PtCl_6 (1)	TMDS (5)	25
8	$Zn(OAc)_2.2H_2O$ (5)	TMDS (5)	0
9	TBAF (1M in THF) (5)	TMDS (5)	0
10	$Fe(acac)_3$ (5)	TMDS (5)	0
11	$Ni(acac)_2$ (5)	TMDS (5)	0
12	$Co(acac)_3$ (5)	TMDS (5)	0
13	$Mn(acac)_3$ (5)	TMDS (5)	0
14	$AlCl_3$ (5)	TMDS (5)	0
15	KHMDS (1M in THF) (5)	TMDS (5)	0
16	$B(C_6F_5)_3$ (5)	PMHS (6)	55
17	$Fe_3(CO)_{12}$ (5)	PMHS (6)	57
18	H_2PtCl_6 (1)	PMHS (6)	64
19	H_2PtCl_6 (4)	PMHS (6)	76
20	$Zn(OAc)_2.2H_2O$ (5)	PMHS (6)	0

(continued)

S. No.	Catalyst (mol%)	Silane (equiv)	**6b** (LC relative area%)
21	$B(C_6F_5)_3$ (5)	Et_3SiH (8)	60

Example 7: Formation of compound **6a** from compound **5a,** wherein R is H

[0086]



[0087] A 10 mL tube reactor was charged with compound **5a** (75 mg) and THF (2 mL). The reaction mixture was cooled to 0 °C while stirring. To this was added BH_3·THF (0.91 mL, 3 equiv, 1 M in THF) slowly. The reaction mixture was slowly warmed to 50 °C with stirring and left for 4 h at that temperature. To this was slowly added methanol (0.3 mL) and stirred for 2 h. After cooling to room temperature, the crude mixture was concentrated under vacuum and the residue was redissolved in 2-methyltetrahydrofuram (3 mL) and heated to 50 °C, followed by addition of aq.H_2SO_4 (0.5 mL, 4 eq, 2.28M in water). After 2h, the solution was neutralized by addition of aq. NaOH (0.35 mL, 4.5 eq, 12.5 mass% in water) followed by phase separation and concentration in vacuo provided product **6a** (60 mg, 80% assay, 72% yield).

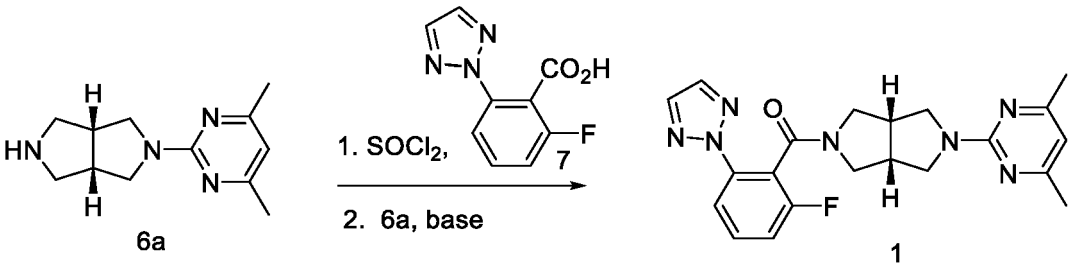
Example 8: Formation of compound **6a** from compound **6b**

[0088]

[0089] 5.8 g of 10w% Pd/C (wet) was added to a solution of 58 g (188 mmol) of compound **6b** in 406 ml of methanol. The resulting suspension was heated to 60 °C before a solution of 13 g (206 mmol) of ammonium formate in 174 ml of methanol was added over an hour. The reaction mixture was then stirred 3 hours at 60 °C before being cooled to room temperature. The catalyst was filtered off and filtrate was concentrated under vacuum to obtain 40.7 g of compound **6a** as a slightly yellow solid. Yield: 97%. ^{1}H NMR (DMSO-d_6) δ: 6.35 (s, 1H), 3.68 (dd, J=11.3, 7.9 Hz, 2H), 3.32 (dd, J=11.3, 3.4 Hz, 2H), 2.93 (br dd, J=10.2, 6.0 Hz, 2H), 2.76 (br s, 2H), 2.61 (br d, J=9.4 Hz, 2H), 2.21 (s, 6H). ^{13}C NMR (DMSO-d_6) δ: 166.1, 160.2, 107.9, 53.1, 51.6, 42.9, 23.4. High resolution MS (ES, *m/z):* calcd for $C_{12}H_{19}N_4$ $(M + H)^+$: 219.1610; found: 219.1624. m.p.: 99-100 °C.

