25 NOV 2005

1,6-DIHYDRO-7H-PYRAZOLO[4,3-D]PYRIMIDIN-7-ONE COMPOUND FOR THE TREATMENT OF IMPOTENCE

TECHNICAL FIELD

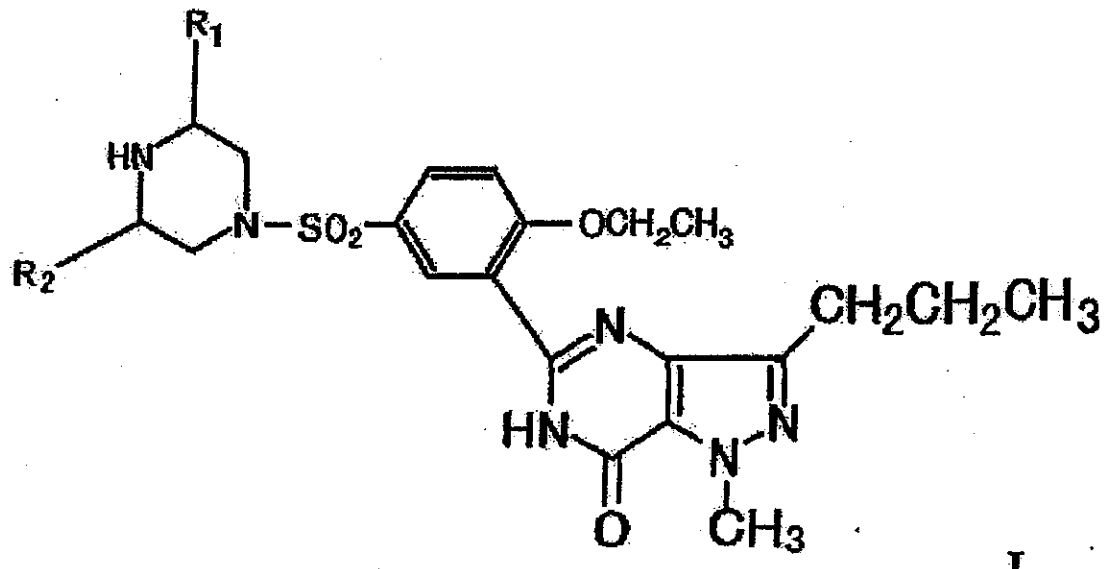
This invention relates to new compounds for the treatment of impotence. In particular, the present invention relates to new compounds for the treatment of impotence, their preparation method and their use.

BACKGROUND OF THE INVENTION

Sildenafil is a selective inhibitor of phosphodiesterase whose chemical name is 1-[[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenylsulphonyl]]-4-methylpiperazine. This compound and its preparation method as well as its use in treating cardiovascular diseases was disclosed in CN1124926A; CN1057464A disclosed the use of this compound in preparing medicine for treating erection dysfunction of male animals. CN1168376A disclosed a new method for preparing sildenafil. CN1246478A disclosed another method for preparing sildenafil. Although sidenafil is very effective on treating male erectile dysfunction, the toxicity and side effects of the compound is high.

SUMMERY OF THE INVENTION

The present invention provides a new selective inhibitor of phosphodiesterase, i.e. the compound of formula (I) and its pharmaceutically acceptable salts or its stereoisomers. Such compound has the structure of formula (I):



I

Wherein, R_1 and R_2 may be the same or different, and independently be C_{1-6} alkyl, and preferably methyl, more preferably, R_1 and R_2 are both in the cis-form of piperazine ring and are both methyl.

Another object of the present invention is to provide the method for preparing the compound of formula (I).

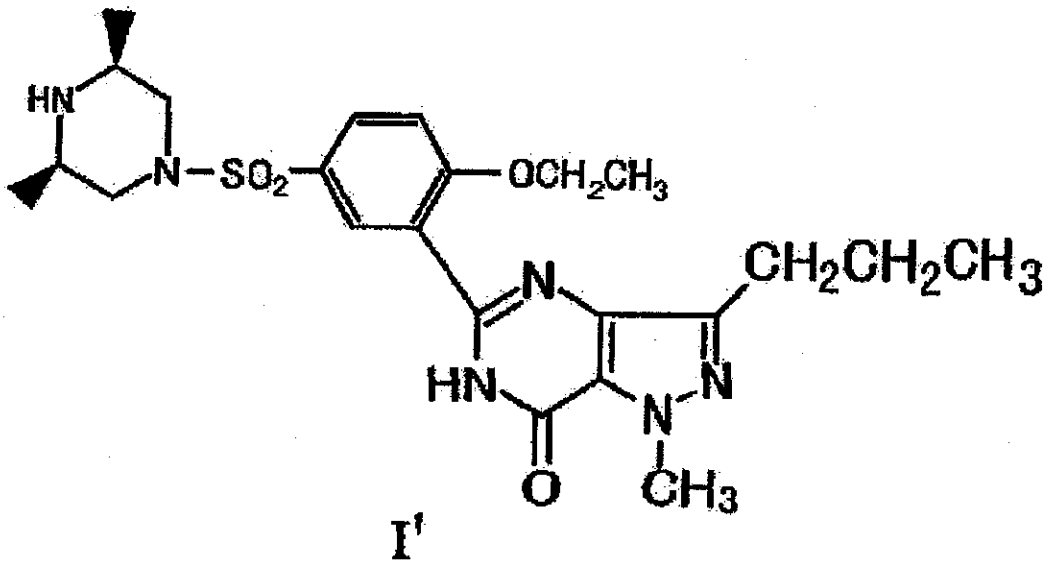
There are some new intermediates involved in the synthetic route of the present invention. Therefore, another object of the invention is to provide the intermediates for preparing of compounds of formula (I).

