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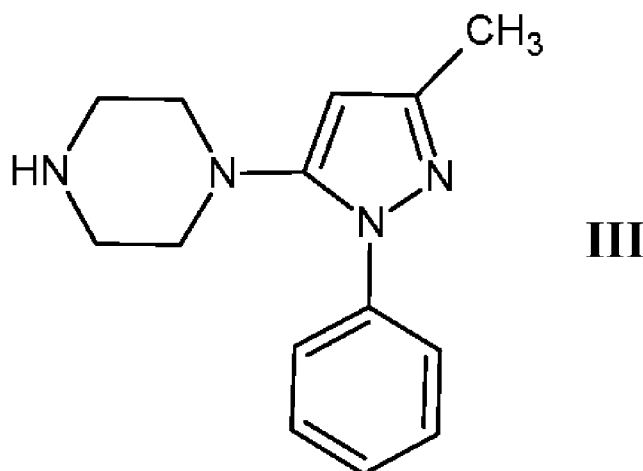
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(54) Title: PROCESS FOR THE PREPARATION OF 1-(3-METHYL-1-PHENYL-1H-PYRAZOL-5-YL)PIPERAZINE

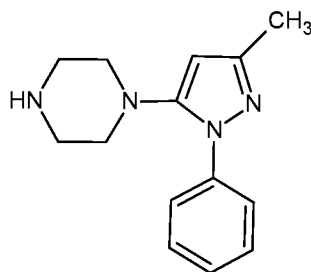


(57) Abstract: The present invention provides a process for the preparation of 1-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazine of Formula III, or salts thereof. The invention also provides a process for the preparation of {(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone of Formula II, or salts thereof, using the 1-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazine of Formula III, or salts thereof.

PROCESS FOR THE PREPARATION OF 1-(3-METHYL-1-PHENYL-1H-PYRAZOL-5-YL)PIPERAZINE

Field of the Invention

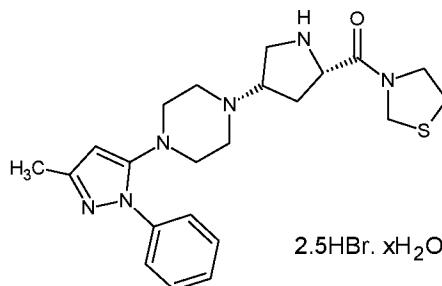
The present invention provides a process for the preparation of 1-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazine of Formula III, or salts thereof. The invention also provides a process for the preparation of {(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone of Formula II, or salts thereof, using the 1-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazine of Formula III, or salts thereof.



Formula III

Background of the Invention

Teneligliptin hydrobromide hydrate, chemically described as {(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone hemipentahydrobromide hydrate, represented by Formula I, is marketed in Japan for the treatment of type 2 diabetes mellitus.

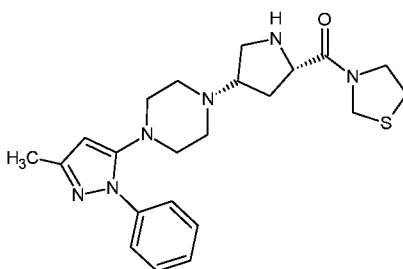


Formula I

U.S. Patent No. 7,074,794 at Example 222 discloses a process for the preparation of 1-(3-methyl-1-phenyl-5-pyrazolyl)piperazine of Formula III, or salts thereof,

comprising the reaction of 1-acetoacetyl-4-tert-butoxycarbonylpiperazine with phenylhydrazine in the presence of methanesulfonic acid, followed by cyclization with phosphorus oxychloride in pyridine to obtain 1-tert-butoxycarbonyl-4-(3-methyl-1-phenyl-5-pyrazolyl)piperazine as an oil; and its deprotection with trifluoroacetic acid. The compound of Formula III, thus prepared, is then converted to {(2S,4S)-4-[4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone of Formula II, or salts thereof.

The process for the preparation of a compound of Formula III, involving the use of phosphorous oxychloride as a cyclizing agent, is time consuming and results in a loss of purity and yield of 1-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazine of Formula III, and {(2S,4S)-4-[4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone of Formula II, or salts thereof.