Example 9: Formation of (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone **(1)** from compound **6a** and compound **7**

[0090]

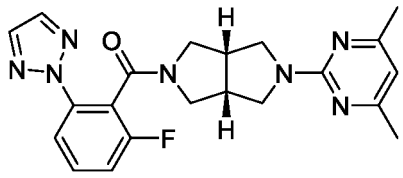


[0091] 4.3 ml (60 mmol) of thionyl chloride was added to a suspension of 9.5 g (46 mmol) of compound **7** in 110 ml of toluene before being heated to 55 °C for 2.5 hours then concentrated under vacuum to a residual volume of about 100 ml (about 20 ml of solvent distilled). The resulting solution of intermediate acyl chloride in toluene was added to a well stirred biphasic mixture of 10.2 g (45.7 mmol) of compound **6a** in 44 ml of toluene and 7.26 g (68.5 mmol) of sodium carbonate in 44 ml of water. The resulting biphasic mixture was stirred at 30 °C for 3.5 hours before being heating to 70 °C. The water layer was discarded and the organic one was washed twice with 57 ml of water and concentrated under vacuum to a residual volume of about 64 ml. The concentrated mixture was heated to 90 °C to obtain a solution before cooling to room temperature and addition of 64 ml of cyclohexane. The resulting suspension was stirred overnight. 18.1 g of (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone **(1)** was obtained as a solid after filtration, wash with 12 ml of cyclohexane and 11 ml of water and drying under vacuum. Yield: 97%. ^{1}H NMR (400 MHz, pyridine-d_5) δ ppm 2.33 (s, 12 H) 2.81 - 2.97 (m, 4 H) 3.27 (dd, *J*=10.6, 5.0 Hz, 1 H) 3.33 (dd, *J*=10.5, 4.7 Hz, 1 H) 3.57 (br t, *J*=7.1 Hz, 1 H) 3.59 (br t, *J*=7.0 Hz, 1 H) 3.67 (dd, *J*=11.7, 4.5 Hz, 1 H) 3.70 - 3.75 (m, 1 H) 3.75 - 3.82 (m, 2 H) 3.82 - 3.98 (m, 7 H) 4.11 (dd, *J*=12.4, 7.6 Hz, 1 H) 6.29 (s, 1 H) 6.29 (s, 1 H) 7.19 (td, *J*=8.7, 1.0 Hz, 1 H) 7.26 (td, *J*=8.6, 0.9 Hz, 1 H) 7.46 (td, *J*=8.3, 6.2 Hz, 1 H) 7.46 (td, *J*=8.3, 6.0 Hz, 1 H) 7.90 (dt, *J*=8.2, 0.8 Hz, 1 H) 7.90 (s, 2 H) 7.98 (dt, *J*=8.2, 0.8 Hz, 1 H) 8.04 (s, 2 H). ^{13}C NMR (101 MHz, pyridine-d_5) δ ppm 24.47, 24.48, 41.74, 41.82, 42.71, 42.93, 50.76, 50.82, 50.90, 51.03, 51.43, 51.62, 51.87, 52.06, 109.27, 109.44, 115.88 (br d, *J*=22.4 Hz), 115.89 (br d, *J*=22.4 Hz), 118.82 (br d, *J*=3.3 Hz), 118.97 (br d, *J*=3.3 Hz), 120.48 (d, *J*=24.9 Hz), 120.55 (d, *J*=24.6 Hz), 131.53 (br d, *J*=9.2 Hz), 131.54 (d, *J*=9.2 Hz), 137.33, 137.47, 138.04 (d, *J*=7.0 Hz), 138.07 (br d, *J*=7.0 Hz), 159.71 (d, *J*=245.8 Hz), 159.81 (d, *J*=245.4 Hz), 161.53, 161.61, 162.99 (d, *J*=7.3 Hz), 162.99 (d, *J*=7.3 Hz), 167.61, 167.63. High resolution MS (ES, *m/z):* calcd for $C_{21}H_{23}FN_7O$ (M + H)$^+$: 408.1943; found: 408.1946.

