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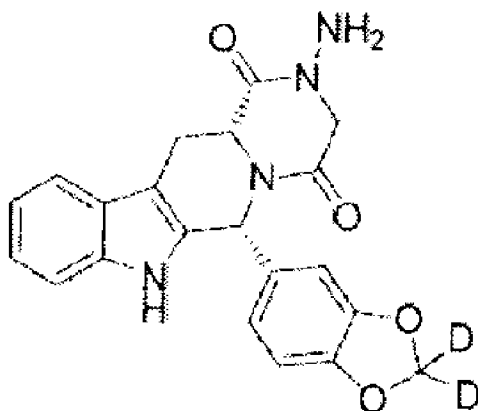
(72) Inventeurs/Inventors:
CHEN, ZHONGZHU, CN;
XU, ZHIGANG, CN;
TANG, DIANYONG, CN

(73) Propriétaire/Owner:
CHONGQING DIKANG ERLE PHARMA CO. LTD., CN

(74) Agent: SMART & BIGGAR LLP

(54) Titre : DERIVES DE 6-(BENZO[D][1,3]DIOXOL-5-YL)-2-SUBSTITUE-2,3,12,12A-TETRAHYDROPYRAZINO
[1',2':1,6]PYRIDO[3,4-B]INDOLE-1,4(6H,7H)-DIONE COMME INHIBITEURS DE PHOSPHODIESTERASE DE TYPE
5

(54) Title: 6-(BENZO[D][1,3]DIOXOL-5-YL)-2-SUBSTITUTED-2,3,12,12A-
TETRAHYDROPYRAZINO[1',2':1,6]PYRIDO[3,4-B]INDOLE-1,4(6H,7H)-DIONE DERIVATIVES AS
PHOSPHODIESTERASE TYPE-5 INHIBITORS



Compound DDCI-01

(57) **Abrégé/Abstract:**

Disclosed are a compound represented by general formula (I) as a phosphodiesterase type-5 inhibitor or pharmaceutically acceptable salt thereof and use thereof in treating and/or preventing diseases or disease states related to the phosphodiesterase type-5 in mammals.

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- (71) 申请人: 重庆文理学院 (CHONGQING UNIVERSITY OF ARTS AND SCIENCES) [CN/CN]; 中国重庆市永川区红河大道 319 号, Chongqing 402160 (CN)。
- (72) 发明人: 陈中祝 (CHEN, Zhongzhu); 中国重庆市永川区红河大道 319 号重庆文理学院新药创制中心, Chongqing 402160 (CN)。 徐志刚 (XU, Zhigang); 中国重庆市永川区红河大道 319 号重庆文理学院新药创制中心, Chongqing 402160 (CN)。 唐典勇 (TANG, Dianyong); 中国重庆市永川区红河大道 319 号重庆文理学院新药创制中心, Chongqing 402160 (CN)。
- (74) 代理人: 北京英赛嘉华知识产权代理有限公司 (INSIGHT INTELLECTUAL PROPERTY LIM-

ITED); 中国北京市海淀区知春路甲 48 号盈都大厦 A 座 19A, Beijing 100098 (CN)。

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— 包括国际检索报告(条约第 21 条(3))。

(54) Title: NOVEL PHOSPHODIESTERASE TYPE-5 INHIBITOR AND APPLICATION THEREOF

(54) 发明名称: 新的 5 型磷酸二酯酶抑制剂及其应用

(57) Abstract: Disclosed are a compound represented by general formula (I) as a phosphodiesterase type-5 inhibitor or pharmaceutically acceptable salt thereof and use thereof in treating and/or preventing diseases or disease states related to the phosphodiesterase type-5 in mammals.

(57) 摘要: 公开了作为 5 型磷酸二酯酶抑制剂的通式(I)表示的化合物或其药物可接受的盐及其在治疗和/或预防哺乳动物的与 5 型磷酸二酯酶相关的疾病或疾病状态中的用途

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6-(Benzo[d][1,3]dioxol-5-yl)-2-Substituted-2,3,12,12a-Tetrahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4(6H,7H)-dione Derivatives as Phosphodiesterase Type-5 Inhibitors

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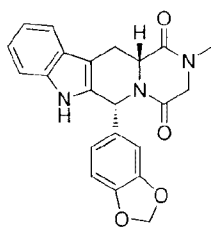
TECHNICAL FIELD

The present application relates to a pharmaceutical field. In Particular, the present application relates to selective inhibitors of phosphodiesterase type 5 (PDE5) and their utilities in the treatment and/or prevention of disease or conditions, wherein such inhibition is considered beneficial.

10

BACKGROUND

Erectile dysfunction (ED) has a significant impact on male mentality and physiology. It has been found that an inhibitor of PDE5 can effectively treat ED, such as Cialis from Eli Lilly and Company, whose chemical structure is shown as follows :



15

Cialis.

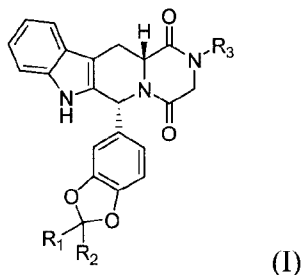
PDE5 inhibitors were found to improve erectile dysfunction caused by a variety of factors, and as for an onset time, there is no significant difference among various PDE5 inhibitors. However, in respect of a half-life, there is a greater difference among these pharmaceutical compounds. For example, Cialis has a half-life of up to 24-36 hours in a human body, while Viagra from Pfizer and Levitra from Bayer both have a half-life of about 4-5 hours.

Because of different half-life of a pharmaceutical compound, patients having different ages and different physical conditions will select pharmaceutical products with different half-lives to meet different requirements. However, there is a greater difference among the above-mentioned PDE5 inhibitors in half-life. Therefore, there is an urgent need for a novel PDE5 inhibitor.

25

SUMMARY

In one aspect, the present application is directed to a compound represented by formula (I) or a pharmaceutically acceptable salt thereof,



5 wherein

R₁ and R₂ are independently selected from the group consisting of hydrogen and deuterium;

R₃ is selected from the group consisting of hydrogen, -Q-OR₆, mercapto and -Q-NR₄R₅;

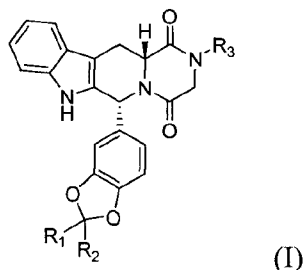
10 Q is absent or C₁-C₆ alkylene;

R₄ and R₅ are independently selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H; and

R₆ is selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H;

with the proviso that if both R₁ and R₂ are hydrogen, then R₃ is -Q-NR₄R₅, wherein Q is absent or C₁-C₆ alkylene, and one of R₄ and R₅ is hydrogen while the other of R₄ and R₅ is selected from the group consisting of -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H.

In another aspect, the present application is directed to a pharmaceutical composition, comprising a compound represented by formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient or diluent,



wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen and deuterium;

5 R_3 is selected from the group consisting of hydrogen, $-Q-OR_6$, mercapto and $-Q-NR_4R_5$;

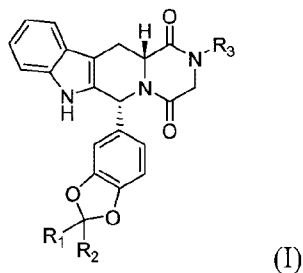
Q is absent or C_1-C_6 alkylene;

R_4 and R_5 are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, $-C(O)-C_1-C_6$ alkyl, $-C(O)-H$, $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$,
10 $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$; and

R_6 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, $-C(O)-C_1-C_6$ alkyl, $-C(O)-H$, $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$, $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$;

with the proviso that if both R_1 and R_2 are hydrogen, then R_3 is $-Q-NR_4R_5$, wherein
15 Q is absent or C_1-C_6 alkylene, and one of R_4 and R_5 is hydrogen while the other of R_4 and R_5 is selected from the group consisting of $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$, $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$.

In another aspect, the present application is directed to a use of a compound represented by formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical
20 composition comprising the same in the preparation of a medicament for treating and/or preventing a disease or condition related with phosphodiesterase type 5 in a mammal wherein an inhibition of phosphodiesterase type 5 is considered beneficial,



wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen and deuterium;

5 R_3 is selected from the group consisting of hydrogen, $-Q-OR_6$, mercapto and $-Q-NR_4R_5$;

Q is absent or C_1-C_6 alkylene;

R_4 and R_5 are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, $-C(O)-C_1-C_6$ alkyl, $-C(O)-H$, $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$, $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$; and

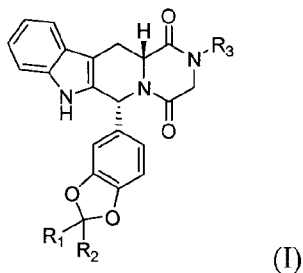
R_6 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, $-C(O)-C_1-C_6$ alkyl, $-C(O)-H$, $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$, $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$;

with the proviso that if both R_1 and R_2 are hydrogen, then R_3 is $-Q-NR_4R_5$, wherein

15 Q is absent or C_1-C_6 alkylene, and one of R_4 and R_5 is hydrogen while the other of R_4 and R_5 is selected from the group consisting of $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$, $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$.

In yet another aspect, the present application is directed to a method for treating and/or preventing a disease or condition related with phosphodiesterase type 5 in a mammal

20 wherein an inhibition of phosphodiesterase type 5 is considered beneficial, comprising administering to the mammal in need thereof a therapeutically effective amount of a compound represented by formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the same,



wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen and deuterium,

5 R_3 is selected from the group consisting of hydrogen, $-Q-OR_6$, mercapto and $-Q-NR_4R_5$,

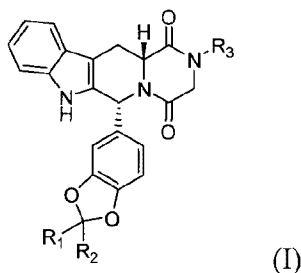
Q is absent or C_1-C_6 alkylene,

R_4 and R_5 are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, $-C(O)-C_1-C_6$ alkyl, $-C(O)-H$, $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$,
10 $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$, and

R_6 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, $-C(O)-C_1-C_6$ alkyl, $-C(O)-H$, $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$, $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$;

with the proviso that if both R_1 and R_2 are hydrogen, then R_3 is $-Q-NR_4R_5$, wherein
15 Q is absent or C_1-C_6 alkylene, and one of R_4 and R_5 is hydrogen while the other of R_4 and R_5 is selected from the group consisting of $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$, $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$.