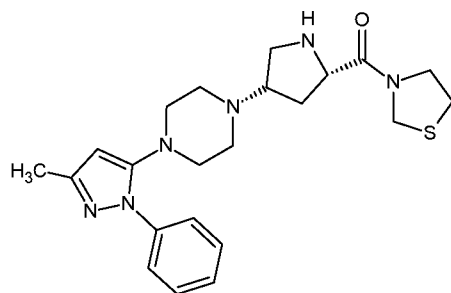


Formula II

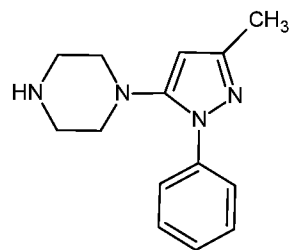
Additionally, pyridine is toxic and therefore its use as a solvent should be avoided for industrial production of a pharmaceutical ingredient. Thus, there is a need in the art to develop a process for the preparation of a compound of Formula III that avoids the use of pyridine as a solvent.

Summary of the Invention

The present invention provides an improved, economical, and industrially advantageous process for the preparation of 1-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazine of Formula III, {(2S,4S)-4-[4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone of Formula II, or salts thereof.

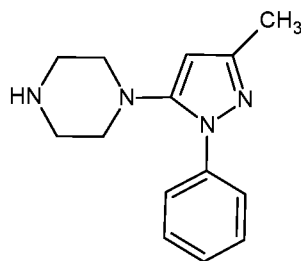


Formula II



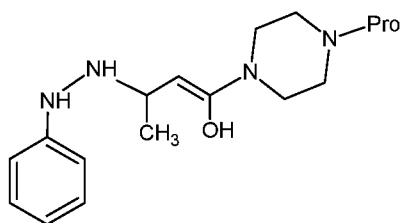
Formula III

A first aspect of the present invention provides a process for the preparation of 1-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazine of Formula III, or salts thereof,

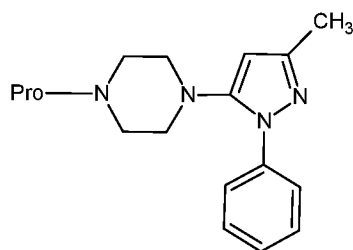


Formula III

wherein the process comprises cyclizing a compound of Formula V in the presence of a Lawesson's reagent to obtain a compound of Formula VI,



Formula V

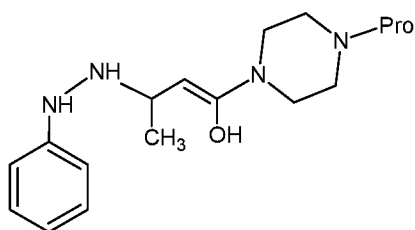
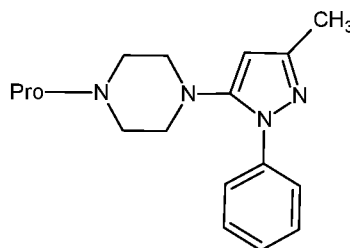


Formula VI

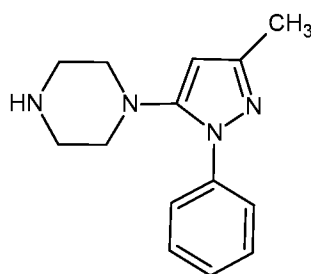
wherein 'Pro' is a protecting group.

A second aspect of the present invention provides a process for the preparation of {(2*S*,4*S*)-4-[4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone of Formula II, or salts thereof, wherein the process comprises:

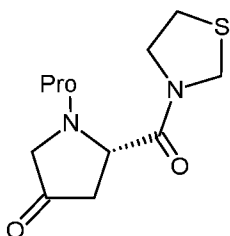
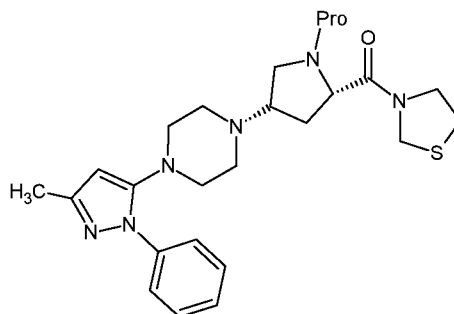
- a) cyclizing a compound of Formula V in the presence of Lawesson's reagent to obtain a compound of Formula VI;

**Formula V****Formula VI**

- b) deprotecting the compound of Formula VI to obtain a compound of Formula III;

**Formula III**

- c) reacting the compound of Formula III or a salt thereof with a compound of Formula VII to obtain a compound of Formula VIII; and

**Formula VII****Formula VIII**

- d) deprotecting the compound of Formula VIII to obtain {(2*S*,4*S*)-4-[4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone of Formula II or salts thereof,

wherein 'Pro' is a protecting group.