[0092] While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

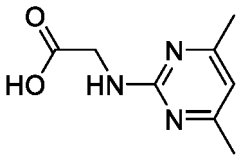
Claims

1. A process of preparing (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

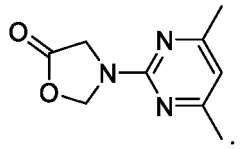


said process comprising step described below:

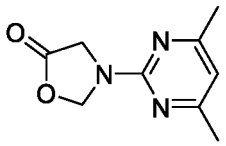
a) Oxazolidination of (4,6-dimethylpyrimidin-2-yl)glycine,



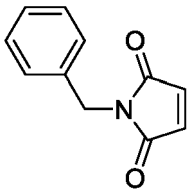
wherein said oxazolidination is **characterized by** the use of formaldehyde or paraformaldehyde to obtain 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



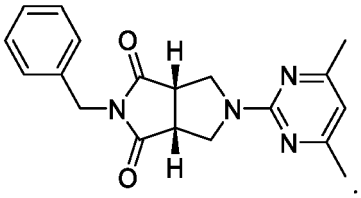
2. The process of claim 1, said process further comprising reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



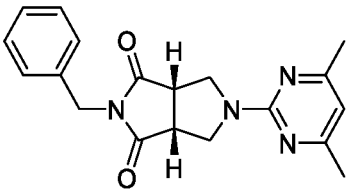
with 1-benzyl-1H-pyrrole-2,5-dione



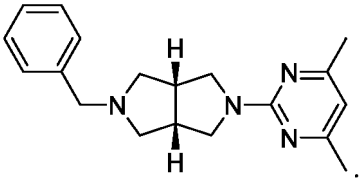
at a temperature greater than 250 °C to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



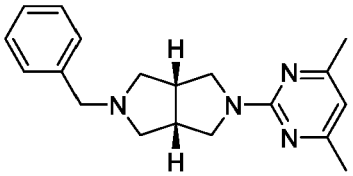
3. The process of claim 2, said process further comprising reduction of (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



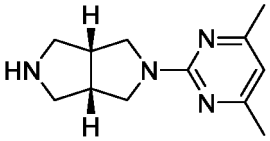
to form (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



4. The process of claim 3, said process further comprising deprotection of (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole

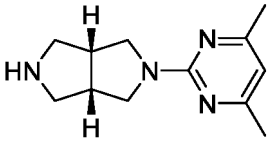


to form (3a*R*,6a*S*)-2-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3 ,4-c]pyrrole

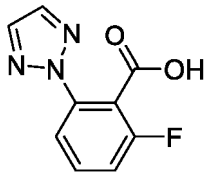


by means of 10% (w/w) Pd/C and ammonium formate.

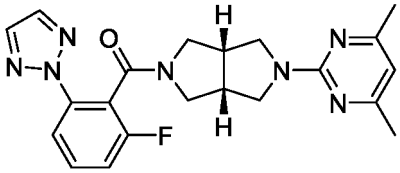
5. The process of claim 4, said process further comprising amidation of (3a*R*,6a*S*)-2-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



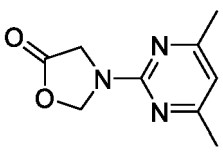
with 2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)benzoic acid



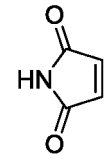
by means of $SOCl_2$ to form (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2-(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone



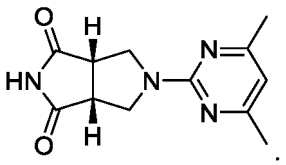
6. The process of claim 1, said process further comprising reaction of 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



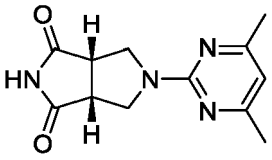
with 1*H*-pyrrole-2,5-dione



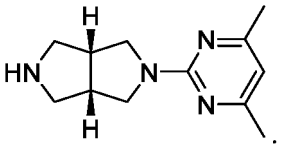
at a temperature greater than 250 °C to form (3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