In yet another aspect, the present application is directed to a compound represented by formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition
20 comprising the same for use in a method for treating and/or preventing a disease or condition related with phosphodiesterase type 5 in a mammal wherein an inhibition of phosphodiesterase type 5 is considered beneficial,



wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen and deuterium;

5 R_3 is selected from the group consisting of hydrogen, $-Q-OR_6$, mercapto and $-Q-NR_4R_5$;

Q is absent or C_1-C_6 alkylene;

R_4 and R_5 are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, $-C(O)-C_1-C_6$ alkyl, $-C(O)-H$, $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$,
10 $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$; and

R_6 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, $-C(O)-C_1-C_6$ alkyl, $-C(O)-H$, $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$, $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$;

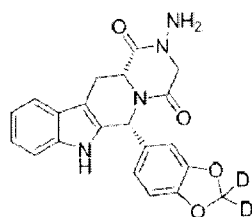
with the proviso that if both R_1 and R_2 are hydrogen, then R_3 is $-Q-NR_4R_5$, wherein
15 Q is absent or C_1-C_6 alkylene, and one of R_4 and R_5 is hydrogen while the other of R_4 and R_5 is selected from the group consisting of $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$, $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$.

In another aspect, the present application is directed to a method for inhibiting the activity of phosphodiesterase type 5, comprising contacting a compound represented by
20 formula (I) or a pharmaceutically acceptable salt thereof as defined in the above with phosphodiesterase type 5 in vitro or in vivo.

In another aspect, the present application is directed to a use of a compound represented by formula (I) or a pharmaceutically acceptable salt thereof as defined in the above as an inhibitor of phosphodiesterase type 5.

In yet another aspect, the present application is directed to a use of a compound represented by formula (I) or a pharmaceutically acceptable salt thereof as defined in the above as a medicament for treating and/or preventing erectile dysfunction in a human.

Various embodiments of the disclosure relate to a compound or a pharmaceutically acceptable salt thereof, wherein the compound is:



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Compound DDCI-01.

The claimed compound may be useful for treating and/or preventing a disease or condition related with a phosphodiesterase type 5 in a mammal.

The compound represented by formula (I) or a pharmaceutically acceptable salt thereof according to the present application has a good inhibition effect on PDE5 and a suitable half-life and an appropriate biological metabolism in body. Therefore, it is prone to being developed as a clinical drug.

15

DETAILED DESCRIPTION

In the following description, certain specific details are included to provide a thorough understanding of various disclosed embodiments. One of ordinary skill in the relevant art, however, will recognize that the embodiments may be practiced without one or more of these specific details, or with other methods, components, materials etc.

20

Unless the context required otherwise, throughout the specification and claims which follows, the term “comprise” and variations thereof, such as “comprises” and “comprising” are to be construed in an open, inclusive sense, which is as “include, but not limited to”.

25

Reference throughout this specification to “one embodiment”, or “an embodiment”, or “in another embodiment”, or “in some embodiments” means that a particular referent feature,

structure or characteristics described in connection with the embodiment is included in at least one embodiment. Therefore, the appearance of the phrases “in one embodiment” or “in the embodiment” or “in another embodiment” or “in some embodiments” in various places throughout this specification are not necessarily all referring to the same embodiment.

- 5 Moreover, the particular features, structures or characteristics may be combined in any suitable manner in one or more embodiments.

It should be noted that, as used in this specification and the appended claims, the singular forms “a”, “an” and “the” include plural referents unless the context clearly stated otherwise. It should be also noted that the use of “or” means “and/or” unless stated otherwise.

Definitions

Certain chemical groups named herein are preceded by a shorthand notation indicating the total number of carbon atoms that are to be found in the indicated chemical group. For example; C₁-C₆ alkyl describes an alkyl group, as defined below, having a total of 1 to 6 carbon atoms. The total number of carbons in the shorthand notation does not include carbons that may exist in substituents of the group described. As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated:

“Mercapto” refers to -SH.

“Cyano” refers to -CN.

“Amino” refers to -NH₂.

“Hydroxy” refers to -OH.

“Halo” refers to fluoro, chloro, bromo or iodo.

“Carboxy group” refers to -COOH.

“Sulfonic group” refers to -SO₃H.

“Sulfinic group” refers to -SO₂H.

“Alkyl” refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to six carbon atoms, and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), and the like. When specifically stated in the specification, an alkyl group may be optionally substituted by one or more of the following groups: alkyl, halo, cyano, hydroxy, mercapto, amino, carboxy, sulfonic group, and sulfinic group.

“Alkylene” or “alkylene chain” refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group or linking two parts of the molecule, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to six carbon atoms, *e.g.*, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene

chain links the rest of the molecule to a radical group or links two parts of the molecule through one carbon atom or any two carbon atoms in the alkylene chain.

“Optional” or “optionally” means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, “optionally substituted alkyl” means that the alkyl radical may or may not be substituted and that the description includes both substituted alkyl radicals and alkyl radicals having no substitution (“unsubstituted”).

The term “carrier” defines a compound that facilitates the incorporation of a compound into cells or tissues. For example, dimethylsulfoxide (DMSO) is generally used as a carrier, as it facilitates the uptake of many organic compounds into cells or tissues of an organism.

The term “pharmaceutically acceptable carrier” includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isosmotic agent, solvent, or emulsifier, *etc*, which has been approved by the China Food and Drug Administration as being acceptable for use in humans or animals and have no side effect on a pharmaceutical composition.

The term “pharmaceutically acceptable salts” means those salts which retain the biological effectiveness and properties of the PDE5 inhibitor used in the present application, and which are not biologically or otherwise undesirable. For example, a pharmaceutically acceptable salt does not interfere with the beneficial effect of an agent of the present application in inhibiting PDE5. The term “pharmaceutically acceptable salts” includes pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

The term “a pharmaceutically acceptable acid addition salt” refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as, but not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid

and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphanic acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleinic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, *p*-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid and the like.

The term "Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are

isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

The term “mammal” includes humans and both domestic animals, such as laboratory animals and household pets (e.g. cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and
5 non-domestic animals such as wildlife and the like.

The term “pharmaceutical composition” refers to a formulation of a compound of the present application and a medium generally acceptable in the art for the delivery of the biologically active compound to mammals, *e.g.* humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients. The pharmaceutical composition
10 is conducive to administration of a compound to an organism. There are various routes of administration of a compound or a pharmaceutical composition in the art including, but not limited to oral administration, injection administration, aerosol administration, parenteral administration and topical administration.

The term “pharmaceutically acceptable” defines a carrier, excipient or diluent that
15 does not abrogate the biological activities and properties of a compound.

The term “therapeutically effective amount” refers to that amount of a compound of the present application which, when administered to a mammal, preferably a human, is sufficient to effect treatment of a disease or condition related with PDE5 in a mammal, preferably a human. The amount of a compound of the present application which constitutes a
20 “therapeutically effective amount” will vary depending on the compound, the condition and its severity, and the age of the mammal to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

The term “treating” or “treatment” as used herein covers the treatment of the disease or condition of interest in a mammal, preferably a human, having the disease or disorder of
25 interest, and includes:

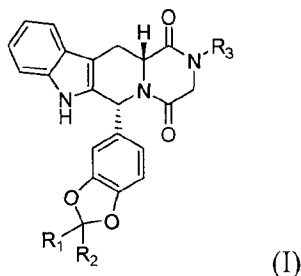
(i) preventing the disease or condition from occurring in a mammal, in particular, when such mammal is predisposed to the condition but has not yet been diagnosed as having it;

(ii) inhibiting the disease or condition, *i.e.* arresting its development; or

(iii) relieving the disease or condition, *i.e.* causing regression of the disease or condition.

Specific Embodiments

5 In one aspect, the present application is directed to a compound represented by formula (I) or a pharmaceutically acceptable salt thereof,



wherein

R₁ and R₂ are independently selected from the group consisting of hydrogen and
10 deuterium;

R₃ is selected from the group consisting of hydrogen, -Q-OR₆, mercapto and
-Q-NR₄R₅;

Q is absent or C₁-C₆ alkylene;

R₄ and R₅ are independently selected from the group consisting of hydrogen,
15 optionally substituted C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H,
-S(O)-C₁-C₆ alkyl, and -S(O)-H; and

R₆ is selected from the group consisting of hydrogen, optionally substituted C₁-C₆
alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and
-S(O)-H;

20 with the proviso that if both R₁ and R₂ are hydrogen, then R₃ is -Q-NR₄R₅, wherein
Q is absent or C₁-C₆ alkylene, and one of R₄ and R₅ is hydrogen while the other of R₄ and R₅
is selected from the group consisting of -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and
-S(O)-H.

In some embodiments, the present application is directed to the compound represented by formula (I) or a pharmaceutically acceptable salt thereof, wherein

R_1 and R_2 are both deuterium, or one of R_1 and R_2 is hydrogen and the other is deuterium;

5 R_3 is selected from the group consisting of hydrogen, -Q-OR₆, mercapto and -Q-NR₄R₅;

Q is absent or C₁-C₆ alkylene;

R_4 and R_5 are independently selected from the group consisting of hydrogen; -C(O)-C₁-C₆ alkyl; -C(O)-H; -S(O)₂-C₁-C₆ alkyl; -S(O)₂-H; -S(O)-C₁-C₆ alkyl; -S(O)-H; and
10 C₁-C₆ alkyl optionally substituted with a substituent selected from the group consisting of halo, cyano, hydroxy, amino, mercapto, carboxyl, sulfonic group, and sulfinic group; and

R_6 is selected from the group consisting of hydrogen; -C(O)-C₁-C₆ alkyl; -C(O)-H; -S(O)₂-C₁-C₆ alkyl; -S(O)₂-H; -S(O)-C₁-C₆ alkyl; -S(O)-H; and C₁-C₆ alkyl optionally substituted with a substituent selected from the group consisting of halo, cyano, hydroxy,
15 amino, mercapto, carboxyl, sulfonic group, and sulfinic group.

In some embodiments, the present application is directed to the compound represented by formula (I) or a pharmaceutically acceptable salt thereof, wherein

R_1 and R_2 are both deuterium, or one of R_1 and R_2 is hydrogen and the other is deuterium;

20 R_3 is selected from the group consisting of hydrogen, -Q-OR₆, mercapto and -Q-NR₄R₅;

Q is absent or (CH₂)_n, wherein n is an integer of 1-6;

R_4 and R_5 are independently selected from the group consisting of hydrogen, unsubstituted C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H,
25 -S(O)-C₁-C₆ alkyl, and -S(O)-H; and

R_6 is selected from the group consisting of hydrogen, unsubstituted C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H.