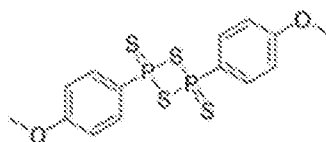
Detailed Description of the Invention

The term “about”, as used herein, refers to any value which lies within the range defined by a number up to $\pm 10\%$ of the value.

The term “protecting group (Pro)”, as used herein, refers to an amino-protecting group. Examples of amino-protecting groups include 9-fluorenylmethyl carbamate (Fmoc), 2,2,2-trichloroethyl carbamate (Troc), ethyl carbamate, t-butyl carbamate (Boc), 2-(trimethylsilyl)ethyl carbamate (Teoc), allyl carbamate (Alloc), carboxybenzyl (Cbz), trifluoroacetamide, benzylamine, allylamine, and tritylamine.

In the context of the present invention, “salts” refer to inorganic acid addition salts, organic acid addition salts, and salts formed with amino acids. Examples of inorganic acid addition salts include salts formed with hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, and phosphoric acid. Examples of organic acid addition salts include salts formed with methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, formic acid, acetic acid, trifluoroacetic acid, oxalic acid, citric acid, malonic acid, fumaric acid, glutaric acid, adipic acid, maleic acid, tartaric acid, succinic acid, mandelic acid, malic acid, and pantothenic acid. Examples of amino acid salts include salts formed with glutamic acid and aspartic acid.

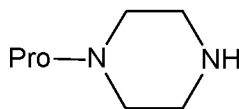
Lawesson’s reagent, chemically designated as 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide is represented by Formula IX.



Formula IX

The compound of Formula V is cyclized using Lawesson’s reagent in the presence of a base to obtain a compound of Formula VI. Types of bases include inorganic and organic bases. Examples of inorganic bases include sodium carbonate, sodium bicarbonate, potassium carbonate, and potassium bicarbonate. Examples of organic bases include methyl amine, ethylamine, triethylamine, and pyridine.

The compound of Formula V used in the above process is prepared by reacting N-protected piperazine of Formula IV with acetoacetic acid or its ester, followed by the reaction with phenylhydrazine.

**Formula IV**

The compound of Formula V may or may not be isolated. In the context of the present invention, the compound of Formula V is not isolated.

5 The compound of Formula VI is deprotected to obtain a compound of Formula III. The deprotection may be performed using conventional methods disclosed in Greene and Wuts, *Protective Groups in Organic Synthesis*, 4th Edition, 2006.

 The compound of Formula III is reacted with a compound of Formula VII in the presence of a metal hydrogen complex to obtain a compound of Formula VIII. Examples
10 of metal hydrogen complexes include sodium borohydride, sodium cyanoborohydride, and sodium triacetoxyborohydride.

 The compound of Formula VII may be prepared by the processes disclosed in U.S. Patent Nos. 7,074,794 and 8,003,790 or Indian Patent Application Nos. 2350/DEL/2013 and 2347/DEL/2013, which are incorporated herein by reference for their teachings of
15 processes of preparing the compound according to Formula VII.

 The reaction of the compound of Formula III with the compound of Formula VII may also be carried out in the presence of an acid catalyst. Examples of acid catalysts include acetic acid, p-toluenesulfonic acid, and boron trifluoride.

 The compound of Formula VIII is deprotected to obtain {(2S,4S)-4-[4-(3-methyl-
20 1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone of Formula II, or salts thereof. The deprotection is performed using conventional methods as disclosed in Greene and Wuts, *Protective Groups in Organic Synthesis*, 4th Edition, 2006.

 The compound of Formula III may also be converted into {(2S,4S)-4-[4-(3-methyl-
25 1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone of Formula II, or salts thereof, by following the processes disclosed in U.S. Patent Nos. 7,074,794 and 8,003,790 or Indian Patent Application Nos. 2350/DEL/2013 and 2347/DEL/2013, which are incorporated herein as reference for their teachings of these conversion processes.