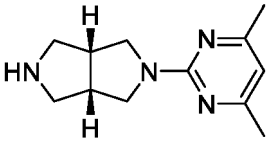
7. The process of claim 6, said process further comprising reduction of (3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



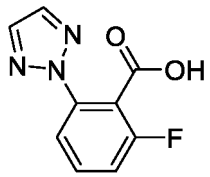
to form (3a*R*,6a*S*)-2-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3 ,4-c]pyrrole



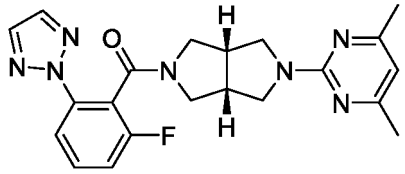
8. The process of claim 7, said process further comprising amidation of (3a*R*,6a*S*)-2-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole


with

2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)benzoic acid



by means of $SOCl_2$ to form (((3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl)metlianone



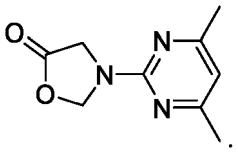
9. The process of claim 2, wherein said 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one is not isolated prior to reaction with said 1-benzyl-1*H*-pyrrole-2,5-dione.

10. The process of claim 2, wherein said 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one is isolated prior to reaction with said 1-benzyl-1*H*-pyrrole-2,5-dione.

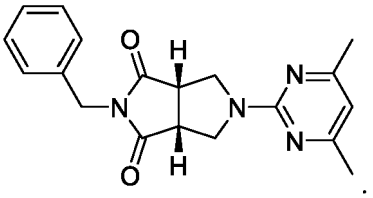
11. The process of claim 6, wherein said 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one is not isolated prior to reaction with said 1*H*-pyrrole-2,5-dione.

12. The process of claim 6, wherein said 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one is isolated prior to reaction with said 1*H*-pyrrole-2,5-dione.

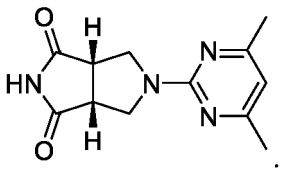
13. A compound which is 3-(4,6-dimethylpyrimidin-2-yl)oxazolidin-5-one



14. A compound which is (3a*R*,6a*S*)-2-benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione

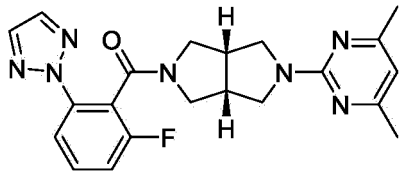


15. A compound which is (3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



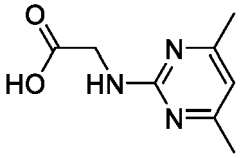
Patentansprüche

1. Verfahren zur Herstellung von (((3a*R*,6a*S*)-5-(4,6-Dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluor-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanon

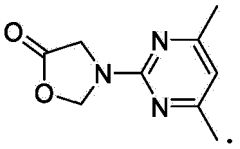


wobei das Verfahren den nachstehend beschriebenen Schritt umfasst:

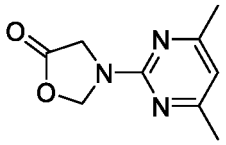
a) Oxazolidinierung von (4,6-Dimethylpyrimidin-2-yl)glycin,



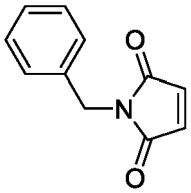
wobei die Oxazolidinierung durch die Verwendung von Formaldehyd oder Paraformaldehyd gekennzeichnet ist, zum Erhalt von 3-(4,6-Dimethylpyrimidin-2-yl)oxazolidin-5-on