In some embodiments, the present application is directed to the compound represented by formula (I) or a pharmaceutically acceptable salt thereof, wherein

R₁ and R₂ are both deuterium, or one of R₁ and R₂ is hydrogen and the other is deuterium;

5 R₃ is selected from the group consisting of hydrogen, -Q-OR₆, and -Q-NR₄R₅;

Q is absent or (CH₂)_n, wherein n is an integer of 1-6;

R₄ and R₅ are independently selected from the group consisting of hydrogen, unsubstituted C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H; and

10 R₆ is selected from the group consisting of hydrogen and unsubstituted C₁-C₆ alkyl.

In some embodiments, the present application is directed to the compound represented by formula (I) or a pharmaceutically acceptable salt thereof, wherein

R₁ and R₂ are both deuterium, or one of R₁ and R₂ is hydrogen and the other is deuterium, and preferably R₁ and R₂ are both deuterium;

15 R₃ is -Q-NR₄R₅;

Q is absent or C₁-C₆ alkylene; and

R₄ and R₅ are independently selected from the group consisting of hydrogen; -C(O)-C₁-C₆ alkyl; -C(O)-H; -S(O)₂-C₁-C₆ alkyl; -S(O)₂-H; -S(O)-C₁-C₆ alkyl; -S(O)-H; and C₁-C₆ alkyl optionally substituted with a substituent selected from the group consisting of
20 halo, cyano, hydroxy, amino, mercapto, carboxy, sulfonic group, and sulfinic group.

In some embodiments, the present application is directed to the compound represented by formula (I) or a pharmaceutically acceptable salt thereof, wherein

R₁ and R₂ are both deuterium, or one of R₁ and R₂ is hydrogen and the other is deuterium, and preferably R₁ and R₂ are both deuterium;

25 R₃ is -Q-NR₄R₅;

Q is absent or (CH₂)_n, wherein n is an integer of 1-6; and

R₄ and R₅ are independently selected from the group consisting of hydrogen and unsubstituted C₁-C₆ alkyl.

In some embodiments, the present application is directed to the compound represented by formula (I) or a pharmaceutically acceptable salt thereof, wherein

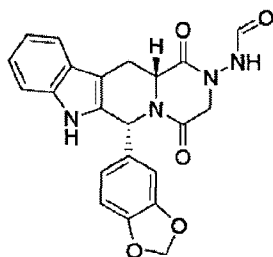
5 R₁ and R₂ are both hydrogen;

R₃ is -Q-NR₄R₅;

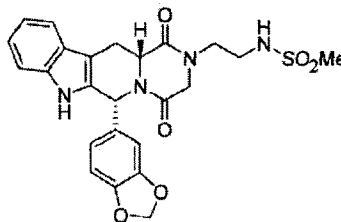
Q is absent or C₁-C₆ alkylene; and

one of R₄ and R₅ is hydrogen and the other is selected from the group consisting of -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H.

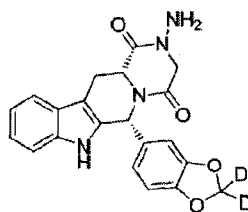
10 In some embodiments, the PDE5 inhibitor of the present application is preferably the following compounds:



Compound 1,



Compound 2, and



Compound 3.

The compound represented by formula (I) according to the present application is a
15 potent and selective inhibitor of PDE5, has a suitable half-life and an appropriate biological metabolism in body, and can meet a patient's requirement.

Pharmaceutical Compositions

In another aspect, the present application is directed to a pharmaceutical composition
20 comprising a pharmaceutically acceptable carrier, excipient, or diluent and a therapeutically

C1=CC=C2C(=C1)C(=C3C(=C2)C(=C4C(=C3)C(=C5C(=C4)C(=C6C(=C5)C(=C7C(=C6)C(=C8C(=C7)C(=C9C(=C8)C(=C10C(=C9)C(=C11C(=C10)C(=C12C(=C11)C(=C13C(=C12)C(=C14C(=C13)C(=C15C(=C14)C(=C16C(=C15)C(=C17C(=C16)C(=C18C(=C17)C(=C19C(=C18)C(=C20C(=C19)C(=C21C(=C20)C(=C22C(=C21)C(=C23C(=C22)C(=C24C(=C23)C(=C25C(=C24)C(=C26C(=C25)C(=C27C(=C26)C(=C28C(=C27)C(=C29C(=C28)C(=C30C(=C29)C(=C31C(=C30)C(=C32C(=C31)C(=C33C(=C32)C(=C34C(=C33)C(=C35C(=C34)C(=C36C(=C35)C(=C37C(=C36)C(=C38C(=C37)C(=C39C(=C38)C(=C40C(=C39)C(=C41C(=C40)C(=C42C(=C41)C(=C43C(=C42)C(=C44C(=C43)C(=C45C(=C44)C(=C46C(=C45)C(=C47C(=C46)C(=C48C(=C47)C(=C49C(=C48)C(=C50C(=C49)C(=C51C(=C50)C(=C52C(=C51)C(=C53C(=C52)C(=C54C(=C53)C(=C55C(=C54)C(=C56C(=C55)C(=C57C(=C56)C(=C58C(=C57)C(=C59C(=C58)C(=C60C(=C59)C(=C61C(=C60)C(=C62C(=C61)C(=C63C(=C62)C(=C64C(=C63)C(=C65C(=C64)C(=C66C(=C65)C(=C67C(=C66)C(=C68C(=C67)C(=C69C(=C68)C(=C70C(=C69)C(=C71C(=C70)C(=C72C(=C71)C(=C73C(=C72)C(=C74C(=C73)C(=C75C(=C74)C(=C76C(=C75)C(=C77C(=C76)C(=C78C(=C77)C(=C79C(=C78)C(=C80C(=C79)C(=C81C(=C80)C(=C82C(=C81)C(=C83C(=C82)C(=C84C(=C83)C(=C85C(=C84)C(=C86C(=C85)C(=C87C(=C86)C(=C88C(=C87)C(=C89C(=C88)C(=C90C(=C89)C(=C91C(=C90)C(=C92C(=C91)C(=C93C(=C92)C(=C94C(=C93)C(=C95C(=C94)C(=C96C(=C95)C(=C97C(=C96)C(=C98C(=C97)C(=C99C(=C98)C(=C100C(=C99)C(=C101C(=C100)C(=C102C(=C101)C(=C103C(=C102)C(=C104C(=C103)C(=C105C(=C104)C(=C106C(=C105)C(=C107C(=C106)C(=C108C(=C107)C(=C109C(=C108)C(=C110C(=C109)C(=C111C(=C110)C(=C112C(=C111)C(=C113C(=C112)C(=C114C(=C113)C(=C115C(=C114)C(=C116C(=C115)C(=C117C(=C116)C(=C118C(=C117)C(=C119C(=C118)C(=C120C(=C119)C(=C121C(=C120)C(=C122C(=C121)C(=C123C(=C122)C(=C124C(=C123)C(=C125C(=C124)C(=C126C(=C125)C(=C127C(=C126)C(=C128C(=C127)C(=C129C(=C128)C(=C130C(=C129)C(=C131C(=C130)C(=C132C(=C131)C(=C133C(=C132)C(=C134C(=C133)C(=C135C(=C134)C(=C136C(=C135)C(=C137C(=C136)C(=C138C(=C137)C(=C139C(=C138)C(=C140C(=C139)C(=C141C(=C140)C(=C142C(=C141)C(=C143C(=C142)C(=C144C(=C143)C(=C145C(=C144)C(=C146C(=C145)C(=C147C(=C146)C(=C148C(=C147)C(=C149C(=C148)C(=C150C(=C149)C(=C151C(=C150)C(=C152C(=C151)C(=C153C(=C152)C(=C154C(=C153)C(=C155C(=C154)C(=C156C(=C155)C(=C157C(=C156)C(=C158C(=C157)C(=C159C(=C158)C(=C160C(=C159)C(=C161C(=C160)C(=C162C(=C161)C(=C163C(=C162)C(=C164C(=C163)C(=C165C(=C164)C(=C166C(=C165)C(=C167C(=C166)C(=C168C(=C167)C(=C169C(=C168)C(=C170C(=C169)C(=C171C(=C170)C(=C172C(=C171)C(=C173C(=C172)C(=C174C(=C173)C(=C175C(=C174)C(=C176C(=C175)C(=C177C(=C176)C(=C178C(=C177)C(=C179C(=C178)C(=C180C(=C179)C(=C181C(=C180)C(=C182C(=C181)C(=C183C(=C182)C(=C184C(=C183)C(=C185C(=C184)C(=C186C(=C185)C(=C187C(=C186)C(=C188C(=C187)C(=C189C(=C188)C(=C190C(=C189)C(=C191C(=C190)C(=C192C(=C191)C(=C193C(=C192)C(=C194C(=C193)C(=C195C(=C194)C(=C196C(=C195)C(=C197C(=C196)C(=C198C(=C197)C(=C199C(=C198)C(=C200C(=C199)C(=C201C(=C200)C(=C202C(=C201)C(=C203C(=C202)C(=C204C(=C203)C(=C205C(=C204)C(=C206C(=C205)C(=C207C(=C206)C(=C208C(=C207)C(=C209C(=C208)C(=C210C(=C209)C(=C211C(=C210)C(=C212C(=C211)C(=C213C(=C212)C(=C214C(=C213)C(=C215C(=C214)C(=C216C(=C215)C(=C217C(=C216)C(=C218C(=C217)C(=C219C(=C218)C(=C220C(=C219)C(=C221C(=C220)C(=C222C(=C221)C(=C223C(=C222)C(=C224C(=C223)C(=C225C(=C224)C(=C226C(=C225)C(=C227C(=C226)C(=C228C(=C227)C(=C229C(=C228)C(=C230C(=C229)C(=C231C(=C230)C(=C232C(=C231)C(=C233C(=C232)C(=C234C(=C233)C(=C235C(=C234)C(=C236C(=C235)C(=C237C(=C236)C(=C238C(=C237)C(=C239C(=C238)C(=C240C(=C239)C(=C241C(=C240)C(=C242C(=C241)C(=C243C(=C242)C(=C244C(=C243)C(=C245C(=C244)C(=C246C(=C245)C(=C247C(=C246)C(=C248C(=C247)C(=C249C(=C248)C(=C250C(=C249)C(=C251C(=C250)C(=C252C(=C251)C(=C253C(=C252)C(=C254C(=C253)C(=C255C(=C254)C(=C256C(=C255)C(=C257C(=C256)C(=C258C(=C257)C(=C259C(=C258)C(=C260C(=C259)C(=C261C(=C260)C(=C262C(=C261)C(=C263C(=C262)C(=C264C(=C263)C(=C265C(=C264)C(=C266C(=C265)C(=C267C(=C266)C(=C268C(=C267)C(=C269C(=C268)C(=C270C(=C269)C(=C271C(=C270)C(=C272C(=C271)C(=C273C(=C272)C(=C274C(=C273)C(=C275C(=C274)C(=C276C(=C275)C(=C277C(=C276)C(=C278C(=C277)C(=C279C(=C278)C(=C280C(=C279)C(=C281C(=C280)C(=C282C(=C281)C(=C283C(=C282)C(=C284C(=C283)C(=C285C(=C284)C(=C286C(=C285)C(=C287C(=C286)C(=C288C(=C287)C(

R₁ and R₂ are both deuterium, or one of R₁ and R₂ is hydrogen and the other is deuterium, and preferably R₁ and R₂ are both deuterium;

R₃ is -Q-NR₄R₅;

Q is absent or C₁-C₆ alkylene; and

R₄ and R₅ are independently selected from the group consisting of hydrogen; -C(O)-C₁-C₆ alkyl; -C(O)-H; -S(O)₂-C₁-C₆ alkyl; -S(O)₂-H; -S(O)-C₁-C₆ alkyl; -S(O)-H; and
5 C₁-C₆ alkyl optionally substituted with a substituent selected from the group consisting of halo, cyano, hydroxy, amino, mercapto, carboxy, sulfonic group, and sulfinic group.