The examples are set forth to aid the understanding of the invention but are not intended to and should not be construed to limit its scope in any way.

Methods

5 The HPLC purity was determined using a Gemini[®] C18 (250 x 4.6 mm), 5 μ m column with a flow rate of 1.0 mL/minute with gradient elution; column oven temperature: 35°C; sample tray temperature: 25°C to 35°C; detector UV: 215 nm; injection volume: 10 μ L; run time: 65 minutes.

EXAMPLES

10 Example 1: Preparation of 1-(3-Methyl-1-phenyl-1H-pyrazol-5-yl)piperazine acetate (Formula III)

Ethyl acetoacetate (82.2 g) was added to a solution of ethyl piperazine-1-carboxylate (Formula IV; 100 g) in toluene (1000 mL), and the reaction mixture was heated at 100°C to 110°C for 24 hours. The reaction mixture was cooled to 0°C to 5°C. Phenyl hydrazine (68.4 g) was slowly added to the reaction mixture at 0°C to 10°C over a
15 period of 15 minutes to 20 minutes. The reaction mixture was heated to 20°C to 25°C, and stirred at the same temperature for 3 hours. After completion of the reaction, the reaction mixture was concentrated at a temperature of about 55°C under reduced pressure to obtain a residue. The residue was dissolved in tetrahydrofuran (350 mL), and sodium carbonate (134 g) was added to it at 20°C to 22°C to obtain a solution. Lawesson's
20 reagent (281.2 g) was slowly added to the solution over a period of 30 minutes. The reaction mixture was stirred at 20°C to 35°C for 90 minutes. The reaction mixture was heated to 50°C to 55°C, and stirred at the same temperature for 3 hours. After completion of the reaction, the reaction mixture was allowed to cool to 35°C to 40°C. The reaction mixture was quenched with toluene (500 mL) and deionized water (500 mL). The reaction
25 mixture was stirred at 35°C to 40°C for 30 minutes. The reaction mixture was allowed to settle for about 15 minutes and cooled to 25°C to 30°C.

The reaction mixture then was filtered through a Hyflo[®] bed. The Hyflo[®] bed was washed with toluene (2 x 200 mL). The organic layer was separated and the aqueous layer was extracted with toluene (2 x 200 mL) at 25°C to 30°C. The combined organic layers
30 were washed with de-ionized water (500 mL) at 25°C to 30°C. The organic layer was concentrated at about 55°C under reduced pressure to obtain a residue. The residue was dissolved in methanol (200 mL), and concentrated at 55°C under reduced pressure to

obtain a residue. The residue was again dissolved in methanol (500 mL). Deionized water (250 mL) was added to it. Potassium hydroxide (301.4 g) was added, and the reaction mixture was heated to about 80°C to 85°C for 2 hours to 3 hours. The reaction mixture was allowed to cool to 50°C to 55°C, and quenched with toluene (500 mL) and deionized water (100 mL). The reaction mixture was allowed to settle for 15 minutes, and the layers were separated at about 50°C to 55°C. The aqueous layer was extracted with toluene (2 x 200 mL) at 50°C to 55°C. The organic layers were combined and washed with an aqueous solution of sodium chloride (3 x 200 mL; prepared by adding 120 g sodium chloride to 600 mL deionized water) at 50°C to 55°C. The organic layer was separated, washed with deionized water (100 mL) at 52°C to 55°C, and concentrated at 100°C to 110°C under atmospheric pressure to a volume of about 500 mL. The concentrated solution was cooled to 50°C to 55°C, and glacial acetic acid (28.5 g) was slowly added at 50°C to 55°C. The reaction mixture was stirred at the same temperature for 60 minutes, allowed to cool to 20°C to 25°C, and stirred at the same temperature for 60 minutes. The reaction mixture was then cooled to about 0°C to about 5°C, and stirred at the same temperature for 60 minutes. The reaction mixture was filtered. The solid obtained was washed with toluene (100 mL) at 0°C to 5°C, and then dried in an air oven at 40°C to 45°C for 15 hours to 20 hours to obtain 1-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazine acetate.