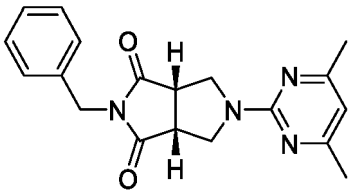
2. Verfahren nach Anspruch 1, wobei das Verfahren ferner die Umsetzung von 3-(4,6-Dimethylpyrimidin-2-yl)oxazolidin-5-on



mit 1-Benzyl-1H-pyrrol-2,5-dion

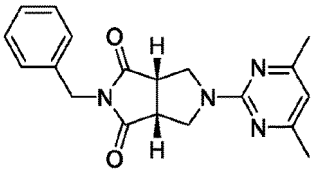


bei einer Temperatur von mehr als 250 °C zur Bildung von (3aR,6aS)-2-Benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrol-1, 3 (2H, 3aH) -dion

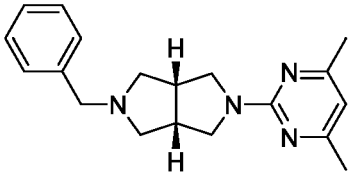


umfasst.

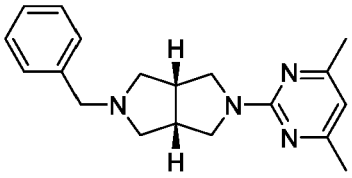
3. Verfahren nach Anspruch 2, wobei das Verfahren ferner die Reduktion von (3a*R*,6a*S*)-2-Benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrol-1,3(2*H*3a*H*)-dion



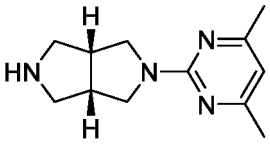
zur Bildung von (3a*R*,6a*S*)-2-Benzyl-5-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrol umfasst.



4. Verfahren nach Anspruch 3, wobei das Verfahren ferner die Entschützung von (3a*R*,6a*S*)-2-Benzyl-5-(4,6-dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrol

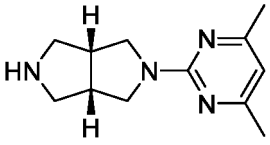


zur Bildung von(3a*R*,6a*S*)-2-(4,6-Dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrol

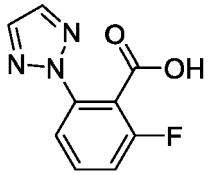


mit Hilfe von 10 % (w/w) Pd/C und Ammoniumformiat umfasst.

5. Verfahren nach Anspruch 4, wobei das Verfahren ferner die Amidierung von (3a*R*,6a*S*)-2-(4,6-Dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrol

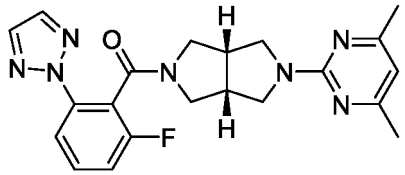


mit 2-Fluor-6-(2*H*-1,2,3-triazol-2-yl)benzoesäure



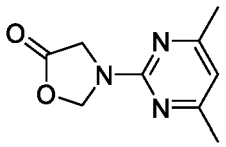
mit Hilfe von $SOCl_2$ zur Bildung von (((3a*R*,6a*S*)-5-(4,6-Dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-

2(1*H*)-yl) (2-fluor-6-(2H-1,2,3-triazol-2-yl)phenyl)methanon

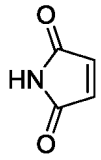


umfasst.

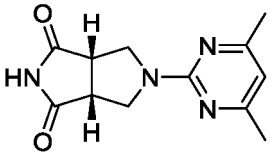
6. Verfahren nach Anspruch 1, wobei das Verfahren ferner die Umsetzung von 3-(4,6-Dimethylpyrimidin-2-yl)oxazolidin-5-on



mit 1*H*-Pyrrol-2,5-dion

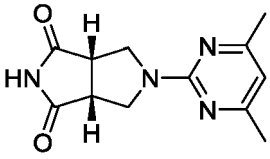


bei einer Temperatur von mehr als 250 °C zur Bildung von (3a*R*,6a*S*)-5-(4,6-Dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrol-1,3(2*H*,3a*H*)-dion

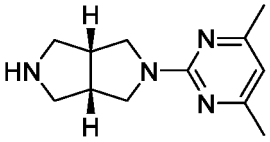


umfasst.