In some embodiments, when R₁ and R₂ are both deuterium, R₃ is -Q-NR₄R₅; Q is absent; and R₄ and R₅ are both hydrogen.

In some embodiments, when R₁ and R₂ are both hydrogen, R₃ is -Q-NR₄R₅; Q is
10 absent or C₁-C₆ alkylene; and one of R₄ and R₅ is hydrogen and the other is selected from the group consisting of -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H.

In some embodiments, the pharmaceutical composition is formulated into a dosage form suitable for oral administration, buccal administration, intravenous injection, intraperitoneal injection, subcutaneous injection, intramuscular injection, inhalation, or
15 epidermal administration, preferable oral administration and buccal administration.

In some embodiments, the pharmaceutical composition is formulated into tablets, lozenges, pills, capsules, granules, powders, solutions, emulsions, suspensions, dispersions, syrups, gels, or aerosols.

In some embodiments, the pharmaceutical composition further comprises
20 pharmaceutically acceptable surfactants, film forming substances, coating assistants, stabilizers, dyes, flavoring agents, fragrances, excipients, lubricants, disintegrants, glidants, solubilizers, fillers, solvents, diluents, suspending agents, osmoregulators, buffers, preservatives, antioxidants, sweetening agents, colorants and/or binders. Acceptable excipients, carriers or diluents for therapeutic use are well-known in the art, and are described,
25 for example, in Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co., Easton, PA (1990), which is incorporated herein by reference in its entirety.

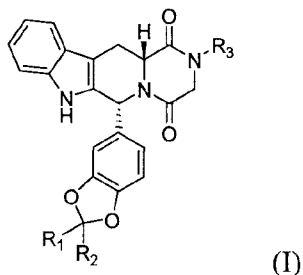
Pharmaceutical compositions of the present application may be manufactured in manner that is itself known, for example, by means of conventional mixing, dissolving,

granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or tableting processes.

Pharmaceutical compositions for use in accordance with the present application therefore may be formulated by a conventional manner using one or more pharmaceutically acceptable carriers, excipients, diluents and/or auxiliaries which facilitate processing the active compounds into a pharmaceutical preparation. Proper formulation is dependent on the selected administration route. Any of the suitable formulation techniques, carriers and excipients in the art can be used in the preparation of the pharmaceutical composition.

10 Therapeutic Uses and Methods of Treatment

In another aspect, the present application is directed to a use of a compound represented by formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the same in the preparation of a medicament for treating and/or preventing a disease or condition related with phosphodiesterase type 5 in a mammal wherein an inhibition of phosphodiesterase type 5 is considered beneficial,



wherein

R₁ and R₂ are independently selected from the group consisting of hydrogen and deuterium;

20 R₃ is selected from the group consisting of hydrogen, -Q-OR₆, mercapto and -Q-NR₄R₅;

Q is absent or C₁-C₆ alkylene;

R₄ and R₅ are independently selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H; and

R₆ is selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H;

with the proviso that if both R₁ and R₂ are hydrogen, then R₃ is -Q-NR₄R₅, wherein Q is absent or C₁-C₆ alkylene, and one of R₄ and R₅ is hydrogen while the other of R₄ and R₅ is selected from the group consisting of -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H.

In some embodiments, the present application is directed to the compound represented by formula (I) or a pharmaceutically acceptable salt thereof, wherein

R₁ and R₂ are both deuterium, or one of R₁ and R₂ is hydrogen and the other is deuterium, and preferably R₁ and R₂ are both deuterium;

R₃ is -Q-NR₄R₅;

Q is absent or C₁-C₆ alkylene; and

R₄ and R₅ are independently selected from the group consisting of hydrogen; -C(O)-C₁-C₆ alkyl; -C(O)-H; -S(O)₂-C₁-C₆ alkyl; -S(O)₂-H; -S(O)-C₁-C₆ alkyl; -S(O)-H; and C₁-C₆ alkyl optionally substituted with a substituent selected from the group consisting of halo, cyano, hydroxy, amino, mercapto, carboxy, sulfonic group, and sulfinic group.

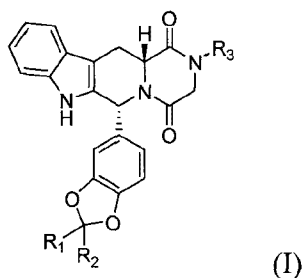
In some embodiments, when R₁ and R₂ are both deuterium, R₃ is -Q-NR₄R₅; Q is absent; and R₄ and R₅ are both hydrogen.

In some embodiments, when R₁ and R₂ are both hydrogen, R₃ is -Q-NR₄R₅; Q is absent or C₁-C₆ alkylene; and one of R₄ and R₅ is hydrogen and the other is selected from the group consisting of -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H.

In some embodiments, the mammal is preferably a human.

In some embodiments, the disease or condition related with phosphodiesterase type 5 is erectile dysfunction.

In yet another aspect, the present application is directed to a method for treating and/or preventing a disease or condition related with phosphodiesterase type 5 in a mammal wherein an inhibition of phosphodiesterase type 5 is considered beneficial, comprising administering to the mammal in need thereof a therapeutically effective amount of a compound represented by formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the same,



wherein

R₁ and R₂ are independently selected from the group consisting of hydrogen and deuterium;

R₃ is selected from the group consisting of hydrogen, -Q-OR₆, mercapto and -Q-NR₄R₅;

Q is absent or C₁-C₆ alkylene;

R₄ and R₅ are independently selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H; and

R₆ is selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H;

with the proviso that if both R₁ and R₂ are hydrogen, then R₃ is -Q-NR₄R₅, wherein Q is absent or C₁-C₆ alkylene, and one of R₄ and R₅ is hydrogen while the other of R₄ and R₅

is selected from the group consisting of $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$, $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$.

In some embodiments, the present application is directed to the compound represented by formula (I) or a pharmaceutically acceptable salt thereof, wherein R_1 and R_2 are both deuterium, or one of R_1 and R_2 is hydrogen and the other is deuterium, and preferably R_1 and R_2 are both deuterium; R_3 is $-Q-NR_4R_5$; Q is absent or C_1-C_6 alkylene; and R_4 and R_5 are independently selected from the group consisting of hydrogen; $-C(O)-C_1-C_6$ alkyl; $-C(O)-H$; $-S(O)_2-C_1-C_6$ alkyl; $-S(O)_2-H$; $-S(O)-C_1-C_6$ alkyl; $-S(O)-H$; and C_1-C_6 alkyl optionally substituted with a substituent selected from the group consisting of halo, cyano, hydroxy, amino, mercapto, carboxy, sulfonic group, and sulfinic group.

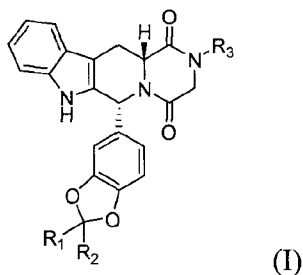
In some embodiments, when R_1 and R_2 are both deuterium, R_3 is $-Q-NR_4R_5$; Q is absent; and R_4 and R_5 are both hydrogen.

In some embodiments, when R_1 and R_2 are both hydrogen; R_3 is $-Q-NR_4R_5$; Q is absent or C_1-C_6 alkylene; and one of R_4 and R_5 is hydrogen and the other is selected from the group consisting of $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$, $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$.

In some embodiments, the mammal in the method for treating and/or preventing a disease or condition related with PDE5 is preferably a human.

In some embodiments, the disease or condition related with phosphodiesterase type 5 in the method for treating and/or preventing a disease or condition related with PDE5 is erectile dysfunction.

In yet another aspect, the present application is directed to a compound represented by formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the same for use in a method for treating and/or preventing a disease or condition related with phosphodiesterase type 5 in a mammal wherein an inhibition of phosphodiesterase type 5 is considered beneficial,



wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen and deuterium;

5 R_3 is selected from the group consisting of hydrogen, $-Q-OR_6$, mercapto and $-Q-NR_4R_5$;

Q is absent or C_1-C_6 alkylene;

R_4 and R_5 are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, $-C(O)-C_1-C_6$ alkyl, $-C(O)-H$, $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$,
10 $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$; and

R_6 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, $-C(O)-C_1-C_6$ alkyl, $-C(O)-H$, $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$, $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$;

with the proviso that if both R_1 and R_2 are hydrogen, then R_3 is $-Q-NR_4R_5$, wherein
15 Q is absent or C_1-C_6 alkylene, and one of R_4 and R_5 is hydrogen while the other of R_4 and R_5 is selected from the group consisting of $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$, $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$.

In some embodiments, the present application is directed to the compound represented by formula (I) or a pharmaceutically acceptable salt thereof, wherein

20 R_1 and R_2 are both deuterium, or one of R_1 and R_2 is hydrogen and the other is deuterium, and preferably R_1 and R_2 are both deuterium;

R_3 is $-Q-NR_4R_5$;

Q is absent or C_1-C_6 alkylene; and

R_4 and R_5 are independently selected from the group consisting of hydrogen; -C(O)-C₁-C₆ alkyl; -C(O)-H; -S(O)₂-C₁-C₆ alkyl; -S(O)₂-H; -S(O)-C₁-C₆ alkyl; -S(O)-H; and C₁-C₆ alkyl optionally substituted with a substituent selected from the group consisting of halo, cyano, hydroxy, amino, mercapto, carboxy, sulfonic group, and sulfinic group.

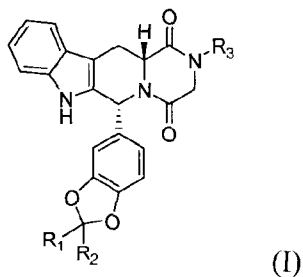
5 In some embodiments, when R_1 and R_2 are both deuterium, R_3 is -Q-NR₄R₅; Q is absent; and R_4 and R_5 are both hydrogen.

In some embodiments, when R_1 and R_2 are both hydrogen, R_3 is -Q-NR₄R₅; Q is absent or C₁-C₆ alkylene; and one of R_4 and R_5 is hydrogen and the other is selected from the group consisting of -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H.