Still another object of the invention is to provide the pharmaceutical composition comprising the compound of formula (I) as active component.

Another object of the invention is to provide the use of the compounds of formula (I) for preparing medicine for the treatment of impotence diseases.

According to the present invention, there are two substituted groups, R_1 and R_2, and two asymmetrical carbon atoms on piperazine ring of the compounds of formula (I). R_1 and R_2 can be in cis- or trans- form of the piperazine ring. Therefore, the compounds of formula (I) are presented as various stereoisomers. These isomers and their pharmaceutically acceptable salts are all in the scope of compounds of the present invention.

Preferably, the compound of the present invention is the compounds of formula (I) wherein R_1 and R_2 are in the cis-form, and most preferably is the compound wherein R_1 and R_2 are both methyl and in cis-form. Its chemical name is: 5-[[2-ethoxy-5-(cis-2,6-dimethylpiperazin-4-ylsulphonyl)phenyl]]-1-methyl-3-n-propyl-7,6-dihydro-1H- pyrazolo [4,3-d] pyrimidin-7-one, i.e., the compound of formula (I'):



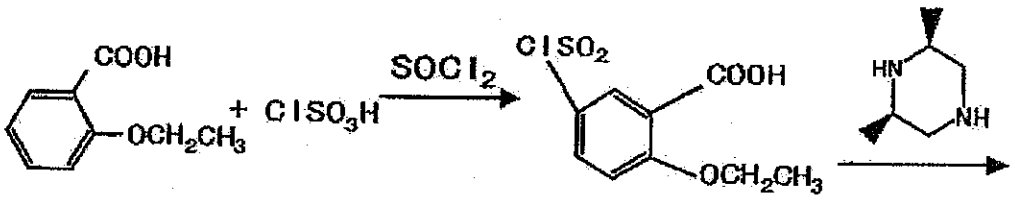
I'

The compound of formula (I) of the present invention is not only effective for the treatment of impotence diseases, such as male erectile dysfunction, but also have such features as long-lasting medical effectiveness and lower toxicity.

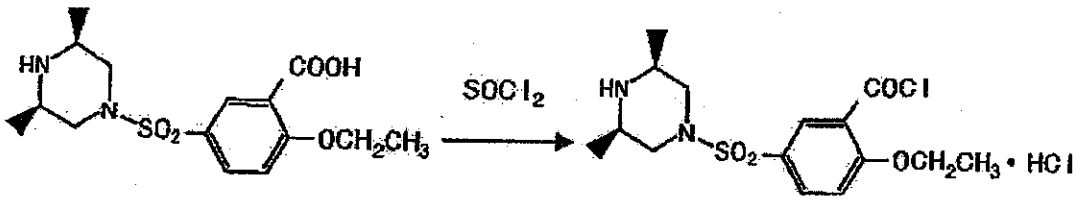
The method for preparing the compound of formula (I) is hereinafter described on the basis of taking formula (I') compound as an example.

The synthetic route of the compounds of formula (I') of the present invention is

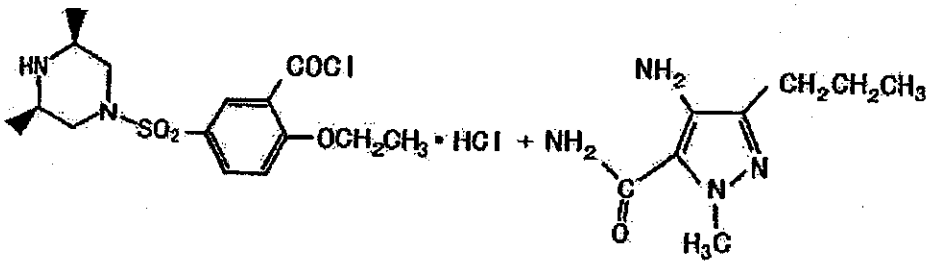
illustrated as follows:



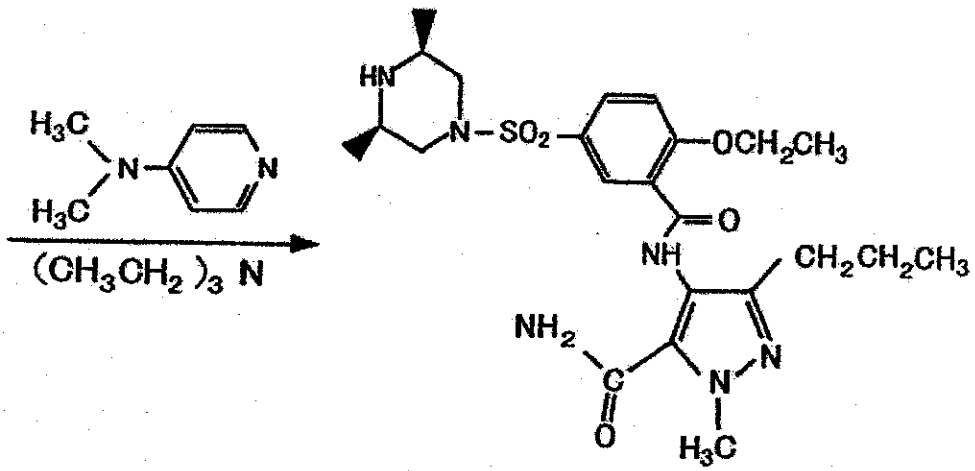
II



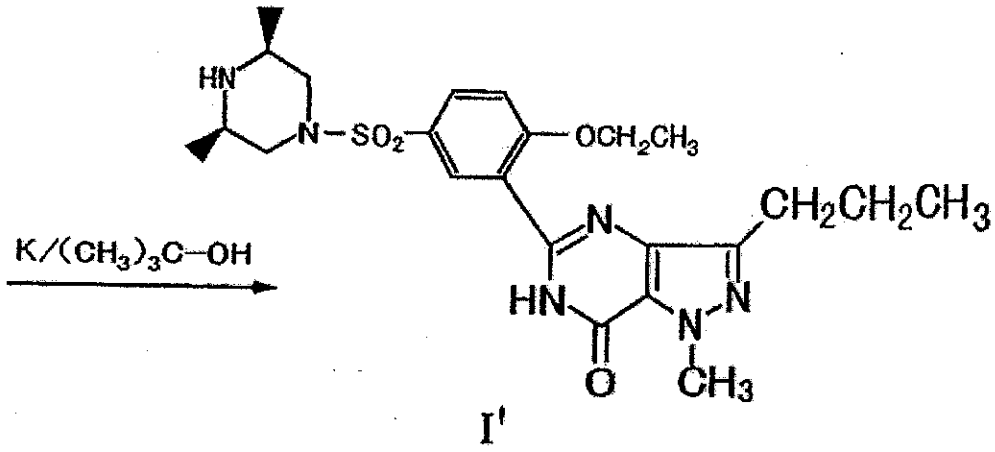
III IV



IV V



VI



I'

The compound of formula (I') was prepared as follow: reacting 2-ethoxy benzoic acid as raw materials with chlorosulfonic acid in the present of sulfoxide dichloride, obtained 5-chlorosulphonyl-2-ethoxy benzoic acid (compound II); reacting compound II with cis-2,6-dimethyl piperazine (see, Zhongguo Yiyao Gongye Zazhi, 1997, vol.28(11), page 524~525), obtained 2-ethoxy-5-(cis-2,6-dimethylpiperazin-4-ylsulphonyl) benzoic acid (compound III); acylation of compound (III), which is a new compound, obtained 2-ethoxy-5-(cis-2,6-dimethylpiperazin-4-ylsulphonyl) benzoyl chloride (compound IV); reacting compound IV with compound V (see the synthesis method of the compound of formula IX in CN1246478A), in the present of 4-dimethylaminopyridine and triethylamine, obtained 4-[[2-ethoxy-5-(cis-2,6-dimethylpiperazin-4-ylsulphonyl)benzamido]]-1-methyl-3-n-propylpyrazole-5-carbox amide(compound VI), this compound is a new compound; cyclization of compound VI in the present of potassium t-butoxide, obtained 5-[[2-ethoxy-5-(cis-2,6-dimethylpiperazin-4-ylsulphonyl) phenyl]]-1-methyl-3-n-propyl-7,6-dihydro-1H-pyrazolo[4,3-d] pyrimidin-7-one (compound I').

DETAILED DESCRIPTION OF THE INVENTION

The method for preparing the compounds of formula (I') of the present invention and their pharmaceutically acceptable salts is hereinafter described by examples. It should be understood that the examples of the preparation methods are only for the purpose of illustrating the present invention and the invention is not limited to the examples. Any modifications under the concept of the present invention to the preparation methods of the present invention all belong to the scopes of the present invention.