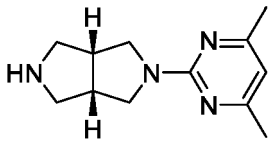
7. Verfahren nach Anspruch 6, wobei das Verfahren ferner die Reduktion von (3a*R*,6a*S*)-5-(4,6-Dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrol-1,3(2*H*,3a*H*)-dion



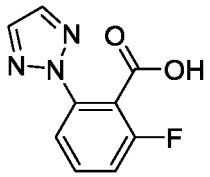
zur Bildung von (3a*R*,6a*S*)-2-(4,6-Dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrol umfasst.



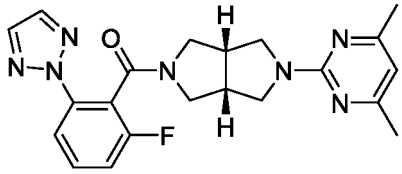
8. Verfahren nach Anspruch 7, wobei das Verfahren ferner die Amidierung von (3a*R*,6a*S*)-2-(4,6-Dimethylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrol



mit 2-Fluor-6-(2*H*-1,2,3-triazol-2-yl)benzoesäure



mit Hilfe von $SOCl_2$ zur Bildung von (((3a*R*,6a*S*)-5-(4,6-Dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl) (2-fluor-6-(2H-1,2,3-triazol-2-yl)phenyl)methanon



umfasst.

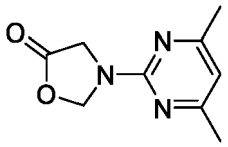
9. Verfahren nach Anspruch 2, wobei das 3-(4,6-Dimethylpyrimidin-2-yl)oxazolidin-5-on vor der Umsetzung mit dem 1-Benzyl-1H-pyrrol-2,5-dion nicht isoliert wird.

10. Verfahren nach Anspruch 2, wobei das 3-(4,6-Dimethylpyrimidin-2-yl)oxazolidin-5-on vor der Umsetzung mit dem 1-Benzyl-1H-pyrrol-2,5-dion isoliert wird.

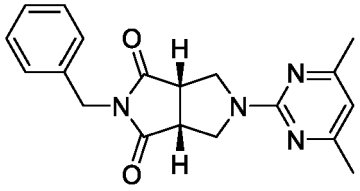
11. Verfahren nach Anspruch 6, wobei das 3-(4,6-Dimethylpyrimidin-2-yl)oxazolidin-5-on vor der Umsetzung mit dem 1*H*-Pyrrol-2,5-dion nicht isoliert wird.

12. Verfahren nach Anspruch 6, wobei das 3-(4,6-Dimethylpyrimidin-2-yl)oxazolidin-5-on vor der Umsetzung mit dem 1*H*-Pyrrol-2,5-dion isoliert wird.

13. Verbindung, bei der es sich um 3-(4,6-Dimethylpyrimidin-2-yl)oxazolidin-5-on handelt.

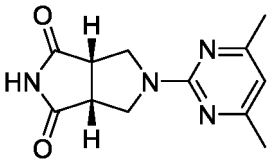


14. Verbindung, bei der es sich um (3a*R*,6a*S*)-2-Benzyl-5-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrol-1,3(2*H*,3a*H*)-dion



handelt.

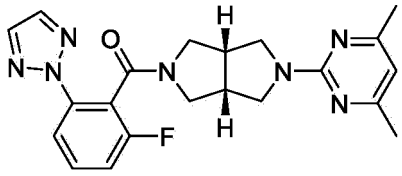
15. Verbindung, bei der es sich um (3a*R*,6a*S*)-5-(4,6-Dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrol-1,3(2*H*,3a*H*)-dion



handelt.