10 In some embodiments, the mammal is preferably a human.

In some embodiments, the disease or condition related with phosphodiesterase type 5 is erectile dysfunction.

In another aspect, the present application is directed to a method for inhibiting the activity of phosphodiesterase type 5, comprising contacting a compound represented by
15 formula (I) or a pharmaceutically acceptable salt thereof with phosphodiesterase type 5 in vitro or in vivo,



wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen and
20 deuterium;

R_3 is selected from the group consisting of hydrogen, -Q-OR₆, mercapto and -Q-NR₄R₅;

Q is absent or C₁-C₆ alkylene;

R₄ and R₅ are independently selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H; and

R₆ is selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H;

with the proviso that if both R₁ and R₂ are hydrogen, then R₃ is -Q-NR₄R₅, wherein Q is absent or C₁-C₆ alkylene, and one of R₄ and R₅ is hydrogen while the other of R₄ and R₅ is selected from the group consisting of -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H.

In some embodiments, the present application is directed to the compound represented by formula (I) or a pharmaceutically acceptable salt thereof, wherein

R₁ and R₂ are both deuterium, or one of R₁ and R₂ is hydrogen and the other is deuterium, and preferably R₁ and R₂ are both deuterium;

R₃ is -Q-NR₄R₅;

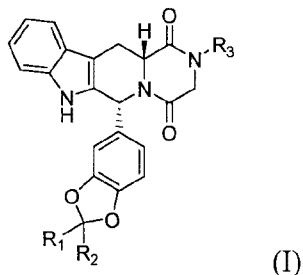
Q is absent or C₁-C₆ alkylene; and

R₄ and R₅ are independently selected from the group consisting of hydrogen; -C(O)-C₁-C₆ alkyl; -C(O)-H; -S(O)₂-C₁-C₆ alkyl; -S(O)₂-H; -S(O)-C₁-C₆ alkyl; -S(O)-H; and C₁-C₆ alkyl optionally substituted with a substituent selected from the group consisting of halo, cyano, hydroxy, amino, mercapto, carboxy, sulfonic group, and sulfinic group.

In some embodiments, when R₁ and R₂ are both deuterium, R₃ is -Q-NR₄R₅; Q is absent; and R₄ and R₅ are both hydrogen.

In some embodiments, when R₁ and R₂ are both hydrogen, R₃ is -Q-NR₄R₅; Q is absent or C₁-C₆ alkylene; and one of R₄ and R₅ is hydrogen and the other is selected from the group consisting of -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H.

In yet another aspect, the present application is directed to a compound represented by formula (I) or a pharmaceutically acceptable salt thereof used as an inhibitor of phosphodiesterase type 5,



5 wherein

R₁ and R₂ are independently selected from the group consisting of hydrogen and deuterium;

R₃ is selected from the group consisting of hydrogen, -Q-OR₆, mercapto and -Q-NR₄R₅;

10 Q is absent or C₁-C₆ alkylene;

R₄ and R₅ are independently selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H; and

R₆ is selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H;

15 with the proviso that if both R₁ and R₂ are hydrogen, then R₃ is -Q-NR₄R₅, wherein Q is absent or C₁-C₆ alkylene, and one of R₄ and R₅ is hydrogen while the other of R₄ and R₅ is selected from the group consisting of -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and
20 -S(O)-H.

In some embodiments, the present application is directed to the compound represented by formula (I) or a pharmaceutically acceptable salt thereof, wherein

R_1 and R_2 are both deuterium, or one of R_1 and R_2 is hydrogen and the other is deuterium, and preferably R_1 and R_2 are both deuterium;

R_3 is $-Q-NR_4R_5$;

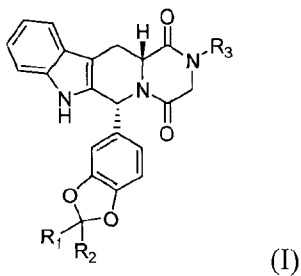
Q is absent or C_1 - C_6 alkylene; and

5 R_4 and R_5 are independently selected from the group consisting of hydrogen; $-C(O)-C_1-C_6$ alkyl; $-C(O)-H$; $-S(O)_2-C_1-C_6$ alkyl; $-S(O)_2-H$; $-S(O)-C_1-C_6$ alkyl; $-S(O)-H$; and C_1-C_6 alkyl optionally substituted with a substituent selected from the group consisting of halo, cyano, hydroxy, amino, mercapto, carboxy, sulfonic group, and sulfinic group.

10 In some embodiments, when R_1 and R_2 are both deuterium, R_3 is $-Q-NR_4R_5$; Q is absent; and R_4 and R_5 are both hydrogen.

In some embodiments, when R_1 and R_2 are both hydrogen, R_3 is $-Q-NR_4R_5$; Q is absent or C_1 - C_6 alkylene; and one of R_4 and R_5 is hydrogen and the other is selected from the group consisting of $-S(O)_2-C_1-C_6$ alkyl, $-S(O)_2-H$, $-S(O)-C_1-C_6$ alkyl, and $-S(O)-H$.

15 In yet another aspect, the present application is directed to a method for treating erectile dysfunction in a human, comprising administering to the human in need thereof a compound represented by formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the same,



wherein

20 R_1 and R_2 are independently selected from the group consisting of hydrogen and deuterium;

R_3 is selected from the group consisting of hydrogen, $-Q-OR_6$, mercapto and $-Q-NR_4R_5$;

Q is absent or C_1 - C_6 alkylene;

R₄ and R₅ are independently selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H; and

R₆ is selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, -C(O)-C₁-C₆ alkyl, -C(O)-H, -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H;

with the proviso that if both R₁ and R₂ are hydrogen, then R₃ is -Q-NR₄R₅, wherein Q is absent or C₁-C₆ alkylene, and one of R₄ and R₅ is hydrogen while the other of R₄ and R₅ is selected from the group consisting of -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H.

In some embodiments, the present application is directed to the compound represented by formula (I) or a pharmaceutically acceptable salt, wherein R₁ and R₂ are both deuterium, or one of R₁ and R₂ is hydrogen and the other is deuterium, and preferably R₁ and R₂ are both deuterium; R₃ is -Q-NR₄R₅; Q is absent or C₁-C₆ alkylene; and R₄ and R₅ are independently selected from the group consisting of hydrogen; -C(O)-C₁-C₆ alkyl; -C(O)-H; -S(O)₂-C₁-C₆ alkyl; -S(O)₂-H; -S(O)-C₁-C₆ alkyl; -S(O)-H; and C₁-C₆ alkyl optionally substituted with a substituent selected from the group consisting of halo, cyano, hydroxy, amino, mercapto, carboxy, sulfonic group, and sulfinic group.

In some embodiments, when R₁ and R₂ are both deuterium, R₃ is -Q-NR₄R₅; Q is absent; and R₄ and R₅ are both hydrogen.

In some embodiments, when R₁ and R₂ are both hydrogen, R₃ is -Q-NR₄R₅; Q is absent or C₁-C₆ alkylene; and one of R₄ and R₅ is hydrogen and the other is selected from the group consisting of -S(O)₂-C₁-C₆ alkyl, -S(O)₂-H, -S(O)-C₁-C₆ alkyl, and -S(O)-H.

25 Formulations, Routes of Administration, and Effective Doses

In yet another aspect, the present application relates to formulations comprising the compound represented by formula (I) or the pharmaceutically acceptable salt thereof, routes

of administration and effective doses for the formulations. Such pharmaceutical formulations can be used to treat a disease or condition related with PDE5 as described above.

The compound represented by formula (I) or the pharmaceutically acceptable salt thereof of the present application can be administered as pharmaceutical formulations, including but not limited to those suitable for oral (including buccal and sub-lingual), topical, or parenteral (including intramuscular, intradermal, intraperitoneal, subcutaneous and intravenous) administration or in a form suitable for administration by aerosolization, inhalation or insufflation. General information on drug delivery systems can be found in Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems (Lippencott Williams & Wilkins, Baltimore Md. (1999)).

In various aspects, the pharmaceutical formulations includes carriers and excipients (including but not limited to buffers, carbohydrates, antioxidants, bacteriostats, chelating agents, suspending agents, thickening agents and/or preservatives), water, oils, saline solutions, flavoring agents, coloring agents, detackifiers and other acceptable additives, adjuvants, or binders, other pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH buffering agents, tonicity adjusting agents, emulsifying agents, wetting agents, preservatives and the like. It will be recognized that, while any suitable carrier known to those of ordinary skill in the art can be employed to administer the pharmaceutical formulations of the present application, the type of carrier will vary depending on the routes of administration.

The concentration of the compound can be adjusted, the pH of the solution can be buffered and the isotonicity can be adjusted to be compatible with intravenous injection, as is well known in the art.

The compound represented by formula (I) or the pharmaceutically acceptable salt thereof of the present application can be formulated as a sterile solution or suspension, in suitable vehicles, well known in the art. The pharmaceutical compositions can be sterilized by conventional, well-known sterilization techniques, or can be sterile filtered. The resulting

aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile solution prior to administration.

For oral administration, the compound represented by formula (I) or the pharmaceutically acceptable salt thereof of the present application can be formulated readily
5 by combining the active agent with pharmaceutically acceptable carriers well known in the art. Such carriers enable the agent of the present application to be formulated as tablets, pills, dragees, capsules, lozenges, liquids, gels, syrups, powders, suspensions, elixirs, and the like, for oral ingestion by a patient to be treated.

Pharmaceutical compositions suitable for use in the present application include
10 compositions wherein the active ingredients are present in an effective amount, i.e., in an amount effective to achieve therapeutic and/or prophylactic benefit in a subject. The actual amount effective for a particular application will depend on the condition or conditions being treated, the condition of the subject, the formulation, and the route of administration, as well as other factors known to those of skill in the art. Determination of an effective amount of a
15 PDE5 inhibitor is well within the capabilities of those skilled in the art, in light of the disclosure herein, and the effective amount will be determined using routine optimization techniques.

The effective amount for use in humans can be determined from animal models. For example, a dose for humans can be formulated to achieve circulating, liver, topical and/or
20 gastrointestinal concentrations that have been found to be effective in animals. One skilled in the art can determine the effective amount for human use, especially in light of the animal model experimental data described herein. Based on animal data, and other types of similar data, those skilled in the art can determine the effective amounts of compositions of the present application appropriate for humans.

25 The effective amount when referring to an inhibitor of PDE5 of the present application will generally mean the dose ranges, routes of administration, formulations, etc., that have been recommended or approved by any of the various regulatory or advisory

organizations in the medical or pharmaceutical arts (e.g., FDA, SDA) or by the manufacturer or supplier.

Further, appropriate doses for a PDE5 inhibitor can be determined based on in vitro experimental results. For example, the in vitro potency of an agent in inhibiting PDE5 provides information useful in the development of effective in vivo dosages to achieve similar biological effects.