Example 1 Preparation of 5-chlorosulphonyl-2-ethoxy benzoic acid (II)

In a 250ml three-neck flack, 2-ethoxy benzoic acid (50g, 0.30mol) was added dropwise to an ice-cooled mixtures of sulfoxide dichloride (22 ml, 0.30mol)and chlorosulfonic acid (82.6ml, 1.24mol) under stirring. At the same time, the

temperature of the reacting mixture was kept below 25℃. The resulting mixture was stirred at room temperature for 18 hours and then poured into ice water with stirring, and white deposit appeared. The reaction mixture was stirred for another 1 hour and filtered, washed with water and dried in vacuum, gave 64.4g of crude product as white solid (II) (yield 81%). m.p. 108-110℃. The crude product was used directly in the next step without further purification.

Example 2 Preparation of 2-ethoxy-5-(cis-2,6-dimethypiperazin-4-ylsulphonyl) benzoic acid (III)

In 250ml three-neck flask, 52.6g(0.23mol)of cis-2, 6-dimethylpiperazine was added to the suspension of compound (II) (53g, 0.20mol)in water (170ml) at about 10 ℃ with stirring, at the same time the temperature of reacting mixture was kept below 20℃. The reaction was then stirred at 10℃ for another 2 hours. The precipitate was filtered, ice-water washed, dried, and refluxed in acetone for 1 hour, and purified, gave 48g compound (III)(yield 70%) as white crystalline, m.p. 260.5-273.0 ℃ (Dec.). HNMR(DMSO) δ : 7.72-7.75(2H, H-4 and H-6 on benzene ring), 7.26-7.28(1H, H-3 on benzene ring),4.12-4.17(2H, $-CH_2-$ on $-OCH_2CH_3$), 3.5-3.53(2H, $-CH_2-$on piperazine ring), 2.89-2.92(2H, -CH- on piperazine ring), 1.80-1.86(2H, $-CH_2-$on piperazine ring), 1.31-1.34(3H, $-CH_3$ on $-OCH_2CH_3$), 1.0-1.04(6H, $-CH_3$ on piperazine ring).

Example 3 Preparation of 2-ethoxy-5-(cis-2,6-dimethylpiperazin-4-ylsulphonyl) benzoyl chloride(IV)

Compound (III) (34.2g, 0.1mol) and sulfoxide dichloride (73.0ml, 0.5mol) was charged into a 250ml three-neck flask and the resulting mixture was heated under reflux for 3 hours. The unreacted sulfoxide dichloride was then evaporated under vacuum. The ethyl acetate was added into the residue, and stirred. The precipitate was filtered, washed with ethyl acetate, dried under vacuum, gave 29.4g (74%) compound (IV) as a yellow solid. m.p., 206.0-209.5℃. HNMR(D_2O) δ : 8.0(1H, H-6 on benzene), 7.74-7.76(1H, H-4 on benzene), 7.14-7.16(1H, H-3 on benzene), 4.08-4.11(2H, $-CH_2-$ on $-OCH_2CH_3$), 3.74-3.77(2H, $-CH_2-$on piperazine ring), 3.32(2H, -CH -on piperazine ring), 2.19-2.25(2H, $-CH_2-$ on piperazine ring), 1.24-1.27(3H, $-CH_3$ on $-OCH_2CH_3$), 1.09-1.10(6H, $-CH_3$ on piperazine ring).

Example 4 Preparation of 4-[-2-ethoxy-5-(cis-2,6-dimethylpiperazin-4-ylsulphonyl) benzamide] -1-methyl-3-n-propyl pyrazole-5-carboxamide(VI)

In a 500ml three-neck flask, 125ml of methylene chloride, 9.1g(0.05mol) of 1-methyl-4-amino-3-n-propyl pyrazole-5-formamide (V), 0.06g(0.0005mol) of 4-dimethylaminopyridine and 10.1g(0.1mol)of triethylamine were added successively and then the mixture was cooled to below 10℃. A solution of of the compound (IV) (25.80g, 0.065mol) in methylene chloride (125ml) was added dropwise into the mixture and then stirred at this temperature for 2 hours. The solvent was evaporated, then water was added to the residue. The solid was filtered and

washed with ethyl acetate, gave 19.2g compound (VI) as a grey-white solid , m.p.197-198.5℃ (yield 76%). HNMR($CDCl_3$) δ : 8.62(1H, H-6 on benzene ring), 7.90-7.92(1H, H-4 on benzene ring), 7.90(1H, -CO-NH-), 7.17-7.27(1H, H-3 on benzene ring), 5.73(1H, -NH- on piperazine ring), 4.37-4.41(2H, $-OCH_2CH_3$), 4.06(3H, $N-CH_3$), 3.63-3.66(2H, $-CH_2-$ on piperazine ring), 3.0(2H, -CH- on piperazine ring), 2.52-2.56(2H, $-CH_2CH_2CH_3$), 1.84-1.90(2H, $-CH_2-$ on piperazine ring), 1.65-1.69(2H, $-CH_2CH_2CH_3$), 1.58-1.63(3H, $-OCH_2CH_3$), 1.03-1.05(6H, $-CH_3$ on piperazine ring), 0.94-0.97(3H, $-CH_2CH_2CH_3$).