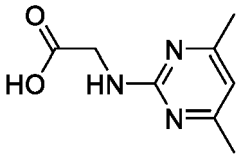
Revendications

1. Procédé de préparation de (((3a*R*,6a*S*)-5-(4,6-diméthylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phényl)méthanone

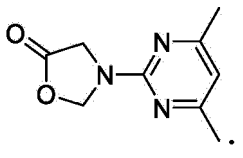


ledit procédé comprenant l'étape décrite ci-dessous :

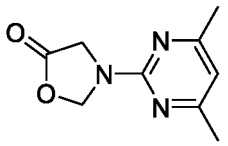
a) l'oxazolidinisation de (4,6-diméthylpyrimidin-2-yl)glycine,



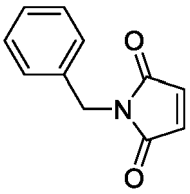
dans lequel ladite oxazolidinisation est **caractérisée par** l'utilisation de formaldéhyde ou de paraformaldéhyde pour obtenir de la 3-(4,6-diméthylpyrimidin-2-yl)oxazolidin-5-one



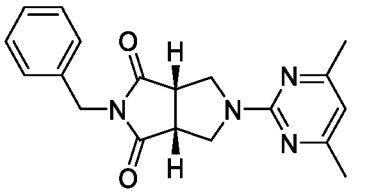
2. Procédé selon la revendication 1, ledit procédé comprenant en outre la réaction de 3-(4,6-diméthylpyrimidin-2-yl)oxazolidin-5-one



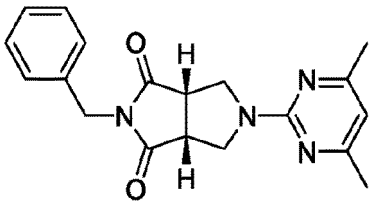
avec de la 1-benzyl-1H-pyrrole-2,5-dione



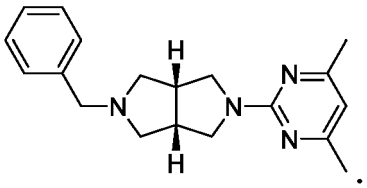
à une température supérieure à 250 °C pour former de la (3a*R*,6a*S*)-2-benzyl-5-(4,6-diméthylpyrimidin-2-yl)tétrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



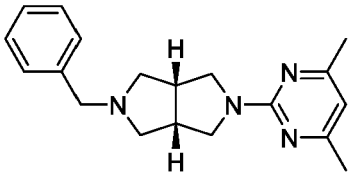
3. Procédé selon la revendication 2, ledit procédé comprenant en outre la réduction de (3a*R*,6a*S*)-2-benzyl-5-(4,6-diméthylpyrimidin-2-yl)tétrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



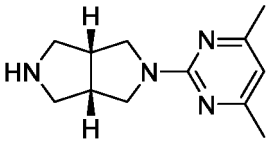
pour former du (3a*R*,6a*S*)-2-benzyl-5-(4,6-diméthylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



4. Procédé selon la revendication 3, ledit procédé comprenant en outre la déprotection de (3a*R*,6a*S*)-2-benzyl-5-(4,6-diméthylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole

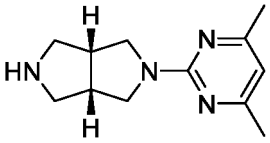


pour former du (3a*R*,6a*S*)-2-(4,6-diméthylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole

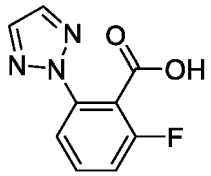


au moyen de 10 % (p/p) de Pd/C et de formiate d'ammonium.

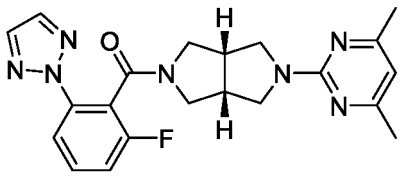
5. Procédé selon la revendication 4, ledit procédé comprenant en outre l'amidation de (3a*R*,6a*S*)-2-(4,6-diméthylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



avec de l'acide 2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)benzoïque



au moyen de $SOCl_2$ pour former de la (((3a*R*,6a*S*)-5-(4,6-diméthylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2H-1,2,3-triazol-2-yl)phényl)méthanone