Having now generally described various aspects of the present application, the same will be more readily understood through reference to the following examples which are provided by way of illustration, and are not intended to be limiting, unless specified.

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EXAMPLES

Example 1 Synthesis of Compound 3 (Compound No. DDCI01)

Step 1.

15

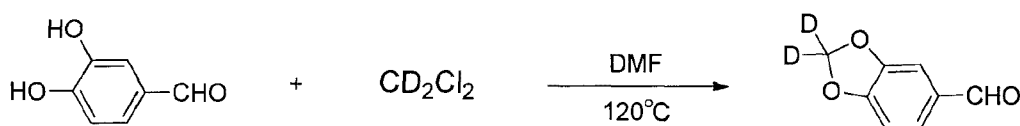


Table A

Reagent	Mw.	eq.	Wt. or Vol.
3,4-Dihydroxybenzaldehyde	138	1.0eq	27.6g (0.2mol)
CD_2Cl_2	87	3.0eq	50.0g (0.6mol)
Cs_2CO_3	326	1.5eq	100g
KI	166	0.1eq	4.0g
DMF			200mL

To 500 mL round bottle flask equipped with a reflux condenser were added the reagents and solvents as showed in Table A. The resulting reaction mixture was heated and

refluxed at 120 °C for 6 h under nitrogen atmosphere and stirring or until TLC indicated the completion of the reaction. Then, the reaction mixture was allowed to cool to room temperature, filtered to remove Cs₂CO₃ solid, and the filter cake was washed with dichloromethane. Subsequently, the filtrate was concentrated to dryness under reduced pressure, and the resulting residue was dissolved in dichloromethane, and washed sequentially with water and a saturated solution of NaCl. The organic phase was dried over anhydrous MgSO₄, filtered, and concentrated to dryness under reduced pressure to give a crude product. The crude product was purified by a silica gel column chromatography to afford 24.4 g of pure title compound as a white solid with 80% yield.

Step 2.

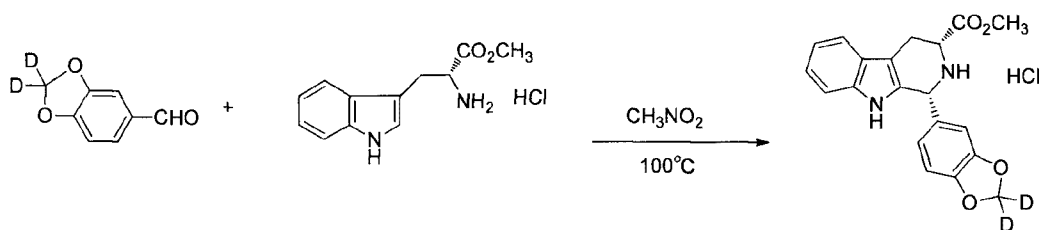


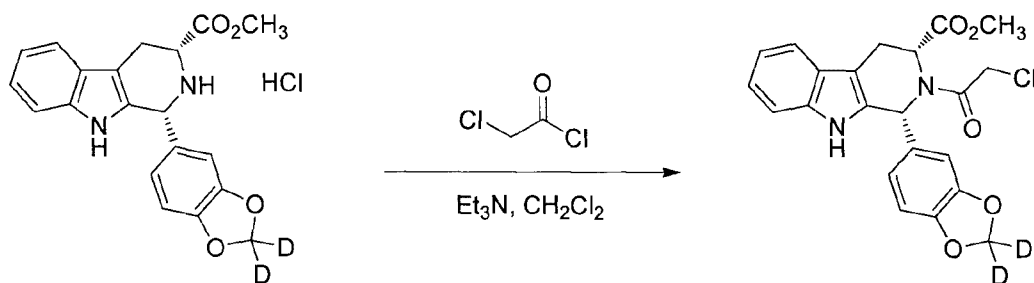
Table B

reagent	Mw.	eq.	Wt. or Vol.
Product obtained from Step 1	152	1.0eq	24.4g (0.16mol)
D-tryptophan methyl ester hydrochloride	255	1.0eq	41.0g (0.16mol)
CH ₃ NO ₂			200mL

To 500 mL round bottle flask equipped with a reflux condenser were added the reagents and solvents as showed in Table B. The resulting reaction mixture was refluxed at 100 °C for 6 h under stirring or until TLC indicated the completion of the reaction. Then, the reaction mixture was cooled to room temperature, then cooled to 0 °C and was allowed to stand at 0 °C overnight to precipitate a solid. The resulting solid was filtered and washed with

a small amount of CH_3NO_2 and subsequently with dichloromethane. After dried in vacuum, 60.0g of title compound as a white solid was obtained with 96% of yield.

Step 3.



5

Table C

Reagent	Mw.	eq.	Wt. or Vol.
Product obtained from Step 2	389	1.0eq	44.0g (0.11mol)
Et_3N	101	3.0eq	45mL (0.33mol)
chloroacetyl chloride	113	1.5	17.0g (0.22mol)
CH_2Cl_2			500mL

400 mL dichloromethane, the product obtained from Step 2 (44.0g, 0.11 mol) and Et_3N (45.0 mL, 0.33 mol) were added to a 1000 mL of round bottle flask and stirred to obtain a clear solution at room temperature. After cooling to 0 °C in an ice bath, a solution of chloroacetyl chloride (17.0g, 0.22 mol) in 100 mL dichloromethane was slowly added dropwise, and meanwhile the reaction temperature was kept at 0 °C to 5 °C. After the completion of addition, the resulting reaction mixture was continuously stirred in an ice bath (0 °C to 5 °C) until TLC indicated the completion of the reaction. The resulting reaction mixture was filtered and the filter cake was washed with a small amount of dichloromethane and dried to give 32.4g of white solid that contains $\text{Et}_3\text{N} \cdot \text{HCl}$ salt and was used for the next reaction without purification.

10

15

The filtrate was washed with 10% K_2CO_3 aqueous solution and then a saturated aqueous solution of NaCl. The resulting organic phase was dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was recrystallized with $CH_3OH:H_2O=4:1$ to give 31.0 g of the title compound as a light brown solid.

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Step 4.

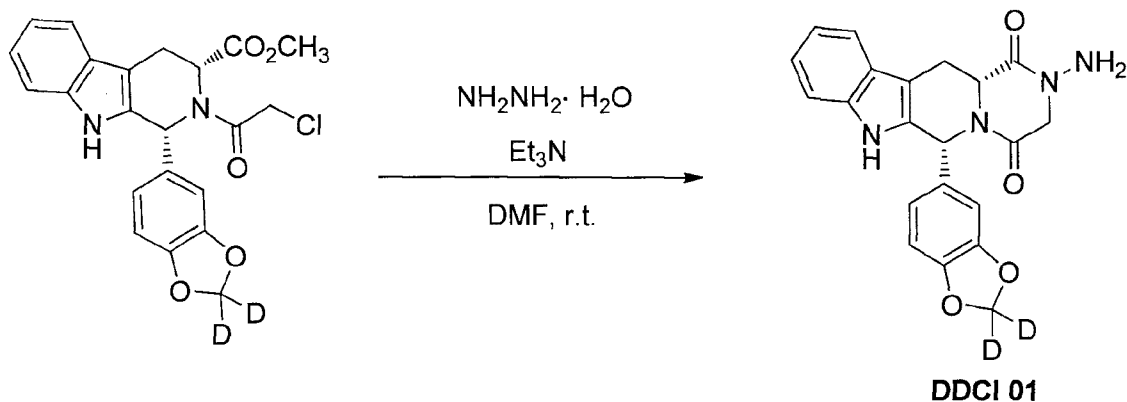


Table D

reagent	Mw.	eq.	Wt. or Vol.
Product obtained from Step 3	429	1.0eq	63.4g
Et_3N	101	3.0eq	60mL
hydrazine hydrate	50	5.0eq	35g
DMF			400mL

To a 1000 mL round bottle flask were added the product obtained from Step 3 (63.4g), Et_3N (60 mL) and DMF, and then a solution of hydrazine hydrate (35.0g) in DMF was slowly added dropwise at room temperature. The resulting reaction mixture was stirred overnight at room temperature until TLC indicated the completion of the reaction. 3 times volume of purified water was slowly added to the resulting reaction mixture at 0 °C with vigorous stirring for 2h. A white solid was precipitated, filtered and washed with water and

15

isopropyl alcohol to obtain a crude product. The crude product was dried in vacuum and diluted with a small amount of CHCl_3 and refluxed for 20 min. The solid was filtered again and dried in vacuum to give 35.5g of pure title compound as a white solid with 82% yield for two steps.

5 ^1H NMR (d-DMSO, 400M): 11.01 (s, 1H), 7.55 (d, $J = 7.6$ Hz, 1H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.07 (t, $J = 7.2$ Hz, 1H), 7.02 (t, $J = 7.2$ Hz, 1H), 6.87 (d, $J = 1.2$ Hz, 1H), 6.80 (dd, $J = 8.4, 1.6$ Hz, 1H), 6.77 (d, $J = 8.0$ Hz, 1H), 6.09 (s, 1H), 5.12 (s, 2H), 4.44 (dd, $J = 11.6, 3.6$ Hz, 1H), 4.26 (dd, $J = 16.8, 1.6$ Hz, 1H), 3.96 (d, $J = 17.2$ Hz, 1H), 3.56 (dd, $J = 16.0, 4.4$ Hz, 1H), 2.98 (dd, $J = 15.6, 12.0$ Hz, 1H).

10 ^{13}C NMR (d-DMSO, 100M): 166.76, 165.09, 147.53, 146.54, 137.56, 136.7, 134.50, 126.23, 121.73, 119.77, 119.35, 118.59, 111.79, 108.43, 107.40, 105.27, 56.05, 55.89, 53.81, 23.94.

Example 2 Synthesis of Compound 1

15 Except for omitting Step 1 and replacing the product obtained from Step 1 with piperonal (3,4-(methylenedioxy)benzaldehyde) in step 2, Compound 1 was prepared by using a similar synthesis process to that in Example 1.

^1H NMR (500M, *d*-DMSO): δ 11.06 (s, 1 H), 9.50(s, 1H), 8.65(s, 1H), 7.50 (d, $J = 7.7$ Hz, 1 H), 7.24 (d, $J = 7.9$ Hz, 1 H), 7.01 (t, $J = 7.3$ Hz, 1 H), 6.95 (t, $J = 7.3$ Hz, 1 H), 6.84 (s, 1 H), 6.80 - 6.70 (m, 2H), 6.10 (s, 1 H), 5.84 (s, 2H), 4.33 (dd, $J = 11.5, 3.8$ Hz, 1 H), 4.10 (d, $J = 17.1$ Hz, 1 H), 3.87 (d, $J = 17.2$ Hz, 1 H), 3.46-3.40 (m, 1 H), 3.00 - 2.90 (m, 1 H).