Example 5 Preparation of 5-[[2-ethoxy-5-(cis-2,6-dimethylpiperazin-4-ylsulphonyl)phenyl]]-1-methyl-3-n-propyl-7,6-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7- one (I')

In a 250ml three-neck flask, 1.8g(0.046mol)of metallic potassium and 96ml of dry tert-butyl alcohol were added, then to the mixture 19g(0.0387mol) of compound (VI) was added. The mixture was heated to reflux with stirring for 8 hours, then cooled to room temperature. 96ml of water was added and the pH was adjusted to 7.0 by adding 0.5mol/l of hydrochloric acid, giving precipitate and then standing for 1 hour at a temperature below 10℃. The precipitate was filtered, washed with ice-water, dried and gave 17.0g compound (I') (yield 93%) as white crystalline. m.p. 202.2-203.2 ℃. HNMR(MeOD) δ : 8.15(1H, H-6 on benzene ring), 7.90-7.93(1H, H-4 benzene ring), 7.36-7.38(1H, H-3 on benzene ring), 4.32(2H, $-OCH_2CH_3$), 4.23(3H, $N-CH_3$), 3.75-3.78(2H, $-CH_2-$ on piperazine ring), 3.10(2H, -CH- on piperazine ring), 2.86-2.89(2H, $-CH_2CH_2CH_3$), 2.04-2.10(2H, $-CH_2-$ on piperazine ring), 1.80-1.84(2H, $-OCH_2CH_2CH_3$), 1.45-1.48(3H, $-OCH_2CH_3$), 1.14-1.17(6H, $-CH_3$ on piperazine ring), 0.97-1.01(3H, $-CH_2CH_2CH_3$). If necessary, the compound of formula (I') may be converted into its pharmaceutically acceptable salts by conventional method.

The inventors of the present invention discovered that the compound of the present invention is very effective for treating male erectile dysfunction diseases and has lower toxicity and side effects. Specific results of pharmacodynamics and toxicity test are summarized as follows:

Example 6 Pharmacodynamics test

Test 1. Penis erection test of the compound formula (I') in rats with testis removed

The result indicates that the latent period of penis erection by electric irritation (10V) can be significantly shortened ($P<0.05$ and $P<0.01$) in rats administered the compound formula (I') at the dosage of 24mg/kg and 12mg/kg, respectively. This result is the same as another compound sildenafil ($P<0.01$)。

Test 2. Effect of the compound formula (I') on the sexual function in mice with testis removed

Result a. The result shows that latent period which male mice catch female mice can be significantly shortened ($P<0.05$ and $P<0.01$) after administration of the compound of formula (I') at the dosage of 24mg/kg and 12mg/kg, respectively.

Result b. The result shows that the times of back-climbing on female mice by male mice (times of sexual intercourse) can be significantly increased ($P<0.05$ and $P<0.01$) when the male mice was administrated the compound formula (I') at the dosage of 24mg/kg and 12mg/kg, respectively.

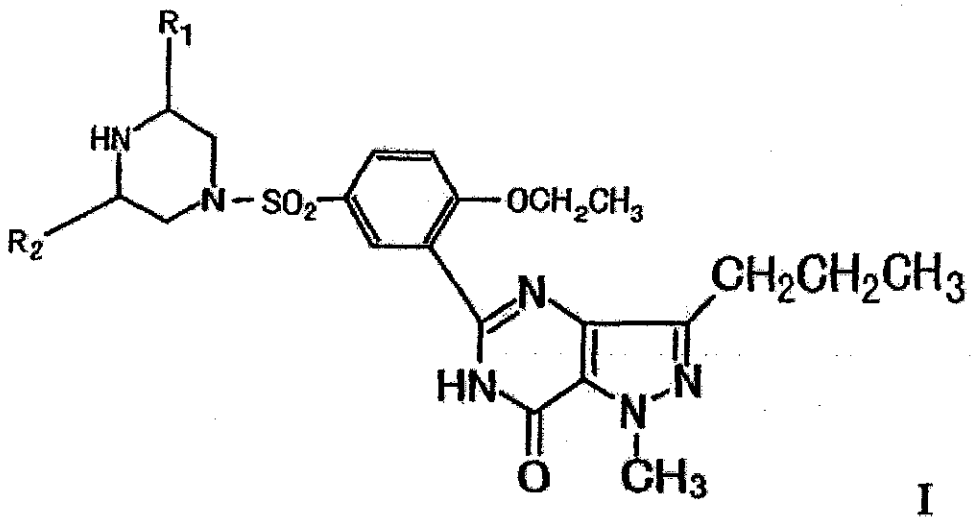
Example 7 Toxicity test

It was observed by using Bliss method that the half-lethal dosage(LD_{50}) is 901.5 mg/kg when mice were administrated the compound formula (I') orally by gavage. The confidence limit of 95% is 772.5-1052.1mg/kg.