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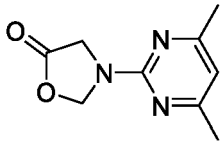
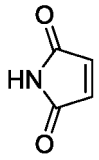
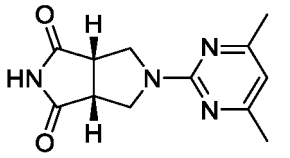
6. Procédé selon la revendication 1, ledit procédé comprenant en outre la réaction de 3-(4,6-diméthylpyrimidin-2-yl)oxazolidin-5-one



avec de la 1*H*-pyrrole-2,5-dione

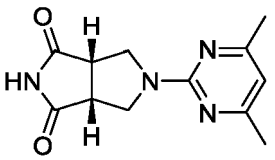


à une température supérieure à 250 °C pour former de la (3a*R*,6a*S*)-5-(4,6-diméthylpyrimidin-2-yl)tétrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione

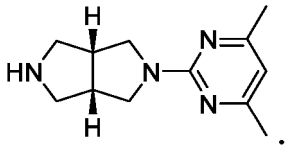


.

7. Procédé selon la revendication 6, ledit procédé comprenant en outre la réduction de (3a*R*,6a*S*)-5-(4,6-diméthylpyrimidin-2-yl)tétrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



pour former du (3a*R*,6a*S*)-2-(4,6-diméthylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



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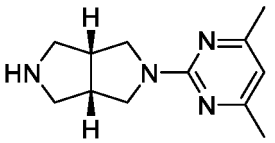
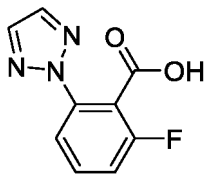
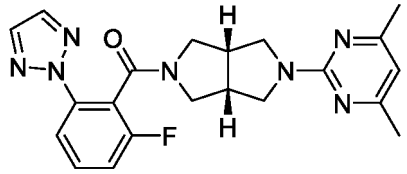
8. Procédé selon la revendication 7, ledit procédé comprenant en outre l'amidation de (3a*R*,6a*S*)-2-(4,6-diméthylpyrimidin-2-yl)octahydropyrrolo[3,4-c]pyrrole



avec de l'acide 2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)benzoïque



au moyen de $SOCl_2$ pour former de la (((3a*R*,6a*S*)-5-(4,6-diméthylpyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1*H*)-yl)(2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phényl)méthanone



.

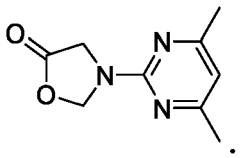
9. Procédé selon la revendication 2, dans lequel ladite 3-(4,6-diméthylpyrimidin-2-yl)oxazolidin-5-one n'est pas isolée avant la réaction avec ladite 1-benzyl-1*H*-pyrrole-2,5-dione.

10. Procédé selon la revendication 2, dans lequel ladite 3-(4,6-diméthylpyrimidin-2-yl)oxazolidin-5-one est isolée avant la réaction avec ladite 1-benzyl-1H-pyrrole-2,5-dione.

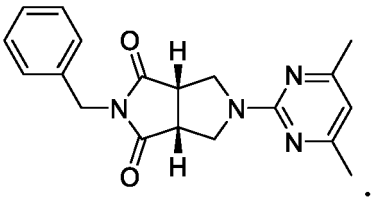
11. Procédé selon la revendication 6, dans lequel ladite 3-(4,6-diméthylpyrimidin-2-yl)oxazolidin-5-one n'est pas isolée avant la réaction avec ladite 1*H*-pyrrole-2,5-dione.

12. Procédé selon la revendication 6, dans lequel ladite 3-(4,6-diméthylpyrimidin-2-yl)oxazolidin-5-one est isolée avant la réaction avec ladite 1*H*-pyrrole-2,5-dione.

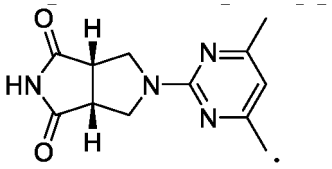
13. Composé qui est la 3-(4,6-diméthylpyrimidin-2-yl)oxazolidin-5-one



14. Composé qui est la (3a*R*,6a*S*)-2-benzyl-5-(4,6-diméthylpyrimidin-2-yl)tétrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



15. Composé qui est la (3a*R*,6a*S*)-5-(4,6-diméthylpyrimidin-2-yl)tétrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione



REFERENCES CITED IN THE DESCRIPTION

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