Example 3 Synthesis of Compound 2

25 Except for omitting Step 1 and replacing the product obtained from Step 1 with piperonal (3,4-(methylenedioxy)benzaldehyde) in step 2, Compound 2 was prepared by using a similar synthesis process to that in Example 1.

¹HNMR (500M, *d*-DMSO): δ 11.16 (s, 1 H), 7.52 (d, *J* = 7.7 Hz, 1 H), 7.31 (d, *J* = 7.9 Hz, 1 H), 7.07 (t, *J* = 7.3 Hz, 1 H), 7.01 (t, *J* = 7.3 Hz, 1 H), 6.90 (s, 1 H), 6.80 - 6.70 (m, 2H), 6.11 (s, 1 H), 5.91 (s, 2H), 4.41 (dd, *J* = 1 1.5, 3.8 Hz, 1 H), 4.10 (d, *J* = 17.1 Hz, 1 H), 3.91 (d, *J* = 17.2 Hz, 1 H), 3.51-3.40 (m, 1 H), 3.21 (s, 3H), 3.02 - 2.95 (m, 1 H), 3.00-2.95(m, 4H).

5

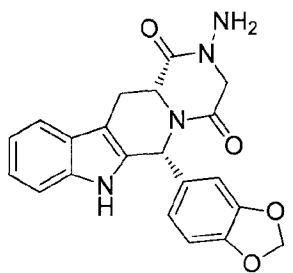
Example 4: Inhibition against PDE5

Method: IC₅₀ of an inhibition effect on PDE5A (E904, SIGMA-ALDRICH) of test compounds was determined by using Sildenafil (S1431, selleck) as a positive control sample and the method of Homogenous Time Resolve Fluoresce, HTF (Cat. No. 62GM2PEB, Cisbio.)

10

Test compounds	IC ₅₀ values
Cialis	111.6 nM
DDCI-01	33.6 nM
DDCI02 ^{note}	566.2 nM

Note: the chemical structure of Compound DDCI02 was shown as follows:



Example 5: Study on pharmacokinetics

15

Experimental methods:

Stock Solution Preparation: Cialis 1.13 mg, DDCI02 1.15 mg, DDCI-01 1.23 mg were weighed and dissolved in 1.13 mL, 1.15 mL, 1.23 mL of DMSO respectively, to achieve the concentration of 1.00 mg·mL⁻¹.

Sample Preparation Method: One step protein precipitation

Precipitant: ACN, with concentration of Verapamil (5.00 ng·mL⁻¹)

Calibration Curve and QC samples Preparation: 5.00 µL each of the calibration or QC working solution and 45.0 µL of blank plasma were transferred into a 1.5-mL microcentrifuge tube. Final standard curve concentration levels were 1.00, 2.50, 5.00, 10.0, 50.0, 100, 500 and 1000 ng·mL⁻¹. The QC sample concentration levels were 2.50 or 5.00, 50.0 and 800 ng·mL⁻¹. Dilution QC sample concentration level was 5000 ng·mL⁻¹.

Plasma Samples Preparation: Aliquots of 10.0 µL of real samples, calibration curve samples and QC samples were supplemented with 100 µL of precipitant. After vortexed for 3.00 min and centrifuged at 12000 rpm for 5.00 min, the supernatant 10 µL was injected for LC-MS/MS analysis.

Number of Rats/Group: 3/group

Administration Route: oral administration

Blood Collection Time: 0min, 15min, 30min, 1h, 2h, 4h, 6h, 8h, 24h

DDCI-01:

PK Parameters		PO-1	PO-2	PO-3	Mean	SD	RSD (%)
Dose	mg·kg ⁻¹	10.0					
K _{el}	h ⁻¹	0.327	0.269	0.319	0.305	0.032	10
t _{1/2}	h	2.12	2.58	2.17	2.29	0.251	11
t _{max}	h	2.00	2.00	2.00	2.00	0	0
C _{max}	ng·mL ⁻¹	1304	1574	1528	1468.7	144	10
AUC _{0-t}	h·ng·mL ⁻¹	9970	11202	11080	10750	679	6.3
AUC _{0-inf}	h·ng·mL ⁻¹	9976	11221	11087	10761	683	6.3
AUMC _{0-t}	h·h·ng·mL ⁻¹	48497	50539	50911	49982	1300	2.6
AUMC _{0-inf}	h·h·ng·mL ⁻¹	48665	51065	51110	50280	1399	2.8
MRT _{PO}	h	4.88	4.55	4.61	4.68	0.174	3.7

DDCI02

PK Parameters		PO-7	PO-8	PO-9	Mean	SD	RSD (%)
Dose	mg·kg ⁻¹	10.0					
K _{el}	h ⁻¹	0.143	0.221	0.216	0.193	0.0437	23
t _{1/2}	h	4.85	3.14	3.21	3.73	0.969	26
t _{max}	h	0.250	0.250	0.250	0.250	0	0
C _{max}	ng·mL ⁻¹	4583	4288	5171	4681	450	10
AUC _{0-t}	h·ng·mL ⁻¹	18125	15563	14723	16137	1772	11
AUC _{0-inf}	h·ng·mL ⁻¹	18576	15617	14794	16329	1989	12
AUMC _{0-t}	h·h·ng·mL ⁻¹	85428	56156	50008	63864	18926	30
AUMC _{0-inf}	h·h·ng·mL ⁻¹	99393	57718	52047	69719	25854	37
MRT _{PO}	h	5.35	3.70	3.52	4.19	1.01	24

Cialis

PK Parameters		PO-1	PO-2	PO-3	Mean	SD	RSD (%)
Dose	mg·kg ⁻¹	10.0					
K _{el}	h ⁻¹	0.200	0.197	0.346	0.248	0.0851	34
t _{1/2}	h	3.46	3.51	2.00	2.99	0.858	29
t _{max}	h	4.00	4.00	4.00	4.00	0	0
C _{max}	ng·mL ⁻¹	747	676	1356	926	374	40
AUC _{0-t}	h·ng·mL ⁻¹	8717	5993	11723	8811	2866	33
AUC _{0-inf}	h·ng·mL ⁻¹	8812	6051	11729	8864	2839	32
AUMC _{0-t}	h·h·ng·mL ⁻¹	53611	32747	71748	52702	19516	37
AUMC _{0-inf}	h·h·ng·mL ⁻¹	56364	34440	71915	54240	18828	35
MRT _{PO}	h	6.40	5.69	6.13	6.07	0.356	5.9

The above pharmacokinetics results indicated that both C_{max} and AUC of DDCI-01 were greater than those of Cialis. Furthermore, the half-life ($T_{1/2}$) of DDCI-01 in SD rat was slightly shorter than that of Cialis and significantly shorter than that of DDCI02.

5 Example 6: Pharmacology Study on Erectile Function of Normal Rat

Measurement of Change in Blood Pressure and Intracavernous Pressure

Rats were anesthetized with 2% pentobarbital (3 mg/kg), then incision was made in the right side of neck, a PE-50 silicon tube connected with a pressure transducer was inserted into the carotid artery, to record the change of the blood pressure (The blood pressure began to drop rapidly when an electronic stimulation started, and the blood pressure quickly returned to normal when the electronic stimulation ended).

Via the incision in the inferior abdomen, exposing the lateral surface of prostate, a 23-gauge needle was inserted into the corpus cavernosum, filled with heparin (250 U/mL), and connected with a pressure sensor. The erectile activity was induced by a bipolar stainless-steel, stimulus parameters at a pulse width of 2.56 ms, stimulation frequency of 7.98 Hz, current of 3 mA, stimulation duration of 40 s, and then record the intracavernous pressure (ICP).

Assessment of erectile function: ICP, BP, change of ICP and detumescence time were monitored through electric cavernous nerve stimulation at 2, 6 and 24 hours post dosing. Erectile function was evaluated by change of ICP and detumescence time.

Table 1: The blood pressure of study groups-2 hours after dosing (Mean± SD)

Group	BP before stimulation (mmHg)#	BP after stimulation (mmHg)	Change of BP (mmHg)
Vehicle	102.44±13.66	52.17±14.97	50.27±5.17
Cialis	100.98±4.48	64.14±9.86	36.85±7.34 *
DDCI-01 Low dose	97.43±11.45	63.89±2.93	33.54±13.57 *
DDCI-01 Middle dose	96.49±7.55	70.38±7.82	26.12±3.04 **
DDCI-01 High dose	91.86±21.57	60.97±19.95	30.89±4.09 *

Note: * P<0.05 , ** P<0.01 compared with Vehicle group.

Table 2: The intracavernous pressure of study groups-2 hours after dosing (Mean± SD)

Group	ICP before stimulation (mmHg)	ICP after stimulation (mmHg)	Change of ICP (mmHg)
Vehicle	8.81±3.06	26.55±4.33	18.75±4.48
Cialis	7.38±1.75	39.19±8.58 *	31.82±7.63 *
DDCI-01 Low dose	11.48±4.57	42.86±5.14 *	31.38±3.09 *
DDCI-01 Middle dose	8.49±2.06	41.58±7.94 *	33.09±7.46 *
DDCI-01 High dose	11.05±3.25	52.25±9.49 **	41.20±9.83 **

Note: * P<0.05 , ** P<0.01 compared with Vehicle group.

Table 3: The detumescence time of study groups-2 hours after dosing (Mean± SD)

Group	Change of BP /change of ICP	Detumescence Time(s)
Vehicle	38.14±13.17	9.75±4.92
Cialis	89.75±33.30	40.50±21.14 *
DDCI-01 Low dose	105.52±41.17 *	38.00±10.42 *
DDCI-01 Middle dose	128.64±35.20 *	40.75±4.79 *
DDCI-01 High dose	136.85±41.98 **	101.00±21.56 **

Note: * P<0.05 , ** P<0.01 compared with Vehicle group.

Table 4: The blood pressure of study groups-6 hours after dosing (Mean± SD)

Group	BP before stimulation (mmHg)	BP after stimulation (mmHg)	Change of BP (mmHg)
Vehicle	95.97±4.28	52.58±1.62	43.40±4.78
Cialis	91.20±28.48	58.14±14.30	33.07±17.13
DDCI-01 Low dose	95.73±18.25	61.78±17.93	33.95±3.20
DDCI-01 Middle dose	92.91±19.51	61.03±12.64	31.88±7.39
DDCI-01 High dose	76.38±21.11	50.09±22.36	26.29±1.54

Note: Compared with Vehicle group, all no significance.