According to the "Chinese Journal of Clinical Pharmacology and Therapeutics", 1999, 4(3), 237-240, the LD_{50} of the compound sidenafil is 625mg/kg when male mice were administrated orally in the single dose, and the confidence limit of 95% is 50-672mg/kg.

Claims

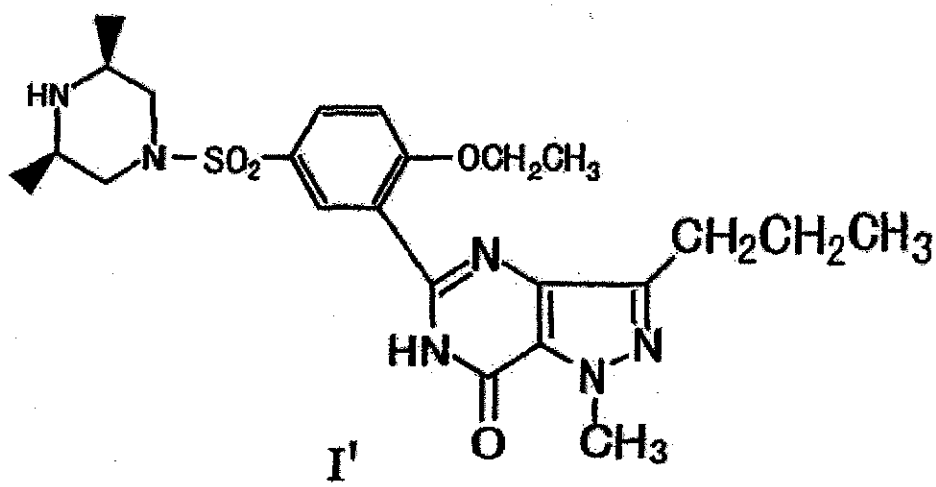
1. A compound of formula (I), or a pharmaceutically acceptable salt or a stereoisomer thereof:



I

Wherein, R_1 and R_2 may be the same or different and independently be C_{1-6} alkyl.

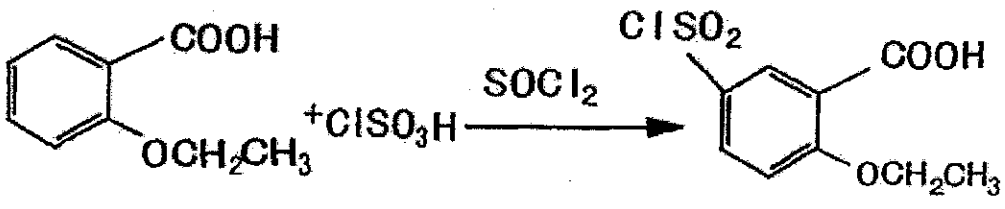
2. The compound according to claim 1, wherein said compound is 5-[[2-ethoxy-5-(cis-2,6-dimethypiperazin-4-ylsulphonyl)phenyl]]-1-methyl-3-n-propy l-7,6-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one, and said compound has the structure of formula (I') as follows:



I'

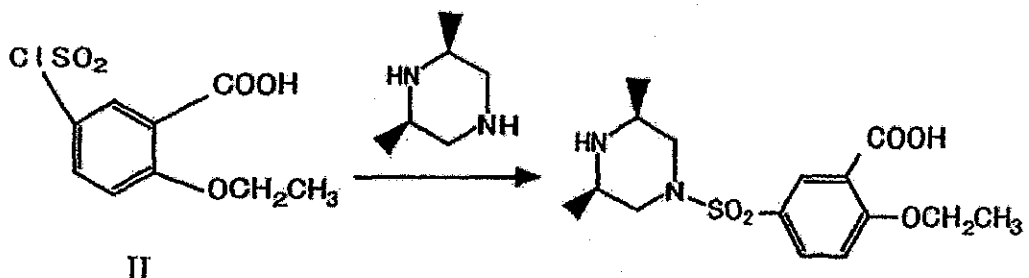
3. A method for preparing the compound of formula (I'), comprising the following steps:

a. reacting 2-ethoxy benzoic acid, as raw materials, with chlorosulfonic acid in the prensent of sulfoxide dichloride, obtained 5-chlorosulphonyl-2-ethoxy benzoic acid (compound II);