Yield: 73.8%

HPLC Purity: 99.69%

Example 2: Preparation of *tert*-butyl (2*S*)-4-[4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]-2-(1,3-thiazolidin-3-ylcarbonyl)pyrrolidine-1-carboxylate (Formula VIII)

A solution of sodium triacetoxo borohydride (98.8 g) in toluene (300 mL) was added to a mixture of *tert*-butyl (2*S*)-4-oxo-2-(1,3-thiazolidin-3-yl carbonyl)pyrrolidine-1-carboxylate (100 g) and 1-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazine acetate (Formula III; 100.7 g; prepared according to Example 1) in toluene (800 mL) at 5°C to 10°C. The reaction mixture was stirred at 20°C to 25°C for 3 hours. The progress of the reaction was monitored by HPLC. After completion of the reaction, the reaction mixture was quenched with deionized water (600 mL) and stirred for 10 minutes. The reaction mixture was allowed to settle for about 15 minutes. The organic layer was separated and washed with an aqueous sodium bicarbonate solution (60 g sodium carbonate in 600 mL

deionized water). The organic layer was washed with deionized water (600 mL), and concentrated at about 50°C under reduced pressure to obtain a residue. The residue was dissolved in isopropyl alcohol (500 mL) and the solution was concentrated at 50°C under reduced pressure to obtain *tert*-butyl (2*S*)-4-[4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]-2-(1,3-thiazolidin-3-ylcarbonyl)pyrrolidine-1-carboxylate. The residue was used as such in the next step.

Example 3: Preparation of {(2*S*,4*S*)-4-[4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone hemipentahydrobromide hydrate (Formula I)

Activated carbon (10 g) was added to a solution of the residue of Formula VIII (prepared according to Example 2) in isopropyl alcohol (1000 mL) at 30°C to 35°C. The reaction mixture was stirred at the same temperature for 30 minutes. The reaction mixture was filtered through a Hyflo[®] bed. The filtrate was heated to 70°C to 75°C. Hydrobromic acid (48%; 168 g) was slowly added to the filtrate at 70°C to 75°C over a period of 10 minutes to 15 minutes. The reaction mixture was stirred at 70°C to 77°C for 2 hours to 3 hours. The progress of the reaction was monitored by HPLC. After completion of the reaction, the reaction mixture was cooled to 20°C to 25°C, and stirred at the same temperature for 60 minutes. The reaction mixture was filtered to obtain a solid. The solid obtained was washed with isopropyl alcohol (2 x 200 mL), and then dried at 50°C under reduced pressure for 15 hours to obtain {(2*S*,4*S*)-4-[4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone hemipentahydrobromide hydrate.

Yield: 90%

Example 4: Purification of {(2*S*,4*S*)-4-[4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone hemipentahydrobromide hydrate (Formula I)

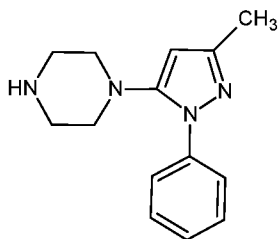
A mixture of {(2*S*,4*S*)-4-[4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone hemipentahydrobromide hydrate (Formula I; 100 g; prepared according to the process of Example 3) in ethanol (700 mL) was heated to 70°C to 75°C to obtain a clear solution. The solution was filtered at the same temperature, and the residue was washed with hot ethanol (100 mL; 70°C to 75°C). The filtrate was allowed to cool to 65°C to 68°C and deionized water (10 mL) was added

at the same temperature. The solution was cooled to 55°C to 60°C, and stirred at the same temperature for 2 hours. The solution was further cooled to 20°C to 25°C, and stirred at the same temperature for 60 minutes to obtain a solid. The solid was filtered, washed with ethanol (100 mL), and then dried at 45°C to 50°C under reduced pressure for 18 hours to
5 20 hours to obtain pure {(2S,4S)-4-[4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone hemipentahydrobromide hydrate.