Table 5: The intracavernous pressure of study groups -6 hours after dosing (Mean± SD)

Group	ICP before stimulation (mmHg)	ICP after stimulation (mmHg)	Change of ICP (mmHg)
Vehicle	8.78±2.46	25.37±3.87	16.59±5.11
Cialis	7.61±1.53	41.76±6.49 *	34.15±6.99 *
DDCI-01 Low dose	8.98±3.06	40.36±5.92 *	31.38±7.73 *
DDCI-01 Middle dose	6.72±3.14	40.21±8.37 *	33.49±8.09 *
DDCI-01 High dose	9.20±8.79	50.94±11.12 **	41.74±7.92 **

Note: * P<0.05 , ** P<0.01 compared with Vehicle group.

Table 6: The detumescence time of study groups-6 hours after dosing (Mean± SD)

Group	Change of BP /change of ICP	Detumescence Time(s)
Vehicle	39.30±15.86	9.50±2.52
Cialis	117.16±42.07 *	44.25±13.35 **
DDCI-01 Low dose	94.70±33.16 *	47.75±11.79 *
DDCI-01 Middle dose	106.19±16.03 *	48.00±23.85 *
DDCI-01 High dose	159.65±33.86 **	64.00±19.37 **

5 Note: * P<0.05 , ** P<0.01 compared with Vehicle group.

Table 7: The blood pressure of study groups-24 hours after dosing (Mean± SD)

Group	BP before stimulation(mmHg)	BP after stimulation(mmHg)	Change of BP(mmHg)
Vehicle	100.82±10.18	61.53±12.03	39.30±3.70
Cialis	112.26±7.30	78.00±2.68	34.26±7.18
DDCI-01 Low dose	108.36±8.89	72.34±12.33	36.03±10.90
DDCI-01 Middle dose	102.18±15.12	69.85±12.70	32.33±8.76
DDCI-01 High dose	94.16±9.79	52.95±14.12	41.21±11.98

Note: Compared with Vehicle group, all no significance.

Table 8: The intracavernous pressure of study groups-24 hours after dosing (Mean± SD)

Group	ICP before stimulation (mmHg)	ICP after stimulation (mmHg)	Change of ICP(mmHg)
Vehicle	7.42±2.26	27.02±5.41	19.61±3.44
Cialis	7.63±4.03	43.01±6.19 **	35.38±4.55 **
DDCI-01 Low dose	12.91±5.02	43.55±5.05 **	30.65±0.98 **
DDCI-01 Middle dose	8.41±1.86	40.00±5.56 **	31.58±5.75 **
DDCI-01 High dose	9.41±3.81	52.77±2.07 **	43.36±4.90 **

5

Note : ** P<0.01 compared with Vehicle group.

Table 9: The detumescence time of study groups-24 hours after dosing (Mean± SD)

Group	Change of BP /change of ICP	Detumescence Time(s)
Vehicle	49.67±5.59	8.75±1.71
Cialis	107.99±32.42	41.25±10.34 *
DDCI-01 Low dose	92.05±31.72	23.75±12.84
DDCI-01 Middle dose	106.03±44.12	41.25±14.50 *
DDCI-01 High dose	113.00±38.23	60.75±24.14 **

Note : * P<0.05 , ** P<0.01 comparing with Vehicle group.

Experimental results in Tables 1-9 showed that after the test compound DDCI-01 was administered to the normal rat model, all three different doses of DDCI-01, including high, middle, and low doses, significantly improved the erectile function of the normal rat model by prolonging the detumescence time and significantly increasing the ICP in the normal rat model. The dose of Cialis used in this experiment was close to human normal dose.

10 Example 7: The Efficacy Study of DDCI-01

Experiment procedure

1.1.1 Compound preparation

Serial dilute compounds in DMSO

- ◆ 3-fold serial dilute Cialis and DDCI-01 from 10mM of stock solution in DMSO;

1.1.2 Compound treatment

- i. Supplementing 99 μ l assay buffer per well, then adding 1 μ l compound in DMSO dilution to wells of V96 MicroWell Plates and uniformly mixing;
- ii. Adding 5 μ l compound in assay buffer dilution to each well of 96-well microplate; the final concentration of compound as below:

10000, 3333, 1111, 370.4, 123.5, 41.2, 13.7, 4.6, 1.5, 0.51, 0.17 [nM];

The inhibitory potential of test compounds on several types of phosphodiesterase (PDE) activity was determined according to the protocol of assay kit. The screening results were shown in Table 10.

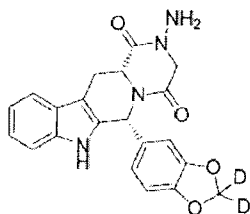
5 Table 10 The inhibition effect of test compounds on several types of PDE activity

PDE	IC ₅₀ (μM)	
	Cialis (ref.)	DDCI-01
PDE1A	>10	>10
PDE2A	>10	>10
PDE3A	>10	>10
PDE3A	>10	>10
PDE4A	>10	>10
PDE6C	12.53	14.67
PDE7A	>10	>10
PDE11A	1.60	2.64

The above results showed that among the 7 other PDE isoforms, DDCI-01 showed weak inhibitory activity against PDE6C (IC₅₀>10 μM) and PDE11A (IC₅₀=2.6 μM), while had no inhibition effect (0% inhibition at 10 μM) on PDE1A, 2A, 3A, 4A1A, and 7A.

What is claimed is:

1. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is:



Compound DDCI-01.

2. A pharmaceutical composition comprising: a compound or a pharmaceutically acceptable salt thereof as defined in claim 1; and a pharmaceutically acceptable carrier, excipient or diluent.

3. Use of a compound or a pharmaceutically acceptable salt thereof as defined in claim 1 in the preparation of a medicament for treating and/or preventing a disease or condition related with phosphodiesterase type 5 in a mammal.

4. Use of a pharmaceutical composition as defined in claim 2 in the preparation of a medicament for treating and/or preventing a disease or condition related with phosphodiesterase type 5 in a mammal.

5. The use of claim 3 or 4, wherein the medicament is for oral administration, local administration, intramuscular administration, intradermal administration, intraperitoneal administration, subcutaneous administration, intravenous administration, or inhalation administration.

6. The use of claim 3 or 4, wherein the medicament is for oral administration.
7. The use of any one of claims 3 to 6, wherein the medicament is formulated into tablets, capsules, lozenges, dragees, pills, granules, powders, solutions, emulsions, suspensions, dispersions, syrups, gels, or aerosols.
8. Use of a compound or a pharmaceutically acceptable salt thereof as defined in claim 1 for treating and/or preventing a disease or condition related with phosphodiesterase type 5 in a mammal.
9. The use of claim 8, wherein the compound or a pharmaceutically acceptable salt thereof is for oral administration, local administration, intramuscular administration, intradermal administration, intraperitoneal administration, subcutaneous administration, intravenous administration, or inhalation administration.
10. The use of claim 8, wherein the compound or a pharmaceutically acceptable salt thereof is for oral administration.
11. The use of claim 8, wherein the compound or a pharmaceutically acceptable salt thereof is formulated into tablets, capsules, lozenges, dragees, pills, granules, powders, solutions, emulsions, suspensions, dispersions, syrups, gels, or aerosols.
12. Use of a pharmaceutical composition as defined in claim 2 for treating and/or preventing a disease or condition related with phosphodiesterase type 5 in a mammal.
13. The use of claim 12, wherein the pharmaceutical composition is for oral administration, local administration, intramuscular administration, intradermal administration,

intraperitoneal administration, subcutaneous administration, intravenous administration, or inhalation administration.

14. The use of claim 12, wherein the pharmaceutical composition is for oral administration.

15. The use of claims 12, wherein the pharmaceutical composition is formulated into tablets, capsules, lozenges, dragees, pills, granules, powders, solutions, emulsions, suspensions, dispersions, syrups, gels, or aerosols.

16. The use of any one of claims 3 to 15, wherein the disease or condition related with phosphodiesterase type 5 is erectile dysfunction.

17. Use of a compound or a pharmaceutically acceptable salt thereof as defined in claim 1 for inhibiting phosphodiesterase type 5 in a mammal.

18. Use of a pharmaceutical composition as defined in claim 2 for inhibiting phosphodiesterase type 5 in a mammal.

19. The use of any one of claims 3 to 18, wherein the mammal is a human.

20. A compound or a pharmaceutically acceptable salt thereof of as defined in claim 1 for treating and/or preventing a disease or condition related with phosphodiesterase type 5 in a mammal.

21. The compound or pharmaceutically acceptable salt thereof of claim 20, wherein the mammal is a human.

22. The compound or pharmaceutically acceptable salt thereof of claim 20 or 21, wherein the disease or condition related with phosphodiesterase type 5 is erectile dysfunction.

23. The compound or pharmaceutically acceptable salt thereof of claim 20, 21, or 22, wherein the compound or pharmaceutically acceptable salt thereof is used for oral administration, local administration, intramuscular administration, intradermal administration, intraperitoneal administration, subcutaneous administration, intravenous administration, or inhalation administration.

24. The compound or pharmaceutically acceptable salt thereof of claim 20, 21, or 22, wherein the compound or pharmaceutically acceptable salt thereof is used for oral administration.

25. The compound or pharmaceutically acceptable salt thereof of claim 20, 21, or 22, wherein the compound or pharmaceutically acceptable salt thereof is formulated into tablets, capsules, lozenges, dragees, pills, granules, powders, solutions, emulsions, suspensions, dispersions, syrups, gels, or aerosols.

26. A pharmaceutical composition as defined in claim 2 for treating and/or preventing a disease or condition related with phosphodiesterase type 5 in a mammal.

27. The pharmaceutical composition of claim 26, wherein the mammal is a human.

28. The pharmaceutical composition of claim 26 or 27, wherein the disease or condition related with phosphodiesterase type 5 is erectile dysfunction.

29. The pharmaceutical composition of claim 26, 27, or 28, wherein the pharmaceutical composition is used for oral administration, local administration, intramuscular administration, intradermal administration, intraperitoneal administration, subcutaneous administration, intravenous administration, or inhalation administration.

30. The pharmaceutical composition of claim 26, 27, or 28, wherein the pharmaceutical composition is used for oral administration.

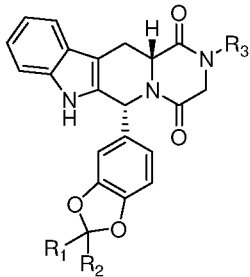
31. The pharmaceutical composition of claim 26, 27, or 28, wherein the pharmaceutical composition is formulated into tablets, capsules, lozenges, dragees, pills, granules, powders, solutions, emulsions, suspensions, dispersions, syrups, gels, or aerosols.

32. A compound or a pharmaceutically acceptable salt thereof as defined in claim 1 for inhibiting phosphodiesterase type 5 in a mammal.

33. The compound or a pharmaceutically acceptable salt thereof of claim 32, wherein the mammal is a human.

34. A pharmaceutical composition as defined in claim 2 for inhibiting phosphodiesterase type 5 in a mammal.

35. The pharmaceutical composition of claim 34, wherein the mammal is a human.



(I)