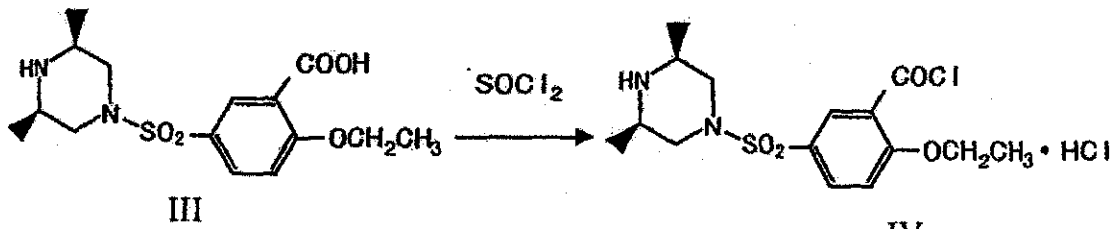
II

b. reacting the compound II with cis-2,6-dimethyl piperazine, obtained 2-ethoxy-5-(cis-2, 6-dimethyl piperazin-4-ylsulphonyl) benzoic acid (compound III);



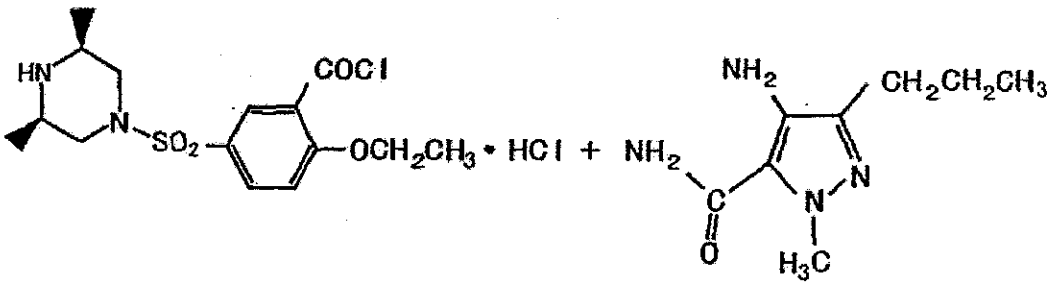
II III

c. acylation of the compound III, obtained 2-ethoxy-5-(cis-2,6-dimethylpiperazin-4-ylsulphonyl)benzoylchloride(IV);

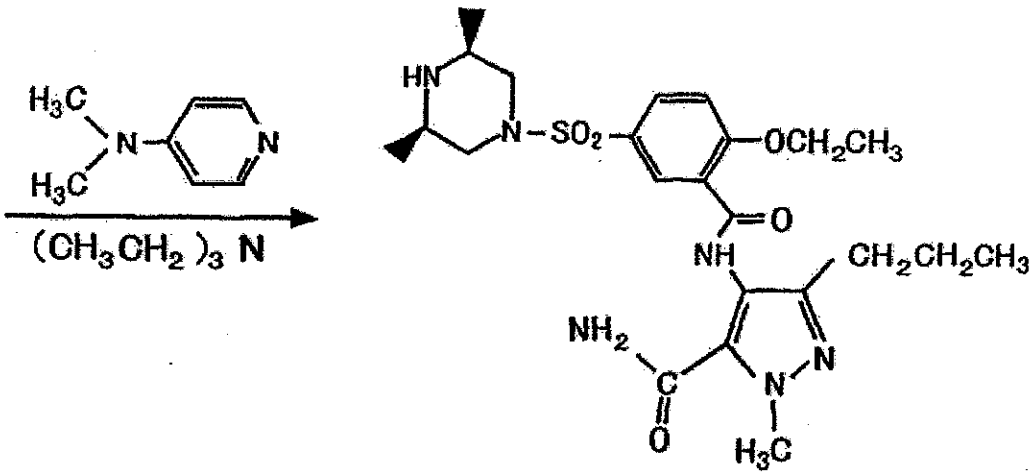


III IV

d. reacting the compound (IV) with the compound (V) in the present of 4-dimethylaminopyridine and triethylamine, obtained 4-[2-ethoxy-5-(cis-2,6-dimethylpiperazin-4-ylsulphonyl)benzamido]-1-methyl-3-n-prophlpyrazole-5-carboxamide (compound VI);