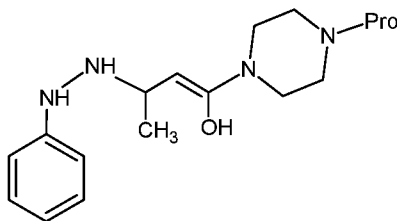
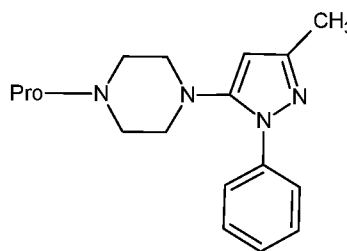
Yield: 90%

We claim:

- 1 1. A process for the preparation of 1-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazine
 2 of Formula III, or salts thereof,

**Formula III**

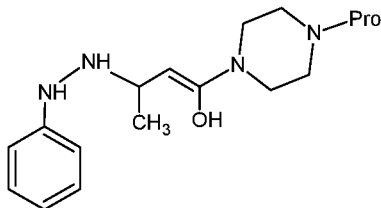
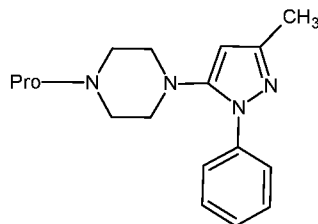
- 5 wherein the process comprises cyclizing a compound of Formula V in the presence of
 6 Lawesson's reagent to obtain a compound of Formula VI,

**Formula V****Formula VI**

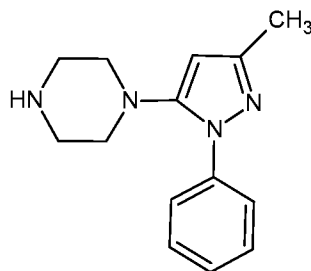
- 9 wherein 'Pro' is a protecting group.

- 1 2. A process for the preparation of {(2*S*,4*S*)-4-[4-(3-methyl-1-phenyl-1*H*-pyrazol-5-
 2 yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone of Formula II, or salts
 3 thereof, wherein the process comprises:

- 4 a) cyclizing a compound of Formula V in the presence of Lawesson's reagent to
 5 obtain a compound of Formula VI;

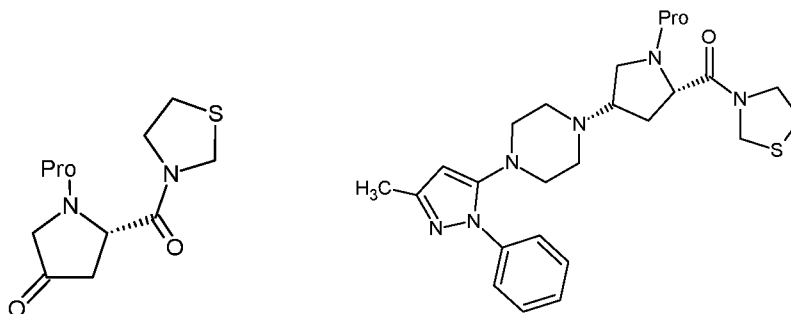
**Formula V****Formula VI**

8 b) deprotecting the compound of Formula VI to obtain a compound of Formula
9 III;



Formula III

12 c) reacting the compound of Formula III, or a salt thereof, with a compound of
13 Formula VII to obtain a compound of Formula VIII; and



Formula VII

Formula VIII

16 d) deprotecting the compound of Formula VIII to obtain {(2S,4S)-4-[4-(3-
17 methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-
18 thiazolidin-3-yl)methanone of Formula II, or salts thereof,

19 wherein 'Pro' is a protecting group.

1 3. The process according to claim 1 or claim 2, wherein the step of cyclization is
2 carried out in the presence of a base.

1 4. The process according to claim 3, wherein the base is an inorganic base or an
2 organic base.

5. The process according to claim 4, wherein the inorganic base is selected from the group consisting of sodium carbonate, sodium bicarbonate, potassium carbonate, and potassium bicarbonate.

1 6. The process according to claim 4, wherein the organic base is selected from the
2 group consisting of methyl amine, ethylamine, triethylamine, and pyridine.

1 7. The process according to claim 2, wherein step b) is carried out in the presence of
2 an acid catalyst.

1 8. The process according to claim 7, wherein the acid catalyst is selected from the
2 group consisting of acetic acid, p-tolunesulfonic acid, and boron trifluoride.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/065699

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 7 074 794 B2 (KITAJIMA HIROSHI [JP] ET AL) 11 July 2006 (2006-07-11) example 222 ----- -/--	1-8



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

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Date of the actual completion of the international search

8 January 2015

Date of mailing of the international search report

22/01/2015

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INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2014/065699

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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International application No

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