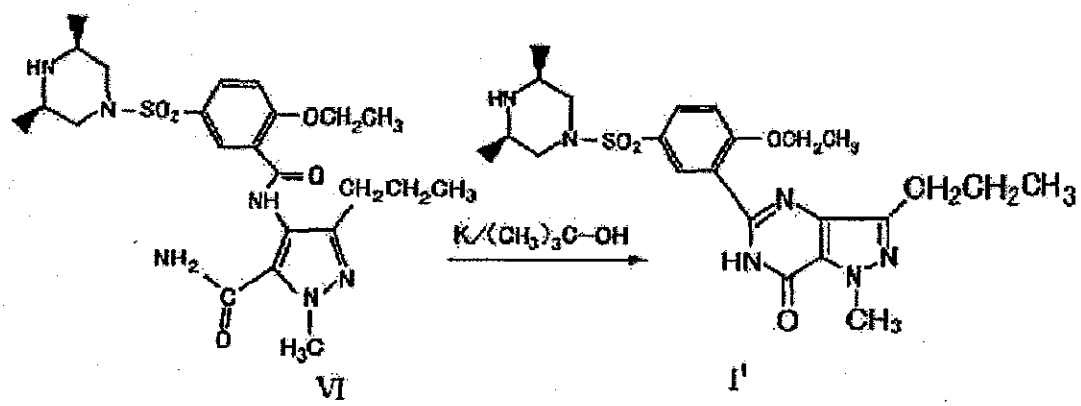


IV V



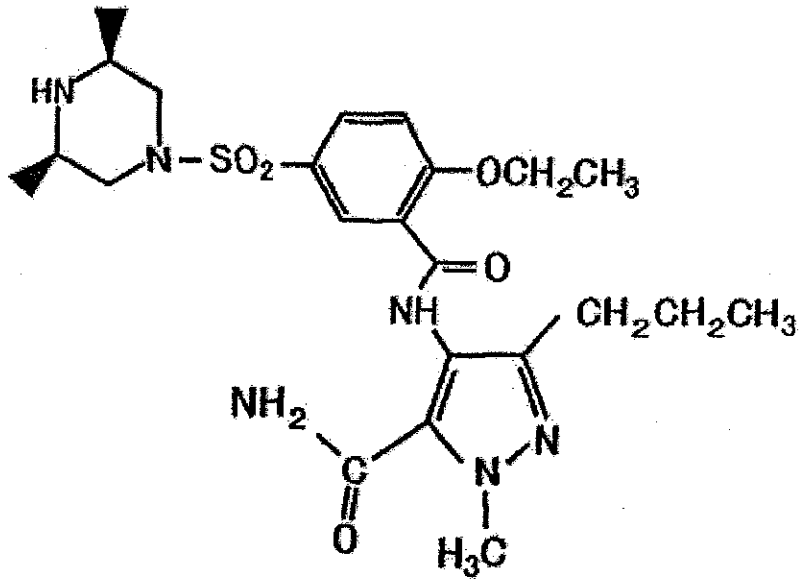
VI

e. cyclization of the compound VI in the present of potassium t-butoxide, obtained 5-[[2-ethoxy-5-(cis-2,6-dimethylpiperazin-4-ylsulphonyl)phenyl]]-1-methyl-3-n-propyl-7,6-dihydro-1H-pyrazolo[4,3-d] pyrimidin-7-one (I') .



VI I'

4. A compound of formula (VI), which is 4-[2-ethoxy-5-(cis-2,6-dimethylpiperazin-4-ylsulphonyl)benzamido]-1-methyl-3-n-propyl-pyrazole-5-carbox amide, having the structure as follow:



VI

5. A pharmaceutical composition for treating impotence, comprising a therapeutically effective amount of a compound of formula (I), its pharmaceutically acceptable salts or stereoisomers, as an active component, and a pharmaceutical acceptable carrier.

6. The pharmaceutical composition according to claim 5, wherein the compound of formula (I) is 5-[[2-ethoxy-5-(cis-2,6-dimethylpiperazin-4-ylsulphonyl)phenyl]] -1-methyl-3-n-propyl-7,6-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one.

7. Use of a compound of formula (I) in preparing medicine for the treatment of impotence diseases.

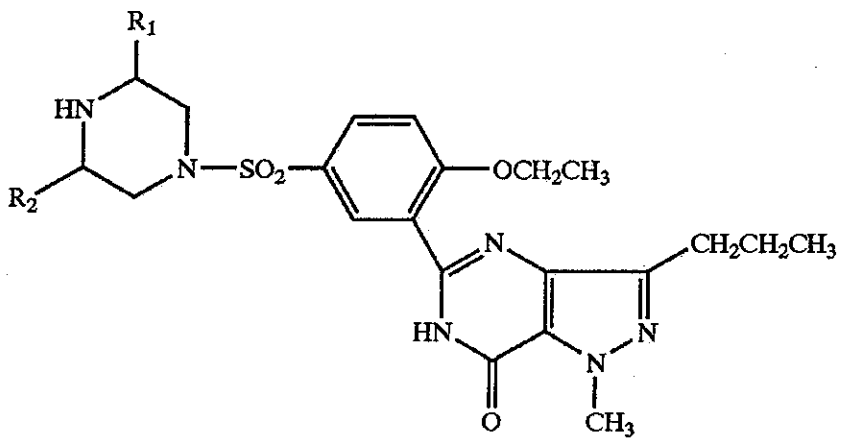
8. The use according to claim 7, wherein the compound of formula (I) is 5-[[2-ethoxy-5-(cis-2,6-dimethylpiperazin-4-ylsulphonyl)phenyl]]-1-methyl-3-n-prop yl-7,6-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one.

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ABSTRACT

The present invention relates to new 1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one compounds of formula (I), or a pharmaceutically acceptable salt or a stereoisomer thereof, useful for treatment of impotence diseases:

I



wherein R_1 and R_2 may be the same or different and independently be C_{1-6} alkyl. The present invention also provides a method of preparing the compounds of formula (I).